16. APPENDICES

APPENDIX 16.1: TRIAL INFORMATION

APPENDIX 16.1.1: PROTOCOL AND PROTOCOL AMENDMENTS

PROTOCOL CLARIFICATION MEMORANDUM

PROTOCOL NUMBER ZP4207-16051

AMENDMENT NUMBER 7.0, 06 January 2017

MEMORANDUM DATE: 25 January 2017

PROTOCOL TITLE: The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

PROTOCOL CLARIFICATION AND RATIONALE:

This memorandum was developed to clarify the glucose testing being performed at the study site during the treatment visits (Visits 3 and 4).

Section 7.4.1 and section 9.2 of the protocol currently state –

At Visit 3 and Visit 4, plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.

Whole blood samples are drawn from the subject's IV and used for both the YSI 2300 STAT Plus and the Nova StatStrip Xpress glucose measurements. Since the YSI 2300 STAT Plus is configured to report glucose results as whole blood glucose values, these results are being converted to equivalent plasma glucose values using a conversion factor of 1.12 by study staff on-site during the treatment visits. The conversion is performed based on the manufacturer's instructions in Appendix 15 of the YSI 2300 STAT Plus user manual, and the conversion factor of 1.12 assumes a normal average hematocrit of approximately 45. For the Nova StatStrip Xpress, the glucose results are automatically converted by the glucometer and reported as plasma glucose values, so no manual conversion of this data is required.

The conversion of whole blood glucose results from the YSI 2300 STAT Plus to plasma glucose results is necessary for comparability of all blood glucose data across the study.

It is important to note that throughout the protocol the term "blood glucose" (BG) is used to refer to "plasma glucose" or equivalent values regardless of which equipment is used to perform the measurement.

Clinical decisions including increased frequency of blood glucose sampling are made based on the plasma glucose values. AE reporting for hypoglycemia (see protocol section 10.5) is performed based on the plasma glucose values.

These clarifications will be incorporated into the protocol if a subsequent amendment occurs.

Approval Signature

[redacted] MD
Vice President, Clinical Development
Zealand Pharma A/S

Date

[redacted] DVM, PhD
Principal Clinical Pharmacologist
Zealand Pharma A/S

Date

Investigator Agreement

I have received and read this protocol clarification memorandum dated 25 January 2017.

[redacted]
Investigator's Signature
Steven J. Russell, MD, PhD
Diabetes Research Center
Massachusetts General Hospital

Date

[redacted]

SUMMARY OF CHANGES DOCUMENT

PROTOCOL NUMBER ZP4207-16051

AMENDMENT NUMBER 7.0

PROTOCOL TITLE: The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

AMENDMENT DATE: 06 January 2017

SUMMARY AND JUSTIFICATION OF CHANGES:

This amendment was developed to include operational changes regarding basal insulin rate adjustments, blood glucose (BG) levels during exercise, safety lab sampling, questionnaires, Investigational Medicinal Product (IMP) accountability, and Sponsor discontinuation criteria.

After the basal rate of the patient's own insulin infusion pump is changed to be 2-fold higher than weighted mean of the basal rate during the trial period (intended to increase the usage of glucagon during the treatment visit), the basal insulin rate may be decreased during the treatment visit at the discretion of the Investigator. To the extent possible, the same basal rate should be used at Visit 3 and Visit 4.

If, during exercise, the patient's BG is <50 mg/dL, the exercise will be terminated regardless of heart beats achieved.

Chemistry and hematology samples will be collected immediately after end of exercise.

The patient questionnaires have been removed.

Accountability for used pre-filled syringes will be made in accordance with the IMP standard operating procedures (SOPs).

The Sponsor, Investigator, or a pertinent regulatory authority may decide to stop the trial or part of the trial at any time (e.g., upon completion of Part 1 [iPhone-based BP]), but agreement on procedures to be followed must be obtained.

The schedule of procedures was updated to reflect the changes specified in this document. Other minor edits were made throughout the protocol to provide greater clarity and consistency.

SUMMARY OF CHANGES:

The amended protocol sections and the details of the changes are summarized in the following sections. Revisions to the protocol are presented as strikethrough (ie, ~~subject~~) for text that was removed and bold (ie, **subject**) for text that was added.

Section 6.2, Storage and Drug Accountability of IMPs, Page 27

Original Text:

All used, partly used, and unused vials or prefilled syringes must be kept by the Investigator and stored between +2ºC and +8ºC (unused) or at room temperature (partly used and used). Used and unused pre-filled syringes must be stored separately.

New Text:

All used, partly used, and unused vials ~~or prefilled syringes~~ must be kept by the Investigator and stored between +2ºC and +8ºC (unused) or at room temperature (partly used and used). ~~Used and unused~~ **Accountability for used** pre-filled syringes ~~must~~ **will** be ~~stored separately~~ **made in accordance with the IMP standard operating procedures (SOPs)**.

Section 7.4.1, Visit Procedures, Page 34

Original Text:

- The control algorithm will be initialized only with the patient's weight. Diagnostics will be performed to ensure that the CGM device is appropriately calibrated and that all of the components of the BP systems are in working order.
- The basal rate of the patient's own insulin infusion pump will be changed to be 2-fold higher than weighted mean of the basal rate during the trial period. This is intended to increase the usage of glucagon during the treatment visit.
- The patients will continue to wear their own infusion pump infusing at the temporary 2-fold basal rate throughout the visit until the start of the structured exercise period, in addition to the BP.

New Text:

- The control algorithm will be initialized only with the patient's weight. Diagnostics will be performed to ensure that the CGM device is appropriately calibrated and that all of the components of the BP systems are in working order.
- The basal rate of the patient's own insulin infusion pump will be changed to be 2-fold higher than weighted mean of the basal rate during the trial period. This is intended to increase the usage of glucagon during the treatment visit. **The basal insulin rate may be decreased during the treatment visit at the discretion of the Investigator. To the extent possible, the same basal rate should be used at Visit 3 and Visit 4.**
- The patients will continue to wear their own infusion pump infusing at the temporary ~~2-fold~~ basal rate throughout the visit until the start of the structured exercise period, in addition to the BP.

Section 7.4.1, Visit Procedures, Page 35

Original Text:

- At approximately 15 minutes before the meal, patients will administer a bolus for the meal with their own insulin pump based on the carbohydrate count for the meal.
- After lunch is completed, the patients will not be allowed any carbohydrate intake (non-caloric drinks will be permitted) until the trial is completed (except as necessary to treat hypoglycemia), to allow the BP to control the post-prandial BG without further interruption.

New Text:

- At approximately 15 minutes before the meal, patients will administer a bolus for the meal with their own insulin pump based on the carbohydrate count for the meal **in agreement with the Investigator**.
- After lunch is completed, the patients will not be allowed any carbohydrate intake (non-caloric drinks will be permitted) until the trial is completed (except as necessary to treat hypoglycemia), to allow the BP to control the post-prandial BG without further interruption.

Section 7.4.1, Visit Procedures, Page 35

Original Text:

- Patients will exercise on a stationary bike with a heart rate from 120-140 beats per minute for a total of 4,000 heart beats (approximately 30 minutes). Patients will rate their exercise intensity using the Borg scale every 5 minutes, with the target intensity level between 12 and 14. Heart rate will be measured every 5 minutes.
- BG measurements will be obtained off of the IV line every 10 minutes. If BG is <80 mg/dL, BG measurements will be obtained off of the IV line every 5 minutes.
    - Carbohydrates will be given for any BG <50 mg/dL according to the following protocol: Dextrose (g) = BSA (m^2)/[1.7 m^2 (women) or 1.9 m^2 (men)] *15 g.
    - Repeat treatments will be given at 15-minute intervals as long as BG remains <50 mg/dL.

New Text:

- Patients will exercise on a stationary bike with a heart rate from 120-140 beats per minute for a total of 4,000 heart beats (approximately 30 minutes). Patients will rate their exercise intensity using the Borg scale every 5 minutes, with the target intensity level between 12 and 14. Heart rate will be measured every 5 minutes.
- **Chemistry and hematology samples will be collected immediately after end of exercise (see Appendix B).**
- BG measurements will be obtained off of the IV line every 10 minutes. If BG is <80 mg/dL, BG measurements will be obtained off of the IV line every 5 minutes.
    - **If BG is <50 mg/dL, the exercise will be terminated regardless of heart beats achieved.**
    - Carbohydrates will be given for any BG <50 mg/dL according to the following protocol: Dextrose (g) = BSA (m^2)/[1.7 m^2 (women) or 1.9 m^2 (men)] *15 g.
    - Repeat treatments will be given at 15-minute intervals as long as BG remains <50 mg/dL.

Section 7.4.1, Visit Procedures, Page 36

Original Text:

- Patients will answer questionnaires (see Appendix C).
- Chemistry and hematology samples will be collected at visit end (see Appendix B).
- The BP and glucose meters will be collected and downloaded.

New Text:

- ~~Patients will answer questionnaires (see Appendix C).~~
- ~~Chemistry and hematology samples will be collected at visit end (see Appendix B).~~
- The BP and glucose meters will be collected and downloaded.

Section 7.4.2, Data Collected During the Treatment Visits, Page 36

Original Text:

- Timing and amount of carbohydrates taken for hypoglycemia
- Data from a questionnaire about attitudes and expectations regarding the BP before and after each treatment arm (see Appendix C)
- Time patients were not under BP control for any reason

New Text:

- Timing and amount of carbohydrates taken for hypoglycemia
- ~~Data from a questionnaire about attitudes and expectations regarding the BP before and after each treatment arm (see Appendix C)~~
- Time patients were not under BP control for any reason

Section 7.4.2, Data Collected During the Treatment Visits, Page 37

Original Text:

- Concomitant medications
- Chemistry and hematology samples (see Appendix B) at visit start and visit end
- ADA (Visit 3 only)

New Text:

- Concomitant medications
- Chemistry and hematology samples (see Appendix B) at visit start and ~~visit~~ **immediately after** end **of exercise**
- ADA (Visit 3 only)

Section 12.3, Data Entry, Page 50

Original Text:

Data must be recorded using the electronic data capture (EDC) system as the trial is in progress. The patient questionnaires will be transcribed into the EDC system by site personnel. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct trial data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

[redacted]

New Text:

Data must be recorded using the electronic data capture (EDC) system as the trial is in progress. ~~The patient questionnaires will be transcribed into the EDC system by site personnel.~~ All site personnel must log into the system using their secure user name and password in order to enter, review, or correct trial data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

Section 13.9, Sponsor Discontinuation Criteria, Page 54

Original Text:

The Sponsor, Investigator, or a pertinent regulatory authority may decide to stop the trial or part of the trial at any time but agreement on procedures to be followed must be obtained.

New Text:

The Sponsor, Investigator, or a pertinent regulatory authority may decide to stop the trial or part of the trial at any time **(e.g., upon completion of Part 1 [iPhone-based BP]),** but agreement on procedures to be followed must be obtained.

Appendix A, Schedule of Procedures, Footnote 10, Page 60

Original Text:

10. At visit start and visit end

New Text:

10. At visit start and ~~visit~~ **immediately after** end **of exercise**

[redacted]

Clinical Trial Protocol
ZP4207-16051

Version number: 8.0
Amendment 7.0
Date: 06 January 2017

CLINICAL TRIAL PROTOCOL

The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

Investigational Product: ZP4207
Protocol Number: ZP4207-16051
IND Number: 129980
Phase: 2

Principal Investigator:
Steven J. Russell, MD, PhD[1]

Co-Investigator:
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Original Version: 03 May 2016
Amendment Number 1.0: 28 June 2016
Amendment Number 2.0: 03 August 2016
Amendment Number 3.0: 17 August 2016
Amendment Number 4.0: 02 September 2016
Amendment Number 5.0: 09 September 2016
Amendment Number 6.0: 28 September 2016
Amendment Number: 7.0
Protocol Version Number: 8.0

Date: 06 January 2017

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Date: 06 January 2017

SIGNATURE PAGE

TRIAL TITLE: The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the trial.

Signature [redacted] Date [redacted]

[redacted] MD
Vice President, Clinical Development
Zealand Pharma A/S

[redacted] [redacted]

[redacted] DVM, PhD
Principal Clinical Pharmacologist
Zealand Pharma A/S

Clinical Trial Protocol
ZP4207-16051

Version number: 8.0
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Date: 06 January 2017

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the trial as described. I will conduct this trial in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the trial within the time designated. I will provide copies of this protocol and access to all information furnished by Zealand Pharma A/S to trial personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the trial product and trial procedures. I will let them know that this information is confidential and proprietary to Zealand Pharma A/S and that it may not be further disclosed to third parties. I understand that the trial may be terminated or enrollment suspended at any time by Zealand Pharma A/S, with or without cause, or by me if it becomes necessary to protect the best interests of the trial patients.

I agree to conduct this trial in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations, and ICH Guidelines for Good Clinical Practices.

[redacted]

Investigator's Signature

January 9, 2017
Date

Steven J. Russell, MD, PhD
Investigator's Printed Name

[redacted]

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SYNOPSIS

TITLE: The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

PROTOCOL NUMBER: ZP4207-16051

INVESTIGATIONAL PRODUCT: ZP4207

PHASE: 2

INDICATION: ZP4207 is an anti-hypoglycemic glucagon analog in a ready-to-use liquid formulation which is being studied to improve glycemic control in adults (and children) with type 1 diabetes mellitus (T1DM) as part of a bihormonal bionic pancreas (BP).

OBJECTIVES:

Primary: The primary objective is to conduct a trial testing the safety and tolerability of the BP using either the iLet or the iPhone platform when used with ZP4207 in 20 adult (≥18 years of age) patients with T1DM.

Secondary: The secondary objectives are to measure glycemic regulation, including hypoglycemia exposure (percent of time spent with continuous glucose monitor [CGM] glucose <60 mg/dL), evaluate BP device reliability, and to document the satisfaction of patients with the BP with the goal of optimizing the functionality and user interface of the BP.

POPULATION: Up to 40 adult (≥18 years of age) patients who already manage their T1DM using continuous subcutaneous (SC) insulin infusion pump therapy can be enrolled. It is expected that up to 10 patients will complete each part of the trial protocol.

TRIAL DESIGN: This trial is a single-center, open-label, 2-part, randomized cross-over trial. The trial will enroll adult patients with T1DM and will assess the safety and efficacy of the BP using either the iLet or the iPhone platform using the glucagon analog ZP4207 versus Lilly glucagon. In Part 1, up to 10 patients will participate in two 1-day treatment arms in random order (iPhone-based BP using ZP4207 and iPhone-based BP using Lilly glucagon) according to a pre-generated randomization scheme. In Part 2, up to 10 new patients will participate in two 1-day treatment arms in random order (iLet using ZP4207 and iLet using Lilly glucagon) according to a pre-generated randomization scheme. Patients can only participate in 1 part of the trial. An interim database lock may occur upon completion of Part 1 of the trial to analyze the iPhone-based BP data. The iLet and the iPhone-based BP will also administer insulin (insulin lispro, Lilly Humalog) using the same blood glucose (BG) control algorithm for all 4 treatment arms. The trial will be conducted at a single center, the Massachusetts General Hospital Diabetes Center in Boston, MA.

TRIAL TREATMENT: The trial involves SC administration of insulin lispro (Humalog, Lilly), which is commercially available by prescription and is indicated for patients with T1DM, but not for use in a BP.

[redacted]

The trial also involves SC administration of Lilly glucagon in 1 iLet arm and 1 iPhone-based BP arm. Lilly glucagon is commercially available by prescription and is indicated for patients with T1DM in severe hypoglycemia, but not for use in a BP.

The trial also involves SC administration of the glucagon analog ZP4207, 1 mg/mL, in the other iLet arm and the other iPhone-based BP arm. ZP4207 will be made available by Zealand Pharma A/S, Denmark as liquid formulation in prefilled syringes of 0.6 mL.

PRIMARY ENDPOINT: The primary endpoint is the safety and tolerability of ZP4207 in the BP using either the iLet or the iPhone platform as assessed by:

- Number and type of adverse events (AEs)
- Clinical laboratory measurements
- Vital signs
- 12-lead electrocardiogram (ECG)
- Local tolerability and infusion site reactions as measured with the Draize scale
- Immunogenicity as measured by anti-drug antibodies
- Pain as measured on a 10 cm visual analog scale (VAS)
- Nausea as measured on a 10 cm VAS

SECONDARY ENDPOINTS: The secondary endpoints include measurements of BP function as well as glycemic and non-glycemic measurements.

Bionic Pancreas Function
This endpoint data will be generated from the BP data during each treatment visit:

- Average percent insulin dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
    - Average percent glucagon/ZP4207 dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts calculated by the BP algorithm that are successfully issued to the pump by the BP (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts calculated by the BP control algorithm that are successfully issued by the BP
    - Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully issued by the BP
- Average percent of 5-minute steps during which the BP is functioning nominally in all respects based on real-time CGM data (new CGM glucose reading captured, dose calculated, and dose issued to pumps)

[redacted]

- Average percent of 5-minute steps during which the BP is functioning nominally with or without a new CGM glucose reading captured (dose calculated and dose issued to pumps). If a CGM signal is not available, the dose calculated may be based on weight or historical basal rates.
- CGM reliability index, calculated as percent of possible values actually recorded by CGM
- CGM Mean Absolute Relative Difference versus time-stamped BG values from meter download
- List of technical faults associated with the BP including cause and resolution

Glycemic
All of following metrics will be generated from the Dexcom G4 Platinum CGM data during each treatment visit:

- Fraction of time spent within each of the following glucose ranges:
  - <50 mg/dL
  - <60 mg/dL
  - <70 mg/dL
  - 70-120 mg/dL
  - 70-140 mg/dL
  - 70-180 mg/dL
  - >180 mg/dL
  - >250 mg/dL
  - >300 mg/dL
- Number of severe hypoglycemic events (patients unable to self-treat, requiring the assistance of another person)
- Number of episodes of symptomatic hypoglycemia
- Number of carbohydrate interventions for hypoglycemia
- Total grams of carbohydrates taken for hypoglycemia
- Mean CGM glucose

Non-glycemic

- Glucagon/ZP4207 total delivery per kg of body mass
- Insulin total delivery per kg of body mass
- Number of unscheduled infusion set replacements
- Number of unscheduled CGM sensor changes

EVALUATION OF TRIAL DATA: The following variables will be evaluated according to treatment for safety purposes: AEs, local tolerability, laboratory safety assessments, physical examination, vital signs, and 12-lead ECGs.

The analysis of BP function endpoints and glycemic endpoints will be on an intention-to-treat basis. In cases where a treatment arm was not completed (and that arm was not repeated according to protocol criteria), available data from that arm will be used in the data analysis.

The Shapiro-Wilk test will be used to determine the normality of the residuals for each comparison. Summary tables that display descriptive statistics, including percentages, means or medians, and standard deviation and/or ranges, as appropriate, will be provided.

[redacted]

A paired t-test or the Wilcoxon signed rank test for comparison of means with normally or non-normally distributed residuals, respectively, will be used. In a secondary analysis any period effect and any interaction between treatment and period will be looked for, although no such interaction is predicted for the efficacy outcome.

The number of patients and proportions of severe hypoglycemic events, symptomatic hypoglycemia, and carbohydrate interventions due to hypoglycemia with the event counts will be summarized descriptively, and the proportions will be analyzed by a Fisher's exact test if data allow.

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LIST OF FIGURES

[redacted]

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibodies
AE	Adverse event
BG	Blood glucose
BP	Bionic pancreas
BTLE	Bluetooth Low Energy
BU	Boston University
CFR	Code of Federal Regulations
CGM	Continuous glucose monitor
CRO	Contract research organization
DBP	Diastolic blood pressure
DBR	Database review
DPP-4	Dipeptidyl peptidase-4
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FDA	Food and Drug Administration
FHD	First Human Dose
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GUI	Graphical user interface
HCG	Human chorionic gonadotropin
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IM	Intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
MD	Doctor of Medicine
MedDRA	Medical Dictionary for Regulatory Activities
MGH	Massachusetts General Hospital

[redacted]

Abbreviation	Definition
MPC	Model-predictive control
PD	Pharmacodynamic
PK	Pharmacokinetic
RN	Registered nurse
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SC	Subcutaneous
SGLT-2	Sodium-glucose co-transporter-2
SIV	Site Initiation Visit
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 diabetes mellitus
TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
ULN	Upper limit of normal
VAS	Visual analog scale

[redacted]

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Background and Rationale

To date, clinical trials conducted by Boston University (BU) and Massachusetts General Hospital (MGH) in patients with type 1 diabetes mellitus (T1DM) have demonstrated the practicality of a wearable automated bionic pancreas (BP) control system for robust glucose regulation using a continuous glucose monitor (CGM) to provide the input to the control system. Despite current technical limitations in CGMs and infusion pumps, the trials by BU/MGH have shown that a bihormonal BP is capable of achieving safe and effective blood glucose (BG) control automatically, with minimal hypoglycemia during 11 continuous days in the face of unrestrained meals and exercise and with trivial patient input (optional announcement of meals).

The BP provides automatic BG regulation and reduces hypoglycemic episodes. Additionally, the system spares the wearer the relentless tasks of carbohydrate counting, frequent BG monitoring, estimating the effects of specific meals and exercise activity on BG levels, and manual drug administration, which are inexact, demanding, aggravating, and require continuous diligence and vigilance. The degree of glycemic control achieved by the BP is predicted to dramatically reduce the deleterious and debilitating complications of T1DM.

In its last tested embodiment, the BP consisted of a Dexcom G4 CGM, and an iPhone that are hardwired together, with the iPhone running the control algorithm and communicating via Bluetooth with 2 Tandem t:slim pumps to dose insulin and glucagon. The connections are repeatedly lost among these 4 components throughout the day, an issue that has the potential to adversely impact BG control, whether due to missed CGM values or missed doses. In addition, the troubleshooting required to repair these recurring disconnections can be burdensome to the user. Integrating these components into a single device would establish seamless connectivity among them, which would eliminate the need for such troubleshooting. This would lead to smoother device operation with fewer interruptions, which would enhance its user friendliness, optimize its BG control potential, and further improve the quality of life of its users.

The BU Investigators have recently designed, built, and tested a proprietary first-generation of such a fully integrated BP system, referred to as the iLet and the iLet infusion set. The iLet is a dual-chamber infusion system that currently incorporates the Dexcom G4 CGM technology, a custom user interface with touchscreen display, and all of the mathematical dosing algorithms that were tested in and validated using the iPhone-based BP in outpatient studies over the past 3 years. The iLet infusion set provides 2 independent subcutaneous (SC) fluid pathways from the iLet to the patient (1 for insulin and the other for glucagon). One tube connects to the prefilled insulin cartridge and the other tube connects to the fillable (single-use) glucagon cartridge.

In order to provide automatic BG regulation, the iLet and the iPhone-based BP have the ability to deliver both insulin and glucagon. However, currently available glucagon formulations have limited stability at room temperature, necessitating frequent changes to the glucagon infusion set. Therefore, the current trial is designed to test the glucagon analog ZP4207 in the iLet and the iPhone-based BP, as this peptide analog of human glucagon is provided in a liquid formulation stable at room temperature.

[redacted]

The current trial is a first feasibility trial designed to use the first-generation iLet and iLet infusion set and the iPhone-based BP to compare ZP4207 with marketed glucagon (Lilly). The trial is intended to demonstrate the safety and tolerability of ZP4207 in the iLet and the iPhone-based BP and the feasibility of achieving comparable autonomous glycemic control. It is not intended to comprehensively demonstrate the definitive efficacy of the BP in extended, continuous daily use, but rather to demonstrate its functionality and accuracy in a practical, albeit very controlled, clinical setting. The trial is expected to provide practical information that will benefit the design of a next-generation iLet and iLet infusion set and help pave the way for a more comprehensive outpatient home-use Phase 2 trial and ultimately a pivotal trial where comprehensive safety and efficacy through continuous full daily use of the iLet with ZP4207 will be documented.

The data derived from this trial will permit evaluation of the robustness of the iLet as well as the safety and efficacy of ZP4207 when used in conjunction with the iLet and the iPhone-based BP. The data obtained will be used to further improve the iLet and will allow BU/MGH to expand to larger outpatient trials using the iLet or the iPhone-based BP with ZP4207.

1.2 Bihormonal Bionic Pancreas System

The BP is an autonomous, self-learning system that requires only the patient's weight for initialization, and then autonomously adapts, modestly or dramatically, as needed, to cope with the wide range of insulin requirements of adults, adolescents, and pre-adolescents with T1DM. The BP obviates the need for the patient to know, or even appreciate, their insulin requirements, and renders obsolete any need for patients or caregivers to know carbohydrate-to-insulin ratios, basal rates, or insulin correction factors.

The core technology is a suite of control algorithms that orchestrate the automated dosing of insulin and glucagon to regulate BG levels. An insulin controller orchestrates all SC insulin dosing. At its centerpiece is a model-predictive control (MPC) algorithm, which bases insulin doses on the glucose data and insulin absorption kinetics, compensating for the slow absorption rate of SC insulin analogs (peak time in blood of 30-90 minutes, clearance in 4-8 hours). This enables the algorithm to refrain from stacking and overdosing insulin. Furthermore, the MPC algorithm automatically adjusts its insulin-dosing aggressiveness continuously and in real-time to different insulin needs between individuals and variable needs within the same individual. Running in parallel with the MPC algorithm is an algorithm that automatically modulates basal insulin delivery over multiple time scales, and another algorithm that automatically adapts insulin doses in response to optional meal announcements. Unlike current insulin pumps and the insulin-only control algorithms, the adaptive basal insulin algorithm obviates the need for the user to set, or even know, his or her “basal-rate profile.” Instead, it is capable of automatically adapting to, and compensating for, changes in an individual's basal insulin need, such as might occur over a period of hours, days, or weeks (e.g., circadian hormonal fluctuations, intercurrent illness, physical activity, or emotional state) or as might occur over a period of months or years due to developmental changes (e.g., hormonal changes that occur during puberty or menopause). The adaptive meal dose controller obviates the need for the user to set, or even know, his or her “carbohydrate-to-insulin ratios,” as it makes automatic adjustments based on dosing history for similar meal announcements made on previous days, and customizes the dose for each individual and for time of day.

The BP also includes a proportional-derivative algorithm governing SC micro-doses of glucagon to help prevent impending hypoglycemia. Glucagon dosing is based on the glucose level and rate of descent. It may occur preemptively even if glucose is above range, and it includes a feedback term to account for the pending effects of recent glucagon doses.

Taken together, these mathematical algorithms provide a universal framework for a glycemic control strategy that requires no quantitative input from, or participation by, the user (besides entering body weight to initialize the system), but which automatically adapts insulin and glucagon dosing to meet the individual needs of each user. Another challenge met is enabling the technology to remain completely autonomous in managing insulin and glucagon delivery even when the CGM is offline. Specifically, when the CGM is offline, the BP invokes the high-resolution “basal rate profile” that it had recently learned and stored when the CGM was online. On the basis of what the system learned and stored about meal announcements when the CGM was online, it is able to respond to meal announcements in the same manner when the CGM is offline. Finally, it automatically responds to user-entered BG values when the CGM is offline by issuing a correction dose of insulin or glucagon based on what it learned about the user's insulin and glucagon needs when the CGM was online. Thus, the BP never relies on, or burdens the user with, the determination of subjective dosing decisions, which inevitably vary in quality and reliability among different users. The BP provides a turnkey solution for people with T1DM that comprehensively manages glycemia across a broad range of individual needs and across a large spectrum of circumstances and challenges to glycemic control.

A significant challenge for the use of glucagon in a bihormonal BP is the lack of a commercially available glucagon formation that is stable and well-suited to infusion over several days in a pump reservoir. However, BU/MGH have proceeded with studies using a relatively unstable marketed formulation that must be reconstituted from a lyophilized powder on a daily basis. This allowed BU/MGH to proceed with studies of the bihormonal system while awaiting the production of stable glucagon formulations or stable glucagon analogs.

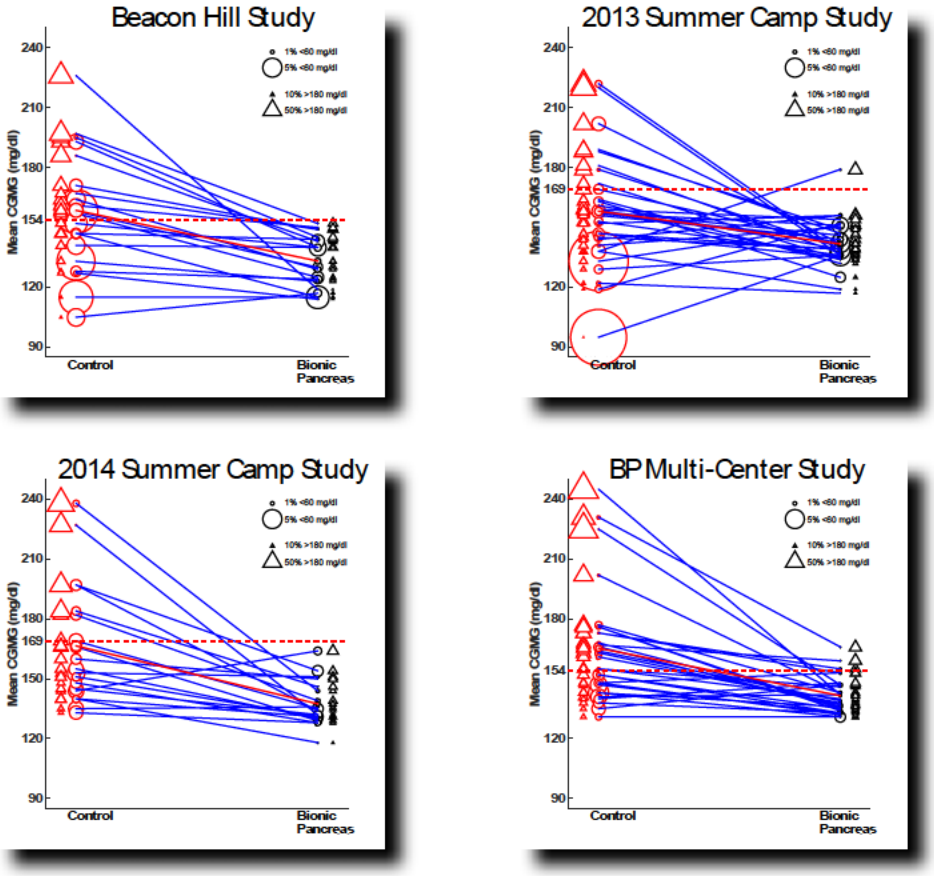
1.3 Preliminary Studies with the Bihormonal Bionic Pancreas System

The BP hardware platform has evolved over the years from a laptop-driven system, which was used in all inpatient studies to the first truly mobile wearable iPhone-driven platform, which has been used in a number of outpatient studies. Using the iPhone-based BP system, >110 outpatient experiments of 5-11 days in duration in each subject have been conducted (>800 patient days or >2 patient years of data) across subjects ranging in age between 6 and 76 years old and in body mass between 21 and 128 kg. The robust adaptation capabilities of the BP is evident in the fact that the average total daily dose of insulin among these subjects varied by over 13-fold (from 11 to 145 units/day).

In November 2012, Food and Drug Administration (FDA) approval was obtained to conduct the first outpatient study testing the BP in adults 21 years or older with T1DM. This study, referred to as the Beacon Hill Study, followed a random-order cross-over design in which 20 adults with T1DM participated in 5 days on the iPhone-based BP and 5 days of usual care in which they wore a CGM with blinded display and muted alarms. In the BP arm, subjects kept to a 3-square-mile geographic area centered around the Beacon Hill neighborhood in Boston. They ate as they chose at local restaurants, and exercised at will with access to 2 gyms. Analysis was pre-specified to focus on Days 2-5, since glycemic control is more representative of BP performance after most of the adaptation by the BP occurs on Day 1 (Russell, 2014). Results are summarized in Figure 1.

[redacted]

Figure 1. Outpatient Results Summarizing the Distribution of Mean CGM Glucose Levels and Hypoglycemia in the BP and Control Arms



Study	Age (years)	Bionic Pancreas (BP) Mean CGM glucose level (mg/dl)	Bionic Pancreas (BP) % of CGM glucose levels <50 mg/dl (%)	Bionic Pancreas (BP) % of CGM glucose levels 70–180 mg/dl (%)	Control Mean CGM glucose level (mg/dl)	Control % of CGM goucose values <50 mg/dl (%)	Control % of CGM goucose values 70–180 mg/dl (%)	*p* value (BP versus Control) for: Mean CGM glucose level	*p* value (BP versus Control) for: % of CGM glucose values <50 mg/dl	*p* value (BP versus Control) for: % of CGM glucose values 70–180 mg/dl
Beacon Hill (n 20, 5-day experiments)	≥21	133	1.5	80	159	3.7	59	<0.001	0.020	<0.001
2013 Summer Camp (n 32, 5-day experiments)	12–20	142	1.3	76	158	2.2	65	0.004	0.192	<0.001
2014 Summer Camp (n 19, 5-day experiments)	6–11	137	1.2	81	168	2.8	58	0.004	0.001	<0.001
BP Multi Center (n 39, 11-day experiments)	≥18	141	0.6	78	162	1.9	62	<0.001	<0.001	<0.001

Mean CGM glucose levels for each subject under usual care (red circles) are connected with the subject's mean CGM glucose level on the BP (black circles). The diameters of the circles shown are proportional to the percentage of CGM glucose values <60 mg/dL, and the size of the triangle is proportional to the percentage of CGM glucose values >180 mg/dL. The horizontal red dashed line refers to the glucose level corresponding to the American Diabetes Association therapy goal for each age group tested, which corresponds to 154 mg/dL (HbA1c of 7%) for adults and 169 mg/dL (HbA1c of 7.5%) for children. Results are summarized in the table, where the co-primary outcomes (mean CGM glucose level and percentage of CGM glucose values <60 mg/dL) for the BP arm are highlighted in red for each of the 4 studies.
BP = bionic pancreas; CGM = continuous glucose monitoring; HbA1c = hemoglobin A1c.

In April 2013, FDA approval was obtained to conduct the first outpatient study testing the BP in adolescents 12-20 years old with T1DM. This study, referred to as the 2013 Summer Camp Study, followed a random-order cross-over design in which 32 adolescents with T1DM participated in 5 days on the BP and 5 days of supervised camp care in which they wore a CGM with blinded display and muted alarms. Subjects were fully integrated into normal camp activities without restrictions on diet or exercise. The study used the same iPhone-based BP that was used in the Beacon Hill Study. Results are summarized in Figure 1 (Russell, 2014). In April 2014, FDA approval was obtained to conduct the first outpatient study testing the BP in pre-adolescents 6-11 years old with T1DM. This study, referred to as the 2014 Summer Camp Study, was similar in design to the 2013 Summer Camp Study. Results are summarized in Figure 1 (Russell, 2016).

In April 2014, FDA approval was obtained to conduct the first multi-center study, which was also the first home study, to test the BP in adults 18 years or older with T1DM. This study, referred to as the Bionic Pancreas Multi-Center Study, followed a random-order cross-over design in which 39 adults participated in 11 days on the BP and 11 days of usual care. Participants went to work as usual, and lived and slept at home, all without clinical supervision. There were no restrictions placed on diet or exercise. The study included 4 medical centers (10 subjects per center), which included MGH, the University of Massachusetts Medical School, Stanford University, and the University of North Carolina at Chapel Hill. Results are summarized in Figure 1.

All of these studies used marketed glucagon (glucagon for injection, Eli Lilly). Due to its limited stability, Lilly glucagon must be reconstituted immediately before use. Animal studies have previously shown that despite its limited chemical stability, Lilly glucagon maintains its biological activity for up to 7 days in solution. Using this data, an Investigational New Drug (IND) exemption was obtained from the FDA for its use in a pump for up to 27 hours. This allowed these studies to be performed by asking volunteers to reconstitute a new vial of glucagon and fill the glucagon pump at approximately the same time every day. However, marketed Lilly glucagon has no path forward for approval for chronic BP use.

1.4 ZP4207

ZP4207 is a peptide analog of human glucagon that is being developed to treat hypoglycemia in patients with T1DM and type 2 diabetes mellitus. ZP4207 exhibits improved physical and chemical stability in aqueous media and is suitable for liquid formulation. ZP4207 is comprised of 29 amino acids and has 7 amino acid substitutions when compared to native glucagon.

Two clinical Phase 1 trials have been conducted to establish safety and tolerability of ZP4207 after single and multiple dosing to healthy patients and T1DM patients under insulin-induced hypoglycemic conditions.

The First Human Dose (FHD) trial (ZP4207-14013) was finalized in April 2015. The trial was a randomized, double-blinded trial with the objectives to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of ZP4207 as compared to an active comparator. Part 1 included a single ascending dose in healthy volunteers in cohorts of 8. In each cohort, the patients were randomized 3:1 to ZP4207 (n=6) or Novo Nordisk GlucaGen® (n=2). Five cohorts with SC administration (0.01, 0.1, 0.3, 1.0, and 2.0 mg ZP4207 compared to 1 mg GlucaGen) and 3 cohorts with intramuscular (IM) administration (0.3, 1.0, and 2.0 mg ZP4207 compared to 1 mg GlucaGen) were included. Part 2 included 2 sequence groups of

[redacted]

10 hypoglycemic T1DM patients. The patients were treated with fixed single IM doses of 0.7 mg ZP4207 and 1.0 mg GlucaGen in a sequential cross-over design in a randomized treatment order.

The second clinical trial (ZP4207-15007) was a single-center, double-blind, Phase 1b trial investigating the safety and tolerability, PK and PD of ZP4207 following repeated administration in healthy volunteers compared to placebo. It was finalized in July 2015. Each of the 3 cohorts comprised 8 subjects, who received 5 repeated SC doses of ZP4207 or placebo in a 3:1 treatment allocation. The first cohort started with the lowest dose of 0.1 mg. Cohort 2 and 3 continued with 0.3 and 1.0 mg, respectively.

The Phase 1 results did not give rise to specific safety concerns, beyond those related to the pharmacological effect of ZP4207. All adverse events (AEs) recorded in the trials were of mild or moderate severity. The most frequent systemic AE related to treatment with ZP4207 was nausea, which is a known side-effect following administration of glucagon. The most frequent injection site reaction was transient erythema, occurring in all ZP4207, glucagon, and placebo treatment groups, irrespective of dose. No anti-drug antibodies (ADA) incidences were observed.

The observed PD response, in terms of increased plasma glucose, in insulin-induced hypoglycemic patients with T1DM following dosing with 0.7 mg ZP4207 administered IM was similar to that observed following IM dosing with 1.0 mg glucagon (GlucaGen, Novo Nordisk). An increase in plasma glucose of ≥20 mg/dL from hypoglycemic levels was achieved within 30 minutes for all patients.

In terms of PK, ZP4207 had a short half-life and high clearance and dose proportionality for both maximum plasma concentration and area under the concentration-time curve from time 0 to 300 minutes in the dose range 0.1 to 2.0 mg following SC administration. Following IM administration, dose proportionality was shown in the investigated dose range of 0.3 to 2.0 mg. The PK properties of 0.7 mg ZP4207 IM were comparable with those of 1.0 mg glucagon (GlucaGen, Novo Nordisk) with IM administration.

1.5 Risk/Benefit

While the potential risks are minimal, the findings of this trial may reveal information that can substantially improve medical care for persons with diabetes. Therefore, the overall risk/benefit for patients participating in this trial is assessed as acceptable.

Potential Risks and Discomforts

Trial patients will be informed by the Investigator of the potential risks of ZP4207 and other trial-related procedures before they enter the trial.

In this trial, patients with T1DM will be included to test the safety and efficacy of the BP using either the iLet or the iPhone platform when used with ZP4207 versus Lilly glucagon. The cross-over design with inclusion of 1 group of 10 T1DM patients into the 2 iLet treatment arms and the inclusion of a second group of 10 T1DM patients into the 2 iPhone-based BP treatment arms in a randomized order will allow for a direct comparison of the safety and efficacy of the 2 treatments, based on intra-patient variability only.

[redacted]

Patients may experience mild discomfort associated with the insertion of the infusion sets and sensor into the SC tissues. The risk of discomfort due to insertion of infusion sets and sensors is expected to be slightly greater than in their lives outside the trial because more infusion sets will be inserted and a CGM sensor will be inserted. Most patients will use only 1 infusion set and not all will use a CGM sensor in usual care.

There is a potential risk of hypoglycemia, since recombinant insulin analog will be administered. Due to frequent monitoring of glucose and direct supervision by a registered nurse (RN) or Doctor of Medicine (MD) at all times, the risk of a hypoglycemic episodes leading to significant harm to patients is expected to be substantially lower than their risk during their usual therapy.

There is a risk of hyperglycemia. This risk is expected to be less than the risk during the patients' lives outside of the trial based on data from earlier BP trials and the design of this trial.

Treatment with ZP4207 and marketed glucagon can result in undesired effects or complaints. Undesired effects and complaints such as gastrointestinal side effects including nausea, vomiting, and diarrhea are known side effects of glucagon administration at higher dose levels. The frequency of nausea associated with the administration of 1 mg of glucagon according to the Summary of Product Characteristics (SPC) for Glucagon is described to be between 1/10 and 1/100. The frequency of vomiting is described to be between 1/100 and 1/1000 (Novo Nordisk, 2015). Similar gastrointestinal side effects have also been observed to a limited degree in the 2 clinical trials conducted with ZP4207, again at higher dose levels. The individual doses of ZP4207 and Lilly glucagon delivered by the BP are expected to be significantly lower than doses typically associated with nausea. Episodes of low blood pressure have also been observed after administration of higher doses of glucagon and ZP4207. As with every novel drug substance, new and yet unknown side effects may also occur.

There are limited data available to describe the immunogenic potential of glucagon products available on the market, but the data available indicate that marketed glucagon only has a small immunogenic potential. A Phase 1 trial performed with recombinant human glucagon and animal derived glucagon in 75 healthy patients did not show signs of ADA measured 13 weeks after trial product administration (Eli Lilly, 2005). In the ZP4207 FHD trial, ZP4207-14013, no confirmed anti-ZP4207 or anti-glucagon antibodies were detected in any of the samples. In addition, the 5 sequential administrations of ZP4207, as applied in trial ZP4207-15007, were not associated with the development of antibodies against ZP4207 in the 18 subjects enrolled to receive ZP4207. The optimized formulation of ZP4207, as applied in the present trial is not expected to change the immunogenic potential of the Investigational Medicinal Product (IMP).

In relation to diabetes therapy, development of insulin-antibodies is documented more substantially and route of administration has been shown to influence immunogenic potential of insulins. However, these antibodies against insulin generally do not have an impact on insulin action and are thus not clinically relevant.

In terms of consequence, development of high titer antibodies against ZP4207 could, in theory reduce the activity of endogenous glucagon, which again, in theory could influence

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hypoglycemic episodes. However, most patients with T1DM do not secrete glucagon normally in response to hypoglycemia, so they would be less likely to be negatively impacted by anti-glucagon antibodies. Limited suppression of glucagon would, however, not be considered critical, as low glucose levels can also be corrected by other means, including oral intake of glucose and by other endogenous hormones such as oxyntomodulin.

Overall, ZP4207 is judged to be a low-risk molecule, based upon the available clinical data as well as the outcome of the risk-based approach to the immunogenicity assessment made. The present trial will include sampling for measurement of antibodies against ZP4207 prior to first dosing (Visit 3), at the ADA Assessment Visit (Visit 5), and at the Follow-up Visit (Visit 6). In line with regulatory guidance documents, these samples will be appropriately analyzed and the results will be included in the overall assessment of the immunogenic potential of ZP4207 after completion of each trial and as the clinical development program advances.

Administration of ZP4207 may be associated with a risk of allergic reactions similar to those observed for other therapeutic peptides or proteins. Patients with known or suspected allergies to the trial products or related products will be excluded from the trial. Mild or moderate allergic reactions may include symptoms of rash, fever, flu-like symptoms, nausea, headache, and myalgia. Acute generalized hypersensitivity reactions are usually very rare but may include symptoms of flushing, sweating, dizziness, change in blood pressure, and difficulties in breathing. The risk of acute hypersensitivity reactions is described to be less than 1/10,000 for native glucagon. No severe acute hypersensitivity reactions have been observed in the 2 clinical trials conducted with ZP4207.

Potential Benefits

Based on experiences from previous trials of the BP and the design of this trial, patients enrolled in the trial may benefit from a reduction in risk of hypoglycemia and hyperglycemia and a better mean glucose compared to their usual diabetes care during their short trial participation.

The data derived from this trial will allow evaluation of safety and tolerability of ZP4207 in the iLet and the iPhone-based BP, and the robustness and effectiveness of the new BP control system. The data obtained will be used to further improve the iLet and will allow the expansion to larger outpatient trials using the iLet or the iPhone-based BP with ZP4207.

This trial is a necessary step in preparing the BP with ZP4207 to become available to people with T1DM. Wide availability of the BP with ZP4207 could improve the medical care of adults and children with T1DM.

[redacted]

2 TRIAL OBJECTIVES

2.1 Primary Objective

The primary objective is to conduct a trial testing the safety and tolerability of the BP using either the iLet or the iPhone platform when used with ZP4207 in 20 adult (≥18 years of age) patients with T1DM.

2.2 Secondary Objectives

The secondary objectives are to measure glycemic regulation, including hypoglycemia exposure (percent of time spent with CGM glucose <60 mg/dL), evaluate BP device reliability, and to document the satisfaction of patients with the BP with the goal of optimizing the functionality and user interface of the BP.

3 TRIAL DESCRIPTION

3.1 Summary of Trial Design

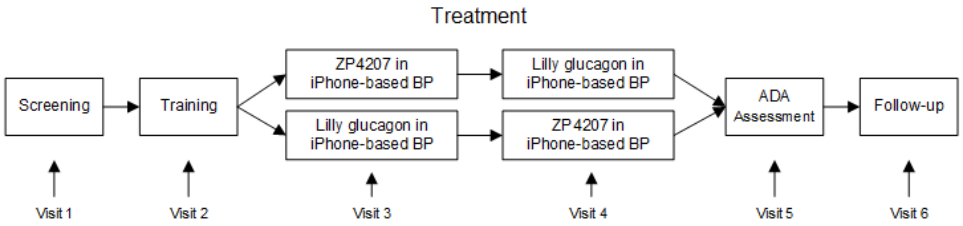
This trial is a single-center, open-label, 2-part, randomized cross-over trial. The trial will enroll adult patients with T1DM and will assess the safety and efficacy of the BP using either the iLet or the iPhone platform using the glucagon analog ZP4207 versus Lilly glucagon. In Part 1, up to 10 patients will participate in two 1-day treatment arms in random order (iPhone-based BP using ZP4207 and iPhone-based BP using Lilly glucagon) according to a pre-generated randomization scheme. In Part 2, up to 10 new patients will participate in two 1-day treatment arms in random order (iLet using ZP4207 and iLet using Lilly glucagon) according to a pre-generated randomization scheme. Patients can only participate in 1 part of the trial. An interim database lock may occur upon completion of Part 1 of the trial to analyze the iPhone-based BP data. The iLet and the iPhone-based BP will also administer insulin (insulin lispro, Lilly Humalog) using the same BG control algorithm for all 4 treatment arms. The trial will be conducted at a single center, the MGH Diabetes Center in Boston, MA.

The overall trial design schematic is displayed in Figure 2.

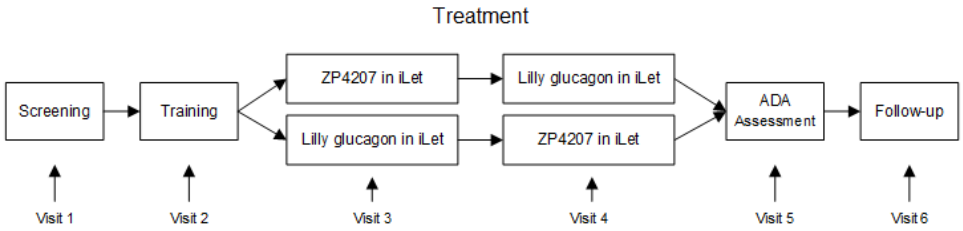
[redacted]

Figure 2. Trial Design Schematic

Part 1:



Part 2:



Patients can only participate in 1 part of the trial.
ADA = anti-drug antibodies; BP = bionic pancreas.

3.2 Indication

ZP4207 is an anti-hypoglycemic glucagon analog in a ready-to-use liquid formulation which is being studied to improve glycemic control in adults (and children) with T1DM as part of a bihormonal BP.

3.3 Number of Patients

Up to 40 adult patients with T1DM can be enrolled. The upper bound is based on the expectation that some patients will be excluded after the Screening Visit and the possibility that some patients may have to be discontinued before completion (due to, for instance, inter-current illness or patient withdrawal). It is expected that up to 10 patients will complete each part of the trial protocol.

4 SELECTION AND WITHDRAWAL OF PATIENTS

The trial will enroll patients who already manage their T1DM using continuous SC insulin infusion pump therapy. This requirement is imposed because multiple daily injection therapy involves the use of medium-acting or long-acting basal insulin that would require an extended washout period.

4.1 Inclusion Criteria

1. Male and female patients with T1DM for at least 1 year, as defined by the American Diabetes Association
2. Age ≥18 years
3. Diabetes managed using an insulin pump for ≥6 months
4. Prescription medication regimen stable for >1 month (except for medications that will not affect the safety of the trial and are not expected to affect any outcome of the trial, in the judgment of the Investigator)
5. Informed consent obtained before any trial-related activities (trial-related activities are any procedure that would not have been performed during normal management of the patient)
6. Patients in good health according to age (medical history, physical examination, vital signs, 12-lead electrocardiograms [ECGs], laboratory assessments), as judged by the Investigator

4.2 Exclusion Criteria

1. Unable to provide informed consent (e.g., impaired cognition or judgment)
2. Unable to safely comply with trial procedures and reporting requirements (e.g., impairment of vision or dexterity that prevents safe operation of the BP, impaired memory, unable to speak and read English)
3. Participation in another clinical trial of an investigational agent or device concurrently or within 1 month (or 5 half-lives) prior to the Screening Visit
4. Previous exposure to ZP4207
5. Females of childbearing potential who are pregnant (positive urine human chorionic gonadotropin [HCG]), breast feeding, plan to become pregnant in the immediate future, or sexually active without using highly effective contraception methods (highly effective methods are considered those with a failure rate less than 1% undesired pregnancies per year including surgical sterilization, hormonal intrauterine devices [coil], oral hormonal contraceptives, sexual abstinence, or a surgically sterilized partner) or postmenopausal women amenorrheic for less than 1 year with serum follicle-stimulating hormone (FSH) level ≤40 IU/L and not using highly effective contraceptive methods during the trial and until 1 month after last dosing in the trial
6. Male who is sexually active and not surgically sterilized who or whose partner(s) is not using highly effective contraceptive methods (highly effective contraceptive measures include surgical sterilization, hormonal intrauterine devices [coil], oral hormonal contraceptives, each in combination with spermicide-coated condoms), or who is not willing to refrain from sexual intercourse from the first dosing until 1 month after last dosing in the trial
7. Current alcohol abuse (intake averaging >3 drinks daily in last 30 days) or use within the last 6 months of controlled substances without a prescription (other than marijuana)
8. New onset clinically significant illness within 4 weeks prior to screening, as judged by the Investigator
9. Unwilling or unable to refrain on the treatment visits from:
    a. Acetaminophen in any form
    b. Use of drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the trial (use of beta blockers will be allowed as long as the dose is stable and the patient does not meet the criteria for hypoglycemia unawareness while

[redacted]

taking that stable dose, but use of benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the Investigator)

10. History of liver disease that is expected to interfere with the anti-hypoglycemia action of glucagon (e.g., liver failure or cirrhosis). Other liver disease (i.e., active hepatitis, steatosis, active biliary disease, any tumor of the liver, hemochromatosis, glycogen storage disease) may exclude the patient if it causes significant compromise to liver function or may do so in an unpredictable fashion.
11. Aspartate aminotransferase >2 × upper limit of normal (ULN), alanine aminotransferase >2 × ULN, or bilirubin >1.5 × ULN on screening laboratories
12. Renal failure on dialysis or estimated glomerular filtration rate <30 mL/min/1.73 m^2 on screening laboratories
13. Hemoglobin <12 gm/dL for men and <11 gm/dL for women
14. Personal history of cystic fibrosis, pancreatitis, pancreatic tumor, or any other pancreatic disease besides T1DM
15. Any known history of coronary artery disease including, but not limited to, history of myocardial infarction, stress test showing ischemia, history of angina, or history of intervention such as coronary artery bypass grafting, percutaneous coronary intervention, or enzymatic lysis of a presumed coronary occlusion)
16. Congestive heart failure with New York Heart Association Functional Classification III or IV
17. History of transient ischemic attack or stroke in the last 12 months
18. Seizure disorder, history of any non-hypoglycemic seizure within the last 2 years, or ongoing treatment with anticonvulsants
19. History of hypoglycemic seizures (grand-mal) or coma in the last 12 months
20. History of hypoglycemic unawareness in the last 12 months
21. History of pheochromocytoma: fractionated metanephrines will be tested in patients with history increasing the risk for a catecholamine secreting tumor:
    a. Episodic or treatment refractory (requiring 4 or more medications to achieve normotension) hypertension
    b. Paroxysms of tachycardia, pallor, or headache
    c. Personal or family history of MEN 2A, MEN 2B, neurofibromatosis, or von Hippel-Lindau disease
22. History of adrenal disease or tumor
23. Hypertension with systolic blood pressure (SBP) ≥160 mm Hg or diastolic blood pressure (DBP) ≥100 mm Hg despite treatment
24. Hypotension (SBP <90 mm Hg or DBP <60 mm Hg), either sitting or standing, or orthostatic hypotension (decrease in SBP >20 mm Hg or decrease in DBP >10 mm Hg within 3 minutes of standing from a seated position)
25. Untreated or inadequately treated mental illness (indicators would include symptoms such as psychosis, hallucinations, mania, and any psychiatric hospitalization in the last year), or treatment with anti-psychotic medications that are known to affect glucose regulation
26. Electrically powered implants (e.g., cochlear implants, neurostimulators) that might be susceptible to radio frequency interference
27. History of adverse reaction to glucagon (including allergy) besides nausea and vomiting
28. History of severe hypersensitivity to milk proteins or lactose
29. Established history of allergy or severe reaction to adhesive or tape that must be used in the trial

[redacted]

30. Use of oral anti-diabetic medications (e.g., thiazolidinediones, biguanides, sulfonylureas, glitinides, dipeptidyl peptidase-4 [DPP-4] inhibitors, sodium-glucose co-transporter-2 [SGLT-2] inhibitors)
31. Inadequate venous access as determined by trial nurse or physician at time of screening
32. Any factors that, in the opinion of the Investigator, would interfere with trial endpoints or the safe completion of the trial

4.3 Target Population

Patients who meet all of the inclusion and none of the exclusion criteria will be considered as candidates for this trial. Individuals who have previously inquired about participation in BU/MGH trials and have asked to have their contact information kept on file will be contacted. In addition, advertisements for the trial may be posted at the MGH Diabetes Center and other places, and may be distributed in the weekly broadcast e-mail of research studies seeking volunteers. A letter may be sent to adult endocrinologists in the Boston metropolitan as well as selected nearby endocrinologists informing them of the trial and asking them to refer any eligible patients who might be interested. Information will be posted about the trial along with contact information on the BU/MGH website www.bionicpancreas.org and on www.clinicaltrials.gov.

4.4 Withdrawal Criteria

The participation of individual patients will be discontinued if they experience:

- Seizure or unconsciousness associated with hypoglycemia and associated with participation in the trial
- Persistent nausea and vomiting thought to be related to glucagon dosing associated with participation in the trial
- Hospitalization associated with participation in the trial
- Pregnancy
- Diabetic ketoacidosis

If more than 1 patient must be withdrawn from the trial for these reasons, the trial will stop and a vote of the Data and Safety Monitoring Board (DSMB) will be required to restart it. All AEs that are serious and unexpected but related will be reported to the DSMB within 5 working days.

Note that patients may discontinue participation at any time. Patients may be removed from the trial for other reasons, for instance, failure to comply with trial procedures or intercurrent illness that is unrelated to the BP but that precludes safe participation. Discontinuation of participation for these reasons will not contribute to a decision to discontinue the trial.

5 ASSIGNMENT TO TREATMENT GROUPS

This trial is an open-label, 2-part, randomized cross-over trial. Patients who have completed the Screening Visit and meet all of the inclusion and none of exclusion criteria will be enrolled into the trial. In Part 1, up to 10 patients will participate in two 1-day treatment arms in random order (iPhone-based BP using ZP4207 and iPhone-based BP using Lilly glucagon) according to a pre-generated randomization scheme. In Part 2, up to 10 new patients will participate in two 1-day treatment arms in random order (iLet using ZP4207 and iLet using Lilly glucagon)

[redacted]

according to a pre-generated randomization scheme. Up to 2 patients may participate in the trial per day. The order of the treatment visits will be randomized in blocks of 2 patients.

6 TRIAL TREATMENT

6.1 Investigational Medicinal Products

Insulin: The trial involves SC administration of insulin lispro *(*Humalog, Lilly*)*, which is commercially available by prescription and is indicated for patients with T1DM, but not for use in a BP.

Glucagon: The trial also involves SC administration of Lilly glucagon in 1 iLet arm and 1 iPhone-based BP arm. Lilly glucagon is commercially available by prescription and is indicated for patients with T1DM in severe hypoglycemia, but not for use in a BP.

ZP4207: The trial also involves SC administration of the glucagon analog ZP4207, 1 mg/mL, in the other iLet arm and the other iPhone-based BP arm. ZP4207 will be made available by Zealand Pharma A/S, Denmark as liquid formulation in prefilled syringes of 0.6 mL.

6.2 Storage and Drug Accountability of IMPs

All IMPs will be stored and handled in accordance with the Sponsor's instructions and/or the product labeling at the Investigator's site, e.g., refrigerated (+2ºC to +8ºC) and should not be exposed to excessive heat, direct sunlight and never be frozen.

All used, partly used, and unused vials must be kept by the Investigator and stored between +2ºC and +8ºC (unused) or at room temperature (partly used and used). Accountability for used pre-filled syringes will be made in accordance with the IMP standard operating procedures (SOPs).

The Investigator must ensure the availability of proper storage conditions and record and evaluate the temperature. Temperature of the refrigerator used for drug storage is monitored continuously, an alarm system is established. The Investigator must inform the monitor immediately if any IMP has been stored outside specified conditions (e.g., outside temperature storage). Investigational Medicinal Product that has been stored improperly must not be dispensed to any patient before it has been re-evaluated and approved for further use. The Investigator must take appropriate action to ensure correct storage.

For the IMP, the Investigator must keep an accurate record of all IMPs received and the products used for each patient in a Drug Accountability Record. Storage locations, batch numbers, and expiry dates are also documented in this form.

The drug accountability must be performed in a timely manner by the monitor.

6.3 Dispensing and Return of IMPs

No IMPs may be dispensed to any person not enrolled in the trial.

Upon completion of the trial, the Sponsor will be responsible for destruction or storage of IMPs (used, partially used, or unused). These duties can be delegated to a contract research organization (CRO) and must be documented in the trial files.

[redacted]

6.4 Doses

The iLet and the iPhone-based BP can administer isolated insulin-glucagon doses once every 5 minutes. A single automated bolus of insulin will not exceed 3 units per 5-minute dose (30 µl of U-100 insulin) in both systems, and a single meal-priming dose, in response to a meal announcement made by the user, will not exceed 12 units (120 µl of U-100 insulin). A single bolus of glucagon will not exceed 80 µg (80 µl of 1 mg/mL Lilly glucagon or 1 mg/mL ZP4207). In prior studies, typical doses of glucagon were in the range of 2.5-40 µg per dose. The iLet and the iPhone-based BP are capable of administering as little as ~0.5 µl (0.05 units of U-100 insulin or 0.5 µg of 1 mg/mL ZP4207).

It is expected that the mean total daily doses of glucagon/ZP4207 will be <1.0 mg daily as in previous studies. The mean daily glucagon dose in a previous 11-day outpatient trial was 0.5 mg/day (range 0.2-0.9 mg/day). Currently, single doses of up to 2 mg ZP4207 have been administered in clinical trials. The recommended dose of marketed glucagon for adult patients suffering from severe hypoglycemia is 1 mg as a single injection. Mean glucagon levels in previous inpatient studies have been above the normal fasting range for glucagon only 1% of the time. Therefore, the glucagon exposure of patients is expected to be modest.

6.5 iPhone-based Bionic Pancreas

Infusion Set: Patients will wear 2 FDA-approved commercially available infusion sets, 1 for insulin infusion and 1 for glucagon infusion. Infusion sets that are compatible with the Tandem t:slim infusion pump (luer lock connection) will be provided.

Continuous Glucose Monitors: One transcutaneous glucose sensor for the Dexcom G4 Platinum (Garcia, 2013) will be inserted in the abdominal SC tissue and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to the sensor and the whole assembly is held to the skin with an adhesive patch and communicates wirelessly with the BP. If the G4 sensor fails for any reason during the trial (loss of CGM signal), it will be replaced promptly.

Bionic Pancreas Control Unit: The control unit consists of a stock iPhone 4S and a Dexcom G4 Platinum receiver connected with a custom hardware interface and placed back-to-back in a custom enclosure. The G4 receiver converts the raw wireless signal from the transmitter into an estimated BG signal that is sent via a hardwired connection to the iPhone.

The iPhone runs iOS 6 in “Guided Access” mode, where the only app accessible to the patient is the Beta Bionics app, which runs the control algorithm. The home screen, where typical user options reside, is password protected. Access to other functions on the iPhone (primarily the Settings options) is separately password protected and only accessible to the study staff. This prevents accidental activation of other apps that could interfere with the function of the BP. The control algorithm app has a graphical user interface (GUI) that displays the current CGM glucose, a graphical history of the CGM glucose, and doses of insulin and glucagon delivered by the control algorithm. The GUI can also be used to input meal announcements, designating the size of the meal as larger than typical, typical in size, smaller than typical, or just a bite, and the type of meal as breakfast, lunch, or dinner. This will trigger a partial meal-priming bolus the size of which will adapt during the course of the trial to meet a target of 75% of the insulin needs for that size and type of meal.

[redacted]

The target glucose level will be programmed to 100 mg/dL by the study engineers prior to the start of each experiment. This will be locked for each arm of the study; the patient will be unable to accidentally change or tamper with this setting.

The GUI can be used to manage meal boluses and correction boluses during periods when the CGM is offline, such as the period after a sensor is replaced and before the new sensor has been calibrated. During these times the control algorithm will determine and direct the administration of insulin basal rates based on the patient's weight. The controller will also administer insulin and/or glucagon as appropriate in response to any entered BG values, just as if they were CGM values.

The GUI also displays visual alarms associated with an audio signal if communication is dropped between the CGM transmitter and the BP control unit or between the control unit and the 2 insulin pumps.

The iPhone communicates wirelessly via the Bluetooth Low Energy (BTLE) protocol with 2 Tandem t:slim insulin pumps to deliver insulin and glucagon.

Tandem t:slim Pumps: These pumps are FDA-approved insulin pumps with reservoirs capable of holding 300 units (3 mL) of insulin or 3 mL of glucagon or ZP4207 solution. The pumps have a mechanical dosing resolution of 1/120 (0.00833) unit and can deliver liquids at a maximal rate of ~33 µl per minute (2 mL per hour). They are slave to the BP control unit and are controlled wirelessly via the BTLE protocol by the iPhone 4S.

6.6 iLet Bionic Pancreas

Infusion Set: A novel, dual cannula infusion set has been designed specifically for use with the iLet. Patients will wear dual channel tubing that will be attached to 2 infusion sets with 1 steel cannula each, 1 for insulin infusion and the other for glucagon infusion. The tubing and infusion sets will have undergone sterilization prior to being delivered in a sealed pouch. The steel cannulae will be inserted in the abdominal SC tissue.

Continuous Glucose Monitors: One transcutaneous glucose sensor for the Dexcom G4 Platinum (Garcia, 2013) will be inserted in the abdominal SC tissue and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to the sensor and the whole assembly is held to the skin with an adhesive patch and communicates wirelessly with the BP. If the G4 sensor fails for any reason during the trial (loss of CGM signal), it will be replaced promptly.

Bionic Pancreas Control Unit: The iLet is being built according to Class III medical device standards, adheres to a comprehensive and robust quality system, and is fully compliant with International Organization for Standardization (ISO) 13485 standards and document control practices. The iLet is a fully-integrated dual-hormone BP system that integrates the CGM technology (currently the Dexcom G4 Share system) as well as 2 independent motor-drivetrain pumping assemblies, which independently actuate the delivery of insulin and glucagon from pre-filled cartridges that are separately loaded into the iLet housing. Each drivetrain assembly utilizes a lead screw, which is driven by a precision micromotor, a gear case assembly, and a motor controller unit, in a manner similar to what is commonly found in most insulin infusion pumps on the market today. The iLet has dosing accuracy that is comparable to FDA-approved insulin pumps currently on the market. The iLet has a built-in BTLE radio that

also allows automatic communication with the paired CGM, as well as the Nova StatStrip® Xpress BG meter (Nova Biomedical). The iLet does not contain a cellular nor a WiFi radio, and does not accept input data from another mobile device (e.g., smartphone), other than the paired CGM and BG meter(s).

The mathematical control algorithms (which are the same as those used in the iPhone-based BP), the CGM glucose engine (Dexcom), and the native user interface software, are all interconnected through controller framework software and reside as embedded systems on printed circuit boards contained within the device housing. The touchscreen-enabled, menu-driven user interface and onboard processor provide a comprehensive and standalone platform, which allows the iLet to operate independently of smartphones or other devices and without the need for internet support during routine operation. The graphical user interface of the iLet has the same user options and capabilities of the iPhone BP, including having its home screen password protected and its settings options only accessible to trial staff via a separate password.

6.7 Other Trial Devices

YSI 2300 STAT Plus™ (Yellow Springs Instruments): The YSI 2300 STAT Plus is an FDA-approved glucose analyzer. Blood glucose measurements using the YSI 2300 STAT Plus will be obtained off of the intravenous (IV) line during both treatment visits.

Nova Biomedical StatStrip Xpress Glucose Meter: The Nova StatStrip Xpress glucose meter is an FDA-approved glucose meter that is commercially available. Blood glucose measurements for CGM calibration will be obtained with the Nova StatStrip Xpress during both treatment visits if the YSI 2300 STAT Plus fails and via fingerstick with the Nova StatStrip Xpress during any periods when IV blood samples are not available for any reason or the IV fails.

Exercise Bike: The trial will utilize a stationary exercise bike (ergometer) for the in-clinic exercise at the treatment visits. This bike will be stored at the Diabetes Research Center when not in use.

6.8 Concomitant Medications

6.8.1 Permitted Medications and/or Procedures

Patients may take any over-the-counter medications that they wish during the trial, with the exception of any medication containing acetaminophen as that may cause interference with CGM sensing. All concomitant medications, including over-the-counter medications, should be recorded.

Use of beta blockers will be allowed as long as the dose is stable and the patient does not meet the criteria for hypoglycemia unawareness while taking that stable dose.

If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.

6.8.2 Excluded Medications and/or Procedures

During the trial, patients will not use any recreational drugs or drugs of abuse. The need to take prescription drugs that dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder appropriate decision-making may be grounds for exclusion from the trial or discontinuation of participation, a decision that will be made by the Investigator.

Use of benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the Investigator. Use of oral anti-diabetic medications (e.g., thiazolidinediones, biguanides, sulfonylureas, glitinides, DPP-4 inhibitors, SGLT-2 inhibitors) will also be excluded.

7 TRIAL PROCEDURES

7.1 Informed Consent

After potential patients have had time to review the consent document, and prior to any trial-related activities, they will meet with a trial MD or designee who will explain the trial, answer any questions, and administer informed consent. In the event that a volunteer is a patient of 1 of the trial MDs, another staff MD or designee will answer questions and administer consent. The patients will be fully informed of their responsibilities and their rights while participating in the trial as well as of the possible risks and potential benefits of participation in the trial. They will have the opportunity to discuss all questions and ample time to consider participation.

Trial-related activities are any procedures that would not have been performed during normal management of the patient. Patients who wish to participate in the trial will be asked to personally date and sign an informed consent form (ICF). Likewise, the Investigator must also personally date and sign the ICF. All patients will be provided with a copy of their own signed and dated ICF.

Trial staff will answer any questions that the patients may have during their participation. They will share any new information in a timely manner that may be relevant to the patient's willingness to continue participating in the trial. The patients may choose to discontinue their participation at any time.

7.2 Screening Visit (Visit 1)

All patients will have a Screening Visit to confirm eligibility. The patient will be interviewed and the electronic Case Report Form (eCRF) will be completed by trial staff to establish whether the patient is eligible.

Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator.

Once all of the results have been returned, a trial MD will review the eCRF to determine patient eligibility. If a patient is not eligible to continue in the trial, the results of abnormal tests will be reported to the patient and to a health care provider of their choosing.

[redacted]

7.2.1 Data Collected at Screening

- Age, sex, race, and ethnicity
- Date of last menstrual period in female patients
- Medical, surgical, and social history, allergies, and review of systems relevant to inclusion and exclusion criteria, including:
  - Date of diabetes diagnosis
  - Duration of insulin pump use and type of insulin used in pump
  - Type/model of insulin pump
  - Insulin regimen (basal rate, sensitivity factor, and carbohydrate ratio)
  - Average total daily dose of insulin in the last 30 days as available (from pump history)
  - Usage of CGM, if any (type of CGM, days per month worn, usage of data, whether insulin is dosed based on CGM alone, alarm settings)
- Concomitant illness (any illness present at screening)
- Concomitant medications (prescription and non-prescription) and date of last change in medication regimen
- Height, weight, physical examination, and vital signs including body temperature and blood pressure
- Orthostatic vital signs (heart rate and blood pressure) in the seated position and within 3 minutes of standing
- 12-lead ECG
- Hemoglobin A1c
- Chemistry and hematology samples (see Appendix B)
- Urine HCG pregnancy test for women of childbearing potential
- FSH level for postmenopausal women amenorrheic for less than 1 year
- Fractionated plasma metanephrines (if indicated by history)

7.3 Training Visit (Visit 2)

A Training Visit will take place before the first treatment visit. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor and trial policies and procedures. Trial staff will verify that the patients have understood the material and are competent to participate safely in the trial. Concomitant medications will also be reviewed.

Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator. The goals of diabetes management for patients during the fasting period are to avoid hypoglycemia, to treat hypoglycemia if it occurs, and to arrive at the treatment visit in the morning with a BG between 80 and 250 mg/dL. If insulin pump basal rates are properly configured, patients should be able to fast from 12:00 AM until the time of arrival for the visit without a high likelihood that they will become hypoglycemic or severely hyperglycemic. Patients will be asked whether they believe that they can safely fast from 12:00 AM until their arrival time at approximately 7:00 AM without adjusting their basal rates. If they have concerns, a trial physician will consult with them regarding pump basal rate adjustments. In all cases, subjects will be instructed to self-treat with carbohydrates according to the 15/15 rule (15 grams of carbohydrates, repeated in 15 minutes if necessary) during the overnight fasting period and at any time prior to their arrival at the trial site for the treatment visits.

[redacted]

7.4 Treatment Visits (Visit 3 and Visit 4)

- Visit 3 will take place at least 48 hours after screening (Visit 1) and no more than 30 days after screening (Visit 1).
- There will be a 24-hour minimum washout between Visit 3 and Visit 4 and a maximum of 3 weeks between Visit 3 and Visit 4.
- Up to 2 patients may participate per day.
- In Part 1, each patient will participate in 2 treatment visits: 1 with the iPhone-based BP using ZP4207 and 1 with the iPhone-based BP using Lilly glucagon in a randomized order.
- In Part 2, each patient will participate in 2 treatment visits: 1 with the iLet using ZP4207 and 1 with the iLet using Lilly glucagon in a randomized order.
- The night before the treatment visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be instructed to call if they encounter any difficulty with their CGM.
- Patients will be responsible for their own medications other than insulin during the trial. Any medical advice needed by the patients during their participation that is not directly related to BG control should be obtained from them in their usual manner. Patients may take any over-the-counter medications that they wish during the trial, with the exception of any medication containing acetaminophen as that may cause interference with CGM sensing. If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.
- During the trial, patients will not use any recreational drugs or drugs of abuse. The need to take prescription drugs that dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder appropriate decision-making may be grounds for exclusion from the trial or discontinuation of participation, a decision that will be made by the Investigator.
- Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator.
- Patients will not tamper with the BP, including changing any settings.
- Patients may not remove the BP during the trial unless the BP failed or they are withdrawing from the trial.
- The exact time of each procedure and assessment will be documented.

7.4.1 Visit Procedures

- Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window. If BG is <50 mg/dL, the patient will be treated with simple carbohydrate according to the 15/15 rule (15 grams of carbohydrates, repeated in 15 minutes if necessary). The visit will not need to be rescheduled unless the patient experiences a severe hypoglycemic event and requires treatment with glucagon or IV dextrose. If the visit needs to be rescheduled due to hypoglycemia or hyperglycemia, trial staff will assist the patient with insulin or medication adjustments to address glycemic control.

[redacted]

The patient will be instructed to contact trial staff later in the day if his or her BG remains uncontrolled.

- Upon arrival to the visit, the patient's weight and vital signs including body temperature and blood pressure will be documented.
- Orthostatic vital signs (heart rate and blood pressure) will be measured in the seated position and within 3 minutes of standing.
- Patient reports of symptoms, any other complaints, and AEs will be reviewed.
- Concomitant medications will be recorded.
- Chemistry and hematology samples will be collected at visit start (see Appendix B).
- ADA samples will be collected before the start of dosing (Visit 3 only).
- A 12-lead ECG will be performed.
- A urine HCG pregnancy test will be performed in female patients of childbearing potential. If the test is positive, the patient will be informed of the result and the visit will be ended.
- Patients will complete a baseline survey about their attitudes and experience with their usual diabetes care.
- An IV catheter will be placed for blood sampling.
- Trial staff will assist the patient to calibrate their CGM, review the trial procedures again and assist with the setup of the BP system, including inserting and priming infusion sets.
- The control algorithm will be initialized only with the patient's weight. Diagnostics will be performed to ensure that the CGM device is appropriately calibrated and that all of the components of the BP systems are in working order.
- The basal rate of the patient's own insulin infusion pump will be changed to be 2-fold higher than weighted mean of the basal rate during the trial period. This is intended to increase the usage of glucagon during the treatment visit. The basal insulin rate may be decreased during the treatment visit at the discretion of the Investigator. To the extent possible, the same basal rate should be used at Visit 3 and Visit 4.
- The patients will continue to wear their own infusion pump infusing at the temporary basal rate throughout the visit until the start of the structured exercise period, in addition to the BP.
- The staff will start the BP as close as possible to a minute divisible by 5 minutes (i.e., on a 5-minute mark). The starting time will be considered Hour 0.
- Additional calibrations will be performed at any of the BG checks throughout the day if the CGM value does not meet the ISO standard (<15 mg/dL difference for BG values <75 mg/dL; <20% absolute difference for BG values >75 mg/dL) at the time of the BG measurement AND it is a good time to calibrate (the CGM trend arrow is flat and there has been no carbohydrate intake in the last 30 minutes or glucagon boluses in the last 15 minutes).
- Blood samples will be taken from the IV at least hourly and processed for plasma ZP4207/glucagon. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator. The actual time of sampling will be recorded in the eCRF.
- Plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then

[redacted]

sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.

- Patients will be asked to rate any nausea and/or infusion site pain on 10 cm visual analog scales (VAS) at the beginning of the visit once the infusion sites have been placed but no drug has yet been administered, then approximately at the top of every hour during the visit, and at the end of the visit. Trial staff will also evaluate their infusion sites to document any erythema or edema at the same times. If moderate or severe pain is reported or swelling or redness occurs at the infusion site, the infusion site will be replaced in a different location. If moderate or severe pain, swelling, or redness continues at the old site for more than 30 minutes after the infusion site is removed, or if moderate or severe pain, swelling, or redness occurs at the new site, all infusion sites will be removed and the patient will be discontinued from the study. Any such symptoms will be followed until resolution.
- From the start of closed loop control until approximately Hour 3, the patients will continue to fast.
- Between approximately Hour 3 and Hour 4, patients will be provided with a lunch meal of their choice in the Diabetes Research Center from a menu of choices from nearby restaurants. They will be asked to choose a meal that is a “typical meal” for them. The content of their meal will not be restricted in any way, with the exception that the number of carbohydrates should be in the “typical” range for them at lunch, and that they must eat the same meal at the same time during both visits.
- At approximately 15 minutes before the meal, patients will administer a bolus for the meal with their own insulin pump based on the carbohydrate count for the meal in agreement with the Investigator.
- After lunch is completed, the patients will not be allowed any carbohydrate intake (non-caloric drinks will be permitted) until the trial is completed (except as necessary to treat hypoglycemia), to allow the BP to control the post-prandial BG without further interruption.
- Between approximately Hour 6 and Hour 7, the patients will start a period of structured exercise.
- At the start of the exercise period, patients will restore their normal basal insulin profile so that they will not have elevated insulin levels at the end of the study period when they are to transition back to their usual care.
- Patients will exercise on a stationary bike with a heart rate from 120-140 beats per minute for a total of 4,000 heart beats (approximately 30 minutes). Patients will rate their exercise intensity using the Borg scale every 5 minutes, with the target intensity level between 12 and 14. Heart rate will be measured every 5 minutes.
- Chemistry and hematology samples will be collected immediately after end of exercise (see Appendix B).
- BG measurements will be obtained off of the IV line every 10 minutes. If BG is <80 mg/dL, BG measurements will be obtained off of the IV line every 5 minutes.
    - If BG is <50 mg/dL, the exercise will be terminated regardless of heart beats achieved.
    - Carbohydrates will be given for any BG <50 mg/dL according to the following protocol: Dextrose (g) = BSA (m^2)/[1.7 m^2 (women) or 1.9 m^2 (men)] *15 g.
    - Repeat treatments will be given at 15-minute intervals as long as BG remains <50 mg/dL.

- If there is an interruption in the Dexcom CGM output, trial staff will assist the patient in recovering CGM data streaming. If this requires replacement of the CGM sensor, BGs will be checked every 10 minutes (every 5 minutes if BG is <80 mg/dL) using blood from the IV until the CGM is able to be calibrated again. These BGs will be entered into the BP, which will treat them as CGM values and dose insulin and/or glucagon appropriately.
- If there is a complete failure of the BP operation, patients will take over their own BG control using their personal insulin pump until the BP can be brought back online. If BP control cannot be promptly resumed (e.g., within 30 minutes), the patient may be asked to repeat that trial day once.
- Patients may choose to withdraw from the trial at any time. If they withdraw from the trial, they should alert a provider immediately.
- Just prior to the end of the study visit, vital signs including body temperature and blood pressure will be obtained and a 12-lead ECG will be performed. Orthostatic vital signs (heart rate and blood pressure) will be measured in the seated position and within 3 minutes of standing. If patients have hypotension or orthostatic hypotension, discharge will be delayed until their blood pressure is normal and stable.
- After approximately Hour 8, but not earlier than at least 60 minutes after end of exercise, the BP will be stopped and the patient will continue with their personal insulin pump.
- If the patient experiences seizure or unconsciousness, persistent nausea or vomiting, diabetic ketoacidosis, persistent hyperglycemia with ketonemia, hemodynamic changes such as hypotension, or other medically significant findings, a longer observation period at the trial site may be necessary until the patient is considered stable for discharge. If the Investigator or trial staff determines that the patient requires further observation or treatment, the patient may be transferred to the emergency room for additional monitoring and/or medical care. At discharge, patients will be provided with any necessary instructions concerning personal insulin pump usage, food intake, and driving arrangements.
- The maximum amount of blood loss per study visit will be approximately 230 mL. The total blood loss for the entire study will be up to 460 mL.
- The BP and glucose meters will be collected and downloaded.
- A trial MD will review the last several hours of insulin and glucagon dosing and assist the patient in resuming their usual diabetes care. A longer observation period at the trial site may be necessary. Patients will be instructed to call trial staff with any questions, issues, or concerns.

7.4.2 Data Collected During the Treatment Visits

- CGM glucose every 5 minutes from the Dexcom G4 Platinum CGM
- All BG measurements taken
- Insulin total dose by the BP and the patient's own insulin pump
- Glucagon total dose
- Timing and content of the meal eaten and carbohydrate amount
- Timing of meal announcement and size of meal announced
- Timing and glucose values at calibrations
- Timing and amount of carbohydrates taken for hypoglycemia
- Time patients were not under BP control for any reason
- List of technical faults associated with the BP including cause and resolution

[redacted]

- ZP4207/glucagon sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.
- Plasma glucose sampling will be collected at least hourly in parallel with ZP4207/glucagon exposure sampling. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
- Nausea and infusion site pain on a VAS at visit start (after insertion and before any drug administration), hourly, and at visit end
- Infusion site reaction according to the Draize scale at visit start (after insertion and before any drug administration), hourly, and at visit end
- Patient reports of symptoms, any other complaints, and AEs
- Vital signs including body temperature and blood pressure (at visit start and visit end) and weight
- Orthostatic vital signs (heart rate and blood pressure) in the seated position and within 3 minutes of standing
- Concomitant medications
- Chemistry and hematology samples (see Appendix B) at visit start and immediately after end of exercise
- ADA (Visit 3 only)
- 12-lead ECG at visit start and visit end
- Urine HCG pregnancy test for women of childbearing potential

7.4.3 Response to Hypoglycemia

- Patients are encouraged to check their BG for any symptoms of hypoglycemia.
- Patients will be permitted to take 15 grams of carbohydrates for any BG value <60 mg/dL. Trial staff will ensure proper functioning of the BP, infusion set, and insulin pump, and will encourage the patient to wait for the BP to treat the low blood sugar for as long as they feel comfortable.
- Patients will be required to take 15 grams of carbohydrates for any BG value <50 mg/dL. After treatment of hypoglycemia, a follow-up measurement will be taken 15 minutes later. Repeated measurements will be taken every 15 minutes until the BG is >60 mg/dL. Treatment will be repeated if subsequent BG values are still <50 mg/dL. All carbohydrate treatments for hypoglycemia will be documented by trial staff (amount and time).
- Trial staff will check the infusion site, BP, and insulin pump for normal operation any time hypoglycemia occurs. If there is any suspicion of infusion set malfunction, the site should be replaced. Trial staff will check the BP for any malfunction and correct any problems that are found.
- If no correctable fault is found, but there is doubt regarding the correct function of the BP system, an entirely new backup BP system may be started.
- If a patient experiences a seizure or unconsciousness associated with hypoglycemia, his or her participation in the trial will be discontinued.

[redacted]

7.4.4 Response to Hyperglycemia

- Trial staff will check the infusion site, BP, and insulin pump for normal operation any time BG is >300 mg/dL. If there is any suspicion of infusion set malfunction, the site should be replaced. Trial staff will check the BP for any malfunction and correct any problems that are found. If the BG remains >300 mg/dL for 2 hours despite troubleshooting, blood ketones will be measured. If the blood ketone result is >1.5 mmol/L, the visit will be stopped and rescheduled. The patient will be provided with insulin and a syringe to give an injection based on their correction factor.
- If a patient experiences diabetic ketoacidosis, his or her participation in the trial will be discontinued.
- If no correctable fault is found, but there is doubt regarding the correct function of the BP system, the treatment visit may be stopped and the visit rescheduled.

7.4.5 Response to Nausea/Vomiting

If significant nausea (e.g., that prevents the patient from eating normally) or any vomiting occurs, trial staff will notify the Investigator. Trial staff will assist the patient in troubleshooting, such as checking BG and the calibration of the CGM (excessive glucagon dosing may occur if the CGM is reading lower than the true BG). If a patient experiences persistent nausea and vomiting thought to be related to glucagon dosing, his or her participation in the trial will be discontinued.

7.4.6 Response to Other Medical Needs

If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.

7.4.7 Monitoring of Bionic Pancreas Performance

Bionic pancreas inventors and developers [redacted], [redacted], and/or an engineer trained by them will be readily available by phone for consultation for the trial staff at all times during the course of the trial.

7.4.8 Supervision by Trial Staff

A trial MD will be on call at all times during the course of the trial. An RN or MD will be with the trial patients in the Diabetes Research Center at all times.

7.5 Anti-drug Antibodies Assessment Visit (Visit 5)

Patients will return for an ADA Assessment Visit 10 days ±3 days following the last day of dosing (Visit 4) for ADA sampling and a review of AEs and concomitant medications.

7.6 Follow-up Visit (Visit 6)

Patients will return for a Follow-up Visit 25 days ±4 days following the last day of dosing (Visit 4), for chemistry, hematology, and ADA sampling, and a review of AEs and concomitant medications.

8 ENDPOINTS

8.1 Primary Endpoint

The primary endpoint is the safety and tolerability of ZP4207 in the BP using either the iLet or the iPhone platform as assessed by:

- Number and type of AEs
- Clinical laboratory measurements
- Vital signs
- 12-lead ECG
- Local tolerability and infusion site reactions as measured with the Draize scale
- Immunogenicity as measured by ADA
- Pain as measured on a 10 cm VAS
- Nausea as measured on a 10 cm VAS

8.2 Secondary Endpoints

The secondary endpoints include measurements of BP function as well as glycemic and non-glycemic measurements.

8.2.1 Bionic Pancreas Function

This endpoint data will be generated from the BP data during each treatment visit:

- Average percent insulin dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
    - Average percent glucagon/ZP4207 dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts calculated by the BP algorithm that are successfully issued to the pump by the BP (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts calculated by the BP control algorithm that are successfully issued by the BP
    - Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully issued by the BP
- Average percent of 5-minute steps during which the BP is functioning nominally in all respects based on real-time CGM data (new CGM glucose reading captured, dose calculated, and dose issued to pumps)
- Average percent of 5-minute steps during which the BP is functioning nominally with or without a new CGM glucose reading captured (dose calculated and dose issued to pumps). If a CGM signal is not available, the dose calculated may be based on weight or historical basal rates.
- CGM reliability index, calculated as percent of possible values actually recorded by CGM

[redacted]

- CGM Mean Absolute Relative Difference versus time-stamped BG values from meter download
- List of technical faults associated with the BP including cause and resolution

8.2.2 Glycemic

All of following metrics will be generated from the Dexcom G4 Platinum CGM data during each treatment visit:

- Fraction of time spent within each of the following glucose ranges:
  - <50 mg/dL
  - <60 mg/dL
  - <70 mg/dL
  - 70-120 mg/dL
  - 70-140 mg/dL
  - 70-180 mg/dL
  - >180 mg/dL
  - >250 mg/dL
  - >300 mg/dL
- Number of severe hypoglycemic events (patients unable to self-treat, requiring the assistance of another person)
- Number of episodes of symptomatic hypoglycemia
- Number of carbohydrate interventions for hypoglycemia
- Total grams of carbohydrates taken for hypoglycemia
- Mean CGM glucose

8.2.3 Non-glycemic

- Glucagon/ZP4207 total delivery per kg of body mass
- Insulin total delivery per kg of body mass
- Number of unscheduled infusion set replacements
- Number of unscheduled CGM sensor changes

9 LABORATORY ASSESSMENTS

Descriptions of sample handling and sample processing, storage, and shipment at the site will be included in the laboratory manual.

The responsible laboratories are listed in the address list.

9.1 Safety Laboratory Assessments

Chemistry and hematology samples will be collected at specified time points. See Appendix A for the schedule of procedures and Appendix B for a list of clinical laboratory analytes.

9.2 Pharmacodynamic Assessments (Plasma Glucose)

At Visit 3 and Visit 4, plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is

[redacted]

<100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.

9.3 Exposure Assessments (ZP4207 and Glucagon)

At Visit 3 and Visit 4, ZP4207/glucagon exposure sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator. The actual time of sampling will be recorded in the eCRF.

Bioanalytical Reports will be prepared.

9.4 Anti-drug Antibodies Assessments

Blood samples (including back-up samples) for serum anti-ZP4207 and anti-glucagon antibodies will be taken at Visit 3, the ADA Assessment Visit (Visit 5), and the Follow-up Visit (Visit 6). Any patient that tests positive for ADA will be monitored until the ADA levels return to baseline.

Bioanalytical Reports will be prepared.

10 SAFETY REPORTING

10.1 Adverse Events

An AE is any untoward medical occurrence in a trial patient administered an IMP and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP. Patients should be instructed to report any AE they experience to the Investigator.
Note: This includes events from the first trial-related activity from Visit 3.

AEs for ZP4207 include:

- A clinically significant worsening of a concomitant illness
- A clinical laboratory abnormality which is clinically significant, i.e., any abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example, change of medicine dose or more frequent follow-up due to the abnormality.
- Hypoglycemic episodes
- Injection site reactions

The following should **not** be recorded as AEs, if recorded prior to randomization (on the Screening Form or the eCRF):

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial-related activity from Visit 3.
- Pre-existing conditions found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).

For known (listed) AEs for Glucagon and Humalog, please refer to SPC for Glucagon and Humalog.

[redacted]

10.1.1 Follow-up of Adverse Events

All AEs that are ongoing at the end of the patient's participation in the trial will be followed-up until the event is resolved or reaches a satisfactory outcome as deemed by the Investigator. Follow-up actions for all serious adverse events (SAEs) will be performed according to appropriate clinical care practices and may depend on the nature of the event. These will be determined after internal review and/or Sponsor review. The follow-up information should only include new (updated and/or additional) information that reflects the situation at the time of the Investigator's signature.

Follow-up information on (S)AEs will be updated using the (S)AE Form. If a non-serious event becomes serious during the follow-up, the AE Form and SAE Form must be used and reporting timelines follow those of an SAE.

The Investigator must forward follow-up information on SAEs, and if previously non-serious AEs become SAEs, to the Sponsor.

10.1.2 Precautions

Normal precautions taken for a human trial will be taken during this trial. Qualified and well-trained physicians and medical staff will instruct the patients. During a patient's participation in the trial, the Investigator should ensure that adequate medical care is provided to the patient for any AEs, including clinically significant laboratory values related to the trial. The Investigator should inform the patient when medical care is needed for intercurrent illnesses of which the Investigator becomes aware.

For further information on safety precautions for ZP4207, Lilly glucagon, and Lilly Humalog, please refer to the current version of the Investigator's Brochure (IB) for ZP4207 (Zealand Pharma A/S, 2015, or any updates hereof), and the SPC for Glucagon (Eli Lilly, 2012) and Humalog (Eli Lilly, 2015), respectively.

10.1.3 Assessment of Adverse Events by the Investigator

Intensity of an Adverse Event

The maximum intensity (severity) of all AEs must be assessed by the Investigator and documented. Severity should be graded when the AE outcome is known:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

A "severe" reaction does not necessarily deem the AE as "serious," and an SAE may not be "severe" in nature.

Causality Relationship to IMP
Insulin (insulin lispro, Lilly Humalog), glucagon (glucagon for injection, Eli Lilly), and ZP4207 are all regarded as IMP.

The causality of each AE should be assessed by the Investigator according to the following classification:

- Related: Good reason and sufficient documentation to assume a causal relationship.
- Not related: No relationship to trial product can be established.

Outcome of an Adverse Event
The outcome of all AEs must be assessed by the Investigator and documented by his/her staff. The following definitions should be used:

- Recovered/resolved: The patient has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity from Visit 3.
- Recovering/resolving: The condition is improving and the patient is expected to recover from the event. This term is only applicable if the patient has completed the trial.
- Recovered/resolved with sequelae: The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment, or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- Not recovered/not resolved: The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known.
- Fatal: This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as “recovered/resolved,” “recovering/resolving,” “recovered/resolved with sequelae,” or “not recovered/not resolved.” An AE with a fatal outcome must be reported as an SAE.
- Unknown: This term is only applicable if the patient is lost to follow-up.

10.2 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Medically important

Medical judgement must be exercised in deciding whether an AE is believed to be “medically important.” Medically important events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above.

Suspected Unexpected Serious Adverse Reactions (SUSAR)
A SUSAR is an AE fulfilling 1 of the criteria of seriousness and being assessed as related to an IMP, the nature or severity of which is not consistent with the applicable reference document (e.g., ZP4207 IB or package leaflet/SPC for an approved product).

Unanticipated Adverse Device Effect (UADE)
A UADE is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

10.3 Adverse Event Reporting – Procedures for Investigators

The Principal Investigator and co-investigators will review any AEs and report any SAEs to the Sponsor as soon as possible and within 24 hours of obtaining knowledge of the event. The Principal Investigator and co-investigators will promptly report AEs to the Partner's Institutional Review Board (IRB) and to the BU IRB (unless oversight is ceded by the BU IRB to the Partners IRB), in accordance with local requirements.

Ed Damiano is the Sponsor of the Investigational Device Exception for the BP and Zealand Pharma A/S is the Sponsor of the IND for ZP4207.

Reports of AEs will be submitted to the FDA in compliance with the terms of the Code of Federal Regulations.

All events meeting the definition of an AE must be collected and reported from the first trial-related activity from Visit 3 until the end of the post-treatment follow-up period. At each contact with the site (visit or telephone, excluding safety visits, where the patient is not seeing the Investigator or staff [e.g., visits to the laboratory], the patient must be asked about AEs. All AEs, either observed by the Investigator or reported by the patient, must be recorded by the Investigator and evaluated.

The Investigator should record the diagnosis, if possible. If no diagnosis can be made, the Investigator should record each sign and symptom as individual AEs.
All AEs must be recorded by the Investigator. One single AE Form must be used per AE from start to resolution. For SAEs, the SAE Form must also be completed.

AE information should include the following:

- Patient identification number on all pages
- Date and time of treatment start
- Date and time of onset and date of outcome
- Date and time of Investigator's first information on the (S)AE
- Seriousness
- Severity
- Causal relationship with IMP ZP4207
- Causal relationship with IMP insulin
- Causal relationship with IMP glucagon
- Causal relationship with medical device
- Causal relationship with procedures
- Interruption or withdrawal of treatment with IMP or medical device and other measures taken
- Outcome

[redacted]

All AEs are coded; details are described in the trial specific Data Management Plan.

The Investigator must report initial information in writing on the SAE Form for all SAEs to the Sponsor's responsible pharmacovigilance unit (here: Lindeq) immediately (within 24 hours) after obtaining knowledge about the event.

Name: [redacted]
Company: Lindeq
Address: Lyskær 8, 2730 Herlev, Denmark
Tel: [redacted]
Fax:
Mobile:
E-mail: drugsafety@lindeq.com

In addition and meeting the same timeline, Investigators must report all SAEs to Zealand Pharma A/S by forwarding the SAE Form electronically within 24 hours of obtaining knowledge of the event to the representatives of Zealand Pharma A/S.

Names: [redacted] and [redacted]
Address: Smedeland 36, DK-2600 Glostrup, Denmark
Tel: [redacted]
E-mails: [redacted]

It is the responsibility of Lindeq to report all SUSARs that occur in this trial to the Competent Authorities and to the Investigators. It is the responsibility of the Investigators to report the SUSARs to the IRBs in accordance with the local requirements in force and the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP). The trial monitor must be informed accordingly.

It is the responsibility of Lindeq to report all serious adverse reactions on insulin lispro and glucagon for injection to the Eli Lilly Pharmacovigilance department within 5 days.

It is the responsibility of the Investigators to report all UADEs to Beta Bionics within 24 hours of the time they are detected. It is the responsibility of the Investigators to report all UADEs to the IRB in accordance with the local requirements in force and the ICH GCP. It is the responsibility of Beta Bionics to report all UADEs to the Competent Authorities.

All device deficiencies should be documented and should be reported to Beta Bionics within 24 hours. Device deficiencies are inadequacies of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

Name: [redacted]
Company: Beta Bionics, Inc.
Address: Business Innovation Center, Photonics Center, 8 Saint Mary's Street, Suite 936
Boston, Massachusetts 02215-2421, United States
Tel: [redacted]
E-mail: [redacted]

[redacted]

10.4 Pregnancy Reporting

Female patients must be instructed to notify the Investigator immediately if they become pregnant or if they suspect to be pregnant during the trial. The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical trial.

Male patients must be instructed to notify the Investigator immediately if their partner becomes pregnant or suspects to be pregnant. The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical trial. During an information meeting at the trial site, the patient's partner will be fully informed by a physician of her participation in capturing the outcome data, and will be asked to provide her written consent.

The Investigator must report all information on pregnancies, including AEs in the patient/patient's partner, the fetus, and newborn infant/ toddler. The pregnancy report must be forwarded to the Sponsor preferably electronically as PDF or by fax.

The Investigator must follow the pregnancy until the pregnancy outcome and the newborn infant(s) until the age of 1 month. The Investigator must collect information on the pregnancy and pregnancy complications as well as the pregnancy outcome including the health of the newborn infant(s) on the pregnancy forms.

The following must be collected:

- Initial information of the pregnancy
- Information on the outcome of the pregnancy, including the health status of the newborn infant(s) at the age of 1 month
- All AEs in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms. It must be clear in the description if the event occurs in the patient/patient's partner, the fetus, or the newborn infant.
- All SAEs in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms following the same timelines as required for other SAEs. It must be clear in the description if the event occurs in the patient/patient's partner, the fetus, or the newborn infant.

The SAEs that must be reported include abnormal outcome – such as congenital anomalies, fetal death, and termination of pregnancy (spontaneous or elective abortion), including any anomalies of the fetus observed at gross examination or during autopsy – as well as other pregnancy complications (ectopic pregnancy) fulfilling the criteria of an SAE.

10.5 Hypoglycemia

Hypoglycemia will be regarded as an AE and will be recorded and documented on an AE Form. For the purposes of AE reporting, the following definitions of hypoglycemia will be used:

- Symptomatic hypoglycemia: an event during which typical symptoms of hypoglycemia are accompanied by a BG concentration ≤70 mg/dL
- Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with a BG concentration ≤50 mg/dL
- Severe hypoglycemia: an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions

[redacted]

10.6 Safety Monitoring

10.6.1 Data and Safety Monitoring Board

An external DSMB will oversee the conduct of the trial, as set forth in the DSMB Charter. Additionally, the DSMB will be informed in the event of any serious and unexpected AEs. The DSMB will be informed if there are any changes to the trial protocol that could significantly impact the safety or scientific validity of the trial. A final DSMB meeting will convene after the completion of the trial.

The participation of individual patients will be discontinued if they experience:

- Seizure or unconsciousness associated with hypoglycemia and associated with participation in the trial
- Persistent nausea and vomiting thought to be related to glucagon dosing associated with participation in the trial
- Hospitalization associated with participation in the trial
- Pregnancy
- Diabetic ketoacidosis

If more than 1 patient must be withdrawn from the trial for these reasons, the trial will stop and a vote of the DSMB will be required to restart it. All AEs that are serious and unexpected but related will be reported to the DSMB within 5 working days.

Note that patients may discontinue participation at any time. Patients may be removed from the trial for other reasons, for instance, failure to comply with trial procedures or intercurrent illness that is unrelated to the BP but that precludes safe participation. Discontinuation of participation for these reasons will not contribute to a decision to discontinue the trial.

10.6.2 Zealand Pharma Safety Committee

The internal Zealand Pharma Safety Committee is constituted to perform ongoing safety surveillance of clinical trials within ZP4207, including this trial.

If safety signals are observed either based on reported SAEs, periodic review of laboratory parameters, planned review of all AEs reported between the safety committee meetings, or on notification of significant findings, the Safety Committee will take appropriate measures to safeguard the patients.

11 STATISTICS

For all analysis, the 2 treatment arms from Part 1 (iPhone-based BP) will be compared, and the 2 treatment arms from Part 2 (iLet) will be compared. The analysis of Part 1 will be completely separate from the analysis of Part 2.

11.1 Analysis Populations

The following analysis sets are defined in accordance with the ICH-E9 guidance:

The Full Analysis Set is based on the intention-to-treat principle and includes all randomized patients. In exceptional cases, patients from the Full Analysis Set may be excluded (will be

[redacted]

decided in the database review [DBR] meeting). In such cases, the exclusion will be justified and documented. Patients will contribute to the evaluation “as randomized.”

The Per-Protocol Set includes all patients of the Full Analysis Set who completed the trial without any major protocol violations. Patients in the Per-Protocol Set will contribute to the evaluation “as treated.” This analysis will only be used if it is different than the Full Analysis Set.

The Safety Analysis Set includes all patients receiving at least 1 dose of the IMP. Patients in the Safety Analysis Set will contribute to the evaluation “as treated.”

Analyses of efficacy endpoints will be based on the Full Analysis Set (and the Per-Protocol Set if necessary). This decision will be made in the DBR meeting. The analysis of the safety endpoints will be based on the Safety Analysis Set.

Before data are released for statistical analysis, a blinded review of all data will take place to identify protocol deviations that may potentially affect the results. At this time, it will be determined if patients and/or data should be excluded from the analysis. Furthermore, outliers will be identified by data review according to ICH-E9.

Obviously erroneous data points may be excluded from the analyses or re-analyzed (e.g., serum concentrations). The decision to re-analyze or exclude data points from the statistical analysis is the joint responsibility of the Sponsor, the Principal Investigator, and the Trial Statistician.

The patients or observations to be excluded and the reason for their exclusion will be documented and signed by those responsible prior to database release. The documentation will be stored together with the remaining trial documentation. The patients and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

11.2 Statistical Methods

Medpace will be responsible for the statistical analysis. The statistical planning and conduct of analyses of the data from this trial will follow the principles defined in relevant ICH guidelines and Medpace’s biostatistical SOPs. A general description of the statistical methods to be used is given in this section, specific details will be provided in the Statistical Analysis Plan (SAP), which will be prepared before database lock. All statistical analyses will be performed using SAS® (SAS Institute Inc., Cary, North Carolina, USA), version 9.3 or later.

11.2.1 Analysis of Safety

The following variables will be evaluated according to treatment for safety purposes:

Adverse Events
All AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Individual AEs will be presented in a listing including relationship to trial product/device, severity, and treatment period at onset. If more than 20 treatment-emergent AEs (AEs with onset after [first] dosing at Visit 3 until the Follow-up Visit 6) are registered, a summary table including number of AEs, number of patients with at least 1 AE, and percentage

[redacted]

of exposed patients with at least 1 AE will be made by system organ class and treatment period at onset.

Local Tolerability
Local tolerability at the injection site will be summarized using descriptive statistics as appropriate.

Laboratory Safety Assessments
Laboratory assessments will be summarized. A listing of abnormal values will be provided.

Physical Examination
A frequency table will show the number and percentage of physical examination results.

Vital Signs
Vital signs will be summarized using descriptive statistics.

12-lead ECG
The Investigator's evaluations of 12-lead ECGs will be summarized and abnormal individual evaluations will be listed together with the Investigator's comments. Changes in 12-lead ECG between measurements will be recorded as AEs if the Investigator judges them to be clinically significant.

11.2.2 Analysis of Efficacy

The analysis of BP function endpoints and glycemic endpoints will be on an intention-to-treat basis. In cases where a treatment arm was not completed (and that arm was not repeated according to protocol criteria), available data from that arm will be used in the data analysis.

The Shapiro-Wilk test will be used to determine the normality of the residuals for each comparison. Summary tables that display descriptive statistics, including percentages, means or medians, and standard deviation and/or ranges, as appropriate, will be provided.

A paired t-test or the Wilcoxon signed rank test for comparison of means with normally or non-normally distributed residuals, respectively, will be used. In a secondary analysis, any period effect and any interaction between treatment and period will be looked for, although no such interaction is predicted for the efficacy outcome. Further details will be included in the SAP.

The number of patients and proportions of severe hypoglycemic events, symptomatic hypoglycemia, and carbohydrate interventions due to hypoglycemia with the event counts will be summarized descriptively, and the proportions will be analyzed by a Fisher's exact test if data allow.

11.2.3 Interim Analysis

An interim database lock may occur upon completion of Part 1 of the trial to analyze the iPhone-based BP data.

11.2.4 Sample Size Determination

No formal sample size calculations were made. It is expected that between 20 and 24 patients will be randomized in the trial. The sample size is based on a clinical rather than statistical

[redacted]

rationale. The sample size is considered adequate to address the primary trial objective of exploring the safety of ZP4207 when used in the BP and with reference to Lilly glucagon used in the BP.

12 DATA MANAGEMENT AND RECORD KEEPING

Data Management is the responsibility of Medpace. The complete Data Management process will be described in detail and agreed on in the Data Management Plan for this trial.

12.1 Data Handling

Case Report Forms
Electronic Case Report Forms will be used in this trial. The Data Management Department of Medpace will provide the eCRFs. All further information regarding the eCRFs and the data flow will be described and agreed on in the Data Management Plan.

Device-Related Data
During the trial, CGM data, calibration data, insulin dosing data, and glucagon dosing data will be automatically stored in the BP device (from which it will be downloaded at intervals), combined in a single database that will be compared against the primary data files for integrity, and ultimately transferred to Medpace.

12.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

12.3 Data Entry

Data must be recorded using the electronic data capture (EDC) system as the trial is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct trial data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

12.4 Medical Information Coding

Adverse events and medical history will be coded using the latest version of MedDRA. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary.

12.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

[redacted]

12.6 Record Keeping

Medpace will be responsible for hosting the TMF. Records of patients, source documents, monitoring visit logs, eCRFs, inventory of trial product, regulatory documents, and other Sponsor correspondence pertaining to the trial must be kept in the appropriate trial files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the evaluation and reconstruction of the clinical trial. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Trial Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

13 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

13.1 Ethical Conduct of the Trial

The trial will be conducted according to Medpace, MGH, and/or the Sponsor's written instructions (SOPs, working instructions, or process descriptions). Content and definitions of the written instructions are based on the Declaration of Helsinki and the ICH GCP.

13.2 Institutional Review Board

Written favorable opinion must be obtained from the responsible IRB prior to commencement of the trial. Clinical trial submission and reporting requirements before, during, and after completion of the trial will be performed in accordance with national law and local regulations.

All amendments that affect patient safety or the trial integrity (substantial amendments) must not be implemented before favorable opinion has been obtained, unless necessary to eliminate hazards to the patients. Non-substantial amendments do not require favorable opinion by the IRB, but the respective IRB will be notified according to local requirements.

The Sponsor and Investigator must approve any amendment in writing before its implementation.

The Sponsor must maintain an accurate and complete record of all submissions made to the IRB. The records should be filed in the Sponsor's Trial Master File (TMF).

13.3 Informed Consent

In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirement(s) and adhere to the ICH GCP guideline and the requirements in the Declaration of Helsinki.

Prior to any trial-related activity, the Investigator must give the patient oral and written information in a form that the patient can read and understand about all aspects of the trial that are relevant to the patient's decision to participate. The patient will be given ample time to decide whether or not to participate in the trial.

The patient must be informed that his/her personal trial-related data will be used in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

[redacted]

The patient must be informed that his/her medical records may be examined by authorized monitors or Clinical Quality Assurance auditors appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

A voluntary, personally signed and dated ICF must be obtained from the patient prior to any trial-related activity. The ICF must also be signed and dated by the physician or designee who conducted the informed consent procedure. A signed copy of the ICF and any additional patient information must be given to each patient.

The responsibility for taking informed consent must remain with that of a research physician or designee. If information becomes available that may be relevant to the patient's willingness to continue participating in the trial, the Investigator must inform the patient in a timely manner, and a revised written informed consent must be obtained.

Should a protocol amendment become necessary, the ICF may need to be revised to reflect the changes to the protocol. It is the responsibility of the Sponsor to ensure that an amended consent form is reviewed and has received favorable opinion from IRB, and the Investigator must ensure that the amended consent form is signed by all patients subsequently entered into the trial and those currently in the trial, if affected by the amendment.

13.4 Trial Monitoring Requirements

The monitoring procedures for this trial are described in detail in the Monitoring Manual. The objectives of the monitoring procedures are to ensure that (i) the safety and rights of the trial patients are respected, (ii) that accurate, valid, and complete data are collected, and (iii) that the trial is conducted in accordance with the trial protocol, the principles of GCP, and local legislation, including drug accountability.

The monitor must be given direct access to the investigational site files and source documents (original documents, data, and records). Direct access includes permission to examine, analyze, verify, and reproduce any record(s) and report(s) that are important to evaluation of the clinical trial.

Key tasks of the monitor include verifying the presence of informed consent, the adherence to the inclusion/exclusion criteria, the documentation of SAEs, and the recording of all safety and efficacy variables. The monitor will also confirm the completeness of patient records, the adherence to the protocol, ICH GCP, and the progress in patient enrollment and perform drug accountability.

Because no information that could reveal the identity of patients may ever be removed from the trial site, the monitor will visit the site at regular intervals to perform these monitoring tasks. Other contact between the Investigator and monitors will be maintained as required through telephone calls and e-mail. The Investigator and/or key members of staff involved in the trial must be available to assist the monitors during all visits.

Site Initiation Visit
During the Site Initiation Visit (SIV) the CRO, Sponsor, and/or monitors will go through information on the IMP, the protocol, the eCRFs, and other key aspects of the trial with the Investigator and the key members of staff involved in the trial. The topics of the SIV are

[redacted]

documented in a SIV report made available to the Investigator. Documentation on the SIV (e.g., power point presentation) should be filed by both Investigator and Sponsor.

13.5 Disclosure of Data

Data generated by this trial must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the trial is confidential and disclosure to third parties other than those noted above is prohibited.

13.6 Retention of Records

Massachusetts General Hospital will maintain the patient's medical file according to local regulations. MGH will archive the documentation pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. MGH should not destroy any documents without prior permission from the Sponsor.

The documentation includes all the raw data generated during the clinical trial, the investigational site files, and a copy of the clinical trial report. The documents will be retained for a period of at least 15 years at archives by MGH, or its sub-contractor. After this period, the Sponsor will be contacted and their advice sought on the return or further retention of the trial records.

The Sponsor will maintain the documentation pertaining to the trial in accordance with national regulations.

13.7 Publication Policy

The Principal Investigator of the trial will review and sign the clinical trial report. A summary of the final clinical trial report will be submitted to the IRB and Competent Authority.

According to the Declaration of Helsinki Investigators and Sponsors "have ethical obligations with regard to the publication and dissemination of the results of research." The trial design and results may be published as 1 or more original research manuscripts/abstracts and presented at a scientific meeting. The Investigator and Sponsor reserve the right to review any proposed presentation of the results of this trial before they are submitted for publication. Authorship on any publication(s) resulting from this clinical trial will be assigned according to the recommendations of the International Committee of Medicinal Journal Editors.

Participating patients will not be identified by name in any published reports about the clinical trial.

The Sponsor is responsible for trial registration at ClinicalTrials.gov (www.clinicaltrials.gov) according to the requirements from the FDA.

13.8 Legal Aspects

An implicit or explicit approval must be obtained from the Competent Authority prior to commencement of the trial. Clinical trial submission and reporting requirements before, during, and after completion of the trial will be performed in accordance with national law and local regulations.

An implicit or explicit approval will also be mandatory before implementation of substantial changes. Non-substantial amendments do not require approval from the Competent Authority but will be notified according to local requirements.

The Sponsor and Investigator must approve the amendment in writing before its implementation.

The Sponsor must maintain an accurate and complete record of all submissions made to the Competent Authority. The records should be filed in the Sponsor's TMF.

Audits and Inspections
In the event of an audit, representatives of the Sponsor or designee, or national and international regulatory authorities may request access to all trial records for inspection and copying. Such access must be stated in the ICF signed by the patient.

13.9 Sponsor Discontinuation Criteria

The Sponsor, Investigator, or a pertinent regulatory authority may decide to stop the trial or part of the trial at any time (e.g., upon completion of Part 1 [iPhone-based BP]), but agreement on procedures to be followed must be obtained.

Conditions that may warrant termination of the clinical trial include, but are not limited to:

- Safety or administrative reasons
- The discovery of an unexpected, relevant, or unacceptable risk to the patients enrolled in the clinical trial
- A decision of the Sponsor to suspend or discontinue investigation of the IMP

If the trial is prematurely terminated or suspended, the Investigator should promptly inform the patients and assure appropriate therapy and follow-up. Furthermore, the Sponsor should promptly inform the IRB and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

If after the termination of the trial the risk/benefit analysis has changed, the new evaluation should be provided to the IRB in case it will have an impact on the planned follow-up of the patients who have participated in the trial. Necessary actions needed to protect the patients should be described.

13.10 Patient Compensation

Financial compensation will be provided to all patients who complete the Screening Visit. Patients will be paid $25 for completing the Screening Visit whether or not they are eligible to participate in the trial. Patients will be compensated $25 for completing the Training Visit. Patients will be compensated $100 for completing each of the 2 treatment visits, $25 for completing the ADA Assessment Visit, and $25 for completing the Follow-up Visit. Thus, the

[redacted]

total compensation for a patient who completes the trial would be $300. Patients who are unable to complete the trial or choose to stop participation will receive prorated compensation for each visit. In addition to the monetary compensation, the cost of the patients' lunch meals during their participation in the trial, as well as the patients' parking at each visit, will be covered by trial funds.

14 TRIAL ADMINISTRATIVE INFORMATION

14.1 Protocol Amendments

Any amendments to the trial protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

14.2 Address List

14.2.1 Sponsor

Zealand Pharma A/S
Smedeland 36
DK-2600 Glostrup (Copenhagen)
Denmark
Tel: +45 88 77 36 00
Fax: +45 88 77 38 98

14.2.2 Supplier of Device

[redacted], PhD
Beta Bionics, Inc.
Business Innovation Center, Photonics Center
8 Saint Mary's Street, Suite 936
Boston, Massachusetts 02215-2421
United States
Tel: [redacted]

14.2.3 Principal Investigator (Site)

Steven J. Russell, M.D., Ph.D.
MGH Diabetes Center
50 Staniford Street Suite 301
Boston, Massachusetts 02114
United States
Tel: [redacted]
Fax: [redacted]

14.2.4 Contract Research Organization (Including Monitoring)

Medpace, Inc.
5375 Medpace Way
Cincinnati, Ohio 45227
United States
Tel: +1-513-579-9911
Fax: +1-513-579-0444

14.2.5 Medical Monitoring

Medpace Clinical Safety
5375 Medpace Way
Cincinnati, OH 45227
United States
Tel: +1-800-730-5779, Dial 3 **or** +1-513-579-9911, Dial 3
Fax: +1-866-336-5320 **or** +1-513-579-0444
E-mail: medpace-safetynotification@medpace.com

14.2.6 Pharmacovigilance

Lindeq
Lyskær 8
2730 Herlev
Denmark
Tel: [redacted]
Fax: [redacted]
Mobile: [redacted]
E-mail: drugsafety@lindeq.com

14.2.7 Central Laboratory (Safety Laboratory and Plasma Glucose)

Medpace Reference Laboratories, LLC
5365 Medpace Way
Cincinnati, OH 45227
United States
Tel: +1-513-366-3270
Fax: +1-513-366-3273

14.2.8 Special Laboratory (ZP4207 Exposure and ADA Analyses)

Unilabs – York Bioanalytical Solutions
[redacted]
Cedar House
Northminster Business Park
Upper Poppleton
York YO26 6QR
Great Britain
Tel: [redacted]
Fax: [redacted]

14.2.9 Special Laboratory (Glucagon Exposure)

MLM Medical Labs GmbH
Dr. [redacted]
Dohrweg 63
D-41066 Mönchengladbach
Germany
Tel: [redacted]
Fax: [redacted]

[redacted]

15 REFERENCES

1. Russell SJ, El-Khatib FH, Sinha M, et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. N Engl J Med. 2014;371(4):313-325.
2. Russell SJ, Hillard MA, Balliro C, et al. Day and night glycemic control with a bionic pancreas versus conventional insulin pump therapy in preadolescent children with type 1 diabetes: a randomized crossover trial. Lancet Diabetes Endocrinol. 2016;4(3):233-243.
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5. Garcia A, Rack-Gomer AL, Bhavaraju NC, et al. Dexcom G4AP: an advanced continuous glucose monitor for the artificial pancreas. J Diabetes Sci Technol. 2013;7(6):1436-1445.
6. Zealand Pharma A/S. Investigator's Brochure for ZP4207. Edition No. 2, 14 December 2015, or any updates hereof.
7. Summary of Product Characteristics. Glucagon for Injection. Indianapolis, IN, USA; Eli Lilly and Company:2012.
8. Summary of Product Characteristics. Humalog (insulin lispro injection). Indianapolis, IN, USA; Eli Lilly and Company:2015.
9. ICH Harmonised Tripartite Guideline. Statistical Principles for Clinical Trials E9. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf. 5 February 1998.
10. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R1). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf. 10 June 1996.

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Clinical Trial Protocol
ZP4207-16051

Version number: 8.0
Amendment 7.0
Date: 06 January 2017

APPENDIX A: SCHEDULE OF PROCEDURES – PARTS 1 AND 2

Trial Visit	**Visit 1 [1] Screening**	**Visit 2 Training**	**Visit 3 [2] [3] [4] [5] (1st Treatment Visit)**	**Visit 4 [2] [3] [5] (2nd Treatment Visit)**	**Visit 5 ADA Assessment Visit [6]**	**Visit 6 Follow-Up [7]**
Informed consent	X					
Assess/confirm elig bility	X	X				
Demographics	X					
Medical, surgical, and social history; allergies	X					
Concomitant illness	X					
Concomitant medications	X	X	X	X	X	X
Height, weight, physical examination, and vital signs including body temperature and blood pressure [8]	X		X [9]	X [9]		
12-lead ECG	X		X [10]	X [10]		
Urine HCG pregnancy test and menstrual history [11]	X		X	X		
FSH [12]	X					
Screening labs – HbA1c, optional fractionated metanephrines [13]	X					
Safety lab sampling including chemistry and hematology	X		X [10]	X [10]		X
Training on devices [14]		X				
Monitored BP use			X	X		
Plasma glucose sampling [15]			X	X		
ZP4207/glucagon exposure sampling [16]			X	X		
Nausea and infusion site pain VAS and infusion site reaction Draize scale (visit start [17], hourly, & visit end)			X	X		
Standardized lunch [18]			X	X		
In-clinic exercise [19]			X	X		
ADA			X [20]		X	X
Adverse event review			X	X	X	X

[redacted]

1. Once the patient has been enrolled and eligibility has been established, the order of the treatment visits will be randomized in blocks of 2 patients.
2. In Part 1, each patient will participate in 2 treatment visits: 1 with the iPhone-based BP using ZP4207 and 1 with the iPhone-based BP using Lilly glucagon in a randomized order. In Part 2, each patient will participate in 2 treatment visits: 1 with the iLet using ZP4207 and 1 with the iLet using Lilly glucagon in a randomized order. Up to 2 patients may participate in the trial per day.
3. The night before the visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be asked to arrive at he visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM he night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window. If BG is <50 mg/dL, the patient will be treated with simple carbohydrate according to the 15/15 rule (15 grams of carbohydrates, repeated in 15 minutes if necessary). The visit will not need to be rescheduled unless the patient experiences a severe hypoglycemic event and requires treatment with glucagon or intravenous dextrose.
4. Visit 3 will take place at least 48 hours after screening (Visit 1) and no more than 30 days after screening (Visit 1).
5. There will be a 24-hour minimum washout between Visit 3 and Visit 4 and a maximum of 3 weeks between Visit 3 and Visit 4.
6. Visit 5 will take place 10 days ±3 days from Visit 4.
7. Visit 6 will take place 25 days ±4 days from Visit 4.
8. Height and physical examination will be measured at Visit 1 only.
9. Vital signs including body temperature and blood pressure will be obtained at visit start and visit end. Blood pressure and heart rate will be measured in the seated position and within 3 minutes of standing.
10. At visit start and immediately after end of exercise.
11. Urine HCG pregnancy test only for women of childbearing potential. The date of the last menstrual period in female patients will be obtained at Visit 1 only.
12. Test for FSH level only for postmenopausal women amenorrheic for less than 1 year.
13. If indicated by history.
14. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor, diabetes management (e g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits, and trial policies and procedures.
15. Collected at least hourly. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
16. Collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.
17. Once the infusion sites have been placed but no drug has yet been administered.
18. Between approximately Hour 3 and Hour 4.
19. Between approximately Hour 6 and Hour 7.
20. Before the start of dosing.

ADA = anti-drug antibodies; BG = blood glucose; BP = bionic pancreas; CGM = continuous glucose monitor; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HCG = human chorionic gonadotropin; VAS = visual analog scale.

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APPENDIX B: CLINICAL LABORATORY ANALYTES

Chemistry

Alanine aminotransferase	Aspartate aminotransferase
Alkaline phosphatase	Total protein
Albumin	Total and direct bilirubin
Gamma-glutamyl transferase	Glucose
Creatinine	Estimated glomerular filtration rate
Blood urea nitrogen	Uric acid
Bicarbonate	Sodium
Potassium	Calcium
Chloride	Phosphorus

Hematology

Hemoglobin	Hematocrit
Red blood cell count	White blood cell count and differential
Platelets	Mean corpuscular volume
Mean corpuscular hemoglobin	Mean corpuscular hemoglobin concentration

Pregnancy Test
A urine HCG pregnancy test will be performed at screening, Visit 3, and Visit 4 only for women of childbearing potential.

Anti-drug Antibodies Assessments
Blood samples (including back-up samples) for serum anti-ZP4207 and anti-glucagon antibodies will be taken prior to first dosing (Visit 3), at the ADA Assessment Visit (Visit 5), and at the Follow-up Visit (Visit 6).

ZP4207/Glucagon Exposure Sampling
At Visit 3 and Visit 4, ZP4207/glucagon exposure sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.

Screening Visit Only
Test for FSH level only for postmenopausal women amenorrheic for less than 1 year
Optional fractionated plasma metanephrines (if indicated by history)
Hemoglobin A1c

[redacted]

SUMMARY OF CHANGES DOCUMENT

PROTOCOL NUMBER ZP4207-16051

AMENDMENT NUMBER 6.0

PROTOCOL TITLE: The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

AMENDMENT DATE: 28 September 2016

SUMMARY AND JUSTIFICATION OF CHANGES:

This amendment was developed in response to FDA feedback regarding patients with hypotension or orthostatic hypotension, the diabetes management instruction for patients during the fasting period, and the management of patients who arrive at the treatment visits with hypoglycemia.

Patients with hypotension (systolic blood pressure [SBP] <90 mm Hg or diastolic blood pressure [DBP] <60 mm Hg), either sitting or standing, or orthostatic hypotension (decrease in SBP >20 mm Hg or decrease in DBP >10 mm Hg within 3 minutes of standing from a seated position) at screening will be excluded from participation in the trial.

At screening and at the start and end of the treatment visits, orthostatic vital signs (heart rate and blood pressure) will be measured in the seated position and within 3 minutes of standing. Prior to discharge, if patients have hypotension or orthostatic hypotension, discharge will be delayed until their blood pressure is normal and stable.

The instructions patients will receive concerning diabetes management during the fasting period have been clarified.

Upon arrival at the treatment visit, if blood glucose is <50 mg/dL, the patient will be treated with simple carbohydrate according to the 15/15 rule (15 grams of carbohydrates, repeated in 15 minutes if necessary). The visit will not need to be rescheduled unless the patient experiences a severe hypoglycemic event and requires treatment with glucagon or intravenous dextrose.

The schedule of procedures was updated to reflect the changes specified in this document. Other minor edits were made throughout the protocol to provide greater clarity and consistency.

SUMMARY OF CHANGES:

The amended protocol sections and the details of the changes are summarized in the following sections. Revisions to the protocol are presented as strikethrough (ie, ~~subject~~) for text that was removed and bold (ie, **subject**) for text that was added.

[redacted]

Section 4.2, Exclusion Criteria, Page 25

Original Text:

23. Hypertension with systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg despite treatment
24. Untreated or inadequately treated mental illness (indicators would include symptoms such as psychosis, hallucinations, mania, and any psychiatric hospitalization in the last year), or treatment with anti-psychotic medications that are known to affect glucose regulation

New Text:

23. Hypertension with systolic blood pressure **(SBP)** ≥160 mm Hg or diastolic blood pressure **(DBP)** ≥100 mm Hg despite treatment
24. **Hypotension (SBP <90 mm Hg or DBP <60 mm Hg), either sitting or standing, or orthostatic hypotension (decrease in SBP >20 mm Hg or decrease in DBP >10 mm Hg within 3 minutes of standing from a seated position)**
~~24~~**25**. Untreated or inadequately treated mental illness (indicators would include symptoms such as psychosis, hallucinations, mania, and any psychiatric hospitalization in the last year), or treatment with anti-psychotic medications that are known to affect glucose regulation

Section 7.2.1, Data Collected at Screening, Page 32

Original Text:

- Height, weight, physical examination, and vital signs including body temperature and blood pressure
- 12-lead ECG

New Text:

- Height, weight, physical examination, and vital signs including body temperature and blood pressure
- **Orthostatic vital signs (heart rate and blood pressure) in the seated position and within 3 minutes of standing**
- 12-lead ECG

Section 7.3, Training Visit (Visit 2), Page 32

Original Text:

A Training Visit will take place before the first treatment visit. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor and trial policies and procedures. Trial staff will verify that the patients have understood the material and are competent to participate safely in the trial. Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator. Concomitant medications will also be reviewed.

New Text:
A Training Visit will take place before the first treatment visit. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor and trial policies and procedures. Trial staff will verify that the patients have understood the material and are competent to participate safely in the trial. **Concomitant medications will also be reviewed.**

Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator. ~~Concomitant medications will also be reviewed.~~ **The goals of diabetes management for patients during the fasting period are to avoid hypoglycemia, to treat hypoglycemia if it occurs, and to arrive at the treatment visit in the morning with a BG between 80 and 250 mg/dL. If insulin pump basal rates are properly configured, patients should be able to fast from 12:00 AM until the time of arrival for the visit without a high likelihood that they will become hypoglycemic or severely hyperglycemic. Patients will be asked whether they believe that they can safely fast from 12:00 AM until their arrival time at approximately 7:00 AM without adjusting their basal rates. If they have concerns, a trial physician will consult with them regarding pump basal rate adjustments. In all cases, subjects will be instructed to self-treat with carbohydrates according to the 15/15 rule (15 grams of carbohydrates, repeated in 15 minutes if necessary) during the overnight fasting period and at any time prior to their arrival at the trial site for the treatment visits.**

Section 7.4.1, Visit Procedures, Page 34

Original Text:

- Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window. If BG is <50 mg/dL, treatment with simple carbohydrate is allowed. If the patient experiences persistent hypoglycemia, the visit will be rescheduled within the visit window. If the visit needs to be rescheduled due to hypoglycemia or hyperglycemia, trial staff will assist the patient with insulin or medication adjustments to address glycemic control. The patient will be instructed to contact trial staff later in the day if his or her BG remains uncontrolled.
- Upon arrival to the visit, the patient's weight and vital signs including body temperature and blood pressure will be documented.
- Patient reports of symptoms, any other complaints, and AEs will be reviewed.

New Text:

- Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window. If BG is <50 mg/dL, ~~treatment~~ **the patient will be treated** with simple carbohydrate ~~is allowed. If the patient experiences persistent hypoglycemia,~~ **according to** the **15/15 rule (15 grams of carbohydrates, repeated in 15 minutes if necessary). The** visit will **not need to** be rescheduled ~~within the visit window~~ **unless the patient experiences a severe hypoglycemic event and requires treatment with glucagon or IV dextrose**. If the visit needs to be rescheduled due to hypoglycemia or hyperglycemia, trial staff will assist the

patient with insulin or medication adjustments to address glycemic control. The patient will be instructed to contact trial staff later in the day if his or her BG remains uncontrolled.
- Upon arrival to the visit, the patient's weight and vital signs including body temperature and blood pressure will be documented.
- **Orthostatic vital signs (heart rate and blood pressure) will be measured in the seated position and within 3 minutes of standing.**
- Patient reports of symptoms, any other complaints, and AEs will be reviewed.

Section 7.4.1, Visit Procedures, Page 36

Original Text:

- Patients may choose to withdraw from the trial at any time. If they withdraw from the trial, they should alert a provider immediately.
- Just prior to the end of the study visit, vital signs including body temperature and blood pressure will be obtained and a 12-lead ECG will be performed.
- After approximately Hour 8, but not earlier than at least 60 minutes after end of exercise, the BP will be stopped and the patient will continue with their personal insulin pump.

New Text:

- Patients may choose to withdraw from the trial at any time. If they withdraw from the trial, they should alert a provider immediately.
- Just prior to the end of the study visit, vital signs including body temperature and blood pressure will be obtained and a 12-lead ECG will be performed. **Orthostatic vital signs (heart rate and blood pressure) will be measured in the seated position and within 3 minutes of standing. If patients have hypotension or orthostatic hypotension, discharge will be delayed until their blood pressure is normal and stable.**
- After approximately Hour 8, but not earlier than at least 60 minutes after end of exercise, the BP will be stopped and the patient will continue with their personal insulin pump.

Section 7.4.2, Data Collected During the Treatment Visits, Page 37

Original Text:

- Vital signs including body temperature and blood pressure (at visit start and visit end) and weight
- Concomitant medications

New Text:

- Vital signs including body temperature and blood pressure (at visit start and visit end) and weight
- **Orthostatic vital signs (heart rate and blood pressure) in the seated position and within 3 minutes of standing**
- Concomitant medications

[redacted]

Appendix A, Schedule of Procedures, Footnote 3, Page 60

Original Text:

3. The night before the visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window. If BG is <50 mg/dL, treatment with simple carbohydrate is allowed. If the patient experiences persistent hypoglycemia, the visit will be rescheduled within the visit window.

New Text:

3. The night before the visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window. If BG is <50 mg/dL, ~~treatment~~ **the patient will be treated** with simple carbohydrate ~~is allowed. If the patient experiences persistent hypoglycemia,~~ **according to** the **15/15 rule (15 grams of carbohydrates, repeated in 15 minutes if necessary). The** visit will **not need to** be rescheduled ~~within the visit window~~ **unless the patient experiences a severe hypoglycemic event and requires treatment with glucagon or intravenous dextrose.**

Appendix A, Schedule of Procedures, Footnote 9, Page 60

Original Text:

9. Vital signs including body temperature and blood pressure will be obtained at visit start and visit end.

New Text:

9. Vital signs including body temperature and blood pressure will be obtained at visit start and visit end. **Blood pressure and heart rate will be measured in the seated position and within 3 minutes of standing.**

[redacted]

Clinical Trial Protocol
ZP4207-16051

Version number: 7.0
Amendment 6.0
Date: 28 September 2016

CLINICAL TRIAL PROTOCOL

The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

Investigational Product: ZP4207
Protocol Number: ZP4207-16051
IND Number: 129980
Phase: 2

Principal Investigator:
Steven J. Russell, MD, PhD[1]

Co-Investigator:
[redacted], RN, CDE[1]

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Original Version: 03 May 2016
Amendment Number 1.0: 28 June 2016
Amendment Number 2.0: 03 August 2016
Amendment Number 3.0: 17 August 2016
Amendment Number 4.0: 02 September 2016
Amendment Number 5.0: 09 September 2016
Amendment Number: 6.0
Protocol Version Number: 7.0

Date: 28 September 2016

Clinical Trial Protocol
ZP4207-16051

Version number: 7.0
Amendment 6.0
Date: 28 September 2016

SIGNATURE PAGE

TRIAL TITLE: The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the trial.

Signature [redacted] Date [redacted]

[redacted] MD
Vice President, Clinical Development
Zealand Pharma A/S

[redacted] DVM, PhD
Principal Clinical Pharmacologist
Zealand Pharma A/S

Clinical Trial Protocol
ZP4207-16051

Version number: 7.0
Amendment 6.0
Date: 28 September 2016

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the trial as described. I will conduct this trial in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the trial within the time designated. I will provide copies of this protocol and access to all information furnished by Zealand Pharma A/S to trial personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the trial product and trial procedures. I will let them know that this information is confidential and proprietary to Zealand Pharma A/S and that it may not be further disclosed to third parties. I understand that the trial may be terminated or enrollment suspended at any time by Zealand Pharma A/S, with or without cause, or by me if it becomes necessary to protect the best interests of the trial patients.

I agree to conduct this trial in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and ICH Guidelines for Good Clinical Practices.

[redacted] 9/28/2016

Investigator's Signature Date

Steven J. Russell, MD, PhD

Investigator's Printed Name

Clinical Trial Protocol
ZP4207-16051

Version number: 7.0
Amendment 6.0
Date: 28 September 2016

SYNOPSIS

TITLE: The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

PROTOCOL NUMBER: ZP4207-16051

INVESTIGATIONAL PRODUCT: ZP4207

PHASE: 2

INDICATION: ZP4207 is an anti-hypoglycemic glucagon analog in a ready-to-use liquid formulation which is being studied to improve glycemic control in adults (and children) with type 1 diabetes mellitus (T1DM) as part of a bihormonal bionic pancreas (BP).

OBJECTIVES:

Primary: The primary objective is to conduct a trial testing the safety and tolerability of the BP using either the iLet or the iPhone platform when used with ZP4207 in 20 adult (≥18 years of age) patients with T1DM.

Secondary: The secondary objectives are to measure glycemic regulation, including hypoglycemia exposure (percent of time spent with continuous glucose monitor [CGM] glucose <60 mg/dL), evaluate BP device reliability, and to document the satisfaction of patients with the BP with the goal of optimizing the functionality and user interface of the BP.

POPULATION: Up to 40 adult (≥18 years of age) patients who already manage their T1DM using continuous subcutaneous (SC) insulin infusion pump therapy can be enrolled. It is expected that up to 10 patients will complete each part of the trial protocol.

TRIAL DESIGN: This trial is a single-center, open-label, 2-part, randomized cross-over trial. The trial will enroll adult patients with T1DM and will assess the safety and efficacy of the BP using either the iLet or the iPhone platform using the glucagon analog ZP4207 versus Lilly glucagon. In Part 1, up to 10 patients will participate in two 1-day treatment arms in random order (iPhone-based BP using ZP4207 and iPhone-based BP using Lilly glucagon) according to a pre-generated randomization scheme. In Part 2, up to 10 new patients will participate in two 1-day treatment arms in random order (iLet using ZP4207 and iLet using Lilly glucagon) according to a pre-generated randomization scheme. Patients can only participate in 1 part of the trial. An interim database lock may occur upon completion of Part 1 of the trial to analyze the iPhone-based BP data. The iLet and the iPhone-based BP will also administer insulin (insulin lispro, Lilly Humalog) using the same blood glucose (BG) control algorithm for all 4 treatment arms. The trial will be conducted at a single center, the Massachusetts General Hospital Diabetes Center in Boston, MA.

TRIAL TREATMENT: The trial involves SC administration of insulin lispro (Humalog, Lilly), which is commercially available by prescription and is indicated for patients with T1DM, but not for use in a BP.

[redacted]

The trial also involves SC administration of Lilly glucagon in 1 iLet arm and 1 iPhone-based BP arm. Lilly glucagon is commercially available by prescription and is indicated for patients with T1DM in severe hypoglycemia, but not for use in a BP.

The trial also involves SC administration of the glucagon analog ZP4207, 1 mg/mL, in the other iLet arm and the other iPhone-based BP arm. ZP4207 will be made available by Zealand Pharma A/S, Denmark as liquid formulation in prefilled syringes of 0.6 mL.

PRIMARY ENDPOINT:
The primary endpoint is the safety and tolerability of ZP4207 in the BP using either the iLet or the iPhone platform as assessed by:

- Number and type of adverse events (AEs)
- Clinical laboratory measurements
- Vital signs
- 12-lead electrocardiogram (ECG)
- Local tolerability and infusion site reactions as measured with the Draize scale
- Immunogenicity as measured by anti-drug antibodies
- Pain as measured on a 10 cm visual analog scale (VAS)
- Nausea as measured on a 10 cm VAS

SECONDARY ENDPOINTS:
The secondary endpoints include measurements of BP function as well as glycemic and non-glycemic measurements.

Bionic Pancreas Function
This endpoint data will be generated from the BP data during each treatment visit:

- Average percent insulin dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
    - Average percent glucagon/ZP4207 dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts calculated by the BP algorithm that are successfully issued to the pump by the BP (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts calculated by the BP control algorithm that are successfully issued by the BP
    - Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully issued by the BP
- Average percent of 5-minute steps during which the BP is functioning nominally in all respects based on real-time CGM data (new CGM glucose reading captured, dose calculated, and dose issued to pumps)

[redacted]

- Average percent of 5-minute steps during which the BP is functioning nominally with or without a new CGM glucose reading captured (dose calculated and dose issued to pumps). If a CGM signal is not available, the dose calculated may be based on weight or historical basal rates.
- CGM reliability index, calculated as percent of possible values actually recorded by CGM
- CGM Mean Absolute Relative Difference versus time-stamped BG values from meter download
- List of technical faults associated with the BP including cause and resolution

Glycemic
All of following metrics will be generated from the Dexcom G4 Platinum CGM data during each treatment visit:

- Fraction of time spent within each of the following glucose ranges:
  - <50 mg/dL
  - <60 mg/dL
  - <70 mg/dL
  - 70-120 mg/dL
  - 70-140 mg/dL
  - 70-180 mg/dL
  - >180 mg/dL
  - >250 mg/dL
  - >300 mg/dL
- Number of severe hypoglycemic events (patients unable to self-treat, requiring the assistance of another person)
- Number of episodes of symptomatic hypoglycemia
- Number of carbohydrate interventions for hypoglycemia
- Total grams of carbohydrates taken for hypoglycemia
- Mean CGM glucose

Non-glycemic

- Glucagon/ZP4207 total delivery per kg of body mass
- Insulin total delivery per kg of body mass
- Number of unscheduled infusion set replacements
- Number of unscheduled CGM sensor changes

EVALUATION OF TRIAL DATA: The following variables will be evaluated according to treatment for safety purposes: AEs, local tolerability, laboratory safety assessments, physical examination, vital signs, and 12-lead ECGs.

The analysis of BP function endpoints and glycemic endpoints will be on an intention-to-treat basis. In cases where a treatment arm was not completed (and that arm was not repeated according to protocol criteria), available data from that arm will be used in the data analysis.

The Shapiro-Wilk test will be used to determine the normality of the residuals for each comparison. Summary tables that display descriptive statistics, including percentages, means or medians, and standard deviation and/or ranges, as appropriate, will be provided.

[redacted]

A paired t-test or the Wilcoxon signed rank test for comparison of means with normally or non-normally distributed residuals, respectively, will be used. In a secondary analysis any period effect and any interaction between treatment and period will be looked for, although no such interaction is predicted for the efficacy outcome.
The number of patients and proportions of severe hypoglycemic events, symptomatic hypoglycemia, and carbohydrate interventions due to hypoglycemia with the event counts will be summarized descriptively, and the proportions will be analyzed by a Fisher's exact test if data allow.

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[redacted]

Clinical Trial Protocol
ZP4207-16051

Version number: 7.0
Amendment 6.0
Date: 28 September 2016

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibodies
AE	Adverse event
BG	Blood glucose
BP	Bionic pancreas
BTLE	Bluetooth Low Energy
BU	Boston University
CFR	Code of Federal Regulations
CGM	Continuous glucose monitor
CRO	Contract research organization
DBP	Diastolic blood pressure
DBR	Database review
DPP-4	Dipeptidyl peptidase-4
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FDA	Food and Drug Administration
FHD	First Human Dose
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GUI	Graphical user interface
HCG	Human chorionic gonadotropin
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IM	Intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
MD	Doctor of Medicine
MedDRA	Medical Dictionary for Regulatory Activities
MGH	Massachusetts General Hospital

[redacted]

Abbreviation	Definition
MPC	Model-predictive control
PD	Pharmacodynamic
PK	Pharmacokinetic
RN	Registered nurse
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SC	Subcutaneous
SGLT-2	Sodium-glucose co-transporter-2
SIV	Site Initiation Visit
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 diabetes mellitus
TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
ULN	Upper limit of normal
VAS	Visual analog scale

[redacted]

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Background and Rationale

To date, clinical trials conducted by Boston University (BU) and Massachusetts General Hospital (MGH) in patients with type 1 diabetes mellitus (T1DM) have demonstrated the practicality of a wearable automated bionic pancreas (BP) control system for robust glucose regulation using a continuous glucose monitor (CGM) to provide the input to the control system. Despite current technical limitations in CGMs and infusion pumps, the trials by BU/MGH have shown that a bihormonal BP is capable of achieving safe and effective blood glucose (BG) control automatically, with minimal hypoglycemia during 11 continuous days in the face of unrestrained meals and exercise and with trivial patient input (optional announcement of meals).

The BP provides automatic BG regulation and reduces hypoglycemic episodes. Additionally, the system spares the wearer the relentless tasks of carbohydrate counting, frequent BG monitoring, estimating the effects of specific meals and exercise activity on BG levels, and manual drug administration, which are inexact, demanding, aggravating, and require continuous diligence and vigilance. The degree of glycemic control achieved by the BP is predicted to dramatically reduce the deleterious and debilitating complications of T1DM.

In its last tested embodiment, the BP consisted of a Dexcom G4 CGM, and an iPhone that are hardwired together, with the iPhone running the control algorithm and communicating via Bluetooth with 2 Tandem t:slim pumps to dose insulin and glucagon. The connections are repeatedly lost among these 4 components throughout the day, an issue that has the potential to adversely impact BG control, whether due to missed CGM values or missed doses. In addition, the troubleshooting required to repair these recurring disconnections can be burdensome to the user. Integrating these components into a single device would establish seamless connectivity among them, which would eliminate the need for such troubleshooting. This would lead to smoother device operation with fewer interruptions, which would enhance its user friendliness, optimize its BG control potential, and further improve the quality of life of its users.

The BU Investigators have recently designed, built, and tested a proprietary first-generation of such a fully integrated BP system, referred to as the iLet and the iLet infusion set. The iLet is a dual-chamber infusion system that currently incorporates the Dexcom G4 CGM technology, a custom user interface with touchscreen display, and all of the mathematical dosing algorithms that were tested in and validated using the iPhone-based BP in outpatient studies over the past 3 years. The iLet infusion set provides 2 independent subcutaneous (SC) fluid pathways from the iLet to the patient (1 for insulin and the other for glucagon). One tube connects to the prefilled insulin cartridge and the other tube connects to the fillable (single-use) glucagon cartridge.

In order to provide automatic BG regulation, the iLet and the iPhone-based BP have the ability to deliver both insulin and glucagon. However, currently available glucagon formulations have limited stability at room temperature, necessitating frequent changes to the glucagon infusion set. Therefore, the current trial is designed to test the glucagon analog ZP4207 in the iLet and the iPhone-based BP, as this peptide analog of human glucagon is provided in a liquid formulation stable at room temperature.

[redacted]

The current trial is a first feasibility trial designed to use the first-generation iLet and iLet infusion set and the iPhone-based BP to compare ZP4207 with marketed glucagon (Lilly). The trial is intended to demonstrate the safety and tolerability of ZP4207 in the iLet and the iPhone-based BP and the feasibility of achieving comparable autonomous glycemic control. It is not intended to comprehensively demonstrate the definitive efficacy of the BP in extended, continuous daily use, but rather to demonstrate its functionality and accuracy in a practical, albeit very controlled, clinical setting. The trial is expected to provide practical information that will benefit the design of a next-generation iLet and iLet infusion set and help pave the way for a more comprehensive outpatient home-use Phase 2 trial and ultimately a pivotal trial where comprehensive safety and efficacy through continuous full daily use of the iLet with ZP4207 will be documented.

The data derived from this trial will permit evaluation of the robustness of the iLet as well as the safety and efficacy of ZP4207 when used in conjunction with the iLet and the iPhone-based BP. The data obtained will be used to further improve the iLet and will allow BU/MGH to expand to larger outpatient trials using the iLet or the iPhone-based BP with ZP4207.

1.2 Bihormonal Bionic Pancreas System

The BP is an autonomous, self-learning system that requires only the patient's weight for initialization, and then autonomously adapts, modestly or dramatically, as needed, to cope with the wide range of insulin requirements of adults, adolescents, and pre-adolescents with T1DM. The BP obviates the need for the patient to know, or even appreciate, their insulin requirements, and renders obsolete any need for patients or caregivers to know carbohydrate-to-insulin ratios, basal rates, or insulin correction factors.

The core technology is a suite of control algorithms that orchestrate the automated dosing of insulin and glucagon to regulate BG levels. An insulin controller orchestrates all SC insulin dosing. At its centerpiece is a model-predictive control (MPC) algorithm, which bases insulin doses on the glucose data and insulin absorption kinetics, compensating for the slow absorption rate of SC insulin analogs (peak time in blood of 30-90 min, clearance in 4-8 hr). This enables the algorithm to refrain from stacking and overdosing insulin. Furthermore, the MPC algorithm automatically adjusts its insulin-dosing aggressiveness continuously and in real-time to different insulin needs between individuals and variable needs within the same individual. Running in parallel with the MPC algorithm is an algorithm that automatically modulates basal insulin delivery over multiple time scales, and another algorithm that automatically adapts insulin doses in response to optional meal announcements. Unlike current insulin pumps and the insulin-only control algorithms, the adaptive basal insulin algorithm obviates the need for the user to set, or even know, his or her “basal-rate profile.” Instead, it is capable of automatically adapting to, and compensating for, changes in an individual's basal insulin need, such as might occur over a period of hours, days, or weeks (e.g., circadian hormonal fluctuations, intercurrent illness, physical activity, or emotional state) or as might occur over a period of months or years due to developmental changes (e.g., hormonal changes that occur during puberty or menopause). The adaptive meal dose controller obviates the need for the user to set, or even know, his or her “carbohydrate-to-insulin ratios,” as it makes automatic adjustments based on dosing history for similar meal announcements made on previous days, and customizes the dose for each individual and for time of day.

[redacted]

The BP also includes a proportional-derivative algorithm governing SC micro-doses of glucagon to help prevent impending hypoglycemia. Glucagon dosing is based on the glucose level and rate of descent. It may occur preemptively even if glucose is above range, and it includes a feedback term to account for the pending effects of recent glucagon doses.

Taken together, these mathematical algorithms provide a universal framework for a glycemic control strategy that requires no quantitative input from, or participation by, the user (besides entering body weight to initialize the system), but which automatically adapts insulin and glucagon dosing to meet the individual needs of each user. Another challenge met is enabling the technology to remain completely autonomous in managing insulin and glucagon delivery even when the CGM is offline. Specifically, when the CGM is offline, the BP invokes the high-resolution “basal rate profile” that it had recently learned and stored when the CGM was online. On the basis of what the system learned and stored about meal announcements when the CGM was online, it is able to respond to meal announcements in the same manner when the CGM is offline. Finally, it automatically responds to user-entered BG values when the CGM is offline by issuing a correction dose of insulin or glucagon based on what it learned about the user's insulin and glucagon needs when the CGM was online. Thus, the BP never relies on, or burdens the user with, the determination of subjective dosing decisions, which inevitably vary in quality and reliability among different users. The BP provides a turnkey solution for people with T1DM that comprehensively manages glycemia across a broad range of individual needs and across a large spectrum of circumstances and challenges to glycemic control.

A significant challenge for the use of glucagon in a bihormonal BP is the lack of a commercially available glucagon formation that is stable and well-suited to infusion over several days in a pump reservoir. However, BU/MGH have proceeded with studies using a relatively unstable marketed formulation that must be reconstituted from a lyophilized powder on a daily basis. This allowed BU/MGH to proceed with studies of the bihormonal system while awaiting the production of stable glucagon formulations or stable glucagon analogs.

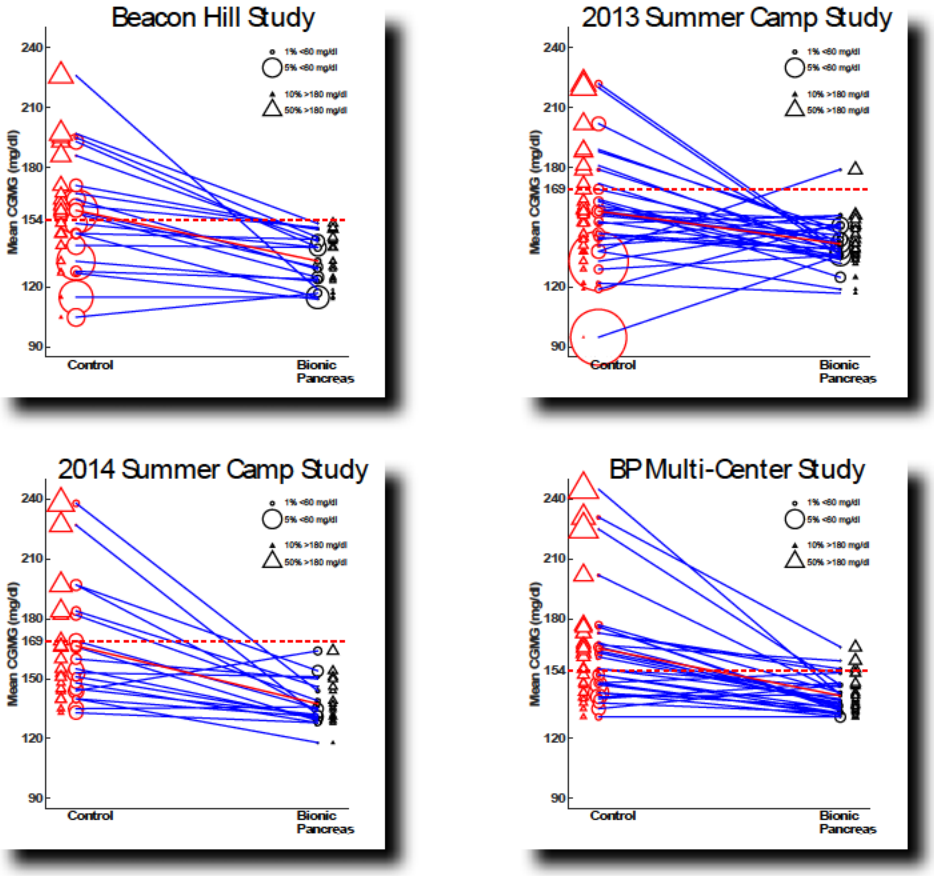
1.3 Preliminary Studies with the Bihormonal Bionic Pancreas System

The BP hardware platform has evolved over the years from a laptop-driven system, which was used in all inpatient studies to the first truly mobile wearable iPhone-driven platform, which has been used in a number of outpatient studies. Using the iPhone-based BP system, >110 outpatient experiments of 5-11 days in duration in each subject have been conducted (>800 patient days or >2 patient years of data) across subjects ranging in age between 6 and 76 years old and in body mass between 21 and 128 kg. The robust adaptation capabilities of the BP is evident in the fact that the average total daily dose of insulin among these subjects varied by over 13-fold (from 11 to 145 units/day).

In November 2012, Food and Drug Administration (FDA) approval was obtained to conduct the first outpatient study testing the BP in adults 21 years or older with T1DM. This study, referred to as the Beacon Hill Study, followed a random-order cross-over design in which 20 adults with T1DM participated in 5 days on the iPhone-based BP and 5 days of usual care in which they wore a CGM with blinded display and muted alarms. In the BP arm, subjects kept to a 3-square-mile geographic area centered around the Beacon Hill neighborhood in Boston. They ate as they chose at local restaurants, and exercised at will with access to 2 gyms. Analysis was pre-specified to focus on Days 2-5, since glycemic control is more representative of BP performance after most of the adaptation by the BP occurs on Day 1 (Russell, 2014). Results are summarized in Figure 1.

[redacted]

Figure 1. Outpatient Results Summarizing the Distribution of Mean CGM Glucose Levels and Hypoglycemia in the BP and Control Arms



Study	Age (years)	Bionic Pancreas (BP) Mean CGM glucose level (mg/dl)	Bionic Pancreas (BP) % of CGM glucose levels <50 mg/dl (%)	Bionic Pancreas (BP) % of CGM glucose levels 70–180 mg/dl (%)	Control Mean CGM glucose level (mg/dl)	Control % of CGM goucose values <50 mg/dl (%)	Control % of CGM goucose values 70–180 mg/dl (%)	p value (BP versus Control) for: Mean CGM glucose level	p value (BP versus Control) for: % of CGM glucose values <50 mg/dl	p value (BP versus Control) for: % of CGM glucose values 70–180 mg/dl
Beacon Hill (n 20, 5-day experiments)	≥21	133	1.5	80	159	3.7	59	<0.001	0.020	<0.001
2013 Summer Camp (n 32, 5-day experiments)	12–20	142	1.3	76	158	2.2	65	0.004	0.192	<0.001
2014 Summer Camp (n 19, 5-day experiments)	6–11	137	1.2	81	168	2.8	58	0.004	0.001	<0.001
BP Multi Center (n 39, 11-day experiments)	≥18	141	0.6	78	162	1.9	62	<0.001	<0.001	<0.001

Mean CGM glucose levels for each subject under usual care (red circles) are connected with the subject's mean CGM glucose level on the BP (black circles). The diameters of the circles shown are proportional to the percentage of CGM glucose values <60 mg/dL, and the size of the triangle is proportional to the percentage of CGM glucose values >180 mg/dL. The horizontal red dashed line refers to the glucose level corresponding to the American Diabetes Association therapy goal for each age group tested, which corresponds to 154 mg/dL (HbA1c of 7%) for adults and 169 mg/dL (HbA1c of 7.5%) for children. Results are summarized in the table, where the co-primary outcomes (mean CGM glucose level and percentage of CGM glucose values <60 mg/dL) for the BP arm are highlighted in red for each of the 4 studies.
BP = bionic pancreas; CGM = continuous glucose monitoring; HbA1c = hemoglobin A1c.

In April 2013, FDA approval was obtained to conduct the first outpatient study testing the BP in adolescents 12-20 years old with T1DM. This study, referred to as the 2013 Summer Camp Study, followed a random-order cross-over design in which 32 adolescents with T1DM participated in 5 days on the BP and 5 days of supervised camp care in which they wore a CGM with blinded display and muted alarms. Subjects were fully integrated into normal camp activities without restrictions on diet or exercise. The study used the same iPhone-based BP that was used in the Beacon Hill Study. Results are summarized in Figure 1 (Russell, 2014). In April 2014, FDA approval was obtained to conduct the first outpatient study testing the BP in pre-adolescents 6-11 years old with T1DM. This study, referred to as the 2014 Summer Camp Study, was similar in design to the 2013 Summer Camp Study. Results are summarized in Figure 1 (Russell, 2016).

In April 2014, FDA approval was obtained to conduct the first multi-center study, which was also the first home study, to test the BP in adults 18 years or older with T1DM. This study, referred to as the Bionic Pancreas Multi-Center Study, followed a random-order cross-over design in which 39 adults participated in 11 days on the BP and 11 days of usual care. Participants went to work as usual, and lived and slept at home, all without clinical supervision. There were no restrictions placed on diet or exercise. The study included 4 medical centers (10 subjects per center), which included MGH, the University of Massachusetts Medical School, Stanford University, and the University of North Carolina at Chapel Hill. Results are summarized in Figure 1.

All of these studies used marketed glucagon (glucagon for injection, Eli Lilly). Due to its limited stability, Lilly glucagon must be reconstituted immediately before use. Animal studies have previously shown that despite its limited chemical stability, Lilly glucagon maintains its biological activity for up to 7 days in solution. Using this data, an Investigational New Drug (IND) exemption was obtained from the FDA for its use in a pump for up to 27 hours. This allowed these studies to be performed by asking volunteers to reconstitute a new vial of glucagon and fill the glucagon pump at approximately the same time every day. However, marketed Lilly glucagon has no path forward for approval for chronic BP use.

1.4 ZP4207

ZP4207 is a peptide analog of human glucagon that is being developed to treat hypoglycemia in patients with T1DM and type 2 diabetes mellitus. ZP4207 exhibits improved physical and chemical stability in aqueous media and is suitable for liquid formulation. ZP4207 is comprised of 29 amino acids and has 7 amino acid substitutions when compared to native glucagon.

Two clinical Phase 1 trials have been conducted to establish safety and tolerability of ZP4207 after single and multiple dosing to healthy patients and T1DM patients under insulin-induced hypoglycemic conditions.

The First Human Dose (FHD) trial (ZP4207-14013) was finalized in April 2015. The trial was a randomized, double-blinded trial with the objectives to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of ZP4207 as compared to an active comparator. Part 1 included a single ascending dose in healthy volunteers in cohorts of 8. In each cohort, the patients were randomized 3:1 to ZP4207 (n=6) or Novo Nordisk GlucaGen® (n=2). Five cohorts with SC administration (0.01, 0.1, 0.3, 1.0, and 2.0 mg ZP4207 compared to 1 mg GlucaGen) and 3 cohorts with intramuscular (IM) administration (0.3, 1.0, and 2.0 mg ZP4207 compared to 1 mg GlucaGen) were included. Part 2 included 2 sequence groups of

[redacted]

10 hypoglycemic T1DM patients. The patients were treated with fixed single IM doses of 0.7 mg ZP4207 and 1.0 mg GlucaGen in a sequential cross-over design in a randomized treatment order.

The second clinical trial (ZP4207-15007) was a single-center, double-blind, Phase 1b trial investigating the safety and tolerability, PK and PD of ZP4207 following repeated administration in healthy volunteers compared to placebo. It was finalized in July 2015. Each of the 3 cohorts comprised 8 subjects, who received 5 repeated SC doses of ZP4207 or placebo in a 3:1 treatment allocation. The first cohort started with the lowest dose of 0.1 mg. Cohort 2 and 3 continued with 0.3 and 1.0 mg, respectively.

The Phase 1 results did not give rise to specific safety concerns, beyond those related to the pharmacological effect of ZP4207. All adverse events (AEs) recorded in the trials were of mild or moderate severity. The most frequent systemic AE related to treatment with ZP4207 was nausea, which is a known side-effect following administration of glucagon. The most frequent injection site reaction was transient erythema, occurring in all ZP4207, glucagon, and placebo treatment groups, irrespective of dose. No anti-drug antibodies (ADA) incidences were observed.

The observed PD response, in terms of increased plasma glucose, in insulin-induced hypoglycemic patients with T1DM following dosing with 0.7 mg ZP4207 administered IM was similar to that observed following IM dosing with 1.0 mg glucagon (GlucaGen, Novo Nordisk). An increase in plasma glucose of ≥20 mg/dL from hypoglycemic levels was achieved within 30 minutes for all patients.

In terms of PK, ZP4207 had a short half-life and high clearance and dose proportionality for both maximum plasma concentration and area under the concentration-time curve from time 0 to 300 minutes in the dose range 0.1 to 2.0 mg following SC administration. Following IM administration, dose proportionality was shown in the investigated dose range of 0.3 to 2.0 mg. The PK properties of 0.7 mg ZP4207 IM were comparable with those of 1.0 mg glucagon (GlucaGen, Novo Nordisk) with IM administration.

1.5 Risk/Benefit

While the potential risks are minimal, the findings of this trial may reveal information that can substantially improve medical care for persons with diabetes. Therefore, the overall risk/benefit for patients participating in this trial is assessed as acceptable.

Potential Risks and Discomforts

Trial patients will be informed by the Investigator of the potential risks of ZP4207 and other trial-related procedures before they enter the trial.

In this trial, patients with T1DM will be included to test the safety and efficacy of the BP using either the iLet or the iPhone platform when used with ZP4207 versus Lilly glucagon. The cross-over design with inclusion of 1 group of 10 T1DM patients into the 2 iLet treatment arms and the inclusion of a second group of 10 T1DM patients into the 2 iPhone-based BP treatment arms in a randomized order will allow for a direct comparison of the safety and efficacy of the 2 treatments, based on intra-patient variability only.

Patients may experience mild discomfort associated with the insertion of the infusion sets and sensor into the SC tissues. The risk of discomfort due to insertion of infusion sets and sensors is expected to be slightly greater than in their lives outside the trial because more infusion sets will be inserted and a CGM sensor will be inserted. Most patients will use only 1 infusion set and not all will use a CGM sensor in usual care.

There is a potential risk of hypoglycemia, since recombinant insulin analog will be administered. Due to frequent monitoring of glucose and direct supervision by a registered nurse (RN) or Doctor of Medicine (MD) at all times, the risk of a hypoglycemic episodes leading to significant harm to patients is expected to be substantially lower than their risk during their usual therapy.

There is a risk of hyperglycemia. This risk is expected to be less than the risk during the patients' lives outside of the trial based on data from earlier BP trials and the design of this trial.

Treatment with ZP4207 and marketed glucagon can result in undesired effects or complaints. Undesired effects and complaints such as gastrointestinal side effects including nausea, vomiting, and diarrhea are known side effects of glucagon administration at higher dose levels. The frequency of nausea associated with the administration of 1 mg of glucagon according to the Summary of Product Characteristics (SPC) for Glucagon is described to be between 1/10 and 1/100. The frequency of vomiting is described to be between 1/100 and 1/1000 (Novo Nordisk, 2015). Similar gastrointestinal side effects have also been observed to a limited degree in the 2 clinical trials conducted with ZP4207, again at higher dose levels. The individual doses of ZP4207 and Lilly glucagon delivered by the BP are expected to be significantly lower than doses typically associated with nausea. Episodes of low blood pressure have also been observed after administration of higher doses of glucagon and ZP4207. As with every novel drug substance, new and yet unknown side effects may also occur.

There are limited data available to describe the immunogenic potential of glucagon products available on the market, but the data available indicate that marketed glucagon only has a small immunogenic potential. A Phase 1 trial performed with recombinant human glucagon and animal derived glucagon in 75 healthy patients did not show signs of ADA measured 13 weeks after trial product administration (Eli Lilly, 2005). In the ZP4207 FHD trial, ZP4207-14013, no confirmed anti-ZP4207 or anti-glucagon antibodies were detected in any of the samples. In addition, the 5 sequential administrations of ZP4207, as applied in trial ZP4207-15007, were not associated with the development of antibodies against ZP4207 in the 18 subjects enrolled to receive ZP4207. The optimized formulation of ZP4207, as applied in the present trial is not expected to change the immunogenic potential of the Investigational Medicinal Product (IMP).

In relation to diabetes therapy, development of insulin-antibodies is documented more substantially and route of administration has been shown to influence immunogenic potential of insulins. However, these antibodies against insulin generally do not have an impact on insulin action and are thus not clinically relevant.

In terms of consequence, development of high titer antibodies against ZP4207 could, in theory reduce the activity of endogenous glucagon, which again, in theory could influence

[redacted]

hypoglycemic episodes. However, most patients with T1DM do not secrete glucagon normally in response to hypoglycemia, so they would be less likely to be negatively impacted by anti-glucagon antibodies. Limited suppression of glucagon would, however, not be considered critical, as low glucose levels can also be corrected by other means, including oral intake of glucose and by other endogenous hormones such as oxyntomodulin.

Overall, ZP4207 is judged to be a low-risk molecule, based upon the available clinical data as well as the outcome of the risk-based approach to the immunogenicity assessment made. The present trial will include sampling for measurement of antibodies against ZP4207 prior to first dosing (Visit 3), at the ADA Assessment Visit (Visit 5), and at the Follow-up Visit (Visit 6). In line with regulatory guidance documents, these samples will be appropriately analyzed and the results will be included in the overall assessment of the immunogenic potential of ZP4207 after completion of each trial and as the clinical development program advances.

Administration of ZP4207 may be associated with a risk of allergic reactions similar to those observed for other therapeutic peptides or proteins. Patients with known or suspected allergies to the trial products or related products will be excluded from the trial. Mild or moderate allergic reactions may include symptoms of rash, fever, flu-like symptoms, nausea, headache, and myalgia. Acute generalized hypersensitivity reactions are usually very rare but may include symptoms of flushing, sweating, dizziness, change in blood pressure, and difficulties in breathing. The risk of acute hypersensitivity reactions is described to be less than 1/10,000 for native glucagon. No severe acute hypersensitivity reactions have been observed in the 2 clinical trials conducted with ZP4207.

Potential Benefits

Based on experiences from previous trials of the BP and the design of this trial, patients enrolled in the trial may benefit from a reduction in risk of hypoglycemia and hyperglycemia and a better mean glucose compared to their usual diabetes care during their short trial participation.

The data derived from this trial will allow evaluation of safety and tolerability of ZP4207 in the iLet and the iPhone-based BP, and the robustness and effectiveness of the new BP control system. The data obtained will be used to further improve the iLet and will allow the expansion to larger outpatient trials using the iLet or the iPhone-based BP with ZP4207.

This trial is a necessary step in preparing the BP with ZP4207 to become available to people with T1DM. Wide availability of the BP with ZP4207 could improve the medical care of adults and children with T1DM.

[redacted]

2 TRIAL OBJECTIVES

2.1 Primary Objective

The primary objective is to conduct a trial testing the safety and tolerability of the BP using either the iLet or the iPhone platform when used with ZP4207 in 20 adult (≥18 years of age) patients with T1DM.

2.2 Secondary Objectives

The secondary objectives are to measure glycemic regulation, including hypoglycemia exposure (percent of time spent with CGM glucose <60 mg/dL), evaluate BP device reliability, and to document the satisfaction of patients with the BP with the goal of optimizing the functionality and user interface of the BP.

3 TRIAL DESCRIPTION

3.1 Summary of Trial Design

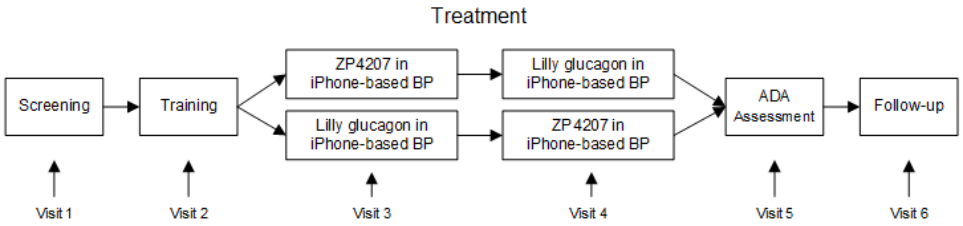
This trial is a single-center, open-label, 2-part, randomized cross-over trial. The trial will enroll adult patients with T1DM and will assess the safety and efficacy of the BP using either the iLet or the iPhone platform using the glucagon analog ZP4207 versus Lilly glucagon. In Part 1, up to 10 patients will participate in two 1-day treatment arms in random order (iPhone-based BP using ZP4207 and iPhone-based BP using Lilly glucagon) according to a pre-generated randomization scheme. In Part 2, up to 10 new patients will participate in two 1-day treatment arms in random order (iLet using ZP4207 and iLet using Lilly glucagon) according to a pre-generated randomization scheme. Patients can only participate in 1 part of the trial. An interim database lock may occur upon completion of Part 1 of the trial to analyze the iPhone-based BP data. The iLet and the iPhone-based BP will also administer insulin (insulin lispro, Lilly Humalog) using the same BG control algorithm for all 4 treatment arms. The trial will be conducted at a single center, the MGH Diabetes Center in Boston, MA.

The overall trial design schematic is displayed in Figure 2.

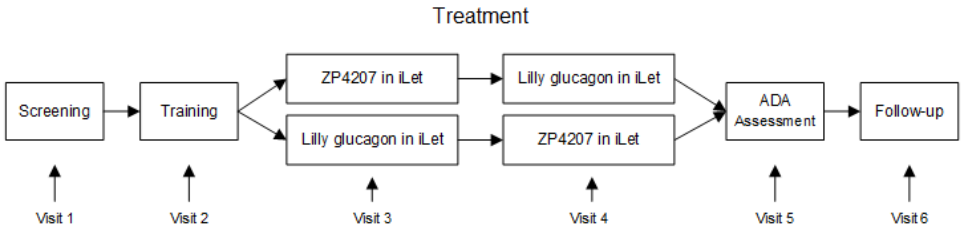
[redacted]

Figure 2. Trial Design Schematic

Part 1:



Part 2:



Patients can only participate in 1 part of the trial.
ADA = anti-drug antibodies; BP = bionic pancreas.

3.2 Indication

ZP4207 is an anti-hypoglycemic glucagon analog in a ready-to-use liquid formulation which is being studied to improve glycemic control in adults (and children) with T1DM as part of a bihormonal BP.

3.3 Number of Patients

Up to 40 adult patients with T1DM can be enrolled. The upper bound is based on the expectation that some patients will be excluded after the Screening Visit and the possibility that some patients may have to be discontinued before completion (due to, for instance, inter-current illness or patient withdrawal). It is expected that up to 10 patients will complete each part of the trial protocol.

4 SELECTION AND WITHDRAWAL OF PATIENTS

The trial will enroll patients who already manage their T1DM using continuous SC insulin infusion pump therapy. This requirement is imposed because multiple daily injection therapy involves the use of medium-acting or long-acting basal insulin that would require an extended washout period.

4.1 Inclusion Criteria

1. Male and female patients with T1DM for at least 1 year, as defined by the American Diabetes Association
2. Age ≥18 years
3. Diabetes managed using an insulin pump for ≥6 months
4. Prescription medication regimen stable for >1 month (except for medications that will not affect the safety of the trial and are not expected to affect any outcome of the trial, in the judgment of the Investigator)
5. Informed consent obtained before any trial-related activities (trial-related activities are any procedure that would not have been performed during normal management of the patient)
6. Patients in good health according to age (medical history, physical examination, vital signs, 12-lead electrocardiograms [ECGs], laboratory assessments), as judged by the Investigator

4.2 Exclusion Criteria

1. Unable to provide informed consent (e.g., impaired cognition or judgment)
2. Unable to safely comply with trial procedures and reporting requirements (e.g., impairment of vision or dexterity that prevents safe operation of the BP, impaired memory, unable to speak and read English)
3. Participation in another clinical trial of an investigational agent or device concurrently or within 1 month (or 5 half-lives) prior to the Screening Visit
4. Previous exposure to ZP4207
5. Females of childbearing potential who are pregnant (positive urine human chorionic gonadotropin [HCG]), breast feeding, plan to become pregnant in the immediate future, or sexually active without using highly effective contraception methods (highly effective methods are considered those with a failure rate less than 1% undesired pregnancies per year including surgical sterilization, hormonal intrauterine devices [coil], oral hormonal contraceptives, sexual abstinence, or a surgically sterilized partner) or postmenopausal women amenorrheic for less than 1 year with serum follicle-stimulating hormone (FSH) level ≤40 IU/L and not using highly effective contraceptive methods during the trial and until 1 month after last dosing in the trial
6. Male who is sexually active and not surgically sterilized who or whose partner(s) is not using highly effective contraceptive methods (highly effective contraceptive measures include surgical sterilization, hormonal intrauterine devices [coil], oral hormonal contraceptives, each in combination with spermicide-coated condoms), or who is not willing to refrain from sexual intercourse from the first dosing until 1 month after last dosing in the trial
7. Current alcohol abuse (intake averaging >3 drinks daily in last 30 days) or use within the last 6 months of controlled substances without a prescription (other than marijuana)
8. New onset clinically significant illness within 4 weeks prior to screening, as judged by the Investigator
9. Unwilling or unable to refrain on the treatment visits from:
    a. Acetaminophen in any form
    b. Use of drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the trial (use of beta blockers will be allowed as long as the dose is stable and the patient does not meet the criteria for hypoglycemia unawareness while

[redacted]

taking that stable dose, but use of benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the Investigator)

10. History of liver disease that is expected to interfere with the anti-hypoglycemia action of glucagon (e.g., liver failure or cirrhosis). Other liver disease (i.e., active hepatitis, steatosis, active biliary disease, any tumor of the liver, hemochromatosis, glycogen storage disease) may exclude the patient if it causes significant compromise to liver function or may do so in an unpredictable fashion.
11. Aspartate aminotransferase >2 × upper limit of normal (ULN), alanine aminotransferase >2 × ULN, or bilirubin >1.5 × ULN on screening laboratories
12. Renal failure on dialysis or estimated glomerular filtration rate <30 mL/min/1.73 m^2 on screening laboratories
13. Hemoglobin <12 gm/dL for men and <11 gm/dL for women
14. Personal history of cystic fibrosis, pancreatitis, pancreatic tumor, or any other pancreatic disease besides T1DM
15. Any known history of coronary artery disease including, but not limited to, history of myocardial infarction, stress test showing ischemia, history of angina, or history of intervention such as coronary artery bypass grafting, percutaneous coronary intervention, or enzymatic lysis of a presumed coronary occlusion)
16. Congestive heart failure with New York Heart Association Functional Classification III or IV
17. History of transient ischemic attack or stroke in the last 12 months
18. Seizure disorder, history of any non-hypoglycemic seizure within the last 2 years, or ongoing treatment with anticonvulsants
19. History of hypoglycemic seizures (grand-mal) or coma in the last 12 months
20. History of hypoglycemic unawareness in the last 12 months
21. History of pheochromocytoma: fractionated metanephrines will be tested in patients with history increasing the risk for a catecholamine secreting tumor:
    a. Episodic or treatment refractory (requiring 4 or more medications to achieve normotension) hypertension
    b. Paroxysms of tachycardia, pallor, or headache
    c. Personal or family history of MEN 2A, MEN 2B, neurofibromatosis, or von Hippel-Lindau disease
22. History of adrenal disease or tumor
23. Hypertension with systolic blood pressure (SBP) ≥160 mm Hg or diastolic blood pressure (DBP) ≥100 mm Hg despite treatment
24. Hypotension (SBP <90 mm Hg or DBP <60 mm Hg), either sitting or standing, or orthostatic hypotension (decrease in SBP >20 mm Hg or decrease in DBP >10 mm Hg within 3 minutes of standing from a seated position)
25. Untreated or inadequately treated mental illness (indicators would include symptoms such as psychosis, hallucinations, mania, and any psychiatric hospitalization in the last year), or treatment with anti-psychotic medications that are known to affect glucose regulation
26. Electrically powered implants (e.g., cochlear implants, neurostimulators) that might be susceptible to radio frequency interference
27. History of adverse reaction to glucagon (including allergy) besides nausea and vomiting
28. History of severe hypersensitivity to milk proteins or lactose
29. Established history of allergy or severe reaction to adhesive or tape that must be used in the trial

[redacted]

30. Use of oral anti-diabetic medications (e.g., thiazolidinediones, biguanides, sulfonylureas, glitinides, dipeptidyl peptidase-4 [DPP-4] inhibitors, sodium-glucose co-transporter-2 [SGLT-2] inhibitors)
31. Inadequate venous access as determined by trial nurse or physician at time of screening
32. Any factors that, in the opinion of the Investigator, would interfere with trial endpoints or the safe completion of the trial

4.3 Target Population

Patients who meet all of the inclusion and none of the exclusion criteria will be considered as candidates for this trial. Individuals who have previously inquired about participation in BU/MGH trials and have asked to have their contact information kept on file will be contacted. In addition, advertisements for the trial may be posted at the MGH Diabetes Center and other places, and may be distributed in the weekly broadcast e-mail of research studies seeking volunteers. A letter may be sent to adult endocrinologists in the Boston metropolitan as well as selected nearby endocrinologists informing them of the trial and asking them to refer any eligible patients who might be interested. Information will be posted about the trial along with contact information on the BU/MGH website www.bionicpancreas.org and on www.clinicaltrials.gov.

4.4 Withdrawal Criteria

The participation of individual patients will be discontinued if they experience:

- Seizure or unconsciousness associated with hypoglycemia and associated with participation in the trial
- Persistent nausea and vomiting thought to be related to glucagon dosing associated with participation in the trial
- Hospitalization associated with participation in the trial
- Pregnancy
- Diabetic ketoacidosis

If more than 1 patient must be withdrawn from the trial for these reasons, the trial will stop and a vote of the Data and Safety Monitoring Board (DSMB) will be required to restart it. All AEs that are serious and unexpected but related will be reported to the DSMB within 5 working days.

Note that patients may discontinue participation at any time. Patients may be removed from the trial for other reasons, for instance, failure to comply with trial procedures or intercurrent illness that is unrelated to the BP but that precludes safe participation. Discontinuation of participation for these reasons will not contribute to a decision to discontinue the trial.

5 ASSIGNMENT TO TREATMENT GROUPS

This trial is an open-label, 2-part, randomized cross-over trial. Patients who have completed the Screening Visit and meet all of the inclusion and none of exclusion criteria will be enrolled into the trial. In Part 1, up to 10 patients will participate in two 1-day treatment arms in random order (iPhone-based BP using ZP4207 and iPhone-based BP using Lilly glucagon) according to a pre-generated randomization scheme. In Part 2, up to 10 new patients will participate in two 1-day treatment arms in random order (iLet using ZP4207 and iLet using Lilly glucagon)

[redacted]

according to a pre-generated randomization scheme. Up to 2 patients may participate in the trial per day. The order of the treatment visits will be randomized in blocks of 2 patients.

6 TRIAL TREATMENT

6.1 Investigational Medicinal Products

Insulin: The trial involves SC administration of insulin lispro *(*Humalog, Lilly*)*, which is commercially available by prescription and is indicated for patients with T1DM, but not for use in a BP.

Glucagon: The trial also involves SC administration of Lilly glucagon in 1 iLet arm and 1 iPhone-based BP arm. Lilly glucagon is commercially available by prescription and is indicated for patients with T1DM in severe hypoglycemia, but not for use in a BP.

ZP4207: The trial also involves SC administration of the glucagon analog ZP4207, 1 mg/mL, in the other iLet arm and the other iPhone-based BP arm. ZP4207 will be made available by Zealand Pharma A/S, Denmark as liquid formulation in prefilled syringes of 0.6 mL.

6.2 Storage and Drug Accountability of IMPs

All IMPs will be stored and handled in accordance with the Sponsor's instructions and/or the product labeling at the Investigator's site, e.g., refrigerated (+2ºC to +8ºC) and should not be exposed to excessive heat, direct sunlight and never be frozen.

All used, partly used, and unused vials or prefilled syringes must be kept by the Investigator and stored between +2ºC and +8ºC (unused) or at room temperature (partly used and used). Used and unused pre-filled syringes must be stored separately.

The Investigator must ensure the availability of proper storage conditions and record and evaluate the temperature. Temperature of the refrigerator used for drug storage is monitored continuously, an alarm system is established. The Investigator must inform the monitor immediately if any IMP has been stored outside specified conditions (e.g., outside temperature storage). Investigational Medicinal Product that has been stored improperly must not be dispensed to any patient before it has been re-evaluated and approved for further use. The Investigator must take appropriate action to ensure correct storage.

For the IMP, the Investigator must keep an accurate record of all IMPs received and the products used for each patient in a Drug Accountability Record. Storage locations, batch numbers, and expiry dates are also documented in this form.

The drug accountability must be performed in a timely manner by the monitor.

6.3 Dispensing and Return of IMPs

No IMPs may be dispensed to any person not enrolled in the trial.

Upon completion of the trial, the Sponsor will be responsible for destruction or storage of IMPs (used, partially used, or unused). These duties can be delegated to a contract research organization (CRO) and must be documented in the trial files.

[redacted]

6.4 Doses

The iLet and the iPhone-based BP can administer isolated insulin-glucagon doses once every 5 minutes. A single automated bolus of insulin will not exceed 3 units per 5-minute dose (30 µl of U-100 insulin) in both systems, and a single meal-priming dose, in response to a meal announcement made by the user, will not exceed 12 units (120 µl of U-100 insulin). A single bolus of glucagon will not exceed 80 µg (80 µl of 1 mg/mL Lilly glucagon or 1 mg/mL ZP4207). In prior studies, typical doses of glucagon were in the range of 2.5-40 µg per dose. The iLet and the iPhone-based BP are capable of administering as little as ~0.5 µl (0.05 units of U-100 insulin or 0.5 µg of 1 mg/mL ZP4207).

It is expected that the mean total daily doses of glucagon/ZP4207 will be <1.0 mg daily as in previous studies. The mean daily glucagon dose in a previous 11-day outpatient trial was 0.5 mg/day (range 0.2-0.9 mg/day). Currently, single doses of up to 2 mg ZP4207 have been administered in clinical trials. The recommended dose of marketed glucagon for adult patients suffering from severe hypoglycemia is 1 mg as a single injection. Mean glucagon levels in previous inpatient studies have been above the normal fasting range for glucagon only 1% of the time. Therefore, the glucagon exposure of patients is expected to be modest.

6.5 iPhone-based Bionic Pancreas

Infusion Set: Patients will wear 2 FDA-approved commercially available infusion sets, 1 for insulin infusion and 1 for glucagon infusion. Infusion sets that are compatible with the Tandem t:slim infusion pump (luer lock connection) will be provided.

Continuous Glucose Monitors: One transcutaneous glucose sensor for the Dexcom G4 Platinum (Garcia, 2013) will be inserted in the abdominal SC tissue and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to the sensor and the whole assembly is held to the skin with an adhesive patch and communicates wirelessly with the BP. If the G4 sensor fails for any reason during the trial (loss of CGM signal), it will be replaced promptly.

Bionic Pancreas Control Unit: The control unit consists of a stock iPhone 4S and a Dexcom G4 Platinum receiver connected with a custom hardware interface and placed back-to-back in a custom enclosure. The G4 receiver converts the raw wireless signal from the transmitter into an estimated BG signal that is sent via a hardwired connection to the iPhone.

The iPhone runs iOS 6 in “Guided Access” mode, where the only app accessible to the patient is the Beta Bionics app, which runs the control algorithm. The home screen, where typical user options reside, is password protected. Access to other functions on the iPhone (primarily the Settings options) is separately password protected and only accessible to the study staff. This prevents accidental activation of other apps that could interfere with the function of the BP. The control algorithm app has a graphical user interface (GUI) that displays the current CGM glucose, a graphical history of the CGM glucose, and doses of insulin and glucagon delivered by the control algorithm. The GUI can also be used to input meal announcements, designating the size of the meal as larger than typical, typical in size, smaller than typical, or just a bite, and the type of meal as breakfast, lunch, or dinner. This will trigger a partial meal-priming bolus the size of which will adapt during the course of the trial to meet a target of 75% of the insulin needs for that size and type of meal.

The target glucose level will be programmed to 100 mg/dL by the study engineers prior to the start of each experiment. This will be locked for each arm of the study; the patient will be unable to accidentally change or tamper with this setting.

The GUI can be used to manage meal boluses and correction boluses during periods when the CGM is offline, such as the period after a sensor is replaced and before the new sensor has been calibrated. During these times the control algorithm will determine and direct the administration of insulin basal rates based on the patient's weight. The controller will also administer insulin and/or glucagon as appropriate in response to any entered BG values, just as if they were CGM values.

The GUI also displays visual alarms associated with an audio signal if communication is dropped between the CGM transmitter and the BP control unit or between the control unit and the 2 insulin pumps.

The iPhone communicates wirelessly via the Bluetooth Low Energy (BTLE) protocol with 2 Tandem t:slim insulin pumps to deliver insulin and glucagon.

Tandem t:slim Pumps: These pumps are FDA-approved insulin pumps with reservoirs capable of holding 300 units (3 mL) of insulin or 3 mL of glucagon or ZP4207 solution. The pumps have a mechanical dosing resolution of 1/120 (0.00833) unit and can deliver liquids at a maximal rate of ~33 µl per minute (2 mL per hour). They are slave to the BP control unit and are controlled wirelessly via the BTLE protocol by the iPhone 4S.

6.6 iLet Bionic Pancreas

Infusion Set: A novel, dual cannula infusion set has been designed specifically for use with the iLet. Patients will wear dual channel tubing that will be attached to 2 infusion sets with 1 steel cannula each, 1 for insulin infusion and the other for glucagon infusion. The tubing and infusion sets will have undergone sterilization prior to being delivered in a sealed pouch. The steel cannulae will be inserted in the abdominal SC tissue.

Continuous Glucose Monitors: One transcutaneous glucose sensor for the Dexcom G4 Platinum (Garcia, 2013) will be inserted in the abdominal SC tissue and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to the sensor and the whole assembly is held to the skin with an adhesive patch and communicates wirelessly with the BP. If the G4 sensor fails for any reason during the trial (loss of CGM signal), it will be replaced promptly.

Bionic Pancreas Control Unit: The iLet is being built according to Class III medical device standards, adheres to a comprehensive and robust quality system, and is fully compliant with International Organization for Standardization (ISO) 13485 standards and document control practices. The iLet is a fully-integrated dual-hormone BP system that integrates the CGM technology (currently the Dexcom G4 Share system) as well as 2 independent motor-drivetrain pumping assemblies, which independently actuate the delivery of insulin and glucagon from pre-filled cartridges that are separately loaded into the iLet housing. Each drivetrain assembly utilizes a lead screw, which is driven by a precision micromotor, a gear case assembly, and a motor controller unit, in a manner similar to what is commonly found in most insulin infusion pumps on the market today. The iLet has dosing accuracy that is comparable to FDA-approved insulin pumps currently on the market. The iLet has a built-in BTLE radio that

also allows automatic communication with the paired CGM, as well as the Nova StatStrip® Xpress BG meter (Nova Biomedical). The iLet does not contain a cellular nor a WiFi radio, and does not accept input data from another mobile device (e.g., smartphone), other than the paired CGM and BG meter(s).

The mathematical control algorithms (which are the same as those used in the iPhone-based BP), the CGM glucose engine (Dexcom), and the native user interface software, are all interconnected through controller framework software and reside as embedded systems on printed circuit boards contained within the device housing. The touchscreen-enabled, menu-driven user interface and onboard processor provide a comprehensive and standalone platform, which allows the iLet to operate independently of smartphones or other devices and without the need for internet support during routine operation. The graphical user interface of the iLet has the same user options and capabilities of the iPhone BP, including having its home screen password protected and its settings options only accessible to trial staff via a separate password.

6.7 Other Trial Devices

YSI 2300 STAT Plus™ (Yellow Springs Instruments): The YSI 2300 STAT Plus is an FDA-approved glucose analyzer. Blood glucose measurements using the YSI 2300 STAT Plus will be obtained off of the intravenous (IV) line during both treatment visits.

Nova Biomedical StatStrip Xpress Glucose Meter: The Nova StatStrip Xpress glucose meter is an FDA-approved glucose meter that is commercially available. Blood glucose measurements for CGM calibration will be obtained with the Nova StatStrip Xpress during both treatment visits if the YSI 2300 STAT Plus fails and via fingerstick with the Nova StatStrip Xpress during any periods when IV blood samples are not available for any reason or the IV fails.

Exercise Bike: The trial will utilize a stationary exercise bike (ergometer) for the in-clinic exercise at the treatment visits. This bike will be stored at the Diabetes Research Center when not in use.

6.8 Concomitant Medications

6.8.1 Permitted Medications and/or Procedures

Patients may take any over-the-counter medications that they wish during the trial, with the exception of any medication containing acetaminophen as that may cause interference with CGM sensing. All concomitant medications, including over-the-counter medications, should be recorded.

Use of beta blockers will be allowed as long as the dose is stable and the patient does not meet the criteria for hypoglycemia unawareness while taking that stable dose.

If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.

6.8.2 Excluded Medications and/or Procedures

During the trial, patients will not use any recreational drugs or drugs of abuse. The need to take prescription drugs that dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder appropriate decision-making may be grounds for exclusion from the trial or discontinuation of participation, a decision that will be made by the Investigator.

Use of benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the Investigator. Use of oral anti-diabetic medications (e.g., thiazolidinediones, biguanides, sulfonylureas, glitinides, DPP-4 inhibitors, SGLT-2 inhibitors) will also be excluded.

7 TRIAL PROCEDURES

7.1 Informed Consent

After potential patients have had time to review the consent document, and prior to any trial-related activities, they will meet with a trial MD or designee who will explain the trial, answer any questions, and administer informed consent. In the event that a volunteer is a patient of 1 of the trial MDs, another staff MD or designee will answer questions and administer consent. The patients will be fully informed of their responsibilities and their rights while participating in the trial as well as of the possible risks and potential benefits of participation in the trial. They will have the opportunity to discuss all questions and ample time to consider participation.

Trial-related activities are any procedures that would not have been performed during normal management of the patient. Patients who wish to participate in the trial will be asked to personally date and sign an informed consent form (ICF). Likewise, the Investigator must also personally date and sign the ICF. All patients will be provided with a copy of their own signed and dated ICF.

Trial staff will answer any questions that the patients may have during their participation. They will share any new information in a timely manner that may be relevant to the patient's willingness to continue participating in the trial. The patients may choose to discontinue their participation at any time.

7.2 Screening Visit (Visit 1)

All patients will have a Screening Visit to confirm eligibility. The patient will be interviewed and the electronic Case Report Form (eCRF) will be completed by trial staff to establish whether the patient is eligible.

Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator.

Once all of the results have been returned, a trial MD will review the eCRF to determine patient eligibility. If a patient is not eligible to continue in the trial, the results of abnormal tests will be reported to the patient and to a health care provider of their choosing.

[redacted]

7.2.1 Data Collected at Screening

- Age, sex, race, and ethnicity
- Date of last menstrual period in female patients
- Medical, surgical, and social history, allergies, and review of systems relevant to inclusion and exclusion criteria, including:
  - Date of diabetes diagnosis
  - Duration of insulin pump use and type of insulin used in pump
  - Type/model of insulin pump
  - Insulin regimen (basal rate, sensitivity factor, and carbohydrate ratio)
  - Average total daily dose of insulin in the last 30 days as available (from pump history)
  - Usage of CGM, if any (type of CGM, days per month worn, usage of data, whether insulin is dosed based on CGM alone, alarm settings)
- Concomitant illness (any illness present at screening)
- Concomitant medications (prescription and non-prescription) and date of last change in medication regimen
- Height, weight, physical examination, and vital signs including body temperature and blood pressure
- Orthostatic vital signs (heart rate and blood pressure) in the seated position and within 3 minutes of standing
- 12-lead ECG
- Hemoglobin A1c
- Chemistry and hematology samples (see Appendix B)
- Urine HCG pregnancy test for women of childbearing potential
- FSH level for postmenopausal women amenorrheic for less than 1 year
- Fractionated plasma metanephrines (if indicated by history)

7.3 Training Visit (Visit 2)

A Training Visit will take place before the first treatment visit. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor and trial policies and procedures. Trial staff will verify that the patients have understood the material and are competent to participate safely in the trial. Concomitant medications will also be reviewed.

Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator. The goals of diabetes management for patients during the fasting period are to avoid hypoglycemia, to treat hypoglycemia if it occurs, and to arrive at the treatment visit in the morning with a BG between 80 and 250 mg/dL. If insulin pump basal rates are properly configured, patients should be able to fast from 12:00 AM until the time of arrival for the visit without a high likelihood that they will become hypoglycemic or severely hyperglycemic. Patients will be asked whether they believe that they can safely fast from 12:00 AM until their arrival time at approximately 7:00 AM without adjusting their basal rates. If they have concerns, a trial physician will consult with them regarding pump basal rate adjustments. In all cases, subjects will be instructed to self-treat with carbohydrates according to the 15/15 rule (15 grams of carbohydrates, repeated in 15 minutes if necessary) during the overnight fasting period and at any time prior to their arrival at the trial site for the treatment visits.

7.4 Treatment Visits (Visit 3 and Visit 4)

- Visit 3 will take place at least 48 hours after screening (Visit 1) and no more than 30 days after screening (Visit 1).
- There will be a 24-hour minimum washout between Visit 3 and Visit 4 and a maximum of 3 weeks between Visit 3 and Visit 4.
- Up to 2 patients may participate per day.
- In Part 1, each patient will participate in 2 treatment visits: 1 with the iPhone-based BP using ZP4207 and 1 with the iPhone-based BP using Lilly glucagon in a randomized order.
- In Part 2, each patient will participate in 2 treatment visits: 1 with the iLet using ZP4207 and 1 with the iLet using Lilly glucagon in a randomized order.
- The night before the treatment visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be instructed to call if they encounter any difficulty with their CGM.
- Patients will be responsible for their own medications other than insulin during the trial. Any medical advice needed by the patients during their participation that is not directly related to BG control should be obtained from them in their usual manner. Patients may take any over-the-counter medications that they wish during the trial, with the exception of any medication containing acetaminophen as that may cause interference with CGM sensing. If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.
- During the trial, patients will not use any recreational drugs or drugs of abuse. The need to take prescription drugs that dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder appropriate decision-making may be grounds for exclusion from the trial or discontinuation of participation, a decision that will be made by the Investigator.
- Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator.
- Patients will not tamper with the BP, including changing any settings.
- Patients may not remove the BP during the trial unless the BP failed or they are withdrawing from the trial.
- The exact time of each procedure and assessment will be documented.

[redacted]

7.4.1 Visit Procedures

- Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window. If BG is <50 mg/dL, the patient will be treated with simple carbohydrate according to the 15/15 rule (15 grams of carbohydrates, repeated in 15 minutes if necessary). The visit will not need to be rescheduled unless the patient experiences a severe hypoglycemic event and requires treatment with glucagon or IV dextrose. If the visit needs to be rescheduled due to hypoglycemia or hyperglycemia, trial staff will assist the patient with insulin or medication adjustments to address glycemic control. The patient will be instructed to contact trial staff later in the day if his or her BG remains uncontrolled.
- Upon arrival to the visit, the patient's weight and vital signs including body temperature and blood pressure will be documented.
- Orthostatic vital signs (heart rate and blood pressure) will be measured in the seated position and within 3 minutes of standing.
- Patient reports of symptoms, any other complaints, and AEs will be reviewed.
- Concomitant medications will be recorded.
- Chemistry and hematology samples will be collected at visit start (see Appendix B).
- ADA samples will be collected before the start of dosing (Visit 3 only).
- A 12-lead ECG will be performed.
- A urine HCG pregnancy test will be performed in female patients of childbearing potential. If the test is positive, the patient will be informed of the result and the visit will be ended.
- Patients will complete a baseline survey about their attitudes and experience with their usual diabetes care.
- An IV catheter will be placed for blood sampling.
- Trial staff will assist the patient to calibrate their CGM, review the trial procedures again and assist with the setup of the BP system, including inserting and priming infusion sets.
- The control algorithm will be initialized only with the patient's weight. Diagnostics will be performed to ensure that the CGM device is appropriately calibrated and that all of the components of the BP systems are in working order.
- The basal rate of the patient's own insulin infusion pump will be changed to be 2-fold higher than weighted mean of the basal rate during the trial period. This is intended to increase the usage of glucagon during the treatment visit.
- The patients will continue to wear their own infusion pump infusing at the temporary 2-fold basal rate throughout the visit until the start of the structured exercise period, in addition to the BP.
- The staff will start the BP as close as possible to a minute divisible by 5 minutes (i.e., on a 5-minute mark). The starting time will be considered Hour 0.
- Additional calibrations will be performed at any of the BG checks throughout the day if the CGM value does not meet the ISO standard (<15 mg/dL difference for BG values <75 mg/dL; <20% absolute difference for BG values >75 mg/dL) at the time of the BG measurement AND it is a good time to calibrate (the CGM trend arrow is flat and there has been no carbohydrate intake in the last 30 minutes or glucagon boluses in the last 15 minutes).

[redacted]

- Blood samples will be taken from the IV at least hourly and processed for plasma ZP4207/glucagon. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator. The actual time of sampling will be recorded in the eCRF.
- Plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.
- Patients will be asked to rate any nausea and/or infusion site pain on 10 cm visual analog scales (VAS) at the beginning of the visit once the infusion sites have been placed but no drug has yet been administered, then approximately at the top of every hour during the visit, and at the end of the visit. Trial staff will also evaluate their infusion sites to document any erythema or edema at the same times. If moderate or severe pain is reported or swelling or redness occurs at the infusion site, the infusion site will be replaced in a different location. If moderate or severe pain, swelling, or redness continues at the old site for more than 30 minutes after the infusion site is removed, or if moderate or severe pain, swelling, or redness occurs at the new site, all infusion sites will be removed and the patient will be discontinued from the study. Any such symptoms will be followed until resolution.
- From the start of closed loop control until approximately Hour 3, the patients will continue to fast.
- Between approximately Hour 3 and Hour 4, patients will be provided with a lunch meal of their choice in the Diabetes Research Center from a menu of choices from nearby restaurants. They will be asked to choose a meal that is a “typical meal” for them. The content of their meal will not be restricted in any way, with the exception that the number of carbohydrates should be in the “typical” range for them at lunch, and that they must eat the same meal at the same time during both visits.
- At approximately 15 minutes before the meal, patients will administer a bolus for the meal with their own insulin pump based on the carbohydrate count for the meal.
- After lunch is completed, the patients will not be allowed any carbohydrate intake (non-caloric drinks will be permitted) until the trial is completed (except as necessary to treat hypoglycemia), to allow the BP to control the post-prandial BG without further interruption.
- Between approximately Hour 6 and Hour 7, the patients will start a period of structured exercise.
- At the start of the exercise period, patients will restore their normal basal insulin profile so that they will not have elevated insulin levels at the end of the study period when they are to transition back to their usual care.
- Patients will exercise on a stationary bike with a heart rate from 120-140 beats per minute for a total of 4,000 heart beats (approximately 30 minutes). Patients will rate their exercise intensity using the Borg scale every 5 minutes, with the target intensity level between 12 and 14. Heart rate will be measured every 5 minutes.

[redacted]

- BG measurements will be obtained off of the IV line every 10 minutes. If BG is <80 mg/dL, BG measurements will be obtained off of the IV line every 5 minutes.
  - Carbohydrates will be given for any BG <50 mg/dL according to the following protocol: Dextrose (g) = BSA (m^2)/[1.7 m^2 (women) or 1.9 m^2 (men)] *15 g.
  - Repeat treatments will be given at 15-minute intervals as long as BG remains <50 mg/dL.
- If there is an interruption in the Dexcom CGM output, trial staff will assist the patient in recovering CGM data streaming. If this requires replacement of the CGM sensor, BGs will be checked every 10 minutes (every 5 minutes if BG is <80 mg/dL) using blood from the IV until the CGM is able to be calibrated again. These BGs will be entered into the BP, which will treat them as CGM values and dose insulin and/or glucagon appropriately.
- If there is a complete failure of the BP operation, patients will take over their own BG control using their personal insulin pump until the BP can be brought back online. If BP control cannot be promptly resumed (e.g., within 30 minutes), the patient may be asked to repeat that trial day once.
- Patients may choose to withdraw from the trial at any time. If they withdraw from the trial, they should alert a provider immediately.
- Just prior to the end of the study visit, vital signs including body temperature and blood pressure will be obtained and a 12-lead ECG will be performed. Orthostatic vital signs (heart rate and blood pressure) will be measured in the seated position and within 3 minutes of standing. If patients have hypotension or orthostatic hypotension, discharge will be delayed until their blood pressure is normal and stable.
- After approximately Hour 8, but not earlier than at least 60 minutes after end of exercise, the BP will be stopped and the patient will continue with their personal insulin pump.
- If the patient experiences seizure or unconsciousness, persistent nausea or vomiting, diabetic ketoacidosis, persistent hyperglycemia with ketonemia, hemodynamic changes such as hypotension, or other medically significant findings, a longer observation period at the trial site may be necessary until the patient is considered stable for discharge. If the Investigator or trial staff determines that the patient requires further observation or treatment, the patient may be transferred to the emergency room for additional monitoring and/or medical care. At discharge, patients will be provided with any necessary instructions concerning personal insulin pump usage, food intake, and driving arrangements.
- The maximum amount of blood loss per study visit will be approximately 230 mL. The total blood loss for the entire study will be up to 460 mL.
- Patients will answer questionnaires (see Appendix C).
- Chemistry and hematology samples will be collected at visit end (see Appendix B).
- The BP and glucose meters will be collected and downloaded.
- A trial MD will review the last several hours of insulin and glucagon dosing and assist the patient in resuming their usual diabetes care. A longer observation period at the trial site may be necessary. Patients will be instructed to call trial staff with any questions, issues, or concerns.

7.4.2 Data Collected During the Treatment Visits

- CGM glucose every 5 minutes from the Dexcom G4 Platinum CGM
- All BG measurements taken

- Insulin total dose by the BP and the patient's own insulin pump
- Glucagon total dose
- Timing and content of the meal eaten and carbohydrate amount
- Timing of meal announcement and size of meal announced
- Timing and glucose values at calibrations
- Timing and amount of carbohydrates taken for hypoglycemia
- Data from a questionnaire about attitudes and expectations regarding the BP before and after each treatment arm (see Appendix C)
- Time patients were not under BP control for any reason
- List of technical faults associated with the BP including cause and resolution
- ZP4207/glucagon sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.
- Plasma glucose sampling will be collected at least hourly in parallel with ZP4207/glucagon exposure sampling. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
- Nausea and infusion site pain on a VAS at visit start (after insertion and before any drug administration), hourly, and at visit end
- Infusion site reaction according to the Draize scale at visit start (after insertion and before any drug administration), hourly, and at visit end
- Patient reports of symptoms, any other complaints, and AEs
- Vital signs including body temperature and blood pressure (at visit start and visit end) and weight
- Orthostatic vital signs (heart rate and blood pressure) in the seated position and within 3 minutes of standing
- Concomitant medications
- Chemistry and hematology samples (see Appendix B) at visit start and visit end
- ADA (Visit 3 only)
- 12-lead ECG at visit start and visit end
- Urine HCG pregnancy test for women of childbearing potential

7.4.3 Response to Hypoglycemia

- Patients are encouraged to check their BG for any symptoms of hypoglycemia.
- Patients will be permitted to take 15 grams of carbohydrates for any BG value <60 mg/dL. Trial staff will ensure proper functioning of the BP, infusion set, and insulin pump, and will encourage the patient to wait for the BP to treat the low blood sugar for as long as they feel comfortable.
- Patients will be required to take 15 grams of carbohydrates for any BG value <50 mg/dL. After treatment of hypoglycemia, a follow-up measurement will be taken 15 minutes later. Repeated measurements will be taken every 15 minutes until the BG is >60 mg/dL. Treatment will be repeated if subsequent BG values are still <50 mg/dL. All carbohydrate treatments for hypoglycemia will be documented by trial staff (amount and time).

[redacted]

- Trial staff will check the infusion site, BP, and insulin pump for normal operation any time hypoglycemia occurs. If there is any suspicion of infusion set malfunction, the site should be replaced. Trial staff will check the BP for any malfunction and correct any problems that are found.
- If no correctable fault is found, but there is doubt regarding the correct function of the BP system, an entirely new backup BP system may be started.
- If a patient experiences a seizure or unconsciousness associated with hypoglycemia, his or her participation in the trial will be discontinued.

7.4.4 Response to Hyperglycemia

- Trial staff will check the infusion site, BP, and insulin pump for normal operation any time BG is >300 mg/dL. If there is any suspicion of infusion set malfunction, the site should be replaced. Trial staff will check the BP for any malfunction and correct any problems that are found. If the BG remains >300 mg/dL for 2 hours despite troubleshooting, blood ketones will be measured. If the blood ketone result is >1.5 mmol/L, the visit will be stopped and rescheduled. The patient will be provided with insulin and a syringe to give an injection based on their correction factor.
- If a patient experiences diabetic ketoacidosis, his or her participation in the trial will be discontinued.
- If no correctable fault is found, but there is doubt regarding the correct function of the BP system, the treatment visit may be stopped and the visit rescheduled.

7.4.5 Response to Nausea/Vomiting

If significant nausea (e.g., that prevents the patient from eating normally) or any vomiting occurs, trial staff will notify the Investigator. Trial staff will assist the patient in troubleshooting, such as checking BG and the calibration of the CGM (excessive glucagon dosing may occur if the CGM is reading lower than the true BG). If a patient experiences persistent nausea and vomiting thought to be related to glucagon dosing, his or her participation in the trial will be discontinued.

7.4.6 Response to Other Medical Needs

If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.

7.4.7 Monitoring of Bionic Pancreas Performance

Bionic pancreas inventors and developers [redacted], [redacted], and/or an engineer trained by them will be readily available by phone for consultation for the trial staff at all times during the course of the trial.

7.4.8 Supervision by Trial Staff

A trial MD will be on call at all times during the course of the trial. An RN or MD will be with the trial patients in the Diabetes Research Center at all times.

7.5 Anti-drug Antibodies Assessment Visit (Visit 5)

Patients will return for an ADA Assessment Visit 10 days ±3 days following the last day of dosing (Visit 4) for ADA sampling and a review of AEs and concomitant medications.

7.6 Follow-up Visit (Visit 6)

Patients will return for a Follow-up Visit 25 days ±4 days following the last day of dosing (Visit 4), for chemistry, hematology, and ADA sampling, and a review of AEs and concomitant medications.

8 ENDPOINTS

8.1 Primary Endpoint

The primary endpoint is the safety and tolerability of ZP4207 in the BP using either the iLet or the iPhone platform as assessed by:

- Number and type of AEs
- Clinical laboratory measurements
- Vital signs
- 12-lead ECG
- Local tolerability and infusion site reactions as measured with the Draize scale
- Immunogenicity as measured by ADA
- Pain as measured on a 10 cm VAS
- Nausea as measured on a 10 cm VAS

8.2 Secondary Endpoints

The secondary endpoints include measurements of BP function as well as glycemic and non-glycemic measurements.

8.2.1 Bionic Pancreas Function

This endpoint data will be generated from the BP data during each treatment visit:

- Average percent insulin dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
    - Average percent glucagon/ZP4207 dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts calculated by the BP algorithm that are successfully issued to the pump by the BP (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts calculated by the BP control algorithm that are successfully issued by the BP
    - Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully issued by the BP
- Average percent of 5-minute steps during which the BP is functioning nominally in all respects based on real-time CGM data (new CGM glucose reading captured, dose calculated, and dose issued to pumps)

- Average percent of 5-minute steps during which the BP is functioning nominally with or without a new CGM glucose reading captured (dose calculated and dose issued to pumps). If a CGM signal is not available, the dose calculated may be based on weight or historical basal rates.
- CGM reliability index, calculated as percent of possible values actually recorded by CGM
- CGM Mean Absolute Relative Difference versus time-stamped BG values from meter download
- List of technical faults associated with the BP including cause and resolution

8.2.2 Glycemic

All of following metrics will be generated from the Dexcom G4 Platinum CGM data during each treatment visit:

- Fraction of time spent within each of the following glucose ranges:
  - <50 mg/dL
  - <60 mg/dL
  - <70 mg/dL
  - 70-120 mg/dL
  - 70-140 mg/dL
  - 70-180 mg/dL
  - >180 mg/dL
  - >250 mg/dL
  - >300 mg/dL
- Number of severe hypoglycemic events (patients unable to self-treat, requiring the assistance of another person)
- Number of episodes of symptomatic hypoglycemia
- Number of carbohydrate interventions for hypoglycemia
- Total grams of carbohydrates taken for hypoglycemia
- Mean CGM glucose

8.2.3 Non-glycemic

- Glucagon/ZP4207 total delivery per kg of body mass
- Insulin total delivery per kg of body mass
- Number of unscheduled infusion set replacements
- Number of unscheduled CGM sensor changes

9 LABORATORY ASSESSMENTS

Descriptions of sample handling and sample processing, storage, and shipment at the site will be included in the laboratory manual.

The responsible laboratories are listed in the address list.

9.1 Safety Laboratory Assessments

Chemistry and hematology samples will be collected at specified time points. See Appendix A for the schedule of procedures and Appendix B for a list of clinical laboratory analytes.

[redacted]

9.2 Pharmacodynamic Assessments (Plasma Glucose)

At Visit 3 and Visit 4, plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.

9.3 Exposure Assessments (ZP4207 and Glucagon)

At Visit 3 and Visit 4, ZP4207/glucagon exposure sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator. The actual time of sampling will be recorded in the eCRF.

Bioanalytical Reports will be prepared.

9.4 Anti-drug Antibodies Assessments

Blood samples (including back-up samples) for serum anti-ZP4207 and anti-glucagon antibodies will be taken at Visit 3, the ADA Assessment Visit (Visit 5), and the Follow-up Visit (Visit 6). Any patient that tests positive for ADA will be monitored until the ADA levels return to baseline.

Bioanalytical Reports will be prepared.

10 SAFETY REPORTING

10.1 Adverse Events

An AE is any untoward medical occurrence in a trial patient administered an IMP and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP. Patients should be instructed to report any AE they experience to the Investigator.
Note: This includes events from the first trial-related activity from Visit 3.

AEs for ZP4207 include:

- A clinically significant worsening of a concomitant illness
- A clinical laboratory abnormality which is clinically significant, i.e., any abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example, change of medicine dose or more frequent follow-up due to the abnormality.
- Hypoglycemic episodes
- Injection site reactions

[redacted]

The following should **not** be recorded as AEs, if recorded prior to randomization (on the Screening Form or the eCRF):

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial-related activity from Visit 3.
- Pre-existing conditions found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).

For known (listed) AEs for Glucagon and Humalog, please refer to SPC for Glucagon and Humalog.

10.1.1 Follow-up of Adverse Events

All AEs that are ongoing at the end of the patient's participation in the trial will be followed-up until the event is resolved or reaches a satisfactory outcome as deemed by the Investigator. Follow-up actions for all serious adverse events (SAEs) will be performed according to appropriate clinical care practices and may depend on the nature of the event. These will be determined after internal review and/or Sponsor review. The follow-up information should only include new (updated and/or additional) information that reflects the situation at the time of the Investigator's signature.

Follow-up information on (S)AEs will be updated using the (S)AE Form. If a non-serious event becomes serious during the follow-up, the AE Form and SAE Form must be used and reporting timelines follow those of an SAE.

The Investigator must forward follow-up information on SAEs, and if previously non-serious AEs become SAEs, to the Sponsor.

10.1.2 Precautions

Normal precautions taken for a human trial will be taken during this trial. Qualified and well-trained physicians and medical staff will instruct the patients. During a patient's participation in the trial, the Investigator should ensure that adequate medical care is provided to the patient for any AEs, including clinically significant laboratory values related to the trial. The Investigator should inform the patient when medical care is needed for intercurrent illnesses of which the Investigator becomes aware.

For further information on safety precautions for ZP4207, Lilly glucagon, and Lilly Humalog, please refer to the current version of the Investigator's Brochure (IB) for ZP4207 (Zealand Pharma A/S, 2015, or any updates hereof), and the SPC for Glucagon (Eli Lilly, 2012) and Humalog (Eli Lilly, 2015), respectively.

10.1.3 Assessment of Adverse Events by the Investigator

Intensity of an Adverse Event

The maximum intensity (severity) of all AEs must be assessed by the Investigator and documented. Severity should be graded when the AE outcome is known:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

A "severe" reaction does not necessarily deem the AE as "serious," and an SAE may not be "severe" in nature.

Causality Relationship to IMP
Insulin (insulin lispro, Lilly Humalog), glucagon (glucagon for injection, Eli Lilly), and ZP4207 are all regarded as IMP.

The causality of each AE should be assessed by the Investigator according to the following classification:

- Related: Good reason and sufficient documentation to assume a causal relationship.
- Not related: No relationship to trial product can be established.

Outcome of an Adverse Event
The outcome of all AEs must be assessed by the Investigator and documented by his/her staff. The following definitions should be used:

- Recovered/resolved: The patient has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity from Visit 3.
- Recovering/resolving: The condition is improving and the patient is expected to recover from the event. This term is only applicable if the patient has completed the trial.
- Recovered/resolved with sequelae: The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment, or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- Not recovered/not resolved: The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known.
- Fatal: This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as "recovered/resolved," "recovering/resolving," "recovered/resolved with sequelae," or "not recovered/not resolved." An AE with a fatal outcome must be reported as an SAE.
- Unknown: This term is only applicable if the patient is lost to follow-up.

10.2 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Medically important

[redacted]

Medical judgement must be exercised in deciding whether an AE is believed to be "medically important." Medically important events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above.

Suspected Unexpected Serious Adverse Reactions (SUSAR)
A SUSAR is an AE fulfilling 1 of the criteria of seriousness and being assessed as related to an IMP, the nature or severity of which is not consistent with the applicable reference document (e.g., ZP4207 IB or package leaflet/SPC for an approved product).

Unanticipated Adverse Device Effect (UADE)
A UADE is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

10.3 Adverse Event Reporting – Procedures for Investigators

The Principal Investigator and co-investigators will review any AEs and report any SAEs to the Sponsor as soon as possible and within 24 hours of obtaining knowledge of the event. The Principal Investigator and co-investigators will promptly report AEs to the Partner's Institutional Review Board (IRB) and to the BU IRB (unless oversight is ceded by the BU IRB to the Partners IRB), in accordance with local requirements.

Ed Damiano is the Sponsor of the Investigational Device Exception for the BP and Zealand Pharma A/S is the Sponsor of the IND for ZP4207.

Reports of AEs will be submitted to the FDA in compliance with the terms of the Code of Federal Regulations.

All events meeting the definition of an AE must be collected and reported from the first trial-related activity from Visit 3 until the end of the post-treatment follow-up period. At each contact with the site (visit or telephone, excluding safety visits, where the patient is not seeing the Investigator or staff [e.g., visits to the laboratory], the patient must be asked about AEs. All AEs, either observed by the Investigator or reported by the patient, must be recorded by the Investigator and evaluated.

The Investigator should record the diagnosis, if possible. If no diagnosis can be made, the Investigator should record each sign and symptom as individual AEs.
All AEs must be recorded by the Investigator. One single AE Form must be used per AE from start to resolution. For SAEs, the SAE Form must also be completed.

AE information should include the following:

- Patient identification number on all pages
- Date and time of treatment start
- Date and time of onset and date of outcome
- Date and time of Investigator's first information on the (S)AE
- Seriousness

[redacted]

- Severity
- Causal relationship with IMP ZP4207
- Causal relationship with IMP insulin
- Causal relationship with IMP glucagon
- Causal relationship with medical device
- Causal relationship with procedures
- Interruption or withdrawal of treatment with IMP or medical device and other measures taken
- Outcome

All AEs are coded; details are described in the trial specific Data Management Plan.

The Investigator must report initial information in writing on the SAE Form for all SAEs to the Sponsor's responsible pharmacovigilance unit (here: Lindeq) immediately (within 24 hours) after obtaining knowledge about the event.

Name: [redacted]
Company: Lindeq
Address: Lyskær 8, 2730 Herlev, Denmark
Tel: [redacted]
Fax:
Mobile:
E-mail: drugsafety@lindeq.com

In addition and meeting the same timeline, Investigators must report all SAEs to Zealand Pharma A/S by forwarding the SAE Form electronically within 24 hours of obtaining knowledge of the event to the representatives of Zealand Pharma A/S.

Names: [redacted] and [redacted]
Address: Smedeland 36, DK-2600 Glostrup, Denmark
Tel: [redacted] / [redacted]
E-mails: [redacted] / [redacted]

It is the responsibility of Lindeq to report all SUSARs that occur in this trial to the Competent Authorities and to the Investigators. It is the responsibility of the Investigators to report the SUSARs to the IRBs in accordance with the local requirements in force and the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP). The trial monitor must be informed accordingly.

It is the responsibility of Lindeq to report all serious adverse reactions on insulin lispro and glucagon for injection to the Eli Lilly Pharmacovigilance department within 5 days.

It is the responsibility of the Investigators to report all UADEs to Beta Bionics within 24 hours of the time they are detected. It is the responsibility of the Investigators to report all UADEs to the IRB in accordance with the local requirements in force and the ICH GCP. It is the responsibility of Beta Bionics to report all UADEs to the Competent Authorities.

All device deficiencies should be documented and should be reported to Beta Bionics within 24 hours. Device deficiencies are inadequacies of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

Name: [redacted]
Company: Beta Bionics, Inc.
Address: Business Innovation Center, Photonics Center, 8 Saint Mary's Street, Suite 936 Boston, Massachusetts 02215-2421, United States
Tel: [redacted]
E-mail: [redacted]

10.4 Pregnancy Reporting

Female patients must be instructed to notify the Investigator immediately if they become pregnant or if they suspect to be pregnant during the trial. The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical trial.

Male patients must be instructed to notify the Investigator immediately if their partner becomes pregnant or suspects to be pregnant. The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical trial. During an information meeting at the trial site, the patient's partner will be fully informed by a physician of her participation in capturing the outcome data, and will be asked to provide her written consent.

The Investigator must report all information on pregnancies, including AEs in the patient/patient's partner, the fetus, and newborn infant/ toddler. The pregnancy report must be forwarded to the Sponsor preferably electronically as PDF or by fax.

The Investigator must follow the pregnancy until the pregnancy outcome and the newborn infant(s) until the age of 1 month. The Investigator must collect information on the pregnancy and pregnancy complications as well as the pregnancy outcome including the health of the newborn infant(s) on the pregnancy forms.

The following must be collected:

- Initial information of the pregnancy
- Information on the outcome of the pregnancy, including the health status of the newborn infant(s) at the age of 1 month
- All AEs in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms. It must be clear in the description if the event occurs in the patient/patient's partner, the fetus, or the newborn infant.
- All SAEs in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms following the same timelines as required for other SAEs. It must be clear in the description if the event occurs in the patient/patient's partner, the fetus, or the newborn infant.

The SAEs that must be reported include abnormal outcome – such as congenital anomalies, fetal death, and termination of pregnancy (spontaneous or elective abortion), including any anomalies of the fetus observed at gross examination or during autopsy – as well as other pregnancy complications (ectopic pregnancy) fulfilling the criteria of an SAE.

[redacted]

10.5 Hypoglycemia

Hypoglycemia will be regarded as an AE and will be recorded and documented on an AE Form. For the purposes of AE reporting, the following definitions of hypoglycemia will be used:

- Symptomatic hypoglycemia: an event during which typical symptoms of hypoglycemia are accompanied by a BG concentration ≤70 mg/dL
- Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with a BG concentration ≤50 mg/dL
- Severe hypoglycemia: an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions

10.6 Safety Monitoring

10.6.1 Data and Safety Monitoring Board

An external DSMB will oversee the conduct of the trial, as set forth in the DSMB Charter. Additionally, the DSMB will be informed in the event of any serious and unexpected AEs. The DSMB will be informed if there are any changes to the trial protocol that could significantly impact the safety or scientific validity of the trial. A final DSMB meeting will convene after the completion of the trial.

The participation of individual patients will be discontinued if they experience:

- Seizure or unconsciousness associated with hypoglycemia and associated with participation in the trial
- Persistent nausea and vomiting thought to be related to glucagon dosing associated with participation in the trial
- Hospitalization associated with participation in the trial
- Pregnancy
- Diabetic ketoacidosis

If more than 1 patient must be withdrawn from the trial for these reasons, the trial will stop and a vote of the DSMB will be required to restart it. All AEs that are serious and unexpected but related will be reported to the DSMB within 5 working days.

Note that patients may discontinue participation at any time. Patients may be removed from the trial for other reasons, for instance, failure to comply with trial procedures or intercurrent illness that is unrelated to the BP but that precludes safe participation. Discontinuation of participation for these reasons will not contribute to a decision to discontinue the trial.

10.6.2 Zealand Pharma Safety Committee

The internal Zealand Pharma Safety Committee is constituted to perform ongoing safety surveillance of clinical trials within ZP4207, including this trial.

If safety signals are observed either based on reported SAEs, periodic review of laboratory parameters, planned review of all AEs reported between the safety committee meetings, or on notification of significant findings, the Safety Committee will take appropriate measures to safeguard the patients.

11 STATISTICS

For all analysis, the 2 treatment arms from Part 1 (iPhone-based BP) will be compared, and the 2 treatment arms from Part 2 (iLet) will be compared. The analysis of Part 1 will be completely separate from the analysis of Part 2.

11.1 Analysis Populations

The following analysis sets are defined in accordance with the ICH-E9 guidance:

The Full Analysis Set is based on the intention-to-treat principle and includes all randomized patients. In exceptional cases, patients from the Full Analysis Set may be excluded (will be decided in the database review [DBR] meeting). In such cases, the exclusion will be justified and documented. Patients will contribute to the evaluation “as randomized.”

The Per-Protocol Set includes all patients of the Full Analysis Set who completed the trial without any major protocol violations. Patients in the Per-Protocol Set will contribute to the evaluation “as treated.” This analysis will only be used if it is different than the Full Analysis Set.

The Safety Analysis Set includes all patients receiving at least 1 dose of the IMP. Patients in the Safety Analysis Set will contribute to the evaluation “as treated.”

Analyses of efficacy endpoints will be based on the Full Analysis Set (and the Per-Protocol Set if necessary). This decision will be made in the DBR meeting. The analysis of the safety endpoints will be based on the Safety Analysis Set.

Before data are released for statistical analysis, a blinded review of all data will take place to identify protocol deviations that may potentially affect the results. At this time, it will be determined if patients and/or data should be excluded from the analysis. Furthermore, outliers will be identified by data review according to ICH-E9.

Obviously erroneous data points may be excluded from the analyses or re-analyzed (e.g., serum concentrations). The decision to re-analyze or exclude data points from the statistical analysis is the joint responsibility of the Sponsor, the Principal Investigator, and the Trial Statistician.

The patients or observations to be excluded and the reason for their exclusion will be documented and signed by those responsible prior to database release. The documentation will be stored together with the remaining trial documentation. The patients and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

11.2 Statistical Methods

Medpace will be responsible for the statistical analysis. The statistical planning and conduct of analyses of the data from this trial will follow the principles defined in relevant ICH guidelines and Medpace’s biostatistical standard operating procedures (SOPs). A general description of the statistical methods to be used is given in this section, specific details will be provided in the Statistical Analysis Plan (SAP), which will be prepared before database lock. All statistical

[redacted]

analyses will be performed using SAS® (SAS Institute Inc., Cary, North Carolina, USA), version 9.3 or later.

11.2.1 Analysis of Safety

The following variables will be evaluated according to treatment for safety purposes:

Adverse Events
All AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Individual AEs will be presented in a listing including relationship to trial product/device, severity, and treatment period at onset. If more than 20 treatment-emergent AEs (AEs with onset after [first] dosing at Visit 3 until the Follow-up Visit 6) are registered, a summary table including number of AEs, number of patients with at least 1 AE, and percentage of exposed patients with at least 1 AE will be made by system organ class and treatment period at onset.

Local Tolerability
Local tolerability at the injection site will be summarized using descriptive statistics as appropriate.

Laboratory Safety Assessments
Laboratory assessments will be summarized. A listing of abnormal values will be provided.

Physical Examination
A frequency table will show the number and percentage of physical examination results.

Vital Signs
Vital signs will be summarized using descriptive statistics.

12-lead ECG
The Investigator's evaluations of 12-lead ECGs will be summarized and abnormal individual evaluations will be listed together with the Investigator's comments. Changes in 12-lead ECG between measurements will be recorded as AEs if the Investigator judges them to be clinically significant.

11.2.2 Analysis of Efficacy

The analysis of BP function endpoints and glycemic endpoints will be on an intention-to-treat basis. In cases where a treatment arm was not completed (and that arm was not repeated according to protocol criteria), available data from that arm will be used in the data analysis.

The Shapiro-Wilk test will be used to determine the normality of the residuals for each comparison. Summary tables that display descriptive statistics, including percentages, means or medians, and standard deviation and/or ranges, as appropriate, will be provided.
A paired t-test or the Wilcoxon signed rank test for comparison of means with normally or non-normally distributed residuals, respectively, will be used. In a secondary analysis, any period effect and any interaction between treatment and period will be looked for, although no such interaction is predicted for the efficacy outcome. Further details will be included in the SAP.

[redacted]

The number of patients and proportions of severe hypoglycemic events, symptomatic hypoglycemia, and carbohydrate interventions due to hypoglycemia with the event counts will be summarized descriptively, and the proportions will be analyzed by a Fisher's exact test if data allow.

11.2.3 Interim Analysis

An interim database lock may occur upon completion of Part 1 of the trial to analyze the iPhone-based BP data.

11.2.4 Sample Size Determination

No formal sample size calculations were made. It is expected that between 20 and 24 patients will be randomized in the trial. The sample size is based on a clinical rather than statistical rationale. The sample size is considered adequate to address the primary trial objective of exploring the safety of ZP4207 when used in the BP and with reference to Lilly glucagon used in the BP.

12 DATA MANAGEMENT AND RECORD KEEPING

Data Management is the responsibility of Medpace. The complete Data Management process will be described in detail and agreed on in the Data Management Plan for this trial.

12.1 Data Handling

Case Report Forms
Electronic Case Report Forms will be used in this trial. The Data Management Department of Medpace will provide the eCRFs. All further information regarding the eCRFs and the data flow will be described and agreed on in the Data Management Plan.

Device-Related Data
During the trial, CGM data, calibration data, insulin dosing data, and glucagon dosing data will be automatically stored in the BP device (from which it will be downloaded at intervals), combined in a single database that will be compared against the primary data files for integrity, and ultimately transferred to Medpace.

12.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

12.3 Data Entry

Data must be recorded using the electronic data capture (EDC) system as the trial is in progress. The patient questionnaires will be transcribed into the EDC system by site personnel. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct trial data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

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12.4 Medical Information Coding

Adverse events and medical history will be coded using the latest version of MedDRA. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary.

12.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

12.6 Record Keeping

Medpace will be responsible for hosting the TMF. Records of patients, source documents, monitoring visit logs, eCRFs, inventory of trial product, regulatory documents, and other Sponsor correspondence pertaining to the trial must be kept in the appropriate trial files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the evaluation and reconstruction of the clinical trial. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Trial Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

13 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

13.1 Ethical Conduct of the Trial

The trial will be conducted according to Medpace, MGH, and/or the Sponsor's written instructions (SOPs, working instructions, or process descriptions). Content and definitions of the written instructions are based on the Declaration of Helsinki and the ICH GCP.

13.2 Institutional Review Board

Written favorable opinion must be obtained from the responsible IRB prior to commencement of the trial. Clinical trial submission and reporting requirements before, during, and after completion of the trial will be performed in accordance with national law and local regulations.

All amendments that affect patient safety or the trial integrity (substantial amendments) must not be implemented before favorable opinion has been obtained, unless necessary to eliminate hazards to the patients. Non-substantial amendments do not require favorable opinion by the IRB, but the respective IRB will be notified according to local requirements.

The Sponsor and Investigator must approve any amendment in writing before its implementation.

The Sponsor must maintain an accurate and complete record of all submissions made to the IRB. The records should be filed in the Sponsor's Trial Master File (TMF).

13.3 Informed Consent

In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirement(s) and adhere to the ICH GCP guideline and the requirements in the Declaration of Helsinki.

Prior to any trial-related activity, the Investigator must give the patient oral and written information in a form that the patient can read and understand about all aspects of the trial that are relevant to the patient's decision to participate. The patient will be given ample time to decide whether or not to participate in the trial.

The patient must be informed that his/her personal trial-related data will be used in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by authorized monitors or Clinical Quality Assurance auditors appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

A voluntary, personally signed and dated ICF must be obtained from the patient prior to any trial-related activity. The ICF must also be signed and dated by the physician or designee who conducted the informed consent procedure. A signed copy of the ICF and any additional patient information must be given to each patient.

The responsibility for taking informed consent must remain with that of a research physician or designee. If information becomes available that may be relevant to the patient's willingness to continue participating in the trial, the Investigator must inform the patient in a timely manner, and a revised written informed consent must be obtained.

Should a protocol amendment become necessary, the ICF may need to be revised to reflect the changes to the protocol. It is the responsibility of the Sponsor to ensure that an amended consent form is reviewed and has received favorable opinion from IRB, and the Investigator must ensure that the amended consent form is signed by all patients subsequently entered into the trial and those currently in the trial, if affected by the amendment.

13.4 Trial Monitoring Requirements

The monitoring procedures for this trial are described in detail in the Monitoring Manual. The objectives of the monitoring procedures are to ensure that (i) the safety and rights of the trial patients are respected, (ii) that accurate, valid, and complete data are collected, and (iii) that the trial is conducted in accordance with the trial protocol, the principles of GCP, and local legislation, including drug accountability.

The monitor must be given direct access to the investigational site files and source documents (original documents, data, and records). Direct access includes permission to examine, analyze, verify, and reproduce any record(s) and report(s) that are important to evaluation of the clinical trial.

Key tasks of the monitor include verifying the presence of informed consent, the adherence to the inclusion/exclusion criteria, the documentation of SAEs, and the recording of all safety and efficacy variables. The monitor will also confirm the completeness of patient records, the

adherence to the protocol, ICH GCP, and the progress in patient enrollment and perform drug accountability.

Because no information that could reveal the identity of patients may ever be removed from the trial site, the monitor will visit the site at regular intervals to perform these monitoring tasks. Other contact between the Investigator and monitors will be maintained as required through telephone calls and e-mail. The Investigator and/or key members of staff involved in the trial must be available to assist the monitors during all visits.

Site Initiation Visit
During the Site Initiation Visit (SIV) the CRO, Sponsor, and/or monitors will go through information on the IMP, the protocol, the eCRFs, and other key aspects of the trial with the Investigator and the key members of staff involved in the trial. The topics of the SIV are documented in a SIV report made available to the Investigator. Documentation on the SIV (e.g., power point presentation) should be filed by both Investigator and Sponsor.

13.5 Disclosure of Data

Data generated by this trial must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the trial is confidential and disclosure to third parties other than those noted above is prohibited.

13.6 Retention of Records

Massachusetts General Hospital will maintain the patient's medical file according to local regulations. MGH will archive the documentation pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. MGH should not destroy any documents without prior permission from the Sponsor.

The documentation includes all the raw data generated during the clinical trial, the investigational site files, and a copy of the clinical trial report. The documents will be retained for a period of at least 15 years at archives by MGH, or its sub-contractor. After this period, the Sponsor will be contacted and their advice sought on the return or further retention of the trial records.

The Sponsor will maintain the documentation pertaining to the trial in accordance with national regulations.

13.7 Publication Policy

The Principal Investigator of the trial will review and sign the clinical trial report. A summary of the final clinical trial report will be submitted to the IRB and Competent Authority.

According to the Declaration of Helsinki Investigators and Sponsors "have ethical obligations with regard to the publication and dissemination of the results of research." The trial design and results may be published as 1 or more original research manuscripts/abstracts and presented at a scientific meeting. The Investigator and Sponsor reserve the right to review any

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proposed presentation of the results of this trial before they are submitted for publication. Authorship on any publication(s) resulting from this clinical trial will be assigned according to the recommendations of the International Committee of Medicinal Journal Editors.

Participating patients will not be identified by name in any published reports about the clinical trial.

The Sponsor is responsible for trial registration at ClinicalTrials.gov (www.clinicaltrials.gov) according to the requirements from the FDA.

13.8 Legal Aspects

An implicit or explicit approval must be obtained from the Competent Authority prior to commencement of the trial. Clinical trial submission and reporting requirements before, during, and after completion of the trial will be performed in accordance with national law and local regulations.

An implicit or explicit approval will also be mandatory before implementation of substantial changes. Non-substantial amendments do not require approval from the Competent Authority but will be notified according to local requirements.

The Sponsor and Investigator must approve the amendment in writing before its implementation.

The Sponsor must maintain an accurate and complete record of all submissions made to the Competent Authority. The records should be filed in the Sponsor's TMF.

Audits and Inspections
In the event of an audit, representatives of the Sponsor or designee, or national and international regulatory authorities may request access to all trial records for inspection and copying. Such access must be stated in the ICF signed by the patient.

13.9 Sponsor Discontinuation Criteria

The Sponsor, Investigator, or a pertinent regulatory authority may decide to stop the trial or part of the trial at any time but agreement on procedures to be followed must be obtained.

Conditions that may warrant termination of the clinical trial include, but are not limited to:

- Safety or administrative reasons
- The discovery of an unexpected, relevant, or unacceptable risk to the patients enrolled in the clinical trial
- A decision of the Sponsor to suspend or discontinue investigation of the IMP

If the trial is prematurely terminated or suspended, the Investigator should promptly inform the patients and assure appropriate therapy and follow-up. Furthermore, the Sponsor should promptly inform the IRB and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

If after the termination of the trial the risk/benefit analysis has changed, the new evaluation should be provided to the IRB in case it will have an impact on the planned follow-up of the

patients who have participated in the trial. Necessary actions needed to protect the patients should be described.

13.10 Patient Compensation

Financial compensation will be provided to all patients who complete the Screening Visit. Patients will be paid $25 for completing the Screening Visit whether or not they are eligible to participate in the trial. Patients will be compensated $25 for completing the Training Visit. Patients will be compensated $100 for completing each of the 2 treatment visits, $25 for completing the ADA Assessment Visit, and $25 for completing the Follow-up Visit. Thus, the total compensation for a patient who completes the trial would be $300. Patients who are unable to complete the trial or choose to stop participation will receive prorated compensation for each visit. In addition to the monetary compensation, the cost of the patients' lunch meals during their participation in the trial, as well as the patients' parking at each visit, will be covered by trial funds.

14 TRIAL ADMINISTRATIVE INFORMATION

14.1 Protocol Amendments

Any amendments to the trial protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

14.2 Address List

14.2.1 Sponsor

Zealand Pharma A/S
Smedeland 36
DK-2600 Glostrup (Copenhagen)
Denmark
Telephone: +45 88 77 36 00
Facsimile: +45 88 77 38 98

14.2.2 Supplier of Device

[redacted], PhD
Beta Bionics, Inc.
Business Innovation Center, Photonics Center
8 Saint Mary's Street, Suite 936
Boston, Massachusetts 02215-2421
United States
Telephone: [redacted]

14.2.3 Principal Investigator (Site)

Steven J. Russell, M.D., Ph.D.
MGH Diabetes Center
50 Staniford Street Suite 301
Boston, Massachusetts 02114
Telephone: [redacted]
Facsimile: [redacted]

14.2.4 Contract Research Organization (Including Monitoring)

Medpace, Inc.
5375 Medpace Way
Cincinnati, Ohio 45227
Telephone: +1-513-579-9911
Facsimile: +1-513-579-0444

14.2.5 Medical Monitoring

Medpace Clinical Safety
5375 Medpace Way
Cincinnati, OH 45227
United States
Telephone: +1-800-730-5779, ext. 2999 or +1-513-579-9911, ext. 2999
Facsimile: +1-866-336-5320 or +1-513-579-0444
E-mail: medpace-safetynotification@medpace.com

14.2.6 Pharmacovigilance

Lindeq
Lyskær 8
2730 Herlev
Denmark
Telephone: [redacted]
Facsimile: [redacted]
Mobile: [redacted]
E-mail: drugsafety@lindeq.com

14.2.7 Central Laboratory (Safety Laboratory and Plasma Glucose)

Medpace Reference Laboratories, LLC
5365 Medpace Way
Cincinnati, OH 45227
United States
Telephone: +1-513-366-3270
Facsimile: +1-513-366-3273

14.2.8 Special Laboratory (ZP4207 Exposure and ADA Analyses)

Unilabs – York Bioanalytical Solutions
[redacted]
Cedar House
Northminster Business Park
Upper Poppleton
York YO26 6QR
Great Britain
Telephone: [redacted]
Facsimile: [redacted]

14.2.9 Special Laboratory (Glucagon Exposure)

MLM Medical Labs GmbH
Dr. [redacted]
Dohrweg 63
D-41066 Mönchengladbach
Germany
Telephone: [redacted]
Facsimile: [redacted]

15 REFERENCES

1. Russell SJ, El-Khatib FH, Sinha M, et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. N Engl J Med. 2014;371(4):313-325.
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ZP4207-16051

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Amendment 6.0
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APPENDIX A: SCHEDULE OF PROCEDURES – PARTS 1 AND 2

Trial Visit	**Visit 1 [1] Screening**	**Visit 2 Training**	**Visit 3 [2] [3] [4] [5] (1st Treatment Visit)**	**Visit 4 [2] [3] [5] (2nd Treatment Visit)**	**Visit 5 ADA Assessment Visit [6]**	**Visit 6 Follow-Up [7]**
Informed consent	X					
Assess/confirm elig bility	X	X				
Demographics	X					
Medical, surgical, and social history; allergies	X					
Concomitant illness	X					
Concomitant medications	X	X	X	X	X	X
Height, weight, physical examination, and vital signs including body temperature and blood pressure [8]	X		X [9]	X [9]		
12-lead ECG	X		X [10]	X [10]		
Urine HCG pregnancy test and menstrual history [11]	X		X	X		
FSH [12]	X					
Screening labs – HbA1c, optional fractionated metanephrines [13]	X					
Safety lab sampling including chemistry and hematology	X		X [10]	X [10]		X
Training on devices [14]		X				
Monitored BP use			X	X		
Plasma glucose sampling [15]			X	X		
ZP4207/glucagon exposure sampling [16]			X	X		
Nausea and infusion site pain VAS and infusion site reaction Draize scale (visit start [17], hourly, & visit end)			X	X		
Standardized lunch [18]			X	X		
In-clinic exercise [19]			X	X		
Questionnaires (pre & post BP)			X	X		
ADA			X [20]		X	X
Adverse event review			X	X	X	X

[redacted]

1. Once the patient has been enrolled and eligibility has been established, the order of the treatment visits will be randomized in blocks of 2 patients.
2. In Part 1, each patient will participate in 2 treatment visits: 1 with the iPhone-based BP using ZP4207 and 1 with the iPhone-based BP using Lilly glucagon in a randomized order. In Part 2, each patient will participate in 2 treatment visits: 1 with the iLet using ZP4207 and 1 with the iLet using Lilly glucagon in a randomized order. Up to 2 patients may participate in the trial per day.
3. The night before the visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be asked to arrive at he visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window. If BG is <50 mg/dL, the patient will be treated with simple carbohydrate according to the 15/15 rule (15 grams of carbohydrates, repeated in 15 minutes if necessary). The visit will not need to be rescheduled unless the patient experiences a severe hypoglycemic event and requires treatment with glucagon or intravenous dextrose.
4. Visit 3 will take place at least 48 hours after screening (Visit 1) and no more than 30 days after screening (Visit 1).
5. There will be a 24-hour minimum washout between Visit 3 and Visit 4 and a maximum of 3 weeks between Visit 3 and Visit 4.
6. Visit 5 will take place 10 days ±3 days from Visit 4.
7. Visit 6 will take place 25 days ±4 days from Visit 4.
8. Height and physical examination will be measured at Visit 1 only.
9. Vital signs including body temperature and blood pressure will be obtained at visit start and visit end. Blood pressure and heart rate will be measured in the seated position and within 3 minutes of standing.
10. At visit start and visit end.
11. Urine HCG pregnancy test only for women of childbearing potential. The date of the last menstrual period in female patients will be obtained at Visit 1 only.
12. Test for FSH level only for postmenopausal women amenorrheic for less than 1 year.
13. If indicated by history.
14. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor, diabetes management (e g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits, and trial policies and procedures.
15. Collected at least hourly. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
16. Collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.
17. Once the infusion sites have been placed but no drug has yet been administered.
18. Between approximately Hour 3 and Hour 4.
19. Between approximately Hour 6 and Hour 7.
20. Before the start of dosing.

ADA = anti-drug antibodies; BG = blood glucose; BP = bionic pancreas; CGM = continuous glucose monitor; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HCG = human chorionic gonadotropin; VAS = visual analog scale.

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APPENDIX B: CLINICAL LABORATORY ANALYTES

Chemistry

Alanine aminotransferase	Aspartate aminotransferase
Alkaline phosphatase	Total protein
Albumin	Total and direct bilirubin
Gamma-glutamyl transferase	Glucose
Creatinine	Estimated glomerular filtration rate
Blood urea nitrogen	Uric acid
Bicarbonate	Sodium
Potassium	Calcium
Chloride	Phosphorus

Hematology

Hemoglobin	Hematocrit
Red blood cell count	White blood cell count and differential
Platelets	Mean corpuscular volume
Mean corpuscular hemoglobin	Mean corpuscular hemoglobin concentration

Pregnancy Test
A urine HCG pregnancy test will be performed at screening, Visit 3, and Visit 4 only for women of childbearing potential.

Anti-drug Antibodies Assessments
Blood samples (including back-up samples) for serum anti-ZP4207 and anti-glucagon antibodies will be taken prior to first dosing (Visit 3), at the ADA Assessment Visit (Visit 5), and at the Follow-up Visit (Visit 6).

ZP4207/Glucagon Exposure Sampling
At Visit 3 and Visit 4, ZP4207/glucagon exposure sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.

Screening Visit Only
Test for FSH level only for postmenopausal women amenorrheic for less than 1 year
Optional fractionated plasma metanephrines (if indicated by history)
Hemoglobin A1c

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APPENDIX C: BRIEF DESCRIPTION OF QUESTIONNAIRES

Diabetes Treatment Satisfaction Questionnaire – Status (DTSQs)
The DTSQs measures patient satisfaction with diabetes treatment. It consists of a 6 item scale for assessing treatment satisfaction and two additional items assessing perceived frequency of hyperglycemia and hypoglycemia. The DTSQs is meant for adults and older children. Dr. Clare Bradley has produced a version that is appropriate for bionic pancreas studies for this use, along with a version for younger children. It is administered before the intervention. The DTSQs is valid and reliable. Administration time is less than 5 minutes.

Diabetes Treatment Satisfaction Questionnaire – Change (DTSQc)
Although the DTSQ is responsive to treatment changes, ceiling effects are often seen with this instrument, where maximum or close-to-maximum scores at baseline provide little opportunity for registering improvement. The DTSQc contains the same items as the DTSQs version but asks patients to consider their satisfaction with their current treatment compared with their previous treatment. The DTSQc is meant for adults and older children. Dr. Clare Bradley has produced a version that is appropriate for bionic pancreas studies for our use, along with a version for younger children. It is administered during and at the end of the intervention. The DTSQc is valid and reliable. Administration time is less than 5 minutes.

T1-Diabetes Distress Scale (T1-DDS)
The T1-DDS is a 28-item survey that assesses seven sources of diabetes distress for type 1 adults. It captures feelings of powerlessness; management distress; hypoglycemia distress; negative social perceptions by others; eating distress; physician (health care) distress; and friend/family distress. Items are scored on a 6-point scale from not a problem to a very serious problem. It is administered before, during, and at the end of the intervention. The scale is valid and reliable, and has been shown to be sensitive to change over time. Administration time is 5 minutes.

Problem Areas in Diabetes Survey (PAID)
There are three versions of the PAID: Teen (PAID-T), Parent (PAID-P), and Child (PAID-C) versions. This measure of diabetes-specific emotional distress in youth with diabetes and their parents is 26 items. A total score is generated. It is administered before, during, and at the end of the intervention. The PAID-T and PAID-P are valid and reliable. Psychometric analysis of the PAID-C is in progress. Administration time is 5 minutes.

Hypoglycemia Fear Survey (HFS)
There are three versions of the HFS, Adult (HFS), Youth (HFS-Y) and Parent (HFS-P). The HFS measures several dimensions of fear of hypoglycemia among adults with type 1 diabetes. It consists of 23 items and produces two sub-scale scores; a Behavior sub-scale that measures behaviors involved in avoidance and/or over-treatment of hypoglycemia and a Worry sub-scale that measures anxiety and fear surrounding hypoglycemia. The HFS-Y consists of 25 items and the HFS-P consists of 26 items; both produce sub-scale scores similar to the Adult HFS. It is administered before, during, and at the end of the intervention. All versions of the HFS are valid and reliable. Administration time is 5-10 minutes.

[redacted]

Impact of Daily Diabetes Demands (IDDD)
There are four versions of the IDDD; Adult (IDDD-A), Youth (IDDD-Y), Parent (IDDD-P), and Significant Other (IDDD-SO). This instrument measures the burden related to the demands of the daily diabetes regimen and is 22 items. A total score is generated. It is administered before, during, and at the end of the intervention. Psychometric analysis of the IDDD-Y is in progress using the data from the second Bionic Pancreas Camp Study in pre-adolescent children, and of the IDDD-A is in progress using data from the Bionic Pancreas Multicenter Study in adults. Administration time is 5 minutes.

Bionic Pancreas User Opinion Survey (BPUOS)
There are four versions of the BPUOS; Adult (BPUOS-A), Youth (BPUOS-Y), Parent (BPUOS-P), and Significant Other (BPUOS-SO). This measure assessing both the benefits from, and difficulties with, use of the bionic pancreas, and consists of 38 items. A total score is generated. It is administered during and at the end of the intervention. Psychometric analysis of the BPUOS-Y is in progress using the data from the second Bionic Pancreas Camp Study in pre-adolescent children, and of the BPUOS -A is in progress using data from the Bionic Pancreas Multicenter Study in adults. Administration time is 10 minutes.

[redacted]

SUMMARY OF CHANGES DOCUMENT

PROTOCOL NUMBER ZP4207-16051

AMENDMENT NUMBER 5.0

PROTOCOL TITLE: The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

AMENDMENT DATE: 09 September 2016

SUMMARY AND JUSTIFICATION OF CHANGES:

This amendment was developed to include additional anti-drug antibodies (ADA) sampling at 10 days ±3 days following the last day of dosing (Visit 4). Visit 5 has been changed from a phone call 7 days ±3 days following the last day of dosing (Visit 4) to an ADA Assessment Visit at the trial site 10 days ±3 days following the last day of dosing (Visit 4). In addition, language has been added that any patient that tests positive for ADA will be monitored until the ADA levels return to baseline. The schedule of procedures was updated to reflect the changes specified in this document. Other minor edits were made throughout the protocol to provide greater clarity and consistency.

SUMMARY OF CHANGES:

The amended protocol sections and the details of the changes are summarized in the following sections. Revisions to the protocol are presented as strikethrough (ie, ~~subject~~) for text that was removed and bold (ie, **subject**) for text that was added.

Section 1.5, Risk/Benefit, Page 21

Original Text:

Overall, ZP4207 is judged to be a low-risk molecule, based upon the available clinical data as well as the outcome of the risk-based approach to the immunogenicity assessment made. The present trial will include sampling for measurement of antibodies against ZP4207 prior to first dosing (Visit 3) and at the Follow-up Visit. In line with regulatory guidance documents, these samples will be appropriately analyzed and the results will be included in the overall assessment of the immunogenic potential of ZP4207 after completion of each trial and as the clinical development program advances.

New Text:

Overall, ZP4207 is judged to be a low-risk molecule, based upon the available clinical data as well as the outcome of the risk-based approach to the immunogenicity assessment made. The present trial will include sampling for measurement of antibodies against ZP4207 prior to first dosing (Visit 3)**, at the ADA Assessment Visit (Visit 5),** and at the Follow-up Visit **(Visit 6)**. In line with regulatory guidance documents, these samples will be appropriately analyzed and the results will be included in the overall assessment of the immunogenic potential of ZP4207 after completion of each trial and as the clinical development program advances.

Section 7.5, Anti-drug Antibodies Assessment Visit (Visit 5), Page 38

Original Text:

7.5 Phone Call (Visit 5)

A phone call will be conducted 7 days ±3 days following the last day of dosing (Visit 4) to review AEs and concomitant medications.

New Text:

7.5 ~~Phone Call~~ **Anti-drug Antibodies Assessment Visit** (Visit 5)

~~A phone call~~ **Patients** will ~~be conducted~~ **return for an ADA Assessment Visit** ~~7~~ **10** days ±3 days following the last day of dosing (Visit 4) ~~to~~ **for ADA sampling and a** review **of** AEs and concomitant medications.

Section 9.4, Anti-drug Antibodies Assessments, Page 40

Original Text:

Blood samples (including back-up samples) for serum anti-ZP4207 and anti-glucagon antibodies will be taken at Visit 3 and the Follow-up Visit 6.

New Text:

Blood samples (including back-up samples) for serum anti-ZP4207 and anti-glucagon antibodies will be taken at Visit 3**, the ADA Assessment Visit (Visit 5),** and the Follow-up Visit **(Visit** 6). **Any patient that tests positive for ADA will be monitored until the ADA levels return to baseline.**

[redacted]

Section 13.10, Patient Compensation, Page 54

Original Text:

Patients will be compensated $100 for completing each of the 2 treatment visits, $25 for completing the phone call, and $25 for completing the Follow-up Visit. Thus, the total compensation for a patient who completes the trial would be $300. Patients who are unable to complete the trial or choose to stop participation will receive prorated compensation for each visit. In addition to the monetary compensation, the cost of the patients' lunch meals during their participation in the trial, as well as the patients' parking at each visit, will be covered by trial funds.

New Text:

Patients will be compensated $100 for completing each of the 2 treatment visits, $25 for completing the ~~phone call~~ **ADA Assessment Visit**, and $25 for completing the Follow-up Visit. Thus, the total compensation for a patient who completes the trial would be $300. Patients who are unable to complete the trial or choose to stop participation will receive prorated compensation for each visit. In addition to the monetary compensation, the cost of the patients' lunch meals during their participation in the trial, as well as the patients' parking at each visit, will be covered by trial funds.

Appendix B, Clinical Laboratory Analytes, Page 60

Original Text:

Blood samples (including back-up samples) for serum anti-ZP4207 and anti-glucagon antibodies will be taken prior to first dosing (Visit 3) and at the Follow-up Visit (Visit 6).

New Text:

Blood samples (including back-up samples) for serum anti-ZP4207 and anti-glucagon antibodies will be taken prior to first dosing (Visit 3)**, at the ADA Assessment Visit (Visit 5),** and at the Follow-up Visit (Visit 6).

Appendix A, Schedule of Procedures – Parts 1 and 2, Page 58-59

Original Text:

APPENDIX A: SCHEDULE OF PROCEDURES – PARTS 1 AND 2

Trial Visit	Visit 1 [1] Screening	Visit 2 Training	Visit 3 [2] [3] [4] [5] (1st Treatment Visit)	Visit 4 [2] [3] [5] (2nd Treatment Visit)	Visit 5 Phone Call [6]	Visit 6 Follow-Up [7]
Informed consent	X					
Assess/confirm eligibility	X	X				
Demographics	X					
Medical, surgical, and social history; allergies	X					
Concomitant illness	X					
Concomitant medications	X	X	X	X	X	X
Height, weight, physical examination, and vital signs including body temperature and blood pressure [8]	X		X [9]	X [9]		
12-lead ECG	X		X [10]	X [10]		
Urine HCG pregnancy test and menstrual history [11]	X		X	X		
FSH [12]	X					
Screening labs – HbA1c, optional fractionated metanephrines [13]	X					
Safety lab sampling including chemistry and hematology	X		X [10]	X [10]		X
Training on devices [14]		X				
Monitored BP use			X	X		
Plasma glucose sampling [15]			X	X		
ZP4207/glucagon exposure sampling [16]			X	X		
Nausea and infusion site pain VAS and infusion site reaction Draize scale (visit start [17], hourly, & visit end)			X	X		

Summary of Changes, Amendment 5.0, ZP4207-16051

Trial Visit	Visit 1 [1] Screening	Visit 2 Training	Visit 3 [2] [3] [4] [5] (1st Treatment Visit)	Visit 4 [2] [3] [5] (2nd Treatment Visit)	Visit 5 Phone Call [6]	Visit 6 Follow-Up [7]
Standardized lunch [18]			X	X		
In-clinic exercise [19]			X	X		
Questionnaires (pre & post BP)			X	X		
ADA			X [20]			X
Adverse event review			X	X	X	X

1. Once the patient has been enrolled and eligibility has been established, the order of the treatment visits will be randomized in blocks of 2 pa ients.
2. In Part 1, each patient will participate in 2 treatment visits: 1 with the iPhone-based BP using ZP4207 and 1 with the iPhone-based BP using Lilly glucagon in a randomized order. In Part 2, each patient will participate in 2 treatment visits: 1 with he iLet using ZP4207 and 1 with the iLet using Lilly glucagon in a randomized order. Up to 2 patients may participate in the trial per day.
3. The night before the visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Pa ients will be asked to arrive at the visit at least 1 hour in advance of the start of he BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window. If BG is <50 mg/dL, treatment with simple carbohydrate is allowed. If the pa ient experiences persistent hypoglycemia, the visit will be rescheduled within the visit window.
4. Visit 3 will take place at least 48 hours after screening (Visit 1) and no more han 30 days after screening (Visit 1).
5. There will be a 24-hour minimum washout between Visit 3 and Visit 4 and a maximum of 3 weeks between Visit 3 and Visit 4.
6. Visit 5 will take place 7 days ±3 days from Visit 4.
7. Visit 6 will take place 25 days ±4 days from Visit 4.
8. Height and physical examination will be measured at Visit 1 only.
9. Vital signs including body temperature and blood pressure will be obtained at visit start and visit end.
10. At visit start and visit end.
11. Urine HCG pregnancy test only for women of childbearing poten ial. The date of the last menstrual period in female patients will be obtained at Visit 1 only.
12. Test for FSH level only for postmenopausal women amenorrheic for less than 1 year.
13. If indicated by history.
14. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor, diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fas ing prior to and between the treatment visits, and trial policies and procedures.
15. Collected at least hourly. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, hen sampling will be every 10 minutes.
16. Collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.
17. Once the infusion sites have been placed but no drug has yet been administered.
18. Between approximately Hour 3 and Hour 4.
19. Between approximately Hour 6 and Hour 7.
20. Before the start of dosing.

ADA = anti-drug antibodies; BG = blood glucose; BP = bionic pancreas; CGM = continuous glucose monitor; ECG = electrocardiogram; FSH = follicle-stimula ing hormone; HbA1c = hemoglobin A1c; HCG = human chorionic gonadotropin; VAS = visual analog scale.

New Text:

APPENDIX A: SCHEDULE OF PROCEDURES – PARTS 1 AND 2

Trial Visit	Visit 1 [1] Screening	Visit 2 Training	Visit 3 [2] [3] [4] [5] (1st Treatment Visit)	Visit 4 [2] [3] [5] (2nd Treatment Visit)	Visit 5 ~~Phone Call~~ **ADA Assessment Visit** [6]	Visit 6 Follow-Up [7]
Informed consent	X					
Assess/confirm eligibility	X	X				
Demographics	X					
Medical, surgical, and social history; allergies	X					
Concomitant illness	X					
Concomitant medications	X	X	X	X	X	X
Height, weight, physical examination, and vital signs including body temperature and blood pressure [8]	X		X [9]	X [9]		
12-lead ECG	X		X [10]	X [10]		
Urine HCG pregnancy test and menstrual history [11]	X		X	X		
FSH [12]	X					
Screening labs – HbA1c, optional fractionated metanephrines [13]	X					
Safety lab sampling including chemistry and hematology	X		X [10]	X [10]		X
Training on devices [14]		X				
Monitored BP use			X	X		
Plasma glucose sampling [15]			X	X		
ZP4207/glucagon exposure sampling [16]			X	X		
Nausea and infusion site pain VAS and infusion site reaction Draize scale (visit start [17], hourly, & visit end)			X	X		

Summary of Changes, Amendment 5.0, ZP4207-16051

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Standardized lunch [18]			X	X		
In-clinic exercise [19]			X	X		
Questionnaires (pre & post BP)			X	X		
ADA			X [20]		**X**	X
Adverse event review			X	X	X	X

1. Once the patient has been enrolled and eligibility has been established, the order of the treatment visits will be randomized in blocks of 2 patients.
2. In Part 1, each patient will participate in 2 treatment visits: 1 with the iPhone-based BP using ZP4207 and 1 with the iPhone-based BP using Lilly glucagon in a randomized order. In Part 2, each patient will participate in 2 treatment visits: 1 with the iLet using ZP4207 and 1 with the iLet using Lilly glucagon in a randomized order. Up to 2 patients may participate in the trial per day.
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[redacted]

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ZP4207-16051

Version number: 6.0
Amendment 5.0
Date: 09 September 2016

CLINICAL TRIAL PROTOCOL

The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

Investigational Product: ZP4207
Protocol Number: ZP4207-16051
IND Number: 129980
Phase: 2

Principal Investigator:
Steven J. Russell, MD, PhD[1]

Co-Investigator:
[redacted], RN, CDE[1]
[redacted], MD[1]

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Original Version: 03 May 2016
Amendment Number 1.0: 28 June 2016
Amendment Number 2.0: 03 August 2016
Amendment Number 3.0: 17 August 2016
Amendment Number 4.0: 02 September 2016
Amendment Number 5.0
Protocol Version Number: 6.0

Date: 09 September 2016

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Date: 09 September 2016

SIGNATURE PAGE

TRIAL TITLE: The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the trial.

Signature [redacted] Date [redacted]

[redacted], MD
Vice President, Clinical Development
Zealand Pharma A/S

[redacted] [redacted]

[redacted], DVM, PhD
Principal Clinical Pharmacologist
Zealand Pharma A/S

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INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the trial as described. I will conduct this trial in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the trial within the time designated. I will provide copies of this protocol and access to all information furnished by Zealand Pharma A/S to trial personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the trial product and trial procedures. I will let them know that this information is confidential and proprietary to Zealand Pharma A/S and that it may not be further disclosed to third parties. I understand that the trial may be terminated or enrollment suspended at any time by Zealand Pharma A/S, with or without cause, or by me if it becomes necessary to protect the best interests of the trial patients.

I agree to conduct this trial in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and ICH Guidelines for Good Clinical Practices.

[redacted]

Investigator's Signature

9/12/2016

Date

Steven J. Russell, MD, PhD

Investigator's Printed Name

[redacted]

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SYNOPSIS

TITLE: The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

PROTOCOL NUMBER: ZP4207-16051

INVESTIGATIONAL PRODUCT: ZP4207

PHASE: 2

INDICATION: ZP4207 is an anti-hypoglycemic glucagon analog in a ready-to-use liquid formulation which is being studied to improve glycemic control in adults (and children) with type 1 diabetes mellitus (T1DM) as part of a bihormonal bionic pancreas (BP).

OBJECTIVES:

Primary: The primary objective is to conduct a trial testing the safety and tolerability of the BP using either the iLet or the iPhone platform when used with ZP4207 in 20 adult (≥18 years of age) patients with T1DM.

Secondary: The secondary objectives are to measure glycemic regulation, including hypoglycemia exposure (percent of time spent with continuous glucose monitor [CGM] glucose <60 mg/dL), evaluate BP device reliability, and to document the satisfaction of patients with the BP with the goal of optimizing the functionality and user interface of the BP.

POPULATION: Up to 40 adult (≥18 years of age) patients who already manage their T1DM using continuous subcutaneous (SC) insulin infusion pump therapy can be enrolled. It is expected that up to 10 patients will complete each part of the trial protocol.

TRIAL DESIGN: This trial is a single-center, open-label, 2-part, randomized cross-over trial. The trial will enroll adult patients with T1DM and will assess the safety and efficacy of the BP using either the iLet or the iPhone platform using the glucagon analog ZP4207 versus Lilly glucagon. In Part 1, up to 10 patients will participate in two 1-day treatment arms in random order (iPhone-based BP using ZP4207 and iPhone-based BP using Lilly glucagon) according to a pre-generated randomization scheme. In Part 2, up to 10 new patients will participate in two 1-day treatment arms in random order (iLet using ZP4207 and iLet using Lilly glucagon) according to a pre-generated randomization scheme. Patients can only participate in 1 part of the trial. An interim database lock may occur upon completion of Part 1 of the trial to analyze the iPhone-based BP data. The iLet and the iPhone-based BP will also administer insulin (insulin lispro, Lilly Humalog) using the same blood glucose (BG) control algorithm for all 4 treatment arms. The trial will be conducted at a single center, the Massachusetts General Hospital Diabetes Center in Boston, MA.

TRIAL TREATMENT: The trial involves SC administration of insulin lispro (Humalog, Lilly), which is commercially available by prescription and is indicated for patients with T1DM, but not for use in a BP.

The trial also involves SC administration of Lilly glucagon in 1 iLet arm and 1 iPhone-based BP arm. Lilly glucagon is commercially available by prescription and is indicated for patients with T1DM in severe hypoglycemia, but not for use in a BP.

The trial also involves SC administration of the glucagon analog ZP4207, 1 mg/mL, in the other iLet arm and the other iPhone-based BP arm. ZP4207 will be made available by Zealand Pharma A/S, Denmark as liquid formulation in prefilled syringes of 0.6 mL.

PRIMARY ENDPOINT:
The primary endpoint is the safety and tolerability of ZP4207 in the BP using either the iLet or the iPhone platform as assessed by:

- Number and type of adverse events (AEs)
- Clinical laboratory measurements
- Vital signs
- 12-lead electrocardiogram (ECG)
- Local tolerability and infusion site reactions as measured with the Draize scale
- Immunogenicity as measured by anti-drug antibodies
- Pain as measured on a 10 cm visual analog scale (VAS)
- Nausea as measured on a 10 cm VAS

SECONDARY ENDPOINTS:
The secondary endpoints include measurements of BP function as well as glycemic and non-glycemic measurements.

Bionic Pancreas Function
This endpoint data will be generated from the BP data during each treatment visit:

- Average percent insulin dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
    - Average percent glucagon/ZP4207 dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts calculated by the BP algorithm that are successfully issued to the pump by the BP (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts calculated by the BP control algorithm that are successfully issued by the BP
    - Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully issued by the BP
- Average percent of 5-minute steps during which the BP is functioning nominally in all respects based on real-time CGM data (new CGM glucose reading captured, dose calculated, and dose issued to pumps)

- Average percent of 5-minute steps during which the BP is functioning nominally with or without a new CGM glucose reading captured (dose calculated and dose issued to pumps). If a CGM signal is not available, the dose calculated may be based on weight or historical basal rates.
- CGM reliability index, calculated as percent of possible values actually recorded by CGM
- CGM Mean Absolute Relative Difference versus time-stamped BG values from meter download
- List of technical faults associated with the BP including cause and resolution

Glycemic
All of following metrics will be generated from the Dexcom G4 Platinum CGM data during each treatment visit:

- Fraction of time spent within each of the following glucose ranges:
  - <50 mg/dL
  - <60 mg/dL
  - <70 mg/dL
  - 70-120 mg/dL
  - 70-140 mg/dL
  - 70-180 mg/dL
  - >180 mg/dL
  - >250 mg/dL
  - >300 mg/dL
- Number of severe hypoglycemic events (patients unable to self-treat, requiring the assistance of another person)
- Number of episodes of symptomatic hypoglycemia
- Number of carbohydrate interventions for hypoglycemia
- Total grams of carbohydrates taken for hypoglycemia
- Mean CGM glucose

Non-glycemic

- Glucagon/ZP4207 total delivery per kg of body mass
- Insulin total delivery per kg of body mass
- Number of unscheduled infusion set replacements
- Number of unscheduled CGM sensor changes

EVALUATION OF TRIAL DATA: The following variables will be evaluated according to treatment for safety purposes: AEs, local tolerability, laboratory safety assessments, physical examination, vital signs, and 12-lead ECGs.

The analysis of BP function endpoints and glycemic endpoints will be on an intention-to-treat basis. In cases where a treatment arm was not completed (and that arm was not repeated according to protocol criteria), available data from that arm will be used in the data analysis.

The Shapiro-Wilk test will be used to determine the normality of the residuals for each comparison. Summary tables that display descriptive statistics, including percentages, means or medians, and standard deviation and/or ranges, as appropriate, will be provided.

[redacted]

A paired t-test or the Wilcoxon signed rank test for comparison of means with normally or non-normally distributed residuals, respectively, will be used. In a secondary analysis any period effect and any interaction between treatment and period will be looked for, although no such interaction is predicted for the efficacy outcome.
The number of patients and proportions of severe hypoglycemic events, symptomatic hypoglycemia, and carbohydrate interventions due to hypoglycemia with the event counts will be summarized descriptively, and the proportions will be analyzed by a Fisher's exact test if data allow.

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LIST OF FIGURES

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibodies
AE	Adverse event
BG	Blood glucose
BP	Bionic pancreas
BTLE	Bluetooth Low Energy
BU	Boston University
CFR	Code of Federal Regulations
CGM	Continuous glucose monitor
CRO	Contract research organization
DBR	Database review
DPP-4	Dipeptidyl peptidase-4
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FDA	Food and Drug Administration
FHD	First Human Dose
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GUI	Graphical user interface
HCG	Human chorionic gonadotropin
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IM	Intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
MD	Doctor of Medicine
MedDRA	Medical Dictionary for Regulatory Activities
MGH	Massachusetts General Hospital
MPC	Model-predictive control

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Abbreviation	Definition
PD	Pharmacodynamic
PK	Pharmacokinetic
RN	Registered nurse
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SGLT-2	Sodium-glucose co-transporter-2
SIV	Site Initiation Visit
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 diabetes mellitus
TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
ULN	Upper limit of normal
VAS	Visual analog scale

[redacted]

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Background and Rationale

To date, clinical trials conducted by Boston University (BU) and Massachusetts General Hospital (MGH) in patients with type 1 diabetes mellitus (T1DM) have demonstrated the practicality of a wearable automated bionic pancreas (BP) control system for robust glucose regulation using a continuous glucose monitor (CGM) to provide the input to the control system. Despite current technical limitations in CGMs and infusion pumps, the trials by BU/MGH have shown that a bihormonal BP is capable of achieving safe and effective blood glucose (BG) control automatically, with minimal hypoglycemia during 11 continuous days in the face of unrestrained meals and exercise and with trivial patient input (optional announcement of meals).

The BP provides automatic BG regulation and reduces hypoglycemic episodes. Additionally, the system spares the wearer the relentless tasks of carbohydrate counting, frequent BG monitoring, estimating the effects of specific meals and exercise activity on BG levels, and manual drug administration, which are inexact, demanding, aggravating, and require continuous diligence and vigilance. The degree of glycemic control achieved by the BP is predicted to dramatically reduce the deleterious and debilitating complications of T1DM.

In its last tested embodiment, the BP consisted of a Dexcom G4 CGM, and an iPhone that are hardwired together, with the iPhone running the control algorithm and communicating via Bluetooth with 2 Tandem t:slim pumps to dose insulin and glucagon. The connections are repeatedly lost among these 4 components throughout the day, an issue that has the potential to adversely impact BG control, whether due to missed CGM values or missed doses. In addition, the troubleshooting required to repair these recurring disconnections can be burdensome to the user. Integrating these components into a single device would establish seamless connectivity among them, which would eliminate the need for such troubleshooting. This would lead to smoother device operation with fewer interruptions, which would enhance its user friendliness, optimize its BG control potential, and further improve the quality of life of its users.

The BU Investigators have recently designed, built, and tested a proprietary first-generation of such a fully integrated BP system, referred to as the iLet and the iLet infusion set. The iLet is a dual-chamber infusion system that currently incorporates the Dexcom G4 CGM technology, a custom user interface with touchscreen display, and all of the mathematical dosing algorithms that were tested in and validated using the iPhone-based BP in outpatient studies over the past 3 years. The iLet infusion set provides 2 independent subcutaneous (SC) fluid pathways from the iLet to the patient (1 for insulin and the other for glucagon). One tube connects to the prefilled insulin cartridge and the other tube connects to the fillable (single-use) glucagon cartridge.

In order to provide automatic BG regulation, the iLet and the iPhone-based BP have the ability to deliver both insulin and glucagon. However, currently available glucagon formulations have limited stability at room temperature, necessitating frequent changes to the glucagon infusion set. Therefore, the current trial is designed to test the glucagon analog ZP4207 in the iLet and the iPhone-based BP, as this peptide analog of human glucagon is provided in a liquid formulation stable at room temperature.

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The current trial is a first feasibility trial designed to use the first-generation iLet and iLet infusion set and the iPhone-based BP to compare ZP4207 with marketed glucagon (Lilly). The trial is intended to demonstrate the safety and tolerability of ZP4207 in the iLet and the iPhone-based BP and the feasibility of achieving comparable autonomous glycemic control. It is not intended to comprehensively demonstrate the definitive efficacy of the BP in extended, continuous daily use, but rather to demonstrate its functionality and accuracy in a practical, albeit very controlled, clinical setting. The trial is expected to provide practical information that will benefit the design of a next-generation iLet and iLet infusion set and help pave the way for a more comprehensive outpatient home-use Phase 2 trial and ultimately a pivotal trial where comprehensive safety and efficacy through continuous full daily use of the iLet with ZP4207 will be documented.

The data derived from this trial will permit evaluation of the robustness of the iLet as well as the safety and efficacy of ZP4207 when used in conjunction with the iLet and the iPhone-based BP. The data obtained will be used to further improve the iLet and will allow BU/MGH to expand to larger outpatient trials using the iLet or the iPhone-based BP with ZP4207.

1.2 Bihormonal Bionic Pancreas System

The BP is an autonomous, self-learning system that requires only the patient's weight for initialization, and then autonomously adapts, modestly or dramatically, as needed, to cope with the wide range of insulin requirements of adults, adolescents, and pre-adolescents with T1DM. The BP obviates the need for the patient to know, or even appreciate, their insulin requirements, and renders obsolete any need for patients or caregivers to know carbohydrate-to-insulin ratios, basal rates, or insulin correction factors.

The core technology is a suite of control algorithms that orchestrate the automated dosing of insulin and glucagon to regulate BG levels. An insulin controller orchestrates all SC insulin dosing. At its centerpiece is a model-predictive control (MPC) algorithm, which bases insulin doses on the glucose data and insulin absorption kinetics, compensating for the slow absorption rate of SC insulin analogs (peak time in blood of 30-90 min, clearance in 4-8 hr). This enables the algorithm to refrain from stacking and overdosing insulin. Furthermore, the MPC algorithm automatically adjusts its insulin-dosing aggressiveness continuously and in real-time to different insulin needs between individuals and variable needs within the same individual. Running in parallel with the MPC algorithm is an algorithm that automatically modulates basal insulin delivery over multiple time scales, and another algorithm that automatically adapts insulin doses in response to optional meal announcements. Unlike current insulin pumps and the insulin-only control algorithms, the adaptive basal insulin algorithm obviates the need for the user to set, or even know, his or her “basal-rate profile.” Instead, it is capable of automatically adapting to, and compensating for, changes in an individual's basal insulin need, such as might occur over a period of hours, days, or weeks (e.g., circadian hormonal fluctuations, intercurrent illness, physical activity, or emotional state) or as might occur over a period of months or years due to developmental changes (e.g., hormonal changes that occur during puberty or menopause). The adaptive meal dose controller obviates the need for the user to set, or even know, his or her “carbohydrate-to-insulin ratios,” as it makes automatic adjustments based on dosing history for similar meal announcements made on previous days, and customizes the dose for each individual and for time of day.

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The BP also includes a proportional-derivative algorithm governing SC micro-doses of glucagon to help prevent impending hypoglycemia. Glucagon dosing is based on the glucose level and rate of descent. It may occur preemptively even if glucose is above range, and it includes a feedback term to account for the pending effects of recent glucagon doses.

Taken together, these mathematical algorithms provide a universal framework for a glycemic control strategy that requires no quantitative input from, or participation by, the user (besides entering body weight to initialize the system), but which automatically adapts insulin and glucagon dosing to meet the individual needs of each user. Another challenge met is enabling the technology to remain completely autonomous in managing insulin and glucagon delivery even when the CGM is offline. Specifically, when the CGM is offline, the BP invokes the high-resolution “basal rate profile” that it had recently learned and stored when the CGM was online. On the basis of what the system learned and stored about meal announcements when the CGM was online, it is able to respond to meal announcements in the same manner when the CGM is offline. Finally, it automatically responds to user-entered BG values when the CGM is offline by issuing a correction dose of insulin or glucagon based on what it learned about the user's insulin and glucagon needs when the CGM was online. Thus, the BP never relies on, or burdens the user with, the determination of subjective dosing decisions, which inevitably vary in quality and reliability among different users. The BP provides a turnkey solution for people with T1DM that comprehensively manages glycemia across a broad range of individual needs and across a large spectrum of circumstances and challenges to glycemic control.

A significant challenge for the use of glucagon in a bihormonal BP is the lack of a commercially available glucagon formation that is stable and well-suited to infusion over several days in a pump reservoir. However, BU/MGH have proceeded with studies using a relatively unstable marketed formulation that must be reconstituted from a lyophilized powder on a daily basis. This allowed BU/MGH to proceed with studies of the bihormonal system while awaiting the production of stable glucagon formulations or stable glucagon analogs.

1.3 Preliminary Studies with the Bihormonal Bionic Pancreas System

The BP hardware platform has evolved over the years from a laptop-driven system, which was used in all inpatient studies to the first truly mobile wearable iPhone-driven platform, which has been used in a number of outpatient studies. Using the iPhone-based BP system, >110 outpatient experiments of 5-11 days in duration in each subject have been conducted (>800 patient days or >2 patient years of data) across subjects ranging in age between 6 and 76 years old and in body mass between 21 and 128 kg. The robust adaptation capabilities of the BP is evident in the fact that the average total daily dose of insulin among these subjects varied by over 13-fold (from 11 to 145 units/day).

In November 2012, Food and Drug Administration (FDA) approval was obtained to conduct the first outpatient study testing the BP in adults 21 years or older with T1DM. This study, referred to as the Beacon Hill Study, followed a random-order cross-over design in which 20 adults with T1DM participated in 5 days on the iPhone-based BP and 5 days of usual care in which they wore a CGM with blinded display and muted alarms. In the BP arm, subjects kept to a 3-square-mile geographic area centered around the Beacon Hill neighborhood in Boston. They ate as they chose at local restaurants, and exercised at will with access to 2 gyms. Analysis was pre-specified to focus on Days 2-5, since glycemic control is more representative of BP performance after most of the adaptation by the BP occurs on Day 1 (Russell, 2014). Results are summarized in Figure 1.

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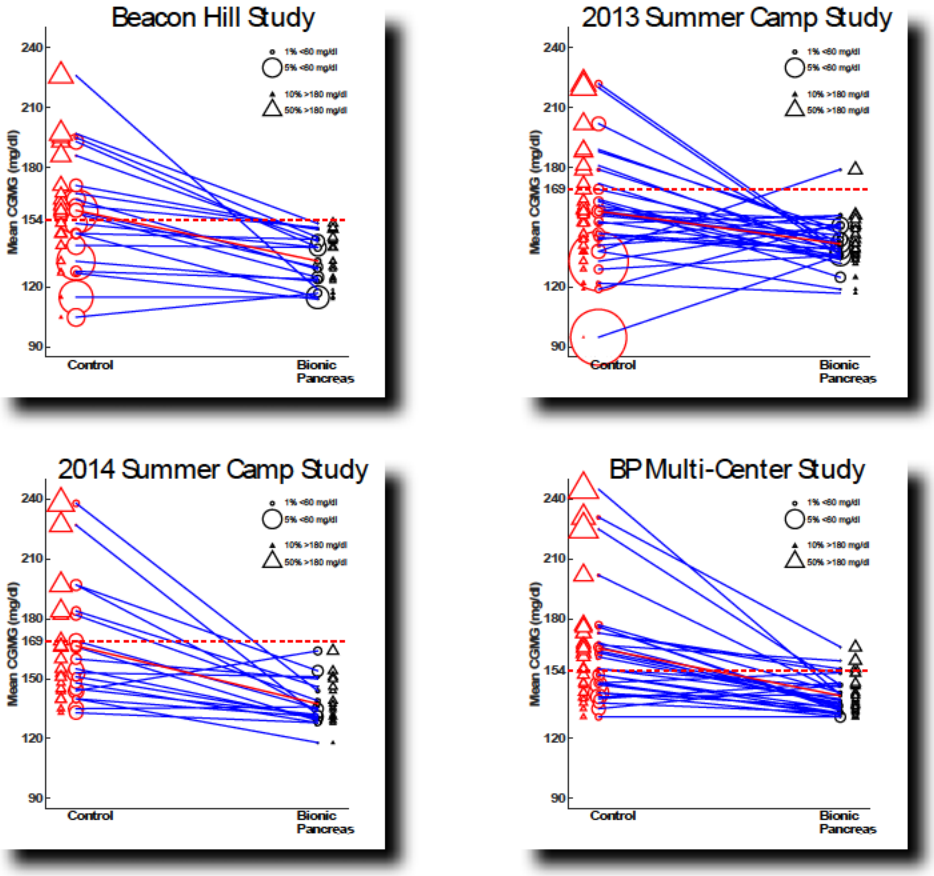
Figure 1. Outpatient Results Summarizing the Distribution of Mean CGM Glucose Levels and Hypoglycemia in the BP and Control Arms



Study	Age (years)	Bionic Pancreas (BP) Mean CGM glucose level (mg/dl)	Bionic Pancreas (BP) % of CGM glucose levels <50 mg/dl (%)	Bionic Pancreas (BP) % of CGM glucose levels 70–180 mg/dl (%)	Control Mean CGM glucose level (mg/dl)	Control % of CGM goucose values <50 mg/dl (%)	Control % of CGM goucose values 70–180 mg/dl (%)	p value (BP versus Control) for: Mean CGM glucose level	p value (BP versus Control) for: % of CGM glucose values <50 mg/dl	p value (BP versus Control) for: % of CGM glucose values 70–180 mg/dl
Beacon Hill (n 20, 5-day experiments)	≥21	133	1.5	80	159	3.7	59	<0.001	0.020	<0.001
2013 Summer Camp (n 32, 5-day experiments)	12–20	142	1.3	76	158	2.2	65	0.004	0.192	<0.001
2014 Summer Camp (n 19, 5-day experiments)	6–11	137	1.2	81	168	2.8	58	0.004	0.001	<0.001
BP Multi Center (n 39, 11-day experiments)	≥18	141	0.6	78	162	1.9	62	<0.001	<0.001	<0.001

Mean CGM glucose levels for each subject under usual care (red circles) are connected with the subject's mean CGM glucose level on the BP (black circles). The diameters of the circles shown are proportional to the percentage of CGM glucose values <60 mg/dL, and the size of the triangle is proportional to the percentage of CGM glucose values >180 mg/dL. The horizontal red dashed line refers to the glucose level corresponding to the American Diabetes Association therapy goal for each age group tested, which corresponds to 154 mg/dL (HbA1c of 7%) for adults and 169 mg/dL (HbA1c of 7.5%) for children. Results are summarized in the table, where the co-primary outcomes (mean CGM glucose level and percentage of CGM glucose values <60 mg/dL) for the BP arm are highlighted in red for each of the 4 studies.
BP = bionic pancreas; CGM = continuous glucose monitoring; HbA1c = hemoglobin A1c.

In April 2013, FDA approval was obtained to conduct the first outpatient study testing the BP in adolescents 12-20 years old with T1DM. This study, referred to as the 2013 Summer Camp Study, followed a random-order cross-over design in which 32 adolescents with T1DM participated in 5 days on the BP and 5 days of supervised camp care in which they wore a CGM with blinded display and muted alarms. Subjects were fully integrated into normal camp activities without restrictions on diet or exercise. The study used the same iPhone-based BP that was used in the Beacon Hill Study. Results are summarized in Figure 1 (Russell, 2014). In April 2014, FDA approval was obtained to conduct the first outpatient study testing the BP in pre-adolescents 6-11 years old with T1DM. This study, referred to as the 2014 Summer Camp Study, was similar in design to the 2013 Summer Camp Study. Results are summarized in Figure 1 (Russell, 2016).

In April 2014, FDA approval was obtained to conduct the first multi-center study, which was also the first home study, to test the BP in adults 18 years or older with T1DM. This study, referred to as the Bionic Pancreas Multi-Center Study, followed a random-order cross-over design in which 39 adults participated in 11 days on the BP and 11 days of usual care. Participants went to work as usual, and lived and slept at home, all without clinical supervision. There were no restrictions placed on diet or exercise. The study included 4 medical centers (10 subjects per center), which included MGH, the University of Massachusetts Medical School, Stanford University, and the University of North Carolina at Chapel Hill. Results are summarized in Figure 1.

All of these studies used marketed glucagon (glucagon for injection, Eli Lilly). Due to its limited stability, Lilly glucagon must be reconstituted immediately before use. Animal studies have previously shown that despite its limited chemical stability, Lilly glucagon maintains its biological activity for up to 7 days in solution. Using this data, an Investigational New Drug (IND) exemption was obtained from the FDA for its use in a pump for up to 27 hours. This allowed these studies to be performed by asking volunteers to reconstitute a new vial of glucagon and fill the glucagon pump at approximately the same time every day. However, marketed Lilly glucagon has no path forward for approval for chronic BP use.

1.4 ZP4207

ZP4207 is a peptide analog of human glucagon that is being developed to treat hypoglycemia in patients with T1DM and type 2 diabetes mellitus. ZP4207 exhibits improved physical and chemical stability in aqueous media and is suitable for liquid formulation. ZP4207 is comprised of 29 amino acids and has 7 amino acid substitutions when compared to native glucagon.

Two clinical Phase 1 trials have been conducted to establish safety and tolerability of ZP4207 after single and multiple dosing to healthy patients and T1DM patients under insulin-induced hypoglycemic conditions.

The First Human Dose (FHD) trial (ZP4207-14013) was finalized in April 2015. The trial was a randomized, double-blinded trial with the objectives to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of ZP4207 as compared to an active comparator. Part 1 included a single ascending dose in healthy volunteers in cohorts of 8. In each cohort, the patients were randomized 3:1 to ZP4207 (n=6) or Novo Nordisk GlucaGen® (n=2). Five cohorts with SC administration (0.01, 0.1, 0.3, 1.0, and 2.0 mg ZP4207 compared to 1 mg GlucaGen) and 3 cohorts with intramuscular (IM) administration (0.3, 1.0, and 2.0 mg ZP4207 compared to 1 mg GlucaGen) were included. Part 2 included 2 sequence groups of

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10 hypoglycemic T1DM patients. The patients were treated with fixed single IM doses of 0.7 mg ZP4207 and 1.0 mg GlucaGen in a sequential cross-over design in a randomized treatment order.

The second clinical trial (ZP4207-15007) was a single-center, double-blind, Phase 1b trial investigating the safety and tolerability, PK and PD of ZP4207 following repeated administration in healthy volunteers compared to placebo. It was finalized in July 2015. Each of the 3 cohorts comprised 8 subjects, who received 5 repeated SC doses of ZP4207 or placebo in a 3:1 treatment allocation. The first cohort started with the lowest dose of 0.1 mg. Cohort 2 and 3 continued with 0.3 and 1.0 mg, respectively.

The Phase 1 results did not give rise to specific safety concerns, beyond those related to the pharmacological effect of ZP4207. All adverse events (AEs) recorded in the trials were of mild or moderate severity. The most frequent systemic AE related to treatment with ZP4207 was nausea, which is a known side-effect following administration of glucagon. The most frequent injection site reaction was transient erythema, occurring in all ZP4207, glucagon, and placebo treatment groups, irrespective of dose. No anti-drug antibodies (ADA) incidences were observed.

The observed PD response, in terms of increased plasma glucose, in insulin-induced hypoglycemic patients with T1DM following dosing with 0.7 mg ZP4207 administered IM was similar to that observed following IM dosing with 1.0 mg glucagon (GlucaGen, Novo Nordisk). An increase in plasma glucose of ≥20 mg/dL from hypoglycemic levels was achieved within 30 minutes for all patients.

In terms of PK, ZP4207 had a short half-life and high clearance and dose proportionality for both maximum plasma concentration and area under the concentration-time curve from time 0 to 300 minutes in the dose range 0.1 to 2.0 mg following SC administration. Following IM administration, dose proportionality was shown in the investigated dose range of 0.3 to 2.0 mg. The PK properties of 0.7 mg ZP4207 IM were comparable with those of 1.0 mg glucagon (GlucaGen, Novo Nordisk) with IM administration.

1.5 Risk/Benefit

While the potential risks are minimal, the findings of this trial may reveal information that can substantially improve medical care for persons with diabetes. Therefore, the overall risk/benefit for patients participating in this trial is assessed as acceptable.

Potential Risks and Discomforts

Trial patients will be informed by the Investigator of the potential risks of ZP4207 and other trial-related procedures before they enter the trial.

In this trial, patients with T1DM will be included to test the safety and efficacy of the BP using either the iLet or the iPhone platform when used with ZP4207 versus Lilly glucagon. The cross-over design with inclusion of 1 group of 10 T1DM patients into the 2 iLet treatment arms and the inclusion of a second group of 10 T1DM patients into the 2 iPhone-based BP treatment arms in a randomized order will allow for a direct comparison of the safety and efficacy of the 2 treatments, based on intra-patient variability only.

Patients may experience mild discomfort associated with the insertion of the infusion sets and sensor into the SC tissues. The risk of discomfort due to insertion of infusion sets and sensors is expected to be slightly greater than in their lives outside the trial because more infusion sets will be inserted and a CGM sensor will be inserted. Most patients will use only 1 infusion set and not all will use a CGM sensor in usual care.

There is a potential risk of hypoglycemia, since recombinant insulin analog will be administered. Due to frequent monitoring of glucose and direct supervision by a registered nurse (RN) or Doctor of Medicine (MD) at all times, the risk of a hypoglycemic episodes leading to significant harm to patients is expected to be substantially lower than their risk during their usual therapy.

There is a risk of hyperglycemia. This risk is expected to be less than the risk during the patients' lives outside of the trial based on data from earlier BP trials and the design of this trial.

Treatment with ZP4207 and marketed glucagon can result in undesired effects or complaints. Undesired effects and complaints such as gastrointestinal side effects including nausea, vomiting, and diarrhea are known side effects of glucagon administration at higher dose levels. The frequency of nausea associated with the administration of 1 mg of glucagon according to the Summary of Product Characteristics (SPC) for Glucagon is described to be between 1/10 and 1/100. The frequency of vomiting is described to be between 1/100 and 1/1000 (Novo Nordisk, 2015). Similar gastrointestinal side effects have also been observed to a limited degree in the 2 clinical trials conducted with ZP4207, again at higher dose levels. The individual doses of ZP4207 and Lilly glucagon delivered by the BP are expected to be significantly lower than doses typically associated with nausea. Episodes of low blood pressure have also been observed after administration of higher doses of glucagon and ZP4207. As with every novel drug substance, new and yet unknown side effects may also occur.

There are limited data available to describe the immunogenic potential of glucagon products available on the market, but the data available indicate that marketed glucagon only has a small immunogenic potential. A Phase 1 trial performed with recombinant human glucagon and animal derived glucagon in 75 healthy patients did not show signs of ADA measured 13 weeks after trial product administration (Eli Lilly, 2005). In the ZP4207 FHD trial, ZP4207-14013, no confirmed anti-ZP4207 or anti-glucagon antibodies were detected in any of the samples. In addition, the 5 sequential administrations of ZP4207, as applied in trial ZP4207-15007, were not associated with the development of antibodies against ZP4207 in the 18 subjects enrolled to receive ZP4207. The optimized formulation of ZP4207, as applied in the present trial is not expected to change the immunogenic potential of the Investigational Medicinal Product (IMP).

In relation to diabetes therapy, development of insulin-antibodies is documented more substantially and route of administration has been shown to influence immunogenic potential of insulins. However, these antibodies against insulin generally do not have an impact on insulin action and are thus not clinically relevant.

In terms of consequence, development of high titer antibodies against ZP4207 could, in theory reduce the activity of endogenous glucagon, which again, in theory could influence

hypoglycemic episodes. However, most patients with T1DM do not secrete glucagon normally in response to hypoglycemia, so they would be less likely to be negatively impacted by anti-glucagon antibodies. Limited suppression of glucagon would, however, not be considered critical, as low glucose levels can also be corrected by other means, including oral intake of glucose and by other endogenous hormones such as oxyntomodulin.

Overall, ZP4207 is judged to be a low-risk molecule, based upon the available clinical data as well as the outcome of the risk-based approach to the immunogenicity assessment made. The present trial will include sampling for measurement of antibodies against ZP4207 prior to first dosing (Visit 3), at the ADA Assessment Visit (Visit 5), and at the Follow-up Visit (Visit 6). In line with regulatory guidance documents, these samples will be appropriately analyzed and the results will be included in the overall assessment of the immunogenic potential of ZP4207 after completion of each trial and as the clinical development program advances.

Administration of ZP4207 may be associated with a risk of allergic reactions similar to those observed for other therapeutic peptides or proteins. Patients with known or suspected allergies to the trial products or related products will be excluded from the trial. Mild or moderate allergic reactions may include symptoms of rash, fever, flu-like symptoms, nausea, headache, and myalgia. Acute generalized hypersensitivity reactions are usually very rare but may include symptoms of flushing, sweating, dizziness, change in blood pressure, and difficulties in breathing. The risk of acute hypersensitivity reactions is described to be less than 1/10,000 for native glucagon. No severe acute hypersensitivity reactions have been observed in the 2 clinical trials conducted with ZP4207.

Potential Benefits

Based on experiences from previous trials of the BP and the design of this trial, patients enrolled in the trial may benefit from a reduction in risk of hypoglycemia and hyperglycemia and a better mean glucose compared to their usual diabetes care during their short trial participation.

The data derived from this trial will allow evaluation of safety and tolerability of ZP4207 in the iLet and the iPhone-based BP, and the robustness and effectiveness of the new BP control system. The data obtained will be used to further improve the iLet and will allow the expansion to larger outpatient trials using the iLet or the iPhone-based BP with ZP4207.

This trial is a necessary step in preparing the BP with ZP4207 to become available to people with T1DM. Wide availability of the BP with ZP4207 could improve the medical care of adults and children with T1DM.

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2 TRIAL OBJECTIVES

2.1 Primary Objective

The primary objective is to conduct a trial testing the safety and tolerability of the BP using either the iLet or the iPhone platform when used with ZP4207 in 20 adult (≥18 years of age) patients with T1DM.

2.2 Secondary Objectives

The secondary objectives are to measure glycemic regulation, including hypoglycemia exposure (percent of time spent with CGM glucose <60 mg/dL), evaluate BP device reliability, and to document the satisfaction of patients with the BP with the goal of optimizing the functionality and user interface of the BP.

3 TRIAL DESCRIPTION

3.1 Summary of Trial Design

This trial is a single-center, open-label, 2-part, randomized cross-over trial. The trial will enroll adult patients with T1DM and will assess the safety and efficacy of the BP using either the iLet or the iPhone platform using the glucagon analog ZP4207 versus Lilly glucagon. In Part 1, up to 10 patients will participate in two 1-day treatment arms in random order (iPhone-based BP using ZP4207 and iPhone-based BP using Lilly glucagon) according to a pre-generated randomization scheme. In Part 2, up to 10 new patients will participate in two 1-day treatment arms in random order (iLet using ZP4207 and iLet using Lilly glucagon) according to a pre-generated randomization scheme. Patients can only participate in 1 part of the trial. An interim database lock may occur upon completion of Part 1 of the trial to analyze the iPhone-based BP data. The iLet and the iPhone-based BP will also administer insulin (insulin lispro, Lilly Humalog) using the same BG control algorithm for all 4 treatment arms. The trial will be conducted at a single center, the MGH Diabetes Center in Boston, MA.

The overall trial design schematic is displayed in Figure 2.

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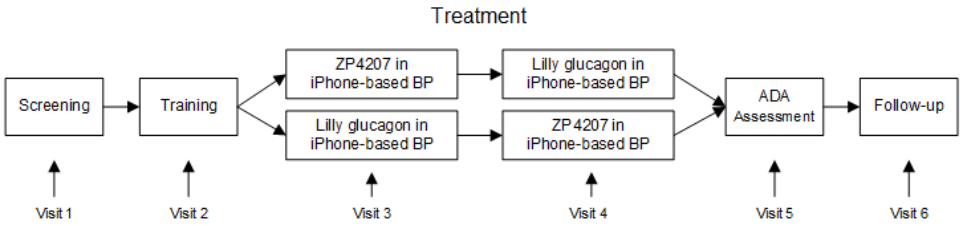
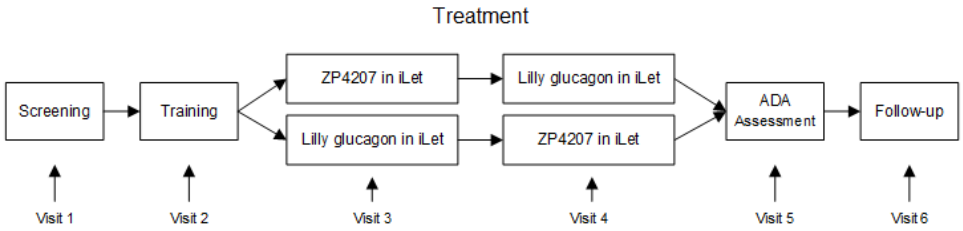
Figure 2. Trial Design Schematic

Part 1:



Part 2:



Patients can only participate in 1 part of the trial.
ADA = anti-drug antibodies; BP = bionic pancreas.

3.2 Indication

ZP4207 is an anti-hypoglycemic glucagon analog in a ready-to-use liquid formulation which is being studied to improve glycemic control in adults (and children) with T1DM as part of a bihormonal BP.

3.3 Number of Patients

Up to 40 adult patients with T1DM can be enrolled. The upper bound is based on the expectation that some patients will be excluded after the Screening Visit and the possibility that some patients may have to be discontinued before completion (due to, for instance, inter-current illness or patient withdrawal). It is expected that up to 10 patients will complete each part of the trial protocol.

4 SELECTION AND WITHDRAWAL OF PATIENTS

The trial will enroll patients who already manage their T1DM using continuous SC insulin infusion pump therapy. This requirement is imposed because multiple daily injection therapy involves the use of medium-acting or long-acting basal insulin that would require an extended washout period.

4.1 Inclusion Criteria

1. Male and female patients with T1DM for at least 1 year, as defined by the American Diabetes Association
2. Age ≥18 years
3. Diabetes managed using an insulin pump for ≥6 months
4. Prescription medication regimen stable for >1 month (except for medications that will not affect the safety of the trial and are not expected to affect any outcome of the trial, in the judgment of the Investigator)
5. Informed consent obtained before any trial-related activities (trial-related activities are any procedure that would not have been performed during normal management of the patient)
6. Patients in good health according to age (medical history, physical examination, vital signs, 12-lead electrocardiograms [ECGs], laboratory assessments), as judged by the Investigator

4.2 Exclusion Criteria

1. Unable to provide informed consent (e.g., impaired cognition or judgment)
2. Unable to safely comply with trial procedures and reporting requirements (e.g., impairment of vision or dexterity that prevents safe operation of the BP, impaired memory, unable to speak and read English)
3. Participation in another clinical trial of an investigational agent or device concurrently or within 1 month (or 5 half-lives) prior to the Screening Visit
4. Previous exposure to ZP4207
5. Females of childbearing potential who are pregnant (positive urine human chorionic gonadotropin [HCG]), breast feeding, plan to become pregnant in the immediate future, or sexually active without using highly effective contraception methods (highly effective methods are considered those with a failure rate less than 1% undesired pregnancies per year including surgical sterilization, hormonal intrauterine devices [coil], oral hormonal contraceptives, sexual abstinence, or a surgically sterilized partner) or postmenopausal women amenorrheic for less than 1 year with serum follicle-stimulating hormone (FSH) level ≤40 IU/L and not using highly effective contraceptive methods during the trial and until 1 month after last dosing in the trial
6. Male who is sexually active and not surgically sterilized who or whose partner(s) is not using highly effective contraceptive methods (highly effective contraceptive measures include surgical sterilization, hormonal intrauterine devices [coil], oral hormonal contraceptives, each in combination with spermicide-coated condoms), or who is not willing to refrain from sexual intercourse from the first dosing until 1 month after last dosing in the trial
7. Current alcohol abuse (intake averaging >3 drinks daily in last 30 days) or use within the last 6 months of controlled substances without a prescription (other than marijuana)
8. New onset clinically significant illness within 4 weeks prior to screening, as judged by the Investigator
9. Unwilling or unable to refrain on the treatment visits from:
    a. Acetaminophen in any form
    b. Use of drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the trial (use of beta blockers will be allowed as long as the dose is stable and the patient does not meet the criteria for hypoglycemia unawareness while

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taking that stable dose, but use of benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the Investigator)

10. History of liver disease that is expected to interfere with the anti-hypoglycemia action of glucagon (e.g., liver failure or cirrhosis). Other liver disease (i.e., active hepatitis, steatosis, active biliary disease, any tumor of the liver, hemochromatosis, glycogen storage disease) may exclude the patient if it causes significant compromise to liver function or may do so in an unpredictable fashion.
11. Aspartate aminotransferase >2 × upper limit of normal (ULN), alanine aminotransferase >2 × ULN, or bilirubin >1.5 × ULN on screening laboratories
12. Renal failure on dialysis or estimated glomerular filtration rate <30 mL/min/1.73 m^2 on screening laboratories
13. Hemoglobin <12 gm/dL for men and <11 gm/dL for women
14. Personal history of cystic fibrosis, pancreatitis, pancreatic tumor, or any other pancreatic disease besides T1DM
15. Any known history of coronary artery disease including, but not limited to, history of myocardial infarction, stress test showing ischemia, history of angina, or history of intervention such as coronary artery bypass grafting, percutaneous coronary intervention, or enzymatic lysis of a presumed coronary occlusion)
16. Congestive heart failure with New York Heart Association Functional Classification III or IV
17. History of transient ischemic attack or stroke in the last 12 months
18. Seizure disorder, history of any non-hypoglycemic seizure within the last 2 years, or ongoing treatment with anticonvulsants
19. History of hypoglycemic seizures (grand-mal) or coma in the last 12 months
20. History of hypoglycemic unawareness in the last 12 months
21. History of pheochromocytoma: fractionated metanephrines will be tested in patients with history increasing the risk for a catecholamine secreting tumor:
    a. Episodic or treatment refractory (requiring 4 or more medications to achieve normotension) hypertension
    b. Paroxysms of tachycardia, pallor, or headache
    c. Personal or family history of MEN 2A, MEN 2B, neurofibromatosis, or von Hippel-Lindau disease
22. History of adrenal disease or tumor
23. Hypertension with systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg despite treatment
24. Untreated or inadequately treated mental illness (indicators would include symptoms such as psychosis, hallucinations, mania, and any psychiatric hospitalization in the last year), or treatment with anti-psychotic medications that are known to affect glucose regulation
25. Electrically powered implants (e.g., cochlear implants, neurostimulators) that might be susceptible to radio frequency interference
26. History of adverse reaction to glucagon (including allergy) besides nausea and vomiting
27. History of severe hypersensitivity to milk proteins or lactose
28. Established history of allergy or severe reaction to adhesive or tape that must be used in the trial
29. Use of oral anti-diabetic medications (e.g., thiazolidinediones, biguanides, sulfonylureas, glitinides, dipeptidyl peptidase-4 [DPP-4] inhibitors, sodium-glucose co-transporter-2 [SGLT-2] inhibitors)

30. Inadequate venous access as determined by trial nurse or physician at time of screening
31. Any factors that, in the opinion of the Investigator, would interfere with trial endpoints or the safe completion of the trial

4.3 Target Population

Patients who meet all of the inclusion and none of the exclusion criteria will be considered as candidates for this trial. Individuals who have previously inquired about participation in BU/MGH trials and have asked to have their contact information kept on file will be contacted. In addition, advertisements for the trial may be posted at the MGH Diabetes Center and other places, and may be distributed in the weekly broadcast e-mail of research studies seeking volunteers. A letter may be sent to adult endocrinologists in the Boston metropolitan as well as selected nearby endocrinologists informing them of the trial and asking them to refer any eligible patients who might be interested. Information will be posted about the trial along with contact information on the BU/MGH website www.bionicpancreas.org and on www.clinicaltrials.gov.

4.4 Withdrawal Criteria

The participation of individual patients will be discontinued if they experience:

- Seizure or unconsciousness associated with hypoglycemia and associated with participation in the trial
- Persistent nausea and vomiting thought to be related to glucagon dosing associated with participation in the trial
- Hospitalization associated with participation in the trial
- Pregnancy
- Diabetic ketoacidosis

If more than 1 patient must be withdrawn from the trial for these reasons, the trial will stop and a vote of the Data and Safety Monitoring Board (DSMB) will be required to restart it. All AEs that are serious and unexpected but related will be reported to the DSMB within 5 working days.

Note that patients may discontinue participation at any time. Patients may be removed from the trial for other reasons, for instance, failure to comply with trial procedures or intercurrent illness that is unrelated to the BP but that precludes safe participation. Discontinuation of participation for these reasons will not contribute to a decision to discontinue the trial.

5 ASSIGNMENT TO TREATMENT GROUPS

This trial is an open-label, 2-part, randomized cross-over trial. Patients who have completed the Screening Visit and meet all of the inclusion and none of exclusion criteria will be enrolled into the trial. In Part 1, up to 10 patients will participate in two 1-day treatment arms in random order (iPhone-based BP using ZP4207 and iPhone-based BP using Lilly glucagon) according to a pre-generated randomization scheme. In Part 2, up to 10 new patients will participate in two 1-day treatment arms in random order (iLet using ZP4207 and iLet using Lilly glucagon) according to a pre-generated randomization scheme. Up to 2 patients may participate in the trial per day. The order of the treatment visits will be randomized in blocks of 2 patients.

6 TRIAL TREATMENT

6.1 Investigational Medicinal Products

Insulin: The trial involves SC administration of insulin lispro (Humalog, Lilly), which is commercially available by prescription and is indicated for patients with T1DM, but not for use in a BP.

Glucagon: The trial also involves SC administration of Lilly glucagon in 1 iLet arm and 1 iPhone-based BP arm. Lilly glucagon is commercially available by prescription and is indicated for patients with T1DM in severe hypoglycemia, but not for use in a BP.

ZP4207: The trial also involves SC administration of the glucagon analog ZP4207, 1 mg/mL, in the other iLet arm and the other iPhone-based BP arm. ZP4207 will be made available by Zealand Pharma A/S, Denmark as liquid formulation in prefilled syringes of 0.6 mL.

6.2 Storage and Drug Accountability of IMPs

All IMPs will be stored and handled in accordance with the Sponsor's instructions and/or the product labeling at the Investigator's site, e.g., refrigerated (+2ºC to +8ºC) and should not be exposed to excessive heat, direct sunlight and never be frozen.

All used, partly used, and unused vials or prefilled syringes must be kept by the Investigator and stored between +2ºC and +8ºC (unused) or at room temperature (partly used and used). Used and unused pre-filled syringes must be stored separately.

The Investigator must ensure the availability of proper storage conditions and record and evaluate the temperature. Temperature of the refrigerator used for drug storage is monitored continuously, an alarm system is established. The Investigator must inform the monitor immediately if any IMP has been stored outside specified conditions (e.g., outside temperature storage). Investigational Medicinal Product that has been stored improperly must not be dispensed to any patient before it has been re-evaluated and approved for further use. The Investigator must take appropriate action to ensure correct storage.

For the IMP, the Investigator must keep an accurate record of all IMPs received and the products used for each patient in a Drug Accountability Record. Storage locations, batch numbers, and expiry dates are also documented in this form.

The drug accountability must be performed in a timely manner by the monitor.

6.3 Dispensing and Return of IMPs

No IMPs may be dispensed to any person not enrolled in the trial.

Upon completion of the trial, the Sponsor will be responsible for destruction or storage of IMPs (used, partially used, or unused). These duties can be delegated to a contract research organization (CRO) and must be documented in the trial files.

[redacted]

6.4 Doses

The iLet and the iPhone-based BP can administer isolated insulin-glucagon doses once every 5 minutes. A single automated bolus of insulin will not exceed 3 units per 5-minute dose (30 µl of U-100 insulin) in both systems, and a single meal-priming dose, in response to a meal announcement made by the user, will not exceed 12 units (120 µl of U-100 insulin). A single bolus of glucagon will not exceed 80 µg (80 µl of 1 mg/mL Lilly glucagon or 1 mg/mL ZP4207). In prior studies, typical doses of glucagon were in the range of 2.5-40 µg per dose. The iLet and the iPhone-based BP are capable of administering as little as ~0.5 µl (0.05 units of U-100 insulin or 0.5 µg of 1 mg/mL ZP4207).

It is expected that the mean total daily doses of glucagon/ZP4207 will be <1.0 mg daily as in previous studies. The mean daily glucagon dose in a previous 11-day outpatient trial was 0.5 mg/day (range 0.2-0.9 mg/day). Currently, single doses of up to 2 mg ZP4207 have been administered in clinical trials. The recommended dose of marketed glucagon for adult patients suffering from severe hypoglycemia is 1 mg as a single injection. Mean glucagon levels in previous inpatient studies have been above the normal fasting range for glucagon only 1% of the time. Therefore, the glucagon exposure of patients is expected to be modest.

6.5 iPhone-based Bionic Pancreas

Infusion Set: Patients will wear 2 FDA-approved commercially available infusion sets, 1 for insulin infusion and 1 for glucagon infusion. Infusion sets that are compatible with the Tandem t:slim infusion pump (luer lock connection) will be provided.

Continuous Glucose Monitors: One transcutaneous glucose sensor for the Dexcom G4 Platinum (Garcia, 2013) will be inserted in the abdominal SC tissue and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to the sensor and the whole assembly is held to the skin with an adhesive patch and communicates wirelessly with the BP. If the G4 sensor fails for any reason during the trial (loss of CGM signal), it will be replaced promptly.

Bionic Pancreas Control Unit: The control unit consists of a stock iPhone 4S and a Dexcom G4 Platinum receiver connected with a custom hardware interface and placed back-to-back in a custom enclosure. The G4 receiver converts the raw wireless signal from the transmitter into an estimated BG signal that is sent via a hardwired connection to the iPhone.

The iPhone runs iOS 6 in “Guided Access” mode, where the only app accessible to the patient is the Beta Bionics app, which runs the control algorithm. The home screen, where typical user options reside, is password protected. Access to other functions on the iPhone (primarily the Settings options) is separately password protected and only accessible to the study staff. This prevents accidental activation of other apps that could interfere with the function of the BP. The control algorithm app has a graphical user interface (GUI) that displays the current CGM glucose, a graphical history of the CGM glucose, and doses of insulin and glucagon delivered by the control algorithm. The GUI can also be used to input meal announcements, designating the size of the meal as larger than typical, typical in size, smaller than typical, or just a bite, and the type of meal as breakfast, lunch, or dinner. This will trigger a partial meal-priming bolus the size of which will adapt during the course of the trial to meet a target of 75% of the insulin needs for that size and type of meal.

[redacted]

The target glucose level will be programmed to 100 mg/dL by the study engineers prior to the start of each experiment. This will be locked for each arm of the study; the patient will be unable to accidentally change or tamper with this setting.

The GUI can be used to manage meal boluses and correction boluses during periods when the CGM is offline, such as the period after a sensor is replaced and before the new sensor has been calibrated. During these times the control algorithm will determine and direct the administration of insulin basal rates based on the patient's weight. The controller will also administer insulin and/or glucagon as appropriate in response to any entered BG values, just as if they were CGM values.

The GUI also displays visual alarms associated with an audio signal if communication is dropped between the CGM transmitter and the BP control unit or between the control unit and the 2 insulin pumps.

The iPhone communicates wirelessly via the Bluetooth Low Energy (BTLE) protocol with 2 Tandem t:slim insulin pumps to deliver insulin and glucagon.

Tandem t:slim Pumps: These pumps are FDA-approved insulin pumps with reservoirs capable of holding 300 units (3 mL) of insulin or 3 mL of glucagon or ZP4207 solution. The pumps have a mechanical dosing resolution of 1/120 (0.00833) unit and can deliver liquids at a maximal rate of ~33 µl per minute (2 mL per hour). They are slave to the BP control unit and are controlled wirelessly via the BTLE protocol by the iPhone 4S.

6.6 iLet Bionic Pancreas

Infusion Set: A novel, dual cannula infusion set has been designed specifically for use with the iLet. Patients will wear dual channel tubing that will be attached to 2 infusion sets with 1 steel cannula each, 1 for insulin infusion and the other for glucagon infusion. The tubing and infusion sets will have undergone sterilization prior to being delivered in a sealed pouch. The steel cannulae will be inserted in the abdominal SC tissue.

Continuous Glucose Monitors: One transcutaneous glucose sensor for the Dexcom G4 Platinum (Garcia, 2013) will be inserted in the abdominal SC tissue and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to the sensor and the whole assembly is held to the skin with an adhesive patch and communicates wirelessly with the BP. If the G4 sensor fails for any reason during the trial (loss of CGM signal), it will be replaced promptly.

Bionic Pancreas Control Unit: The iLet is being built according to Class III medical device standards, adheres to a comprehensive and robust quality system, and is fully compliant with International Organization for Standardization (ISO) 13485 standards and document control practices. The iLet is a fully-integrated dual-hormone BP system that integrates the CGM technology (currently the Dexcom G4 Share system) as well as 2 independent motor-drivetrain pumping assemblies, which independently actuate the delivery of insulin and glucagon from pre-filled cartridges that are separately loaded into the iLet housing. Each drivetrain assembly utilizes a lead screw, which is driven by a precision micromotor, a gear case assembly, and a motor controller unit, in a manner similar to what is commonly found in most insulin infusion pumps on the market today. The iLet has dosing accuracy that is comparable to FDA-approved insulin pumps currently on the market. The iLet has a built-in BTLE radio that

also allows automatic communication with the paired CGM, as well as the Nova StatStrip® Xpress BG meter (Nova Biomedical). The iLet does not contain a cellular nor a WiFi radio, and does not accept input data from another mobile device (e.g., smartphone), other than the paired CGM and BG meter(s).

The mathematical control algorithms (which are the same as those used in the iPhone-based BP), the CGM glucose engine (Dexcom), and the native user interface software, are all interconnected through controller framework software and reside as embedded systems on printed circuit boards contained within the device housing. The touchscreen-enabled, menu-driven user interface and onboard processor provide a comprehensive and standalone platform, which allows the iLet to operate independently of smartphones or other devices and without the need for internet support during routine operation. The graphical user interface of the iLet has the same user options and capabilities of the iPhone BP, including having its home screen password protected and its settings options only accessible to trial staff via a separate password.

6.7 Other Trial Devices

YSI 2300 STAT Plus™ (Yellow Springs Instruments): The YSI 2300 STAT Plus is an FDA-approved glucose analyzer. Blood glucose measurements using the YSI 2300 STAT Plus will be obtained off of the intravenous (IV) line during both treatment visits.

Nova Biomedical StatStrip Xpress Glucose Meter: The Nova StatStrip Xpress glucose meter is an FDA-approved glucose meter that is commercially available. Blood glucose measurements for CGM calibration will be obtained with the Nova StatStrip Xpress during both treatment visits if the YSI 2300 STAT Plus fails and via fingerstick with the Nova StatStrip Xpress during any periods when IV blood samples are not available for any reason or the IV fails.

Exercise Bike: The trial will utilize a stationary exercise bike (ergometer) for the in-clinic exercise at the treatment visits. This bike will be stored at the Diabetes Research Center when not in use.

6.8 Concomitant Medications

6.8.1 Permitted Medications and/or Procedures

Patients may take any over-the-counter medications that they wish during the trial, with the exception of any medication containing acetaminophen as that may cause interference with CGM sensing. All concomitant medications, including over-the-counter medications, should be recorded.

Use of beta blockers will be allowed as long as the dose is stable and the patient does not meet the criteria for hypoglycemia unawareness while taking that stable dose.

If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.

[redacted]

6.8.2 Excluded Medications and/or Procedures

During the trial, patients will not use any recreational drugs or drugs of abuse. The need to take prescription drugs that dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder appropriate decision-making may be grounds for exclusion from the trial or discontinuation of participation, a decision that will be made by the Investigator.

Use of benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the Investigator. Use of oral anti-diabetic medications (e.g., thiazolidinediones, biguanides, sulfonylureas, glitinides, DPP-4 inhibitors, SGLT-2 inhibitors) will also be excluded.

7 TRIAL PROCEDURES

7.1 Informed Consent

After potential patients have had time to review the consent document, and prior to any trial-related activities, they will meet with a trial MD or designee who will explain the trial, answer any questions, and administer informed consent. In the event that a volunteer is a patient of 1 of the trial MDs, another staff MD or designee will answer questions and administer consent. The patients will be fully informed of their responsibilities and their rights while participating in the trial as well as of the possible risks and potential benefits of participation in the trial. They will have the opportunity to discuss all questions and ample time to consider participation.

Trial-related activities are any procedures that would not have been performed during normal management of the patient. Patients who wish to participate in the trial will be asked to personally date and sign an informed consent form (ICF). Likewise, the Investigator must also personally date and sign the ICF. All patients will be provided with a copy of their own signed and dated ICF.

Trial staff will answer any questions that the patients may have during their participation. They will share any new information in a timely manner that may be relevant to the patient's willingness to continue participating in the trial. The patients may choose to discontinue their participation at any time.

7.2 Screening Visit (Visit 1)

All patients will have a Screening Visit to confirm eligibility. The patient will be interviewed and the electronic Case Report Form (eCRF) will be completed by trial staff to establish whether the patient is eligible.
Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator.

Once all of the results have been returned, a trial MD will review the eCRF to determine patient eligibility. If a patient is not eligible to continue in the trial, the results of abnormal tests will be reported to the patient and to a health care provider of their choosing.

[redacted]

7.2.1 Data Collected at Screening

- Age, sex, race, and ethnicity
- Date of last menstrual period in female patients
- Medical, surgical, and social history, allergies, and review of systems relevant to inclusion and exclusion criteria, including:
  - Date of diabetes diagnosis
  - Duration of insulin pump use and type of insulin used in pump
  - Type/model of insulin pump
  - Insulin regimen (basal rate, sensitivity factor, and carbohydrate ratio)
  - Average total daily dose of insulin in the last 30 days as available (from pump history)
  - Usage of CGM, if any (type of CGM, days per month worn, usage of data, whether insulin is dosed based on CGM alone, alarm settings)
- Concomitant illness (any illness present at screening)
- Concomitant medications (prescription and non-prescription) and date of last change in medication regimen
- Height, weight, physical examination, and vital signs including body temperature and blood pressure
- 12-lead ECG
- Hemoglobin A1c
- Chemistry and hematology samples (see Appendix B)
- Urine HCG pregnancy test for women of childbearing potential
- FSH level for postmenopausal women amenorrheic for less than 1 year
- Fractionated plasma metanephrines (if indicated by history)

7.3 Training Visit (Visit 2)

A Training Visit will take place before the first treatment visit. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor and trial policies and procedures. Trial staff will verify that the patients have understood the material and are competent to participate safely in the trial. Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator. Concomitant medications will also be reviewed.

7.4 Treatment Visits (Visit 3 and Visit 4)

- Visit 3 will take place at least 48 hours after screening (Visit 1) and no more than 30 days after screening (Visit 1).
- There will be a 24-hour minimum washout between Visit 3 and Visit 4 and a maximum of 3 weeks between Visit 3 and Visit 4.
- Up to 2 patients may participate per day.
- In Part 1, each patient will participate in 2 treatment visits: 1 with the iPhone-based BP using ZP4207 and 1 with the iPhone-based BP using Lilly glucagon in a randomized order.
- In Part 2, each patient will participate in 2 treatment visits: 1 with the iLet using ZP4207 and 1 with the iLet using Lilly glucagon in a randomized order.

[redacted]

- The night before the treatment visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be instructed to call if they encounter any difficulty with their CGM.
- Patients will be responsible for their own medications other than insulin during the trial. Any medical advice needed by the patients during their participation that is not directly related to BG control should be obtained from them in their usual manner. Patients may take any over-the-counter medications that they wish during the trial, with the exception of any medication containing acetaminophen as that may cause interference with CGM sensing. If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.
- During the trial, patients will not use any recreational drugs or drugs of abuse. The need to take prescription drugs that dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder appropriate decision-making may be grounds for exclusion from the trial or discontinuation of participation, a decision that will be made by the Investigator.
- Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator.
- Patients will not tamper with the BP, including changing any settings.
- Patients may not remove the BP during the trial unless the BP failed or they are withdrawing from the trial.
- The exact time of each procedure and assessment will be documented.

7.4.1 Visit Procedures

- Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window. If BG is <50 mg/dL, treatment with simple carbohydrate is allowed. If the patient experiences persistent hypoglycemia, the visit will be rescheduled within the visit window. If the visit needs to be rescheduled due to hypoglycemia or hyperglycemia, trial staff will assist the patient with insulin or medication adjustments to address glycemic control. The patient will be instructed to contact trial staff later in the day if his or her BG remains uncontrolled.
- Upon arrival to the visit, the patient's weight and vital signs including body temperature and blood pressure will be documented.
- Patient reports of symptoms, any other complaints, and AEs will be reviewed.
- Concomitant medications will be recorded.
- Chemistry and hematology samples will be collected at visit start (see Appendix B).
- ADA samples will be collected before the start of dosing (Visit 3 only).
- A 12-lead ECG will be performed.
- A urine HCG pregnancy test will be performed in female patients of childbearing potential. If the test is positive, the patient will be informed of the result and the visit will be ended.

[redacted]

- Patients will complete a baseline survey about their attitudes and experience with their usual diabetes care.
- An IV catheter will be placed for blood sampling.
- Trial staff will assist the patient to calibrate their CGM, review the trial procedures again and assist with the setup of the BP system, including inserting and priming infusion sets.
- The control algorithm will be initialized only with the patient's weight. Diagnostics will be performed to ensure that the CGM device is appropriately calibrated and that all of the components of the BP systems are in working order.
- The basal rate of the patient's own insulin infusion pump will be changed to be 2-fold higher than weighted mean of the basal rate during the trial period. This is intended to increase the usage of glucagon during the treatment visit.
- The patients will continue to wear their own infusion pump infusing at the temporary 2-fold basal rate throughout the visit until the start of the structured exercise period, in addition to the BP.
- The staff will start the BP as close as possible to a minute divisible by 5 minutes (i.e., on a 5-minute mark). The starting time will be considered Hour 0.
- Additional calibrations will be performed at any of the BG checks throughout the day if the CGM value does not meet the ISO standard (<15 mg/dL difference for BG values <75 mg/dL; <20% absolute difference for BG values >75 mg/dL) at the time of the BG measurement AND it is a good time to calibrate (the CGM trend arrow is flat and there has been no carbohydrate intake in the last 30 minutes or glucagon boluses in the last 15 minutes).
- Blood samples will be taken from the IV at least hourly and processed for plasma ZP4207/glucagon. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator. The actual time of sampling will be recorded in the eCRF.
- Plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.
- Patients will be asked to rate any nausea and/or infusion site pain on 10 cm visual analog scales (VAS) at the beginning of the visit once the infusion sites have been placed but no drug has yet been administered, then approximately at the top of every hour during the visit, and at the end of the visit. Trial staff will also evaluate their infusion sites to document any erythema or edema at the same times. If moderate or severe pain is reported or swelling or redness occurs at the infusion site, the infusion site will be replaced in a different location. If moderate or severe pain, swelling, or redness continues at the old site for more than 30 minutes after the infusion site is removed, or if moderate or severe pain, swelling, or redness occurs at the new site, all infusion sites will be removed and the patient will be discontinued from the study. Any such symptoms will be followed until resolution.
- From the start of closed loop control until approximately Hour 3, the patients will continue to fast.

- Between approximately Hour 3 and Hour 4, patients will be provided with a lunch meal of their choice in the Diabetes Research Center from a menu of choices from nearby restaurants. They will be asked to choose a meal that is a "typical meal" for them. The content of their meal will not be restricted in any way, with the exception that the number of carbohydrates should be in the "typical" range for them at lunch, and that they must eat the same meal at the same time during both visits.
- At approximately 15 minutes before the meal, patients will administer a bolus for the meal with their own insulin pump based on the carbohydrate count for the meal.
- After lunch is completed, the patients will not be allowed any carbohydrate intake (non-caloric drinks will be permitted) until the trial is completed (except as necessary to treat hypoglycemia), to allow the BP to control the post-prandial BG without further interruption.
- Between approximately Hour 6 and Hour 7, the patients will start a period of structured exercise.
- At the start of the exercise period, patients will restore their normal basal insulin profile so that they will not have elevated insulin levels at the end of the study period when they are to transition back to their usual care.
- Patients will exercise on a stationary bike with a heart rate from 120-140 beats per minute for a total of 4,000 heart beats (approximately 30 minutes). Patients will rate their exercise intensity using the Borg scale every 5 minutes, with the target intensity level between 12 and 14. Heart rate will be measured every 5 minutes.
- BG measurements will be obtained off of the IV line every 10 minutes. If BG is <80 mg/dL, BG measurements will be obtained off of the IV line every 5 minutes.
    - Carbohydrates will be given for any BG <50 mg/dL according to the following protocol: Dextrose (g) = BSA (m^2)/[1.7 m^2 (women) or 1.9 m^2 (men)] *15 g.
    - Repeat treatments will be given at 15-minute intervals as long as BG remains <50 mg/dL.
- If there is an interruption in the Dexcom CGM output, trial staff will assist the patient in recovering CGM data streaming. If this requires replacement of the CGM sensor, BGs will be checked every 10 minutes (every 5 minutes if BG is <80 mg/dL) using blood from the IV until the CGM is able to be calibrated again. These BGs will be entered into the BP, which will treat them as CGM values and dose insulin and/or glucagon appropriately.
- If there is a complete failure of the BP operation, patients will take over their own BG control using their personal insulin pump until the BP can be brought back online. If BP control cannot be promptly resumed (e.g., within 30 minutes), the patient may be asked to repeat that trial day once.
- Patients may choose to withdraw from the trial at any time. If they withdraw from the trial, they should alert a provider immediately.
- Just prior to the end of the study visit, vital signs including body temperature and blood pressure will be obtained and a 12-lead ECG will be performed.
- After approximately Hour 8, but not earlier than at least 60 minutes after end of exercise, the BP will be stopped and the patient will continue with their personal insulin pump.

- If the patient experiences seizure or unconsciousness, persistent nausea or vomiting, diabetic ketoacidosis, persistent hyperglycemia with ketonemia, hemodynamic changes such as hypotension, or other medically significant findings, a longer observation period at the trial site may be necessary until the patient is considered stable for discharge. If the Investigator or trial staff determines that the patient requires further observation or treatment, the patient may be transferred to the emergency room for additional monitoring and/or medical care. At discharge, patients will be provided with any necessary instructions concerning personal insulin pump usage, food intake, and driving arrangements.
- The maximum amount of blood loss per study visit will be approximately 230 mL. The total blood loss for the entire study will be up to 460 mL.
- Patients will answer questionnaires (see Appendix C).
- Chemistry and hematology samples will be collected at visit end (see Appendix B).
- The BP and glucose meters will be collected and downloaded.
- A trial MD will review the last several hours of insulin and glucagon dosing and assist the patient in resuming their usual diabetes care. A longer observation period at the trial site may be necessary. Patients will be instructed to call trial staff with any questions, issues, or concerns.

7.4.2 Data Collected During the Treatment Visits

- CGM glucose every 5 minutes from the Dexcom G4 Platinum CGM
- All BG measurements taken
- Insulin total dose by the BP and the patient's own insulin pump
- Glucagon total dose
- Timing and content of the meal eaten and carbohydrate amount
- Timing of meal announcement and size of meal announced
- Timing and glucose values at calibrations
- Timing and amount of carbohydrates taken for hypoglycemia
- Data from a questionnaire about attitudes and expectations regarding the BP before and after each treatment arm (see Appendix C)
- Time patients were not under BP control for any reason
- List of technical faults associated with the BP including cause and resolution
- ZP4207/glucagon sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.
- Plasma glucose sampling will be collected at least hourly in parallel with ZP4207/glucagon exposure sampling. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
- Nausea and infusion site pain on a VAS at visit start (after insertion and before any drug administration), hourly, and at visit end
- Infusion site reaction according to the Draize scale at visit start (after insertion and before any drug administration), hourly, and at visit end
- Patient reports of symptoms, any other complaints, and AEs
- Vital signs including body temperature and blood pressure (at visit start and visit end) and weight
- Concomitant medications

[redacted]

- Chemistry and hematology samples (see Appendix B) at visit start and visit end
- ADA (Visit 3 only)
- 12-lead ECG at visit start and visit end
- Urine HCG pregnancy test for women of childbearing potential

7.4.3 Response to Hypoglycemia

- Patients are encouraged to check their BG for any symptoms of hypoglycemia.
- Patients will be permitted to take 15 grams of carbohydrates for any BG value <60 mg/dL. Trial staff will ensure proper functioning of the BP, infusion set, and insulin pump, and will encourage the patient to wait for the BP to treat the low blood sugar for as long as they feel comfortable.
- Patients will be required to take 15 grams of carbohydrates for any BG value <50 mg/dL. After treatment of hypoglycemia, a follow-up measurement will be taken 15 minutes later. Repeated measurements will be taken every 15 minutes until the BG is >60 mg/dL. Treatment will be repeated if subsequent BG values are still <50 mg/dL. All carbohydrate treatments for hypoglycemia will be documented by trial staff (amount and time).
- Trial staff will check the infusion site, BP, and insulin pump for normal operation any time hypoglycemia occurs. If there is any suspicion of infusion set malfunction, the site should be replaced. Trial staff will check the BP for any malfunction and correct any problems that are found.
- If no correctable fault is found, but there is doubt regarding the correct function of the BP system, an entirely new backup BP system may be started.
- If a patient experiences a seizure or unconsciousness associated with hypoglycemia, his or her participation in the trial will be discontinued.

7.4.4 Response to Hyperglycemia

- Trial staff will check the infusion site, BP, and insulin pump for normal operation any time BG is >300 mg/dL. If there is any suspicion of infusion set malfunction, the site should be replaced. Trial staff will check the BP for any malfunction and correct any problems that are found. If the BG remains >300 mg/dL for 2 hours despite troubleshooting, blood ketones will be measured. If the blood ketone result is >1.5 mmol/L, the visit will be stopped and rescheduled. The patient will be provided with insulin and a syringe to give an injection based on their correction factor.
- If a patient experiences diabetic ketoacidosis, his or her participation in the trial will be discontinued.
- If no correctable fault is found, but there is doubt regarding the correct function of the BP system, the treatment visit may be stopped and the visit rescheduled.

7.4.5 Response to Nausea/Vomiting

If significant nausea (e.g., that prevents the patient from eating normally) or any vomiting occurs, trial staff will notify the Investigator. Trial staff will assist the patient in troubleshooting, such as checking BG and the calibration of the CGM (excessive glucagon dosing may occur if the CGM is reading lower than the true BG). If a patient experiences persistent nausea and vomiting thought to be related to glucagon dosing, his or her participation in the trial will be discontinued.

[redacted]

7.4.6 Response to Other Medical Needs

If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.

7.4.7 Monitoring of Bionic Pancreas Performance

Bionic pancreas inventors and developers [redacted], [redacted], and/or an engineer trained by them will be readily available by phone for consultation for the trial staff at all times during the course of the trial.

7.4.8 Supervision by Trial Staff

A trial MD will be on call at all times during the course of the trial. An RN or MD will be with the trial patients in the Diabetes Research Center at all times.

7.5 Anti-drug Antibodies Assessment Visit (Visit 5)

Patients will return for an ADA Assessment Visit 10 days ±3 days following the last day of dosing (Visit 4) for ADA sampling and a review of AEs and concomitant medications.

7.6 Follow-up Visit (Visit 6)

Patients will return for a Follow-up Visit 25 days ±4 days following the last day of dosing (Visit 4), for chemistry, hematology, and ADA sampling, and a review of AEs and concomitant medications.

8 ENDPOINTS

8.1 Primary Endpoint

The primary endpoint is the safety and tolerability of ZP4207 in the BP using either the iLet or the iPhone platform as assessed by:

- Number and type of AEs
- Clinical laboratory measurements
- Vital signs
- 12-lead ECG
- Local tolerability and infusion site reactions as measured with the Draize scale
- Immunogenicity as measured by ADA
- Pain as measured on a 10 cm VAS
- Nausea as measured on a 10 cm VAS

8.2 Secondary Endpoints

The secondary endpoints include measurements of BP function as well as glycemic and non-glycemic measurements.

8.2.1 Bionic Pancreas Function

This endpoint data will be generated from the BP data during each treatment visit:

- Average percent insulin dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
    - Average percent glucagon/ZP4207 dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts calculated by the BP algorithm that are successfully issued to the pump by the BP (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts calculated by the BP control algorithm that are successfully issued by the BP
    - Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully issued by the BP
- Average percent of 5-minute steps during which the BP is functioning nominally in all respects based on real-time CGM data (new CGM glucose reading captured, dose calculated, and dose issued to pumps)
- Average percent of 5-minute steps during which the BP is functioning nominally with or without a new CGM glucose reading captured (dose calculated and dose issued to pumps). If a CGM signal is not available, the dose calculated may be based on weight or historical basal rates.
- CGM reliability index, calculated as percent of possible values actually recorded by CGM
- CGM Mean Absolute Relative Difference versus time-stamped BG values from meter download
- List of technical faults associated with the BP including cause and resolution

8.2.2 Glycemic

All of following metrics will be generated from the Dexcom G4 Platinum CGM data during each treatment visit:

- Fraction of time spent within each of the following glucose ranges:
    - <50 mg/dL
    - <60 mg/dL
    - <70 mg/dL
    - 70-120 mg/dL
    - 70-140 mg/dL
    - 70-180 mg/dL
    - >180 mg/dL
    - >250 mg/dL
    - >300 mg/dL
- Number of severe hypoglycemic events (patients unable to self-treat, requiring the assistance of another person)

[redacted]

- Number of episodes of symptomatic hypoglycemia
- Number of carbohydrate interventions for hypoglycemia
- Total grams of carbohydrates taken for hypoglycemia
- Mean CGM glucose

8.2.3 Non-glycemic

- Glucagon/ZP4207 total delivery per kg of body mass
- Insulin total delivery per kg of body mass
- Number of unscheduled infusion set replacements
- Number of unscheduled CGM sensor changes

9 LABORATORY ASSESSMENTS

Descriptions of sample handling and sample processing, storage, and shipment at the site will be included in the laboratory manual.

The responsible laboratories are listed in the address list.

9.1 Safety Laboratory Assessments

Chemistry and hematology samples will be collected at specified time points. See Appendix A for the schedule of procedures and Appendix B for a list of clinical laboratory analytes.

9.2 Pharmacodynamic Assessments (Plasma Glucose)

At Visit 3 and Visit 4, plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.

9.3 Exposure Assessments (ZP4207 and Glucagon)

At Visit 3 and Visit 4, ZP4207/glucagon exposure sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator. The actual time of sampling will be recorded in the eCRF.

Bioanalytical Reports will be prepared.

9.4 Anti-drug Antibodies Assessments

Blood samples (including back-up samples) for serum anti-ZP4207 and anti-glucagon antibodies will be taken at Visit 3, the ADA Assessment Visit (Visit 5), and the Follow-up Visit (Visit 6). Any patient that tests positive for ADA will be monitored until the ADA levels return to baseline.

Bioanalytical Reports will be prepared.

[redacted]

10 SAFETY REPORTING

10.1 Adverse Events

An AE is any untoward medical occurrence in a trial patient administered an IMP and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP. Patients should be instructed to report any AE they experience to the Investigator.
Note: This includes events from the first trial-related activity from Visit 3.

AEs for ZP4207 include:

- A clinically significant worsening of a concomitant illness
- A clinical laboratory abnormality which is clinically significant, i.e., any abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example, change of medicine dose or more frequent follow-up due to the abnormality.
- Hypoglycemic episodes
- Injection site reactions

The following should **not** be recorded as AEs, if recorded prior to randomization (on the Screening Form or the eCRF):

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial-related activity from Visit 3.
- Pre-existing conditions found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).

For known (listed) AEs for Glucagon and Humalog, please refer to SPC for Glucagon and Humalog.

10.1.1 Follow-up of Adverse Events

All AEs that are ongoing at the end of the patient's participation in the trial will be followed-up until the event is resolved or reaches a satisfactory outcome as deemed by the Investigator. Follow-up actions for all serious adverse events (SAEs) will be performed according to appropriate clinical care practices and may depend on the nature of the event. These will be determined after internal review and/or Sponsor review. The follow-up information should only include new (updated and/or additional) information that reflects the situation at the time of the Investigator's signature.

Follow-up information on (S)AEs will be updated using the (S)AE Form. If a non-serious event becomes serious during the follow-up, the AE Form and SAE Form must be used and reporting timelines follow those of an SAE.

The Investigator must forward follow-up information on SAEs, and if previously non-serious AEs become SAEs, to the Sponsor.

[redacted]

10.1.2 Precautions

Normal precautions taken for a human trial will be taken during this trial. Qualified and well-trained physicians and medical staff will instruct the patients. During a patient's participation in the trial, the Investigator should ensure that adequate medical care is provided to the patient for any AEs, including clinically significant laboratory values related to the trial. The Investigator should inform the patient when medical care is needed for intercurrent illnesses of which the Investigator becomes aware.

For further information on safety precautions for ZP4207, Lilly glucagon, and Lilly Humalog, please refer to the current version of the Investigator's Brochure (IB) for ZP4207 (Zealand Pharma A/S, 2015, or any updates hereof), and the SPC for Glucagon (Eli Lilly, 2012) and Humalog (Eli Lilly, 2015), respectively.

10.1.3 Assessment of Adverse Events by the Investigator

Intensity of an Adverse Event
The maximum intensity (severity) of all AEs must be assessed by the Investigator and documented. Severity should be graded when the AE outcome is known:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

A "severe" reaction does not necessarily deem the AE as "serious," and an SAE may not be "severe" in nature.

Causality Relationship to IMP
Insulin (insulin lispro, Lilly Humalog), glucagon (glucagon for injection, Eli Lilly), and ZP4207 are all regarded as IMP.

The causality of each AE should be assessed by the Investigator according to the following classification:

- Related: Good reason and sufficient documentation to assume a causal relationship.
- Not related: No relationship to trial product can be established.

Outcome of an Adverse Event
The outcome of all AEs must be assessed by the Investigator and documented by his/her staff. The following definitions should be used:

- Recovered/resolved: The patient has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity from Visit 3.
- Recovering/resolving: The condition is improving and the patient is expected to recover from the event. This term is only applicable if the patient has completed the trial.

[redacted]

- Recovered/resolved with sequelae: The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment, or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- Not recovered/not resolved: The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known.
- Fatal: This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as "recovered/resolved," "recovering/resolving," "recovered/resolved with sequelae," or "not recovered/not resolved." An AE with a fatal outcome must be reported as an SAE.
- Unknown: This term is only applicable if the patient is lost to follow-up.

10.2 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Medically important

Medical judgement must be exercised in deciding whether an AE is believed to be "medically important." Medically important events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above.

Suspected Unexpected Serious Adverse Reactions (SUSAR)
A SUSAR is an AE fulfilling 1 of the criteria of seriousness and being assessed as related to an IMP, the nature or severity of which is not consistent with the applicable reference document (e.g., ZP4207 IB or package leaflet/SPC for an approved product).

Unanticipated Adverse Device Effect (UADE)
A UADE is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

10.3 Adverse Event Reporting – Procedures for Investigators

The Principal Investigator and co-investigators will review any AEs and report any SAEs to the Sponsor as soon as possible and within 24 hours of obtaining knowledge of the event. The Principal Investigator and co-investigators will promptly report AEs to the Partner's Institutional Review Board (IRB) and to the BU IRB (unless oversight is ceded by the BU IRB to the Partners IRB), in accordance with local requirements.

Ed Damiano is the Sponsor of the Investigational Device Exception for the BP and Zealand Pharma A/S is the Sponsor of the IND for ZP4207.

[redacted]

Reports of AEs will be submitted to the FDA in compliance with the terms of the Code of Federal Regulations.

All events meeting the definition of an AE must be collected and reported from the first trial-related activity from Visit 3 until the end of the post-treatment follow-up period. At each contact with the site (visit or telephone, excluding safety visits, where the patient is not seeing the Investigator or staff [e.g., visits to the laboratory], the patient must be asked about AEs. All AEs, either observed by the Investigator or reported by the patient, must be recorded by the Investigator and evaluated.

The Investigator should record the diagnosis, if possible. If no diagnosis can be made, the Investigator should record each sign and symptom as individual AEs.
All AEs must be recorded by the Investigator. One single AE Form must be used per AE from start to resolution. For SAEs, the SAE Form must also be completed.

AE information should include the following:

- Patient identification number on all pages
- Date and time of treatment start
- Date and time of onset and date of outcome
- Date and time of Investigator's first information on the (S)AE
- Seriousness
- Severity
- Causal relationship with IMP ZP4207
- Causal relationship with IMP insulin
- Causal relationship with IMP glucagon
- Causal relationship with medical device
- Causal relationship with procedures
- Interruption or withdrawal of treatment with IMP or medical device and other measures taken
- Outcome

All AEs are coded; details are described in the trial specific Data Management Plan.

The Investigator must report initial information in writing on the SAE Form for all SAEs to the Sponsor's responsible pharmacovigilance unit (here: Lindeq) immediately (within 24 hours) after obtaining knowledge about the event.

Name: [redacted]
Company: Lindeq
Address: Lyskær 8, 2730 Herlev, Denmark
Tel: [redacted]
Fax:
Mobile:
E-mail: drugsafety@lindeq.com

In addition and meeting the same timeline, Investigators must report all SAEs to Zealand Pharma A/S by forwarding the SAE Form electronically within 24 hours of obtaining knowledge of the event to the representatives of Zealand Pharma A/S.

Names: [redacted] and [redacted]
Address: Smedeland 36, DK-2600 Glostrup, Denmark
Tel: [redacted]
E-mails: [redacted]

It is the responsibility of Lindeq to report all SUSARs that occur in this trial to the Competent Authorities and to the Investigators. It is the responsibility of the Investigators to report the SUSARs to the IRBs in accordance with the local requirements in force and the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP). The trial monitor must be informed accordingly.

It is the responsibility of Lindeq to report all serious adverse reactions on insulin lispro and glucagon for injection to the Eli Lilly Pharmacovigilance department within 5 days.

It is the responsibility of the Investigators to report all UADEs to Beta Bionics within 24 hours of the time they are detected. It is the responsibility of the Investigators to report all UADEs to the IRB in accordance with the local requirements in force and the ICH GCP. It is the responsibility of Beta Bionics to report all UADEs to the Competent Authorities.

All device deficiencies should be documented and should be reported to Beta Bionics within 24 hours. Device deficiencies are inadequacies of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

Name: [redacted]
Company: Beta Bionics, Inc.
Address: Business Innovation Center, Photonics Center, 8 Saint Mary's Street, Suite 936
Boston, Massachusetts 02215-2421, United States
Tel: [redacted]
E-mail: [redacted]

10.4 Pregnancy Reporting

Female patients must be instructed to notify the Investigator immediately if they become pregnant or if they suspect to be pregnant during the trial. The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical trial.

Male patients must be instructed to notify the Investigator immediately if their partner becomes pregnant or suspects to be pregnant. The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical trial. During an information meeting at the trial site, the patient's partner will be fully informed by a physician of her participation in capturing the outcome data, and will be asked to provide her written consent.

The Investigator must report all information on pregnancies, including AEs in the patient/patient's partner, the fetus, and newborn infant/ toddler. The pregnancy report must be forwarded to the Sponsor preferably electronically as PDF or by fax.

The Investigator must follow the pregnancy until the pregnancy outcome and the newborn infant(s) until the age of 1 month. The Investigator must collect information on the pregnancy and pregnancy complications as well as the pregnancy outcome including the health of the newborn infant(s) on the pregnancy forms.

The following must be collected:

- Initial information of the pregnancy
- Information on the outcome of the pregnancy, including the health status of the newborn infant(s) at the age of 1 month
- All AEs in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms. It must be clear in the description if the event occurs in the patient/patient's partner, the fetus, or the newborn infant.
- All SAEs in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms following the same timelines as required for other SAEs. It must be clear in the description if the event occurs in the patient/patient's partner, the fetus, or the newborn infant.

The SAEs that must be reported include abnormal outcome – such as congenital anomalies, fetal death, and termination of pregnancy (spontaneous or elective abortion), including any anomalies of the fetus observed at gross examination or during autopsy – as well as other pregnancy complications (ectopic pregnancy) fulfilling the criteria of an SAE.

10.5 Hypoglycemia

Hypoglycemia will be regarded as an AE and will be recorded and documented on an AE Form. For the purposes of AE reporting, the following definitions of hypoglycemia will be used:

- Symptomatic hypoglycemia: an event during which typical symptoms of hypoglycemia are accompanied by a BG concentration ≤70 mg/dL
- Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with a BG concentration ≤50 mg/dL
- Severe hypoglycemia: an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions

10.6 Safety Monitoring

10.6.1 Data and Safety Monitoring Board

An external DSMB will oversee the conduct of the trial, as set forth in the DSMB Charter. Additionally, the DSMB will be informed in the event of any serious and unexpected AEs. The DSMB will be informed if there are any changes to the trial protocol that could significantly impact the safety or scientific validity of the trial. A final DSMB meeting will convene after the completion of the trial.

The participation of individual patients will be discontinued if they experience:

- Seizure or unconsciousness associated with hypoglycemia and associated with participation in the trial
- Persistent nausea and vomiting thought to be related to glucagon dosing associated with participation in the trial
- Hospitalization associated with participation in the trial
- Pregnancy
- Diabetic ketoacidosis

If more than 1 patient must be withdrawn from the trial for these reasons, the trial will stop and a vote of the DSMB will be required to restart it. All AEs that are serious and unexpected but related will be reported to the DSMB within 5 working days.

[redacted]

Note that patients may discontinue participation at any time. Patients may be removed from the trial for other reasons, for instance, failure to comply with trial procedures or intercurrent illness that is unrelated to the BP but that precludes safe participation. Discontinuation of participation for these reasons will not contribute to a decision to discontinue the trial.

10.6.2 Zealand Pharma Safety Committee

The internal Zealand Pharma Safety Committee is constituted to perform ongoing safety surveillance of clinical trials within ZP4207, including this trial.

If safety signals are observed either based on reported SAEs, periodic review of laboratory parameters, planned review of all AEs reported between the safety committee meetings, or on notification of significant findings, the Safety Committee will take appropriate measures to safeguard the patients.

11 STATISTICS

For all analysis, the 2 treatment arms from Part 1 (iPhone-based BP) will be compared, and the 2 treatment arms from Part 2 (iLet) will be compared. The analysis of Part 1 will be completely separate from the analysis of Part 2.

11.1 Analysis Populations

The following analysis sets are defined in accordance with the ICH-E9 guidance:

The Full Analysis Set is based on the intention-to-treat principle and includes all randomized patients. In exceptional cases, patients from the Full Analysis Set may be excluded (will be decided in the database review [DBR] meeting). In such cases, the exclusion will be justified and documented. Patients will contribute to the evaluation “as randomized.”

The Per-Protocol Set includes all patients of the Full Analysis Set who completed the trial without any major protocol violations. Patients in the Per-Protocol Set will contribute to the evaluation “as treated.” This analysis will only be used if it is different than the Full Analysis Set.

The Safety Analysis Set includes all patients receiving at least 1 dose of the IMP. Patients in the Safety Analysis Set will contribute to the evaluation “as treated.”

Analyses of efficacy endpoints will be based on the Full Analysis Set (and the Per-Protocol Set if necessary). This decision will be made in the DBR meeting. The analysis of the safety endpoints will be based on the Safety Analysis Set.

Before data are released for statistical analysis, a blinded review of all data will take place to identify protocol deviations that may potentially affect the results. At this time, it will be determined if patients and/or data should be excluded from the analysis. Furthermore, outliers will be identified by data review according to ICH-E9.

Obviously erroneous data points may be excluded from the analyses or re-analyzed (e.g., serum concentrations). The decision to re-analyze or exclude data points from the statistical analysis is the joint responsibility of the Sponsor, the Principal Investigator, and the Trial Statistician.

[redacted]

The patients or observations to be excluded and the reason for their exclusion will be documented and signed by those responsible prior to database release. The documentation will be stored together with the remaining trial documentation. The patients and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

11.2 Statistical Methods

Medpace will be responsible for the statistical analysis. The statistical planning and conduct of analyses of the data from this trial will follow the principles defined in relevant ICH guidelines and Medpace's biostatistical standard operating procedures (SOPs). A general description of the statistical methods to be used is given in this section, specific details will be provided in the Statistical Analysis Plan (SAP), which will be prepared before database lock. All statistical analyses will be performed using SAS® (SAS Institute Inc., Cary, North Carolina, USA), version 9.3 or later.

11.2.1 Analysis of Safety

The following variables will be evaluated according to treatment for safety purposes:

Adverse Events
All AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Individual AEs will be presented in a listing including relationship to trial product/device, severity, and treatment period at onset. If more than 20 treatment-emergent AEs (AEs with onset after [first] dosing at Visit 3 until the Follow-up Visit 6) are registered, a summary table including number of AEs, number of patients with at least 1 AE, and percentage of exposed patients with at least 1 AE will be made by system organ class and treatment period at onset.

Local Tolerability
Local tolerability at the injection site will be summarized using descriptive statistics as appropriate.

Laboratory Safety Assessments
Laboratory assessments will be summarized. A listing of abnormal values will be provided.

Physical Examination
A frequency table will show the number and percentage of physical examination results.

Vital Signs
Vital signs will be summarized using descriptive statistics.

12-lead ECG
The Investigator's evaluations of 12-lead ECGs will be summarized and abnormal individual evaluations will be listed together with the Investigator's comments. Changes in 12-lead ECG between measurements will be recorded as AEs if the Investigator judges them to be clinically significant.

11.2.2 Analysis of Efficacy

The analysis of BP function endpoints and glycemic endpoints will be on an intention-to-treat basis. In cases where a treatment arm was not completed (and that arm was not repeated according to protocol criteria), available data from that arm will be used in the data analysis.

The Shapiro-Wilk test will be used to determine the normality of the residuals for each comparison. Summary tables that display descriptive statistics, including percentages, means or medians, and standard deviation and/or ranges, as appropriate, will be provided.
A paired t-test or the Wilcoxon signed rank test for comparison of means with normally or non-normally distributed residuals, respectively, will be used. In a secondary analysis, any period effect and any interaction between treatment and period will be looked for, although no such interaction is predicted for the efficacy outcome. Further details will be included in the SAP.

The number of patients and proportions of severe hypoglycemic events, symptomatic hypoglycemia, and carbohydrate interventions due to hypoglycemia with the event counts will be summarized descriptively, and the proportions will be analyzed by a Fisher's exact test if data allow.

11.2.3 Interim Analysis

An interim database lock may occur upon completion of Part 1 of the trial to analyze the iPhone-based BP data.

11.2.4 Sample Size Determination

No formal sample size calculations were made. It is expected that between 20 and 24 patients will be randomized in the trial. The sample size is based on a clinical rather than statistical rationale. The sample size is considered adequate to address the primary trial objective of exploring the safety of ZP4207 when used in the BP and with reference to Lilly glucagon used in the BP.

12 DATA MANAGEMENT AND RECORD KEEPING

Data Management is the responsibility of Medpace. The complete Data Management process will be described in detail and agreed on in the Data Management Plan for this trial.

12.1 Data Handling

Case Report Forms
Electronic Case Report Forms will be used in this trial. The Data Management Department of Medpace will provide the eCRFs. All further information regarding the eCRFs and the data flow will be described and agreed on in the Data Management Plan.

Device-Related Data
During the trial, CGM data, calibration data, insulin dosing data, and glucagon dosing data will be automatically stored in the BP device (from which it will be downloaded at intervals), combined in a single database that will be compared against the primary data files for integrity, and ultimately transferred to Medpace.

[redacted]

12.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

12.3 Data Entry

Data must be recorded using the electronic data capture (EDC) system as the trial is in progress. The patient questionnaires will be transcribed into the EDC system by site personnel. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct trial data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

12.4 Medical Information Coding

Adverse events and medical history will be coded using the latest version of MedDRA. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary.

12.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

12.6 Record Keeping

Medpace will be responsible for hosting the TMF. Records of patients, source documents, monitoring visit logs, eCRFs, inventory of trial product, regulatory documents, and other Sponsor correspondence pertaining to the trial must be kept in the appropriate trial files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the evaluation and reconstruction of the clinical trial. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Trial Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

13 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

13.1 Ethical Conduct of the Trial

The trial will be conducted according to Medpace, MGH, and/or the Sponsor's written instructions (SOPs, working instructions, or process descriptions). Content and definitions of the written instructions are based on the Declaration of Helsinki and the ICH GCP.

[redacted]

13.2 Institutional Review Board

Written favorable opinion must be obtained from the responsible IRB prior to commencement of the trial. Clinical trial submission and reporting requirements before, during, and after completion of the trial will be performed in accordance with national law and local regulations.

All amendments that affect patient safety or the trial integrity (substantial amendments) must not be implemented before favorable opinion has been obtained, unless necessary to eliminate hazards to the patients. Non-substantial amendments do not require favorable opinion by the IRB, but the respective IRB will be notified according to local requirements.

The Sponsor and Investigator must approve any amendment in writing before its implementation.
The Sponsor must maintain an accurate and complete record of all submissions made to the IRB. The records should be filed in the Sponsor's Trial Master File (TMF).

13.3 Informed Consent

In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirement(s) and adhere to the ICH GCP guideline and the requirements in the Declaration of Helsinki.

Prior to any trial-related activity, the Investigator must give the patient oral and written information in a form that the patient can read and understand about all aspects of the trial that are relevant to the patient's decision to participate. The patient will be given ample time to decide whether or not to participate in the trial.

The patient must be informed that his/her personal trial-related data will be used in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by authorized monitors or Clinical Quality Assurance auditors appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

A voluntary, personally signed and dated ICF must be obtained from the patient prior to any trial-related activity. The ICF must also be signed and dated by the physician or designee who conducted the informed consent procedure. A signed copy of the ICF and any additional patient information must be given to each patient.

The responsibility for taking informed consent must remain with that of a research physician or designee. If information becomes available that may be relevant to the patient's willingness to continue participating in the trial, the Investigator must inform the patient in a timely manner, and a revised written informed consent must be obtained.

Should a protocol amendment become necessary, the ICF may need to be revised to reflect the changes to the protocol. It is the responsibility of the Sponsor to ensure that an amended consent form is reviewed and has received favorable opinion from IRB, and the Investigator must ensure that the amended consent form is signed by all patients subsequently entered into the trial and those currently in the trial, if affected by the amendment.

[redacted]

13.4 Trial Monitoring Requirements

The monitoring procedures for this trial are described in detail in the Monitoring Manual. The objectives of the monitoring procedures are to ensure that (i) the safety and rights of the trial patients are respected, (ii) that accurate, valid, and complete data are collected, and (iii) that the trial is conducted in accordance with the trial protocol, the principles of GCP, and local legislation, including drug accountability.

The monitor must be given direct access to the investigational site files and source documents (original documents, data, and records). Direct access includes permission to examine, analyze, verify, and reproduce any record(s) and report(s) that are important to evaluation of the clinical trial.

Key tasks of the monitor include verifying the presence of informed consent, the adherence to the inclusion/exclusion criteria, the documentation of SAEs, and the recording of all safety and efficacy variables. The monitor will also confirm the completeness of patient records, the adherence to the protocol, ICH GCP, and the progress in patient enrollment and perform drug accountability.

Because no information that could reveal the identity of patients may ever be removed from the trial site, the monitor will visit the site at regular intervals to perform these monitoring tasks. Other contact between the Investigator and monitors will be maintained as required through telephone calls and e-mail. The Investigator and/or key members of staff involved in the trial must be available to assist the monitors during all visits.

Site Initiation Visit
During the Site Initiation Visit (SIV) the CRO, Sponsor, and/or monitors will go through information on the IMP, the protocol, the eCRFs, and other key aspects of the trial with the Investigator and the key members of staff involved in the trial. The topics of the SIV are documented in a SIV report made available to the Investigator. Documentation on the SIV (e.g., power point presentation) should be filed by both Investigator and Sponsor.

13.5 Disclosure of Data

Data generated by this trial must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the trial is confidential and disclosure to third parties other than those noted above is prohibited.

13.6 Retention of Records

Massachusetts General Hospital will maintain the patient's medical file according to local regulations. MGH will archive the documentation pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. MGH should not destroy any documents without prior permission from the Sponsor.

The documentation includes all the raw data generated during the clinical trial, the investigational site files, and a copy of the clinical trial report. The documents will be retained

[redacted]

for a period of at least 15 years at archives by MGH, or its sub-contractor. After this period, the Sponsor will be contacted and their advice sought on the return or further retention of the trial records.

The Sponsor will maintain the documentation pertaining to the trial in accordance with national regulations.

13.7 Publication Policy

The Principal Investigator of the trial will review and sign the clinical trial report. A summary of the final clinical trial report will be submitted to the IRB and Competent Authority.

According to the Declaration of Helsinki Investigators and Sponsors "have ethical obligations with regard to the publication and dissemination of the results of research." The trial design and results may be published as 1 or more original research manuscripts/abstracts and presented at a scientific meeting. The Investigator and Sponsor reserve the right to review any proposed presentation of the results of this trial before they are submitted for publication. Authorship on any publication(s) resulting from this clinical trial will be assigned according to the recommendations of the International Committee of Medicinal Journal Editors.

Participating patients will not be identified by name in any published reports about the clinical trial.

The Sponsor is responsible for trial registration at ClinicalTrials.gov (www.clinicaltrials.gov) according to the requirements from the FDA.

13.8 Legal Aspects

An implicit or explicit approval must be obtained from the Competent Authority prior to commencement of the trial. Clinical trial submission and reporting requirements before, during, and after completion of the trial will be performed in accordance with national law and local regulations.

An implicit or explicit approval will also be mandatory before implementation of substantial changes. Non-substantial amendments do not require approval from the Competent Authority but will be notified according to local requirements.

The Sponsor and Investigator must approve the amendment in writing before its implementation.

The Sponsor must maintain an accurate and complete record of all submissions made to the Competent Authority. The records should be filed in the Sponsor's TMF.

Audits and Inspections
In the event of an audit, representatives of the Sponsor or designee, or national and international regulatory authorities may request access to all trial records for inspection and copying. Such access must be stated in the ICF signed by the patient.

[redacted]

13.9 Sponsor Discontinuation Criteria

The Sponsor, Investigator, or a pertinent regulatory authority may decide to stop the trial or part of the trial at any time but agreement on procedures to be followed must be obtained.

Conditions that may warrant termination of the clinical trial include, but are not limited to:

- Safety or administrative reasons
- The discovery of an unexpected, relevant, or unacceptable risk to the patients enrolled in the clinical trial
- A decision of the Sponsor to suspend or discontinue investigation of the IMP

If the trial is prematurely terminated or suspended, the Investigator should promptly inform the patients and assure appropriate therapy and follow-up. Furthermore, the Sponsor should promptly inform the IRB and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.
If after the termination of the trial the risk/benefit analysis has changed, the new evaluation should be provided to the IRB in case it will have an impact on the planned follow-up of the patients who have participated in the trial. Necessary actions needed to protect the patients should be described.

13.10 Patient Compensation

Financial compensation will be provided to all patients who complete the Screening Visit. Patients will be paid $25 for completing the Screening Visit whether or not they are eligible to participate in the trial. Patients will be compensated $25 for completing the Training Visit. Patients will be compensated $100 for completing each of the 2 treatment visits, $25 for completing the ADA Assessment Visit, and $25 for completing the Follow-up Visit. Thus, the total compensation for a patient who completes the trial would be $300. Patients who are unable to complete the trial or choose to stop participation will receive prorated compensation for each visit. In addition to the monetary compensation, the cost of the patients' lunch meals during their participation in the trial, as well as the patients' parking at each visit, will be covered by trial funds.

14 TRIAL ADMINISTRATIVE INFORMATION

14.1 Protocol Amendments

Any amendments to the trial protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

[redacted]

14.2 Address List

14.2.1 Sponsor

Zealand Pharma A/S
Smedeland 36
DK-2600 Glostrup (Copenhagen)
Denmark
Telephone: +45 88 77 36 00
Facsimile: +45 88 77 38 98

14.2.2 Supplier of Device

[redacted], PhD
Beta Bionics, Inc.
Business Innovation Center, Photonics Center
8 Saint Mary's Street, Suite 936
Boston, Massachusetts 02215-2421
United States
Tel: [redacted]

14.2.3 Principal Investigator (Site)

Steven J. Russell, M.D., Ph.D.
MGH Diabetes Center
50 Staniford Street Suite 301
Boston, Massachusetts 02114
Telephone: [redacted]
Facsimile: [redacted]

14.2.4 Contract Research Organization (Including Monitoring)

Medpace, Inc.
5375 Medpace Way
Cincinnati, Ohio 45227
Telephone: +1-513-579-9911
Facsimile: +1-513-579-0444

14.2.5 Medical Monitoring

Medpace Clinical Safety
5375 Medpace Way
Cincinnati, OH 45227
United States
Telephone: +1-800-730-5779, ext. 2999 or +1-513-579-9911, ext. 2999
Facsimile: +1-866-336-5320 or +1-513-579-0444
E-mail: medpace-safetynotification@medpace.com

14.2.6 Pharmacovigilance

Lindeq
Lyskær 8
2730 Herlev
Denmark
Telephone: [redacted]
Facsimile: [redacted]
Mobile: [redacted]
E-mail: drugsafety@lindeq.com

14.2.7 Central Laboratory (Safety Laboratory and Plasma Glucose)

Medpace Reference Laboratories, LLC
5365 Medpace Way
Cincinnati, OH 45227
United States
Telephone: +1-513-366-3270
Facsimile: +1-513-366-3273

14.2.8 Special Laboratory (ZP4207 Exposure and ADA Analyses)

Unilabs – York Bioanalytical Solutions
[redacted]
Cedar House
Northminster Business Park
Upper Poppleton
York YO26 6QR
Great Britain
Telephone: [redacted]
Facsimile: [redacted]

14.2.9 Special Laboratory (Glucagon Exposure)

MLM Medical Labs GmbH
Dr. [redacted]
Dohrweg 63
D-41066 Mönchengladbach
Germany
Telephone: [redacted]
Facsimile: [redacted]

15 REFERENCES

1. Russell SJ, El-Khatib FH, Sinha M, et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. N Engl J Med. 2014;371(4):313-325.
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9. ICH Harmonised Tripartite Guideline. Statistical Principles for Clinical Trials E9. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf. 5 February 1998.
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Clinical Trial Protocol
ZP4207-16051

Version number: 6.0
Amendment 5.0
Date: 09 September 2016

APPENDIX A: SCHEDULE OF PROCEDURES – PARTS 1 AND 2

Trial Visit	Visit 1 [1] Screening	Visit 2 Training	Visit 3 [2] [3] [4] [5] (1st Treatment Visit)	Visit 4 [2] [3] [5] (2nd Treatment Visit)	Visit 5 ADA Assessment Visit [6]	Visit 6 Follow-Up [7]
Informed consent	X					
Assess/confirm elig bility	X	X				
Demographics	X					
Medical, surgical, and social history; allergies	X					
Concomitant illness	X					
Concomitant medications	X	X	X	X	X	X
Height, weight, physical examination, and vital signs including body temperature and blood pressure [8]	X		X [9]	X [9]		
12-lead ECG	X		X [10]	X [10]		
Urine HCG pregnancy test and menstrual history [11]	X		X	X		
FSH [12]	X					
Screening labs – HbA1c, optional fractionated metanephrines [13]	X					
Safety lab sampling including chemistry and hematology	X		X [10]	X [10]		X
Training on devices [14]		X				
Monitored BP use			X	X		
Plasma glucose sampling [15]			X	X		
ZP4207/glucagon exposure sampling [16]			X	X		
Nausea and infusion site pain VAS and infusion site reaction Draize scale (visit start [17], hourly, & visit end)			X	X		

[redacted]

Clinical Trial Protocol
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Trial Visit	Visit 1 [1] Screening	Visit 2 Training	Visit 3 [2] [3] [4] [5] (1st Treatment Visit)	Visit 4 [2] [3] [5] (2nd Treatment Visit)	Visit 5 ADA Assessment Visit [6]	Visit 6 Follow-Up [7]
Standardized lunch [18]			X	X		
In-clinic exercise [19]			X	X		
Questionnaires (pre & post BP)			X	X		
ADA			X [20]		X	X
Adverse event review			X	X	X	X

1. Once the patient has been enrolled and eligibility has been established, the order of the treatment visits will be randomized in blocks of 2 patients.
2. In Part 1, each patient will participate in 2 treatment visits: 1 with the iPhone-based BP using ZP4207 and 1 with the iPhone-based BP using Lilly glucagon in a randomized order. In Part 2, each patient will participate in 2 treatment visits: 1 with the iLet using ZP4207 and 1 with the iLet using Lilly glucagon in a randomized order. Up to 2 patients may participate in the trial per day.
3. The night before the visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12 00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window. If BG is <50 mg/dL, treatment with simple carbohydrate is allowed. If the patient experiences persistent hypoglycemia, the visit will be rescheduled within the visit window.
4. Visit 3 will take place at least 48 hours after screening (Visit 1) and no more than 30 days after screening (Visit 1).
5. There will be a 24-hour minimum washout between Visit 3 and Visit 4 and a maximum of 3 weeks between Visit 3 and Visit 4.
6. Visit 5 will take place 10 days ±3 days from Visit 4.
7. Visit 6 will take place 25 days ±4 days from Visit 4.
8. Height and physical examination will be measured at Visit 1 only.
9. Vital signs including body temperature and blood pressure will be obtained at visit start and visit end.
10. At visit start and visit end.
11. Urine HCG pregnancy test only for women of childbearing potential. The date of the last menstrual period in female patients will be obtained at Visit 1 only.
12. Test for FSH level only for postmenopausal women amenorrheic for less than 1 year.
13. If indicated by history.
14. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor, diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits, and trial policies and procedures.
15. Collected at least hourly. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
16. Collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.
17. Once the infusion sites have been placed but no drug has yet been administered.
18. Between approximately Hour 3 and Hour 4.
19. Between approximately Hour 6 and Hour 7.
20. Before the start of dosing.

ADA = anti-drug antibodies; BG = blood glucose; BP = bionic pancreas; CGM = continuous glucose monitor; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HCG = human chorionic gonadotropin; VAS = visual analog scale.

[redacted]

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APPENDIX B: CLINICAL LABORATORY ANALYTES

Chemistry

Alanine aminotransferase	Aspartate aminotransferase
Alkaline phosphatase	Total protein
Albumin	Total and direct bilirubin
Gamma-glutamyl transferase	Glucose
Creatinine	Estimated glomerular filtration rate
Blood urea nitrogen	Uric acid
Bicarbonate	Sodium
Potassium	Calcium
Chloride	Phosphorus

Hematology

Hemoglobin	Hematocrit
Red blood cell count	White blood cell count and differential
Platelets	Mean corpuscular volume
Mean corpuscular hemoglobin	Mean corpuscular hemoglobin concentration

Pregnancy Test
A urine HCG pregnancy test will be performed at screening, Visit 3, and Visit 4 only for women of childbearing potential.

Anti-drug Antibodies Assessments
Blood samples (including back-up samples) for serum anti-ZP4207 and anti-glucagon antibodies will be taken prior to first dosing (Visit 3), at the ADA Assessment Visit (Visit 5), and at the Follow-up Visit (Visit 6).

ZP4207/Glucagon Exposure Sampling
At Visit 3 and Visit 4, ZP4207/glucagon exposure sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.

Screening Visit Only
Test for FSH level only for postmenopausal women amenorrheic for less than 1 year
Optional fractionated plasma metanephrines (if indicated by history)
Hemoglobin A1c

[redacted]

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APPENDIX C: BRIEF DESCRIPTION OF QUESTIONNAIRES

Diabetes Treatment Satisfaction Questionnaire – Status (DTSQs)
The DTSQs measures patient satisfaction with diabetes treatment. It consists of a 6 item scale for assessing treatment satisfaction and two additional items assessing perceived frequency of hyperglycemia and hypoglycemia. The DTSQs is meant for adults and older children. Dr. Clare Bradley has produced a version that is appropriate for bionic pancreas studies for this use, along with a version for younger children. It is administered before the intervention. The DTSQs is valid and reliable. Administration time is less than 5 minutes.

Diabetes Treatment Satisfaction Questionnaire – Change (DTSQc)
Although the DTSQ is responsive to treatment changes, ceiling effects are often seen with this instrument, where maximum or close-to-maximum scores at baseline provide little opportunity for registering improvement. The DTSQc contains the same items as the DTSQs version but asks patients to consider their satisfaction with their current treatment compared with their previous treatment. The DTSQc is meant for adults and older children. Dr. Clare Bradley has produced a version that is appropriate for bionic pancreas studies for our use, along with a version for younger children. It is administered during and at the end of the intervention. The DTSQc is valid and reliable. Administration time is less than 5 minutes.

T1-Diabetes Distress Scale (T1-DDS)
The T1-DDS is a 28-item survey that assesses seven sources of diabetes distress for type 1 adults. It captures feelings of powerlessness; management distress; hypoglycemia distress; negative social perceptions by others; eating distress; physician (health care) distress; and friend/family distress. Items are scored on a 6-point scale from not a problem to a very serious problem. It is administered before, during, and at the end of the intervention. The scale is valid and reliable, and has been shown to be sensitive to change over time. Administration time is 5 minutes.

Problem Areas in Diabetes Survey (PAID)
There are three versions of the PAID: Teen (PAID-T), Parent (PAID-P), and Child (PAID-C) versions. This measure of diabetes-specific emotional distress in youth with diabetes and their parents is 26 items. A total score is generated. It is administered before, during, and at the end of the intervention. The PAID-T and PAID-P are valid and reliable. Psychometric analysis of the PAID-C is in progress. Administration time is 5 minutes.

Hypoglycemia Fear Survey (HFS)
There are three versions of the HFS, Adult (HFS), Youth (HFS-Y) and Parent (HFS-P). The HFS measures several dimensions of fear of hypoglycemia among adults with type 1 diabetes. It consists of 23 items and produces two sub-scale scores; a Behavior sub-scale that measures behaviors involved in avoidance and/or over-treatment of hypoglycemia and a Worry sub-scale that measures anxiety and fear surrounding hypoglycemia. The HFS-Y consists of 25 items and the HFS-P consists of 26 items; both produce sub-scale scores similar to the Adult HFS. It is administered before, during, and at the end of the intervention. All versions of the HFS are valid and reliable. Administration time is 5-10 minutes.

[redacted]

Impact of Daily Diabetes Demands (IDDD)
There are four versions of the IDDD; Adult (IDDD-A), Youth (IDDD-Y), Parent (IDDD-P), and Significant Other (IDDD-SO). This instrument measures the burden related to the demands of the daily diabetes regimen and is 22 items. A total score is generated. It is administered before, during, and at the end of the intervention. Psychometric analysis of the IDDD-Y is in progress using the data from the second Bionic Pancreas Camp Study in pre-adolescent children, and of the IDDD-A is in progress using data from the Bionic Pancreas Multicenter Study in adults. Administration time is 5 minutes.

Bionic Pancreas User Opinion Survey (BPUOS)
There are four versions of the BPUOS; Adult (BPUOS-A), Youth (BPUOS-Y), Parent (BPUOS-P), and Significant Other (BPUOS-SO). This measure assessing both the benefits from, and difficulties with, use of the bionic pancreas, and consists of 38 items. A total score is generated. It is administered during and at the end of the intervention. Psychometric analysis of the BPUOS-Y is in progress using the data from the second Bionic Pancreas Camp Study in pre-adolescent children, and of the BPUOS -A is in progress using data from the Bionic Pancreas Multicenter Study in adults. Administration time is 10 minutes.

[redacted]

SUMMARY OF CHANGES DOCUMENT

PROTOCOL NUMBER ZP4207-16051

AMENDMENT NUMBER 4.0

PROTOCOL TITLE: The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

AMENDMENT DATE: 02 September 2016

SUMMARY AND JUSTIFICATION OF CHANGES:

This amendment was developed to indicate that the bionic pancreas (BP) feasibility trial that uses the glucagon analog ZP4207 (Zealand Pharma A/S) will take place in 2 parts. Part 1 will compare the iPhone-based BP using ZP4207 to the iPhone-based BP using Lilly glucagon. Part 2 will compare the iLet using ZP4207 to the iLet using Lilly glucagon. Patients can only participate in 1 part of the trial. The cross-over design with inclusion of 1 group of 10 T1DM patients into the 2 iLet treatment arms and the inclusion of a second group of 10 T1DM patients into the 2 iPhone-based BP treatment arms in a randomized order will allow for a direct comparison of the safety and efficacy of the 2 treatments, based on intra-patient variability only.

The inclusion of Part 1 (the iPhone-based BP arms) will allow the comparison of the performance of ZP4207 to Lilly glucagon in the original iPhone-based BP, which has been well-characterized in a number of outpatient trials in children and adults over the past 3 years. By testing ZP4207 in the original iPhone-based BP, the glucagon used (ZP4207 vs. Lilly glucagon) will be the only new variable. This will allow optimal isolation and identification of differences, if any, that might exist between ZP4207 and Lilly glucagon in the context of automated glycemic control with the well-characterized and extensively tested iPhone-based BP.

The incorporation of Part 1 and Part 2 has been made globally throughout the protocol amendment. It has been specified that for all analysis, the 2 treatment arms from Part 1 (iPhone-based BP) will be compared, and the 2 treatment arms from Part 2 (iLet) will be compared. Additional language has been added to describe the BP infusion set, control unit, and pumps. The schedule of procedures was updated to reflect the changes specified in this document. Other minor edits were made throughout the protocol to provide greater clarity and consistency.

SUMMARY OF CHANGES:

The amended protocol sections and the details of the changes are summarized in the following sections. Revisions to the protocol are presented as strikethrough (ie, ~~subject~~) for text that was removed and bold (ie, **subject**) for text that was added.

[redacted]

Synopsis, Objectives, Page 4; Section 2, Trial Objectives, Page 22

Original Text:

Primary: The primary objective is to conduct a trial testing the safety and tolerability of the iPhone-based bionic pancreas (BP) when used with ZP4207 in 10 adult (≥18 years of age) patients with T1DM.

Secondary: The secondary objectives are to measure glycemic regulation, including hypoglycemia exposure (percent of time spent with continuous glucose monitor [CGM] glucose <60 mg/dL), evaluate BP device reliability, and to document the satisfaction of patients with the iPhone-based BP with the goal of optimizing the functionality and user interface of the iPhone-based BP.

New Text:

Primary: The primary objective is to conduct a trial testing the safety and tolerability of the **BP using either the iLet or the** iPhone ~~-based bionic pancreas (BP)~~ **platform** when used with ZP4207 in ~~10~~ **20** adult (≥18 years of age) patients with T1DM.

Secondary: The secondary objectives are to measure glycemic regulation, including hypoglycemia exposure (percent of time spent with continuous glucose monitor [CGM] glucose <60 mg/dL), evaluate BP device reliability, and to document the satisfaction of patients with the ~~iPhone-based~~ BP with the goal of optimizing the functionality and user interface of the ~~iPhone-based~~ BP.

Synopsis, Population, Page 4

Original Text:

Up to 20 adult (≥18 years of age) patients who already manage their T1DM using continuous subcutaneous (SC) insulin infusion pump therapy can be enrolled. It is expected that up to 10 patients will complete the trial protocol.

New Text:

Up to ~~20~~ **40** adult (≥18 years of age) patients who already manage their T1DM using continuous subcutaneous (SC) insulin infusion pump therapy can be enrolled. It is expected that up to 10 patients will complete **each part of** the trial protocol.

Synopsis, Trial Design, Page 4; Section 3.1, Summary of Trial Design, Page 22

Original Text:

This trial is a single-center, open-label, randomized cross-over trial. The trial will enroll adult patients with T1DM and will assess the safety and efficacy of the iPhone-based BP using the glucagon analog ZP4207 versus the iPhone-based BP using Lilly glucagon. The iPhone-based BP will also administer insulin (insulin lispro, Lilly Humalog) using the same BG control algorithm for both treatment arms. The trial will be conducted at a single center, the MGH Diabetes Center in Boston, MA.

New Text:

This trial is a single-center, open-label, **2-part,** randomized cross-over trial. The trial will enroll adult patients with T1DM and will assess the safety and efficacy of the ~~iPhone-based BP using the glucagon analog ZP4207 versus the iPhone-based BP using Lilly glucagon. The iPhone-~~

BP using either the iLet or the iPhone platform using the glucagon analog ZP4207 versus Lilly glucagon. In Part 1, up to 10 patients will participate in two 1-day treatment arms in random order (iPhone-based BP using ZP4207 and iPhone-based BP using Lilly glucagon) according to a pre-generated randomization scheme. In Part 2, up to 10 new patients will participate in two 1-day treatment arms in random order (iLet using ZP4207 and iLet using Lilly glucagon) according to a pre-generated randomization scheme. Patients can only participate in 1 part of the trial. An interim database lock may occur upon completion of Part 1 of the trial to analyze the iPhone-based BP data. The iLet and the iPhone-based BP will also administer insulin (insulin lispro, Lilly Humalog) using the same BG control algorithm for ~~both~~ **all 4** treatment arms. The trial will be conducted at a single center, the MGH Diabetes Center in Boston, MA.

Synopsis, Trial Treatment, Page 5; Section 6.1, Investigational Medicinal Products, Page 27

Original Text:

The trial also involves SC administration of Lilly glucagon in one iPhone-based BP arm. Lilly glucagon is commercially available by prescription and is indicated for patients with T1DM in severe hypoglycemia, but not for use in a BP.

The trial also involves SC administration of the glucagon analog ZP4207, 1 mg/mL, in the other iPhone-based BP arm. ZP4207 will be made available by Zealand Pharma A/S, Denmark as liquid formulation in prefilled syringes of 0.6 mL.

New Text:

The trial also involves SC administration of Lilly glucagon in ~~one~~ **1 iLet arm and 1** iPhone-based BP arm. Lilly glucagon is commercially available by prescription and is indicated for patients with T1DM in severe hypoglycemia, but not for use in a BP.

The trial also involves SC administration of the glucagon analog ZP4207, 1 mg/mL, in **the other iLet arm and** the other iPhone-based BP arm. ZP4207 will be made available by Zealand Pharma A/S, Denmark as liquid formulation in prefilled syringes of 0.6 mL.

Synopsis, Primary Endpoint, Page 5; Section 8.1, Primary Endpoint, Page 38

Original Text:

The primary endpoint is the safety and tolerability of ZP4207 and the iPhone-based BP as assessed by:

- Number and type of adverse events (AEs)
- Clinical laboratory measurements
- Vital signs
- 12-lead electrocardiogram (ECG)
- Local tolerability and infusion site reactions as measured with the Draize scale
- Immunogenicity as measured by anti-drug antibodies
- Pain as measured on a 10 cm visual analog scale (VAS)
- Nausea as measured on a 10 cm VAS

[redacted]

New Text:

The primary endpoint is the safety and tolerability of ZP4207 ~~and~~ **in the BP using either the iLet or** the iPhone~~-based BP~~ **platform** as assessed by:

- Number and type of adverse events (AEs)
- Clinical laboratory measurements
- Vital signs
- 12-lead electrocardiogram (ECG)
- Local tolerability and infusion site reactions as measured with the Draize scale
- Immunogenicity as measured by anti-drug antibodies
- Pain as measured on a 10 cm visual analog scale (VAS)
- Nausea as measured on a 10 cm VAS

Synopsis, Secondary Endpoints, Page 5; Section 8.2, Secondary Endpoints, Page 38

Original Text:

The secondary endpoints for the iPhone-based BP and ZP4207 include measurements of BP function as well as glycemic and non-glycemic measurements.

New Text:

The secondary endpoints ~~for the iPhone-based BP and ZP4207~~ include measurements of BP function as well as glycemic and non-glycemic measurements.

Section 1.1, Background and Rationale, Page 14-15

Original Text:

In its last tested embodiment, the BP consisted of a Dexcom G4 CGM, and an iPhone that are hardwired together, with the iPhone running the control algorithm and communicating via Bluetooth with 2 Tandem t:slim pumps to dose insulin and glucagon.

In order to provide automatic BG regulation, the iPhone-based BP has the ability to deliver both insulin and glucagon. However, currently available glucagon formulations have limited stability at room temperature, necessitating frequent changes to the glucagon infusion set. Therefore, the current trial is designed to test the glucagon analog ZP4207 in the iPhone-based BP, as this peptide analog of human glucagon is provided in a liquid formulation stable at room temperature.

The current trial is a first feasibility trial designed to use the iPhone-based BP to compare ZP4207 with marketed glucagon (Lilly). The trial is intended to demonstrate the safety and tolerability of ZP4207 in the iPhone-based BP and the feasibility of achieving comparable autonomous glycemic control. It is not intended to comprehensively demonstrate the definitive efficacy of the iPhone-based BP in extended, continuous daily use, but rather to demonstrate its functionality and accuracy in a practical, albeit very controlled, clinical setting. The trial is expected to provide practical information that will benefit the design of a next-generation BP and help pave the way for a more comprehensive outpatient home-use Phase 2 trial and ultimately a pivotal trial where comprehensive safety and efficacy through continuous full daily use of the BP with ZP4207 will be documented.

[redacted]

The data derived from this trial will permit evaluation of the robustness of the iPhone-based BP as well as the safety and efficacy of ZP4207 when used in conjunction with the iPhone-based BP.

New Text:

In its last tested embodiment, the BP consisted of a Dexcom G4 CGM, and an iPhone that are hardwired together, with the iPhone running the control algorithm and communicating via Bluetooth with 2 Tandem t:slim pumps to dose insulin and glucagon. **The connections are repeatedly lost among these 4 components throughout the day, an issue that has the potential to adversely impact BG control, whether due to missed CGM values or missed doses. In addition, the troubleshooting required to repair these recurring disconnections can be burdensome to the user. Integrating these components into a single device would establish seamless connectivity among them, which would eliminate the need for such troubleshooting. This would lead to smoother device operation with fewer interruptions, which would enhance its user friendliness, optimize its BG control potential, and further improve the quality of life of its users.**

The BU Investigators have recently designed, built, and tested a proprietary first-generation of such a fully integrated BP system, referred to as the iLet and the iLet infusion set. The iLet is a dual-chamber infusion system that currently incorporates the Dexcom G4 CGM technology, a custom user interface with touchscreen display, and all of the mathematical dosing algorithms that were tested in and validated using the iPhone-based BP in outpatient studies over the past 3 years. The iLet infusion set provides 2 independent subcutaneous (SC) fluid pathways from the iLet to the patient (1 for insulin and the other for glucagon). One tube connects to the prefilled insulin cartridge and the other tube connects to the fillable (single-use) glucagon cartridge.

In order to provide automatic BG regulation, the **iLet and the** iPhone-based BP ~~has~~ **have** the ability to deliver both insulin and glucagon. However, currently available glucagon formulations have limited stability at room temperature, necessitating frequent changes to the glucagon infusion set. Therefore, the current trial is designed to test the glucagon analog ZP4207 in the **iLet and the** iPhone-based BP, as this peptide analog of human glucagon is provided in a liquid formulation stable at room temperature.

The current trial is a first feasibility trial designed to use the **first-generation iLet and iLet infusion set and the** iPhone-based BP to compare ZP4207 with marketed glucagon (Lilly). The trial is intended to demonstrate the safety and tolerability of ZP4207 in the **iLet and the** iPhone-based BP and the feasibility of achieving comparable autonomous glycemic control. It is not intended to comprehensively demonstrate the definitive efficacy of the ~~iPhone-based~~ BP in extended, continuous daily use, but rather to demonstrate its functionality and accuracy in a practical, albeit very controlled, clinical setting. The trial is expected to provide practical information that will benefit the design of a next-generation ~~BP~~ **iLet and iLet infusion set** and help pave the way for a more comprehensive outpatient home-use Phase 2 trial and ultimately a pivotal trial where comprehensive safety and efficacy through continuous full daily use of the ~~BP~~ **iLet** with ZP4207 will be documented.

The data derived from this trial will permit evaluation of the robustness of the ~~iPhone-based~~ ~~BP~~ **iLet** as well as the safety and efficacy of ZP4207 when used in conjunction with the **iLet and the iPhone-based BP. The data obtained will be used to further improve the iLet and will allow BU/MGH to expand to larger outpatient trials using the iLet or the** iPhone-based BP **with ZP4207**.

Section 1.5, Risk/Benefit, Page 19

Original Text:

Trial patients will be informed by the Investigator of the potential risks of ZP4207 and other trial-related procedures before they enter the trial.

In this trial, patients with T1DM will be included to test the safety and efficacy of the iPhone-based BP using ZP4207 versus the iPhone-based BP using Lilly glucagon. The cross-over design with inclusion of the same T1DM patients into the 2 treatment arms in a randomized order will allow for a direct comparison of the safety and efficacy of the 2 treatments, based on intra-patient variability only.

New Text:

Trial patients will be informed by the Investigator of the potential risks of ZP4207 and other trial-related procedures before they enter the trial.

In this trial, patients with T1DM will be included to test the safety and efficacy of the ~~iPhone based~~ BP using **either the iLet or the iPhone platform when used with** ZP4207 versus ~~the iPhone based BP using~~ Lilly glucagon. The cross-over design with inclusion of ~~the same~~ **1 group of 10** T1DM patients into the 2 **iLet treatment arms and the inclusion of a second group of 10 T1DM patients into the 2 iPhone-based BP** treatment arms in a randomized order will allow for a direct comparison of the safety and efficacy of the 2 treatments, based on intra-patient variability only.

Section 1.5, Risk/Benefit, Page 21

Original Text:

Based on experiences from previous trials of the BP and the design of this trial, patients enrolled in the trial may benefit from a reduction in risk of hypoglycemia and hyperglycemia and a better mean glucose compared to their usual diabetes care during their short trial participation.

The data derived from this trial will allow evaluation of safety and tolerability of ZP4207 in the iPhone-based BP.

New Text:

Based on experiences from previous trials of the BP and the design of this trial, patients enrolled in the trial may benefit from a reduction in risk of hypoglycemia and hyperglycemia and a better mean glucose compared to their usual diabetes care during their short trial participation.

The data derived from this trial will allow evaluation of safety and tolerability of ZP4207 in the ~~iPhone based BP.~~ **iLet and the iPhone-based BP, and the robustness and effectiveness of the new BP control system. The data obtained will be used to further improve the iLet and will allow the expansion to larger outpatient trials using the iLet or the iPhone-based BP with ZP4207.**

Section 3.3, Number of Patients, Page 23

Original Text:

Up to 20 adult patients with T1DM can be enrolled. The upper bound is based on the expectation that some patients will be excluded after the Screening Visit and the possibility that some patients may have to be discontinued before completion (due to, for instance, inter-current illness or patient withdrawal). It is expected that up to 10 patients will complete the trial protocol.

New Text:

Up to ~~20~~ **40** adult patients with T1DM can be enrolled. The upper bound is based on the expectation that some patients will be excluded after the Screening Visit and the possibility that some patients may have to be discontinued before completion (due to, for instance, inter-current illness or patient withdrawal). It is expected that up to 10 patients will complete **each part of** the trial protocol.

Section 5, Assignment to Treatment Groups, Page 26

Original Text:

This trial is an open-label, randomized cross-over trial. Patients who have completed the Screening Visit and meet all of the inclusion and none of exclusion criteria will be enrolled into the trial. All patients will participate in two 1-day treatment arms in random order (iPhone-based BP using ZP4207 and iPhone-based BP using Lilly glucagon) according to a pre-generated randomization scheme. Up to 2 patients may participate in the trial per day. The order of the iPhone-based BP visits will be randomized in blocks of 2 patients.

New Text:

This trial is an open-label, **2-part,** randomized cross-over trial. Patients who have completed the Screening Visit and meet all of the inclusion and none of exclusion criteria will be enrolled into the trial. ~~All~~ **In Part 1, up to 10** patients will participate in two 1-day treatment arms in random order (iPhone-based BP using ZP4207 and iPhone-based BP using Lilly glucagon) according to a pre-generated randomization scheme. **In Part 2, up to 10 new patients will participate in two 1-day treatment arms in random order (iLet using ZP4207 and iLet using Lilly glucagon) according to a pre-generated randomization scheme.** Up to 2 patients may participate in the trial per day. The order of the ~~iPhone-based BP~~ **treatment** visits will be randomized in blocks of 2 patients.

Section 6.4, Doses, Page 28

Original Text:

The iPhone-based BP can administer isolated insulin-glucagon doses once every 5 minutes. A single automated bolus of insulin will not exceed 3 units per 5-minute dose (30 µl of U-100 insulin) in both systems, and a single meal-priming dose, in response to a meal announcement made by the user, will not exceed 12 units (120 µl of U-100 insulin). A single bolus of glucagon will not exceed 80 µg (80 µl of 1 mg/mL Lilly glucagon or 1 mg/mL ZP4207). In prior studies, typical doses of glucagon were in the range of 0.005-0.04 mg per dose. The iPhone-based BP is capable of administering as little as ~0.1 µl (0.011 units of U-100 insulin or 0.1 µg of 1 mg/mL ZP4207).

[redacted]

New Text:

The **iLet and the** iPhone-based BP can administer isolated insulin-glucagon doses once every 5 minutes. A single automated bolus of insulin will not exceed 3 units per 5-minute dose (30 µl of U-100 insulin) in both systems, and a single meal-priming dose, in response to a meal announcement made by the user, will not exceed 12 units (120 µl of U-100 insulin). A single bolus of glucagon will not exceed 80 µg (80 µl of 1 mg/mL Lilly glucagon or 1 mg/mL ZP4207). In prior studies, typical doses of glucagon were in the range of ~~0.005 0.04 mg~~ **2.5-40 µg** per dose. The **iLet and the** iPhone-based BP ~~is~~ **are** capable of administering as little as ~0.**5**~~1~~ µl (0.~~011~~**05** units of U-100 insulin or 0.**5**~~1~~ µg of 1 mg/mL ZP4207).

Section 6.6, iLet Bionic Pancreas, Page 29-30

Original Text:

Not applicable.

New Text:

6.6 iLet Bionic Pancreas

Infusion Set: A novel, dual cannula infusion set has been designed specifically for use with the iLet. Patients will wear dual channel tubing that will be attached to 2 infusion sets with 1 steel cannula each, 1 for insulin infusion and the other for glucagon infusion. The tubing and infusion sets will have undergone sterilization prior to being delivered in a sealed pouch. The steel cannulae will be inserted in the abdominal SC tissue.

Continuous Glucose Monitors: One transcutaneous glucose sensor for the Dexcom G4 Platinum (Garcia, 2013) will be inserted in the abdominal SC tissue and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to the sensor and the whole assembly is held to the skin with an adhesive patch and communicates wirelessly with the BP. If the G4 sensor fails for any reason during the trial (loss of CGM signal), it will be replaced promptly.

Bionic Pancreas Control Unit: The iLet is being built according to Class III medical device standards, adheres to a comprehensive and robust quality system, and is fully compliant with International Organization for Standardization (ISO) 13485 standards and document control practices. The iLet is a fully-integrated dual hormone BP system that integrates the CGM technology (currently the Dexcom G4 Share system) as well as 2 independent motor-drivetrain pumping assemblies, which independently actuate the delivery of insulin and glucagon from pre-filled cartridges that are separately loaded into the iLet housing. Each drivetrain assembly utilizes a lead screw, which is driven by a precision micromotor, a gear case assembly, and a motor controller unit, in a manner similar to what is commonly found in most insulin infusion pumps on the market today. The iLet has dosing accuracy that is comparable to FDA-approved insulin pumps currently on the market. The iLet has a built-in BTLE radio that also allows automatic communication with the paired CGM, as well as the Nova StatStrip® Xpress BG meter (Nova Biomedical). The iLet does not contain a cellular nor a WiFi radio, and does not accept input data from another mobile device (e.g., smartphone), other than the paired CGM and BG meter(s).

The mathematical control algorithms (which are the same as those used in the iPhone-based BP), the CGM glucose engine (Dexcom), and the native user interface software, are all interconnected through controller framework software and reside as embedded systems on printed circuit boards contained within the device housing. The

touchscreen-enabled, menu-driven user interface and onboard processor provide a comprehensive and standalone platform, which allows the iLet to operate independently of smartphones or other devices and without the need for internet support during routine operation. The graphical user interface of the iLet has the same user options and capabilities of the iPhone BP, including having its home screen password protected and its settings options only accessible to trial staff via a separate password.

Section 7.4, Treatment Visits (Visit 3 and Visit 4), Page 32-33

Original Text:

- Up to 2 patients may participate per day.
- Each patient will participate in 2 treatment visits: one with the iPhone-based BP using ZP4207 and one with the iPhone-based BP using Lilly glucagon in a randomized order.
- The night before the treatment visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be instructed to call if they encounter any difficulty with their CGM.

New Text:

- Up to 2 patients may participate per day.
- ~~Each~~ **In Part 1, each** patient will participate in 2 treatment visits: ~~one~~ **1** with the iPhone-based BP using ZP4207 and ~~one~~ **1** with the iPhone-based BP using Lilly glucagon in a randomized order.
- **In Part 2, each patient will participate in 2 treatment visits: 1 with the iLet using ZP4207 and 1 with the iLet using Lilly glucagon in a randomized order.**
- The night before the treatment visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be instructed to call if they encounter any difficulty with their CGM.

Section 11, Statistics, Page 47

Original Text:

Not applicable.

New Text:

For all analysis, the 2 treatment arms from Part 1 (iPhone-based BP) will be compared, and the 2 treatment arms from Part 2 (iLet) will be compared. The analysis of Part 1 will be completely separate from the analysis of Part 2.

Section 11.2.3, Interim Analysis, Page 49

Original Text:

No interim analysis is planned.

New Text:

~~No interim analysis is planned.~~ **An interim database lock may occur upon completion of Part 1 of the trial to analyze the iPhone-based BP data.**

[redacted]

Section 11.2.4, Sample Size Determination, Page 49

Original Text:

No formal sample size calculations were made. It is expected that between 10 and 12 patients will be randomized in the trial. The sample size is based on a clinical rather than statistical rationale. The sample size is considered adequate to address the primary trial objective of exploring the safety of ZP4207 when used in the iPhone-based BP and with reference to Lilly glucagon used in the iPhone-based BP.

New Text:

No formal sample size calculations were made. It is expected that between ~~10~~ **20** and ~~12~~ **24** patients will be randomized in the trial. The sample size is based on a clinical rather than statistical rationale. The sample size is considered adequate to address the primary trial objective of exploring the safety of ZP4207 when used in the ~~iPhone-based~~ BP and with reference to Lilly glucagon used in the ~~iPhone-based~~ BP.

Appendix A, Schedule of Procedures, Footnotes 1 and 2, Page 59

Original Text:

1. Once the patient has been enrolled and eligibility has been established, the order of the iPhone-based BP visits will be randomized in blocks of 2 patients.
2. Each patient will participate in 2 treatment visits: one with the iPhone-based BP using ZP4207 and one with the iPhone-based BP using Lilly glucagon in a randomized order. Up to 2 patients may participate in the trial per day.

New Text:

1. Once the patient has been enrolled and eligibility has been established, the order of the ~~iPhone-based BP~~ **treatment** visits will be randomized in blocks of 2 patients.
2. ~~Each~~ **In Part 1, each** patient will participate in 2 treatment visits: ~~one~~ **1** with the iPhone-based BP using ZP4207 and ~~one~~ **1** with the iPhone-based BP using Lilly glucagon in a randomized order. **In Part 2, each patient will participate in 2 treatment visits: 1 with the iLet using ZP4207 and 1 with the iLet using Lilly glucagon in a randomized order.** Up to 2 patients may participate in the trial per day.

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CLINICAL TRIAL PROTOCOL

The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

Investigational Product: ZP4207
Protocol Number: ZP4207-16051
IND Number: 129980
Phase: 2

Principal Investigator:
Steven J. Russell, MD, PhD[1]

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Original Version: 03 May 2016
Amendment Number 1.0: 28 June 2016
Amendment Number 2.0: 03 August 2016
Amendment Number 3.0: 17 August 2016
Amendment Number: 4.0
Protocol Version Number: 5.0

Date: 02 September 2016

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SIGNATURE PAGE

TRIAL TITLE: The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the trial.

Signature [redacted] Date [redacted]

[redacted] MD
Vice President, Clinical Development
Zealand Pharma A/S

[redacted] [redacted]

[redacted] DVM, PhD
Principal Clinical Pharmacologist
Zealand Pharma A/S

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INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the trial as described. I will conduct this trial in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the trial within the time designated. I will provide copies of this protocol and access to all information furnished by Zealand Pharma A/S to trial personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the trial product and trial procedures. I will let them know that this information is confidential and proprietary to Zealand Pharma A/S and that it may not be further disclosed to third parties. I understand that the trial may be terminated or enrollment suspended at any time by Zealand Pharma A/S, with or without cause, or by me if it becomes necessary to protect the best interests of the trial patients.

I agree to conduct this trial in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and ICH Guidelines for Good Clinical Practices.

[redacted]

Investigator's Signature

9/7/2016

Date

Steven J. Russell, MD, PhD

Investigator's Printed Name

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SYNOPSIS

TITLE: The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

PROTOCOL NUMBER: ZP4207-16051

INVESTIGATIONAL PRODUCT: ZP4207

PHASE: 2

INDICATION: ZP4207 is an anti-hypoglycemic glucagon analog in a ready-to-use liquid formulation which is being studied to improve glycemic control in adults (and children) with type 1 diabetes mellitus (T1DM) as part of a bihormonal bionic pancreas (BP).

OBJECTIVES:

Primary: The primary objective is to conduct a trial testing the safety and tolerability of the BP using either the iLet or the iPhone platform when used with ZP4207 in 20 adult (≥18 years of age) patients with T1DM.

Secondary: The secondary objectives are to measure glycemic regulation, including hypoglycemia exposure (percent of time spent with continuous glucose monitor [CGM] glucose <60 mg/dL), evaluate BP device reliability, and to document the satisfaction of patients with the BP with the goal of optimizing the functionality and user interface of the BP.

POPULATION: Up to 40 adult (≥18 years of age) patients who already manage their T1DM using continuous subcutaneous (SC) insulin infusion pump therapy can be enrolled. It is expected that up to 10 patients will complete each part of the trial protocol.

TRIAL DESIGN: This trial is a single-center, open-label, 2-part, randomized cross-over trial. The trial will enroll adult patients with T1DM and will assess the safety and efficacy of the BP using either the iLet or the iPhone platform using the glucagon analog ZP4207 versus Lilly glucagon. In Part 1, up to 10 patients will participate in two 1-day treatment arms in random order (iPhone-based BP using ZP4207 and iPhone-based BP using Lilly glucagon) according to a pre-generated randomization scheme. In Part 2, up to 10 new patients will participate in two 1-day treatment arms in random order (iLet using ZP4207 and iLet using Lilly glucagon) according to a pre-generated randomization scheme. Patients can only participate in 1 part of the trial. An interim database lock may occur upon completion of Part 1 of the trial to analyze the iPhone-based BP data. The iLet and the iPhone-based BP will also administer insulin (insulin lispro, Lilly Humalog) using the same blood glucose (BG) control algorithm for all 4 treatment arms. The trial will be conducted at a single center, the Massachusetts General Hospital Diabetes Center in Boston, MA.

TRIAL TREATMENT: The trial involves SC administration of insulin lispro (Humalog, Lilly), which is commercially available by prescription and is indicated for patients with T1DM, but not for use in a BP.

[redacted]

The trial also involves SC administration of Lilly glucagon in 1 iLet arm and 1 iPhone-based BP arm. Lilly glucagon is commercially available by prescription and is indicated for patients with T1DM in severe hypoglycemia, but not for use in a BP.

The trial also involves SC administration of the glucagon analog ZP4207, 1 mg/mL, in the other iLet arm and the other iPhone-based BP arm. ZP4207 will be made available by Zealand Pharma A/S, Denmark as liquid formulation in prefilled syringes of 0.6 mL.

PRIMARY ENDPOINT:
The primary endpoint is the safety and tolerability of ZP4207 in the BP using either the iLet or the iPhone platform as assessed by:

- Number and type of adverse events (AEs)
- Clinical laboratory measurements
- Vital signs
- 12-lead electrocardiogram (ECG)
- Local tolerability and infusion site reactions as measured with the Draize scale
- Immunogenicity as measured by anti-drug antibodies
- Pain as measured on a 10 cm visual analog scale (VAS)
- Nausea as measured on a 10 cm VAS

SECONDARY ENDPOINTS:
The secondary endpoints include measurements of BP function as well as glycemic and non-glycemic measurements.

Bionic Pancreas Function
This endpoint data will be generated from the BP data during each treatment visit:

- Average percent insulin dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
    - Average percent glucagon/ZP4207 dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts calculated by the BP algorithm that are successfully issued to the pump by the BP (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts calculated by the BP control algorithm that are successfully issued by the BP
    - Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully issued by the BP
- Average percent of 5-minute steps during which the BP is functioning nominally in all respects based on real-time CGM data (new CGM glucose reading captured, dose calculated, and dose issued to pumps)

[redacted]

- Average percent of 5-minute steps during which the BP is functioning nominally with or without a new CGM glucose reading captured (dose calculated and dose issued to pumps). If a CGM signal is not available, the dose calculated may be based on weight or historical basal rates.
- CGM reliability index, calculated as percent of possible values actually recorded by CGM
- CGM Mean Absolute Relative Difference versus time-stamped BG values from meter download
- List of technical faults associated with the BP including cause and resolution

Glycemic
All of following metrics will be generated from the Dexcom G4 Platinum CGM data during each treatment visit:

- Fraction of time spent within each of the following glucose ranges:
  - <50 mg/dL
  - <60 mg/dL
  - <70 mg/dL
  - 70-120 mg/dL
  - 70-140 mg/dL
  - 70-180 mg/dL
  - >180 mg/dL
  - >250 mg/dL
  - >300 mg/dL
- Number of severe hypoglycemic events (patients unable to self-treat, requiring the assistance of another person)
- Number of episodes of symptomatic hypoglycemia
- Number of carbohydrate interventions for hypoglycemia
- Total grams of carbohydrates taken for hypoglycemia
- Mean CGM glucose

Non-glycemic

- Glucagon/ZP4207 total delivery per kg of body mass
- Insulin total delivery per kg of body mass
- Number of unscheduled infusion set replacements
- Number of unscheduled CGM sensor changes

EVALUATION OF TRIAL DATA: The following variables will be evaluated according to treatment for safety purposes: AEs, local tolerability, laboratory safety assessments, physical examination, vital signs, and 12-lead ECGs.

The analysis of BP function endpoints and glycemic endpoints will be on an intention-to-treat basis. In cases where a treatment arm was not completed (and that arm was not repeated according to protocol criteria), available data from that arm will be used in the data analysis.

The Shapiro-Wilk test will be used to determine the normality of the residuals for each comparison. Summary tables that display descriptive statistics, including percentages, means or medians, and standard deviation and/or ranges, as appropriate, will be provided.

[redacted]

A paired t-test or the Wilcoxon signed rank test for comparison of means with normally or non-normally distributed residuals, respectively, will be used. In a secondary analysis any period effect and any interaction between treatment and period will be looked for, although no such interaction is predicted for the efficacy outcome.
The number of patients and proportions of severe hypoglycemic events, symptomatic hypoglycemia, and carbohydrate interventions due to hypoglycemia with the event counts will be summarized descriptively, and the proportions will be analyzed by a Fisher's exact test if data allow.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibodies
AE	Adverse event
BG	Blood glucose
BP	Bionic pancreas
BTLE	Bluetooth Low Energy
BU	Boston University
CFR	Code of Federal Regulations
CGM	Continuous glucose monitor
CRO	Contract research organization
DBR	Database review
DPP-4	Dipeptidyl peptidase-4
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FDA	Food and Drug Administration
FHD	First Human Dose
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GUI	Graphical user interface
HCG	Human chorionic gonadotropin
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IM	Intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
MD	Doctor of Medicine
MedDRA	Medical Dictionary for Regulatory Activities
MGH	Massachusetts General Hospital
MPC	Model-predictive control

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Abbreviation	Definition
PD	Pharmacodynamic
PK	Pharmacokinetic
RN	Registered nurse
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SGLT-2	Sodium-glucose co-transporter-2
SIV	Site Initiation Visit
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 diabetes mellitus
TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
ULN	Upper limit of normal
VAS	Visual analog scale

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1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Background and Rationale

To date, clinical trials conducted by Boston University (BU) and Massachusetts General Hospital (MGH) in patients with type 1 diabetes mellitus (T1DM) have demonstrated the practicality of a wearable automated bionic pancreas (BP) control system for robust glucose regulation using a continuous glucose monitor (CGM) to provide the input to the control system. Despite current technical limitations in CGMs and infusion pumps, the trials by BU/MGH have shown that a bihormonal BP is capable of achieving safe and effective blood glucose (BG) control automatically, with minimal hypoglycemia during 11 continuous days in the face of unrestrained meals and exercise and with trivial patient input (optional announcement of meals).

The BP provides automatic BG regulation and reduces hypoglycemic episodes. Additionally, the system spares the wearer the relentless tasks of carbohydrate counting, frequent BG monitoring, estimating the effects of specific meals and exercise activity on BG levels, and manual drug administration, which are inexact, demanding, aggravating, and require continuous diligence and vigilance. The degree of glycemic control achieved by the BP is predicted to dramatically reduce the deleterious and debilitating complications of T1DM.

In its last tested embodiment, the BP consisted of a Dexcom G4 CGM, and an iPhone that are hardwired together, with the iPhone running the control algorithm and communicating via Bluetooth with 2 Tandem t:slim pumps to dose insulin and glucagon. The connections are repeatedly lost among these 4 components throughout the day, an issue that has the potential to adversely impact BG control, whether due to missed CGM values or missed doses. In addition, the troubleshooting required to repair these recurring disconnections can be burdensome to the user. Integrating these components into a single device would establish seamless connectivity among them, which would eliminate the need for such troubleshooting. This would lead to smoother device operation with fewer interruptions, which would enhance its user friendliness, optimize its BG control potential, and further improve the quality of life of its users.

The BU Investigators have recently designed, built, and tested a proprietary first-generation of such a fully integrated BP system, referred to as the iLet and the iLet infusion set. The iLet is a dual-chamber infusion system that currently incorporates the Dexcom G4 CGM technology, a custom user interface with touchscreen display, and all of the mathematical dosing algorithms that were tested in and validated using the iPhone-based BP in outpatient studies over the past 3 years. The iLet infusion set provides 2 independent subcutaneous (SC) fluid pathways from the iLet to the patient (1 for insulin and the other for glucagon). One tube connects to the prefilled insulin cartridge and the other tube connects to the fillable (single-use) glucagon cartridge.

In order to provide automatic BG regulation, the iLet and the iPhone-based BP have the ability to deliver both insulin and glucagon. However, currently available glucagon formulations have limited stability at room temperature, necessitating frequent changes to the glucagon infusion set. Therefore, the current trial is designed to test the glucagon analog ZP4207 in the iLet and the iPhone-based BP, as this peptide analog of human glucagon is provided in a liquid formulation stable at room temperature.

[redacted]

The current trial is a first feasibility trial designed to use the first-generation iLet and iLet infusion set and the iPhone-based BP to compare ZP4207 with marketed glucagon (Lilly). The trial is intended to demonstrate the safety and tolerability of ZP4207 in the iLet and the iPhone-based BP and the feasibility of achieving comparable autonomous glycemic control. It is not intended to comprehensively demonstrate the definitive efficacy of the BP in extended, continuous daily use, but rather to demonstrate its functionality and accuracy in a practical, albeit very controlled, clinical setting. The trial is expected to provide practical information that will benefit the design of a next-generation iLet and iLet infusion set and help pave the way for a more comprehensive outpatient home-use Phase 2 trial and ultimately a pivotal trial where comprehensive safety and efficacy through continuous full daily use of the iLet with ZP4207 will be documented.

The data derived from this trial will permit evaluation of the robustness of the iLet as well as the safety and efficacy of ZP4207 when used in conjunction with the iLet and the iPhone-based BP. The data obtained will be used to further improve the iLet and will allow BU/MGH to expand to larger outpatient trials using the iLet or the iPhone-based BP with ZP4207.

1.2 Bihormonal Bionic Pancreas System

The BP is an autonomous, self-learning system that requires only the patient's weight for initialization, and then autonomously adapts, modestly or dramatically, as needed, to cope with the wide range of insulin requirements of adults, adolescents, and pre-adolescents with T1DM. The BP obviates the need for the patient to know, or even appreciate, their insulin requirements, and renders obsolete any need for patients or caregivers to know carbohydrate-to-insulin ratios, basal rates, or insulin correction factors.

The core technology is a suite of control algorithms that orchestrate the automated dosing of insulin and glucagon to regulate BG levels. An insulin controller orchestrates all SC insulin dosing. At its centerpiece is a model-predictive control (MPC) algorithm, which bases insulin doses on the glucose data and insulin absorption kinetics, compensating for the slow absorption rate of SC insulin analogs (peak time in blood of 30-90 min, clearance in 4-8 hr). This enables the algorithm to refrain from stacking and overdosing insulin. Furthermore, the MPC algorithm automatically adjusts its insulin-dosing aggressiveness continuously and in real-time to different insulin needs between individuals and variable needs within the same individual. Running in parallel with the MPC algorithm is an algorithm that automatically modulates basal insulin delivery over multiple time scales, and another algorithm that automatically adapts insulin doses in response to optional meal announcements. Unlike current insulin pumps and the insulin-only control algorithms, the adaptive basal insulin algorithm obviates the need for the user to set, or even know, his or her “basal-rate profile.” Instead, it is capable of automatically adapting to, and compensating for, changes in an individual's basal insulin need, such as might occur over a period of hours, days, or weeks (e.g., circadian hormonal fluctuations, intercurrent illness, physical activity, or emotional state) or as might occur over a period of months or years due to developmental changes (e.g., hormonal changes that occur during puberty or menopause). The adaptive meal dose controller obviates the need for the user to set, or even know, his or her “carbohydrate-to-insulin ratios,” as it makes automatic adjustments based on dosing history for similar meal announcements made on previous days, and customizes the dose for each individual and for time of day.

[redacted]

The BP also includes a proportional-derivative algorithm governing SC micro-doses of glucagon to help prevent impending hypoglycemia. Glucagon dosing is based on the glucose level and rate of descent. It may occur preemptively even if glucose is above range, and it includes a feedback term to account for the pending effects of recent glucagon doses.

Taken together, these mathematical algorithms provide a universal framework for a glycemic control strategy that requires no quantitative input from, or participation by, the user (besides entering body weight to initialize the system), but which automatically adapts insulin and glucagon dosing to meet the individual needs of each user. Another challenge met is enabling the technology to remain completely autonomous in managing insulin and glucagon delivery even when the CGM is offline. Specifically, when the CGM is offline, the BP invokes the high-resolution “basal rate profile” that it had recently learned and stored when the CGM was online. On the basis of what the system learned and stored about meal announcements when the CGM was online, it is able to respond to meal announcements in the same manner when the CGM is offline. Finally, it automatically responds to user-entered BG values when the CGM is offline by issuing a correction dose of insulin or glucagon based on what it learned about the user's insulin and glucagon needs when the CGM was online. Thus, the BP never relies on, or burdens the user with, the determination of subjective dosing decisions, which inevitably vary in quality and reliability among different users. The BP provides a turnkey solution for people with T1DM that comprehensively manages glycemia across a broad range of individual needs and across a large spectrum of circumstances and challenges to glycemic control.

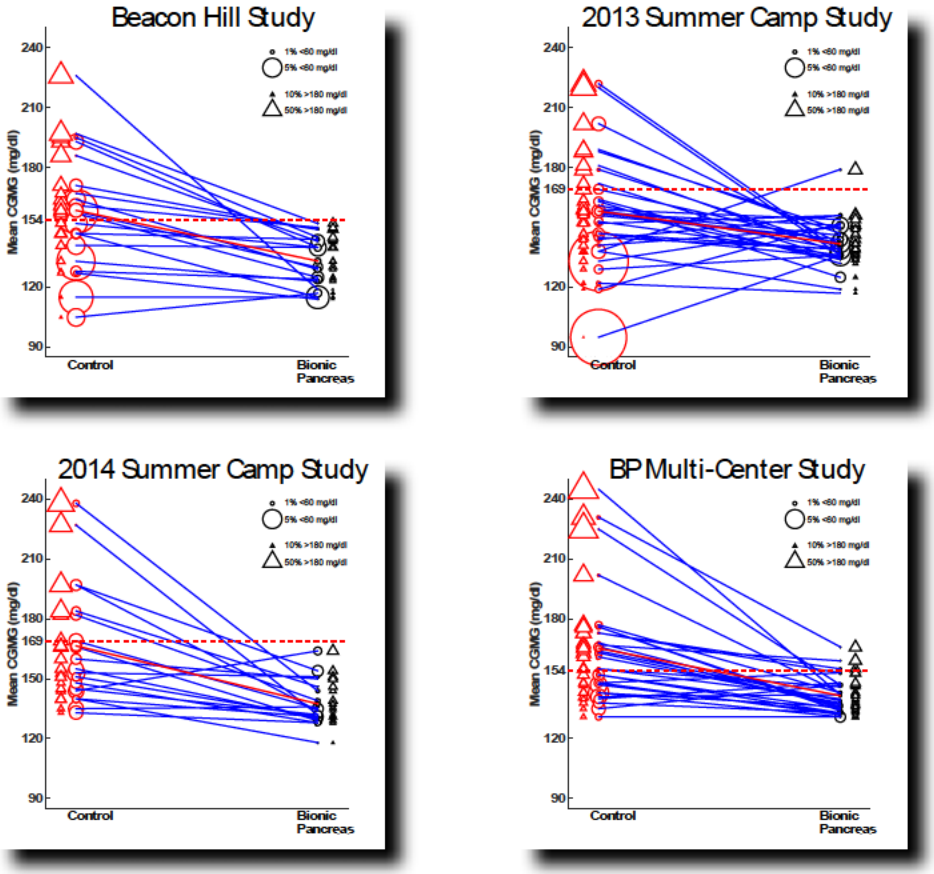
A significant challenge for the use of glucagon in a bihormonal BP is the lack of a commercially available glucagon formation that is stable and well-suited to infusion over several days in a pump reservoir. However, BU/MGH have proceeded with studies using a relatively unstable marketed formulation that must be reconstituted from a lyophilized powder on a daily basis. This allowed BU/MGH to proceed with studies of the bihormonal system while awaiting the production of stable glucagon formulations or stable glucagon analogs.

1.3 Preliminary Studies with the Bihormonal Bionic Pancreas System

The BP hardware platform has evolved over the years from a laptop-driven system, which was used in all inpatient studies to the first truly mobile wearable iPhone-driven platform, which has been used in a number of outpatient studies. Using the iPhone-based BP system, >110 outpatient experiments of 5-11 days in duration in each subject have been conducted (>800 patient days or >2 patient years of data) across subjects ranging in age between 6 and 76 years old and in body mass between 21 and 128 kg. The robust adaptation capabilities of the BP is evident in the fact that the average total daily dose of insulin among these subjects varied by over 13-fold (from 11 to 145 units/day).

In November 2012, Food and Drug Administration (FDA) approval was obtained to conduct the first outpatient study testing the BP in adults 21 years or older with T1DM. This study, referred to as the Beacon Hill Study, followed a random-order cross-over design in which 20 adults with T1DM participated in 5 days on the iPhone-based BP and 5 days of usual care in which they wore a CGM with blinded display and muted alarms. In the BP arm, subjects kept to a 3-square-mile geographic area centered around the Beacon Hill neighborhood in Boston. They ate as they chose at local restaurants, and exercised at will with access to 2 gyms. Analysis was pre-specified to focus on Days 2-5, since glycemic control is more representative of BP performance after most of the adaptation by the BP occurs on Day 1 (Russell, 2014). Results are summarized in Figure 1.

Figure 1. Outpatient Results Summarizing the Distribution of Mean CGM Glucose Levels and Hypoglycemia in the BP and Control Arms



Study	Age (years)	Bionic Pancreas (BP) Mean CGM glucose level (mg/dl)	Bionic Pancreas (BP) % of CGM glucose levels <50 mg/dl (%)	Bionic Pancreas (BP) % of CGM glucose levels 70–180 mg/dl (%)	Control Mean CGM glucose level (mg/dl)	Control % of CGM goucose values <50 mg/dl (%)	Control % of CGM goucose values 70–180 mg/dl (%)	p value (BP versus Control) for: Mean CGM glucose level	p value (BP versus Control) for: % of CGM glucose values <50 mg/dl	p value (BP versus Control) for: % of CGM glucose values 70–180 mg/dl
Beacon Hill (n 20, 5-day experiments)	≥21	133	1.5	80	159	3.7	59	<0.001	0.020	<0.001
2013 Summer Camp (n 32, 5-day experiments)	12–20	142	1.3	76	158	2.2	65	0.004	0.192	<0.001
2014 Summer Camp (n 19, 5-day experiments)	6–11	137	1.2	81	168	2.8	58	0.004	0.001	<0.001
BP Multi Center (n 39, 11-day experiments)	≥18	141	0.6	78	162	1.9	62	<0.001	<0.001	<0.001

Mean CGM glucose levels for each subject under usual care (red circles) are connected with the subject's mean CGM glucose level on the BP (black circles). The diameters of the circles shown are proportional to the percentage of CGM glucose values <60 mg/dL, and the size of the triangle is proportional to the percentage of CGM glucose values >180 mg/dL. The horizontal red dashed line refers to the glucose level corresponding to the American Diabetes Association therapy goal for each age group tested, which corresponds to 154 mg/dL (HbA1c of 7%) for adults and 169 mg/dL (HbA1c of 7.5%) for children. Results are summarized in the table, where the co-primary outcomes (mean CGM glucose level and percentage of CGM glucose values <60 mg/dL) for the BP arm are highlighted in red for each of the 4 studies.
BP = bionic pancreas; CGM = continuous glucose monitoring; HbA1c = hemoglobin A1c.

In April 2013, FDA approval was obtained to conduct the first outpatient study testing the BP in adolescents 12-20 years old with T1DM. This study, referred to as the 2013 Summer Camp Study, followed a random-order cross-over design in which 32 adolescents with T1DM participated in 5 days on the BP and 5 days of supervised camp care in which they wore a CGM with blinded display and muted alarms. Subjects were fully integrated into normal camp activities without restrictions on diet or exercise. The study used the same iPhone-based BP that was used in the Beacon Hill Study. Results are summarized in Figure 1 (Russell, 2014). In April 2014, FDA approval was obtained to conduct the first outpatient study testing the BP in pre-adolescents 6-11 years old with T1DM. This study, referred to as the 2014 Summer Camp Study, was similar in design to the 2013 Summer Camp Study. Results are summarized in Figure 1 (Russell, 2016).

In April 2014, FDA approval was obtained to conduct the first multi-center study, which was also the first home study, to test the BP in adults 18 years or older with T1DM. This study, referred to as the Bionic Pancreas Multi-Center Study, followed a random-order cross-over design in which 39 adults participated in 11 days on the BP and 11 days of usual care. Participants went to work as usual, and lived and slept at home, all without clinical supervision. There were no restrictions placed on diet or exercise. The study included 4 medical centers (10 subjects per center), which included MGH, the University of Massachusetts Medical School, Stanford University, and the University of North Carolina at Chapel Hill. Results are summarized in Figure 1.

All of these studies used marketed glucagon (glucagon for injection, Eli Lilly). Due to its limited stability, Lilly glucagon must be reconstituted immediately before use. Animal studies have previously shown that despite its limited chemical stability, Lilly glucagon maintains its biological activity for up to 7 days in solution. Using this data, an Investigational New Drug (IND) exemption was obtained from the FDA for its use in a pump for up to 27 hours. This allowed these studies to be performed by asking volunteers to reconstitute a new vial of glucagon and fill the glucagon pump at approximately the same time every day. However, marketed Lilly glucagon has no path forward for approval for chronic BP use.

1.4 ZP4207

ZP4207 is a peptide analog of human glucagon that is being developed to treat hypoglycemia in patients with T1DM and type 2 diabetes mellitus. ZP4207 exhibits improved physical and chemical stability in aqueous media and is suitable for liquid formulation. ZP4207 is comprised of 29 amino acids and has 7 amino acid substitutions when compared to native glucagon.

Two clinical Phase 1 trials have been conducted to establish safety and tolerability of ZP4207 after single and multiple dosing to healthy patients and T1DM patients under insulin-induced hypoglycemic conditions.

The First Human Dose (FHD) trial (ZP4207-14013) was finalized in April 2015. The trial was a randomized, double-blinded trial with the objectives to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of ZP4207 as compared to an active comparator. Part 1 included a single ascending dose in healthy volunteers in cohorts of 8. In each cohort, the patients were randomized 3:1 to ZP4207 (n=6) or Novo Nordisk GlucaGen® (n=2). Five cohorts with SC administration (0.01, 0.1, 0.3, 1.0, and 2.0 mg ZP4207 compared to 1 mg GlucaGen) and 3 cohorts with intramuscular (IM) administration (0.3, 1.0, and 2.0 mg ZP4207 compared to 1 mg GlucaGen) were included. Part 2 included 2 sequence groups of

[redacted]

10 hypoglycemic T1DM patients. The patients were treated with fixed single IM doses of 0.7 mg ZP4207 and 1.0 mg GlucaGen in a sequential cross-over design in a randomized treatment order.

The second clinical trial (ZP4207-15007) was a single-center, double-blind, Phase 1b trial investigating the safety and tolerability, PK and PD of ZP4207 following repeated administration in healthy volunteers compared to placebo. It was finalized in July 2015. Each of the 3 cohorts comprised 8 subjects, who received 5 repeated SC doses of ZP4207 or placebo in a 3:1 treatment allocation. The first cohort started with the lowest dose of 0.1 mg. Cohort 2 and 3 continued with 0.3 and 1.0 mg, respectively.

The Phase 1 results did not give rise to specific safety concerns, beyond those related to the pharmacological effect of ZP4207. All adverse events (AEs) recorded in the trials were of mild or moderate severity. The most frequent systemic AE related to treatment with ZP4207 was nausea, which is a known side-effect following administration of glucagon. The most frequent injection site reaction was transient erythema, occurring in all ZP4207, glucagon, and placebo treatment groups, irrespective of dose. No anti-drug antibodies (ADA) incidences were observed.

The observed PD response, in terms of increased plasma glucose, in insulin-induced hypoglycemic patients with T1DM following dosing with 0.7 mg ZP4207 administered IM was similar to that observed following IM dosing with 1.0 mg glucagon (GlucaGen, Novo Nordisk). An increase in plasma glucose of ≥20 mg/dL from hypoglycemic levels was achieved within 30 minutes for all patients.

In terms of PK, ZP4207 had a short half-life and high clearance and dose proportionality for both maximum plasma concentration and area under the concentration-time curve from time 0 to 300 minutes in the dose range 0.1 to 2.0 mg following SC administration. Following IM administration, dose proportionality was shown in the investigated dose range of 0.3 to 2.0 mg. The PK properties of 0.7 mg ZP4207 IM were comparable with those of 1.0 mg glucagon (GlucaGen, Novo Nordisk) with IM administration.

1.5 Risk/Benefit

While the potential risks are minimal, the findings of this trial may reveal information that can substantially improve medical care for persons with diabetes. Therefore, the overall risk/benefit for patients participating in this trial is assessed as acceptable.

Potential Risks and Discomforts

Trial patients will be informed by the Investigator of the potential risks of ZP4207 and other trial-related procedures before they enter the trial.

In this trial, patients with T1DM will be included to test the safety and efficacy of the BP using either the iLet or the iPhone platform when used with ZP4207 versus Lilly glucagon. The cross-over design with inclusion of 1 group of 10 T1DM patients into the 2 iLet treatment arms and the inclusion of a second group of 10 T1DM patients into the 2 iPhone-based BP treatment arms in a randomized order will allow for a direct comparison of the safety and efficacy of the 2 treatments, based on intra-patient variability only.

[redacted]

Patients may experience mild discomfort associated with the insertion of the infusion sets and sensor into the SC tissues. The risk of discomfort due to insertion of infusion sets and sensors is expected to be slightly greater than in their lives outside the trial because more infusion sets will be inserted and a CGM sensor will be inserted. Most patients will use only 1 infusion set and not all will use a CGM sensor in usual care.

There is a potential risk of hypoglycemia, since recombinant insulin analog will be administered. Due to frequent monitoring of glucose and direct supervision by a registered nurse (RN) or Doctor of Medicine (MD) at all times, the risk of a hypoglycemic episodes leading to significant harm to patients is expected to be substantially lower than their risk during their usual therapy.

There is a risk of hyperglycemia. This risk is expected to be less than the risk during the patients' lives outside of the trial based on data from earlier BP trials and the design of this trial.

Treatment with ZP4207 and marketed glucagon can result in undesired effects or complaints. Undesired effects and complaints such as gastrointestinal side effects including nausea, vomiting, and diarrhea are known side effects of glucagon administration at higher dose levels. The frequency of nausea associated with the administration of 1 mg of glucagon according to the Summary of Product Characteristics (SPC) for Glucagon is described to be between 1/10 and 1/100. The frequency of vomiting is described to be between 1/100 and 1/1000 (Novo Nordisk, 2015). Similar gastrointestinal side effects have also been observed to a limited degree in the 2 clinical trials conducted with ZP4207, again at higher dose levels. The individual doses of ZP4207 and Lilly glucagon delivered by the BP are expected to be significantly lower than doses typically associated with nausea. Episodes of low blood pressure have also been observed after administration of higher doses of glucagon and ZP4207. As with every novel drug substance, new and yet unknown side effects may also occur.

There are limited data available to describe the immunogenic potential of glucagon products available on the market, but the data available indicate that marketed glucagon only has a small immunogenic potential. A Phase 1 trial performed with recombinant human glucagon and animal derived glucagon in 75 healthy patients did not show signs of ADA measured 13 weeks after trial product administration (Eli Lilly, 2005). In the ZP4207 FHD trial, ZP4207-14013, no confirmed anti-ZP4207 or anti-glucagon antibodies were detected in any of the samples. In addition, the 5 sequential administrations of ZP4207, as applied in trial ZP4207-15007, were not associated with the development of antibodies against ZP4207 in the 18 subjects enrolled to receive ZP4207. The optimized formulation of ZP4207, as applied in the present trial is not expected to change the immunogenic potential of the Investigational Medicinal Product (IMP).

In relation to diabetes therapy, development of insulin-antibodies is documented more substantially and route of administration has been shown to influence immunogenic potential of insulins. However, these antibodies against insulin generally do not have an impact on insulin action and are thus not clinically relevant.

In terms of consequence, development of high titer antibodies against ZP4207 could, in theory reduce the activity of endogenous glucagon, which again, in theory could influence

[redacted]

hypoglycemic episodes. However, most patients with T1DM do not secrete glucagon normally in response to hypoglycemia, so they would be less likely to be negatively impacted by anti-glucagon antibodies. Limited suppression of glucagon would, however, not be considered critical, as low glucose levels can also be corrected by other means, including oral intake of glucose and by other endogenous hormones such as oxyntomodulin.

Overall, ZP4207 is judged to be a low-risk molecule, based upon the available clinical data as well as the outcome of the risk-based approach to the immunogenicity assessment made. The present trial will include sampling for measurement of antibodies against ZP4207 prior to first dosing (Visit 3) and at the Follow-up Visit. In line with regulatory guidance documents, these samples will be appropriately analyzed and the results will be included in the overall assessment of the immunogenic potential of ZP4207 after completion of each trial and as the clinical development program advances.

Administration of ZP4207 may be associated with a risk of allergic reactions similar to those observed for other therapeutic peptides or proteins. Patients with known or suspected allergies to the trial products or related products will be excluded from the trial. Mild or moderate allergic reactions may include symptoms of rash, fever, flu-like symptoms, nausea, headache, and myalgia. Acute generalized hypersensitivity reactions are usually very rare but may include symptoms of flushing, sweating, dizziness, change in blood pressure, and difficulties in breathing. The risk of acute hypersensitivity reactions is described to be less than 1/10,000 for native glucagon. No severe acute hypersensitivity reactions have been observed in the 2 clinical trials conducted with ZP4207.

Potential Benefits

Based on experiences from previous trials of the BP and the design of this trial, patients enrolled in the trial may benefit from a reduction in risk of hypoglycemia and hyperglycemia and a better mean glucose compared to their usual diabetes care during their short trial participation.

The data derived from this trial will allow evaluation of safety and tolerability of ZP4207 in the iLet and the iPhone-based BP, and the robustness and effectiveness of the new BP control system. The data obtained will be used to further improve the iLet and will allow the expansion to larger outpatient trials using the iLet or the iPhone-based BP with ZP4207.

This trial is a necessary step in preparing the BP with ZP4207 to become available to people with T1DM. Wide availability of the BP with ZP4207 could improve the medical care of adults and children with T1DM.

[redacted]

2 TRIAL OBJECTIVES

2.1 Primary Objective

The primary objective is to conduct a trial testing the safety and tolerability of the BP using either the iLet or the iPhone platform when used with ZP4207 in 20 adult (≥18 years of age) patients with T1DM.

2.2 Secondary Objectives

The secondary objectives are to measure glycemic regulation, including hypoglycemia exposure (percent of time spent with CGM glucose <60 mg/dL), evaluate BP device reliability, and to document the satisfaction of patients with the BP with the goal of optimizing the functionality and user interface of the BP.

3 TRIAL DESCRIPTION

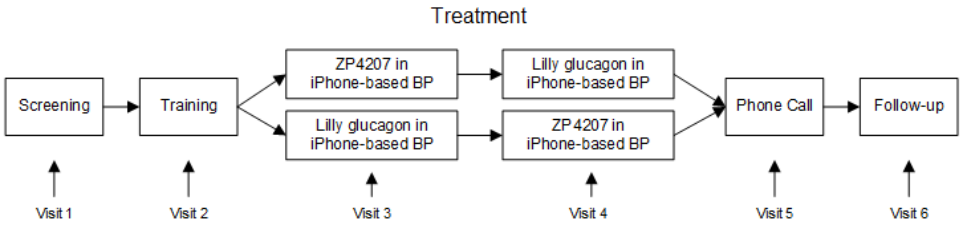
3.1 Summary of Trial Design

This trial is a single-center, open-label, 2-part, randomized cross-over trial. The trial will enroll adult patients with T1DM and will assess the safety and efficacy of the BP using either the iLet or the iPhone platform using the glucagon analog ZP4207 versus Lilly glucagon. In Part 1, up to 10 patients will participate in two 1-day treatment arms in random order (iPhone-based BP using ZP4207 and iPhone-based BP using Lilly glucagon) according to a pre-generated randomization scheme. In Part 2, up to 10 new patients will participate in two 1-day treatment arms in random order (iLet using ZP4207 and iLet using Lilly glucagon) according to a pre-generated randomization scheme. Patients can only participate in 1 part of the trial. An interim database lock may occur upon completion of Part 1 of the trial to analyze the iPhone-based BP data. The iLet and the iPhone-based BP will also administer insulin (insulin lispro, Lilly Humalog) using the same BG control algorithm for all 4 treatment arms. The trial will be conducted at a single center, the MGH Diabetes Center in Boston, MA.

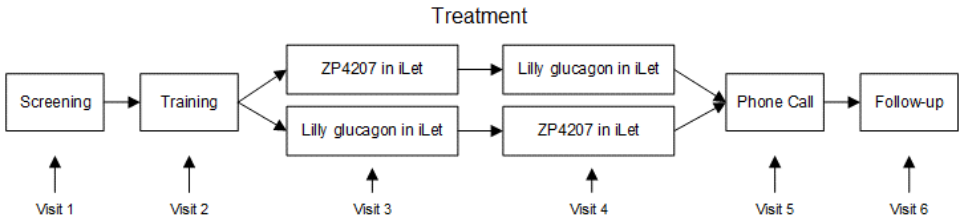
The overall trial design schematic is displayed in Figure 2.

Figure 2. Trial Design Schematic

Part 1:



Part 2:



Patients can only participate in 1 part of the trial.
BP = bionic pancreas.

3.2 Indication

ZP4207 is an anti-hypoglycemic glucagon analog in a ready-to-use liquid formulation which is being studied to improve glycemic control in adults (and children) with T1DM as part of a bihormonal BP.

3.3 Number of Patients

Up to 40 adult patients with T1DM can be enrolled. The upper bound is based on the expectation that some patients will be excluded after the Screening Visit and the possibility that some patients may have to be discontinued before completion (due to, for instance, inter-current illness or patient withdrawal). It is expected that up to 10 patients will complete each part of the trial protocol.

4 SELECTION AND WITHDRAWAL OF PATIENTS

The trial will enroll patients who already manage their T1DM using continuous SC insulin infusion pump therapy. This requirement is imposed because multiple daily injection therapy involves the use of medium-acting or long-acting basal insulin that would require an extended washout period.

4.1 Inclusion Criteria

1. Male and female patients with T1DM for at least 1 year, as defined by the American Diabetes Association
2. Age ≥18 years
3. Diabetes managed using an insulin pump for ≥6 months
4. Prescription medication regimen stable for >1 month (except for medications that will not affect the safety of the trial and are not expected to affect any outcome of the trial, in the judgment of the Investigator)
5. Informed consent obtained before any trial-related activities (trial-related activities are any procedure that would not have been performed during normal management of the patient)
6. Patients in good health according to age (medical history, physical examination, vital signs, 12-lead electrocardiograms [ECGs], laboratory assessments), as judged by the Investigator

4.2 Exclusion Criteria

1. Unable to provide informed consent (e.g., impaired cognition or judgment)
2. Unable to safely comply with trial procedures and reporting requirements (e.g., impairment of vision or dexterity that prevents safe operation of the BP, impaired memory, unable to speak and read English)
3. Participation in another clinical trial of an investigational agent or device concurrently or within 1 month (or 5 half-lives) prior to the Screening Visit
4. Previous exposure to ZP4207
5. Females of childbearing potential who are pregnant (positive urine human chorionic gonadotropin [HCG]), breast feeding, plan to become pregnant in the immediate future, or sexually active without using highly effective contraception methods (highly effective methods are considered those with a failure rate less than 1% undesired pregnancies per year including surgical sterilization, hormonal intrauterine devices [coil], oral hormonal contraceptives, sexual abstinence, or a surgically sterilized partner) or postmenopausal women amenorrheic for less than 1 year with serum follicle-stimulating hormone (FSH) level ≤40 IU/L and not using highly effective contraceptive methods during the trial and until 1 month after last dosing in the trial
6. Male who is sexually active and not surgically sterilized who or whose partner(s) is not using highly effective contraceptive methods (highly effective contraceptive measures include surgical sterilization, hormonal intrauterine devices [coil], oral hormonal contraceptives, each in combination with spermicide-coated condoms), or who is not willing to refrain from sexual intercourse from the first dosing until 1 month after last dosing in the trial
7. Current alcohol abuse (intake averaging >3 drinks daily in last 30 days) or use within the last 6 months of controlled substances without a prescription (other than marijuana)
8. New onset clinically significant illness within 4 weeks prior to screening, as judged by the Investigator
9. Unwilling or unable to refrain on the treatment visits from:
    a. Acetaminophen in any form
    b. Use of drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the trial (use of beta blockers will be allowed as long as the dose is stable and the patient does not meet the criteria for hypoglycemia unawareness while

[redacted]

taking that stable dose, but use of benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the Investigator)

10. History of liver disease that is expected to interfere with the anti-hypoglycemia action of glucagon (e.g., liver failure or cirrhosis). Other liver disease (i.e., active hepatitis, steatosis, active biliary disease, any tumor of the liver, hemochromatosis, glycogen storage disease) may exclude the patient if it causes significant compromise to liver function or may do so in an unpredictable fashion.
11. Aspartate aminotransferase >2 × upper limit of normal (ULN), alanine aminotransferase >2 × ULN, or bilirubin >1.5 × ULN on screening laboratories
12. Renal failure on dialysis or estimated glomerular filtration rate <30 mL/min/1.73 m^2 on screening laboratories
13. Hemoglobin <12 gm/dL for men and <11 gm/dL for women
14. Personal history of cystic fibrosis, pancreatitis, pancreatic tumor, or any other pancreatic disease besides T1DM
15. Any known history of coronary artery disease including, but not limited to, history of myocardial infarction, stress test showing ischemia, history of angina, or history of intervention such as coronary artery bypass grafting, percutaneous coronary intervention, or enzymatic lysis of a presumed coronary occlusion)
16. Congestive heart failure with New York Heart Association Functional Classification III or IV
17. History of transient ischemic attack or stroke in the last 12 months
18. Seizure disorder, history of any non-hypoglycemic seizure within the last 2 years, or ongoing treatment with anticonvulsants
19. History of hypoglycemic seizures (grand-mal) or coma in the last 12 months
20. History of hypoglycemic unawareness in the last 12 months
21. History of pheochromocytoma: fractionated metanephrines will be tested in patients with history increasing the risk for a catecholamine secreting tumor:
    a. Episodic or treatment refractory (requiring 4 or more medications to achieve normotension) hypertension
    b. Paroxysms of tachycardia, pallor, or headache
    c. Personal or family history of MEN 2A, MEN 2B, neurofibromatosis, or von Hippel-Lindau disease
22. History of adrenal disease or tumor
23. Hypertension with systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg despite treatment
24. Untreated or inadequately treated mental illness (indicators would include symptoms such as psychosis, hallucinations, mania, and any psychiatric hospitalization in the last year), or treatment with anti-psychotic medications that are known to affect glucose regulation
25. Electrically powered implants (e.g., cochlear implants, neurostimulators) that might be susceptible to radio frequency interference
26. History of adverse reaction to glucagon (including allergy) besides nausea and vomiting
27. History of severe hypersensitivity to milk proteins or lactose
28. Established history of allergy or severe reaction to adhesive or tape that must be used in the trial
29. Use of oral anti-diabetic medications (e.g., thiazolidinediones, biguanides, sulfonylureas, glitinides, dipeptidyl peptidase-4 [DPP-4] inhibitors, sodium-glucose co-transporter-2 [SGLT-2] inhibitors)

30. Inadequate venous access as determined by trial nurse or physician at time of screening
31. Any factors that, in the opinion of the Investigator, would interfere with trial endpoints or the safe completion of the trial

4.3 Target Population

Patients who meet all of the inclusion and none of the exclusion criteria will be considered as candidates for this trial. Individuals who have previously inquired about participation in BU/MGH trials and have asked to have their contact information kept on file will be contacted. In addition, advertisements for the trial may be posted at the MGH Diabetes Center and other places, and may be distributed in the weekly broadcast e-mail of research studies seeking volunteers. A letter may be sent to adult endocrinologists in the Boston metropolitan as well as selected nearby endocrinologists informing them of the trial and asking them to refer any eligible patients who might be interested. Information will be posted about the trial along with contact information on the BU/MGH website www.bionicpancreas.org and on www.clinicaltrials.gov.

4.4 Withdrawal Criteria

The participation of individual patients will be discontinued if they experience:

- Seizure or unconsciousness associated with hypoglycemia and associated with participation in the trial
- Persistent nausea and vomiting thought to be related to glucagon dosing associated with participation in the trial
- Hospitalization associated with participation in the trial
- Pregnancy
- Diabetic ketoacidosis

If more than 1 patient must be withdrawn from the trial for these reasons, the trial will stop and a vote of the Data and Safety Monitoring Board (DSMB) will be required to restart it. All AEs that are serious and unexpected but related will be reported to the DSMB within 5 working days.

Note that patients may discontinue participation at any time. Patients may be removed from the trial for other reasons, for instance, failure to comply with trial procedures or intercurrent illness that is unrelated to the BP but that precludes safe participation. Discontinuation of participation for these reasons will not contribute to a decision to discontinue the trial.

5 ASSIGNMENT TO TREATMENT GROUPS

This trial is an open-label, 2-part, randomized cross-over trial. Patients who have completed the Screening Visit and meet all of the inclusion and none of exclusion criteria will be enrolled into the trial. In Part 1, up to 10 patients will participate in two 1-day treatment arms in random order (iPhone-based BP using ZP4207 and iPhone-based BP using Lilly glucagon) according to a pre-generated randomization scheme. In Part 2, up to 10 new patients will participate in two 1-day treatment arms in random order (iLet using ZP4207 and iLet using Lilly glucagon) according to a pre-generated randomization scheme. Up to 2 patients may participate in the trial per day. The order of the treatment visits will be randomized in blocks of 2 patients.

[redacted]

6 TRIAL TREATMENT

6.1 Investigational Medicinal Products

Insulin: The trial involves SC administration of insulin lispro (Humalog, Lilly), which is commercially available by prescription and is indicated for patients with T1DM, but not for use in a BP.

Glucagon: The trial also involves SC administration of Lilly glucagon in 1 iLet arm and 1 iPhone-based BP arm. Lilly glucagon is commercially available by prescription and is indicated for patients with T1DM in severe hypoglycemia, but not for use in a BP.

ZP4207: The trial also involves SC administration of the glucagon analog ZP4207, 1 mg/mL, in the other iLet arm and the other iPhone-based BP arm. ZP4207 will be made available by Zealand Pharma A/S, Denmark as liquid formulation in prefilled syringes of 0.6 mL.

6.2 Storage and Drug Accountability of IMPs

All IMPs will be stored and handled in accordance with the Sponsor's instructions and/or the product labeling at the Investigator's site, e.g., refrigerated (+2ºC to +8ºC) and should not be exposed to excessive heat, direct sunlight and never be frozen.

All used, partly used, and unused vials or prefilled syringes must be kept by the Investigator and stored between +2ºC and +8ºC (unused) or at room temperature (partly used and used). Used and unused pre-filled syringes must be stored separately.

The Investigator must ensure the availability of proper storage conditions and record and evaluate the temperature. Temperature of the refrigerator used for drug storage is monitored continuously, an alarm system is established. The Investigator must inform the monitor immediately if any IMP has been stored outside specified conditions (e.g., outside temperature storage). Investigational Medicinal Product that has been stored improperly must not be dispensed to any patient before it has been re-evaluated and approved for further use. The Investigator must take appropriate action to ensure correct storage.

For the IMP, the Investigator must keep an accurate record of all IMPs received and the products used for each patient in a Drug Accountability Record. Storage locations, batch numbers, and expiry dates are also documented in this form.

The drug accountability must be performed in a timely manner by the monitor.

6.3 Dispensing and Return of IMPs

No IMPs may be dispensed to any person not enrolled in the trial.

Upon completion of the trial, the Sponsor will be responsible for destruction or storage of IMPs (used, partially used, or unused). These duties can be delegated to a contract research organization (CRO) and must be documented in the trial files.

[redacted]

6.4 Doses

The iLet and the iPhone-based BP can administer isolated insulin-glucagon doses once every 5 minutes. A single automated bolus of insulin will not exceed 3 units per 5-minute dose (30 µl of U-100 insulin) in both systems, and a single meal-priming dose, in response to a meal announcement made by the user, will not exceed 12 units (120 µl of U-100 insulin). A single bolus of glucagon will not exceed 80 µg (80 µl of 1 mg/mL Lilly glucagon or 1 mg/mL ZP4207). In prior studies, typical doses of glucagon were in the range of 2.5-40 µg per dose. The iLet and the iPhone-based BP are capable of administering as little as ~0.5 µl (0.05 units of U-100 insulin or 0.5 µg of 1 mg/mL ZP4207).

It is expected that the mean total daily doses of glucagon/ZP4207 will be <1.0 mg daily as in previous studies. The mean daily glucagon dose in a previous 11-day outpatient trial was 0.5 mg/day (range 0.2-0.9 mg/day). Currently, single doses of up to 2 mg ZP4207 have been administered in clinical trials. The recommended dose of marketed glucagon for adult patients suffering from severe hypoglycemia is 1 mg as a single injection. Mean glucagon levels in previous inpatient studies have been above the normal fasting range for glucagon only 1% of the time. Therefore, the glucagon exposure of patients is expected to be modest.

6.5 iPhone-based Bionic Pancreas

Infusion Set: Patients will wear 2 FDA-approved commercially available infusion sets, 1 for insulin infusion and 1 for glucagon infusion. Infusion sets that are compatible with the Tandem t:slim infusion pump (luer lock connection) will be provided.

Continuous Glucose Monitors: One transcutaneous glucose sensor for the Dexcom G4 Platinum (Garcia, 2013) will be inserted in the abdominal SC tissue and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to the sensor and the whole assembly is held to the skin with an adhesive patch and communicates wirelessly with the BP. If the G4 sensor fails for any reason during the trial (loss of CGM signal), it will be replaced promptly.

Bionic Pancreas Control Unit: The control unit consists of a stock iPhone 4S and a Dexcom G4 Platinum receiver connected with a custom hardware interface and placed back-to-back in a custom enclosure. The G4 receiver converts the raw wireless signal from the transmitter into an estimated BG signal that is sent via a hardwired connection to the iPhone.

The iPhone runs iOS 6 in “Guided Access” mode, where the only app accessible to the patient is the Beta Bionics app, which runs the control algorithm. The home screen, where typical user options reside, is password protected. Access to other functions on the iPhone (primarily the Settings options) is separately password protected and only accessible to the study staff. This prevents accidental activation of other apps that could interfere with the function of the BP. The control algorithm app has a graphical user interface (GUI) that displays the current CGM glucose, a graphical history of the CGM glucose, and doses of insulin and glucagon delivered by the control algorithm. The GUI can also be used to input meal announcements, designating the size of the meal as larger than typical, typical in size, smaller than typical, or just a bite, and the type of meal as breakfast, lunch, or dinner. This will trigger a partial meal-priming bolus the size of which will adapt during the course of the trial to meet a target of 75% of the insulin needs for that size and type of meal.

[redacted]

The target glucose level will be programmed to 100 mg/dL by the study engineers prior to the start of each experiment. This will be locked for each arm of the study; the patient will be unable to accidentally change or tamper with this setting.

The GUI can be used to manage meal boluses and correction boluses during periods when the CGM is offline, such as the period after a sensor is replaced and before the new sensor has been calibrated. During these times the control algorithm will determine and direct the administration of insulin basal rates based on the patient's weight. The controller will also administer insulin and/or glucagon as appropriate in response to any entered BG values, just as if they were CGM values.

The GUI also displays visual alarms associated with an audio signal if communication is dropped between the CGM transmitter and the BP control unit or between the control unit and the 2 insulin pumps.

The iPhone communicates wirelessly via the Bluetooth Low Energy (BTLE) protocol with 2 Tandem t:slim insulin pumps to deliver insulin and glucagon.

Tandem t:slim Pumps: These pumps are FDA-approved insulin pumps with reservoirs capable of holding 300 units (3 mL) of insulin or 3 mL of glucagon or ZP4207 solution. The pumps have a mechanical dosing resolution of 1/120 (0.00833) unit and can deliver liquids at a maximal rate of ~33 µl per minute (2 mL per hour). They are slave to the BP control unit and are controlled wirelessly via the BTLE protocol by the iPhone 4S.

6.6 iLet Bionic Pancreas

Infusion Set: A novel, dual cannula infusion set has been designed specifically for use with the iLet. Patients will wear dual channel tubing that will be attached to 2 infusion sets with 1 steel cannula each, 1 for insulin infusion and the other for glucagon infusion. The tubing and infusion sets will have undergone sterilization prior to being delivered in a sealed pouch. The steel cannulae will be inserted in the abdominal SC tissue.

Continuous Glucose Monitors: One transcutaneous glucose sensor for the Dexcom G4 Platinum (Garcia, 2013) will be inserted in the abdominal SC tissue and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to the sensor and the whole assembly is held to the skin with an adhesive patch and communicates wirelessly with the BP. If the G4 sensor fails for any reason during the trial (loss of CGM signal), it will be replaced promptly.

Bionic Pancreas Control Unit: The iLet is being built according to Class III medical device standards, adheres to a comprehensive and robust quality system, and is fully compliant with International Organization for Standardization (ISO) 13485 standards and document control practices. The iLet is a fully-integrated dual-hormone BP system that integrates the CGM technology (currently the Dexcom G4 Share system) as well as 2 independent motor-drivetrain pumping assemblies, which independently actuate the delivery of insulin and glucagon from pre-filled cartridges that are separately loaded into the iLet housing. Each drivetrain assembly utilizes a lead screw, which is driven by a precision micromotor, a gear case assembly, and a motor controller unit, in a manner similar to what is commonly found in most insulin infusion pumps on the market today. The iLet has dosing accuracy that is comparable to FDA-approved insulin pumps currently on the market. The iLet has a built-in BTLE radio that

also allows automatic communication with the paired CGM, as well as the Nova StatStrip® Xpress BG meter (Nova Biomedical). The iLet does not contain a cellular nor a WiFi radio, and does not accept input data from another mobile device (e.g., smartphone), other than the paired CGM and BG meter(s).

The mathematical control algorithms (which are the same as those used in the iPhone-based BP), the CGM glucose engine (Dexcom), and the native user interface software, are all interconnected through controller framework software and reside as embedded systems on printed circuit boards contained within the device housing. The touchscreen-enabled, menu-driven user interface and onboard processor provide a comprehensive and standalone platform, which allows the iLet to operate independently of smartphones or other devices and without the need for internet support during routine operation. The graphical user interface of the iLet has the same user options and capabilities of the iPhone BP, including having its home screen password protected and its settings options only accessible to trial staff via a separate password.

6.7 Other Trial Devices

YSI 2300 STAT Plus™ (Yellow Springs Instruments): The YSI 2300 STAT Plus is an FDA-approved glucose analyzer. Blood glucose measurements using the YSI 2300 STAT Plus will be obtained off of the intravenous (IV) line during both treatment visits.

Nova Biomedical StatStrip Xpress Glucose Meter: The Nova StatStrip Xpress glucose meter is an FDA-approved glucose meter that is commercially available. Blood glucose measurements for CGM calibration will be obtained with the Nova StatStrip Xpress during both treatment visits if the YSI 2300 STAT Plus fails and via fingerstick with the Nova StatStrip Xpress during any periods when IV blood samples are not available for any reason or the IV fails.

Exercise Bike: The trial will utilize a stationary exercise bike (ergometer) for the in-clinic exercise at the treatment visits. This bike will be stored at the Diabetes Research Center when not in use.

6.8 Concomitant Medications

6.8.1 Permitted Medications and/or Procedures

Patients may take any over-the-counter medications that they wish during the trial, with the exception of any medication containing acetaminophen as that may cause interference with CGM sensing. All concomitant medications, including over-the-counter medications, should be recorded.

Use of beta blockers will be allowed as long as the dose is stable and the patient does not meet the criteria for hypoglycemia unawareness while taking that stable dose.

If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.

[redacted]

6.8.2 Excluded Medications and/or Procedures

During the trial, patients will not use any recreational drugs or drugs of abuse. The need to take prescription drugs that dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder appropriate decision-making may be grounds for exclusion from the trial or discontinuation of participation, a decision that will be made by the Investigator.

Use of benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the Investigator. Use of oral anti-diabetic medications (e.g., thiazolidinediones, biguanides, sulfonylureas, glitinides, DPP-4 inhibitors, SGLT-2 inhibitors) will also be excluded.

7 TRIAL PROCEDURES

7.1 Informed Consent

After potential patients have had time to review the consent document, and prior to any trial-related activities, they will meet with a trial MD or designee who will explain the trial, answer any questions, and administer informed consent. In the event that a volunteer is a patient of 1 of the trial MDs, another staff MD or designee will answer questions and administer consent. The patients will be fully informed of their responsibilities and their rights while participating in the trial as well as of the possible risks and potential benefits of participation in the trial. They will have the opportunity to discuss all questions and ample time to consider participation.

Trial-related activities are any procedures that would not have been performed during normal management of the patient. Patients who wish to participate in the trial will be asked to personally date and sign an informed consent form (ICF). Likewise, the Investigator must also personally date and sign the ICF. All patients will be provided with a copy of their own signed and dated ICF.

Trial staff will answer any questions that the patients may have during their participation. They will share any new information in a timely manner that may be relevant to the patient's willingness to continue participating in the trial. The patients may choose to discontinue their participation at any time.

7.2 Screening Visit (Visit 1)

All patients will have a Screening Visit to confirm eligibility. The patient will be interviewed and the electronic Case Report Form (eCRF) will be completed by trial staff to establish whether the patient is eligible.
Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator.

Once all of the results have been returned, a trial MD will review the eCRF to determine patient eligibility. If a patient is not eligible to continue in the trial, the results of abnormal tests will be reported to the patient and to a health care provider of their choosing.

[redacted]

7.2.1 Data Collected at Screening

- Age, sex, race, and ethnicity
- Date of last menstrual period in female patients
- Medical, surgical, and social history, allergies, and review of systems relevant to inclusion and exclusion criteria, including:
  - Date of diabetes diagnosis
  - Duration of insulin pump use and type of insulin used in pump
  - Type/model of insulin pump
  - Insulin regimen (basal rate, sensitivity factor, and carbohydrate ratio)
  - Average total daily dose of insulin in the last 30 days as available (from pump history)
  - Usage of CGM, if any (type of CGM, days per month worn, usage of data, whether insulin is dosed based on CGM alone, alarm settings)
- Concomitant illness (any illness present at screening)
- Concomitant medications (prescription and non-prescription) and date of last change in medication regimen
- Height, weight, physical examination, and vital signs including body temperature and blood pressure
- 12-lead ECG
- Hemoglobin A1c
- Chemistry and hematology samples (see Appendix B)
- Urine HCG pregnancy test for women of childbearing potential
- FSH level for postmenopausal women amenorrheic for less than 1 year
- Fractionated plasma metanephrines (if indicated by history)

7.3 Training Visit (Visit 2)

A Training Visit will take place before the first treatment visit. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor and trial policies and procedures. Trial staff will verify that the patients have understood the material and are competent to participate safely in the trial. Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator. Concomitant medications will also be reviewed.

7.4 Treatment Visits (Visit 3 and Visit 4)

- Visit 3 will take place at least 48 hours after screening (Visit 1) and no more than 30 days after screening (Visit 1).
- There will be a 24-hour minimum washout between Visit 3 and Visit 4 and a maximum of 3 weeks between Visit 3 and Visit 4.
- Up to 2 patients may participate per day.
- In Part 1, each patient will participate in 2 treatment visits: 1 with the iPhone-based BP using ZP4207 and 1 with the iPhone-based BP using Lilly glucagon in a randomized order.
- In Part 2, each patient will participate in 2 treatment visits: 1 with the iLet using ZP4207 and 1 with the iLet using Lilly glucagon in a randomized order.

[redacted]

- The night before the treatment visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be instructed to call if they encounter any difficulty with their CGM.
- Patients will be responsible for their own medications other than insulin during the trial. Any medical advice needed by the patients during their participation that is not directly related to BG control should be obtained from them in their usual manner. Patients may take any over-the-counter medications that they wish during the trial, with the exception of any medication containing acetaminophen as that may cause interference with CGM sensing. If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.
- During the trial, patients will not use any recreational drugs or drugs of abuse. The need to take prescription drugs that dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder appropriate decision-making may be grounds for exclusion from the trial or discontinuation of participation, a decision that will be made by the Investigator.
- Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator.
- Patients will not tamper with the BP, including changing any settings.
- Patients may not remove the BP during the trial unless the BP failed or they are withdrawing from the trial.
- The exact time of each procedure and assessment will be documented.

7.4.1 Visit Procedures

- Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window. If BG is <50 mg/dL, treatment with simple carbohydrate is allowed. If the patient experiences persistent hypoglycemia, the visit will be rescheduled within the visit window. If the visit needs to be rescheduled due to hypoglycemia or hyperglycemia, trial staff will assist the patient with insulin or medication adjustments to address glycemic control. The patient will be instructed to contact trial staff later in the day if his or her BG remains uncontrolled.
- Upon arrival to the visit, the patient's weight and vital signs including body temperature and blood pressure will be documented.
- Patient reports of symptoms, any other complaints, and AEs will be reviewed.
- Concomitant medications will be recorded.
- Chemistry and hematology samples will be collected at visit start (see Appendix B).
- ADA samples will be collected before the start of dosing (Visit 3 only).
- A 12-lead ECG will be performed.
- A urine HCG pregnancy test will be performed in female patients of childbearing potential. If the test is positive, the patient will be informed of the result and the visit will be ended.

[redacted]

- Patients will complete a baseline survey about their attitudes and experience with their usual diabetes care.
- An IV catheter will be placed for blood sampling.
- Trial staff will assist the patient to calibrate their CGM, review the trial procedures again and assist with the setup of the BP system, including inserting and priming infusion sets.
- The control algorithm will be initialized only with the patient's weight. Diagnostics will be performed to ensure that the CGM device is appropriately calibrated and that all of the components of the BP systems are in working order.
- The basal rate of the patient's own insulin infusion pump will be changed to be 2-fold higher than weighted mean of the basal rate during the trial period. This is intended to increase the usage of glucagon during the treatment visit.
- The patients will continue to wear their own infusion pump infusing at the temporary 2-fold basal rate throughout the visit until the start of the structured exercise period, in addition to the BP.
- The staff will start the BP as close as possible to a minute divisible by 5 minutes (i.e., on a 5-minute mark). The starting time will be considered Hour 0.
- Additional calibrations will be performed at any of the BG checks throughout the day if the CGM value does not meet the ISO standard (<15 mg/dL difference for BG values <75 mg/dL; <20% absolute difference for BG values >75 mg/dL) at the time of the BG measurement AND it is a good time to calibrate (the CGM trend arrow is flat and there has been no carbohydrate intake in the last 30 minutes or glucagon boluses in the last 15 minutes).
- Blood samples will be taken from the IV at least hourly and processed for plasma ZP4207/glucagon. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator. The actual time of sampling will be recorded in the eCRF.
- Plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.
- Patients will be asked to rate any nausea and/or infusion site pain on 10 cm visual analog scales (VAS) at the beginning of the visit once the infusion sites have been placed but no drug has yet been administered, then approximately at the top of every hour during the visit, and at the end of the visit. Trial staff will also evaluate their infusion sites to document any erythema or edema at the same times. If moderate or severe pain is reported or swelling or redness occurs at the infusion site, the infusion site will be replaced in a different location. If moderate or severe pain, swelling, or redness continues at the old site for more than 30 minutes after the infusion site is removed, or if moderate or severe pain, swelling, or redness occurs at the new site, all infusion sites will be removed and the patient will be discontinued from the study. Any such symptoms will be followed until resolution.
- From the start of closed loop control until approximately Hour 3, the patients will continue to fast.

[redacted]

- Between approximately Hour 3 and Hour 4, patients will be provided with a lunch meal of their choice in the Diabetes Research Center from a menu of choices from nearby restaurants. They will be asked to choose a meal that is a “typical meal” for them. The content of their meal will not be restricted in any way, with the exception that the number of carbohydrates should be in the “typical” range for them at lunch, and that they must eat the same meal at the same time during both visits.
- At approximately 15 minutes before the meal, patients will administer a bolus for the meal with their own insulin pump based on the carbohydrate count for the meal.
- After lunch is completed, the patients will not be allowed any carbohydrate intake (non-caloric drinks will be permitted) until the trial is completed (except as necessary to treat hypoglycemia), to allow the BP to control the post-prandial BG without further interruption.
- Between approximately Hour 6 and Hour 7, the patients will start a period of structured exercise.
- At the start of the exercise period, patients will restore their normal basal insulin profile so that they will not have elevated insulin levels at the end of the study period when they are to transition back to their usual care.
- Patients will exercise on a stationary bike with a heart rate from 120-140 beats per minute for a total of 4,000 heart beats (approximately 30 minutes). Patients will rate their exercise intensity using the Borg scale every 5 minutes, with the target intensity level between 12 and 14. Heart rate will be measured every 5 minutes.
- BG measurements will be obtained off of the IV line every 10 minutes. If BG is <80 mg/dL, BG measurements will be obtained off of the IV line every 5 minutes.
    - Carbohydrates will be given for any BG <50 mg/dL according to the following protocol: Dextrose (g) = BSA (m^2)/[1.7 m^2 (women) or 1.9 m^2 (men)] *15 g.
    - Repeat treatments will be given at 15-minute intervals as long as BG remains <50 mg/dL.
- If there is an interruption in the Dexcom CGM output, trial staff will assist the patient in recovering CGM data streaming. If this requires replacement of the CGM sensor, BGs will be checked every 10 minutes (every 5 minutes if BG is <80 mg/dL) using blood from the IV until the CGM is able to be calibrated again. These BGs will be entered into the BP, which will treat them as CGM values and dose insulin and/or glucagon appropriately.
- If there is a complete failure of the BP operation, patients will take over their own BG control using their personal insulin pump until the BP can be brought back online. If BP control cannot be promptly resumed (e.g., within 30 minutes), the patient may be asked to repeat that trial day once.
- Patients may choose to withdraw from the trial at any time. If they withdraw from the trial, they should alert a provider immediately.
- Just prior to the end of the study visit, vital signs including body temperature and blood pressure will be obtained and a 12-lead ECG will be performed.
- After approximately Hour 8, but not earlier than at least 60 minutes after end of exercise, the BP will be stopped and the patient will continue with their personal insulin pump.

[redacted]

- If the patient experiences seizure or unconsciousness, persistent nausea or vomiting, diabetic ketoacidosis, persistent hyperglycemia with ketonemia, hemodynamic changes such as hypotension, or other medically significant findings, a longer observation period at the trial site may be necessary until the patient is considered stable for discharge. If the Investigator or trial staff determines that the patient requires further observation or treatment, the patient may be transferred to the emergency room for additional monitoring and/or medical care. At discharge, patients will be provided with any necessary instructions concerning personal insulin pump usage, food intake, and driving arrangements.
- The maximum amount of blood loss per study visit will be approximately 230 mL. The total blood loss for the entire study will be up to 460 mL.
- Patients will answer questionnaires (see Appendix C).
- Chemistry and hematology samples will be collected at visit end (see Appendix B).
- The BP and glucose meters will be collected and downloaded.
- A trial MD will review the last several hours of insulin and glucagon dosing and assist the patient in resuming their usual diabetes care. A longer observation period at the trial site may be necessary. Patients will be instructed to call trial staff with any questions, issues, or concerns.

7.4.2 Data Collected During the Treatment Visits

- CGM glucose every 5 minutes from the Dexcom G4 Platinum CGM
- All BG measurements taken
- Insulin total dose by the BP and the patient's own insulin pump
- Glucagon total dose
- Timing and content of the meal eaten and carbohydrate amount
- Timing of meal announcement and size of meal announced
- Timing and glucose values at calibrations
- Timing and amount of carbohydrates taken for hypoglycemia
- Data from a questionnaire about attitudes and expectations regarding the BP before and after each treatment arm (see Appendix C)
- Time patients were not under BP control for any reason
- List of technical faults associated with the BP including cause and resolution
- ZP4207/glucagon sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.
- Plasma glucose sampling will be collected at least hourly in parallel with ZP4207/glucagon exposure sampling. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
- Nausea and infusion site pain on a VAS at visit start (after insertion and before any drug administration), hourly, and at visit end
- Infusion site reaction according to the Draize scale at visit start (after insertion and before any drug administration), hourly, and at visit end
- Patient reports of symptoms, any other complaints, and AEs
- Vital signs including body temperature and blood pressure (at visit start and visit end) and weight
- Concomitant medications

[redacted]

- Chemistry and hematology samples (see Appendix B) at visit start and visit end
- ADA (Visit 3 only)
- 12-lead ECG at visit start and visit end
- Urine HCG pregnancy test for women of childbearing potential

7.4.3 Response to Hypoglycemia

- Patients are encouraged to check their BG for any symptoms of hypoglycemia.
- Patients will be permitted to take 15 grams of carbohydrates for any BG value <60 mg/dL. Trial staff will ensure proper functioning of the BP, infusion set, and insulin pump, and will encourage the patient to wait for the BP to treat the low blood sugar for as long as they feel comfortable.
- Patients will be required to take 15 grams of carbohydrates for any BG value <50 mg/dL. After treatment of hypoglycemia, a follow-up measurement will be taken 15 minutes later. Repeated measurements will be taken every 15 minutes until the BG is >60 mg/dL. Treatment will be repeated if subsequent BG values are still <50 mg/dL. All carbohydrate treatments for hypoglycemia will be documented by trial staff (amount and time).
- Trial staff will check the infusion site, BP, and insulin pump for normal operation any time hypoglycemia occurs. If there is any suspicion of infusion set malfunction, the site should be replaced. Trial staff will check the BP for any malfunction and correct any problems that are found.
- If no correctable fault is found, but there is doubt regarding the correct function of the BP system, an entirely new backup BP system may be started.
- If a patient experiences a seizure or unconsciousness associated with hypoglycemia, his or her participation in the trial will be discontinued.

7.4.4 Response to Hyperglycemia

- Trial staff will check the infusion site, BP, and insulin pump for normal operation any time BG is >300 mg/dL. If there is any suspicion of infusion set malfunction, the site should be replaced. Trial staff will check the BP for any malfunction and correct any problems that are found. If the BG remains >300 mg/dL for 2 hours despite troubleshooting, blood ketones will be measured. If the blood ketone result is >1.5 mmol/L, the visit will be stopped and rescheduled. The patient will be provided with insulin and a syringe to give an injection based on their correction factor.
- If a patient experiences diabetic ketoacidosis, his or her participation in the trial will be discontinued.
- If no correctable fault is found, but there is doubt regarding the correct function of the BP system, the treatment visit may be stopped and the visit rescheduled.

7.4.5 Response to Nausea/Vomiting

If significant nausea (e.g., that prevents the patient from eating normally) or any vomiting occurs, trial staff will notify the Investigator. Trial staff will assist the patient in troubleshooting, such as checking BG and the calibration of the CGM (excessive glucagon dosing may occur if the CGM is reading lower than the true BG). If a patient experiences persistent nausea and vomiting thought to be related to glucagon dosing, his or her participation in the trial will be discontinued.

[redacted]

7.4.6 Response to Other Medical Needs

If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.

7.4.7 Monitoring of Bionic Pancreas Performance

Bionic pancreas inventors and developers [redacted], [redacted], and/or an engineer trained by them will be readily available by phone for consultation for the trial staff at all times during the course of the trial.

7.4.8 Supervision by Trial Staff

A trial MD will be on call at all times during the course of the trial. An RN or MD will be with the trial patients in the Diabetes Research Center at all times.

7.5 Phone Call (Visit 5)

A phone call will be conducted 7 days ±3 days following the last day of dosing (Visit 4) to review AEs and concomitant medications.

7.6 Follow-up Visit (Visit 6)

Patients will return for a Follow-up Visit 25 days ±4 days following the last day of dosing (Visit 4), for chemistry, hematology, and ADA sampling, and a review of AEs and concomitant medications.

8 ENDPOINTS

8.1 Primary Endpoint

The primary endpoint is the safety and tolerability of ZP4207 in the BP using either the iLet or the iPhone platform as assessed by:

- Number and type of AEs
- Clinical laboratory measurements
- Vital signs
- 12-lead ECG
- Local tolerability and infusion site reactions as measured with the Draize scale
- Immunogenicity as measured by ADA
- Pain as measured on a 10 cm VAS
- Nausea as measured on a 10 cm VAS

8.2 Secondary Endpoints

The secondary endpoints include measurements of BP function as well as glycemic and non-glycemic measurements.

8.2.1 Bionic Pancreas Function

This endpoint data will be generated from the BP data during each treatment visit:

- Average percent insulin dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
    - Average percent glucagon/ZP4207 dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts calculated by the BP algorithm that are successfully issued to the pump by the BP (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts calculated by the BP control algorithm that are successfully issued by the BP
    - Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully issued by the BP
- Average percent of 5-minute steps during which the BP is functioning nominally in all respects based on real-time CGM data (new CGM glucose reading captured, dose calculated, and dose issued to pumps)
- Average percent of 5-minute steps during which the BP is functioning nominally with or without a new CGM glucose reading captured (dose calculated and dose issued to pumps). If a CGM signal is not available, the dose calculated may be based on weight or historical basal rates.
- CGM reliability index, calculated as percent of possible values actually recorded by CGM
- CGM Mean Absolute Relative Difference versus time-stamped BG values from meter download
- List of technical faults associated with the BP including cause and resolution

8.2.2 Glycemic

All of following metrics will be generated from the Dexcom G4 Platinum CGM data during each treatment visit:

- Fraction of time spent within each of the following glucose ranges:
    - <50 mg/dL
    - <60 mg/dL
    - <70 mg/dL
    - 70-120 mg/dL
    - 70-140 mg/dL
    - 70-180 mg/dL
    - >180 mg/dL
    - >250 mg/dL
    - >300 mg/dL
- Number of severe hypoglycemic events (patients unable to self-treat, requiring the assistance of another person)

[redacted]

- Number of episodes of symptomatic hypoglycemia
- Number of carbohydrate interventions for hypoglycemia
- Total grams of carbohydrates taken for hypoglycemia
- Mean CGM glucose

8.2.3 Non-glycemic

- Glucagon/ZP4207 total delivery per kg of body mass
- Insulin total delivery per kg of body mass
- Number of unscheduled infusion set replacements
- Number of unscheduled CGM sensor changes

9 LABORATORY ASSESSMENTS

Descriptions of sample handling and sample processing, storage, and shipment at the site will be included in the laboratory manual.

The responsible laboratories are listed in the address list.

9.1 Safety Laboratory Assessments

Chemistry and hematology samples will be collected at specified time points. See Appendix A for the schedule of procedures and Appendix B for a list of clinical laboratory analytes.

9.2 Pharmacodynamic Assessments (Plasma Glucose)

At Visit 3 and Visit 4, plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.

9.3 Exposure Assessments (ZP4207 and Glucagon)

At Visit 3 and Visit 4, ZP4207/glucagon exposure sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator. The actual time of sampling will be recorded in the eCRF.

Bioanalytical Reports will be prepared.

9.4 Anti-drug Antibody Assessments

Blood samples (including back-up samples) for serum anti-ZP4207 and anti-glucagon antibodies will be taken at Visit 3 and the Follow-up Visit 6.

Bioanalytical Reports will be prepared.

[redacted]

10 SAFETY REPORTING

10.1 Adverse Events

An AE is any untoward medical occurrence in a trial patient administered an IMP and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP. Patients should be instructed to report any AE they experience to the Investigator.
Note: This includes events from the first trial-related activity from Visit 3.

AEs for ZP4207 include:

- A clinically significant worsening of a concomitant illness
- A clinical laboratory abnormality which is clinically significant, i.e., any abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example, change of medicine dose or more frequent follow-up due to the abnormality.
- Hypoglycemic episodes
- Injection site reactions

The following should **not** be recorded as AEs, if recorded prior to randomization (on the Screening Form or the eCRF):

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial-related activity from Visit 3.
- Pre-existing conditions found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).

For known (listed) AEs for Glucagon and Humalog, please refer to SPC for Glucagon and Humalog.

10.1.1 Follow-up of Adverse Events

All AEs that are ongoing at the end of the patient's participation in the trial will be followed-up until the event is resolved or reaches a satisfactory outcome as deemed by the Investigator. Follow-up actions for all serious adverse events (SAEs) will be performed according to appropriate clinical care practices and may depend on the nature of the event. These will be determined after internal review and/or Sponsor review. The follow-up information should only include new (updated and/or additional) information that reflects the situation at the time of the Investigator's signature.

Follow-up information on (S)AEs will be updated using the (S)AE Form. If a non-serious event becomes serious during the follow-up, the AE Form and SAE Form must be used and reporting timelines follow those of an SAE.

The Investigator must forward follow-up information on SAEs, and if previously non-serious AEs become SAEs, to the Sponsor.

[redacted]

10.1.2 Precautions

Normal precautions taken for a human trial will be taken during this trial. Qualified and well-trained physicians and medical staff will instruct the patients. During a patient's participation in the trial, the Investigator should ensure that adequate medical care is provided to the patient for any AEs, including clinically significant laboratory values related to the trial. The Investigator should inform the patient when medical care is needed for intercurrent illnesses of which the Investigator becomes aware.

For further information on safety precautions for ZP4207, Lilly glucagon, and Lilly Humalog, please refer to the current version of the Investigator's Brochure (IB) for ZP4207 (Zealand Pharma A/S, 2015, or any updates hereof), and the SPC for Glucagon (Eli Lilly, 2012) and Humalog (Eli Lilly, 2015), respectively.

10.1.3 Assessment of Adverse Events by the Investigator

Intensity of an Adverse Event
The maximum intensity (severity) of all AEs must be assessed by the Investigator and documented. Severity should be graded when the AE outcome is known:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

A "severe" reaction does not necessarily deem the AE as "serious," and an SAE may not be "severe" in nature.

Causality Relationship to IMP
Insulin (insulin lispro, Lilly Humalog), glucagon (glucagon for injection, Eli Lilly), and ZP4207 are all regarded as IMP.

The causality of each AE should be assessed by the Investigator according to the following classification:

- Related: Good reason and sufficient documentation to assume a causal relationship.
- Not related: No relationship to trial product can be established.

Outcome of an Adverse Event
The outcome of all AEs must be assessed by the Investigator and documented by his/her staff. The following definitions should be used:

- Recovered/resolved: The patient has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity from Visit 3.
- Recovering/resolving: The condition is improving and the patient is expected to recover from the event. This term is only applicable if the patient has completed the trial.

[redacted]

- Recovered/resolved with sequelae: The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment, or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- Not recovered/not resolved: The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known.
- Fatal: This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as "recovered/resolved," "recovering/resolving," "recovered/resolved with sequelae," or "not recovered/not resolved." An AE with a fatal outcome must be reported as an SAE.
- Unknown: This term is only applicable if the patient is lost to follow-up.

10.2 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Medically important

Medical judgement must be exercised in deciding whether an AE is believed to be "medically important." Medically important events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above.

Suspected Unexpected Serious Adverse Reactions (SUSAR)
A SUSAR is an AE fulfilling 1 of the criteria of seriousness and being assessed as related to an IMP, the nature or severity of which is not consistent with the applicable reference document (e.g., ZP4207 IB or package leaflet/SPC for an approved product).

Unanticipated Adverse Device Effect (UADE)
A UADE is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

10.3 Adverse Event Reporting – Procedures for Investigators

The Principal Investigator and co-investigators will review any AEs and report any SAEs to the Sponsor as soon as possible and within 24 hours of obtaining knowledge of the event. The Principal Investigator and co-investigators will promptly report AEs to the Partner's Institutional Review Board (IRB) and to the BU IRB (unless oversight is ceded by the BU IRB to the Partners IRB), in accordance with local requirements.

Ed Damiano is the Sponsor of the Investigational Device Exception for the BP and Zealand Pharma A/S is the Sponsor of the IND for ZP4207.

[redacted]

Reports of AEs will be submitted to the FDA in compliance with the terms of the Code of Federal Regulations.

All events meeting the definition of an AE must be collected and reported from the first trial-related activity from Visit 3 until the end of the post-treatment follow-up period. At each contact with the site (visit or telephone, excluding safety visits, where the patient is not seeing the Investigator or staff [e.g., visits to the laboratory], the patient must be asked about AEs. All AEs, either observed by the Investigator or reported by the patient, must be recorded by the Investigator and evaluated.

The Investigator should record the diagnosis, if possible. If no diagnosis can be made, the Investigator should record each sign and symptom as individual AEs.
All AEs must be recorded by the Investigator. One single AE Form must be used per AE from start to resolution. For SAEs, the SAE Form must also be completed.

AE information should include the following:

- Patient identification number on all pages
- Date and time of treatment start
- Date and time of onset and date of outcome
- Date and time of Investigator's first information on the (S)AE
- Seriousness
- Severity
- Causal relationship with IMP ZP4207
- Causal relationship with IMP insulin
- Causal relationship with IMP glucagon
- Causal relationship with medical device
- Causal relationship with procedures
- Interruption or withdrawal of treatment with IMP or medical device and other measures taken
- Outcome

All AEs are coded; details are described in the trial specific Data Management Plan.

The Investigator must report initial information in writing on the SAE Form for all SAEs to the Sponsor's responsible pharmacovigilance unit (here: Lindeq) immediately (within 24 hours) after obtaining knowledge about the event.

Name: [redacted]
Company: Lindeq
Address: Lyskær 8, 2730 Herlev, Denmark
Tel:
Fax: [redacted]
Mobile:
E-mail: drugsafety@lindeq.com

In addition and meeting the same timeline, Investigators must report all SAEs to Zealand Pharma A/S by forwarding the SAE Form electronically within 24 hours of obtaining knowledge of the event to the representatives of Zealand Pharma A/S.

Names: [redacted] and [redacted]
Address: Smedeland 36, DK-2600 Glostrup, Denmark
Tel: [redacted]
E-mails: [redacted]

It is the responsibility of Lindeq to report all SUSARs that occur in this trial to the Competent Authorities and to the Investigators. It is the responsibility of the Investigators to report the SUSARs to the IRBs in accordance with the local requirements in force and the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP). The trial monitor must be informed accordingly.

It is the responsibility of Lindeq to report all serious adverse reactions on insulin lispro and glucagon for injection to the Eli Lilly Pharmacovigilance department within 5 days.

It is the responsibility of the Investigators to report all UADEs to Beta Bionics within 24 hours of the time they are detected. It is the responsibility of the Investigators to report all UADEs to the IRB in accordance with the local requirements in force and the ICH GCP. It is the responsibility of Beta Bionics to report all UADEs to the Competent Authorities.

All device deficiencies should be documented and should be reported to Beta Bionics within 24 hours. Device deficiencies are inadequacies of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

Name: [redacted]
Company: Beta Bionics, Inc.
Address: Business Innovation Center, Photonics Center, 8 Saint Mary's Street, Suite 936
Boston, Massachusetts 02215-2421, United States
Tel: [redacted]
E-mail: [redacted]

10.4 Pregnancy Reporting

Female patients must be instructed to notify the Investigator immediately if they become pregnant or if they suspect to be pregnant during the trial. The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical trial.

Male patients must be instructed to notify the Investigator immediately if their partner becomes pregnant or suspects to be pregnant. The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical trial. During an information meeting at the trial site, the patient's partner will be fully informed by a physician of her participation in capturing the outcome data, and will be asked to provide her written consent.

The Investigator must report all information on pregnancies, including AEs in the patient/patient's partner, the fetus, and newborn infant/ toddler. The pregnancy report must be forwarded to the Sponsor preferably electronically as PDF or by fax.

The Investigator must follow the pregnancy until the pregnancy outcome and the newborn infant(s) until the age of 1 month. The Investigator must collect information on the pregnancy and pregnancy complications as well as the pregnancy outcome including the health of the newborn infant(s) on the pregnancy forms.

The following must be collected:

- Initial information of the pregnancy
- Information on the outcome of the pregnancy, including the health status of the newborn infant(s) at the age of 1 month
- All AEs in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms. It must be clear in the description if the event occurs in the patient/patient's partner, the fetus, or the newborn infant.
- All SAEs in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms following the same timelines as required for other SAEs. It must be clear in the description if the event occurs in the patient/patient's partner, the fetus, or the newborn infant.

The SAEs that must be reported include abnormal outcome – such as congenital anomalies, fetal death, and termination of pregnancy (spontaneous or elective abortion), including any anomalies of the fetus observed at gross examination or during autopsy – as well as other pregnancy complications (ectopic pregnancy) fulfilling the criteria of an SAE.

10.5 Hypoglycemia

Hypoglycemia will be regarded as an AE and will be recorded and documented on an AE Form. For the purposes of AE reporting, the following definitions of hypoglycemia will be used:

- Symptomatic hypoglycemia: an event during which typical symptoms of hypoglycemia are accompanied by a BG concentration ≤70 mg/dL
- Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with a BG concentration ≤50 mg/dL
- Severe hypoglycemia: an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions

10.6 Safety Monitoring

10.6.1 Data and Safety Monitoring Board

An external DSMB will oversee the conduct of the trial, as set forth in the DSMB Charter. Additionally, the DSMB will be informed in the event of any serious and unexpected AEs. The DSMB will be informed if there are any changes to the trial protocol that could significantly impact the safety or scientific validity of the trial. A final DSMB meeting will convene after the completion of the trial.

The participation of individual patients will be discontinued if they experience:

- Seizure or unconsciousness associated with hypoglycemia and associated with participation in the trial
- Persistent nausea and vomiting thought to be related to glucagon dosing associated with participation in the trial
- Hospitalization associated with participation in the trial
- Pregnancy
- Diabetic ketoacidosis

If more than 1 patient must be withdrawn from the trial for these reasons, the trial will stop and a vote of the DSMB will be required to restart it. All AEs that are serious and unexpected but related will be reported to the DSMB within 5 working days.

[redacted]

Note that patients may discontinue participation at any time. Patients may be removed from the trial for other reasons, for instance, failure to comply with trial procedures or intercurrent illness that is unrelated to the BP but that precludes safe participation. Discontinuation of participation for these reasons will not contribute to a decision to discontinue the trial.

10.6.2 Zealand Pharma Safety Committee

The internal Zealand Pharma Safety Committee is constituted to perform ongoing safety surveillance of clinical trials within ZP4207, including this trial.

If safety signals are observed either based on reported SAEs, periodic review of laboratory parameters, planned review of all AEs reported between the safety committee meetings, or on notification of significant findings, the Safety Committee will take appropriate measures to safeguard the patients.

11 STATISTICS

For all analysis, the 2 treatment arms from Part 1 (iPhone-based BP) will be compared, and the 2 treatment arms from Part 2 (iLet) will be compared. The analysis of Part 1 will be completely separate from the analysis of Part 2.

11.1 Analysis Populations

The following analysis sets are defined in accordance with the ICH-E9 guidance:

The Full Analysis Set is based on the intention-to-treat principle and includes all randomized patients. In exceptional cases, patients from the Full Analysis Set may be excluded (will be decided in the database review [DBR] meeting). In such cases, the exclusion will be justified and documented. Patients will contribute to the evaluation “as randomized.”

The Per-Protocol Set includes all patients of the Full Analysis Set who completed the trial without any major protocol violations. Patients in the Per-Protocol Set will contribute to the evaluation “as treated.” This analysis will only be used if it is different than the Full Analysis Set.

The Safety Analysis Set includes all patients receiving at least 1 dose of the IMP. Patients in the Safety Analysis Set will contribute to the evaluation “as treated.”

Analyses of efficacy endpoints will be based on the Full Analysis Set (and the Per-Protocol Set if necessary). This decision will be made in the DBR meeting. The analysis of the safety endpoints will be based on the Safety Analysis Set.

Before data are released for statistical analysis, a blinded review of all data will take place to identify protocol deviations that may potentially affect the results. At this time, it will be determined if patients and/or data should be excluded from the analysis. Furthermore, outliers will be identified by data review according to ICH-E9.

Obviously erroneous data points may be excluded from the analyses or re-analyzed (e.g., serum concentrations). The decision to re-analyze or exclude data points from the statistical analysis is the joint responsibility of the Sponsor, the Principal Investigator, and the Trial Statistician.

[redacted]

The patients or observations to be excluded and the reason for their exclusion will be documented and signed by those responsible prior to database release. The documentation will be stored together with the remaining trial documentation. The patients and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

11.2 Statistical Methods

Medpace will be responsible for the statistical analysis. The statistical planning and conduct of analyses of the data from this trial will follow the principles defined in relevant ICH guidelines and Medpace's biostatistical standard operating procedures (SOPs). A general description of the statistical methods to be used is given in this section, specific details will be provided in the Statistical Analysis Plan (SAP), which will be prepared before database lock. All statistical analyses will be performed using SAS® (SAS Institute Inc., Cary, North Carolina, USA), version 9.3 or later.

11.2.1 Analysis of Safety

The following variables will be evaluated according to treatment for safety purposes:

Adverse Events
All AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Individual AEs will be presented in a listing including relationship to trial product/device, severity, and treatment period at onset. If more than 20 treatment-emergent AEs (AEs with onset after [first] dosing at Visit 3 until the Follow-up Visit 6) are registered, a summary table including number of AEs, number of patients with at least 1 AE, and percentage of exposed patients with at least 1 AE will be made by system organ class and treatment period at onset.

Local Tolerability
Local tolerability at the injection site will be summarized using descriptive statistics as appropriate.

Laboratory Safety Assessments
Laboratory assessments will be summarized. A listing of abnormal values will be provided.

Physical Examination
A frequency table will show the number and percentage of physical examination results.

Vital Signs
Vital signs will be summarized using descriptive statistics.

12-lead ECG
The Investigator's evaluations of 12-lead ECGs will be summarized and abnormal individual evaluations will be listed together with the Investigator's comments. Changes in 12-lead ECG between measurements will be recorded as AEs if the Investigator judges them to be clinically significant.

11.2.2 Analysis of Efficacy

The analysis of BP function endpoints and glycemic endpoints will be on an intention-to-treat basis. In cases where a treatment arm was not completed (and that arm was not repeated according to protocol criteria), available data from that arm will be used in the data analysis.

The Shapiro-Wilk test will be used to determine the normality of the residuals for each comparison. Summary tables that display descriptive statistics, including percentages, means or medians, and standard deviation and/or ranges, as appropriate, will be provided.
A paired t-test or the Wilcoxon signed rank test for comparison of means with normally or non-normally distributed residuals, respectively, will be used. In a secondary analysis, any period effect and any interaction between treatment and period will be looked for, although no such interaction is predicted for the efficacy outcome. Further details will be included in the SAP.

The number of patients and proportions of severe hypoglycemic events, symptomatic hypoglycemia, and carbohydrate interventions due to hypoglycemia with the event counts will be summarized descriptively, and the proportions will be analyzed by a Fisher's exact test if data allow.

11.2.3 Interim Analysis

An interim database lock may occur upon completion of Part 1 of the trial to analyze the iPhone-based BP data.

11.2.4 Sample Size Determination

No formal sample size calculations were made. It is expected that between 20 and 24 patients will be randomized in the trial. The sample size is based on a clinical rather than statistical rationale. The sample size is considered adequate to address the primary trial objective of exploring the safety of ZP4207 when used in the BP and with reference to Lilly glucagon used in the BP.

12 DATA MANAGEMENT AND RECORD KEEPING

Data Management is the responsibility of Medpace. The complete Data Management process will be described in detail and agreed on in the Data Management Plan for this trial.

12.1 Data Handling

Case Report Forms
Electronic Case Report Forms will be used in this trial. The Data Management Department of Medpace will provide the eCRFs. All further information regarding the eCRFs and the data flow will be described and agreed on in the Data Management Plan.

Device-Related Data
During the trial, CGM data, calibration data, insulin dosing data, and glucagon dosing data will be automatically stored in the BP device (from which it will be downloaded at intervals), combined in a single database that will be compared against the primary data files for integrity, and ultimately transferred to Medpace.

12.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

12.3 Data Entry

Data must be recorded using the electronic data capture (EDC) system as the trial is in progress. The patient questionnaires will be transcribed into the EDC system by site personnel. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct trial data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

12.4 Medical Information Coding

Adverse events and medical history will be coded using the latest version of MedDRA. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary.

12.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

12.6 Record Keeping

Medpace will be responsible for hosting the TMF. Records of patients, source documents, monitoring visit logs, eCRFs, inventory of trial product, regulatory documents, and other Sponsor correspondence pertaining to the trial must be kept in the appropriate trial files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the evaluation and reconstruction of the clinical trial. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Trial Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

13 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

13.1 Ethical Conduct of the Trial

The trial will be conducted according to Medpace, MGH, and/or the Sponsor's written instructions (SOPs, working instructions, or process descriptions). Content and definitions of the written instructions are based on the Declaration of Helsinki and the ICH GCP.

[redacted]

13.2 Institutional Review Board

Written favorable opinion must be obtained from the responsible IRB prior to commencement of the trial. Clinical trial submission and reporting requirements before, during, and after completion of the trial will be performed in accordance with national law and local regulations.

All amendments that affect patient safety or the trial integrity (substantial amendments) must not be implemented before favorable opinion has been obtained, unless necessary to eliminate hazards to the patients. Non-substantial amendments do not require favorable opinion by the IRB, but the respective IRB will be notified according to local requirements.

The Sponsor and Investigator must approve any amendment in writing before its implementation.
The Sponsor must maintain an accurate and complete record of all submissions made to the IRB. The records should be filed in the Sponsor's Trial Master File (TMF).

13.3 Informed Consent

In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirement(s) and adhere to the ICH GCP guideline and the requirements in the Declaration of Helsinki.

Prior to any trial-related activity, the Investigator must give the patient oral and written information in a form that the patient can read and understand about all aspects of the trial that are relevant to the patient's decision to participate. The patient will be given ample time to decide whether or not to participate in the trial.

The patient must be informed that his/her personal trial-related data will be used in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by authorized monitors or Clinical Quality Assurance auditors appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

A voluntary, personally signed and dated ICF must be obtained from the patient prior to any trial-related activity. The ICF must also be signed and dated by the physician or designee who conducted the informed consent procedure. A signed copy of the ICF and any additional patient information must be given to each patient.

The responsibility for taking informed consent must remain with that of a research physician or designee. If information becomes available that may be relevant to the patient's willingness to continue participating in the trial, the Investigator must inform the patient in a timely manner, and a revised written informed consent must be obtained.

Should a protocol amendment become necessary, the ICF may need to be revised to reflect the changes to the protocol. It is the responsibility of the Sponsor to ensure that an amended consent form is reviewed and has received favorable opinion from IRB, and the Investigator must ensure that the amended consent form is signed by all patients subsequently entered into the trial and those currently in the trial, if affected by the amendment.

[redacted]

13.4 Trial Monitoring Requirements

The monitoring procedures for this trial are described in detail in the Monitoring Manual. The objectives of the monitoring procedures are to ensure that (i) the safety and rights of the trial patients are respected, (ii) that accurate, valid, and complete data are collected, and (iii) that the trial is conducted in accordance with the trial protocol, the principles of GCP, and local legislation, including drug accountability.

The monitor must be given direct access to the investigational site files and source documents (original documents, data, and records). Direct access includes permission to examine, analyze, verify, and reproduce any record(s) and report(s) that are important to evaluation of the clinical trial.

Key tasks of the monitor include verifying the presence of informed consent, the adherence to the inclusion/exclusion criteria, the documentation of SAEs, and the recording of all safety and efficacy variables. The monitor will also confirm the completeness of patient records, the adherence to the protocol, ICH GCP, and the progress in patient enrollment and perform drug accountability.

Because no information that could reveal the identity of patients may ever be removed from the trial site, the monitor will visit the site at regular intervals to perform these monitoring tasks. Other contact between the Investigator and monitors will be maintained as required through telephone calls and e-mail. The Investigator and/or key members of staff involved in the trial must be available to assist the monitors during all visits.

Site Initiation Visit
During the Site Initiation Visit (SIV) the CRO, Sponsor, and/or monitors will go through information on the IMP, the protocol, the eCRFs, and other key aspects of the trial with the Investigator and the key members of staff involved in the trial. The topics of the SIV are documented in a SIV report made available to the Investigator. Documentation on the SIV (e.g., power point presentation) should be filed by both Investigator and Sponsor.

13.5 Disclosure of Data

Data generated by this trial must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the trial is confidential and disclosure to third parties other than those noted above is prohibited.

13.6 Retention of Records

Massachusetts General Hospital will maintain the patient's medical file according to local regulations. MGH will archive the documentation pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. MGH should not destroy any documents without prior permission from the Sponsor.

The documentation includes all the raw data generated during the clinical trial, the investigational site files, and a copy of the clinical trial report. The documents will be retained

[redacted]

for a period of at least 15 years at archives by MGH, or its sub-contractor. After this period, the Sponsor will be contacted and their advice sought on the return or further retention of the trial records.

The Sponsor will maintain the documentation pertaining to the trial in accordance with national regulations.

13.7 Publication Policy

The Principal Investigator of the trial will review and sign the clinical trial report. A summary of the final clinical trial report will be submitted to the IRB and Competent Authority.

According to the Declaration of Helsinki Investigators and Sponsors "have ethical obligations with regard to the publication and dissemination of the results of research." The trial design and results may be published as 1 or more original research manuscripts/abstracts and presented at a scientific meeting. The Investigator and Sponsor reserve the right to review any proposed presentation of the results of this trial before they are submitted for publication. Authorship on any publication(s) resulting from this clinical trial will be assigned according to the recommendations of the International Committee of Medicinal Journal Editors.

Participating patients will not be identified by name in any published reports about the clinical trial.

The Sponsor is responsible for trial registration at ClinicalTrials.gov (www.clinicaltrials.gov) according to the requirements from the FDA.

13.8 Legal Aspects

An implicit or explicit approval must be obtained from the Competent Authority prior to commencement of the trial. Clinical trial submission and reporting requirements before, during, and after completion of the trial will be performed in accordance with national law and local regulations.

An implicit or explicit approval will also be mandatory before implementation of substantial changes. Non-substantial amendments do not require approval from the Competent Authority but will be notified according to local requirements.

The Sponsor and Investigator must approve the amendment in writing before its implementation.

The Sponsor must maintain an accurate and complete record of all submissions made to the Competent Authority. The records should be filed in the Sponsor's TMF.

Audits and Inspections
In the event of an audit, representatives of the Sponsor or designee, or national and international regulatory authorities may request access to all trial records for inspection and copying. Such access must be stated in the ICF signed by the patient.

[redacted]

13.9 Sponsor Discontinuation Criteria

The Sponsor, Investigator, or a pertinent regulatory authority may decide to stop the trial or part of the trial at any time but agreement on procedures to be followed must be obtained.

Conditions that may warrant termination of the clinical trial include, but are not limited to:

- Safety or administrative reasons
- The discovery of an unexpected, relevant, or unacceptable risk to the patients enrolled in the clinical trial
- A decision of the Sponsor to suspend or discontinue investigation of the IMP

If the trial is prematurely terminated or suspended, the Investigator should promptly inform the patients and assure appropriate therapy and follow-up. Furthermore, the Sponsor should promptly inform the IRB and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.
If after the termination of the trial the risk/benefit analysis has changed, the new evaluation should be provided to the IRB in case it will have an impact on the planned follow-up of the patients who have participated in the trial. Necessary actions needed to protect the patients should be described.

13.10 Patient Compensation

Financial compensation will be provided to all patients who complete the Screening Visit. Patients will be paid $25 for completing the Screening Visit whether or not they are eligible to participate in the trial. Patients will be compensated $25 for completing the Training Visit. Patients will be compensated $100 for completing each of the 2 treatment visits, $25 for completing the phone call, and $25 for completing the Follow-up Visit. Thus, the total compensation for a patient who completes the trial would be $300. Patients who are unable to complete the trial or choose to stop participation will receive prorated compensation for each visit. In addition to the monetary compensation, the cost of the patients' lunch meals during their participation in the trial, as well as the patients' parking at each visit, will be covered by trial funds.

14 TRIAL ADMINISTRATIVE INFORMATION

14.1 Protocol Amendments

Any amendments to the trial protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

[redacted]

14.2 Address List

14.2.1 Sponsor

Zealand Pharma A/S
Smedeland 36
DK-2600 Glostrup (Copenhagen)
Denmark
Telephone: +45 88 77 36 00
Facsimile: +45 88 77 38 98

14.2.2 Supplier of Device

[redacted], PhD
Beta Bionics, Inc.
Business Innovation Center, Photonics Center
8 Saint Mary's Street, Suite 936
Boston, Massachusetts 02215-2421
United States
Tel: [redacted]

14.2.3 Principal Investigator (Site)

Steven J. Russell, M.D., Ph.D.
MGH Diabetes Center
50 Staniford Street Suite 301
Boston, Massachusetts 02114
Telephone: [redacted]
Facsimile: [redacted]

14.2.4 Contract Research Organization (Including Monitoring)

Medpace, Inc.
5375 Medpace Way
Cincinnati, Ohio 45227
Telephone: +1-513-579-9911
Facsimile: +1-513-579-0444

14.2.5 Medical Monitoring

Medpace Clinical Safety
5375 Medpace Way
Cincinnati, OH 45227
United States
Telephone: +1-800-730-5779, ext. 2999 or +1-513-579-9911, ext. 2999
Facsimile: +1-866-336-5320 or +1-513-579-0444
E-mail: medpace-safetynotification@medpace.com

14.2.6 Pharmacovigilance

Lindeq
Lyskær 8
2730 Herlev
Denmark
Telephone: [redacted]
Facsimile: [redacted]
Mobile: [redacted]
E-mail: drugsafety@lindeq.com

14.2.7 Central Laboratory (Safety Laboratory and Plasma Glucose)

Medpace Reference Laboratories, LLC
5365 Medpace Way
Cincinnati, OH 45227
United States
Telephone: +1-513-366-3270
Facsimile: +1-513-366-3273

14.2.8 Special Laboratory (ZP4207 Exposure and ADA Analyses)

Unilabs – York Bioanalytical Solutions
[redacted]
Cedar House
Northminster Business Park
Upper Poppleton
York YO26 6QR
Great Britain
Telephone: [redacted]
Facsimile: [redacted]

14.2.9 Special Laboratory (Glucagon Exposure)

MLM Medical Labs GmbH
Dr. [redacted]
Dohrweg 63
D-41066 Mönchengladbach
Germany
Telephone: [redacted]
Facsimile: [redacted]

15 REFERENCES

1. Russell SJ, El-Khatib FH, Sinha M, et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. N Engl J Med. 2014;371(4):313-325.
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9. ICH Harmonised Tripartite Guideline. Statistical Principles for Clinical Trials E9. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf. 5 February 1998.
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[redacted]

Clinical Trial Protocol
ZP4207-16051

Version number: 5.0
Amendment 4.0
Date: 02 September 2016

APPENDIX A: SCHEDULE OF PROCEDURES – PARTS 1 AND 2

Trial Visit	Visit 1 [1] Screening	Visit 2 Training	Visit 3 [2] [3] [4] [5] (1st Treatment Visit)	Visit 4 [2] [3] [5] (2nd Treatment Visit)	Visit 5 Phone Call [6]	Visit 6 Follow-Up [7]
Informed consent	X					
Assess/confirm elig bility	X	X				
Demographics	X					
Medical, surgical, and social history; allergies	X					
Concomitant illness	X					
Concomitant medications	X	X	X	X	X	X
Height, weight, physical examination, and vital signs including body temperature and blood pressure [8]	X		X [9]	X [9]		
12-lead ECG	X		X [10]	X [10]		
Urine HCG pregnancy test and menstrual history [11]	X		X	X		
FSH [12]	X					
Screening labs – HbA1c, optional fractionated metanephrines [13]	X					
Safety lab sampling including chemistry and hematology	X		X [10]	X [10]		X
Training on devices [14]		X				
Monitored BP use			X	X		
Plasma glucose sampling [15]			X	X		
ZP4207/glucagon exposure sampling [16]			X	X		
Nausea and infusion site pain VAS and infusion site reaction Draize scale (visit start [17], hourly, & visit end)			X	X		

[redacted]

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Trial Visit	Visit 1 [1] Screening	Visit 2 Training	Visit 3 [2] [3] [4] [5] (1st Treatment Visit)	Visit 4 [2] [3] [5] (2nd Treatment Visit)	Visit 5 Phone Call [6]	Visit 6 Follow-Up [7]
Standardized lunch [18]			X	X		
In-clinic exercise [19]			X	X		
Questionnaires (pre & post BP)			X	X		
ADA			X [20]			X
Adverse event review			X	X	X	X

1. Once the patient has been enrolled and eligibility has been established, the order of the treatment visits will be randomized in blocks of 2 patients.
2. In Part 1, each patient will participate in 2 treatment visits: 1 with the iPhone-based BP using ZP4207 and 1 with the iPhone-based BP using Lilly glucagon in a randomized order. In Part 2, each patient will participate in 2 treatment visits: 1 with the iLet using ZP4207 and 1 with the iLet using Lilly glucagon in a randomized order. Up to 2 patients may participate in the trial per day.
3. The night before the visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12 00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window. If BG is <50 mg/dL, treatment with simple carbohydrate is allowed. If the patient experiences persistent hypoglycemia, the visit will be rescheduled within the visit window.
4. Visit 3 will take place at least 48 hours after screening (Visit 1) and no more than 30 days after screening (Visit 1).
5. There will be a 24-hour minimum washout between Visit 3 and Visit 4 and a maximum of 3 weeks between Visit 3 and Visit 4.
6. Visit 5 will take place 7 days ±3 days from Visit 4.
7. Visit 6 will take place 25 days ±4 days from Visit 4.
8. Height and physical examination will be measured at Visit 1 only.
9. Vital signs including body temperature and blood pressure will be obtained at visit start and visit end.
10. At visit start and visit end.
11. Urine HCG pregnancy test only for women of childbearing potential. The date of the last menstrual period in female patients will be obtained at Visit 1 only.
12. Test for FSH level only for postmenopausal women amenorrheic for less than 1 year.
13. If indicated by history.
14. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor, diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits, and trial policies and procedures.
15. Collected at least hourly. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
16. Collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.
17. Once the infusion sites have been placed but no drug has yet been administered.
18. Between approximately Hour 3 and Hour 4.
19. Between approximately Hour 6 and Hour 7.
20. Before the start of dosing.

ADA = anti-drug antibodies; BG = blood glucose; BP = bionic pancreas; CGM = continuous glucose monitor; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HCG = human chorionic gonadotropin; VAS = visual analog scale.

[redacted]

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APPENDIX B: CLINICAL LABORATORY ANALYTES

Chemistry

Alanine aminotransferase	Aspartate aminotransferase
Alkaline phosphatase	Total protein
Albumin	Total and direct bilirubin
Gamma-glutamyl transferase	Glucose
Creatinine	Estimated glomerular filtration rate
Blood urea nitrogen	Uric acid
Bicarbonate	Sodium
Potassium	Calcium
Chloride	Phosphorus

Hematology

Hemoglobin	Hematocrit
Red blood cell count	White blood cell count and differential
Platelets	Mean corpuscular volume
Mean corpuscular hemoglobin	Mean corpuscular hemoglobin concentration

Pregnancy Test
A urine HCG pregnancy test will be performed at screening, Visit 3, and Visit 4 only for women of childbearing potential.

Anti-drug Antibody Assessments
Blood samples (including back-up samples) for serum anti-ZP4207 and anti-glucagon antibodies will be taken prior to first dosing (Visit 3) and at the Follow-up Visit (Visit 6).

ZP4207/Glucagon Exposure Sampling
At Visit 3 and Visit 4, ZP4207/glucagon exposure sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.

Screening Visit Only
Test for FSH level only for postmenopausal women amenorrheic for less than 1 year
Optional fractionated plasma metanephrines (if indicated by history)
Hemoglobin A1c

[redacted]

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APPENDIX C: BRIEF DESCRIPTION OF QUESTIONNAIRES

Diabetes Treatment Satisfaction Questionnaire – Status (DTSQs)
The DTSQs measures patient satisfaction with diabetes treatment. It consists of a 6 item scale for assessing treatment satisfaction and two additional items assessing perceived frequency of hyperglycemia and hypoglycemia. The DTSQs is meant for adults and older children. Dr. Clare Bradley has produced a version that is appropriate for bionic pancreas studies for this use, along with a version for younger children. It is administered before the intervention. The DTSQs is valid and reliable. Administration time is less than 5 minutes.

Diabetes Treatment Satisfaction Questionnaire – Change (DTSQc)
Although the DTSQ is responsive to treatment changes, ceiling effects are often seen with this instrument, where maximum or close-to-maximum scores at baseline provide little opportunity for registering improvement. The DTSQc contains the same items as the DTSQs version but asks patients to consider their satisfaction with their current treatment compared with their previous treatment. The DTSQc is meant for adults and older children. Dr. Clare Bradley has produced a version that is appropriate for bionic pancreas studies for our use, along with a version for younger children. It is administered during and at the end of the intervention. The DTSQc is valid and reliable. Administration time is less than 5 minutes.

T1-Diabetes Distress Scale (T1-DDS)
The T1-DDS is a 28-item survey that assesses seven sources of diabetes distress for type 1 adults. It captures feelings of powerlessness; management distress; hypoglycemia distress; negative social perceptions by others; eating distress; physician (health care) distress; and friend/family distress. Items are scored on a 6-point scale from not a problem to a very serious problem. It is administered before, during, and at the end of the intervention. The scale is valid and reliable, and has been shown to be sensitive to change over time. Administration time is 5 minutes.

Problem Areas in Diabetes Survey (PAID)
There are three versions of the PAID: Teen (PAID-T), Parent (PAID-P), and Child (PAID-C) versions. This measure of diabetes-specific emotional distress in youth with diabetes and their parents is 26 items. A total score is generated. It is administered before, during, and at the end of the intervention. The PAID-T and PAID-P are valid and reliable. Psychometric analysis of the PAID-C is in progress. Administration time is 5 minutes.

Hypoglycemia Fear Survey (HFS)
There are three versions of the HFS, Adult (HFS), Youth (HFS-Y) and Parent (HFS-P). The HFS measures several dimensions of fear of hypoglycemia among adults with type 1 diabetes. It consists of 23 items and produces two sub-scale scores; a Behavior sub-scale that measures behaviors involved in avoidance and/or over-treatment of hypoglycemia and a Worry sub-scale that measures anxiety and fear surrounding hypoglycemia. The HFS-Y consists of 25 items and the HFS-P consists of 26 items; both produce sub-scale scores similar to the Adult HFS. It is administered before, during, and at the end of the intervention. All versions of the HFS are valid and reliable. Administration time is 5-10 minutes.

[redacted]

Impact of Daily Diabetes Demands (IDDD)
There are four versions of the IDDD; Adult (IDDD-A), Youth (IDDD-Y), Parent (IDDD-P), and Significant Other (IDDD-SO). This instrument measures the burden related to the demands of the daily diabetes regimen and is 22 items. A total score is generated. It is administered before, during, and at the end of the intervention. Psychometric analysis of the IDDD-Y is in progress using the data from the second Bionic Pancreas Camp Study in pre-adolescent children, and of the IDDD-A is in progress using data from the Bionic Pancreas Multicenter Study in adults. Administration time is 5 minutes.

Bionic Pancreas User Opinion Survey (BPUOS)
There are four versions of the BPUOS; Adult (BPUOS-A), Youth (BPUOS-Y), Parent (BPUOS-P), and Significant Other (BPUOS-SO). This measure assessing both the benefits from, and difficulties with, use of the bionic pancreas, and consists of 38 items. A total score is generated. It is administered during and at the end of the intervention. Psychometric analysis of the BPUOS-Y is in progress using the data from the second Bionic Pancreas Camp Study in pre-adolescent children, and of the BPUOS -A is in progress using data from the Bionic Pancreas Multicenter Study in adults. Administration time is 10 minutes.

[redacted]

SUMMARY OF CHANGES DOCUMENT

PROTOCOL NUMBER ZP4207-16051

AMENDMENT NUMBER 3.0

PROTOCOL TITLE: The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

AMENDMENT DATE: 17 August 2016

SUMMARY AND JUSTIFICATION OF CHANGES:

This amendment was developed to indicate that the device used in this trial to administer insulin, Lilly glucagon, and the glucagon analog ZP4207, has been changed from the iLet to the iPhone-based bionic pancreas (BP). This change has been made globally throughout the protocol amendment. Additional language has been added to describe the iPhone-based BP infusion set, control unit, and pumps. Other minor edits were made throughout the protocol to provide greater clarity and consistency.

SUMMARY OF CHANGES:

The amended protocol sections and the details of the changes are summarized in the following sections. Revisions to the protocol are presented as strikethrough (ie, ~~subject~~) for text that was removed and bold (ie, **subject**) for text that was added.

[redacted]

Summary of Changes, Amendment 3.0, ZP4207-16051

Global

Original Text:

iLet

New Text:

~~iLet~~ **iPhone-based bionic pancreas**

Protocol Title, Page 1

Original Text:

The iLet Feasibility Trial Testing the iLet, a Fully Integrated Bihormonal Bionic Pancreas with ZP4207

New Text:

The ~~iLet~~ **Bionic Pancreas** Feasibility Trial Testing the ~~iLet, a Fully Integrated Bihormonal~~ Bionic Pancreas with ZP4207

Section 1.1, Background and Rationale, Page 14

Original Text:

In its last tested embodiment, the BP consisted of a Dexcom G4 CGM, and an iPhone that are hardwired together, with the iPhone running the control algorithm and communicating via Bluetooth with 2 Tandem t:slim pumps to dose insulin and glucagon. The connections are repeatedly lost among these 4 components throughout the day, an issue that has the potential to adversely impact BG control, whether due to missed CGM values or missed doses. In addition, the troubleshooting required to repair these recurring disconnections can be burdensome to the user. Integrating these components into a single device would establish seamless connectivity among them, which would eliminate the need for such troubleshooting. This would lead to a smoother device operation with fewer interruptions, which would enhance its user friendliness, optimize its BG control potential, and further improve the quality of life of its users.

The BU Investigators have recently designed, built, and tested a proprietary first-generation of such a fully integrated BP system, referred to as the iLet and the iLet infusion set. The iLet is a dual chamber infusion system that currently incorporates the Dexcom G4 CGM technology, a custom user interface with touchscreen display, and all of the mathematical dosing algorithms that were tested in and validated using the iPhone-based BP in outpatient studies over the past 3 years. The iLet infusion set provides 2 independent subcutaneous (SC) fluid pathways from the iLet to the patient (1 for insulin and the other for glucagon). One tube connects to the prefilled insulin cartridge and the other tube connects to the fillable (single use) glucagon cartridge.

New Text:

In its last tested embodiment, the BP consisted of a Dexcom G4 CGM, and an iPhone that are hardwired together, with the iPhone running the control algorithm and communicating via Bluetooth with 2 Tandem t:slim pumps to dose insulin and glucagon. ~~The connections are repeatedly lost among these 4 components throughout the day, an issue that has the potential to adversely impact BG control, whether due to missed CGM values or missed doses. In addition, the troubleshooting required to repair these recurring disconnections can be~~

[redacted]

~~burdensome to the user. Integrating these components into a single device would establish seamless connectivity among them, which would eliminate the need for such troubleshooting. This would lead to a smoother device operation with fewer interruptions, which would enhance its user friendliness, optimize its BG control potential, and further improve the quality of life of its users.~~

~~The BU Investigators have recently designed, built, and tested a proprietary first generation of such a fully integrated BP system, referred to as the iLet and the iLet infusion set. The iLet is a dual chamber infusion system that currently incorporates the Dexcom G4 CGM technology, a custom user interface with touchscreen display, and all of the mathematical dosing algorithms that were tested in and validated using the iPhone based BP in outpatient studies over the past 3 years. The iLet infusion set provides 2 independent subcutaneous (SC) fluid pathways from the iLet to the patient (1 for insulin and the other for glucagon). One tube connects to the prefilled insulin cartridge and the other tube connects to the fillable (single use) glucagon cartridge.~~

Section 1.1, Background and Rationale, Page 14

Original Text:

The current trial is a first feasibility trial designed to use the first-generation iLet and iLet infusion set to compare ZP4207 with marketed glucagon (Lilly). The trial is intended to demonstrate the safety and tolerability of ZP4207 in the iLet and the feasibility of achieving comparable autonomous glycemic control. It is not intended to comprehensively demonstrate the definitive efficacy of the iLet in extended, continuous daily use, but rather to demonstrate its functionality and accuracy in a practical, albeit very controlled, clinical setting. The trial is expected to provide practical information that will benefit the design of a next-generation iLet and iLet infusion set and help pave the way for a more comprehensive outpatient home-use Phase 2 trial and ultimately a pivotal trial where comprehensive safety and efficacy through continuous full daily use of the iLet with ZP4207 will be documented.

The data derived from this trial will permit evaluation of the robustness of the iLet as well as the safety and efficacy of ZP4207 when used in conjunction with the iLet. The data obtained will be used to further improve the iLet and will allow BU/MGH to expand to larger outpatient trials using the iLet with ZP4207.

New Text:

The current trial is a first feasibility trial designed to use the ~~first generation iLet~~ **iPhone-based BP** ~~and iLet infusion set~~ to compare ZP4207 with marketed glucagon (Lilly). The trial is intended to demonstrate the safety and tolerability of ZP4207 in the ~~iLet~~ **iPhone-based BP** and the feasibility of achieving comparable autonomous glycemic control. It is not intended to comprehensively demonstrate the definitive efficacy of the ~~iLet~~ **iPhone-based BP** in extended, continuous daily use, but rather to demonstrate its functionality and accuracy in a practical, albeit very controlled, clinical setting. The trial is expected to provide practical information that will benefit the design of a next-generation ~~iLet~~ **BP** ~~and iLet infusion set~~ and help pave the way for a more comprehensive outpatient home-use Phase 2 trial and ultimately a pivotal trial where comprehensive safety and efficacy through continuous full daily use of the ~~iLet~~ **BP** with ZP4207 will be documented.

[redacted]

The data derived from this trial will permit evaluation of the robustness of the ~~iLet~~ **iPhone-based BP** as well as the safety and efficacy of ZP4207 when used in conjunction with the ~~iLet~~ **iPhone-based BP**. ~~The data obtained will be used to further improve the iLet and will allow BU/MGH to expand to larger outpatient trials using the iLet with ZP4207.~~

Section 1.5, Risk/Benefit, Page 21

Original Text:

The data derived from this trial will allow evaluation of safety and tolerability of ZP4207 in the iLet, and the robustness and effectiveness of the new BP control system. The data obtained will be used to further improve the iLet and will allow the expansion to larger outpatient trials using the iLet with ZP4207.

New Text:

The data derived from this trial will allow evaluation of safety and tolerability of ZP4207 in the ~~iLet~~ **iPhone-based BP**~~, and the robustness and effectiveness of the new BP control system. The data obtained will be used to further improve the iLet and will allow the expansion to larger outpatient trials using the iLet with ZP4207~~.

Section 6.5, iPhone-based Bionic Pancreas, Page 27-28

Original Text:

6.5 iLet Bionic Pancreas

Infusion set: A novel, dual cannula infusion set has been designed specifically for use with the iLet. Patients will wear dual channel tubing that will be attached to 2 infusion sets with 1 steel cannula each, one for insulin infusion and the other for glucagon infusion. The tubing and infusion sets will have undergone sterilization prior to being delivered in a sealed pouch. The steel cannulae will be inserted in the abdominal SC tissue.

Continuous glucose monitors: The iLet is being built according to Class III medical device standards, adheres to a comprehensive and robust quality system, and is fully compliant with International Organization for Standardization (ISO) 13485 standards and document control practices. The iLet is a fully-integrated dual hormone BP system that integrates the CGM technology (currently the Dexcom G4 Share system) as well as 2 independent motor-drivetrain pumping assemblies, which independently actuate the delivery of insulin and glucagon from pre-filled cartridges that are separately loaded into the iLet housing. Each drivetrain assembly utilizes a lead screw, which is driven by a precision micromotor, a gear case assembly, and a motor controller unit, in a manner similar to what is commonly found in most insulin infusion pumps on the market today. The iLet has dosing accuracy that is comparable to FDA-approved insulin pumps currently on the market. The iLet has a built-in Bluetooth Low Energy radio that also allows automatic communication with the paired CGM, as well as the Nova StatStrip® Xpress BG meter (Nova Biomedical). The iLet does not contain a cellular nor a WiFi radio, and does not accept input data from another mobile device (e.g., smartphone), other than the paired CGM and BG meter(s).

The mathematical control algorithms (which are the same as those used in the iPhone-based BP), the CGM glucose engine (Dexcom), and the native user interface software, are all interconnected through controller framework software and reside as embedded systems on printed circuit boards contained within the device housing. The touchscreen-enabled, menu driven user interface and onboard processor provide a comprehensive and standalone

[redacted]

platform, which allows the iLet to operate independently of smartphones or other devices and without the need for internet support during routine operation. The graphical user interface of the iLet has the same user options and capabilities of the iPhone BP, including having its home screen password protected and its settings options only accessible to trial staff via a separate password.

New Text:

6.5 ~~iLet~~ **iPhone-based Bionic Pancreas**

Infusion ~~s~~**S**et: ~~A novel, dual cannula infusion set has been designed specifically for use with the iLet. Patients will wear dual channel tubing that will be attached to 2 infusion sets with 1 steel cannula each, one for insulin infusion and the other for glucagon infusion. The tubing and infusion sets will have undergone sterilization prior to being delivered in a sealed pouch. The steel cannulae will be inserted in the abdominal SC tissue.~~ **Patients will wear 2 FDA-approved commercially available infusion sets, one for insulin infusion and one for glucagon infusion, when applicable. Infusion sets that are compatible with the Tandem t:slim insulin pump (luer lock connection) will be provided.**

Continuous ~~g~~**G**lucose ~~m~~**M**onitors: One transcutaneous glucose sensor for the Dexcom G4 Platinum (Garcia, 2013) will be inserted in the abdominal SC tissue and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to the sensor and the whole assembly is held to the skin with an adhesive patch and communicates wirelessly with the BP. If the G4 sensor fails for any reason during the trial (loss of CGM signal), it will be replaced promptly.

Bionic Pancreas Control Unit: **The control unit consists of a stock iPhone 4S and a DexCom G4 Platinum receiver connected with a custom hardware interface and placed back-to-back in a custom enclosure. The G4 receiver converts the raw wireless signal from the transmitter into an estimated BG signal that is sent via a hardwired connection to the iPhone.**

The iPhone runs iOS 6 in "Guided Access" mode, where the only app accessible to the patient is the Beta Bionics app, which runs the control algorithm. The home screen, where typical user options reside, is password protected. Access to other functions on the iPhone (primarily the Settings options) is separately password protected and only accessible to the study staff. This prevents accidental activation of other apps that could interfere with the function of the BP. The control algorithm app has a graphical user interface (GUI) that displays the current CGM glucose, a graphical history of the CGM glucose, and doses of insulin and glucagon delivered by the control algorithm. The GUI can also be used to input meal announcements, designating the size of the meal as larger than typical, typical in size, smaller than typical, or just a bite, and the type of meal as breakfast, lunch, or dinner. This will trigger a partial meal-priming bolus the size of which will adapt during the course of the trial to meet a target of 75% of the insulin needs for that size and type of meal.

The target glucose level will be programmed to 100 mg/dL by the study engineers prior to the start of each experiment. This will be locked for each arm of the study; the patient will be unable to accidentally change or tamper with this setting.

The GUI can be used to manage meal boluses and correction boluses during periods when the CGM is offline, such as the period after a sensor is replaced and before the new sensor has been calibrated. During these times the control algorithm will determine

and direct the administration of insulin basal rates based on the patient's weight. The controller will also administer insulin and/or glucagon as appropriate in response to any entered BG values, just as if they were CGM values.

The GUI also displays visual alarms associated with an audio signal if communication is dropped between the CGM transmitter and the BP control unit or between the control unit and the 2 insulin pumps.

The iPhone communicates wirelessly via the Bluetooth Low Energy (BTLE) protocol with 2 Tandem t:slim insulin pumps to deliver insulin and glucagon.

~~The iLet is being built according to Class III medical device standards, adheres to a comprehensive and robust quality system, and is fully compliant with International Organization for Standardization (ISO) 13485 standards and document control practices. The iLet is a fully integrated dual hormone BP system that integrates the CGM technology (currently the Dexcom G4 Share system) as well as 2 independent motor drivetrain pumping assemblies, which independently actuate the delivery of insulin and glucagon from pre filled cartridges that are separately loaded into the iLet housing. Each drivetrain assembly utilizes a lead screw, which is driven by a precision micromotor, a gear case assembly, and a motor controller unit, in a manner similar to what is commonly found in most insulin infusion pumps on the market today. The iLet has dosing accuracy that is comparable to FDA approved insulin pumps currently on the market. The iLet has a built in Bluetooth Low Energy radio that also allows automatic communication with the paired CGM, as well as the Nova StatStrip® Xpress BG meter (Nova Biomedical). The iLet does not contain a cellular nor a WiFi radio, and does not accept input data from another mobile device (e.g., smartphone), other than the paired CGM and BG meter(s).~~

~~The mathematical control algorithms (which are the same as those used in the iPhone based BP), the CGM glucose engine (Dexcom), and the native user interface software, are all interconnected through controller framework software and reside as embedded systems on printed circuit boards contained within the device housing. The touchscreen enabled, menu driven user interface and onboard processor provide a comprehensive and standalone platform, which allows the iLet to operate independently of smartphones or other devices and without the need for internet support during routine operation. The graphical user interface of the iLet has the same user options and capabilities of the iPhone BP, including having its home screen password protected and its settings options only accessible to trial staff via a separate password.~~

Tandem t:slim Pumps: These pumps are FDA-approved insulin pumps with reservoirs capable of holding 300 units (3 mL) of insulin or 3 mL of glucagon or ZP4207 solution. The pumps have a mechanical dosing resolution of 1/120 (0.00833) unit and can deliver liquids at a maximal rate of ~ 33 µl per minute (2 mL per hour). They are slave to the BP control unit and are controlled wirelessly via the BTLE protocol by the iPhone 4S.

[redacted]

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CLINICAL TRIAL PROTOCOL

The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

Investigational Product: ZP4207
Protocol Number: ZP4207-16051
IND Number: 129980
Phase: 2

Principal Investigator:
Steven J. Russell, MD, PhD[1]

Co-Investigator:
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Original Version: 03 May 2016
Amendment Number 1.0: 28 June 2016
Amendment Number 2.0: 03 August 2016
Amendment Number: 3.0
Protocol Version Number: 4.0
Date: 17 August 2016

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SIGNATURE PAGE

TRIAL TITLE: The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the trial.

Signature [redacted] Date [redacted]

Ulrik Mouritzen, MD
Vice President, Clinical Development
Zealand Pharma A/S

[redacted] Date [redacted]

[redacted] DVM, PhD
Principal Clinical Pharmacologist
Zealand Pharma A/S

[redacted]

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INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the trial as described. I will conduct this trial in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the trial within the time designated. I will provide copies of this protocol and access to all information furnished by Zealand Pharma A/S to trial personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the trial product and trial procedures. I will let them know that this information is confidential and proprietary to Zealand Pharma A/S and that it may not be further disclosed to third parties. I understand that the trial may be terminated or enrollment suspended at any time by Zealand Pharma A/S, with or without cause, or by me if it becomes necessary to protect the best interests of the trial patients.

I agree to conduct this trial in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and ICH Guidelines for Good Clinical Practices.

[redacted]

Investigator's Signature

8/17/2016

Date

Steven J. Russell, MD, PhD

Investigator's Printed Name

[redacted]

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SYNOPSIS

TITLE: The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

PROTOCOL NUMBER: ZP4207-16051

INVESTIGATIONAL PRODUCT: ZP4207

PHASE: 2

INDICATION: ZP4207 is an anti-hypoglycemic glucagon analog in a ready-to-use liquid formulation which is being studied to improve glycemic control in adults (and children) with type 1 diabetes mellitus (T1DM) as part of a bihormonal bionic pancreas (BP).

OBJECTIVES:

Primary: The primary objective is to conduct a trial testing the safety and tolerability of the iPhone-based bionic pancreas (BP) when used with ZP4207 in 10 adult (≥18 years of age) patients with T1DM.

Secondary: The secondary objectives are to measure glycemic regulation, including hypoglycemia exposure (percent of time spent with continuous glucose monitor [CGM] glucose <60 mg/dL), evaluate BP device reliability, and to document the satisfaction of patients with the iPhone-based BP with the goal of optimizing the functionality and user interface of the iPhone-based BP.

POPULATION: Up to 20 adult (≥18 years of age) patients who already manage their T1DM using continuous subcutaneous (SC) insulin infusion pump therapy can be enrolled. It is expected that up to 10 patients will complete the trial protocol.

TRIAL DESIGN: This trial is a single-center, open-label, randomized cross-over trial. The trial will enroll adult patients with T1DM and will assess the safety and efficacy of the iPhone-based BP using the glucagon analog ZP4207 versus the iPhone-based BP using Lilly glucagon. The iPhone-based BP will also administer insulin (insulin lispro, Lilly Humalog) using the same blood glucose (BG) control algorithm for both treatment arms. The trial will be conducted at a single center, the Massachusetts General Hospital Diabetes Center in Boston, MA.

TRIAL TREATMENT: The trial involves SC administration of insulin lispro (Humalog, Lilly), which is commercially available by prescription and is indicated for patients with T1DM, but not for use in a BP.

The trial also involves SC administration of Lilly glucagon in one iPhone-based BP arm. Lilly glucagon is commercially available by prescription and is indicated for patients with T1DM in severe hypoglycemia, but not for use in a BP.

The trial also involves SC administration of the glucagon analog ZP4207, 1 mg/mL, in the other iPhone-based BP arm. ZP4207 will be made available by Zealand Pharma A/S, Denmark as liquid formulation in prefilled syringes of 0.6 mL.

PRIMARY ENDPOINT:
The primary endpoint is the safety and tolerability of ZP4207 and the iPhone-based BP as assessed by:

- Number and type of adverse events (AEs)
- Clinical laboratory measurements
- Vital signs
- 12-lead electrocardiogram (ECG)
- Local tolerability and infusion site reactions as measured with the Draize scale
- Immunogenicity as measured by anti-drug antibodies
- Pain as measured on a 10 cm visual analog scale (VAS)
- Nausea as measured on a 10 cm VAS

SECONDARY ENDPOINTS:
The secondary endpoints for the iPhone-based BP and ZP4207 include measurements of BP function as well as glycemic and non-glycemic measurements.

Bionic Pancreas Function
This endpoint data will be generated from the BP data during each treatment visit:

- Average percent insulin dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
    - Average percent glucagon/ZP4207 dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts calculated by the BP algorithm that are successfully issued to the pump by the BP (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts calculated by the BP control algorithm that are successfully issued by the BP
    - Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully issued by the BP
- Average percent of 5-minute steps during which the BP is functioning nominally in all respects based on real-time CGM data (new CGM glucose reading captured, dose calculated, and dose issued to pumps)
- Average percent of 5-minute steps during which the BP is functioning nominally with or without a new CGM glucose reading captured (dose calculated and dose issued to pumps). If a CGM signal is not available, the dose calculated may be based on weight or historical basal rates.
- CGM reliability index, calculated as percent of possible values actually recorded by CGM
- CGM Mean Absolute Relative Difference versus time-stamped BG values from meter download
- List of technical faults associated with the BP including cause and resolution

[redacted]

Glycemic
All of following metrics will be generated from the Dexcom G4 Platinum CGM data during each treatment visit:

- Fraction of time spent within each of the following glucose ranges:
  - <50 mg/dL
  - <60 mg/dL
  - <70 mg/dL
  - 70-120 mg/dL
  - 70-140 mg/dL
  - 70-180 mg/dL
  - >180 mg/dL
  - >250 mg/dL
  - >300 mg/dL
- Number of severe hypoglycemic events (patients unable to self-treat, requiring the assistance of another person)
- Number of episodes of symptomatic hypoglycemia
- Number of carbohydrate interventions for hypoglycemia
- Total grams of carbohydrates taken for hypoglycemia
- Mean CGM glucose

Non-glycemic

- Glucagon/ZP4207 total delivery per kg of body mass
- Insulin total delivery per kg of body mass
- Number of unscheduled infusion set replacements
- Number of unscheduled CGM sensor changes

EVALUATION OF TRIAL DATA: The following variables will be evaluated according to treatment for safety purposes: AEs, local tolerability, laboratory safety assessments, physical examination, vital signs, and 12-lead ECGs.

The analysis of BP function endpoints and glycemic endpoints will be on an intention-to-treat basis. In cases where a treatment arm was not completed (and that arm was not repeated according to protocol criteria), available data from that arm will be used in the data analysis.

The Shapiro-Wilk test will be used to determine the normality of the residuals for each comparison. Summary tables that display descriptive statistics, including percentages, means or medians, and standard deviation and/or ranges, as appropriate, will be provided.

A paired t-test or the Wilcoxon signed rank test for comparison of means with normally or non-normally distributed residuals, respectively, will be used. In a secondary analysis any period effect and any interaction between treatment and period will be looked for, although no such interaction is predicted for the efficacy outcome.

The number of patients and proportions of severe hypoglycemic events, symptomatic hypoglycemia, and carbohydrate interventions due to hypoglycemia with the event counts will be summarized descriptively, and the proportions will be analyzed by a Fisher's exact test if data allow.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibodies
AE	Adverse event
BG	Blood glucose
BP	Bionic pancreas
BTLE	Bluetooth Low Energy
BU	Boston University
CFR	Code of Federal Regulations
CGM	Continuous glucose monitor
CRO	Contract research organization
DBR	Database review
DPP-4	Dipeptidyl peptidase-4
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FDA	Food and Drug Administration
FHD	First Human Dose
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GUI	Graphical user interface
HCG	Human chorionic gonadotropin
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IM	Intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
MD	Doctor of Medicine
MedDRA	Medical Dictionary for Regulatory Activities
MGH	Massachusetts General Hospital
MPC	Model-predictive control
PD	Pharmacodynamic

[redacted]

Abbreviation	Definition
PK	Pharmacokinetic
RN	Registered nurse
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SGLT-2	Sodium-glucose co-transporter-2
SIV	Site Initiation Visit
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 diabetes mellitus
TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
ULN	Upper limit of normal
VAS	Visual analog scale

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1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Background and Rationale

To date, clinical trials conducted by Boston University (BU) and Massachusetts General Hospital (MGH) in patients with type 1 diabetes mellitus (T1DM) have demonstrated the practicality of a wearable automated bionic pancreas (BP) control system for robust glucose regulation using a continuous glucose monitor (CGM) to provide the input to the control system. Despite current technical limitations in CGMs and infusion pumps, the trials by BU/MGH have shown that a bihormonal BP is capable of achieving safe and effective blood glucose (BG) control automatically, with minimal hypoglycemia during 11 continuous days in the face of unrestrained meals and exercise and with trivial patient input (optional announcement of meals).

The BP provides automatic BG regulation and reduces hypoglycemic episodes. Additionally, the system spares the wearer the relentless tasks of carbohydrate counting, frequent BG monitoring, estimating the effects of specific meals and exercise activity on BG levels, and manual drug administration, which are inexact, demanding, aggravating, and require continuous diligence and vigilance. The degree of glycemic control achieved by the BP is predicted to dramatically reduce the deleterious and debilitating complications of T1DM.

In its last tested embodiment, the BP consisted of a Dexcom G4 CGM, and an iPhone that are hardwired together, with the iPhone running the control algorithm and communicating via Bluetooth with 2 Tandem t:slim pumps to dose insulin and glucagon.

In order to provide automatic BG regulation, the iPhone-based BP has the ability to deliver both insulin and glucagon. However, currently available glucagon formulations have limited stability at room temperature, necessitating frequent changes to the glucagon infusion set. Therefore, the current trial is designed to test the glucagon analog ZP4207 in the iPhone-based BP, as this peptide analog of human glucagon is provided in a liquid formulation stable at room temperature.

The current trial is a first feasibility trial designed to use the iPhone-based BP to compare ZP4207 with marketed glucagon (Lilly). The trial is intended to demonstrate the safety and tolerability of ZP4207 in the iPhone-based BP and the feasibility of achieving comparable autonomous glycemic control. It is not intended to comprehensively demonstrate the definitive efficacy of the iPhone-based BP in extended, continuous daily use, but rather to demonstrate its functionality and accuracy in a practical, albeit very controlled, clinical setting. The trial is expected to provide practical information that will benefit the design of a next-generation BP and help pave the way for a more comprehensive outpatient home-use Phase 2 trial and ultimately a pivotal trial where comprehensive safety and efficacy through continuous full daily use of the BP with ZP4207 will be documented.

The data derived from this trial will permit evaluation of the robustness of the iPhone-based BP as well as the safety and efficacy of ZP4207 when used in conjunction with the iPhone-based BP.

[redacted]

1.2 Bihormonal Bionic Pancreas System

The BP is an autonomous, self-learning system that requires only the patient's weight for initialization, and then autonomously adapts, modestly or dramatically, as needed, to cope with the wide range of insulin requirements of adults, adolescents, and pre-adolescents with T1DM. The BP obviates the need for the patient to know, or even appreciate, their insulin requirements, and renders obsolete any need for patients or caregivers to know carbohydrate-to-insulin ratios, basal rates, or insulin correction factors.

The core technology is a suite of control algorithms that orchestrate the automated dosing of insulin and glucagon to regulate BG levels. An insulin controller orchestrates all subcutaneous (SC) insulin dosing. At its centerpiece is a model-predictive control (MPC) algorithm, which bases insulin doses on the glucose data and insulin absorption kinetics, compensating for the slow absorption rate of SC insulin analogs (peak time in blood of 30-90 min, clearance in 4-8 hr). This enables the algorithm to refrain from stacking and overdosing insulin. Furthermore, the MPC algorithm automatically adjusts its insulin-dosing aggressiveness continuously and in real-time to different insulin needs between individuals and variable needs within the same individual. Running in parallel with the MPC algorithm is an algorithm that automatically modulates basal insulin delivery over multiple time scales, and another algorithm that automatically adapts insulin doses in response to optional meal announcements. Unlike current insulin pumps and the insulin-only control algorithms, the adaptive basal insulin algorithm obviates the need for the user to set, or even know, his or her “basal-rate profile.” Instead, it is capable of automatically adapting to, and compensating for, changes in an individual's basal insulin need, such as might occur over a period of hours, days, or weeks (e.g., circadian hormonal fluctuations, intercurrent illness, physical activity, or emotional state) or as might occur over a period of months or years due to developmental changes (e.g., hormonal changes that occur during puberty or menopause). The adaptive meal dose controller obviates the need for the user to set, or even know, his or her “carbohydrate-to-insulin ratios,” as it makes automatic adjustments based on dosing history for similar meal announcements made on previous days, and customizes the dose for each individual and for time of day.

The BP also includes a proportional-derivative algorithm governing SC micro-doses of glucagon to help prevent impending hypoglycemia. Glucagon dosing is based on the glucose level and rate of descent. It may occur preemptively even if glucose is above range, and it includes a feedback term to account for the pending effects of recent glucagon doses.

Taken together, these mathematical algorithms provide a universal framework for a glycemic control strategy that requires no quantitative input from, or participation by, the user (besides entering body weight to initialize the system), but which automatically adapts insulin and glucagon dosing to meet the individual needs of each user. Another challenge met is enabling the technology to remain completely autonomous in managing insulin and glucagon delivery even when the CGM is offline. Specifically, when the CGM is offline, the BP invokes the high-resolution “basal rate profile” that it had recently learned and stored when the CGM was online. On the basis of what the system learned and stored about meal announcements when the CGM was online, it is able to respond to meal announcements in the same manner when the CGM is offline. Finally, it automatically responds to user-entered BG values when the CGM is offline by issuing a correction dose of insulin or glucagon based on what it learned about the user's insulin and glucagon needs when the CGM was online. Thus, the BP never relies on, or burdens the user with, the determination of subjective dosing decisions, which inevitably

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vary in quality and reliability among different users. The BP provides a turnkey solution for people with T1DM that comprehensively manages glycemia across a broad range of individual needs and across a large spectrum of circumstances and challenges to glycemic control.

A significant challenge for the use of glucagon in a bihormonal BP is the lack of a commercially available glucagon formation that is stable and well-suited to infusion over several days in a pump reservoir. However, BU/MGH have proceeded with studies using a relatively unstable marketed formulation that must be reconstituted from a lyophilized powder on a daily basis. This allowed BU/MGH to proceed with studies of the bihormonal system while awaiting the production of stable glucagon formulations or stable glucagon analogs.

1.3 Preliminary Studies with the Bihormonal Bionic Pancreas System

The BP hardware platform has evolved over the years from a laptop-driven system, which was used in all inpatient studies to the first truly mobile wearable iPhone-driven platform, which has been used in a number of outpatient studies. Using the iPhone-based BP system, >110 outpatient experiments of 5-11 days in duration in each subject have been conducted (>800 patient days or >2 patient years of data) across subjects ranging in age between 6 and 76 years old and in body mass between 21 and 128 kg. The robust adaptation capabilities of the BP is evident in the fact that the average total daily dose of insulin among these subjects varied by over 13-fold (from 11 to 145 units/day).

In November 2012, Food and Drug Administration (FDA) approval was obtained to conduct the first outpatient study testing the BP in adults 21 years or older with T1DM. This study, referred to as the Beacon Hill Study, followed a random-order cross-over design in which 20 adults with T1DM participated in 5 days on the iPhone-based BP and 5 days of usual care in which they wore a CGM with blinded display and muted alarms. In the BP arm, subjects kept to a 3-square-mile geographic area centered around the Beacon Hill neighborhood in Boston. They ate as they chose at local restaurants, and exercised at will with access to 2 gyms. Analysis was pre-specified to focus on Days 2-5, since glycemic control is more representative of BP performance after most of the adaptation by the BP occurs on Day 1 (Russell, 2014). Results are summarized in Figure 1.

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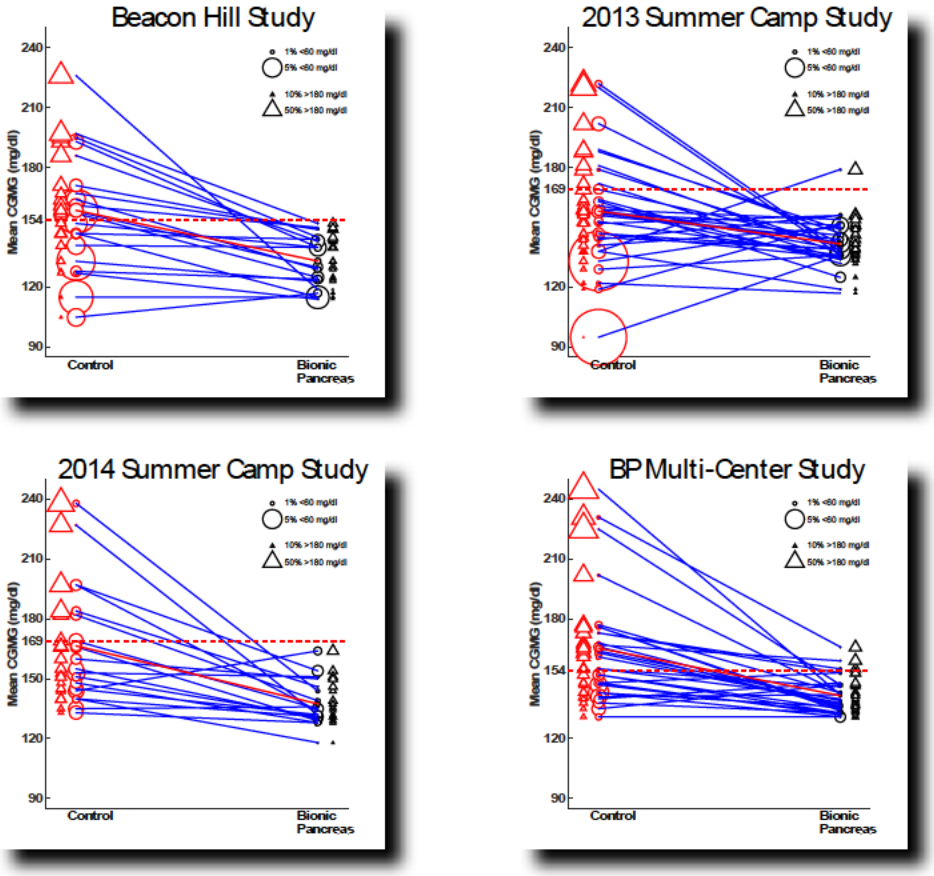
Figure 1. Outpatient Results Summarizing the Distribution of Mean CGM Glucose Levels and Hypoglycemia in the BP and Control Arms



Study	Age (years)	Bionic Pancreas (BP) Mean CGM glucose level (mg/dl)	Bionic Pancreas (BP) % of CGM glucose levels <50 mg/dl (%)	Bionic Pancreas (BP) % of CGM glucose levels 70–180 mg/dl (%)	Control Mean CGM glucose level (mg/dl)	Control % of CGM goucose values <50 mg/dl (%)	Control % of CGM goucose values 70–180 mg/dl (%)	*p* value (BP versus Control) for: Mean CGM glucose level	*p* value (BP versus Control) for: % of CGM glucose values <50 mg/dl	*p* value (BP versus Control) for: % of CGM glucose values 70–180 mg/dl
Beacon Hill (n 20, 5-day experiments)	≥21	133	1.5	80	159	3.7	59	<0.001	0.020	<0.001
2013 Summer Camp (n 32, 5-day experiments)	12–20	142	1.3	76	158	2.2	65	0.004	0.192	<0.001
2014 Summer Camp (n 19, 5-day experiments)	6–11	137	1.2	81	168	2.8	58	0.004	0.001	<0.001
BP Multi Center (n 39, 11-day experiments)	≥18	141	0.6	78	162	1.9	62	<0.001	<0.001	<0.001

Mean CGM glucose levels for each subject under usual care (red circles) are connected with the subject's mean CGM glucose level on the BP (black circles). The diameters of the circles shown are proportional to the percentage of CGM glucose values <60 mg/dL, and the size of the triangle is proportional to the percentage of CGM glucose values >180 mg/dL. The horizontal red dashed line refers to the glucose level corresponding to the American Diabetes Association therapy goal for each age group tested, which corresponds to 154 mg/dL (HbA1c of 7%) for adults and 169 mg/dL (HbA1c of 7.5%) for children. Results are summarized in the table, where the co-primary outcomes (mean CGM glucose level and percentage of CGM glucose values <60 mg/dL) for the BP arm are highlighted in red for each of the 4 studies.
BP = bionic pancreas; CGM = continuous glucose monitoring; HbA1c = hemoglobin A1c.

In April 2013, FDA approval was obtained to conduct the first outpatient study testing the BP in adolescents 12-20 years old with T1DM. This study, referred to as the 2013 Summer Camp Study, followed a random-order cross-over design in which 32 adolescents with T1DM participated in 5 days on the BP and 5 days of supervised camp care in which they wore a CGM with blinded display and muted alarms. Subjects were fully integrated into normal camp activities without restrictions on diet or exercise. The study used the same iPhone-based BP that was used in the Beacon Hill Study. Results are summarized in Figure 1 (Russell, 2014). In April 2014, FDA approval was obtained to conduct the first outpatient study testing the BP in pre-adolescents 6-11 years old with T1DM. This study, referred to as the 2014 Summer Camp Study, was similar in design to the 2013 Summer Camp Study. Results are summarized in Figure 1 (Russell, 2016).

In April 2014, FDA approval was obtained to conduct the first multi-center study, which was also the first home study, to test the BP in adults 18 years or older with T1DM. This study, referred to as the Bionic Pancreas Multi-Center Study, followed a random-order cross-over design in which 39 adults participated in 11 days on the BP and 11 days of usual care. Participants went to work as usual, and lived and slept at home, all without clinical supervision. There were no restrictions placed on diet or exercise. The study included 4 medical centers (10 subjects per center), which included MGH, the University of Massachusetts Medical School, Stanford University, and the University of North Carolina at Chapel Hill. Results are summarized in Figure 1.

All of these studies used marketed glucagon (glucagon for injection, Eli Lilly). Due to its limited stability, Lilly glucagon must be reconstituted immediately before use. Animal studies have previously shown that despite its limited chemical stability, Lilly glucagon maintains its biological activity for up to 7 days in solution. Using this data, an Investigational New Drug (IND) exemption was obtained from the FDA for its use in a pump for up to 27 hours. This allowed these studies to be performed by asking volunteers to reconstitute a new vial of glucagon and fill the glucagon pump at approximately the same time every day. However, marketed Lilly glucagon has no path forward for approval for chronic BP use.

1.4 ZP4207

ZP4207 is a peptide analog of human glucagon that is being developed to treat hypoglycemia in patients with T1DM and type 2 diabetes mellitus. ZP4207 exhibits improved physical and chemical stability in aqueous media and is suitable for liquid formulation. ZP4207 is comprised of 29 amino acids and has 7 amino acid substitutions when compared to native glucagon.

Two clinical Phase 1 trials have been conducted to establish safety and tolerability of ZP4207 after single and multiple dosing to healthy patients and T1DM patients under insulin-induced hypoglycemic conditions.

The First Human Dose (FHD) trial (ZP4207-14013) was finalized in April 2015. The trial was a randomized, double-blinded trial with the objectives to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of ZP4207 as compared to an active comparator. Part 1 included a single ascending dose in healthy volunteers in cohorts of 8. In each cohort, the patients were randomized 3:1 to ZP4207 (n=6) or Novo Nordisk GlucaGen® (n=2). Five cohorts with SC administration (0.01, 0.1, 0.3, 1.0, and 2.0 mg ZP4207 compared to 1 mg GlucaGen) and 3 cohorts with intramuscular (IM) administration (0.3, 1.0, and 2.0 mg ZP4207 compared to 1 mg GlucaGen) were included. Part 2 included 2 sequence groups of

10 hypoglycemic T1DM patients. The patients were treated with fixed single IM doses of 0.7 mg ZP4207 and 1.0 mg GlucaGen in a sequential cross-over design in a randomized treatment order.

The second clinical trial (ZP4207-15007) was a single-center, double-blind, Phase 1b trial investigating the safety and tolerability, PK and PD of ZP4207 following repeated administration in healthy volunteers compared to placebo. It was finalized in July 2015. Each of the 3 cohorts comprised 8 subjects, who received 5 repeated SC doses of ZP4207 or placebo in a 3:1 treatment allocation. The first cohort started with the lowest dose of 0.1 mg. Cohort 2 and 3 continued with 0.3 and 1.0 mg, respectively.

The Phase 1 results did not give rise to specific safety concerns, beyond those related to the pharmacological effect of ZP4207. All adverse events (AEs) recorded in the trials were of mild or moderate severity. The most frequent systemic AE related to treatment with ZP4207 was nausea, which is a known side-effect following administration of glucagon. The most frequent injection site reaction was transient erythema, occurring in all ZP4207, glucagon, and placebo treatment groups, irrespective of dose. No anti-drug antibodies (ADA) incidences were observed.

The observed PD response, in terms of increased plasma glucose, in insulin-induced hypoglycemic patients with T1DM following dosing with 0.7 mg ZP4207 administered IM was similar to that observed following IM dosing with 1.0 mg glucagon (GlucaGen, Novo Nordisk). An increase in plasma glucose of ≥20 mg/dL from hypoglycemic levels was achieved within 30 minutes for all patients.

In terms of PK, ZP4207 had a short half-life and high clearance and dose proportionality for both maximum plasma concentration and area under the concentration-time curve from time 0 to 300 minutes in the dose range 0.1 to 2.0 mg following SC administration. Following IM administration, dose proportionality was shown in the investigated dose range of 0.3 to 2.0 mg. The PK properties of 0.7 mg ZP4207 IM were comparable with those of 1.0 mg glucagon (GlucaGen, Novo Nordisk) with IM administration.

1.5 Risk/Benefit

While the potential risks are minimal, the findings of this trial may reveal information that can substantially improve medical care for persons with diabetes. Therefore, the overall risk/benefit for patients participating in this trial is assessed as acceptable.

Potential Risks and Discomforts

Trial patients will be informed by the Investigator of the potential risks of ZP4207 and other trial-related procedures before they enter the trial.

In this trial, patients with T1DM will be included to test the safety and efficacy of the iPhone-based BP using ZP4207 versus the iPhone-based BP using Lilly glucagon. The cross-over design with inclusion of the same T1DM patients into the 2 treatment arms in a randomized order will allow for a direct comparison of the safety and efficacy of the 2 treatments, based on intra-patient variability only.

[redacted]

Patients may experience mild discomfort associated with the insertion of the infusion sets and sensor into the SC tissues. The risk of discomfort due to insertion of infusion sets and sensors is expected to be slightly greater than in their lives outside the trial because more infusion sets will be inserted and a CGM sensor will be inserted. Most patients will use only one infusion set and not all will use a CGM sensor in usual care.

There is a potential risk of hypoglycemia, since recombinant insulin analog will be administered. Due to frequent monitoring of glucose and direct supervision by a registered nurse (RN) or Doctor of Medicine (MD) at all times, the risk of a hypoglycemic episodes leading to significant harm to patients is expected to be substantially lower than their risk during their usual therapy.

There is a risk of hyperglycemia. This risk is expected to be less than the risk during the patients' lives outside of the trial based on data from earlier BP trials and the design of this trial.

Treatment with ZP4207 and marketed glucagon can result in undesired effects or complaints. Undesired effects and complaints such as gastrointestinal side effects including nausea, vomiting, and diarrhea are known side effects of glucagon administration at higher dose levels. The frequency of nausea associated with the administration of 1 mg of glucagon according to the Summary of Product Characteristics (SPC) for Glucagon is described to be between 1/10 and 1/100. The frequency of vomiting is described to be between 1/100 and 1/1000 (Novo Nordisk, 2015). Similar gastrointestinal side effects have also been observed to a limited degree in the 2 clinical trials conducted with ZP4207, again at higher dose levels. The individual doses of ZP4207 and Lilly glucagon delivered by the BP are expected to be significantly lower than doses typically associated with nausea. Episodes of low blood pressure have also been observed after administration of higher doses of glucagon and ZP4207. As with every novel drug substance, new and yet unknown side effects may also occur.

There are limited data available to describe the immunogenic potential of glucagon products available on the market, but the data available indicate that marketed glucagon only has a small immunogenic potential. A Phase 1 trial performed with recombinant human glucagon and animal derived glucagon in 75 healthy patients did not show signs of ADA measured 13 weeks after trial product administration (Eli Lilly, 2005). In the ZP4207 FHD trial, ZP4207-14013, no confirmed anti-ZP4207 or anti-glucagon antibodies were detected in any of the samples. In addition, the 5 sequential administrations of ZP4207, as applied in trial ZP4207-15007, were not associated with the development of antibodies against ZP4207 in the 18 subjects enrolled to receive ZP4207. The optimized formulation of ZP4207, as applied in the present trial is not expected to change the immunogenic potential of the Investigational Medicinal Product (IMP).

In relation to diabetes therapy, development of insulin-antibodies is documented more substantially and route of administration has been shown to influence immunogenic potential of insulins. However, these antibodies against insulin generally do not have an impact on insulin action and are thus not clinically relevant.

In terms of consequence, development of high titer antibodies against ZP4207 could, in theory reduce the activity of endogenous glucagon, which again, in theory could influence

[redacted]

hypoglycemic episodes. However, most patients with T1DM do not secrete glucagon normally in response to hypoglycemia, so they would be less likely to be negatively impacted by anti-glucagon antibodies. Limited suppression of glucagon would, however, not be considered critical, as low glucose levels can also be corrected by other means, including oral intake of glucose and by other endogenous hormones such as oxyntomodulin.

Overall, ZP4207 is judged to be a low-risk molecule, based upon the available clinical data as well as the outcome of the risk-based approach to the immunogenicity assessment made. The present trial will include sampling for measurement of antibodies against ZP4207 prior to first dosing (Visit 3) and at the Follow-up Visit. In line with regulatory guidance documents, these samples will be appropriately analyzed and the results will be included in the overall assessment of the immunogenic potential of ZP4207 after completion of each trial and as the clinical development program advances.

Administration of ZP4207 may be associated with a risk of allergic reactions similar to those observed for other therapeutic peptides or proteins. Patients with known or suspected allergies to the trial products or related products will be excluded from the trial. Mild or moderate allergic reactions may include symptoms of rash, fever, flu-like symptoms, nausea, headache, and myalgia. Acute generalized hypersensitivity reactions are usually very rare but may include symptoms of flushing, sweating, dizziness, change in blood pressure, and difficulties in breathing. The risk of acute hypersensitivity reactions is described to be less than 1/10,000 for native glucagon. No severe acute hypersensitivity reactions have been observed in the 2 clinical trials conducted with ZP4207.

Potential Benefits

Based on experiences from previous trials of the BP and the design of this trial, patients enrolled in the trial may benefit from a reduction in risk of hypoglycemia and hyperglycemia and a better mean glucose compared to their usual diabetes care during their short trial participation.

The data derived from this trial will allow evaluation of safety and tolerability of ZP4207 in the iPhone-based BP.

This trial is a necessary step in preparing the BP with ZP4207 to become available to people with T1DM. Wide availability of the BP with ZP4207 could improve the medical care of adults and children with T1DM.

2 TRIAL OBJECTIVES

2.1 Primary Objective

The primary objective is to conduct a trial testing the safety and tolerability of the iPhone-based BP when used with ZP4207 in 10 adult (≥18 years of age) patients with T1DM.

2.2 Secondary Objectives

The secondary objectives are to measure glycemic regulation, including hypoglycemia exposure (percent of time spent with CGM glucose <60 mg/dL), evaluate BP device reliability, and to document the satisfaction of patients with the iPhone-based BP with the goal of optimizing the functionality and user interface of the iPhone-based BP.

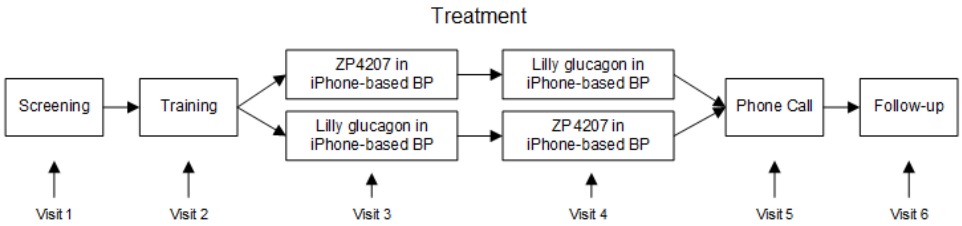
3 TRIAL DESCRIPTION

3.1 Summary of Trial Design

This trial is a single-center, open-label, randomized cross-over trial. The trial will enroll adult patients with T1DM and will assess the safety and efficacy of the iPhone-based BP using the glucagon analog ZP4207 versus the iPhone-based BP using Lilly glucagon. The iPhone-based BP will also administer insulin (insulin lispro, Lilly Humalog) using the same BG control algorithm for both treatment arms. The trial will be conducted at a single center, the MGH Diabetes Center in Boston, MA.

The overall trial design schematic is displayed in Figure 2.

Figure 2. Trial Design Schematic



BP= bionic pancreas.

3.2 Indication

ZP4207 is an anti-hypoglycemic glucagon analog in a ready-to-use liquid formulation which is being studied to improve glycemic control in adults (and children) with T1DM as part of a bihormonal BP.

3.3 Number of Patients

Up to 20 adult patients with T1DM can be enrolled. The upper bound is based on the expectation that some patients will be excluded after the Screening Visit and the possibility that some patients may have to be discontinued before completion (due to, for instance,

inter-current illness or patient withdrawal). It is expected that up to 10 patients will complete the trial protocol.

4 SELECTION AND WITHDRAWAL OF PATIENTS

The trial will enroll patients who already manage their T1DM using continuous SC insulin infusion pump therapy. This requirement is imposed because multiple daily injection therapy involves the use of medium-acting or long-acting basal insulin that would require an extended washout period.

4.1 Inclusion Criteria

1. Male and female patients with T1DM for at least 1 year, as defined by the American Diabetes Association
2. Age ≥18 years
3. Diabetes managed using an insulin pump for ≥6 months
4. Prescription medication regimen stable for >1 month (except for medications that will not affect the safety of the trial and are not expected to affect any outcome of the trial, in the judgment of the Investigator)
5. Informed consent obtained before any trial-related activities (trial-related activities are any procedure that would not have been performed during normal management of the patient)
6. Patients in good health according to age (medical history, physical examination, vital signs, 12-lead electrocardiograms [ECGs], laboratory assessments), as judged by the Investigator

4.2 Exclusion Criteria

1. Unable to provide informed consent (e.g., impaired cognition or judgment)
2. Unable to safely comply with trial procedures and reporting requirements (e.g., impairment of vision or dexterity that prevents safe operation of the BP, impaired memory, unable to speak and read English)
3. Participation in another clinical trial of an investigational agent or device concurrently or within 1 month (or 5 half-lives) prior to the Screening Visit
4. Previous exposure to ZP4207
5. Females of childbearing potential who are pregnant (positive urine human chorionic gonadotropin [HCG]), breast feeding, plan to become pregnant in the immediate future, or sexually active without using highly effective contraception methods (highly effective methods are considered those with a failure rate less than 1% undesired pregnancies per year including surgical sterilization, hormonal intrauterine devices [coil], oral hormonal contraceptives, sexual abstinence, or a surgically sterilized partner) or postmenopausal women amenorrheic for less than 1 year with serum follicle-stimulating hormone (FSH) level ≤40 IU/L and not using highly effective contraceptive methods during the trial and until 1 month after last dosing in the trial
6. Male who is sexually active and not surgically sterilized who or whose partner(s) is not using highly effective contraceptive methods (highly effective contraceptive measures include surgical sterilization, hormonal intrauterine devices [coil], oral hormonal contraceptives, each in combination with spermicide-coated condoms), or who is not willing to refrain from sexual intercourse from the first dosing until 1 month after last dosing in the trial

[redacted]

7. Current alcohol abuse (intake averaging >3 drinks daily in last 30 days) or use within the last 6 months of controlled substances without a prescription (other than marijuana)
8. New onset clinically significant illness within 4 weeks prior to screening, as judged by the Investigator
9. Unwilling or unable to refrain on the treatment visits from:
    a. Acetaminophen in any form
    b. Use of drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the trial (use of beta blockers will be allowed as long as the dose is stable and the patient does not meet the criteria for hypoglycemia unawareness while taking that stable dose, but use of benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the Investigator)
10. History of liver disease that is expected to interfere with the anti-hypoglycemia action of glucagon (e.g., liver failure or cirrhosis). Other liver disease (i.e., active hepatitis, steatosis, active biliary disease, any tumor of the liver, hemochromatosis, glycogen storage disease) may exclude the patient if it causes significant compromise to liver function or may do so in an unpredictable fashion.
11. Aspartate aminotransferase >2 × upper limit of normal (ULN), alanine aminotransferase >2 × ULN, or bilirubin >1.5 × ULN on screening laboratories
12. Renal failure on dialysis or estimated glomerular filtration rate <30 mL/min/1.73 m^2 on screening laboratories
13. Hemoglobin <12 gm/dL for men and <11 gm/dL for women
14. Personal history of cystic fibrosis, pancreatitis, pancreatic tumor, or any other pancreatic disease besides T1DM
15. Any known history of coronary artery disease including, but not limited to, history of myocardial infarction, stress test showing ischemia, history of angina, or history of intervention such as coronary artery bypass grafting, percutaneous coronary intervention, or enzymatic lysis of a presumed coronary occlusion)
16. Congestive heart failure with New York Heart Association Functional Classification III or IV
17. History of transient ischemic attack or stroke in the last 12 months
18. Seizure disorder, history of any non-hypoglycemic seizure within the last 2 years, or ongoing treatment with anticonvulsants
19. History of hypoglycemic seizures (grand-mal) or coma in the last 12 months
20. History of hypoglycemic unawareness in the last 12 months
21. History of pheochromocytoma: fractionated metanephrines will be tested in patients with history increasing the risk for a catecholamine secreting tumor:
    a. Episodic or treatment refractory (requiring 4 or more medications to achieve normotension) hypertension
    b. Paroxysms of tachycardia, pallor, or headache
    c. Personal or family history of MEN 2A, MEN 2B, neurofibromatosis, or von Hippel-Lindau disease
22. History of adrenal disease or tumor
23. Hypertension with systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg despite treatment
24. Untreated or inadequately treated mental illness (indicators would include symptoms such as psychosis, hallucinations, mania, and any psychiatric hospitalization in the last year), or treatment with anti-psychotic medications that are known to affect glucose regulation

[redacted]

25. Electrically powered implants (e.g., cochlear implants, neurostimulators) that might be susceptible to radio frequency interference
26. History of adverse reaction to glucagon (including allergy) besides nausea and vomiting
27. History of severe hypersensitivity to milk proteins or lactose
28. Established history of allergy or severe reaction to adhesive or tape that must be used in the trial
29. Use of oral anti-diabetic medications (e.g., thiazolidinediones, biguanides, sulfonylureas, glitinides, dipeptidyl peptidase-4 [DPP-4] inhibitors, sodium-glucose co-transporter-2 [SGLT-2] inhibitors)
30. Inadequate venous access as determined by trial nurse or physician at time of screening
31. Any factors that, in the opinion of the Investigator, would interfere with trial endpoints or the safe completion of the trial

4.3 Target Population

Patients who meet all of the inclusion and none of the exclusion criteria will be considered as candidates for this trial. Individuals who have previously inquired about participation in BU/MGH trials and have asked to have their contact information kept on file will be contacted. In addition, advertisements for the trial may be posted at the MGH Diabetes Center and other places, and may be distributed in the weekly broadcast e-mail of research studies seeking volunteers. A letter may be sent to adult endocrinologists in the Boston metropolitan as well as selected nearby endocrinologists informing them of the trial and asking them to refer any eligible patients who might be interested. Information will be posted about the trial along with contact information on the BU/MGH website www.bionicpancreas.org and on www.clinicaltrials.gov.

4.4 Withdrawal Criteria

The participation of individual patients will be discontinued if they experience:

- Seizure or unconsciousness associated with hypoglycemia and associated with participation in the trial
- Persistent nausea and vomiting thought to be related to glucagon dosing associated with participation in the trial
- Hospitalization associated with participation in the trial
- Pregnancy
- Diabetic ketoacidosis

If more than 1 patient must be withdrawn from the trial for these reasons, the trial will stop and a vote of the Data and Safety Monitoring Board (DSMB) will be required to restart it. All AEs that are serious and unexpected but related will be reported to the DSMB within 5 working days.

Note that patients may discontinue participation at any time. Patients may be removed from the trial for other reasons, for instance, failure to comply with trial procedures or intercurrent illness that is unrelated to the BP but that precludes safe participation. Discontinuation of participation for these reasons will not contribute to a decision to discontinue the trial.

[redacted]

5 ASSIGNMENT TO TREATMENT GROUPS

This trial is an open-label, randomized cross-over trial. Patients who have completed the Screening Visit and meet all of the inclusion and none of exclusion criteria will be enrolled into the trial. All patients will participate in two 1-day treatment arms in random order (iPhone-based BP using ZP4207 and iPhone-based BP using Lilly glucagon) according to a pre-generated randomization scheme. Up to 2 patients may participate in the trial per day. The order of the iPhone-based BP visits will be randomized in blocks of 2 patients.

6 TRIAL TREATMENT

6.1 Investigational Medicinal Products

Insulin: The trial involves SC administration of insulin lispro *(*Humalog, Lilly*)*, which is commercially available by prescription and is indicated for patients with T1DM, but not for use in a BP.

Glucagon: The trial also involves SC administration of Lilly glucagon in one iPhone-based BP arm. Lilly glucagon is commercially available by prescription and is indicated for patients with T1DM in severe hypoglycemia, but not for use in a BP.

ZP4207: The trial also involves SC administration of the glucagon analog ZP4207, 1 mg/mL, in the other iPhone-based BP arm. ZP4207 will be made available by Zealand Pharma A/S, Denmark as liquid formulation in prefilled syringes of 0.6 mL.

6.2 Storage and Drug Accountability of IMPs

All IMPs will be stored and handled in accordance with the Sponsor's instructions and/or the product labeling at the Investigator's site, e.g., refrigerated (+2ºC to +8ºC) and should not be exposed to excessive heat, direct sunlight and never be frozen.

All used, partly used, and unused vials or prefilled syringes must be kept by the Investigator and stored between +2ºC and +8ºC (unused) or at room temperature (partly used and used). Used and unused pre-filled syringes must be stored separately.

The Investigator must ensure the availability of proper storage conditions and record and evaluate the temperature. Temperature of the refrigerator used for drug storage is monitored continuously, an alarm system is established. The Investigator must inform the monitor immediately if any IMP has been stored outside specified conditions (e.g., outside temperature storage). Investigational Medicinal Product that has been stored improperly must not be dispensed to any patient before it has been re-evaluated and approved for further use. The Investigator must take appropriate action to ensure correct storage.

For the IMP, the Investigator must keep an accurate record of all IMPs received and the products used for each patient in a Drug Accountability Record. Storage locations, batch numbers, and expiry dates are also documented in this form.

The drug accountability must be performed in a timely manner by the monitor.

[redacted]

6.3 Dispensing and Return of IMPs

No IMPs may be dispensed to any person not enrolled in the trial.

Upon completion of the trial, the Sponsor will be responsible for destruction or storage of IMPs (used, partially used, or unused). These duties can be delegated to a contract research organization (CRO) and must be documented in the trial files.

6.4 Doses

The iPhone-based BP can administer isolated insulin-glucagon doses once every 5 minutes. A single automated bolus of insulin will not exceed 3 units per 5-minute dose (30 µl of U-100 insulin) in both systems, and a single meal-priming dose, in response to a meal announcement made by the user, will not exceed 12 units (120 µl of U-100 insulin). A single bolus of glucagon will not exceed 80 µg (80 µl of 1 mg/mL Lilly glucagon or 1 mg/mL ZP4207). In prior studies, typical doses of glucagon were in the range of 0.005-0.04 mg per dose. The iPhone-based BP is capable of administering as little as ~0.1 µl (0.011 units of U-100 insulin or 0.1 µg of 1 mg/mL ZP4207).

It is expected that the mean total daily doses of glucagon/ZP4207 will be <1.0 mg daily as in previous studies. The mean daily glucagon dose in a previous 11-day outpatient trial was 0.5 mg/day (range 0.2-0.9 mg/day). Currently, single doses of up to 2 mg ZP4207 have been administered in clinical trials. The recommended dose of marketed glucagon for adult patients suffering from severe hypoglycemia is 1 mg as a single injection. Mean glucagon levels in previous inpatient studies have been above the normal fasting range for glucagon only 1% of the time. Therefore, the glucagon exposure of patients is expected to be modest.

6.5 iPhone-based Bionic Pancreas

Infusion Set: Patients will wear 2 FDA-approved commercially available infusion sets, one for insulin infusion and one for glucagon infusion, when applicable. Infusion sets that are compatible with the Tandem t:slim infusion pump (luer lock connection) will be provided.

Continuous Glucose Monitors: One transcutaneous glucose sensor for the Dexcom G4 Platinum (Garcia, 2013) will be inserted in the abdominal SC tissue and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to the sensor and the whole assembly is held to the skin with an adhesive patch and communicates wirelessly with the BP. If the G4 sensor fails for any reason during the trial (loss of CGM signal), it will be replaced promptly.

Bionic Pancreas Control Unit: The control unit consists of a stock iPhone 4S and a DexCom G4 Platinum receiver connected with a custom hardware interface and placed back-to-back in a custom enclosure. The G4 receiver converts the raw wireless signal from the transmitter into an estimated BG signal that is sent via a hardwired connection to the iPhone.

The iPhone runs iOS 6 in “Guided Access” mode, where the only app accessible to the patient is the Beta Bionics app, which runs the control algorithm. The home screen, where typical user options reside, is password protected. Access to other functions on the iPhone (primarily the Settings options) is separately password protected and only accessible to the study staff. This prevents accidental activation of other apps that could interfere with the function of the BP. The control algorithm app has a graphical user interface (GUI) that displays the current CGM

glucose, a graphical history of the CGM glucose, and doses of insulin and glucagon delivered by the control algorithm. The GUI can also be used to input meal announcements, designating the size of the meal as larger than typical, typical in size, smaller than typical, or just a bite, and the type of meal as breakfast, lunch, or dinner. This will trigger a partial meal-priming bolus the size of which will adapt during the course of the trial to meet a target of 75% of the insulin needs for that size and type of meal.

The target glucose level will be programmed to 100 mg/dL by the study engineers prior to the start of each experiment. This will be locked for each arm of the study; the patient will be unable to accidentally change or tamper with this setting.

The GUI can be used to manage meal boluses and correction boluses during periods when the CGM is offline, such as the period after a sensor is replaced and before the new sensor has been calibrated. During these times the control algorithm will determine and direct the administration of insulin basal rates based on the patient's weight. The controller will also administer insulin and/or glucagon as appropriate in response to any entered BG values, just as if they were CGM values.

The GUI also displays visual alarms associated with an audio signal if communication is dropped between the CGM transmitter and the BP control unit or between the control unit and the 2 insulin pumps.

The iPhone communicates wirelessly via the Bluetooth Low Energy (BTLE) protocol with 2 Tandem t:slim insulin pumps to deliver insulin and glucagon.

Tandem t:slim Pumps: These pumps are FDA-approved insulin pumps with reservoirs capable of holding 300 units (3 mL) of insulin or 3 mL of glucagon or ZP4207 solution. The pumps have a mechanical dosing resolution of 1/120 (0.00833) unit and can deliver liquids at a maximal rate of ~33 µl per minute (2 ml per hour). They are slave to the BP control unit and are controlled wirelessly via the BTLE protocol by the iPhone 4S.

6.6 Other Trial Devices

YSI 2300 STAT Plus™ (Yellow Springs Instruments): The YSI 2300 STAT Plus is an FDA-approved glucose analyzer. Blood glucose measurements using the YSI 2300 STAT Plus will be obtained off of the IV line during both treatment visits.

Nova Biomedical StatStrip® Xpress Glucose Meter: The Nova StatStrip Xpress glucose meter is an FDA-approved glucose meter that is commercially available. Blood glucose measurements for CGM calibration will be obtained with the Nova StatStrip Xpress during both treatment visits if the YSI 2300 STAT Plus fails and via fingerstick with the Nova StatStrip Xpress during any periods when IV blood samples are not available for any reason or the IV fails.

Exercise Bike: The trial will utilize a stationary exercise bike (ergometer) for the in-clinic exercise at the treatment visits. This bike will be stored at the Diabetes Research Center when not in use.

[redacted]

6.7 Concomitant Medications

6.7.1 Permitted Medications and/or Procedures

Patients may take any over-the-counter medications that they wish during the trial, with the exception of any medication containing acetaminophen as that may cause interference with CGM sensing. All concomitant medications, including over-the-counter medications, should be recorded.

Use of beta blockers will be allowed as long as the dose is stable and the patient does not meet the criteria for hypoglycemia unawareness while taking that stable dose.

If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.

6.7.2 Excluded Medications and/or Procedures

During the trial, patients will not use any recreational drugs or drugs of abuse. The need to take prescription drugs that dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder appropriate decision-making may be grounds for exclusion from the trial or discontinuation of participation, a decision that will be made by the Investigator.

Use of benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the Investigator. Use of oral anti-diabetic medications (e.g., thiazolidinediones, biguanides, sulfonylureas, glitinides, DPP-4 inhibitors, SGLT-2 inhibitors) will also be excluded.

7 TRIAL PROCEDURES

7.1 Informed Consent

After potential patients have had time to review the consent document, and prior to any trial-related activities, they will meet with a trial MD or designee who will explain the trial, answer any questions, and administer informed consent. In the event that a volunteer is a patient of one of the trial MDs, another staff MD or designee will answer questions and administer consent. The patients will be fully informed of their responsibilities and their rights while participating in the trial as well as of the possible risks and potential benefits of participation in the trial. They will have the opportunity to discuss all questions and ample time to consider participation.

Trial-related activities are any procedures that would not have been performed during normal management of the patient. Patients who wish to participate in the trial will be asked to personally date and sign an informed consent form (ICF). Likewise, the Investigator must also personally date and sign the ICF. All patients will be provided with a copy of their own signed and dated ICF.

Trial staff will answer any questions that the patients may have during their participation. They will share any new information in a timely manner that may be relevant to the patient's willingness to continue participating in the trial. The patients may choose to discontinue their participation at any time.

[redacted]

7.2 Screening Visit (Visit 1)

All patients will have a Screening Visit to confirm eligibility. The patient will be interviewed and the electronic Case Report Form (eCRF) will be completed by trial staff to establish whether the patient is eligible.

Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator.

Once all of the results have been returned, a trial MD will review the eCRF to determine patient eligibility. If a patient is not eligible to continue in the trial, the results of abnormal tests will be reported to the patient and to a health care provider of their choosing.

7.2.1 Data Collected at Screening

- Age, sex, race, and ethnicity
- Date of last menstrual period in female patients
- Medical, surgical, and social history, allergies, and review of systems relevant to inclusion and exclusion criteria, including:
    - Date of diabetes diagnosis
    - Duration of insulin pump use and type of insulin used in pump
    - Type/model of insulin pump
    - Insulin regimen (basal rate, sensitivity factor, and carbohydrate ratio)
    - Average total daily dose of insulin in the last 30 days as available (from pump history)
    - Usage of CGM, if any (type of CGM, days per month worn, usage of data, whether insulin is dosed based on CGM alone, alarm settings)
- Concomitant illness (any illness present at screening)
- Concomitant medications (prescription and non-prescription) and date of last change in medication regimen
- Height, weight, physical examination, and vital signs including body temperature and blood pressure
- 12-lead ECG
- Hemoglobin A1c
- Chemistry and hematology samples (see Appendix B)
- Urine HCG pregnancy test for women of childbearing potential
- FSH level for postmenopausal women amenorrheic for less than 1 year
- Fractionated plasma metanephrines (if indicated by history)

7.3 Training Visit (Visit 2)

A Training Visit will take place before the first treatment visit. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor and trial policies and procedures. Trial staff will verify that the patients have understood the material and are competent to participate safely in the trial. Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator. Concomitant medications will also be reviewed.

[redacted]

7.4 Treatment Visits (Visit 3 and Visit 4)

- Visit 3 will take place at least 48 hours after screening (Visit 1) and no more than 30 days after screening (Visit 1).
- There will be a 24-hour minimum washout between Visit 3 and Visit 4 and a maximum of 3 weeks between Visit 3 and Visit 4.
- Up to 2 patients may participate per day.
- Each patient will participate in 2 treatment visits: one with the iPhone-based BP using ZP4207 and one with the iPhone-based BP using Lilly glucagon in a randomized order.
- The night before the treatment visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be instructed to call if they encounter any difficulty with their CGM.
- Patients will be responsible for their own medications other than insulin during the trial. Any medical advice needed by the patients during their participation that is not directly related to BG control should be obtained from them in their usual manner. Patients may take any over-the-counter medications that they wish during the trial, with the exception of any medication containing acetaminophen as that may cause interference with CGM sensing. If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.
- During the trial, patients will not use any recreational drugs or drugs of abuse. The need to take prescription drugs that dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder appropriate decision-making may be grounds for exclusion from the trial or discontinuation of participation, a decision that will be made by the Investigator.
- Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator.
- Patients will not tamper with the BP, including changing any settings.
- Patients may not remove the BP during the trial unless the BP failed or they are withdrawing from the trial.
- The exact time of each procedure and assessment will be documented.

7.4.1 Visit Procedures

- Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window. If BG is <50 mg/dL, treatment with simple carbohydrate is allowed. If the patient experiences persistent hypoglycemia, the visit will be rescheduled within the visit window. If the visit needs to be rescheduled due to hypoglycemia or hyperglycemia, trial staff will assist the patient with insulin or medication adjustments to address glycemic control. The patient will be instructed to contact trial staff later in the day if his or her BG remains uncontrolled.
- Upon arrival to the visit, the patient's weight and vital signs including body temperature and blood pressure will be documented.
- Patient reports of symptoms, any other complaints, and AEs will be reviewed.

[redacted]

- Concomitant medications will be recorded.
- Chemistry and hematology samples will be collected at visit start (see Appendix B).
- ADA samples will be collected before the start of dosing (Visit 3 only).
- A 12-lead ECG will be performed.
- A urine HCG pregnancy test will be performed in female patients of childbearing potential. If the test is positive, the patient will be informed of the result and the visit will be ended.
- Patients will complete a baseline survey about their attitudes and experience with their usual diabetes care.
- An intravenous (IV) catheter will be placed for blood sampling.
- Trial staff will assist the patient to calibrate their CGM, review the trial procedures again and assist with the setup of the BP system, including inserting and priming infusion sets.
- The control algorithm will be initialized only with the patient's weight. Diagnostics will be performed to ensure that the CGM device is appropriately calibrated and that all of the components of the BP systems are in working order.
- The basal rate of the patient's own insulin infusion pump will be changed to be 2-fold higher than weighted mean of the basal rate during the trial period. This is intended to increase the usage of glucagon during the treatment visit.
- The patients will continue to wear their own infusion pump infusing at the temporary 2-fold basal rate throughout the visit until the start of the structured exercise period, in addition to the BP.
- The staff will start the BP as close as possible to a minute divisible by 5 minutes (i.e., on a 5-minute mark). The starting time will be considered Hour 0.
- Additional calibrations will be performed at any of the BG checks throughout the day if the CGM value does not meet the International Organization for Standardization standard (<15 mg/dL difference for BG values <75 mg/dL; <20% absolute difference for BG values >75 mg/dL) at the time of the BG measurement AND it is a good time to calibrate (the CGM trend arrow is flat and there has been no carbohydrate intake in the last 30 minutes or glucagon boluses in the last 15 minutes).
- Blood samples will be taken from the IV at least hourly and processed for plasma ZP4207/glucagon. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator. The actual time of sampling will be recorded in the eCRF.
- Plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.

[redacted]

- Patients will be asked to rate any nausea and/or infusion site pain on 10 cm visual analog scales (VAS) at the beginning of the visit once the infusion sites have been placed but no drug has yet been administered, then approximately at the top of every hour during the visit, and at the end of the visit. Trial staff will also evaluate their infusion sites to document any erythema or edema at the same times. If moderate or severe pain is reported or swelling or redness occurs at the infusion site, the infusion site will be replaced in a different location. If moderate or severe pain, swelling, or redness continues at the old site for more than 30 minutes after the infusion site is removed, or if moderate or severe pain, swelling, or redness occurs at the new site, all infusion sites will be removed and the patient will be discontinued from the study. Any such symptoms will be followed until resolution.
- From the start of closed loop control until approximately Hour 3, the patients will continue to fast.
- Between approximately Hour 3 and Hour 4, patients will be provided with a lunch meal of their choice in the Diabetes Research Center from a menu of choices from nearby restaurants. They will be asked to choose a meal that is a “typical meal” for them. The content of their meal will not be restricted in any way, with the exception that the number of carbohydrates should be in the “typical” range for them at lunch, and that they must eat the same meal at the same time during both visits.
- At approximately 15 minutes before the meal, patients will administer a bolus for the meal with their own insulin pump based on the carbohydrate count for the meal.
- After lunch is completed, the patients will not be allowed any carbohydrate intake (non-caloric drinks will be permitted) until the trial is completed (except as necessary to treat hypoglycemia), to allow the BP to control the post-prandial BG without further interruption.
- Between approximately Hour 6 and Hour 7, the patients will start a period of structured exercise.
- At the start of the exercise period, patients will restore their normal basal insulin profile so that they will not have elevated insulin levels at the end of the study period when they are to transition back to their usual care.
- Patients will exercise on a stationary bike with a heart rate from 120-140 beats per minute for a total of 4,000 heart beats (approximately 30 minutes). Patients will rate their exercise intensity using the Borg scale every 5 minutes, with the target intensity level between 12 and 14. Heart rate will be measured every 5 minutes.
- BG measurements will be obtained off of the IV line every 10 minutes. If BG is <80 mg/dL, BG measurements will be obtained off of the IV line every 5 minutes.
    - Carbohydrates will be given for any BG <50 mg/dL according to the following protocol: Dextrose (g) = BSA (m^2)/[1.7 m^2 (women) or 1.9 m^2 (men)] *15 g.
    - Repeat treatments will be given at 15-minute intervals as long as BG remains <50 mg/dL.
- If there is an interruption in the Dexcom CGM output, trial staff will assist the patient in recovering CGM data streaming. If this requires replacement of the CGM sensor, BGs will be checked every 10 minutes (every 5 minutes if BG is <80 mg/dL) using blood from the IV until the CGM is able to be calibrated again. These BGs will be entered into the BP, which will treat them as CGM values and dose insulin and/or glucagon appropriately.

[redacted]

- If there is a complete failure of the BP operation, patients will take over their own BG control using their personal insulin pump until the BP can be brought back online. If BP control cannot be promptly resumed (e.g., within 30 minutes), the patient may be asked to repeat that trial day once.
- Patients may choose to withdraw from the trial at any time. If they withdraw from the trial, they should alert a provider immediately.
- Just prior to the end of the study visit, vital signs including body temperature and blood pressure will be obtained and a 12-lead ECG will be performed.
- After approximately Hour 8, but not earlier than at least 60 minutes after end of exercise, the BP will be stopped and the patient will continue with their personal insulin pump.
- If the patient experiences seizure or unconsciousness, persistent nausea or vomiting, diabetic ketoacidosis, persistent hyperglycemia with ketonemia, hemodynamic changes such as hypotension, or other medically significant findings, a longer observation period at the trial site may be necessary until the patient is considered stable for discharge. If the Investigator or trial staff determines that the patient requires further observation or treatment, the patient may be transferred to the emergency room for additional monitoring and/or medical care. At discharge, patients will be provided with any necessary instructions concerning personal insulin pump usage, food intake, and driving arrangements.
- The maximum amount of blood loss per study visit will be approximately 230 mL. The total blood loss for the entire study will be up to 460 mL.
- Patients will answer questionnaires (see Appendix C).
- Chemistry and hematology samples will be collected at visit end (see Appendix B).
- The BP and glucose meters will be collected and downloaded.
- A trial MD will review the last several hours of insulin and glucagon dosing and assist the patient in resuming their usual diabetes care. A longer observation period at the trial site may be necessary. Patients will be instructed to call trial staff with any questions, issues, or concerns.

7.4.2 Data Collected During the Treatment Visits

- CGM glucose every 5 minutes from the Dexcom G4 Platinum CGM
- All BG measurements taken
- Insulin total dose by the BP and the patient's own insulin pump
- Glucagon total dose
- Timing and content of the meal eaten and carbohydrate amount
- Timing of meal announcement and size of meal announced
- Timing and glucose values at calibrations
- Timing and amount of carbohydrates taken for hypoglycemia
- Data from a questionnaire about attitudes and expectations regarding the BP before and after each treatment arm (see Appendix C)
- Time patients were not under BP control for any reason
- List of technical faults associated with the BP including cause and resolution
- ZP4207/glucagon sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.

- Plasma glucose sampling will be collected at least hourly in parallel with ZP4207/glucagon exposure sampling. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
- Nausea and infusion site pain on a VAS at visit start (after insertion and before any drug administration), hourly, and at visit end
- Infusion site reaction according to the Draize scale at visit start (after insertion and before any drug administration), hourly, and at visit end
- Patient reports of symptoms, any other complaints, and AEs
- Vital signs including body temperature and blood pressure (at visit start and visit end) and weight
- Concomitant medications
- Chemistry and hematology samples (see Appendix B) at visit start and visit end
- ADA (Visit 3 only)
- 12-lead ECG at visit start and visit end
- Urine HCG pregnancy test for women of childbearing potential

7.4.3 Response to Hypoglycemia

- Patients are encouraged to check their BG for any symptoms of hypoglycemia.
- Patients will be permitted to take 15 grams of carbohydrates for any BG value <60 mg/dL. Trial staff will ensure proper functioning of the BP, infusion set, and insulin pump, and will encourage the patient to wait for the BP to treat the low blood sugar for as long as they feel comfortable.
- Patients will be required to take 15 grams of carbohydrates for any BG value <50 mg/dL. After treatment of hypoglycemia, a follow-up measurement will be taken 15 minutes later. Repeated measurements will be taken every 15 minutes until the BG is >60 mg/dL. Treatment will be repeated if subsequent BG values are still <50 mg/dL. All carbohydrate treatments for hypoglycemia will be documented by trial staff (amount and time).
- Trial staff will check the infusion site, BP, and insulin pump for normal operation any time hypoglycemia occurs. If there is any suspicion of infusion set malfunction, the site should be replaced. Trial staff will check the BP for any malfunction and correct any problems that are found.
- If no correctable fault is found, but there is doubt regarding the correct function of the BP system, an entirely new backup BP system may be started.
- If a patient experiences a seizure or unconsciousness associated with hypoglycemia, his or her participation in the trial will be discontinued.

7.4.4 Response to Hyperglycemia

- Trial staff will check the infusion site, BP, and insulin pump for normal operation any time BG is >300 mg/dL. If there is any suspicion of infusion set malfunction, the site should be replaced. Trial staff will check the BP for any malfunction and correct any problems that are found. If the BG remains >300 mg/dL for 2 hours despite troubleshooting, blood ketones will be measured. If the blood ketone result is >1.5 mmol/L, the visit will be stopped and rescheduled. The patient will be provided with insulin and a syringe to give an injection based on their correction factor.
- If a patient experiences diabetic ketoacidosis, his or her participation in the trial will be discontinued.

[redacted]

- If no correctable fault is found, but there is doubt regarding the correct function of the BP system, the treatment visit may be stopped and the visit rescheduled.

7.4.5 Response to Nausea/Vomiting

If significant nausea (e.g., that prevents the patient from eating normally) or any vomiting occurs, trial staff will notify the Investigator. Trial staff will assist the patient in troubleshooting, such as checking BG and the calibration of the CGM (excessive glucagon dosing may occur if the CGM is reading lower than the true BG). If a patient experiences persistent nausea and vomiting thought to be related to glucagon dosing, his or her participation in the trial will be discontinued.

7.4.6 Response to Other Medical Needs

If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.

7.4.7 Monitoring of Bionic Pancreas Performance

Bionic pancreas inventors and developers [redacted], [redacted], and/or an engineer trained by them will be readily available by phone for consultation for the trial staff at all times during the course of the trial.

7.4.8 Supervision by Trial Staff

A trial MD will be on call at all times during the course of the trial. An RN or MD will be with the trial patients in the Diabetes Research Center at all times.

7.5 Phone Call (Visit 5)

A phone call will be conducted 7 days ±3 days following the last day of dosing (Visit 4) to review AEs and concomitant medications.

7.6 Follow-up Visit (Visit 6)

Patients will return for a Follow-up Visit 25 days ±4 days following the last day of dosing (Visit 4), for chemistry, hematology, and ADA sampling, and a review of AEs and concomitant medications.

8 ENDPOINTS

8.1 Primary Endpoint

The primary endpoint is the safety and tolerability of ZP4207 and the iPhone-based BP as assessed by:

- Number and type of AEs
- Clinical laboratory measurements
- Vital signs
- 12-lead ECG
- Local tolerability and infusion site reactions as measured with the Draize scale
- Immunogenicity as measured by ADA
- Pain as measured on a 10 cm VAS
- Nausea as measured on a 10 cm VAS

8.2 Secondary Endpoints

The secondary endpoints for the iPhone-based BP and ZP4207 include measurements of BP function as well as glycemic and non-glycemic measurements.

8.2.1 Bionic Pancreas Function

This endpoint data will be generated from the BP data during each treatment visit:

- Average percent insulin dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
    - Average percent glucagon/ZP4207 dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts calculated by the BP algorithm that are successfully issued to the pump by the BP (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts calculated by the BP control algorithm that are successfully issued by the BP
    - Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully issued by the BP
- Average percent of 5-minute steps during which the BP is functioning nominally in all respects based on real-time CGM data (new CGM glucose reading captured, dose calculated, and dose issued to pumps)
- Average percent of 5-minute steps during which the BP is functioning nominally with or without a new CGM glucose reading captured (dose calculated and dose issued to pumps). If a CGM signal is not available, the dose calculated may be based on weight or historical basal rates.
- CGM reliability index, calculated as percent of possible values actually recorded by CGM
- CGM Mean Absolute Relative Difference versus time-stamped BG values from meter download
- List of technical faults associated with the BP including cause and resolution

8.2.2 Glycemic

All of following metrics will be generated from the Dexcom G4 Platinum CGM data during each treatment visit:

- Fraction of time spent within each of the following glucose ranges:
    - <50 mg/dL
    - <60 mg/dL
    - <70 mg/dL
    - 70-120 mg/dL
    - 70-140 mg/dL
    - 70-180 mg/dL
    - >180 mg/dL

[redacted]

- >250 mg/dL
- >300 mg/dL

- Number of severe hypoglycemic events (patients unable to self-treat, requiring the assistance of another person)
- Number of episodes of symptomatic hypoglycemia
- Number of carbohydrate interventions for hypoglycemia
- Total grams of carbohydrates taken for hypoglycemia
- Mean CGM glucose

8.2.3 Non-glycemic

- Glucagon/ZP4207 total delivery per kg of body mass
- Insulin total delivery per kg of body mass
- Number of unscheduled infusion set replacements
- Number of unscheduled CGM sensor changes

9 LABORATORY ASSESSMENTS

Descriptions of sample handling and sample processing, storage, and shipment at the site will be included in the laboratory manual.

The responsible laboratories are listed in the address list.

9.1 Safety Laboratory Assessments

Chemistry and hematology samples will be collected at specified time points. See Appendix A for the schedule of procedures and Appendix B for a list of clinical laboratory analytes.

9.2 Pharmacodynamic Assessments (Plasma Glucose)

At Visit 3 and Visit 4, plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.

9.3 Exposure Assessments (ZP4207 and Glucagon)

At Visit 3 and Visit 4, ZP4207/glucagon exposure sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator. The actual time of sampling will be recorded in the eCRF.

Bioanalytical Reports will be prepared.

9.4 Anti-drug Antibody Assessments

Blood samples (including back-up samples) for serum anti-ZP4207 and anti-glucagon antibodies will be taken at Visit 3 and the Follow-up Visit 6.

Bioanalytical Reports will be prepared.

[redacted]

10 SAFETY REPORTING

10.1 Adverse Events

An AE is any untoward medical occurrence in a trial patient administered an IMP and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP. Patients should be instructed to report any AE they experience to the Investigator.
Note: This includes events from the first trial-related activity from Visit 3.

AEs for ZP4207 include:

- A clinically significant worsening of a concomitant illness
- A clinical laboratory abnormality which is clinically significant, i.e., any abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example, change of medicine dose or more frequent follow-up due to the abnormality.
- Hypoglycemic episodes
- Injection site reactions

The following should **not** be recorded as AEs, if recorded prior to randomization (on the Screening Form or the eCRF):

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial-related activity from Visit 3.
- Pre-existing conditions found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).

For known (listed) AEs for Glucagon and Humalog, please refer to SPC for Glucagon and Humalog.

10.1.1 Follow-up of Adverse Events

All AEs that are ongoing at the end of the patient's participation in the trial will be followed-up until the event is resolved or reaches a satisfactory outcome as deemed by the Investigator. Follow-up actions for all serious adverse events (SAEs) will be performed according to appropriate clinical care practices and may depend on the nature of the event. These will be determined after internal review and/or Sponsor review. The follow-up information should only include new (updated and/or additional) information that reflects the situation at the time of the Investigator's signature.

Follow-up information on (S)AEs will be updated using the (S)AE Form. If a non-serious event becomes serious during the follow-up, the AE Form and SAE Form must be used and reporting timelines follow those of an SAE.

The Investigator must forward follow-up information on SAEs, and if previously non-serious AEs become SAEs, to the Sponsor.

[redacted]

10.1.2 Precautions

Normal precautions taken for a human trial will be taken during this trial. Qualified and well-trained physicians and medical staff will instruct the patients. During a patient's participation in the trial, the Investigator should ensure that adequate medical care is provided to the patient for any AEs, including clinically significant laboratory values related to the trial. The Investigator should inform the patient when medical care is needed for intercurrent illnesses of which the Investigator becomes aware.

For further information on safety precautions for ZP4207, Lilly glucagon, Lilly Humalog, and the iPhone-based BP, please refer to the current version of the Investigator's Brochure (IB) for ZP4207 (Zealand Pharma A/S, 2015, or any updates hereof), and the SPC for Glucagon (Eli Lilly, 2012) and Humalog (Eli Lilly, 2015), respectively.

10.1.3 Assessment of Adverse Events by the Investigator

Intensity of an Adverse Event
The maximum intensity (severity) of all AEs must be assessed by the Investigator and documented. Severity should be graded when the AE outcome is known:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

A "severe" reaction does not necessarily deem the AE as "serious," and an SAE may not be "severe" in nature.

Causality Relationship to IMP
Insulin (insulin lispro, Lilly Humalog), glucagon (glucagon for injection, Eli Lilly), and ZP4207 are all regarded as IMP.

The causality of each AE should be assessed by the Investigator according to the following classification:

- Related: Good reason and sufficient documentation to assume a causal relationship.
- Not related: No relationship to trial product can be established.

Outcome of an Adverse Event
The outcome of all AEs must be assessed by the Investigator and documented by his/her staff. The following definitions should be used:

- Recovered/resolved: The patient has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity from Visit 3.
- Recovering/resolving: The condition is improving and the patient is expected to recover from the event. This term is only applicable if the patient has completed the trial.

[redacted]

- Recovered/resolved with sequelae: The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment, or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- Not recovered/not resolved: The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known.
- Fatal: This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as "recovered/resolved," "recovering/resolving," "recovered/resolved with sequelae," or "not recovered/not resolved." An AE with a fatal outcome must be reported as an SAE.
- Unknown: This term is only applicable if the patient is lost to follow-up.

10.2 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Medically important

Medical judgement must be exercised in deciding whether an AE is believed to be "medically important." Medically important events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Suspected Unexpected Serious Adverse Reactions (SUSAR)
A SUSAR is an AE fulfilling one of the criteria of seriousness and being assessed as related to an IMP, the nature or severity of which is not consistent with the applicable reference document (e.g., ZP4207 IB or package leaflet/SPC for an approved product).

Unanticipated Adverse Device Effect (UADE)
A UADE is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

10.3 Adverse Event Reporting – Procedures for Investigators

The Principal Investigator and co-investigators will review any AEs and report any SAEs to the Sponsor as soon as possible and within 24 hours of obtaining knowledge of the event. The Principal Investigator and co-investigators will promptly report AEs to the Partner's Institutional Review Board (IRB) and to the BU IRB (unless oversight is ceded by the BU IRB to the Partners IRB), in accordance with local requirements.

Ed Damiano is the Sponsor of the Investigational Device Exception for the BP and Zealand Pharma A/S is the Sponsor of the IND for ZP4207.

[redacted]

Reports of AEs will be submitted to the FDA in compliance with the terms of the Code of Federal Regulations.

All events meeting the definition of an AE must be collected and reported from the first trial-related activity from Visit 3 until the end of the post-treatment follow-up period. At each contact with the site (visit or telephone, excluding safety visits, where the patient is not seeing the Investigator or staff [e.g., visits to the laboratory], the patient must be asked about AEs. All AEs, either observed by the Investigator or reported by the patient, must be recorded by the Investigator and evaluated.

The Investigator should record the diagnosis, if possible. If no diagnosis can be made, the Investigator should record each sign and symptom as individual AEs.
All AEs must be recorded by the Investigator. One single AE Form must be used per AE from start to resolution. For SAEs, the SAE Form must also be completed.

AE information should include the following:

- Patient identification number on all pages
- Date and time of treatment start
- Date and time of onset and date of outcome
- Date and time of Investigator's first information on the (S)AE
- Seriousness
- Severity
- Causal relationship with IMP ZP4207
- Causal relationship with IMP insulin
- Causal relationship with IMP glucagon
- Causal relationship with medical device
- Causal relationship with procedures
- Interruption or withdrawal of treatment with IMP or medical device and other measures taken
- Outcome

All AEs are coded; details are described in the trial specific Data Management Plan.

The Investigator must report initial information in writing on the SAE Form for all SAEs to the Sponsor's responsible pharmacovigilance unit (here: Lindeq) immediately (within 24 hours) after obtaining knowledge about the event.

Name: [redacted]
Company: Lindeq
Address: Lyskær 8, 2730 Herlev, Denmark
Tel:
Fax: [redacted]
Mobile:
E-mail: drugsafety@lindeq.com

In addition and meeting the same timeline, Investigators must report all SAEs to Zealand Pharma A/S by forwarding the SAE Form electronically within 24 hours of obtaining knowledge of the event to the representatives of Zealand Pharma A/S.

Names: [redacted] and [redacted]
Address: Smedeland 36, DK-2600 Glostrup, Denmark
Tel: [redacted]
E-mails: [redacted]

It is the responsibility of Lindeq to report all SUSARs that occur in this trial to the Competent Authorities and to the Investigators. It is the responsibility of the Investigators to report the SUSARs to the IRBs in accordance with the local requirements in force and the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP). The trial monitor must be informed accordingly.

It is the responsibility of Lindeq to report all serious adverse reactions on insulin lispro and glucagon for injection to the Eli Lilly Pharmacovigilance department within 5 days.

It is the responsibility of the Investigators to report all UADEs to Beta Bionics within 24 hours of the time they are detected. It is the responsibility of the Investigators to report all UADEs to the IRB in accordance with the local requirements in force and the ICH GCP. It is the responsibility of Beta Bionics to report all UADEs to the Competent Authorities.

All device deficiencies should be documented and should be reported to Beta Bionics within 24 hours. Device deficiencies are inadequacies of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

Name: [redacted]
Company: Beta Bionics, Inc.
Address: Business Innovation Center, Photonics Center, 8 Saint Mary's Street, Suite 936
Boston, Massachusetts 02215-2421, United States
Tel: [redacted]
E-mail: [redacted]

10.4 Pregnancy Reporting

Female patients must be instructed to notify the Investigator immediately if they become pregnant or if they suspect to be pregnant during the trial. The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical trial.

Male patients must be instructed to notify the Investigator immediately if their partner becomes pregnant or suspects to be pregnant. The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical trial. During an information meeting at the trial site, the patient's partner will be fully informed by a physician of her participation in capturing the outcome data, and will be asked to provide her written consent.

The Investigator must report all information on pregnancies, including AEs in the patient/patient's partner, the fetus, and newborn infant/ toddler. The pregnancy report must be forwarded to the Sponsor preferably electronically as PDF or by fax.

The Investigator must follow the pregnancy until the pregnancy outcome and the newborn infant(s) until the age of 1 month. The Investigator must collect information on the pregnancy and pregnancy complications as well as the pregnancy outcome including the health of the newborn infant(s) on the pregnancy forms.

The following must be collected:

- Initial information of the pregnancy
- Information on the outcome of the pregnancy, including the health status of the newborn infant(s) at the age of 1 month
- All AEs in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms. It must be clear in the description if the event occurs in the patient/patient's partner, the fetus, or the newborn infant.
- All SAEs in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms following the same timelines as required for other SAEs. It must be clear in the description if the event occurs in the patient/patient's partner, the fetus, or the newborn infant.

The SAEs that must be reported include abnormal outcome – such as congenital anomalies, fetal death, and termination of pregnancy (spontaneous or elective abortion), including any anomalies of the fetus observed at gross examination or during autopsy – as well as other pregnancy complications (ectopic pregnancy) fulfilling the criteria of an SAE.

10.5 Hypoglycemia

Hypoglycemia will be regarded as an AE and will be recorded and documented on an AE Form. For the purposes of AE reporting, the following definitions of hypoglycemia will be used:

- Symptomatic hypoglycemia: an event during which typical symptoms of hypoglycemia are accompanied by a BG concentration ≤70 mg/dL
- Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with a BG concentration ≤50 mg/dL
- Severe hypoglycemia: an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions

10.6 Safety Monitoring

10.6.1 Data and Safety Monitoring Board

An external DSMB will oversee the conduct of the trial, as set forth in the DSMB Charter. Additionally, the DSMB will be informed in the event of any serious and unexpected AEs. The DSMB will be informed if there are any changes to the trial protocol that could significantly impact the safety or scientific validity of the trial. A final DSMB meeting will convene after the completion of the trial.

The participation of individual patients will be discontinued if they experience:

- Seizure or unconsciousness associated with hypoglycemia and associated with participation in the trial
- Persistent nausea and vomiting thought to be related to glucagon dosing associated with participation in the trial
- Hospitalization associated with participation in the trial
- Pregnancy
- Diabetic ketoacidosis

If more than 1 patient must be withdrawn from the trial for these reasons, the trial will stop and a vote of the DSMB will be required to restart it. All AEs that are serious and unexpected but related will be reported to the DSMB within 5 working days.

[redacted]

Note that patients may discontinue participation at any time. Patients may be removed from the trial for other reasons, for instance, failure to comply with trial procedures or intercurrent illness that is unrelated to the BP but that precludes safe participation. Discontinuation of participation for these reasons will not contribute to a decision to discontinue the trial.

10.6.2 Zealand Pharma Safety Committee

The internal Zealand Pharma Safety Committee is constituted to perform ongoing safety surveillance of clinical trials within ZP4207, including this trial.

If safety signals are observed either based on reported SAEs, periodic review of laboratory parameters, planned review of all AEs reported between the safety committee meetings, or on notification of significant findings, the Safety Committee will take appropriate measures to safeguard the patients.

11 STATISTICS

11.1 Analysis Populations

The following analysis sets are defined in accordance with the ICH-E9 guidance:

The Full Analysis Set is based on the intention-to-treat principle and includes all randomized patients. In exceptional cases, patients from the Full Analysis Set may be excluded (will be decided in the database review [DBR] meeting). In such cases, the exclusion will be justified and documented. Patients will contribute to the evaluation “as randomized.”

The Per-Protocol Set includes all patients of the Full Analysis Set who completed the trial without any major protocol violations. Patients in the Per-Protocol Set will contribute to the evaluation “as treated.” This analysis will only be used if it is different than the Full Analysis Set.

The Safety Analysis Set includes all patients receiving at least 1 dose of the IMP. Patients in the Safety Analysis Set will contribute to the evaluation “as treated.”

Analyses of efficacy endpoints will be based on the Full Analysis Set (and the Per-Protocol Set if necessary). This decision will be made in the DBR meeting. The analysis of the safety endpoints will be based on the Safety Analysis Set.

Before data are released for statistical analysis, a blinded review of all data will take place to identify protocol deviations that may potentially affect the results. At this time, it will be determined if patients and/or data should be excluded from the analysis. Furthermore, outliers will be identified by data review according to ICH-E9.

Obviously erroneous data points may be excluded from the analyses or re-analyzed (e.g., serum concentrations). The decision to re-analyze or exclude data points from the statistical analysis is the joint responsibility of the Sponsor, the Principal Investigator, and the Trial Statistician.

The patients or observations to be excluded and the reason for their exclusion will be documented and signed by those responsible prior to database release. The documentation

[redacted]

will be stored together with the remaining trial documentation. The patients and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

11.2 Statistical Methods

Medpace will be responsible for the statistical analysis. The statistical planning and conduct of analyses of the data from this trial will follow the principles defined in relevant ICH guidelines and Medpace's biostatistical standard operating procedures (SOPs). A general description of the statistical methods to be used is given in this section, specific details will be provided in the Statistical Analysis Plan (SAP), which will be prepared before database lock. All statistical analyses will be performed using SAS® (SAS Institute Inc., Cary, North Carolina, USA), version 9.4 or later.

11.2.1 Analysis of Safety

The following variables will be evaluated according to treatment for safety purposes:

Adverse Events
All AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Individual AEs will be presented in a listing including relationship to trial product/device, severity, and treatment period at onset. If more than 20 treatment-emergent AEs (AEs with onset after [first] dosing at Visit 3 until the Follow-up Visit 6) are registered, a summary table including number of AEs, number of patients with at least 1 AE, and percentage of exposed patients with at least 1 AE will be made by system organ class and treatment period at onset.

Local Tolerability
Local tolerability at the injection site will be summarized using descriptive statistics as appropriate.

Laboratory Safety Assessments
Laboratory assessments will be summarized. A listing of abnormal values will be provided.

Physical Examination
A frequency table will show the number and percentage of physical examination results.

Vital Signs
Vital signs will be summarized using descriptive statistics.

12-lead ECG
The Investigator's evaluations of 12-lead ECGs will be summarized and abnormal individual evaluations will be listed together with the Investigator's comments. Changes in 12-lead ECG between measurements will be recorded as AEs if the Investigator judges them to be clinically significant.

11.2.2 Analysis of Efficacy

The analysis of BP function endpoints and glycemic endpoints will be on an intention-to-treat basis. In cases where a treatment arm was not completed (and that arm was not repeated according to protocol criteria), available data from that arm will be used in the data analysis.

The Shapiro-Wilk test will be used to determine the normality of the residuals for each comparison. Summary tables that display descriptive statistics, including percentages, means or medians, and standard deviation and/or ranges, as appropriate, will be provided.
A paired t-test or the Wilcoxon signed rank test for comparison of means with normally or non-normally distributed residuals, respectively, will be used. In a secondary analysis, any period effect and any interaction between treatment and period will be looked for, although no such interaction is predicted for the efficacy outcome. Further details will be included in the SAP.

The number of patients and proportions of severe hypoglycemic events, symptomatic hypoglycemia, and carbohydrate interventions due to hypoglycemia with the event counts will be summarized descriptively, and the proportions will be analyzed by a Fisher's exact test if data allow.

11.2.3 Interim Analysis

No interim analysis is planned.

11.2.4 Sample Size Determination

No formal sample size calculations were made. It is expected that between 10 and 12 patients will be randomized in the trial. The sample size is based on a clinical rather than statistical rationale. The sample size is considered adequate to address the primary trial objective of exploring the safety of ZP4207 when used in the iPhone-based BP and with reference to Lilly glucagon used in the iPhone-based BP.

12 DATA MANAGEMENT AND RECORD KEEPING

Data Management is the responsibility of Medpace. The complete Data Management process will be described in detail and agreed on in the Data Management Plan for this trial.

12.1 Data Handling

Case Report Forms
Electronic Case Report Forms will be used in this trial. The Data Management Department of Medpace will provide the eCRFs. All further information regarding the eCRFs and the data flow will be described and agreed on in the Data Management Plan.

Device-Related Data
During the trial, CGM data, calibration data, insulin dosing data, and glucagon dosing data will be automatically stored in the BP device (from which it will be downloaded at intervals), combined in a single database that will be compared against the primary data files for integrity, and ultimately transferred to Medpace.

12.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

[redacted]

12.3 Data Entry

Data must be recorded using the electronic data capture (EDC) system as the trial is in progress. The patient questionnaires will be transcribed into the EDC system by site personnel. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct trial data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

12.4 Medical Information Coding

Adverse events and medical history will be coded using the latest version of MedDRA. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary.

12.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

12.6 Record Keeping

Medpace will be responsible for hosting the TMF. Records of patients, source documents, monitoring visit logs, eCRFs, inventory of trial product, regulatory documents, and other Sponsor correspondence pertaining to the trial must be kept in the appropriate trial files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the evaluation and reconstruction of the clinical trial. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Trial Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

13 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

13.1 Ethical Conduct of the Trial

The trial will be conducted according to Medpace, MGH, and/or the Sponsor's written instructions (SOPs, working instructions, or process descriptions). Content and definitions of the written instructions are based on the Declaration of Helsinki and the ICH GCP.

13.2 Institutional Review Board

Written favorable opinion must be obtained from the responsible IRB prior to commencement of the trial. Clinical trial submission and reporting requirements before, during, and after completion of the trial will be performed in accordance with national law and local regulations.

[redacted]

All amendments that affect patient safety or the trial integrity (substantial amendments) must not be implemented before favorable opinion has been obtained, unless necessary to eliminate hazards to the patients. Non-substantial amendments do not require favorable opinion by the IRB, but the respective IRB will be notified according to local requirements.

The Sponsor and Investigator must approve any amendment in writing before its implementation.

The Sponsor must maintain an accurate and complete record of all submissions made to the IRB. The records should be filed in the Sponsor's Trial Master File (TMF).

13.3 Informed Consent

In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirement(s) and adhere to the ICH GCP guideline and the requirements in the Declaration of Helsinki.

Prior to any trial-related activity, the Investigator must give the patient oral and written information in a form that the patient can read and understand about all aspects of the trial that are relevant to the patient's decision to participate. The patient will be given ample time to decide whether or not to participate in the trial.

The patient must be informed that his/her personal trial-related data will be used in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by authorized monitors or Clinical Quality Assurance auditors appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

A voluntary, personally signed and dated ICF must be obtained from the patient prior to any trial-related activity. The ICF must also be signed and dated by the physician or designee who conducted the informed consent procedure. A signed copy of the ICF and any additional patient information must be given to each patient.

The responsibility for taking informed consent must remain with that of a research physician or designee. If information becomes available that may be relevant to the patient's willingness to continue participating in the trial, the Investigator must inform the patient in a timely manner, and a revised written informed consent must be obtained.

Should a protocol amendment become necessary, the ICF may need to be revised to reflect the changes to the protocol. It is the responsibility of the Sponsor to ensure that an amended consent form is reviewed and has received favorable opinion from IRB, and the Investigator must ensure that the amended consent form is signed by all patients subsequently entered into the trial and those currently in the trial, if affected by the amendment.

13.4 Trial Monitoring Requirements

The monitoring procedures for this trial are described in detail in the Monitoring Manual. The objectives of the monitoring procedures are to ensure that (i) the safety and rights of the trial patients are respected, (ii) that accurate, valid, and complete data are collected, and (iii) that

[redacted]

the trial is conducted in accordance with the trial protocol, the principles of GCP, and local legislation, including drug accountability.

The monitor must be given direct access to the investigational site files and source documents (original documents, data, and records). Direct access includes permission to examine, analyze, verify, and reproduce any record(s) and report(s) that are important to evaluation of the clinical trial.

Key tasks of the monitor include verifying the presence of informed consent, the adherence to the inclusion/exclusion criteria, the documentation of SAEs, and the recording of all safety and efficacy variables. The monitor will also confirm the completeness of patient records, the adherence to the protocol, ICH GCP, and the progress in patient enrollment and perform drug accountability.

Because no information that could reveal the identity of patients may ever be removed from the trial site, the monitor will visit the site at regular intervals to perform these monitoring tasks. Other contact between the Investigator and monitors will be maintained as required through telephone calls and e-mail. The Investigator and/or key members of staff involved in the trial must be available to assist the monitors during all visits.

Site Initiation Visit
During the Site Initiation Visit (SIV) the CRO, Sponsor, and/or monitors will go through information on the IMP, the protocol, the eCRFs, and other key aspects of the trial with the Investigator and the key members of staff involved in the trial. The topics of the SIV are documented in a SIV report made available to the Investigator. Documentation on the SIV (e.g., power point presentation) should be filed by both Investigator and Sponsor.

13.5 Disclosure of Data

Data generated by this trial must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the trial is confidential and disclosure to third parties other than those noted above is prohibited.

13.6 Retention of Records

Massachusetts General Hospital will maintain the patient's medical file according to local regulations. MGH will archive the documentation pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. MGH should not destroy any documents without prior permission from the Sponsor.

The documentation includes all the raw data generated during the clinical trial, the investigational site files, and a copy of the clinical trial report. The documents will be retained for a period of at least 15 years at archives by MGH, or its sub-contractor. After this period, the Sponsor will be contacted and their advice sought on the return or further retention of the trial records.

[redacted]

The Sponsor will maintain the documentation pertaining to the trial in accordance with national regulations.

13.7 Publication Policy

The Principal Investigator of the trial will review and sign the clinical trial report. A summary of the final clinical trial report will be submitted to the IRB and Competent Authority.

According to the Declaration of Helsinki Investigators and Sponsors "have ethical obligations with regard to the publication and dissemination of the results of research." The trial design and results may be published as one or more original research manuscripts/abstracts and presented at a scientific meeting. The Investigator and Sponsor reserve the right to review any proposed presentation of the results of this trial before they are submitted for publication. Authorship on any publication(s) resulting from this clinical trial will be assigned according to the recommendations of the International Committee of Medicinal Journal Editors.

Participating patients will not be identified by name in any published reports about the clinical trial.

The Sponsor is responsible for trial registration at ClinicalTrials.gov (www.clinicaltrials.gov) according to the requirements from the FDA.

13.8 Legal Aspects

An implicit or explicit approval must be obtained from the Competent Authority prior to commencement of the trial. Clinical trial submission and reporting requirements before, during, and after completion of the trial will be performed in accordance with national law and local regulations.

An implicit or explicit approval will also be mandatory before implementation of substantial changes. Non-substantial amendments do not require approval from the Competent Authority but will be notified according to local requirements.

The Sponsor and Investigator must approve the amendment in writing before its implementation.

The Sponsor must maintain an accurate and complete record of all submissions made to the Competent Authority. The records should be filed in the Sponsor's TMF.

Audits and Inspections
In the event of an audit, representatives of the Sponsor or designee, or national and international regulatory authorities may request access to all trial records for inspection and copying. Such access must be stated in the ICF signed by the patient.

13.9 Sponsor Discontinuation Criteria

The Sponsor, Investigator, or a pertinent regulatory authority may decide to stop the trial or part of the trial at any time but agreement on procedures to be followed must be obtained. Conditions that may warrant termination of the clinical trial include, but are not limited to:

- Safety or administrative reasons

- The discovery of an unexpected, relevant, or unacceptable risk to the patients enrolled in the clinical trial
- A decision of the Sponsor to suspend or discontinue investigation of the IMP

If the trial is prematurely terminated or suspended, the Investigator should promptly inform the patients and assure appropriate therapy and follow-up. Furthermore, the Sponsor should promptly inform the IRB and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.
If after the termination of the trial the risk/benefit analysis has changed, the new evaluation should be provided to the IRB in case it will have an impact on the planned follow-up of the patients who have participated in the trial. Necessary actions needed to protect the patients should be described.

13.10 Patient Compensation

Financial compensation will be provided to all patients who complete the Screening Visit. Patients will be paid $25 for completing the Screening Visit whether or not they are eligible to participate in the trial. Patients will be compensated $25 for completing the Training Visit. Patients will be compensated $100 for completing each of the 2 treatment visits, $25 for completing the phone call, and $25 for completing the Follow-up Visit. Thus, the total compensation for a patient who completes the trial would be $300. Patients who are unable to complete the trial or choose to stop participation will receive prorated compensation for each visit. In addition to the monetary compensation, the cost of the patients' lunch meals during their participation in the trial, as well as the patients' parking at each visit, will be covered by trial funds.

14 TRIAL ADMINISTRATIVE INFORMATION

14.1 Protocol Amendments

Any amendments to the trial protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

14.2 Address List

14.2.1 Sponsor

Zealand Pharma A/S
Smedeland 36
DK-2600 Glostrup (Copenhagen)
Denmark
Telephone: +45 88 77 36 00
Facsimile: +45 88 77 38 98

[redacted]

14.2.2 Supplier of Device

[redacted] PhD
Beta Bionics, Inc.
Business Innovation Center, Photonics Center
8 Saint Mary's Street, Suite 936
Boston, Massachusetts 02215-2421
United States
Tel: [redacted]

14.2.3 Principal Investigator (Site)

Steven J. Russell, M.D., Ph.D.
MGH Diabetes Center
50 Staniford Street Suite 301
Boston, Massachusetts 02114
Telephone: [redacted]
Facsimile: [redacted]

14.2.4 Contract Research Organization (Including Monitoring)

Medpace, Inc.
5375 Medpace Way
Cincinnati, Ohio 45227
Telephone: +1-513-579-9911
Facsimile: +1-513-579-0444

14.2.5 Medical Monitoring

Medpace Clinical Safety
5375 Medpace Way
Cincinnati, OH 45227
United States
Telephone: +1-800-730-5779, ext. 2999 or +1-513-579-9911, ext. 2999
Facsimile: +1-866-336-5320 or +1-513-579-0444
E-mail: medpace-safetynotification@medpace.com

14.2.6 Pharmacovigilance

Lindeq
Lyskær 8
2730 Herlev
Denmark
Telephone: [redacted]
Facsimile: [redacted]
Mobile: [redacted]
E-mail: drugsafety@lindeq.com

14.2.7 Central Laboratory (Safety Laboratory and Plasma Glucose)

Medpace Reference Laboratories, LLC
5365 Medpace Way
Cincinnati, OH 45227
United States
Telephone: +1-513-366-3270
Facsimile: +1-513-366-3273

14.2.8 Special Laboratory (ZP4207 Exposure and ADA Analyses)

Unilabs – York Bioanalytical Solutions
[redacted]
Cedar House
Northminster Business Park
Upper Poppleton
York YO26 6QR
Great Britain
Telephone: [redacted]
Facsimile: [redacted]

14.2.9 Special Laboratory (Glucagon Exposure)

MLM Medical Labs GmbH
Dr. [redacted]
Dohrweg 63
D-41066 Mönchengladbach
Germany
Telephone: [redacted]
Facsimile [redacted]

15 REFERENCES

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9. ICH Harmonised Tripartite Guideline. Statistical Principles for Clinical Trials E9. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf. 5 February 1998.
10. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R1). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf. 10 June 1996.

[redacted]

Clinical Trial Protocol
ZP4207-16051

Version number: 4.0
Amendment 3.0
Date: 17 August 2016

APPENDIX A: SCHEDULE OF PROCEDURES

Trial Visit	Visit 1 [1] Screening	Visit 2 Training	Visit 3 [2] [3] [4] [5] (1st Treatment Visit)	Visit 4 [2] [3] [5] (2nd Treatment Visit)	Visit 5 Phone Call [6]	Visit 6 Follow-Up [7]
Informed consent	X					
Assess/confirm elig bility	X	X				
Demographics	X					
Medical, surgical, and social history; allergies	X					
Concomitant illness	X					
Concomitant medications	X	X	X	X	X	X
Height, weight, physical examination, and vital signs including body temperature and blood pressure [8]	X		X [9]	X [9]		
12-lead ECG	X		X [10]	X [10]		
Urine HCG pregnancy test and menstrual history [11]	X		X	X		
FSH [12]	X					
Screening labs – HbA1c, optional fractionated metanephrines [13]	X					
Safety lab sampling including chemistry and hematology	X		X [10]	X [10]		X
Training on devices [14]		X				
Monitored BP use			X	X		
Plasma glucose sampling [15]			X	X		
ZP4207/glucagon exposure sampling [16]			X	X		
Nausea and infusion site pain VAS and infusion site reaction Draize scale (visit start [17], hourly, & visit end)			X	X		

[redacted]

Trial Visit	Visit 1 [1] Screening	Visit 2 Training	Visit 3 [2] [3] [4] [5] (1st Treatment Visit)	Visit 4 [2] [3] [5] (2nd Treatment Visit)	Visit 5 Phone Call [6]	Visit 6 Follow-Up [7]
Standardized lunch [18]			X	X		
In-clinic exercise [19]			X	X		
Questionnaires (pre & post BP)			X	X		
ADA			X [20]			X
Adverse event review			X	X	X	X

1. Once the patient has been enrolled and eligibility has been established, the order of the iPhone-based BP visits will be randomized in blocks of 2 patients.
2. Each patient will participate in 2 treatment visits: one with the iPhone-based BP using ZP4207 and one with the iPhone-based BP using Lilly glucagon in a randomized order. Up to 2 patients may participate in the trial per day.
3. The night before the visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12 00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window. If BG is <50 mg/dL, treatment with simple carbohydrate is allowed. If the patient experiences persistent hypoglycemia, the visit will be rescheduled within the visit window.
4. Visit 3 will take place at least 48 hours after screening (Visit 1) and no more than 30 days after screening (Visit 1).
5. There will be a 24-hour minimum washout between Visit 3 and Visit 4 and a maximum of 3 weeks between Visit 3 and Visit 4.
6. Visit 5 will take place 7 days ±3 days from Visit 4.
7. Visit 6 will take place 25 days ±4 days from Visit 4.
8. Height and physical examination will be measured at Visit 1 only.
9. Vital signs including body temperature and blood pressure will be obtained at visit start and visit end.
10. At visit start and visit end.
11. Urine HCG pregnancy test only for women of childbearing potential. The date of the last menstrual period in female patients will be obtained at Visit 1 only.
12. Test for FSH level only for postmenopausal women amenorrheic for less than 1 year.
13. If indicated by history.
14. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor, diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits, and trial policies and procedures.
15. Collected at least hourly. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
16. Collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.
17. Once the infusion sites have been placed but no drug has yet been administered.
18. Between approximately Hour 3 and Hour 4.
19. Between approximately Hour 6 and Hour 7.
20. Before the start of dosing.

ADA = anti-drug antibodies; BG = blood glucose; BP = bionic pancreas; CGM = continuous glucose monitor; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HCG = human chorionic gonadotropin; VAS = visual analog scale.

[redacted]

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APPENDIX B: CLINICAL LABORATORY ANALYTES

Chemistry

Alanine aminotransferase	Aspartate aminotransferase
Alkaline phosphatase	Total protein
Albumin	Total and direct bilirubin
Gamma-glutamyl transferase	Glucose
Creatinine	Estimated glomerular filtration rate
Blood urea nitrogen	Uric acid
Bicarbonate	Sodium
Potassium	Calcium
Chloride	Phosphorus

Hematology

Hemoglobin	Hematocrit
Red blood cell count	White blood cell count and differential
Platelets	Mean corpuscular volume
Mean corpuscular hemoglobin	Mean corpuscular hemoglobin concentration

Pregnancy Test
A urine HCG pregnancy test will be performed at screening, Visit 3, and Visit 4 only for women of childbearing potential.

Anti-drug Antibody Assessments
Blood samples (including back-up samples) for serum anti-ZP4207 and anti-glucagon antibodies will be taken prior to first dosing (Visit 3) and at the Follow-up Visit (Visit 6).

ZP4207/Glucagon Exposure Sampling
At Visit 3 and Visit 4, ZP4207/glucagon exposure sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.

Screening Visit Only
Test for FSH level only for postmenopausal women amenorrheic for less than 1 year
Optional fractionated plasma metanephrines (if indicated by history)
Hemoglobin A1c

[redacted]

Clinical Trial Protocol
ZP4207-16051

Version number: 4.0
Amendment 3.0
Date: 17 August 2016

APPENDIX C: BRIEF DESCRIPTION OF QUESTIONNAIRES

Diabetes Treatment Satisfaction Questionnaire – Status (DTSQs)
The DTSQs measures patient satisfaction with diabetes treatment. It consists of a 6 item scale for assessing treatment satisfaction and two additional items assessing perceived frequency of hyperglycemia and hypoglycemia. The DTSQs is meant for adults and older children. Dr. Clare Bradley has produced a version that is appropriate for bionic pancreas studies for this use, along with a version for younger children. It is administered before the intervention. The DTSQs is valid and reliable. Administration time is less than 5 minutes.

Diabetes Treatment Satisfaction Questionnaire – Change (DTSQc)
Although the DTSQ is responsive to treatment changes, ceiling effects are often seen with this instrument, where maximum or close-to-maximum scores at baseline provide little opportunity for registering improvement. The DTSQc contains the same items as the DTSQs version but asks patients to consider their satisfaction with their current treatment compared with their previous treatment. The DTSQc is meant for adults and older children. Dr. Clare Bradley has produced a version that is appropriate for bionic pancreas studies for our use, along with a version for younger children. It is administered during and at the end of the intervention. The DTSQc is valid and reliable. Administration time is less than 5 minutes.

T1-Diabetes Distress Scale (T1-DDS)
The T1-DDS is a 28-item survey that assesses seven sources of diabetes distress for type 1 adults. It captures feelings of powerlessness; management distress; hypoglycemia distress; negative social perceptions by others; eating distress; physician (health care) distress; and friend/family distress. Items are scored on a 6-point scale from not a problem to a very serious problem. It is administered before, during, and at the end of the intervention. The scale is valid and reliable, and has been shown to be sensitive to change over time. Administration time is 5 minutes.

Problem Areas in Diabetes Survey (PAID)
There are three versions of the PAID: Teen (PAID-T), Parent (PAID-P), and Child (PAID-C) versions. This measure of diabetes-specific emotional distress in youth with diabetes and their parents is 26 items. A total score is generated. It is administered before, during, and at the end of the intervention. The PAID-T and PAID-P are valid and reliable. Psychometric analysis of the PAID-C is in progress. Administration time is 5 minutes.

Hypoglycemia Fear Survey (HFS)
There are three versions of the HFS, Adult (HFS), Youth (HFS-Y) and Parent (HFS-P). The HFS measures several dimensions of fear of hypoglycemia among adults with type 1 diabetes. It consists of 23 items and produces two sub-scale scores; a Behavior sub-scale that measures behaviors involved in avoidance and/or over-treatment of hypoglycemia and a Worry sub-scale that measures anxiety and fear surrounding hypoglycemia. The HFS-Y consists of 25 items and the HFS-P consists of 26 items; both produce sub-scale scores similar to the Adult HFS. It is administered before, during, and at the end of the intervention. All versions of the HFS are valid and reliable. Administration time is 5-10 minutes.

[redacted]

Impact of Daily Diabetes Demands (IDDD)
There are four versions of the IDDD; Adult (IDDD-A), Youth (IDDD-Y), Parent (IDDD-P), and Significant Other (IDDD-SO). This instrument measures the burden related to the demands of the daily diabetes regimen and is 22 items. A total score is generated. It is administered before, during, and at the end of the intervention. Psychometric analysis of the IDDD-Y is in progress using the data from the second Bionic Pancreas Camp Study in pre-adolescent children, and of the IDDD-A is in progress using data from the Bionic Pancreas Multicenter Study in adults. Administration time is 5 minutes.

Bionic Pancreas User Opinion Survey (BPUOS)
There are four versions of the BPUOS; Adult (BPUOS-A), Youth (BPUOS-Y), Parent (BPUOS-P), and Significant Other (BPUOS-SO). This measure assessing both the benefits from, and difficulties with, use of the bionic pancreas, and consists of 38 items. A total score is generated. It is administered during and at the end of the intervention. Psychometric analysis of the BPUOS-Y is in progress using the data from the second Bionic Pancreas Camp Study in pre-adolescent children, and of the BPUOS -A is in progress using data from the Bionic Pancreas Multicenter Study in adults. Administration time is 10 minutes.

[redacted]

SUMMARY OF CHANGES DOCUMENT

PROTOCOL NUMBER ZP4207-16051

AMENDMENT NUMBER 2.0

PROTOCOL TITLE: The iLet Feasibility Trial Testing the iLet, a Fully Integrated Bihormonal Bionic Pancreas with ZP4207

AMENDMENT DATE: 03 August 2016

SUMMARY AND JUSTIFICATION OF CHANGES:

This amendment was developed to include additional clinical instructions regarding management of diabetes, low blood glucose (BG), and other medically significant findings during the trial. The main additions include statements that Investigators will instruct patients concerning diabetes management during fasting prior to and between the treatment visits; treatment with simple carbohydrates is allowed when a patient's BG is <50 mg/dL; and a longer observation period at the trial site may be necessary if the patient experiences a medically significant event. In addition, the Exclusion Criteria was updated to exclude patients with a history of hypoglycemic unawareness in the last 12 months and patients with a history of severe hypersensitivity to milk proteins or lactose. The schedule of procedures was updated to reflect the changes specified in this document.

SUMMARY OF CHANGES:

The amended protocol sections and the details of the changes are summarized in the following sections. Revisions to the protocol are presented as strikethrough (ie, ~~subject~~) for text that was removed and bold (ie, **subject**) for text that was added.

[redacted]

Section 1.5, Risk/Benefit, Page 20

Original Text:

Treatment with ZP4207 and marketed glucagon can result in undesired effects or complaints. Undesired effects and complaints such as gastrointestinal side effects including nausea, vomiting, and diarrhea are known side effects of glucagon administration at higher dose levels. The frequency of nausea associated with the administration of 1 mg of glucagon according to the Summary of Product Characteristics (SPC) for Glucagon is described to be between 1/10 and 1/100. The frequency of vomiting is described to be between 1/100 and 1/1000 (Novo Nordisk, 2015). Similar gastrointestinal side effects have also been observed to a limited degree in the 2 clinical trials conducted with ZP4207, again at higher dose levels. The individual doses of ZP4207 and Lilly glucagon delivered by the BP are expected to be significantly lower than doses typically associated with nausea. As with every novel drug substance, new and yet unknown side effects may also occur.

New Text:

Treatment with ZP4207 and marketed glucagon can result in undesired effects or complaints. Undesired effects and complaints such as gastrointestinal side effects including nausea, vomiting, and diarrhea are known side effects of glucagon administration at higher dose levels. The frequency of nausea associated with the administration of 1 mg of glucagon according to the Summary of Product Characteristics (SPC) for Glucagon is described to be between 1/10 and 1/100. The frequency of vomiting is described to be between 1/100 and 1/1000 (Novo Nordisk, 2015). Similar gastrointestinal side effects have also been observed to a limited degree in the 2 clinical trials conducted with ZP4207, again at higher dose levels. The individual doses of ZP4207 and Lilly glucagon delivered by the BP are expected to be significantly lower than doses typically associated with nausea. **Episodes of low blood pressure have also been observed after administration of higher doses of glucagon and ZP4207.** As with every novel drug substance, new and yet unknown side effects may also occur.

Section 4.2, Exclusion Criteria, Page 24

Original Text:

19. History of hypoglycemic seizures (grand-mal) or coma in the last 12 months
20. History of pheochromocytoma: fractionated metanephrines will be tested in patients with history increasing the risk for a catecholamine secreting tumor:
    a. Episodic or treatment refractory (requiring 4 or more medications to achieve normotension) hypertension
    b. Paroxysms of tachycardia, pallor, or headache
    c. Personal or family history of MEN 2A, MEN 2B, neurofibromatosis, or von Hippel-Lindau disease

New Text:

19. History of hypoglycemic seizures (grand-mal) or coma in the last 12 months

20. History of hypoglycemic unawareness in the last 12 months

~~20.~~ **21.** History of pheochromocytoma: fractionated metanephrines will be tested in patients with history increasing the risk for a catecholamine secreting tumor:
   a. Episodic or treatment refractory (requiring 4 or more medications to achieve normotension) hypertension
   b. Paroxysms of tachycardia, pallor, or headache
   c. Personal or family history of MEN 2A, MEN 2B, neurofibromatosis, or von Hippel-Lindau disease

Section 4.2, Exclusion Criteria, Page 25

Original Text:

26. History of adverse reaction to glucagon (including allergy) besides nausea and vomiting
27. Established history of allergy or severe reaction to adhesive or tape that must be used in the trial

New Text:

26. History of adverse reaction to glucagon (including allergy) besides nausea and vomiting

27. History of severe hypersensitivity to milk proteins or lactose

~~27.~~ **28.** Established history of allergy or severe reaction to adhesive or tape that must be used in the trial

Section 7.2, Screening Visit (Visit 1), Page 29

Original Text:

All patients will have a Screening Visit to confirm eligibility. The patient will be interviewed and the electronic Case Report Form (eCRF) will be completed by trial staff to establish whether the patient is eligible.

Once all of the results have been returned, a trial MD will review the eCRF to determine patient eligibility. If a patient is not eligible to continue in the trial, the results of abnormal tests will be reported to the patient and to a health care provider of their choosing.

New Text:

All patients will have a Screening Visit to confirm eligibility. The patient will be interviewed and the electronic Case Report Form (eCRF) will be completed by trial staff to establish whether the patient is eligible.

Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator.

Once all of the results have been returned, a trial MD will review the eCRF to determine patient eligibility. If a patient is not eligible to continue in the trial, the results of abnormal tests will be reported to the patient and to a health care provider of their choosing.

Section 7.3, Training Visit (Visit 2), Page 30

Original Text:

A Training Visit will take place before the first treatment visit. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor and trial policies and procedures. Trial staff will verify that the patients have understood the material and are competent to participate safely in the trial. Concomitant medications will also be reviewed.

New Text:

A Training Visit will take place before the first treatment visit. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor and trial policies and procedures. Trial staff will verify that the patients have understood the material and are competent to participate safely in the trial. **Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator.** Concomitant medications will also be reviewed.

Section 7.4, Treatment Visits (Visit 3 and Visit 4), Page 31

Original Text:

- During the trial, patients will not use any recreational drugs or drugs of abuse. The need to take prescription drugs that dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder appropriate decision-making may be grounds for exclusion from the trial or discontinuation of participation, a decision that will be made by the Investigator.
- Patients will not tamper with the BP, including changing any settings.

New Text:

- During the trial, patients will not use any recreational drugs or drugs of abuse. The need to take prescription drugs that dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder appropriate decision-making may be grounds for exclusion from the trial or discontinuation of participation, a decision that will be made by the Investigator.
- **Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator.**
- Patients will not tamper with the BP, including changing any settings.

Section 7.4.1, Visit Procedures, Page 31

Original Text:

- Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window.
- Upon arrival to the visit, the patient's weight and vital signs including body temperature and blood pressure will be documented.

New Text:

- Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window. **If BG is <50 mg/dL, treatment with simple carbohydrate is allowed. If the patient experiences persistent hypoglycemia, the visit will be rescheduled within the visit window. If the visit needs to be rescheduled due to hypoglycemia or hyperglycemia, trial staff will assist the patient with insulin or medication adjustments to address glycemic control. The patient will be instructed to contact trial staff later in the day if his or her BG remains uncontrolled.**
- Upon arrival to the visit, the patient's weight and vital signs including body temperature and blood pressure will be documented.

Section 7.4.1, Visit Procedures, Page 32

Original Text:

- Patients will be asked to rate any nausea and/or infusion site pain on 10 cm visual analog scales (VAS) at the beginning of the visit once the infusion sites have been placed but no drug has yet been administered, then approximately at the top of every hour during the visit, and at the end of the visit. Trial staff will also evaluate their infusion sites to document any erythema or edema at the same times. If moderate or severe pain is reported or swelling or redness occurs at the infusion site, the infusion site will be replaced in a different location. If moderate or severe pain, swelling, or redness continues at the old site for more than 30 minutes after the infusion site is removed, or if moderate or severe pain, swelling, or redness occurs at the new site, all infusion sites will be removed and the patient will be discontinued from the study.
- From the start of closed loop control until approximately Hour 3, the patients will continue to fast.

New Text:

- Patients will be asked to rate any nausea and/or infusion site pain on 10 cm visual analog scales (VAS) at the beginning of the visit once the infusion sites have been placed but no drug has yet been administered, then approximately at the top of every hour during the visit, and at the end of the visit. Trial staff will also evaluate their infusion sites to document any erythema or edema at the same times. If moderate or severe pain is reported or swelling or redness occurs at the infusion site, the infusion site will be replaced in a different location. If moderate or severe pain, swelling, or redness continues at the old site for more than 30 minutes after the infusion site is removed, or if moderate or severe pain, swelling, or redness occurs at the new site, all infusion sites will be removed and the patient will be discontinued from the study. **Any such symptoms will be followed until resolution.**
- From the start of closed loop control until approximately Hour 3, the patients will continue to fast.

Section 7.4.1, Visit Procedures, Page 33-34

Original Text:

- After approximately Hour 8, but not earlier than at least 60 minutes after end of exercise, the BP will be stopped and the patient will continue with their personal insulin pump.
- The maximum amount of blood loss per study visit will be approximately 230 mL. The total blood loss for the entire study will be up to 460 mL.
- Patients will answer questionnaires (see Appendix C).
- Chemistry and hematology samples will be collected at visit end (see Appendix B).
- The BP and glucose meters will be collected and downloaded.
- A trial MD will review the last several hours of insulin and glucagon dosing and assist the patient in resuming their usual diabetes care. They will be instructed to call trial staff with any questions, issues, or concerns.

New Text:

- After approximately Hour 8, but not earlier than at least 60 minutes after end of exercise, the BP will be stopped and the patient will continue with their personal insulin pump.
- **If the patient experiences seizure or unconsciousness, persistent nausea or vomiting, diabetic ketoacidosis, persistent hyperglycemia with ketonemia, hemodynamic changes such as hypotension, or other medically significant findings, a longer observation period at the trial site may be necessary until the patient is considered stable for discharge. If the Investigator or trial staff determines that the patient requires further observation or treatment, the patient may be transferred to the emergency room for additional monitoring and/or medical care. At discharge, patients will be provided with any necessary instructions concerning personal insulin pump usage, food intake, and driving arrangements.**
- The maximum amount of blood loss per study visit will be approximately 230 mL. The total blood loss for the entire study will be up to 460 mL.
- Patients will answer questionnaires (see Appendix C).
- Chemistry and hematology samples will be collected at visit end (see Appendix B).
- The BP and glucose meters will be collected and downloaded.
- A trial MD will review the last several hours of insulin and glucagon dosing and assist the patient in resuming their usual diabetes care. ~~They~~ **A longer observation period at the trial site may be necessary. Patients** will be instructed to call trial staff with any questions, issues, or concerns.

Appendix A, Schedule of Procedures, Footnote 3, Page 57

Original Text:

3. The night before the visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window.

New Text:

3. The night before the visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window. **If BG is <50 mg/dL, treatment with simple carbohydrate is allowed. If the patient experiences persistent hypoglycemia, the visit will be rescheduled within the visit window.**

Appendix A, Schedule of Procedures, Footnote 14, Page 57

Original Text:

14. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor and trial policies and procedures.

New Text:

14. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor**, diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits,** and trial policies and procedures.

Clinical Trial Protocol
ZP4207-16051

Version number: 3.0
Amendment 2.0
Date: 03 August 2016

CLINICAL TRIAL PROTOCOL

The iLet Feasibility Trial Testing the iLet, a Fully Integrated Bihormonal Bionic Pancreas with ZP4207

Investigational Product: ZP4207
Protocol Number: ZP4207-16051
IND Number: 129980
Phase: 2

Principal Investigator:
Steven J. Russell, MD, PhD[1]

Co-Investigator:
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Original Version: 03 May 2016
Amendment Number 1.0: 28 June 2016
Amendment Number: 2.0
Protocol Version Number: 3.0
Date: 03 August 2016

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Version number: 3.0
Amendment 2.0
Date: 03 August 2016

SIGNATURE PAGE

TRIAL TITLE: The iLet Feasibility Trial Testing the iLet, a Fully Integrated Bihormonal Bionic Pancreas with ZP4207

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the trial.

Signature [redacted] Date [redacted]

[redacted] MD
Vice President, Clinical Development
Zealand Pharma A/S

[redacted] DVM, PhD
Principal Clinical Pharmacologist
Zealand Pharma A/S

Clinical Trial Protocol
ZP4207-16051

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Date: 03 August 2016

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the trial as described. I will conduct this trial in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the trial within the time designated. I will provide copies of this protocol and access to all information furnished by Zealand Pharma A/S to trial personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the trial product and trial procedures. I will let them know that this information is confidential and proprietary to Zealand Pharma A/S and that it may not be further disclosed to third parties. I understand that the trial may be terminated or enrollment suspended at any time by Zealand Pharma A/S, with or without cause, or by me if it becomes necessary to protect the best interests of the trial patients.

I agree to conduct this trial in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and ICH Guidelines for Good Clinical Practices.

[redacted]

Investigator's Signature

8/3/2016
Date

Steven Russell, MD, PhD
Investigator's Printed Name

[redacted]

Clinical Trial Protocol
ZP4207-16051

Version number: 3.0
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Date: 03 August 2016

SYNOPSIS

TITLE: The iLet Feasibility Trial Testing the iLet, a Fully Integrated Bihormonal Bionic Pancreas with ZP4207

PROTOCOL NUMBER: ZP4207-16051

INVESTIGATIONAL PRODUCT: ZP4207

PHASE: 2

INDICATION: ZP4207 is an anti-hypoglycemic glucagon analog in a ready-to-use liquid formulation which is being studied to improve glycemic control in adults (and children) with type 1 diabetes mellitus (T1DM) as part of a bihormonal bionic pancreas (BP).

OBJECTIVES:

Primary: The primary objective is to conduct a trial testing the safety and tolerability of the iLet when used with ZP4207 in 10 adult (≥18 years of age) patients with T1DM.

Secondary: The secondary objectives are to measure glycemic regulation, including hypoglycemia exposure (percent of time spent with continuous glucose monitor [CGM] glucose <60 mg/dL), evaluate BP device reliability, and to document the satisfaction of patients with the iLet with the goal of optimizing the functionality and user interface of the iLet.

POPULATION: Up to 20 adult (≥18 years of age) patients who already manage their T1DM using continuous subcutaneous (SC) insulin infusion pump therapy can be enrolled. It is expected that up to 10 patients will complete the trial protocol.

TRIAL DESIGN: This trial is a single-center, open-label, randomized cross-over trial. The trial will enroll adult patients with T1DM and will assess the safety and efficacy of the iLet using the glucagon analog ZP4207 versus the iLet using Lilly glucagon. The iLet will also administer insulin (insulin lispro, Lilly Humalog) using the same blood glucose (BG) control algorithm for both treatment arms. The trial will be conducted at a single center, the Massachusetts General Hospital Diabetes Center in Boston, MA.

TRIAL TREATMENT: The trial involves SC administration of insulin lispro (Humalog, Lilly), which is commercially available by prescription and is indicated for patients with T1DM, but not for use in a BP.

The trial also involves SC administration of Lilly glucagon in one iLet arm. Lilly glucagon is commercially available by prescription and is indicated for patients with T1DM in severe hypoglycemia, but not for use in a BP.

The trial also involves SC administration of the glucagon analog ZP4207, 1 mg/mL, in the other iLet arm. ZP4207 will be made available by Zealand Pharma A/S, Denmark as liquid formulation in prefilled syringes of 0.6 mL.

PRIMARY ENDPOINT:
The primary endpoint is the safety and tolerability of ZP4207 and the iLet as assessed by:

- Number and type of adverse events (AEs)
- Clinical laboratory measurements
- Vital signs
- 12-lead electrocardiogram (ECG)
- Local tolerability and infusion site reactions as measured with the Draize scale
- Immunogenicity as measured by anti-drug antibodies
- Pain as measured on a 10 cm visual analog scale (VAS)
- Nausea as measured on a 10 cm VAS

SECONDARY ENDPOINTS:
The secondary endpoints for the iLet and ZP4207 include measurements of BP function as well as glycemic and non-glycemic measurements.

Bionic Pancreas Function
This endpoint data will be generated from the BP data during each treatment visit:

- Average percent insulin dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
    - Average percent glucagon/ZP4207 dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts calculated by the BP algorithm that are successfully issued to the pump by the BP (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts calculated by the BP control algorithm that are successfully issued by the BP
    - Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully issued by the BP
- Average percent of 5-minute steps during which the BP is functioning nominally in all respects based on real-time CGM data (new CGM glucose reading captured, dose calculated, and dose issued to pumps)
- Average percent of 5-minute steps during which the BP is functioning nominally with or without a new CGM glucose reading captured (dose calculated and dose issued to pumps). If a CGM signal is not available, the dose calculated may be based on weight or historical basal rates.
- CGM reliability index, calculated as percent of possible values actually recorded by CGM
- CGM Mean Absolute Relative Difference versus time-stamped BG values from meter download
- List of technical faults associated with the BP including cause and resolution

[redacted]

Glycemic
All of following metrics will be generated from the Dexcom G4 Platinum CGM data during each treatment visit.

- Fraction of time spent within each of the following glucose ranges:
  - <50 mg/dL
  - <60 mg/dL
  - <70 mg/dL
  - 70-120 mg/dL
  - 70-140 mg/dL
  - 70-180 mg/dL
  - >180 mg/dL
  - >250 mg/dL
  - >300 mg/dL
- Number of severe hypoglycemic events (patients unable to self-treat, requiring the assistance of another person)
- Number of episodes of symptomatic hypoglycemia
- Number of carbohydrate interventions for hypoglycemia
- Total grams of carbohydrates taken for hypoglycemia
- Mean CGM glucose

Non-glycemic

- Glucagon/ZP4207 total delivery per kg of body mass
- Insulin total delivery per kg of body mass
- Number of unscheduled infusion set replacements
- Number of unscheduled CGM sensor changes

EVALUATION OF TRIAL DATA: The following variables will be evaluated according to treatment for safety purposes: AEs, local tolerability, laboratory safety assessments, physical examination, vital signs, and 12-lead ECGs.

The analysis of BP function endpoints and glycemic endpoints will be on an intention-to-treat basis. In cases where a treatment arm was not completed (and that arm was not repeated according to protocol criteria), available data from that arm will be used in the data analysis.

The Shapiro-Wilk test will be used to determine the normality of the residuals for each comparison. Summary tables that display descriptive statistics, including percentages, means or medians, and standard deviation and/or ranges, as appropriate, will be provided.

A paired t-test or the Wilcoxon signed rank test for comparison of means with normally or non-normally distributed residuals, respectively, will be used. In a secondary analysis any period effect and any interaction between treatment and period will be looked for, although no such interaction is predicted for the efficacy outcome.

The number of patients and proportions of severe hypoglycemic events, symptomatic hypoglycemia, and carbohydrate interventions due to hypoglycemia with the event counts will be summarized descriptively, and the proportions will be analyzed by a Fisher's exact test if data allow.

[redacted]

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Amendment 2.0
Date: 03 August 2016

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LIST OF FIGURES

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibodies
AE	Adverse event
BG	Blood glucose
BP	Bionic pancreas
BU	Boston University
CFR	Code of Federal Regulations
CGM	Continuous glucose monitor
CRO	Contract research organization
DBR	Database review
DPP-4	Dipeptidyl peptidase-4
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FDA	Food and Drug Administration
FHD	First Human Dose
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HCG	Human chorionic gonadotropin
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IM	Intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
MD	Doctor of Medicine
MedDRA	Medical Dictionary for Regulatory Activities
MGH	Massachusetts General Hospital
MPC	Model-predictive control
PD	Pharmacodynamic
PK	Pharmacokinetic

[redacted]

Abbreviation	Definition
RN	Registered nurse
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SGLT-2	Sodium-glucose co-transporter-2
SIV	Site Initiation Visit
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 diabetes mellitus
TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
ULN	Upper limit of normal
VAS	Visual analog scale

[redacted]

Clinical Trial Protocol
ZP4207-16051

Version number: 3.0
Amendment 2.0
Date: 03 August 2016

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Background and Rationale

To date, clinical trials conducted by Boston University (BU) and Massachusetts General Hospital (MGH) in patients with type 1 diabetes mellitus (T1DM) have demonstrated the practicality of a wearable automated bionic pancreas (BP) control system for robust glucose regulation using a continuous glucose monitor (CGM) to provide the input to the control system. Despite current technical limitations in CGMs and infusion pumps, the trials by BU/MGH have shown that a bihormonal BP is capable of achieving safe and effective blood glucose (BG) control automatically, with minimal hypoglycemia during 11 continuous days in the face of unrestrained meals and exercise and with trivial patient input (optional announcement of meals).

The BP provides automatic BG regulation and reduces hypoglycemic episodes. Additionally, the system spares the wearer the relentless tasks of carbohydrate counting, frequent BG monitoring, estimating the effects of specific meals and exercise activity on BG levels, and manual drug administration, which are inexact, demanding, aggravating, and require continuous diligence and vigilance. The degree of glycemic control achieved by the BP is predicted to dramatically reduce the deleterious and debilitating complications of T1DM.

In its last tested embodiment, the BP consisted of a Dexcom G4 CGM, and an iPhone that are hardwired together, with the iPhone running the control algorithm and communicating via Bluetooth with 2 Tandem t:slim pumps to dose insulin and glucagon. The connections are repeatedly lost among these 4 components throughout the day, an issue that has the potential to adversely impact BG control, whether due to missed CGM values or missed doses. In addition, the troubleshooting required to repair these recurring disconnections can be burdensome to the user. Integrating these components into a single device would establish seamless connectivity among them, which would eliminate the need for such troubleshooting. This would lead to a smoother device operation with fewer interruptions, which would enhance its user friendliness, optimize its BG control potential, and further improve the quality of life of its users.

The BU Investigators have recently designed, built, and tested a proprietary first-generation of such a fully integrated BP system, referred to as the iLet and the iLet infusion set. The iLet is a dual-chamber infusion system that currently incorporates the Dexcom G4 CGM technology, a custom user interface with touchscreen display, and all of the mathematical dosing algorithms that were tested in and validated using the iPhone-based BP in outpatient studies over the past 3 years. The iLet infusion set provides 2 independent subcutaneous (SC) fluid pathways from the iLet to the patient (1 for insulin and the other for glucagon). One tube connects to the prefilled insulin cartridge and the other tube connects to the fillable (single-use) glucagon cartridge.

In order to provide automatic BG regulation, the iLet has the ability to deliver both insulin and glucagon. However, currently available glucagon formulations have limited stability at room temperature, necessitating frequent changes to the glucagon infusion set. Therefore, the current trial is designed to test the glucagon analog ZP4207 in the iLet, as this peptide analog of human glucagon is provided in a liquid formulation stable at room temperature.

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The current trial is a first feasibility trial designed to use the first-generation iLet and iLet infusion set to compare ZP4207 with marketed glucagon (Lilly). The trial is intended to demonstrate the safety and tolerability of ZP4207 in the iLet and the feasibility of achieving comparable autonomous glycemic control. It is not intended to comprehensively demonstrate the definitive efficacy of the iLet in extended, continuous daily use, but rather to demonstrate its functionality and accuracy in a practical, albeit very controlled, clinical setting. The trial is expected to provide practical information that will benefit the design of a next-generation iLet and iLet infusion set and help pave the way for a more comprehensive outpatient home-use Phase 2 trial and ultimately a pivotal trial where comprehensive safety and efficacy through continuous full daily use of the iLet with ZP4207 will be documented.

The data derived from this trial will permit evaluation of the robustness of the iLet as well as the safety and efficacy of ZP4207 when used in conjunction with the iLet. The data obtained will be used to further improve the iLet and will allow BU/MGH to expand to larger outpatient trials using the iLet with ZP4207.

1.2 Bihormonal Bionic Pancreas System

The BP is an autonomous, self-learning system that requires only the patient's weight for initialization, and then autonomously adapts, modestly or dramatically, as needed, to cope with the wide range of insulin requirements of adults, adolescents, and pre-adolescents with T1DM. The BP obviates the need for the patient to know, or even appreciate, their insulin requirements, and renders obsolete any need for patients or caregivers to know carbohydrate-to-insulin ratios, basal rates, or insulin correction factors.

The core technology is a suite of control algorithms that orchestrate the automated dosing of insulin and glucagon to regulate BG levels. An insulin controller orchestrates all SC insulin dosing. At its centerpiece is a model-predictive control (MPC) algorithm, which bases insulin doses on the glucose data and insulin absorption kinetics, compensating for the slow absorption rate of SC insulin analogs (peak time in blood of 30-90 min, clearance in 4-8 hr). This enables the algorithm to refrain from stacking and overdosing insulin. Furthermore, the MPC algorithm automatically adjusts its insulin-dosing aggressiveness continuously and in real-time to different insulin needs between individuals and variable needs within the same individual. Running in parallel with the MPC algorithm is an algorithm that automatically modulates basal insulin delivery over multiple time scales, and another algorithm that automatically adapts insulin doses in response to optional meal announcements. Unlike current insulin pumps and the insulin-only control algorithms, the adaptive basal insulin algorithm obviates the need for the user to set, or even know, his or her “basal-rate profile.” Instead, it is capable of automatically adapting to, and compensating for, changes in an individual's basal insulin need, such as might occur over a period of hours, days, or weeks (e.g., circadian hormonal fluctuations, intercurrent illness, physical activity, or emotional state) or as might occur over a period of months or years due to developmental changes (e.g., hormonal changes that occur during puberty or menopause). The adaptive meal dose controller obviates the need for the user to set, or even know, his or her “carbohydrate-to-insulin ratios,” as it makes automatic adjustments based on dosing history for similar meal announcements made on previous days, and customizes the dose for each individual and for time of day.

[redacted]

The BP also includes a proportional-derivative algorithm governing SC micro-doses of glucagon to help prevent impending hypoglycemia. Glucagon dosing is based on the glucose level and rate of descent. It may occur preemptively even if glucose is above range, and it includes a feedback term to account for the pending effects of recent glucagon doses.

Taken together, these mathematical algorithms provide a universal framework for a glycemic control strategy that requires no quantitative input from, or participation by, the user (besides entering body weight to initialize the system), but which automatically adapts insulin and glucagon dosing to meet the individual needs of each user. Another challenge met is enabling the technology to remain completely autonomous in managing insulin and glucagon delivery even when the CGM is offline. Specifically, when the CGM is offline, the BP invokes the high-resolution “basal rate profile” that it had recently learned and stored when the CGM was online. On the basis of what the system learned and stored about meal announcements when the CGM was online, it is able to respond to meal announcements in the same manner when the CGM is offline. Finally, it automatically responds to user-entered BG values when the CGM is offline by issuing a correction dose of insulin or glucagon based on what it learned about the user's insulin and glucagon needs when the CGM was online. Thus, the BP never relies on, or burdens the user with, the determination of subjective dosing decisions, which inevitably vary in quality and reliability among different users. The BP provides a turnkey solution for people with T1DM that comprehensively manages glycemia across a broad range of individual needs and across a large spectrum of circumstances and challenges to glycemic control.

A significant challenge for the use of glucagon in a bihormonal BP is the lack of a commercially available glucagon formation that is stable and well-suited to infusion over several days in a pump reservoir. However, BU/MGH have proceeded with studies using a relatively unstable marketed formulation that must be reconstituted from a lyophilized powder on a daily basis. This allowed BU/MGH to proceed with studies of the bihormonal system while awaiting the production of stable glucagon formulations or stable glucagon analogs.

1.3 Preliminary Studies with the Bihormonal Bionic Pancreas System

The BP hardware platform has evolved over the years from a laptop-driven system, which was used in all inpatient studies to the first truly mobile wearable iPhone-driven platform, which has been used in a number of outpatient studies. Using the iPhone-based BP system, >110 outpatient experiments of 5-11 days in duration in each subject have been conducted (>800 patient days or >2 patient years of data) across subjects ranging in age between 6 and 76 years old and in body mass between 21 and 128 kg. The robust adaptation capabilities of the BP is evident in the fact that the average total daily dose of insulin among these subjects varied by over 13-fold (from 11 to 145 units/day).

In November 2012, Food and Drug Administration (FDA) approval was obtained to conduct the first outpatient study testing the BP in adults 21 years or older with T1DM. This study, referred to as the Beacon Hill Study, followed a random-order cross-over design in which 20 adults with T1DM participated in 5 days on the iPhone-based BP and 5 days of usual care in which they wore a CGM with blinded display and muted alarms. In the BP arm, subjects kept to a 3-square-mile geographic area centered around the Beacon Hill neighborhood in Boston. They ate as they chose at local restaurants, and exercised at will with access to 2 gyms. Analysis was pre-specified to focus on Days 2-5, since glycemic control is more representative of BP performance after most of the adaptation by the BP occurs on Day 1 (Russell, 2014). Results are summarized in Figure 1.

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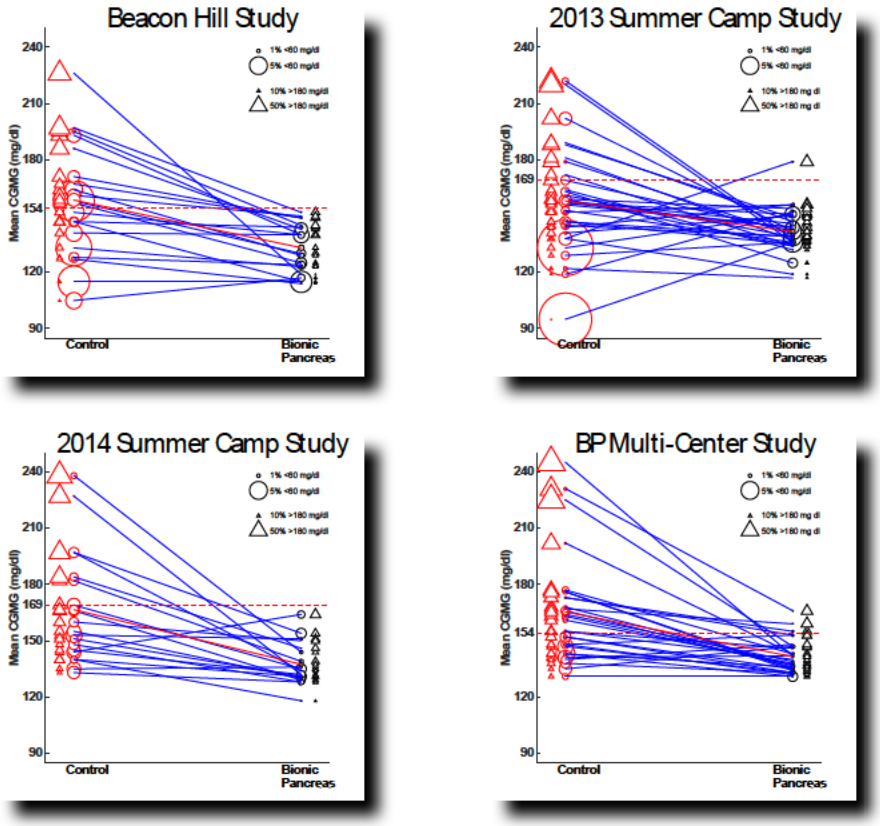
Figure 1. Outpatient Results Summarizing the Distribution of Mean CGM Glucose Levels and Hypoglycemia in the BP and Control Arms



Study	Age (years)	Bionic Pancreas (BP) Mean CGM glucose level (mg/dl)	BP % of CGM glucose levels <50 mg/dl (%)	BP 70–180 mg/dl (%)	Control Mean CGM glucose level (mg/dl)	Control % of CGM glucose values <50 mg/dl (%)	Control 70–180 mg/dl (%)	p value (BP versus Control) for: Mean CGM glucose level	p value for % of CGM glucose values <50 mg/dl	p value for 70–180 mg/dl
Beacon Hill (n 20, 5-day experiments)	≥21	133	1.5	80	159	3.7	59	<0.001	0.020	<0.001
2013 Summer Camp (n 32, 5-day experiments)	12–20	142	1.3	76	158	2.2	65	0.004	0.192	<0.001
2014 Summer Camp (n 19, 5-day experiments)	6–11	137	1.2	81	168	2.8	58	0.004	0.001	<0.001
BP Multi Center (n 39, 11-day experiments)	≥18	141	0.6	78	162	1.9	62	<0.001	<0.001	<0.001

Mean CGM glucose levels for each subject under usual care (red circles) are connected with the subject's mean CGM glucose level on the BP (black circles). The diameters of the circles shown are proportional to the percentage of CGM glucose values <60 mg/dL, and the size of he triangle is proportional to the percentage of CGM glucose values >180 mg/dL. The horizontal red dashed line refers to the glucose level corresponding to the American Diabetes Association therapy goal for each age group tested, which corresponds to 154 mg/dL (HbA1c of 7%) for adults and 169 mg/dL (HbA1c of 7.5%) for children. Results are summarized in the table, where the co-primary outcomes (mean CGM glucose level and percentage of CGM glucose values <60 mg/dL) for the BP arm are highlighted in red for each of the 4 studies.
BP = bionic pancreas; CGM = continuous glucose monitoring; HbA1c = hemoglobin A1c.

In April 2013, FDA approval was obtained to conduct the first outpatient study testing the BP in adolescents 12-20 years old with T1DM. This study, referred to as the 2013 Summer Camp Study, followed a random-order cross-over design in which 32 adolescents with T1DM participated in 5 days on the BP and 5 days of supervised camp care in which they wore a CGM with blinded display and muted alarms. Subjects were fully integrated into normal camp activities without restrictions on diet or exercise. The study used the same iPhone-based BP that was used in the Beacon Hill Study. Results are summarized in Figure 1 (Russell, 2014). In April 2014, FDA approval was obtained to conduct the first outpatient study testing the BP in pre-adolescents 6-11 years old with T1DM. This study, referred to as the 2014 Summer Camp Study, was similar in design to the 2013 Summer Camp Study. Results are summarized in Figure 1 (Russell, 2016).

In April 2014, FDA approval was obtained to conduct the first multi-center study, which was also the first home study, to test the BP in adults 18 years or older with T1DM. This study, referred to as the Bionic Pancreas Multi-Center Study, followed a random-order cross-over design in which 39 adults participated in 11 days on the BP and 11 days of usual care. Participants went to work as usual, and lived and slept at home, all without clinical supervision. There were no restrictions placed on diet or exercise. The study included 4 medical centers (10 subjects per center), which included MGH, the University of Massachusetts Medical School, Stanford University, and the University of North Carolina at Chapel Hill. Results are summarized in Figure 1.

All of these studies used marketed glucagon (glucagon for injection, Eli Lilly). Due to its limited stability, Lilly glucagon must be reconstituted immediately before use. Animal studies have previously shown that despite its limited chemical stability, Lilly glucagon maintains its biological activity for up to 7 days in solution. Using this data, an Investigational New Drug (IND) exemption was obtained from the FDA for its use in a pump for up to 27 hours. This allowed these studies to be performed by asking volunteers to reconstitute a new vial of glucagon and fill the glucagon pump at approximately the same time every day. However, marketed Lilly glucagon has no path forward for approval for chronic BP use.

1.4 ZP4207

ZP4207 is a peptide analog of human glucagon that is being developed to treat hypoglycemia in patients with T1DM and type 2 diabetes mellitus. ZP4207 exhibits improved physical and chemical stability in aqueous media and is suitable for liquid formulation. ZP4207 is comprised of 29 amino acids and has 7 amino acid substitutions when compared to native glucagon.

Two clinical Phase 1 trials have been conducted to establish safety and tolerability of ZP4207 after single and multiple dosing to healthy patients and T1DM patients under insulin-induced hypoglycemic conditions.

The First Human Dose (FHD) trial (ZP4207-14013) was finalized in April 2015. The trial was a randomized, double-blinded trial with the objectives to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of ZP4207 as compared to an active comparator. Part 1 included a single ascending dose in healthy volunteers in cohorts of 8. In each cohort, the patients were randomized 3:1 to ZP4207 (n=6) or Novo Nordisk GlucaGen® (n=2). Five cohorts with SC administration (0.01, 0.1, 0.3, 1.0, and 2.0 mg ZP4207 compared to 1 mg GlucaGen) and 3 cohorts with intramuscular (IM) administration (0.3, 1.0, and 2.0 mg ZP4207 compared to 1 mg GlucaGen) were included. Part 2 included 2 sequence groups of

[redacted]

10 hypoglycemic T1DM patients. The patients were treated with fixed single IM doses of 0.7 mg ZP4207 and 1.0 mg GlucaGen in a sequential cross-over design in a randomized treatment order.

The second clinical trial (ZP4207-15007) was a single-center, double-blind, Phase 1b trial investigating the safety and tolerability, PK and PD of ZP4207 following repeated administration in healthy volunteers compared to placebo. It was finalized in July 2015. Each of the 3 cohorts comprised 8 subjects, who received 5 repeated SC doses of ZP4207 or placebo in a 3:1 treatment allocation. The first cohort started with the lowest dose of 0.1 mg. Cohort 2 and 3 continued with 0.3 and 1.0 mg, respectively.

The Phase 1 results did not give rise to specific safety concerns, beyond those related to the pharmacological effect of ZP4207. All adverse events (AEs) recorded in the trials were of mild or moderate severity. The most frequent systemic AE related to treatment with ZP4207 was nausea, which is a known side-effect following administration of glucagon. The most frequent injection site reaction was transient erythema, occurring in all ZP4207, glucagon, and placebo treatment groups, irrespective of dose. No anti-drug antibodies (ADA) incidences were observed.

The observed PD response, in terms of increased plasma glucose, in insulin-induced hypoglycemic patients with T1DM following dosing with 0.7 mg ZP4207 administered IM was similar to that observed following IM dosing with 1.0 mg glucagon (GlucaGen, Novo Nordisk). An increase in plasma glucose of ≥20 mg/dL from hypoglycemic levels was achieved within 30 minutes for all patients.

In terms of PK, ZP4207 had a short half-life and high clearance and dose proportionality for both maximum plasma concentration and area under the concentration-time curve from time 0 to 300 minutes in the dose range 0.1 to 2.0 mg following SC administration. Following IM administration, dose proportionality was shown in the investigated dose range of 0.3 to 2.0 mg. The PK properties of 0.7 mg ZP4207 IM were comparable with those of 1.0 mg glucagon (GlucaGen, Novo Nordisk) with IM administration.

1.5 Risk/Benefit

While the potential risks are minimal, the findings of this trial may reveal information that can substantially improve medical care for persons with diabetes. Therefore, the overall risk/benefit for patients participating in this trial is assessed as acceptable.

Potential Risks and Discomforts

Trial patients will be informed by the Investigator of the potential risks of ZP4207 and other trial-related procedures before they enter the trial.

In this trial, patients with T1DM will be included to test the safety and efficacy of the iLet using ZP4207 versus the iLet using Lilly glucagon. The cross-over design with inclusion of the same T1DM patients into the 2 treatment arms in a randomized order will allow for a direct comparison of the safety and efficacy of the 2 treatments, based on intra-patient variability only.

[redacted]

Patients may experience mild discomfort associated with the insertion of the infusion sets and sensor into the SC tissues. The risk of discomfort due to insertion of infusion sets and sensors is expected to be slightly greater than in their lives outside the trial because more infusion sets will be inserted and a CGM sensor will be inserted. Most patients will use only one infusion set and not all will use a CGM sensor in usual care.

There is a potential risk of hypoglycemia, since recombinant insulin analog will be administered. Due to frequent monitoring of glucose and direct supervision by a registered nurse (RN) or Doctor of Medicine (MD) at all times, the risk of a hypoglycemic episodes leading to significant harm to patients is expected to be substantially lower than their risk during their usual therapy.

There is a risk of hyperglycemia. This risk is expected to be less than the risk during the patients' lives outside of the trial based on data from earlier BP trials and the design of this trial.

Treatment with ZP4207 and marketed glucagon can result in undesired effects or complaints. Undesired effects and complaints such as gastrointestinal side effects including nausea, vomiting, and diarrhea are known side effects of glucagon administration at higher dose levels. The frequency of nausea associated with the administration of 1 mg of glucagon according to the Summary of Product Characteristics (SPC) for Glucagon is described to be between 1/10 and 1/100. The frequency of vomiting is described to be between 1/100 and 1/1000 (Novo Nordisk, 2015). Similar gastrointestinal side effects have also been observed to a limited degree in the 2 clinical trials conducted with ZP4207, again at higher dose levels. The individual doses of ZP4207 and Lilly glucagon delivered by the BP are expected to be significantly lower than doses typically associated with nausea. Episodes of low blood pressure have also been observed after administration of higher doses of glucagon and ZP4207. As with every novel drug substance, new and yet unknown side effects may also occur.

There are limited data available to describe the immunogenic potential of glucagon products available on the market, but the data available indicate that marketed glucagon only has a small immunogenic potential. A Phase 1 trial performed with recombinant human glucagon and animal derived glucagon in 75 healthy patients did not show signs of ADA measured 13 weeks after trial product administration (Eli Lilly, 2005). In the ZP4207 FHD trial, ZP4207-14013, no confirmed anti-ZP4207 or anti-glucagon antibodies were detected in any of the samples. In addition, the 5 sequential administrations of ZP4207, as applied in trial ZP4207-15007, were not associated with the development of antibodies against ZP4207 in the 18 subjects enrolled to receive ZP4207. The optimized formulation of ZP4207, as applied in the present trial is not expected to change the immunogenic potential of the Investigational Medicinal Product (IMP).

In relation to diabetes therapy, development of insulin-antibodies is documented more substantially and route of administration has been shown to influence immunogenic potential of insulins. However, these antibodies against insulin generally do not have an impact on insulin action and are thus not clinically relevant.

In terms of consequence, development of high titer antibodies against ZP4207 could, in theory reduce the activity of endogenous glucagon, which again, in theory could influence

[redacted]

hypoglycemic episodes. However, most patients with T1DM do not secrete glucagon normally in response to hypoglycemia, so they would be less likely to be negatively impacted by anti-glucagon antibodies. Limited suppression of glucagon would, however, not be considered critical, as low glucose levels can also be corrected by other means, including oral intake of glucose and by other endogenous hormones such as oxyntomodulin.

Overall, ZP4207 is judged to be a low-risk molecule, based upon the available clinical data as well as the outcome of the risk-based approach to the immunogenicity assessment made. The present trial will include sampling for measurement of antibodies against ZP4207 prior to first dosing (Visit 3) and at the Follow-up Visit. In line with regulatory guidance documents, these samples will be appropriately analyzed and the results will be included in the overall assessment of the immunogenic potential of ZP4207 after completion of each trial and as the clinical development program advances.

Administration of ZP4207 may be associated with a risk of allergic reactions similar to those observed for other therapeutic peptides or proteins. Patients with known or suspected allergies to the trial products or related products will be excluded from the trial. Mild or moderate allergic reactions may include symptoms of rash, fever, flu-like symptoms, nausea, headache, and myalgia. Acute generalized hypersensitivity reactions are usually very rare but may include symptoms of flushing, sweating, dizziness, change in blood pressure, and difficulties in breathing. The risk of acute hypersensitivity reactions is described to be less than 1/10,000 for native glucagon. No severe acute hypersensitivity reactions have been observed in the 2 clinical trials conducted with ZP4207.

Potential Benefits

Based on experiences from previous trials of the BP and the design of this trial, patients enrolled in the trial may benefit from a reduction in risk of hypoglycemia and hyperglycemia and a better mean glucose compared to their usual diabetes care during their short trial participation.

The data derived from this trial will allow evaluation of safety and tolerability of ZP4207 in the iLet, and the robustness and effectiveness of the new BP control system. The data obtained will be used to further improve the iLet and will allow the expansion to larger outpatient trials using the iLet with ZP4207.

This trial is a necessary step in preparing the BP with ZP4207 to become available to people with T1DM. Wide availability of the BP with ZP4207 could improve the medical care of adults and children with T1DM.

[redacted]

2 TRIAL OBJECTIVES

2.1 Primary Objective

The primary objective is to conduct a trial testing the safety and tolerability of the iLet when used with ZP4207 in 10 adult (≥18 years of age) patients with T1DM.

2.2 Secondary Objectives

The secondary objectives are to measure glycemic regulation, including hypoglycemia exposure (percent of time spent with CGM glucose <60 mg/dL), evaluate BP device reliability, and to document the satisfaction of patients with the iLet with the goal of optimizing the functionality and user interface of the iLet.

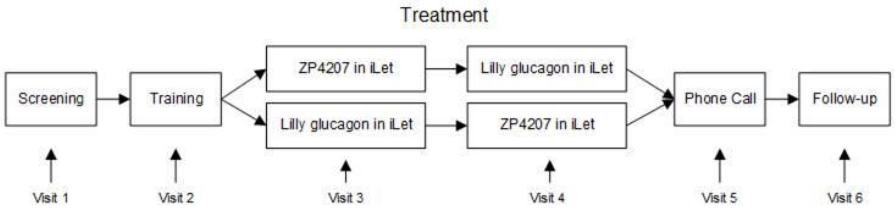
3 TRIAL DESCRIPTION

3.1 Summary of Trial Design

This trial is a single-center, open-label, randomized cross-over trial. The trial will enroll adult patients with T1DM and will assess the safety and efficacy of the iLet using the glucagon analog ZP4207 versus the iLet using Lilly glucagon. The iLet will also administer insulin (insulin lispro, Lilly Humalog) using the same BG control algorithm for both treatment arms. The trial will be conducted at a single center, the MGH Diabetes Center in Boston, MA.

The overall trial design schematic is displayed in Figure 2.

Figure 2. Trial Design Schematic



3.2 Indication

ZP4207 is an anti-hypoglycemic glucagon analog in a ready-to-use liquid formulation which is being studied to improve glycemic control in adults (and children) with T1DM as part of a bihormonal BP.

3.3 Number of Patients

Up to 20 adult patients with T1DM can be enrolled. The upper bound is based on the expectation that some patients will be excluded after the Screening Visit and the possibility that some patients may have to be discontinued before completion (due to, for instance, inter-current illness or patient withdrawal). It is expected that up to 10 patients will complete the trial protocol.

4 SELECTION AND WITHDRAWAL OF PATIENTS

The trial will enroll patients who already manage their T1DM using continuous SC insulin infusion pump therapy. This requirement is imposed because multiple daily injection therapy involves the use of medium-acting or long-acting basal insulin that would require an extended washout period.

4.1 Inclusion Criteria

1. Male and female patients with T1DM for at least 1 year, as defined by the American Diabetes Association
2. Age ≥18 years
3. Diabetes managed using an insulin pump for ≥6 months
4. Prescription medication regimen stable for >1 month (except for medications that will not affect the safety of the trial and are not expected to affect any outcome of the trial, in the judgment of the Investigator)
5. Informed consent obtained before any trial-related activities (trial-related activities are any procedure that would not have been performed during normal management of the patient)
6. Patients in good health according to age (medical history, physical examination, vital signs, 12-lead electrocardiograms [ECGs], laboratory assessments), as judged by the Investigator

4.2 Exclusion Criteria

1. Unable to provide informed consent (e.g., impaired cognition or judgment)
2. Unable to safely comply with trial procedures and reporting requirements (e.g., impairment of vision or dexterity that prevents safe operation of the BP, impaired memory, unable to speak and read English)
3. Participation in another clinical trial of an investigational agent or device concurrently or within 1 month (or 5 half-lives) prior to the Screening Visit
4. Previous exposure to ZP4207
5. Females of childbearing potential who are pregnant (positive urine human chorionic gonadotropin [HCG]), breast feeding, plan to become pregnant in the immediate future, or sexually active without using highly effective contraception methods (highly effective methods are considered those with a failure rate less than 1% undesired pregnancies per year including surgical sterilization, hormonal intrauterine devices [coil], oral hormonal contraceptives, sexual abstinence, or a surgically sterilized partner) or postmenopausal women amenorrheic for less than 1 year with serum follicle-stimulating hormone (FSH) level ≤40 IU/L and not using highly effective contraceptive methods during the trial and until 1 month after last dosing in the trial
6. Male who is sexually active and not surgically sterilized who or whose partner(s) is not using highly effective contraceptive methods (highly effective contraceptive measures include surgical sterilization, hormonal intrauterine devices [coil], oral hormonal contraceptives, each in combination with spermicide-coated condoms), or who is not willing to refrain from sexual intercourse from the first dosing until 1 month after last dosing in the trial
7. Current alcohol abuse (intake averaging >3 drinks daily in last 30 days) or use within the last 6 months of controlled substances without a prescription (other than marijuana)

[redacted]

8. New onset clinically significant illness within 4 weeks prior to screening, as judged by the Investigator
9. Unwilling or unable to refrain on the treatment visits from:
    a. Acetaminophen in any form
    b. Use of drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the trial (use of beta blockers will be allowed as long as the dose is stable and the patient does not meet the criteria for hypoglycemia unawareness while taking that stable dose, but use of benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the Investigator)
10. History of liver disease that is expected to interfere with the anti-hypoglycemia action of glucagon (e.g., liver failure or cirrhosis). Other liver disease (i.e., active hepatitis, steatosis, active biliary disease, any tumor of the liver, hemochromatosis, glycogen storage disease) may exclude the patient if it causes significant compromise to liver function or may do so in an unpredictable fashion.
11. Aspartate aminotransferase >2 × upper limit of normal (ULN), alanine aminotransferase >2 × ULN, or bilirubin >1.5 × ULN on screening laboratories
12. Renal failure on dialysis or estimated glomerular filtration rate <30 mL/min/1.73 m^2 on screening laboratories
13. Hemoglobin <12 gm/dL for men and <11 gm/dL for women
14. Personal history of cystic fibrosis, pancreatitis, pancreatic tumor, or any other pancreatic disease besides T1DM
15. Any known history of coronary artery disease including, but not limited to, history of myocardial infarction, stress test showing ischemia, history of angina, or history of intervention such as coronary artery bypass grafting, percutaneous coronary intervention, or enzymatic lysis of a presumed coronary occlusion)
16. Congestive heart failure with New York Heart Association Functional Classification III or IV
17. History of transient ischemic attack or stroke in the last 12 months
18. Seizure disorder, history of any non-hypoglycemic seizure within the last 2 years, or ongoing treatment with anticonvulsants
19. History of hypoglycemic seizures (grand-mal) or coma in the last 12 months
20. History of hypoglycemic unawareness in the last 12 months
21. History of pheochromocytoma: fractionated metanephrines will be tested in patients with history increasing the risk for a catecholamine secreting tumor:
    a. Episodic or treatment refractory (requiring 4 or more medications to achieve normotension) hypertension
    b. Paroxysms of tachycardia, pallor, or headache
    c. Personal or family history of MEN 2A, MEN 2B, neurofibromatosis, or von Hippel-Lindau disease
22. History of adrenal disease or tumor
23. Hypertension with systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg despite treatment
24. Untreated or inadequately treated mental illness (indicators would include symptoms such as psychosis, hallucinations, mania, and any psychiatric hospitalization in the last year), or treatment with anti-psychotic medications that are known to affect glucose regulation
25. Electrically powered implants (e.g., cochlear implants, neurostimulators) that might be susceptible to radio frequency interference

[redacted]

26. History of adverse reaction to glucagon (including allergy) besides nausea and vomiting
27. History of severe hypersensitivity to milk proteins or lactose
28. Established history of allergy or severe reaction to adhesive or tape that must be used in the trial
29. Use of oral anti-diabetic medications (e.g., thiazolidinediones, biguanides, sulfonylureas, glitinides, dipeptidyl peptidase-4 [DPP-4] inhibitors, sodium-glucose co-transporter-2 [SGLT-2] inhibitors)
30. Inadequate venous access as determined by trial nurse or physician at time of screening
31. Any factors that, in the opinion of the Investigator, would interfere with trial endpoints or the safe completion of the trial

4.3 Target Population

Patients who meet all of the inclusion and none of the exclusion criteria will be considered as candidates for this trial. Individuals who have previously inquired about participation in BU/MGH trials and have asked to have their contact information kept on file will be contacted. In addition, advertisements for the trial may be posted at the MGH Diabetes Center and other places, and may be distributed in the weekly broadcast e-mail of research studies seeking volunteers. A letter may be sent to adult endocrinologists in the Boston metropolitan as well as selected nearby endocrinologists informing them of the trial and asking them to refer any eligible patients who might be interested. Information will be posted about the trial along with contact information on the BU/MGH website www.bionicpancreas.org and on www.clinicaltrials.gov.

4.4 Withdrawal Criteria

The participation of individual patients will be discontinued if they experience:

- Seizure or unconsciousness associated with hypoglycemia and associated with participation in the trial
- Persistent nausea and vomiting thought to be related to glucagon dosing associated with participation in the trial
- Hospitalization associated with participation in the trial
- Pregnancy
- Diabetic ketoacidosis

If more than 1 patient must be withdrawn from the trial for these reasons, the trial will stop and a vote of the Data and Safety Monitoring Board (DSMB) will be required to restart it. All AEs that are serious and unexpected but related will be reported to the DSMB within 5 working days.

Note that patients may discontinue participation at any time. Patients may be removed from the trial for other reasons, for instance, failure to comply with trial procedures or intercurrent illness that is unrelated to the BP but that precludes safe participation. Discontinuation of participation for these reasons will not contribute to a decision to discontinue the trial.

[redacted]

5 ASSIGNMENT TO TREATMENT GROUPS

This trial is an open-label, randomized cross-over trial. Patients who have completed the Screening Visit and meet all of the inclusion and none of exclusion criteria will be enrolled into the trial. All patients will participate in two 1-day treatment arms in random order (iLet using ZP4207 and iLet using Lilly glucagon) according to a pre-generated randomization scheme. Up to 2 patients may participate in the trial per day. The order of the iLet visits will be randomized in blocks of 2 patients.

6 TRIAL TREATMENT

6.1 Investigational Medicinal Products

Insulin: The trial involves SC administration of insulin lispro *(*Humalog, Lilly*)*, which is commercially available by prescription and is indicated for patients with T1DM, but not for use in a BP.

Glucagon: The trial also involves SC administration of Lilly glucagon in one iLet arm. Lilly glucagon is commercially available by prescription and is indicated for patients with T1DM in severe hypoglycemia, but not for use in a BP.

ZP4207: The trial also involves SC administration of the glucagon analog ZP4207, 1 mg/mL, in the other iLet arm. ZP4207 will be made available by Zealand Pharma A/S, Denmark as liquid formulation in prefilled syringes of 0.6 mL.

6.2 Storage and Drug Accountability of IMPs

All IMPs will be stored and handled in accordance with the Sponsor's instructions and/or the product labelling at the Investigator's site, e.g., refrigerated (+2ºC to +8ºC) and should not be exposed to excessive heat, direct sunlight and never be frozen.

All used, partly used, and unused vials or prefilled syringes must be kept by the Investigator and stored between +2ºC and +8ºC (unused) or at room temperature (partly used and used). Used and unused pre-filled syringes must be stored separately.

The Investigator must ensure the availability of proper storage conditions and record and evaluate the temperature. Temperature of the refrigerator used for drug storage is monitored continuously, an alarm system is established. The Investigator must inform the monitor immediately if any IMP has been stored outside specified conditions (e.g., outside temperature storage). Investigational Medicinal Product that has been stored improperly must not be dispensed to any patient before it has been re-evaluated and approved for further use. The Investigator must take appropriate action to ensure correct storage.

For the IMP, the Investigator must keep an accurate record of all IMPs received and the products used for each patient in a Drug Accountability Record. Storage locations, batch numbers, and expiry dates are also documented in this form.

The drug accountability must be performed in a timely manner by the monitor.

[redacted]

6.3 Dispensing and Return of IMPs

No IMPs may be dispensed to any person not enrolled in the trial.

Upon completion of the trial, the Sponsor will be responsible for destruction or storage of IMPs (used, partially used, or unused). These duties can be delegated to a contract research organization (CRO) and must be documented in the trial files.

6.4 Doses

The iLet can administer isolated insulin-glucagon doses once every 5 minutes. A single automated bolus of insulin will not exceed 3 units per 5-minute dose (30 µl of U-100 insulin) in both systems, and a single meal-priming dose, in response to a meal announcement made by the user, will not exceed 12 units (120 µl of U-100 insulin). A single bolus of glucagon will not exceed 80 µg (80 µl of 1 mg/mL Lilly glucagon or 1 mg/mL ZP4207). In prior studies, typical doses of glucagon were in the range of 0.005-0.04 mg per dose. The iLet is capable of administering as little as ~0.1 µl (0.011 units of U-100 insulin or 0.1 µg of 1 mg/mL ZP4207).

It is expected that the mean total daily doses of glucagon/ZP4207 will be <1.0 mg daily as in previous studies. The mean daily glucagon dose in a previous 11-day outpatient trial was 0.5 mg/day (range 0.2-0.9 mg/day). Currently, single doses of up to 2 mg ZP4207 have been administered in clinical trials. The recommended dose of marketed glucagon for adult patients suffering from severe hypoglycemia is 1 mg as a single injection. Mean glucagon levels in previous inpatient studies have been above the normal fasting range for glucagon only 1% of the time. Therefore, the glucagon exposure of patients is expected to be modest.

6.5 iLet Bionic Pancreas

Infusion set: A novel, dual cannula infusion set has been designed specifically for use with the iLet. Patients will wear dual channel tubing that will be attached to 2 infusion sets with 1 steel cannula each, one for insulin infusion and the other for glucagon infusion. The tubing and infusion sets will have undergone sterilization prior to being delivered in a sealed pouch. The steel cannulae will be inserted in the abdominal SC tissue.

Continuous glucose monitors: One transcutaneous glucose sensor for the Dexcom G4 Platinum (Garcia, 2013) will be inserted in the abdominal SC tissue and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to the sensor and the whole assembly is held to the skin with an adhesive patch and communicates wirelessly with the BP. If the G4 sensor fails for any reason during the trial (loss of CGM signal), it will be replaced promptly.

Bionic Pancreas Control Unit: The iLet is being built according to Class III medical device standards, adheres to a comprehensive and robust quality system, and is fully compliant with International Organization for Standardization (ISO) 13485 standards and document control practices. The iLet is a fully-integrated dual-hormone BP system that integrates the CGM technology (currently the Dexcom G4 Share system) as well as 2 independent motor-drivetrain pumping assemblies, which independently actuate the delivery of insulin and glucagon from pre-filled cartridges that are separately loaded into the iLet housing. Each drivetrain assembly utilizes a lead screw, which is driven by a precision micromotor, a gear case assembly, and a motor controller unit, in a manner similar to what is commonly found in most insulin infusion pumps on the market today. The iLet has dosing accuracy that is comparable to

FDA-approved insulin pumps currently on the market. The iLet has a built-in Bluetooth Low Energy radio that also allows automatic communication with the paired CGM, as well as the Nova StatStrip® Xpress BG meter (Nova Biomedical). The iLet does not contain a cellular nor a WiFi radio, and does not accept input data from another mobile device (e.g., smartphone), other than the paired CGM and BG meter(s).

The mathematical control algorithms (which are the same as those used in the iPhone-based BP), the CGM glucose engine (Dexcom), and the native user interface software, are all interconnected through controller framework software and reside as embedded systems on printed circuit boards contained within the device housing. The touchscreen-enabled, menu-driven user interface and onboard processor provide a comprehensive and standalone platform, which allows the iLet to operate independently of smartphones or other devices and without the need for internet support during routine operation. The graphical user interface of the iLet has the same user options and capabilities of the iPhone BP, including having its home screen password protected and its settings options only accessible to trial staff via a separate password.

6.6 Other Trial Devices

YSI 2300 STAT Plus™ (Yellow Springs Instruments): The YSI 2300 STAT Plus is an FDA-approved glucose analyzer. Blood glucose measurements using the YSI 2300 STAT Plus will be obtained off of the IV line during both treatment visits.

Nova Biomedical StatStrip Xpress Glucose Meter: The Nova StatStrip Xpress glucose meter is an FDA-approved glucose meter that is commercially available. Blood glucose measurements for CGM calibration will be obtained with the Nova StatStrip Xpress during both treatment visits if the YSI 2300 STAT Plus fails and via fingerstick with the Nova StatStrip Xpress during any periods when IV blood samples are not available for any reason or the IV fails.

Exercise Bike: The trial will utilize a stationary exercise bike (ergometer) for the in-clinic exercise at the treatment visits. This bike will be stored at the Diabetes Research Center when not in use.

6.7 Concomitant Medications

6.7.1 Permitted Medications and/or Procedures

Patients may take any over-the-counter medications that they wish during the trial, with the exception of any medication containing acetaminophen as that may cause interference with CGM sensing. All concomitant medications, including over-the-counter medications, should be recorded.

Use of beta blockers will be allowed as long as the dose is stable and the patient does not meet the criteria for hypoglycemia unawareness while taking that stable dose.

If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.

[redacted]

6.7.2 Excluded Medications and/or Procedures

During the trial, patients will not use any recreational drugs or drugs of abuse. The need to take prescription drugs that dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder appropriate decision-making may be grounds for exclusion from the trial or discontinuation of participation, a decision that will be made by the Investigator.

Use of benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the Investigator. Use of oral anti-diabetic medications (e.g., thiazolidinediones, biguanides, sulfonylureas, glitinides, DPP-4 inhibitors, SGLT-2 inhibitors) will also be excluded.

7 TRIAL PROCEDURES

7.1 Informed Consent

After potential patients have had time to review the consent document, and prior to any trial-related activities, they will meet with a trial MD or designee who will explain the trial, answer any questions, and administer informed consent. In the event that a volunteer is a patient of one of the trial MDs, another staff MD or designee will answer questions and administer consent. The patients will be fully informed of their responsibilities and their rights while participating in the trial as well as of the possible risks and potential benefits of participation in the trial. They will have the opportunity to discuss all questions and ample time to consider participation.

Trial-related activities are any procedures that would not have been performed during normal management of the patient. Patients who wish to participate in the trial will be asked to personally date and sign an informed consent form (ICF). Likewise, the Investigator must also personally date and sign the ICF. All patients will be provided with a copy of their own signed and dated ICF.

Trial staff will answer any questions that the patients may have during their participation. They will share any new information in a timely manner that may be relevant to the patient's willingness to continue participating in the trial. The patients may choose to discontinue their participation at any time.

7.2 Screening Visit (Visit 1)

All patients will have a Screening Visit to confirm eligibility. The patient will be interviewed and the electronic Case Report Form (eCRF) will be completed by trial staff to establish whether the patient is eligible.

Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator.

Once all of the results have been returned, a trial MD will review the eCRF to determine patient eligibility. If a patient is not eligible to continue in the trial, the results of abnormal tests will be reported to the patient and to a health care provider of their choosing.

7.2.1 Data Collected at Screening

- Age, sex, race, and ethnicity
- Date of last menstrual period in female patients
- Medical, surgical, and social history, allergies, and review of systems relevant to inclusion and exclusion criteria, including:
  - Date of diabetes diagnosis
  - Duration of insulin pump use and type of insulin used in pump
  - Type/model of insulin pump
  - Insulin regimen (basal rate, sensitivity factor, and carbohydrate ratio)
  - Average total daily dose of insulin in the last 30 days as available (from pump history)
  - Usage of CGM, if any (type of CGM, days per month worn, usage of data, whether insulin is dosed based on CGM alone, alarm settings)
- Concomitant illness (any illness present at screening)
- Concomitant medications (prescription and non-prescription) and date of last change in medication regimen
- Height, weight, physical examination, and vital signs including body temperature and blood pressure
- 12-lead ECG
- Hemoglobin A1c
- Chemistry and hematology samples (see Appendix B)
- Urine HCG pregnancy test for women of childbearing potential
- FSH level for postmenopausal women amenorrheic for less than 1 year
- Fractionated plasma metanephrines (if indicated by history)

7.3 Training Visit (Visit 2)

A Training Visit will take place before the first treatment visit. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor and trial policies and procedures. Trial staff will verify that the patients have understood the material and are competent to participate safely in the trial. Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator. Concomitant medications will also be reviewed.

7.4 Treatment Visits (Visit 3 and Visit 4)

- Visit 3 will take place at least 48 hours after screening (Visit 1) and no more than 30 days after screening (Visit 1).
- There will be a 24-hour minimum washout between Visit 3 and Visit 4 and a maximum of 3 weeks between Visit 3 and Visit 4.
- Up to 2 patients may participate per day.
- Each patient will participate in 2 treatment visits: one with the iLet using ZP4207 and one with the iLet using Lilly glucagon in a randomized order.
- The night before the treatment visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be instructed to call if they encounter any difficulty with their CGM.

[redacted]

- Patients will be responsible for their own medications other than insulin during the trial. Any medical advice needed by the patients during their participation that is not directly related to BG control should be obtained from them in their usual manner. Patients may take any over-the-counter medications that they wish during the trial, with the exception of any medication containing acetaminophen as that may cause interference with CGM sensing. If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.
- During the trial, patients will not use any recreational drugs or drugs of abuse. The need to take prescription drugs that dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder appropriate decision-making may be grounds for exclusion from the trial or discontinuation of participation, a decision that will be made by the Investigator.
- Patients will be instructed concerning diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits per the medical judgment of the Investigator.
- Patients will not tamper with the BP, including changing any settings.
- Patients may not remove the BP during the trial unless the BP failed or they are withdrawing from the trial.
- The exact time of each procedure and assessment will be documented.

7.4.1 Visit Procedures

- Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window. If BG is <50 mg/dL, treatment with simple carbohydrate is allowed. If the patient experiences persistent hypoglycemia, the visit will be rescheduled within the visit window. If the visit needs to be rescheduled due to hypoglycemia or hyperglycemia, trial staff will assist the patient with insulin or medication adjustments to address glycemic control. The patient will be instructed to contact trial staff later in the day if his or her BG remains uncontrolled.
- Upon arrival to the visit, the patient's weight and vital signs including body temperature and blood pressure will be documented.
- Patient reports of symptoms, any other complaints, and AEs will be reviewed.
- Concomitant medications will be recorded.
- Chemistry and hematology samples will be collected at visit start (see Appendix B).
- ADA samples will be collected before the start of dosing (Visit 3 only).
- A 12-lead ECG will be performed.
- A urine HCG pregnancy test will be performed in female patients of childbearing potential. If the test is positive, the patient will be informed of the result and the visit will be ended.
- Patients will complete a baseline survey about their attitudes and experience with their usual diabetes care.
- An intravenous (IV) catheter will be placed for blood sampling.

[redacted]

- Trial staff will assist the patient to calibrate their CGM, review the trial procedures again and assist with the setup of the BP system, including inserting and priming infusion sets.
- The control algorithm will be initialized only with the patient's weight. Diagnostics will be performed to ensure that the CGM device is appropriately calibrated and that all of the components of the BP systems are in working order.
- The basal rate of the patient's own insulin infusion pump will be changed to be 2-fold higher than weighted mean of the basal rate during the trial period. This is intended to increase the usage of glucagon during the treatment visit.
- The patients will continue to wear their own infusion pump infusing at the temporary 2-fold basal rate throughout the visit until the start of the structured exercise period, in addition to the BP.
- The staff will start the BP as close as possible to a minute divisible by 5 minutes (i.e., on a 5-minute mark). The starting time will be considered Hour 0.
- Additional calibrations will be performed at any of the BG checks throughout the day if the CGM value does not meet the ISO standard (<15 mg/dL difference for BG values <75 mg/dL; <20% absolute difference for BG values >75 mg/dL) at the time of the BG measurement AND it is a good time to calibrate (the CGM trend arrow is flat and there has been no carbohydrate intake in the last 30 minutes or glucagon boluses in the last 15 minutes).
- Blood samples will be taken from the IV at least hourly and processed for plasma ZP4207/glucagon. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator. The actual time of sampling will be recorded in the eCRF.
- Plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.
- Patients will be asked to rate any nausea and/or infusion site pain on 10 cm visual analog scales (VAS) at the beginning of the visit once the infusion sites have been placed but no drug has yet been administered, then approximately at the top of every hour during the visit, and at the end of the visit. Trial staff will also evaluate their infusion sites to document any erythema or edema at the same times. If moderate or severe pain is reported or swelling or redness occurs at the infusion site, the infusion site will be replaced in a different location. If moderate or severe pain, swelling, or redness continues at the old site for more than 30 minutes after the infusion site is removed, or if moderate or severe pain, swelling, or redness occurs at the new site, all infusion sites will be removed and the patient will be discontinued from the study. Any such symptoms will be followed until resolution.
- From the start of closed loop control until approximately Hour 3, the patients will continue to fast.
- Between approximately Hour 3 and Hour 4, patients will be provided with a lunch meal of their choice in the Diabetes Research Center from a menu of choices from nearby restaurants. They will be asked to choose a meal that is a "typical meal" for them. The content of their meal will not be restricted in any way, with the exception that the

[redacted]

number of carbohydrates should be in the "typical" range for them at lunch, and that they must eat the same meal at the same time during both visits.

- At approximately 15 minutes before the meal, patients will administer a bolus for the meal with their own insulin pump based on the carbohydrate count for the meal.
- After lunch is completed, the patients will not be allowed any carbohydrate intake (non-caloric drinks will be permitted) until the trial is completed (except as necessary to treat hypoglycemia), to allow the BP to control the post-prandial BG without further interruption.
- Between approximately Hour 6 and Hour 7, the patients will start a period of structured exercise.
- At the start of the exercise period, patients will restore their normal basal insulin profile so that they will not have elevated insulin levels at the end of the study period when they are to transition back to their usual care.
- Patients will exercise on a stationary bike with a heart rate from 120-140 beats per minute for a total of 4,000 heart beats (approximately 30 minutes). Patients will rate their exercise intensity using the Borg scale every 5 minutes, with the target intensity level between 12 and 14. Heart rate will be measured every 5 minutes.
- BG measurements will be obtained off of the IV line every 10 minutes. If BG is <80 mg/dL, BG measurements will be obtained off of the IV line every 5 minutes.
    - Carbohydrates will be given for any BG <50 mg/dL according to the following protocol: Dextrose (g) = BSA (m^2)/[1.7 m^2 (women) or 1.9 m^2 (men)] *15 g.
    - Repeat treatments will be given at 15-minute intervals as long as BG remains <50 mg/dL.
- If there is an interruption in the Dexcom CGM output, trial staff will assist the patient in recovering CGM data streaming. If this requires replacement of the CGM sensor, BGs will be checked every 10 minutes (every 5 minutes if BG is <80 mg/dL) using blood from the IV until the CGM is able to be calibrated again. These BGs will be entered into the BP, which will treat them as CGM values and dose insulin and/or glucagon appropriately.
- If there is a complete failure of the BP operation, patients will take over their own BG control using their personal insulin pump until the BP can be brought back online. If BP control cannot be promptly resumed (e.g., within 30 minutes), the patient may be asked to repeat that trial day once.
- Patients may choose to withdraw from the trial at any time. If they withdraw from the trial, they should alert a provider immediately.
- Just prior to the end of the study visit, vital signs including body temperature and blood pressure will be obtained and a 12-lead ECG will be performed.
- After approximately Hour 8, but not earlier than at least 60 minutes after end of exercise, the BP will be stopped and the patient will continue with their personal insulin pump.

[redacted]

- If the patient experiences seizure or unconsciousness, persistent nausea or vomiting, diabetic ketoacidosis, persistent hyperglycemia with ketonemia, hemodynamic changes such as hypotension, or other medically significant findings, a longer observation period at the trial site may be necessary until the patient is considered stable for discharge. If the Investigator or trial staff determines that the patient requires further observation or treatment, the patient may be transferred to the emergency room for additional monitoring and/or medical care. At discharge, patients will be provided with any necessary instructions concerning personal insulin pump usage, food intake, and driving arrangements.
- The maximum amount of blood loss per study visit will be approximately 230 mL. The total blood loss for the entire study will be up to 460 mL.
- Patients will answer questionnaires (see Appendix C).
- Chemistry and hematology samples will be collected at visit end (see Appendix B).
- The BP and glucose meters will be collected and downloaded.
- A trial MD will review the last several hours of insulin and glucagon dosing and assist the patient in resuming their usual diabetes care. A longer observation period at the trial site may be necessary. Patients will be instructed to call trial staff with any questions, issues, or concerns.

7.4.2 Data Collected During the Treatment Visits

- CGM glucose every 5 minutes from the Dexcom G4 Platinum CGM
- All BG measurements taken
- Insulin total dose by the BP and the patient's own insulin pump
- Glucagon total dose
- Timing and content of the meal eaten and carbohydrate amount
- Timing of meal announcement and size of meal announced
- Timing and glucose values at calibrations
- Timing and amount of carbohydrates taken for hypoglycemia
- Data from a questionnaire about attitudes and expectations regarding the BP before and after each treatment arm (see Appendix C)
- Time patients were not under BP control for any reason
- List of technical faults associated with the BP including cause and resolution
- ZP4207/glucagon sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.
- Plasma glucose sampling will be collected at least hourly in parallel with ZP4207/glucagon exposure sampling. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
- Nausea and infusion site pain on a VAS at visit start (after insertion and before any drug administration), hourly, and at visit end
- Infusion site reaction according to the Draize scale at visit start (after insertion and before any drug administration), hourly, and at visit end
- Patient reports of symptoms, any other complaints, and AEs
- Vital signs including body temperature and blood pressure (at visit start and visit end) and weight
- Concomitant medications

[redacted]

- Chemistry and hematology samples (see Appendix B) at visit start and visit end
- ADA (Visit 3 only)
- 12-lead ECG at visit start and visit end
- Urine HCG pregnancy test for women of childbearing potential

7.4.3 Response to Hypoglycemia

- Patients are encouraged to check their BG for any symptoms of hypoglycemia.
- Patients will be permitted to take 15 grams of carbohydrates for any BG value <60 mg/dL. Trial staff will ensure proper functioning of the BP, infusion set, and insulin pump, and will encourage the patient to wait for the BP to treat the low blood sugar for as long as they feel comfortable.
- Patients will be required to take 15 grams of carbohydrates for any BG value <50 mg/dL. After treatment of hypoglycemia, a follow-up measurement will be taken 15 minutes later. Repeated measurements will be taken every 15 minutes until the BG is >60 mg/dL. Treatment will be repeated if subsequent BG values are still <50 mg/dL. All carbohydrate treatments for hypoglycemia will be documented by trial staff (amount and time).
- Trial staff will check the infusion site, BP, and insulin pump for normal operation any time hypoglycemia occurs. If there is any suspicion of infusion set malfunction, the site should be replaced. Trial staff will check the BP for any malfunction and correct any problems that are found.
- If no correctable fault is found, but there is doubt regarding the correct function of the BP system, an entirely new backup BP system may be started.
- If a patient experiences a seizure or unconsciousness associated with hypoglycemia, his or her participation in the trial will be discontinued.

7.4.4 Response to Hyperglycemia

- Trial staff will check the infusion site, BP, and insulin pump for normal operation any time BG is >300 mg/dL. If there is any suspicion of infusion set malfunction, the site should be replaced. Trial staff will check the BP for any malfunction and correct any problems that are found. If the BG remains >300 mg/dL for 2 hours despite troubleshooting, blood ketones will be measured. If the blood ketone result is >1.5 mmol/L, the visit will be stopped and rescheduled. The patient will be provided with insulin and a syringe to give an injection based on their correction factor.
- If a patient experiences diabetic ketoacidosis, his or her participation in the trial will be discontinued.
- If no correctable fault is found, but there is doubt regarding the correct function of the BP system, the treatment visit may be stopped and the visit rescheduled.

7.4.5 Response to Nausea/Vomiting

If significant nausea (e.g., that prevents the patient from eating normally) or any vomiting occurs, trial staff will notify the Investigator. Trial staff will assist the patient in troubleshooting, such as checking BG and the calibration of the CGM (excessive glucagon dosing may occur if the CGM is reading lower than the true BG). If a patient experiences persistent nausea and vomiting thought to be related to glucagon dosing, his or her participation in the trial will be discontinued.

[redacted]

7.4.6 Response to Other Medical Needs

If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.

7.4.7 Monitoring of Bionic Pancreas Performance

Bionic pancreas inventors and developers [redacted], [redacted], and/or an engineer trained by them will be readily available by phone for consultation for the trial staff at all times during the course of the trial.

7.4.8 Supervision by Trial Staff

A trial MD will be on call at all times during the course of the trial. An RN or MD will be with the trial patients in the Diabetes Research Center at all times.

7.5 Phone Call (Visit 5)

A phone call will be conducted 7 days ±3 days following the last day of dosing (Visit 4) to review AEs and concomitant medications.

7.6 Follow-up Visit (Visit 6)

Patients will return for a Follow-up Visit 25 days ±4 days following the last day of dosing (Visit 4), for chemistry, hematology, and ADA sampling, and a review of AEs and concomitant medications.

8 ENDPOINTS

8.1 Primary Endpoint

The primary endpoint is the safety and tolerability of ZP4207 and the iLet as assessed by:

- Number and type of AEs
- Clinical laboratory measurements
- Vital signs
- 12-lead ECG
- Local tolerability and infusion site reactions as measured with the Draize scale
- Immunogenicity as measured by ADA
- Pain as measured on a 10 cm VAS
- Nausea as measured on a 10 cm VAS

8.2 Secondary Endpoints

The secondary endpoints for the iLet and ZP4207 include measurements of BP function as well as glycemic and non-glycemic measurements.

8.2.1 Bionic Pancreas Function

This endpoint data will be generated from the BP data during each treatment visit:

- Average percent insulin dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully delivered by the pump

[redacted]

- Average percent dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
    - Average percent glucagon/ZP4207 dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts calculated by the BP algorithm that are successfully issued to the pump by the BP (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts calculated by the BP control algorithm that are successfully issued by the BP
    - Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully issued by the BP
- Average percent of 5-minute steps during which the BP is functioning nominally in all respects based on real-time CGM data (new CGM glucose reading captured, dose calculated, and dose issued to pumps)
- Average percent of 5-minute steps during which the BP is functioning nominally with or without a new CGM glucose reading captured (dose calculated and dose issued to pumps). If a CGM signal is not available, the dose calculated may be based on weight or historical basal rates.
- CGM reliability index, calculated as percent of possible values actually recorded by CGM
- CGM Mean Absolute Relative Difference versus time-stamped BG values from meter download
- List of technical faults associated with the BP including cause and resolution

8.2.2 Glycemic

All of following metrics will be generated from the Dexcom G4 Platinum CGM data during each treatment visit.

- Fraction of time spent within each of the following glucose ranges:
    - <50 mg/dL
    - <60 mg/dL
    - <70 mg/dL
    - 70-120 mg/dL
    - 70-140 mg/dL
    - 70-180 mg/dL
    - >180 mg/dL
    - >250 mg/dL
    - >300 mg/dL
- Number of severe hypoglycemic events (patients unable to self-treat, requiring the assistance of another person)
- Number of episodes of symptomatic hypoglycemia
- Number of carbohydrate interventions for hypoglycemia
- Total grams of carbohydrates taken for hypoglycemia
- Mean CGM glucose

[redacted]

8.2.3 Non-glycemic

- Glucagon/ZP4207 total delivery per kg of body mass
- Insulin total delivery per kg of body mass
- Number of unscheduled infusion set replacements
- Number of unscheduled CGM sensor changes

9 LABORATORY ASSESSMENTS

Descriptions of sample handling and sample processing, storage, and shipment at the site will be included in the laboratory manual.

The responsible laboratories are listed in the address list.

9.1 Safety Laboratory Assessments

Chemistry and hematology samples will be collected at specified time points. See Appendix A for the schedule of procedures and Appendix B for a list of clinical laboratory analytes.

9.2 Pharmacodynamic Assessments (Plasma Glucose)

At Visit 3 and Visit 4, plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.

9.3 Exposure Assessments (ZP4207 and Glucagon)

At Visit 3 and Visit 4, ZP4207/glucagon exposure sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator. The actual time of sampling will be recorded in the eCRF.

Bioanalytical Reports will be prepared.

9.4 Anti-drug Antibody Assessments

Blood samples (including back-up samples) for serum anti-ZP4207 and anti-glucagon antibodies will be taken at Visit 3 and the Follow-up Visit 6.

A Bioanalytical Report will be prepared.

10 SAFETY REPORTING

10.1 Adverse Events

An AE is any untoward medical occurrence in a trial patient administered an IMP and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP. Patients should be instructed to report any AE they experience to the Investigator.

[redacted]

Note: This includes events from the first trial-related activity from Visit 3.

AEs for ZP4207 include:

- A clinically significant worsening of a concomitant illness
- A clinical laboratory abnormality which is clinically significant, i.e., any abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example, change of medicine dose or more frequent follow-up due to the abnormality.
- Hypoglycemic episodes
- Injection site reactions

The following should **not** be recorded as AEs, if recorded prior to randomization (on the Screening Form or the eCRF):

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial-related activity from Visit 3.
- Pre-existing conditions found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).

For known (listed) AEs for Glucagon and Humalog, please refer to SPC for Glucagon and Humalog.

10.1.1 Follow-up of Adverse Events

All AEs that are ongoing at the end of the patient's participation in the trial will be followed-up until the event is resolved or reaches a satisfactory outcome as deemed by the Investigator. Follow-up actions for all serious adverse events (SAEs) will be performed according to appropriate clinical care practices and may depend on the nature of the event. These will be determined after internal review and/or Sponsor review. The follow-up information should only include new (updated and/or additional) information that reflects the situation at the time of the Investigator's signature.

Follow-up information on (S)AEs will be updated using the (S)AE Form. If a non-serious event becomes serious during the follow-up, the AE Form and SAE Form must be used and reporting timelines follow those of an SAE.

The Investigator must forward follow-up information on SAEs, and if previously non-serious AEs become SAEs, to the Sponsor.

10.1.2 Precautions

Normal precautions taken for a human trial will be taken during this trial. Qualified and well-trained physicians and medical staff will instruct the patients. During a patient's participation in the trial, the Investigator should ensure that adequate medical care is provided to the patient for any AEs, including clinically significant laboratory values related to the trial. The Investigator should inform the patient when medical care is needed for intercurrent illnesses of which the Investigator becomes aware.

For further information on safety precautions for ZP4207, Lilly glucagon, Lilly Humalog, and the iLet, please refer to the current version of the Investigator's Brochure (IB) for ZP4207

[redacted]

(Zealand Pharma A/S, 2015, or any updates hereof), and the SPC for Glucagon (Eli Lilly, 2012) and Humalog (Eli Lilly, 2015), respectively.

10.1.3 Assessment of Adverse Events by the Investigator

Intensity of an Adverse Event
The maximum intensity (severity) of all AEs must be assessed by the Investigator and documented. Severity should be graded when the AE outcome is known:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

A “severe” reaction does not necessarily deem the AE as “serious,” and an SAE may not be “severe” in nature.

Causality Relationship to IMP
Insulin (insulin lispro, Lilly Humalog), glucagon (glucagon for injection, Eli Lilly), and ZP4207 are all regarded as IMP.

The causality of each AE should be assessed by the Investigator according to the following classification:

- Related: Good reason and sufficient documentation to assume a causal relationship.
- Not related: No relationship to trial product can be established.

Outcome of an Adverse Event
The outcome of all AEs must be assessed by the Investigator and documented by his/her staff. The following definitions should be used:

- Recovered/resolved: The patient has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity from Visit 3.
- Recovering/resolving: The condition is improving and the patient is expected to recover from the event. This term is only applicable if the patient has completed the trial.
- Recovered/resolved with sequelae: The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment, or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- Not recovered/not resolved: The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known.
- Fatal: This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as “recovered/resolved,” “recovering/resolving,” “recovered/resolved with sequelae,” or “not recovered/not resolved.” An AE with a fatal outcome must be reported as an SAE.
- Unknown: This term is only applicable if the patient is lost to follow-up.

[redacted]

10.2 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Medically important

Medical judgement must be exercised in deciding whether an AE is believed to be "medically important." Medically important events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Suspected Unexpected Serious Adverse Reactions (SUSAR)
A SUSAR is an AE fulfilling one of the criteria of seriousness and being assessed as related to an IMP, the nature or severity of which is not consistent with the applicable reference document (e.g., ZP4207 IB or package leaflet/SPC for an approved product).

Unanticipated Adverse Device Effect (UADE)
A UADE is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

10.3 Adverse Event Reporting – Procedures for Investigators

The Principal Investigator and co-investigators will review any AEs and report any SAEs to the Sponsor as soon as possible and within 24 hours of obtaining knowledge of the event. The Principal Investigator and co-investigators will promptly report AEs to the Partner's Institutional Review Board (IRB) and to the BU IRB (unless oversight is ceded by the BU IRB to the Partners IRB), in accordance with local requirements.

Ed Damiano is the Sponsor of the Investigational Device Exception for the BP and Zealand Pharma A/S is the Sponsor of the IND for ZP4207.

Reports of AEs will be submitted to the FDA in compliance with the terms of the Code of Federal Regulations.

All events meeting the definition of an AE must be collected and reported from the first trial-related activity from Visit 3 until the end of the post-treatment follow-up period. At each contact with the site (visit or telephone, excluding safety visits, where the patient is not seeing the Investigator or staff [e.g., visits to the laboratory], the patient must be asked about AEs. All AEs, either observed by the Investigator or reported by the patient, must be recorded by the Investigator and evaluated.

The Investigator should record the diagnosis, if possible. If no diagnosis can be made, the Investigator should record each sign and symptom as individual AEs.

[redacted]

All AEs must be recorded by the Investigator. One single AE Form must be used per AE from start to resolution. For SAEs, the SAE Form must also be completed.

AE information should include the following:

- Patient identification number on all pages
- Date and time of treatment start
- Date and time of onset and date of outcome
- Date and time of Investigator's first information on the (S)AE
- Seriousness
- Severity
- Causal relationship with IMP ZP4207
- Causal relationship with IMP insulin
- Causal relationship with IMP glucagon
- Causal relationship with medical device
- Causal relationship with procedures
- Interruption or withdrawal of treatment with IMP or medical device and other measures taken
- Outcome

All AEs are coded; details are described in the trial specific Data Management Plan.

The Investigator must report initial information in writing on the SAE Form for all SAEs to the Sponsor's responsible pharmacovigilance unit (here: Lindeq) immediately (within 24 hours) after obtaining knowledge about the event.

Name: [redacted]
Company: Lindeq
Address: Lyskær 8, 2730 Herlev, Denmark
Tel: [redacted]
Fax:
Mobile:
E-mail: drugsafety@lindeq.com

In addition and meeting the same timeline, Investigators must report all SAEs to Zealand Pharma A/S by forwarding the SAE Form electronically within 24 hours of obtaining knowledge of the event to the representatives of Zealand Pharma A/S.

Names: [redacted] and [redacted]
Address: Smedeland 36, DK-2600 Glostrup, Denmark
Tel: [redacted] / [redacted]
E-mails: [redacted] / [redacted]

It is the responsibility of Lindeq to report all SUSARs that occur in this trial to the Competent Authorities and to the Investigators. It is the responsibility of the Investigators to report the SUSARs to the IRBs in accordance with the local requirements in force and the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP). The trial monitor must be informed accordingly.

It is the responsibility of Lindeq to report all serious adverse reactions on insulin lispro and glucagon for injection to the Eli Lilly Pharmacovigilance department within 5 days.

It is the responsibility of the Investigators to report all UADEs to Beta Bionics within 24 hours of the time they are detected. It is the responsibility of the Investigators to report all UADEs to the IRB in accordance with the local requirements in force and the ICH GCP. It is the responsibility of Beta Bionics to report all UADEs to the Competent Authorities.

All device deficiencies should be documented and should be reported to Beta Bionics within 24 hours. Device deficiencies are inadequacies of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

Name: [redacted]
Company: Beta Bionics, Inc.
Address: Business Innovation Center, Photonics Center, 8 Saint Mary's Street, Suite 936 Boston, Massachusetts 02215-2421, United States
Tel: [redacted]
E-mail: [redacted]

10.4 Pregnancy Reporting

Female patients must be instructed to notify the Investigator immediately if they become pregnant or if they suspect to be pregnant during the trial. The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical trial.

Male patients must be instructed to notify the Investigator immediately if their partner becomes pregnant or suspects to be pregnant. The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical trial. During an information meeting at the trial site, the patient's partner will be fully informed by a physician of her participation in capturing the outcome data, and will be asked to provide her written consent.

The Investigator must report all information on pregnancies, including AEs in the patient/patient's partner, the fetus, and newborn infant/ toddler. The pregnancy report must be forwarded to the Sponsor preferably electronically as PDF or by fax.

The Investigator must follow the pregnancy until the pregnancy outcome and the newborn infant(s) until the age of 1 month. The Investigator must collect information on the pregnancy and pregnancy complications as well as the pregnancy outcome including the health of the newborn infant(s) on the pregnancy forms.
The following must be collected:

- Initial information of the pregnancy
- Information on the outcome of the pregnancy, including the health status of the newborn infant(s) at the age of 1 month
- All AEs in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms. It must be clear in the description if the event occurs in the patient/patient's partner, the fetus, or the newborn infant.

- All SAEs in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms following the same timelines as required for other SAEs. It must be clear in the description if the event occurs in the patient/patient's partner, the fetus, or the newborn infant.

The SAEs that must be reported include abnormal outcome – such as congenital anomalies, fetal death, and termination of pregnancy (spontaneous or elective abortion), including any anomalies of the fetus observed at gross examination or during autopsy – as well as other pregnancy complications (ectopic pregnancy) fulfilling the criteria of an SAE.

10.5 Hypoglycemia

Hypoglycemia will be regarded as an AE and will be recorded and documented on an AE Form. For the purposes of AE reporting, the following definitions of hypoglycemia will be used:

- Symptomatic hypoglycemia: an event during which typical symptoms of hypoglycemia are accompanied by a BG concentration ≤70 mg/dL
- Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with a BG concentration ≤50 mg/dL
- Severe hypoglycemia: an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions

10.6 Safety Monitoring

10.6.1 Data and Safety Monitoring Board

An external DSMB will oversee the conduct of the trial, as set forth in the DSMB Charter. Additionally, the DSMB will be informed in the event of any serious and unexpected AEs. The DSMB will be informed if there are any changes to the trial protocol that could significantly impact the safety or scientific validity of the trial. A final DSMB meeting will convene after the completion of the trial.

The participation of individual patients will be discontinued if they experience:

- Seizure or unconsciousness associated with hypoglycemia and associated with participation in the trial
- Persistent nausea and vomiting thought to be related to glucagon dosing associated with participation in the trial
- Hospitalization associated with participation in the trial
- Pregnancy
- Diabetic ketoacidosis

If more than 1 patient must be withdrawn from the trial for these reasons, the trial will stop and a vote of the DSMB will be required to restart it. All AEs that are serious and unexpected but related will be reported to the DSMB within 5 working days.

Note that patients may discontinue participation at any time. Patients may be removed from the trial for other reasons, for instance, failure to comply with trial procedures or intercurrent illness that is unrelated to the BP but that precludes safe participation. Discontinuation of participation for these reasons will not contribute to a decision to discontinue the trial.

[redacted]

10.6.2 Zealand Pharma Safety Committee

The internal Zealand Pharma Safety Committee is constituted to perform ongoing safety surveillance of clinical trials within ZP4207, including this trial.

If safety signals are observed either based on reported SAEs, periodic review of laboratory parameters, planned review of all AEs reported between the safety committee meetings, or on notification of significant findings, the Safety Committee will take appropriate measures to safeguard the patients.

11 STATISTICS

11.1 Analysis Populations

The following analysis sets are defined in accordance with the ICH-E9 guidance:

The Full Analysis Set is based on the intention-to-treat principle and includes all randomized patients. In exceptional cases, patients from the Full Analysis Set may be excluded (will be decided in the database review [DBR] meeting). In such cases, the exclusion will be justified and documented. Patients will contribute to the evaluation “as randomized.”

The Per-Protocol Set includes all patients of the Full Analysis Set who completed the trial without any major protocol violations. Patients in the Per-Protocol Set will contribute to the evaluation “as treated.” This analysis will only be used if it is different than the Full Analysis Set.

The Safety Analysis Set includes all patients receiving at least 1 dose of the IMP. Patients in the Safety Analysis Set will contribute to the evaluation “as treated.”

Analyses of efficacy endpoints will be based on the Full Analysis Set (and the Per-Protocol Set if necessary). This decision will be made in the DBR meeting. The analysis of the safety endpoints will be based on the Safety Analysis Set.

Before data are released for statistical analysis, a blinded review of all data will take place to identify protocol deviations that may potentially affect the results. At this time, it will be determined if patients and/or data should be excluded from the analysis. Furthermore, outliers will be identified by data review according to ICH-E9.

Obviously erroneous data points may be excluded from the analyses or re-analyzed (e.g., serum concentrations). The decision to re-analyze or exclude data points from the statistical analysis is the joint responsibility of the Sponsor, the Principal Investigator, and the Trial Statistician.

The patients or observations to be excluded and the reason for their exclusion will be documented and signed by those responsible prior to database release. The documentation will be stored together with the remaining trial documentation. The patients and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

[redacted]

11.2 Statistical Methods

Medpace will be responsible for the statistical analysis. The statistical planning and conduct of analyses of the data from this trial will follow the principles defined in relevant ICH guidelines and Medpace's biostatistical standard operating procedures (SOPs). A general description of the statistical methods to be used is given in this section, specific details will be provided in the Statistical Analysis Plan (SAP), which will be prepared before database lock. All statistical analyses will be performed using SAS® (SAS Institute Inc., Cary, North Carolina, USA), version 9.4 or later.

11.2.1 Analysis of Safety

The following variables will be evaluated according to treatment for safety purposes:

Adverse Events
All AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Individual AEs will be presented in a listing including relationship to trial product/device, severity, and treatment period at onset. If more than 20 treatment-emergent AEs (AEs with onset after [first] dosing at Visit 3 until the Follow-up Visit 6) are registered, a summary table including number of AEs, number of patients with at least 1 AE, and percentage of exposed patients with at least 1 AE will be made by system organ class and treatment period at onset.

Local Tolerability
Local tolerability at the injection site will be summarized using descriptive statistics as appropriate.

Laboratory Safety Assessments
Laboratory assessments will be summarized. A listing of abnormal values will be provided.

Physical Examination
A frequency table will show the number and percentage of physical examination results.

Vital Signs
Vital signs will be summarized using descriptive statistics.

12-lead ECG
The Investigator's evaluations of 12-lead ECGs will be summarized and abnormal individual evaluations will be listed together with the Investigator's comments. Changes in 12-lead ECG between measurements will be recorded as AEs if the Investigator judges them to be clinically significant.

11.2.2 Analysis of Efficacy

The analysis of BP function endpoints and glycemic endpoints will be on an intention-to-treat basis. In cases where a treatment arm was not completed (and that arm was not repeated according to protocol criteria), available data from that arm will be used in the data analysis.

The Shapiro-Wilk test will be used to determine the normality of the residuals for each comparison. Summary tables that display descriptive statistics, including percentages, means or medians, and standard deviation and/or ranges, as appropriate, will be provided.

[redacted]

A paired t-test or the Wilcoxon signed rank test for comparison of means with normally or non-normally distributed residuals, respectively, will be used. In a secondary analysis, any period effect and any interaction between treatment and period will be looked for, although no such interaction is predicted for the efficacy outcome. Further details will be included in the SAP.

The number of patients and proportions of severe hypoglycemic events, symptomatic hypoglycemia, and carbohydrate interventions due to hypoglycemia with the event counts will be summarized descriptively, and the proportions will be analyzed by a Fisher's exact test if data allow.

11.2.3 Interim Analysis

No interim analysis is planned.

11.2.4 Sample Size Determination

No formal sample size calculations were made. It is expected that between 10 and 12 patients will be randomized in the trial. The sample size is based on a clinical rather than statistical rationale. The sample size is considered adequate to address the primary trial objective of exploring the safety of ZP4207 when used in the iLet and with reference to Lilly glucagon used in the iLet.

12 DATA MANAGEMENT AND RECORD KEEPING

Data Management is the responsibility of Medpace. The complete Data Management process will be described in detail and agreed on in the Data Management Plan for this trial.

12.1 Data Handling

Case Report Forms
Electronic Case Report Forms will be used in this trial. The Data Management Department of Medpace will provide the eCRFs. All further information regarding the eCRFs and the data flow will be described and agreed on in the Data Management Plan.

Device-Related Data
During the trial, CGM data, calibration data, insulin dosing data, and glucagon dosing data will be automatically stored in the BP device (from which it will be downloaded at intervals), combined in a single database that will be compared against the primary data files for integrity, and ultimately transferred to Medpace.

12.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

12.3 Data Entry

Data must be recorded using the electronic data capture (EDC) system as the trial is in progress. The patient questionnaires will be transcribed into the EDC system by site personnel. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct trial data. These procedures must comply with

[redacted]

Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

12.4 Medical Information Coding

Adverse events and medical history will be coded using the latest version of MedDRA. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary.

12.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

12.6 Record Keeping

Medpace will be responsible for hosting the TMF. Records of patients, source documents, monitoring visit logs, eCRFs, inventory of trial product, regulatory documents, and other Sponsor correspondence pertaining to the trial must be kept in the appropriate trial files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the evaluation and reconstruction of the clinical trial. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Trial Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

13 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

13.1 Ethical Conduct of the Trial

The trial will be conducted according to Medpace, MGH, and/or the Sponsor's written instructions (SOPs, working instructions, or process descriptions). Content and definitions of the written instructions are based on the Declaration of Helsinki and the ICH GCP.

13.2 Institutional Review Board

Written favorable opinion must be obtained from the responsible IRB prior to commencement of the trial. Clinical trial submission and reporting requirements before, during, and after completion of the trial will be performed in accordance with national law and local regulations.

All amendments that affect patient safety or the trial integrity (substantial amendments) must not be implemented before favorable opinion has been obtained, unless necessary to eliminate hazards to the patients. Non-substantial amendments do not require favorable opinion by the IRB, but the respective IRB will be notified according to local requirements.

The Sponsor and Investigator must approve any amendment in writing before its implementation.

[redacted]

The Sponsor must maintain an accurate and complete record of all submissions made to the IRB. The records should be filed in the Sponsor's Trial Master File (TMF).

13.3 Informed Consent

In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirement(s) and adhere to the ICH GCP guideline and the requirements in the Declaration of Helsinki.

Prior to any trial-related activity, the Investigator must give the patient oral and written information in a form that the patient can read and understand about all aspects of the trial that are relevant to the patient's decision to participate. The patient will be given ample time to decide whether or not to participate in the trial.

The patient must be informed that his/her personal trial-related data will be used in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by authorized monitors or Clinical Quality Assurance auditors appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

A voluntary, personally signed and dated ICF must be obtained from the patient prior to any trial-related activity. The ICF must also be signed and dated by the physician or designee who conducted the informed consent procedure. A signed copy of the ICF and any additional patient information must be given to each patient.

The responsibility for taking informed consent must remain with that of a research physician or designee. If information becomes available that may be relevant to the patient's willingness to continue participating in the trial, the Investigator must inform the patient in a timely manner, and a revised written informed consent must be obtained.

Should a protocol amendment become necessary, the ICF may need to be revised to reflect the changes to the protocol. It is the responsibility of the Sponsor to ensure that an amended consent form is reviewed and has received favorable opinion from IRB, and the Investigator must ensure that the amended consent form is signed by all patients subsequently entered into the trial and those currently in the trial, if affected by the amendment.

13.4 Trial Monitoring Requirements

The monitoring procedures for this trial are described in detail in the Monitoring Manual. The objectives of the monitoring procedures are to ensure that (i) the safety and rights of the trial patients are respected, (ii) that accurate, valid, and complete data are collected, and (iii) that the trial is conducted in accordance with the trial protocol, the principles of GCP, and local legislation, including drug accountability.

The monitor must be given direct access to the investigational site files and source documents (original documents, data, and records). Direct access includes permission to examine, analyze, verify, and reproduce any record(s) and report(s) that are important to evaluation of the clinical trial.

[redacted]

Key tasks of the monitor include verifying the presence of informed consent, the adherence to the inclusion/exclusion criteria, the documentation of SAEs, and the recording of all safety and efficacy variables. The monitor will also confirm the completeness of patient records, the adherence to the protocol, ICH GCP, and the progress in patient enrollment and perform drug accountability.

Because no information that could reveal the identity of patients may ever be removed from the trial site, the monitor will visit the site at regular intervals to perform these monitoring tasks. Other contact between the Investigator and monitors will be maintained as required through telephone calls and e-mail. The Investigator and/or key members of staff involved in the trial must be available to assist the monitors during all visits.

Site Initiation Visit
During the Site Initiation Visit (SIV) the CRO, Sponsor, and/or monitors will go through information on the IMP, the protocol, the eCRFs, and other key aspects of the trial with the Investigator and the key members of staff involved in the trial. The topics of the SIV are documented in a SIV report made available to the Investigator. Documentation on the SIV (e.g., power point presentation) should be filed by both Investigator and Sponsor.

13.5 Disclosure of Data

Data generated by this trial must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the trial is confidential and disclosure to third parties other than those noted above is prohibited.

13.6 Retention of Records

Massachusetts General Hospital will maintain the patient's medical file according to local regulations. MGH will archive the documentation pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. MGH should not destroy any documents without prior permission from the Sponsor.

The documentation includes all the raw data generated during the clinical trial, the investigational site files, and a copy of the clinical trial report. The documents will be retained for a period of at least 15 years at archives by MGH, or its sub-contractor. After this period, the Sponsor will be contacted and their advice sought on the return or further retention of the trial records.

The Sponsor will maintain the documentation pertaining to the trial in accordance with national regulations.

13.7 Publication Policy

The Principal Investigator of the trial will review and sign the clinical trial report. A summary of the final clinical trial report will be submitted to the IRB and Competent Authority.

[redacted]

According to the Declaration of Helsinki Investigators and Sponsors "have ethical obligations with regard to the publication and dissemination of the results of research." The trial design and results may be published as one or more original research manuscripts/abstracts and presented at a scientific meeting. The Investigator and Sponsor reserve the right to review any proposed presentation of the results of this trial before they are submitted for publication. Authorship on any publication(s) resulting from this clinical trial will be assigned according to the recommendations of the International Committee of Medicinal Journal Editors.

Participating patients will not be identified by name in any published reports about the clinical trial.
The Sponsor is responsible for trial registration at ClinicalTrials.gov (www.clinicaltrials.gov) according to the requirements from the FDA.

13.8 Legal Aspects

An implicit or explicit approval must be obtained from the Competent Authority prior to commencement of the trial. Clinical trial submission and reporting requirements before, during, and after completion of the trial will be performed in accordance with national law and local regulations.

An implicit or explicit approval will also be mandatory before implementation of substantial changes. Non-substantial amendments do not require approval from the Competent Authority but will be notified according to local requirements.

The Sponsor and Investigator must approve the amendment in writing before its implementation.

The Sponsor must maintain an accurate and complete record of all submissions made to the Competent Authority. The records should be filed in the Sponsor's TMF.

Audits and Inspections
In the event of an audit, representatives of the Sponsor or designee, or national and international regulatory authorities may request access to all trial records for inspection and copying. Such access must be stated in the ICF signed by the patient.

13.9 Sponsor Discontinuation Criteria

The Sponsor, Investigator, or a pertinent regulatory authority may decide to stop the trial or part of the trial at any time but agreement on procedures to be followed must be obtained.
Conditions that may warrant termination of the clinical trial include, but are not limited to:

- Safety or administrative reasons
- The discovery of an unexpected, relevant, or unacceptable risk to the patients enrolled in the clinical trial
- A decision of the Sponsor to suspend or discontinue investigation of the IMP

If the trial is prematurely terminated or suspended, the Investigator should promptly inform the patients and assure appropriate therapy and follow-up. Furthermore, the Sponsor should promptly inform the IRB and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

[redacted]

If after the termination of the trial the risk/benefit analysis has changed, the new evaluation should be provided to the IRB in case it will have an impact on the planned follow-up of the patients who have participated in the trial. Necessary actions needed to protect the patients should be described.

13.10 Patient Compensation

Financial compensation will be provided to all patients who complete the Screening Visit. Patients will be paid $25 for completing the Screening Visit whether or not they are eligible to participate in the trial. Patients will be compensated $25 for completing the Training Visit. Patients will be compensated $100 for completing each of the 2 treatment visits, $25 for completing the phone call, and $25 for completing the Follow-up Visit. Thus, the total compensation for a patient who completes the trial would be $300. Patients who are unable to complete the trial or choose to stop participation will receive prorated compensation for each visit. In addition to the monetary compensation, the cost of the patients' lunch meals during their participation in the trial, as well as the patients' parking at each visit, will be covered by trial funds.

14 TRIAL ADMINISTRATIVE INFORMATION

14.1 Protocol Amendments

Any amendments to the trial protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

14.2 Address List

14.2.1 Sponsor

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14.2.2 Supplier of Device

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14.2.3 Principal Investigator (Site)

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14.2.5 Medical Monitoring

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14.2.6 Pharmacovigilance

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14.2.7 Central Laboratory (Safety Laboratory and Plasma Glucose)

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14.2.8 Special Laboratory (ZP4207 Exposure and ADA Analyses)

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[redacted]
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14.2.9 Special Laboratory (Glucagon Exposure)

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Germany
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Facsimile: [redacted]

15 REFERENCES

1. Russell SJ, El-Khatib FH, Sinha M, et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. N Engl J Med. 2014;371(4):313-325.
2. Russell SJ, Hillard MA, Balliro C, et al. Day and night glycemic control with a bionic pancreas versus conventional insulin pump therapy in preadolescent children with type 1 diabetes: a randomized crossover trial. Lancet Diabetes Endocrinol. 2016;4(3):233-243.
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7. Summary of Product Characteristics. Glucagon for Injection. Indianapolis, IN, USA; Eli Lilly and Company:2012.
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9. ICH Harmonised Tripartite Guideline. Statistical Principles for Clinical Trials E9. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf. 5 February 1998.
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[redacted]

Clinical Trial Protocol
ZP4207-16051

Version number: 3.0
Amendment 2.0
Date: 03 August 2016

APPENDIX A: SCHEDULE OF PROCEDURES

Trial Visit	Visit 1 [1] Screening	Visit 2 Training	Visit 3 [2] [3] [4] [5] (1st Treatment Visit)	Visit 4 [2] [3] [5] (2nd Treatment Visit)	Visit 5 Phone Call [6]	Visit 6 Follow-Up [7]
Informed consent	X					
Assess/confirm eligibility	X	X				
Demographics	X					
Medical, surgical, and social history; allergies	X					
Concomitant illness	X					
Concomitant medications	X	X	X	X	X	X
Height, weight, physical examination, and vital signs including body temperature and blood pressure [8]	X		X [9]	X [9]		
12-lead ECG	X		X [10]	X [10]		
Urine HCG pregnancy test and menstrual history [11]	X		X	X		
FSH [12]	X					
Screening labs – HbA1c, optional fractionated metanephrines [13]	X					
Safety lab sampling including chemistry and hematology	X		X [10]	X [10]		X
Training on devices [14]		X				
Monitored BP use			X	X		
Plasma glucose sampling [15]			X	X		
ZP4207/glucagon exposure sampling [16]			X	X		
Nausea and infusion site pain VAS and infusion site reaction Draize scale (visit start [17], hourly, & visit end)			X	X		

[redacted]

Clinical Trial Protocol
ZP4207-16051

Version number: 3.0
Amendment 2.0
Date: 03 August 2016

Trial Visit	Visit 1 [1] Screening	Visit 2 Training	Visit 3 [2] [3] [4] [5] (1st Treatment Visit)	Visit 4 [2] [3] [5] (2nd Treatment Visit)	Visit 5 Phone Call [6]	Visit 6 Follow-Up [7]
Standardized lunch [18]			X	X		
In-clinic exercise [19]			X	X		
Questionnaires (pre & post BP)			X	X		
ADA			X [20]			X
Adverse event review			X	X	X	X

1. Once the patient has been enrolled and eligibility has been established, the order of the iLet visits will be randomized in blocks of 2 patients.
2. Each patient will participate in 2 treatment visits: one with the iLet using ZP4207 and one with the iLet using Lilly glucagon in a randomized order. Up to 2 patients may participate in the trial per day.
3. The night before the visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12 00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window. If BG is <50 mg/dL, treatment with simple carbohydrate is allowed. If the patient experiences persistent hypoglycemia, the visit will be rescheduled within the visit window.
4. Visit 3 will take place at least 48 hours after screening (Visit 1) and no more than 30 days after screening (Visit 1).
5. There will be a 24-hour minimum washout between Visit 3 and Visit 4 and a maximum of 3 weeks between Visit 3 and Visit 4.
6. Visit 5 will take place 7 days ±3 days from Visit 4.
7. Visit 6 will take place 25 days ±4 days from Visit 4.
8. Height and physical examination will be measured at Visit 1 only.
9. Vital signs including body temperature and blood pressure will be obtained at visit start and visit end.
10. At visit start and visit end.
11. Urine HCG pregnancy test only for women of childbearing potential. The date of the last menstrual period in female patients will be obtained at Visit 1 only.
12. Test for FSH level only for postmenopausal women amenorrheic for less than 1 year.
13. If indicated by history.
14. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor, diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits, and trial policies and procedures.
15. Collected at least hourly. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
16. Collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.
17. Once the infusion sites have been placed but no drug has yet been administered.
18. Between approximately Hour 3 and Hour 4.
19. Between approximately Hour 6 and Hour 7.
20. Before the start of dosing.

ADA = anti-drug antibodies; BG = blood glucose; BP = bionic pancreas; CGM = continuous glucose monitor; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HCG = human chorionic gonadotropin; VAS = visual analog scale.

[redacted]

Clinical Trial Protocol
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Date: 03 August 2016

APPENDIX B: CLINICAL LABORATORY ANALYTES

Chemistry

Alanine aminotransferase	Aspartate aminotransferase
Alkaline phosphatase	Total protein
Albumin	Total and direct bilirubin
Gamma-glutamyl transferase	Glucose
Creatinine	Estimated glomerular filtration rate
Blood urea nitrogen	Uric acid
Bicarbonate	Sodium
Potassium	Calcium
Chloride	Phosphorus

Hematology

Hemoglobin	Hematocrit
Red blood cell count	White blood cell count and differential
Platelets	Mean corpuscular volume
Mean corpuscular hemoglobin	Mean corpuscular hemoglobin concentration

Pregnancy Test
A urine HCG pregnancy test will be performed at screening, Visit 3, and Visit 4 only for women of childbearing potential.

Anti-drug Antibody Assessments
Blood samples (including back-up samples) for serum anti-ZP4207 and anti-glucagon antibodies will be taken prior to first dosing (Visit 3) and at the Follow-up Visit (Visit 6).

ZP4207/Glucagon Exposure Sampling
At Visit 3 and Visit 4, ZP4207/glucagon exposure sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.

Screening Visit Only
Test for FSH level only for postmenopausal women amenorrheic for less than 1 year
Optional fractionated plasma metanephrines (if indicated by history)
Hemoglobin A1c

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Date: 03 August 2016

APPENDIX C: BRIEF DESCRIPTION OF QUESTIONNAIRES

Diabetes Treatment Satisfaction Questionnaire - Status (DTSQs)
The DTSQs measures patient satisfaction with diabetes treatment. It consists of a 6 item scale for assessing treatment satisfaction and two additional items assessing perceived frequency of hyperglycemia and hypoglycemia. The DTSQs is meant for adults and older children. Dr. Clare Bradley has produced a version that is appropriate for bionic pancreas studies for this use, along with a version for younger children. It is administered before the intervention. The DTSQs is valid and reliable. Administration time is less than 5 minutes.

Diabetes Treatment Satisfaction Questionnaire – Change (DTSQc)
Although the DTSQ is responsive to treatment changes, ceiling effects are often seen with this instrument, where maximum or close-to-maximum scores at baseline provide little opportunity for registering improvement. The DTSQc contains the same items as the DTSQs version but asks patients to consider their satisfaction with their current treatment compared with their previous treatment. The DTSQc is meant for adults and older children. Dr. Clare Bradley has produced a version that is appropriate for bionic pancreas studies for our use, along with a version for younger children. It is administered during and at the end of the intervention. The DTSQc is valid and reliable. Administration time is less than 5 minutes.

T1-Diabetes Distress Scale (T1-DDS)
The T1-DDS is a 28-item survey that assesses seven sources of diabetes distress for type 1 adults. It captures feelings of powerlessness; management distress; hypoglycemia distress; negative social perceptions by others; eating distress; physician (health care) distress; and friend/family distress. Items are scored on a 6-point scale from not a problem to a very serious problem. It is administered before, during, and at the end of the intervention. The scale is valid and reliable, and has been shown to be sensitive to change over time. Administration time is 5 minutes.

Problem Areas in Diabetes Survey (PAID)
There are three versions of the PAID: Teen (PAID-T), Parent (PAID-P), and Child (PAID-C) versions. This measure of diabetes-specific emotional distress in youth with diabetes and their parents is 26 items. A total score is generated. It is administered before, during, and at the end of the intervention. The PAID-T and PAID-P are valid and reliable. Psychometric analysis of the PAID-C is in progress. Administration time is 5 minutes.

Hypoglycemia Fear Survey (HFS)
There are three versions of the HFS, Adult (HFS), Youth (HFS-Y) and Parent (HFS-P). The HFS measures several dimensions of fear of hypoglycemia among adults with type 1 diabetes. It consists of 23 items and produces two sub-scale scores; a Behavior sub-scale that measures behaviors involved in avoidance and/or over-treatment of hypoglycemia and a Worry sub-scale that measures anxiety and fear surrounding hypoglycemia. The HFS-Y consists of 25 items and the HFS-P consists of 26 items; both produce sub-scale scores similar to the Adult HFS. It is administered before, during, and at the end of the intervention. All versions of the HFS are valid and reliable. Administration time is 5-10 minutes.

[redacted]

Impact of Daily Diabetes Demands (IDDD)
There are four versions of the IDDD; Adult (IDDD-A), Youth (IDDD-Y), Parent (IDDD-P), and Significant Other (IDDD-SO). This instrument measures the burden related to the demands of the daily diabetes regimen and is 22 items. A total score is generated. It is administered before, during, and at the end of the intervention. Psychometric analysis of the IDDD-Y is in progress using the data from the second Bionic Pancreas Camp Study in pre-adolescent children, and of the IDDD-A is in progress using data from the Bionic Pancreas Multicenter Study in adults. Administration time is 5 minutes.

Bionic Pancreas User Opinion Survey (BPUOS)
There are four versions of the BPUOS; Adult (BPUOS-A), Youth (BPUOS-Y), Parent (BPUOS-P), and Significant Other (BPUOS-SO). This measure assessing both the benefits from, and difficulties with, use of the bionic pancreas, and consists of 38 items. A total score is generated. It is administered during and at the end of the intervention. Psychometric analysis of the BPUOS-Y is in progress using the data from the second Bionic Pancreas Camp Study in pre-adolescent children, and of the BPUOS -A is in progress using data from the Bionic Pancreas Multicenter Study in adults. Administration time is 10 minutes.

[redacted]

SUMMARY OF CHANGES DOCUMENT

PROTOCOL NUMBER ZP4207-16051

AMENDMENT NUMBER 1.0

PROTOCOL TITLE: The iLet Feasibility Trial Testing the iLet, a Fully Integrated Bihormonal Bionic Pancreas with ZP4207

AMENDMENT DATE: 28 June 2016

SUMMARY AND JUSTIFICATION OF CHANGES:

This amendment was developed to include additional safety language and measures and to improve clarity and consistency within the study protocol. The main additions include the maximum blood volume drawn per study visit and for the entire study; blood glucose (BG) checks every 30 minutes if blood glucose is <150 mg/dL; the discontinuation of patients from the trial who experience diabetic ketoacidosis; and blood ketones measurement if the BG remains >300 mg/dL for 2 hours despite troubleshooting. If the blood ketone result is >1.5 mmol/L, the visit will be stopped and rescheduled. The patient will be provided with insulin and a syringe to give an injection based on their correction factor. Blood pressure will be measured at screening as well as Visit 3 and Visit 4. The timing around visit windows was updated, and other minor edits were made throughout the protocol to provide greatly clarity and consistency. The schedule of procedures was updated to reflect the changes specified in this document.

SUMMARY OF CHANGES:

The amended protocol sections and the details of the changes are summarized in the following sections. Revisions to the protocol are presented as strikethrough (ie, ~~subject~~) for text that was removed and bold (ie, **subject**) for text that was added.

Synopsis, Population, Page 4

Original Text:

Up to 20 adult (≥18 years of age) patients who already manage their T1DM using continuous subcutaneous (SC) insulin infusion pump therapy can be enrolled.

New Text:

Up to 20 adult (≥18 years of age) patients who already manage their T1DM using continuous subcutaneous (SC) insulin infusion pump therapy can be enrolled. **It is expected that up to 10 patients will complete the trial protocol**.

Section 3.3, Number of Patients, Page 22

Original Text:

Up to 20 adult patients with T1DM can be enrolled. The upper bound is based on the expectation that some patients will be excluded after the Screening Visit and the possibility that some patients may have to be discontinued before completion (due to, for instance, inter-current illness or patient withdrawal). Eligible patients will be randomized until 10 patients have completed the trial protocol. It is expected that between 10 and 12 patients will be randomized.

New Text:

Up to 20 adult patients with T1DM can be enrolled. The upper bound is based on the expectation that some patients will be excluded after the Screening Visit and the possibility that some patients may have to be discontinued before completion (due to, for instance, inter-current illness or patient withdrawal). ~~Eligible patients will be randomized until~~ **It is expected that up to** 10 patients ~~have completed~~ **will complete** the trial protocol.~~ It is expected that between 10 and 12 patients will be randomized.~~

Section 4.4, Withdrawal Criteria, Page 25; Section 10.6.1, Data and Safety Monitoring Board, Page 43

Original Text:

The participation of individual patients will be discontinued if they experience:

- Seizure or unconsciousness associated with hypoglycemia and associated with participation in the trial
- Persistent nausea and vomiting thought to be related to glucagon dosing associated with participation in the trial
- Hospitalization associated with participation in the trial
- Pregnancy

[redacted]

New Text:

The participation of individual patients will be discontinued if they experience:

- Seizure or unconsciousness associated with hypoglycemia and associated with participation in the trial
- Persistent nausea and vomiting thought to be related to glucagon dosing associated with participation in the trial
- Hospitalization associated with participation in the trial
- Pregnancy
- **Diabetic ketoacidosis**

Section 7.2, Screening Visit (Visit 1), Page 29

Original Text:

7.2 Screening Visit (Visit 1, up to 30 days prior to Visit 2)

New Text:

7.2 Screening Visit (Visit 1~~, up to 30 days prior to Visit 2~~)

Section 7.3, Training Visit (Visit 2), Page 30

Original Text:

7.3 Training Visit (Visit 2) (Day 1)

New Text:

7.3 Training Visit (Visit 2) ~~(Day 1)~~

Section 7.4, Treatment Visits (Visit 3 and Visit 4), Page 30

Original Text:

7.4 Treatment Visits (Visit 3 [Day 8 ±3] and Visit 4 [Day 15 ±3])

- Up to 2 patients may participate per day.
- Each patient will participate in 2 treatment visits: one with the iLet using ZP4207 and one with the iLet using Lilly glucagon in a randomized order.

New Text:

7.4 Treatment Visits (Visit 3 ~~[Day 8 ±3]~~ and Visit 4 ~~[Day 15 ±3]~~)

- **Visit 3 will take place at least 48 hours after screening (Visit 1) and no more than 30 days after screening (Visit 1).**
- **There will be a 24-hour minimum washout between Visit 3 and Visit 4 and a maximum of 3 weeks between Visit 3 and Visit 4.**
- Up to 2 patients may participate per day.
- Each patient will participate in 2 treatment visits: one with the iLet using ZP4207 and one with the iLet using Lilly glucagon in a randomized order.

[redacted]

Section 7.4.1, Visit Procedures, Page 31

Original Text:

- Upon arrival to the visit, the patient's weight and vital signs including body temperature will be documented.
- Patient reports of symptoms, any other complaints, and AEs will be reviewed.

New Text:

- Upon arrival to the visit, the patient's weight and vital signs including body temperature **and blood pressure** will be documented.
- Patient reports of symptoms, any other complaints, and AEs will be reviewed.

Section 7.4.1, Visit Procedures, Page 32

Original Text:

- Blood samples will be taken from the IV at least hourly and processed for plasma ZP4207/glucagon. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.
- Plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.

New Text:

- Blood samples will be taken from the IV at least hourly and processed for plasma ZP4207/glucagon. If BG is ~~<100~~**<150** mg/dL, ~~then sampling will~~ **more frequent samples for plasma ZP4207/glucagon may be** ~~every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes~~ **drawn at the discretion of the Investigator.** The actual time of sampling will be recorded in the eCRF.
- Plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. **If BG is <150 mg/dL, then sampling will be every 30 minutes.** If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.

Section 7.4.1, Visit Procedures, Page 33

Original Text:

- Patients may choose to withdraw from the trial at any time. If they withdraw from the trial, they should alert a provider immediately.
- Just prior to the end of the study visit, vital signs including body temperature will be obtained and a 12-lead ECG will be performed.
- After approximately Hour 8, but not earlier than at least 60 minutes after end of exercise, the BP will be stopped and the patient will continue with their personal insulin pump.
- Patients will answer questionnaires (see Appendix C).

New Text:

- Patients may choose to withdraw from the trial at any time. If they withdraw from the trial, they should alert a provider immediately.
- Just prior to the end of the study visit, vital signs including body temperature **and blood pressure** will be obtained and a 12-lead ECG will be performed.
- After approximately Hour 8, but not earlier than at least 60 minutes after end of exercise, the BP will be stopped and the patient will continue with their personal insulin pump.
- **The maximum amount of blood loss per study visit will be approximately 230 mL. The total blood loss for the entire study will be up to 460 mL.**
- Patients will answer questionnaires (see Appendix C).

Section 7.4.2, Data Collected During the Treatment Visits, Page 33-34

Original Text:

- ZP4207/glucagon sampling collected at least hourly. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
- Plasma glucose sampling will be collected at least hourly in parallel with ZP4207/glucagon exposure sampling. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.

New Text:

- ZP4207/glucagon sampling **will be** collected at least hourly. If BG is <~~100~~**150** mg/dL, ~~then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will~~ **more frequent samples for plasma ZP4207/glucagon may** be ~~every 10 minutes~~ **drawn at the discretion of the Investigator**.
- Plasma glucose sampling will be collected at least hourly in parallel with ZP4207/glucagon exposure sampling. **If BG is <150 mg/dL, then sampling will be every 30 minutes.** If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.

Section 7.4.2, Data Collected During the Treatment Visits, Page 34

Original Text:

- Patient reports of symptoms, any other complaints, and AEs
- Vital signs including body temperature (at visit start and visit end) and weight

New Text:

- Patient reports of symptoms, any other complaints, and AEs
- Vital signs including body temperature **and blood pressure** (at visit start and visit end) and weight

---

Section 7.4.4, Response to Hyperglycemia, Page 34-35

Original Text:

- Trial staff will check the infusion site, BP, and insulin pump for normal operation any time BG is >300 mg/dL. If there is any suspicion of infusion set malfunction, the site should be replaced. Trial staff will check the BP for any malfunction and correct any problems that are found.
- If no correctable fault is found, but there is doubt regarding the correct function of the BP system, the treatment visit may be stopped and the visit rescheduled.

New Text:

- Trial staff will check the infusion site, BP, and insulin pump for normal operation any time BG is >300 mg/dL. If there is any suspicion of infusion set malfunction, the site should be replaced. Trial staff will check the BP for any malfunction and correct any problems that are found. **If the BG remains >300 mg/dL for 2 hours despite troubleshooting, blood ketones will be measured. If the blood ketone result is >1.5 mmol/L, the visit will be stopped and rescheduled. The patient will be provided with insulin and a syringe to give an injection based on their correction factor.**
- **If a patient experiences diabetic ketoacidosis, his or her participation in the trial will be discontinued.**
- If no correctable fault is found, but there is doubt regarding the correct function of the BP system, the treatment visit may be stopped and the visit rescheduled.

Section 7.5, Phone Call (Visit 5), Page 35

Original Text:

7.5 Phone Call (Visit 5) (Day 22 ±3)

A phone call will be conducted 1 week following the last day of dosing (Visit 4) to review AEs and concomitant medications.

New Text:

7.5 Phone Call (Visit 5)~~ (Day 22 ±3)~~

A phone call will be conducted ~~1 week~~ **7 days ±3 days** following the last day of dosing (Visit 4) to review AEs and concomitant medications.

Section 7.6, Follow-up Visit (Visit 6), Page 35

Original Text:

7.6 Follow-up Visit (Visit 6) (Day 40 ±3)

Three to 4 weeks following the last day of dosing (Visit 4), patients will return for a Follow-up Visit for chemistry, hematology, and ADA sampling, and a review of AEs and concomitant medications.

New Text:

7.6 Follow-up Visit (Visit 6) ~~(Day 40 ±3)~~

~~Three to~~ **Patients will return for a Follow-up Visit 25 days ±**4 ~~weeks~~ **days** following the last day of dosing (Visit **4),** ~~patients will return for a Follow-up Visit 4),~~ for chemistry, hematology, and ADA sampling, and a review of AEs and concomitant medications.

Section 9.2, Pharmacodynamic Assessments (Plasma Glucose), Page 37

Original Text:

At Visit 3 and Visit 4, plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.

New Text:

At Visit 3 and Visit 4, plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. **If BG is <150 mg/dL, then sampling will be every 30 minutes.** If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.

Section 9.3, Exposure Assessments (ZP4207 and Glucagon), Page 37; Appendix B, Clinical Laboratory Analytes, Page 57

Original Text:

At Visit 3 and Visit 4, ZP4207/glucagon exposure sampling will be collected at least hourly. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.

New Text:

At Visit 3 and Visit 4, ZP4207/glucagon exposure sampling will be collected at least hourly. If BG is <~~100~~ **150** mg/dL, ~~then sampling will~~ **more frequent samples for plasma ZP4207/glucagon may** be ~~every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes~~ **drawn at the discretion of the Investigator.**

[redacted]

Appendix A, Schedule of Procedures, Page 55-56

Original Text:

APPENDIX A: SCHEDULE OF PROCEDURES

Trial Visit	Visit 1 [1] Screening	Visit 2 Training	Visit 3 [2] [3] Treatment	Visit 4 [2] [3] Treatment	Visit 5 Phone Call	Visit 6 Follow-Up
Trial Day	Up to 30 days prior to Visit 2	Day 1	Day 8 (±3 days)	Day 15 (±3 days)	Day 22 (±3 days)	Day 40 (±3 days)
Informed consent	X					
Assess/confirm eligibility	X	X				
Demographics	X					
Medical, surgical, and social history; allergies	X					
Concomitant illness	X					
Concomitant medications	X	X	X	X	X	X
Height, weight, physical examination, and vital signs including body temperature and blood pressure [4]	X		X [5]	X [5]		
12-lead ECG	X		X [6]	X [6]		
Urine HCG pregnancy test and menstrual history [7]	X		X	X		
FSH [8]	X					
Screening labs – HbA1c, optional fractionated metanephrines [9]	X					
Safety lab sampling including chemistry and hematology	X		X [6]	X [6]		X
Training on devices [10]		X				
Monitored BP use			X	X		
Plasma glucose sampling [11]			X	X		
ZP4207/glucagon exposure sampling [12]			X	X		
Nausea and infusion site pain VAS and infusion site reaction Draize scale (visit start [11], hourly, & visit end)			X	X		
Standardized lunch [13]			X	X		

Trial Visit	Visit 1 [1] Screening	Visit 2 Training	Visit 3 [2] [3] Treatment	Visit 4 [2] [3] Treatment	Visit 5 Phone Call	Visit 6 Follow-Up
Trial Day	Up to 30 days prior to Visit 2	Day 1	Day 8 (±3 days)	Day 15 (±3 days)	Day 22 (±3 days)	Day 40 (±3 days)
In-clinic exercise [14]			X	X		
Questionnaires (pre & post BP)			X	X		
ADA			X [15]			X
Adverse event review			X	X	X	X

1. Once the patient has been enrolled and eligibility has been established, the order of the iLet visits will be randomized in blocks of 2 patients.
2. Each patient will participate in 2 treatment visits: one with the iLet using ZP4207 and one with the iLet using Lilly glucagon in a randomized order. Up to 2 patients can par icipate in the trial per day.
3. The night before the visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Pa ients will arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, he visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window.
4. Height, blood pressure, and physical examination will be measured at Visit 1 only.
5. Vital signs including body temperature will be obtained at visit start and visit end.
6. At visit start and visit end.
7. Urine HCG pregnancy test only for women of childbearing poten ial. The date of the last menstrual period in female patients will be obtained at Visit 1 only.
8. Test for FSH level only for postmenopausal women amenorrheic for less than 1 year.
9. If indicated by history.
10. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor and trial policies and procedures.
11. Collected at least hourly. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
12. Once the infusion sites have been placed but no drug has yet been administered.
13. Between approximately Hour 3 and Hour 4.
14. Between approximately Hour 6 and Hour 7.
15. Before the start of dosing.

ADA = anti-drug antibodies; BG = blood glucose; BP = bionic pancreas; CGM = continuous glucose monitor; ECG = electrocardiogram; FSH = follicle-stimula ing hormone; HbA1c = hemoglobin A1c; HCG = human chorionic gonadotropin; VAS = visual analog scale.

[redacted]

New Text:

APPENDIX A: SCHEDULE OF PROCEDURES

Trial Visit	Visit 1 [1] Screening	Visit 2 Training	Visit 3 [2] [3] **[4] [5]** (1st Treatment **Visit)**	Visit 4 [2] [3] **[5]** (2nd Treatment **Visit)**	Visit 5 Phone Call **[6]**	Visit 6 Follow-Up **[7]**
~~Trial Day~~	~~Up to 30 days prior to Visit 2~~	~~Day 1~~	~~Day 8 (±3 days)~~	~~Day 15 (±3 days)~~	~~Day 22 (±3 days)~~	~~Day 40 (±3 days)~~
Informed consent	X					
Assess/confirm eligibility	X	X				
Demographics	X					
Medical, surgical, and social history; allergies	X					
Concomitant illness	X					
Concomitant medications	X	X	X	X	X	X
Height, weight, physical examination, and vital signs including body temperature and blood pressure [~~4~~**8**]	X		X [~~5~~**9**]	X [~~5~~**9**]		
12-lead ECG	X		X [~~6~~**10**]	X [~~6~~**10**]		
Urine HCG pregnancy test and menstrual history [~~7~~**11**]	X		X	X		
FSH [~~8~~**12**]	X					
Screening labs – HbA1c, optional fractionated metanephrines [~~9~~**13**]	X					
Safety lab sampling including chemistry and hematology	X		X [~~6~~**10**]	X [~~6~~**10**]		X
Training on devices [~~10~~**14**]		X				
Monitored BP use			X	X		
Plasma glucose sampling [~~11~~**15**]			X	X		
ZP4207/glucagon exposure sampling [~~12~~**16**]			X	X		
Nausea and infusion site pain VAS and infusion site reaction Draize scale (visit start [~~11~~**17**], hourly, & visit end)			X	X		

Trial Visit	Visit 1 [1] Screening	Visit 2 Training	Visit 3 [2] [3] **[4] [5]** (**1st** Treatment **Visit)**	Visit 4 [2] [3] **[5]** (**2nd** Treatment **Visit)**	Visit 5 Phone Call **[6]**	Visit 6 Follow-Up **[7]**
~~Trial Day~~	~~Up to 30 days prior to Visit 2~~	~~Day 1~~	~~Day 8 (±3 days)~~	~~Day 15 (±3 days)~~	~~Day 22 (±3 days)~~	~~Day 40 (±3 days)~~
Standardized lunch [~~13~~**18**]			X	X		
In-clinic exercise [~~14~~**19**]			X	X		
Questionnaires (pre & post BP)			X	X		
ADA			X [~~15~~**20**]			X
Adverse event review			X	X	X	X

1. Once the patient has been enrolled and eligibility has been established, the order of the iLet visits will be randomized in blocks of 2 patients.
2. Each patient will participate in 2 treatment visits: one with the iLet using ZP4207 and one with the iLet using Lilly glucagon in a randomized order. Up to 2 patients ~~can~~ **may** participate in the trial per day.
3. The night before the visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Pa ients will **be asked to** arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window.
4. **Visit 3 will take place at least 48 hours after screening (Visit 1) and no more than 30 days after screening (Visit 1).**
5. **There will be a 24-hour minimum washout between Visit 3 and Visit 4 and a maximum of 3 weeks between Visit 3 and Visit 4.**
6. **Visit 5 will take place 7 days ±3 days from Visit 4.**
7. **Visit 6 will take place 25 days ±4 days from Visit 4.**

~~4~~**8**. Height~~, blood pressure,~~ and physical examination will be measured at Visit 1 only.
~~5~~**9**. Vital signs including body temperature **and blood pressure** will be obtained at visit start and visit end.
~~6~~**10**. At visit start and visit end.
~~7~~**11**. Urine HCG pregnancy test only for women of childbearing poten ial. The date of the last menstrual period in female patients will be obtained at Visit 1 only.
~~8~~**12**. Test for FSH level only for postmenopausal women amenorrheic for less than 1 year.
~~9~~**13**. If indicated by history.
~~10~~**14**. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor and trial policies and procedures.
~~11~~**15**. Collected at least hourly. **If BG is <150 mg/dL, then sampling will be every 30 minutes.** If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
16. Collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.
~~12~~**17**. Once the infusion sites have been placed but no drug has yet been administered.
~~13~~**18**. Between approximately Hour 3 and Hour 4.
~~14~~**19**. Between approximately Hour 6 and Hour 7.
~~15~~**20**. Before the start of dosing.

ADA = anti-drug antibodies; BG = blood glucose; BP = bionic pancreas; CGM = continuous glucose monitor; ECG = electrocardiogram; FSH = follicle-stimula ing hormone; HbA1c = hemoglobin A1c; HCG = human chorionic gonadotropin; VAS = visual analog scale.

Clinical Trial Protocol
ZP4207-16051

Version number: 2.0
Amendment 1.0
Date: 28 June 2016

CLINICAL TRIAL PROTOCOL

The iLet Feasibility Trial Testing the iLet, a Fully Integrated Bihormonal Bionic Pancreas with ZP4207

Investigational Product: ZP4207
Protocol Number: ZP4207-16051
IND Number: 129980
Phase: 2

Principal Investigator:
Steven J. Russell, MD, PhD[1]

Co-Investigator:
[redacted], MD[1]

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Original Version: 03 May 2016
Amendment Number: 1.0
Protocol Version Number: 2.0
Date: 28 June 2016

Clinical Trial Protocol
ZP4207-16051

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Date: 28 June 2016

SIGNATURE PAGE

TRIAL TITLE: The iLet Feasibility Trial Testing the iLet, a Fully Integrated Bihormonal Bionic Pancreas with ZP4207

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the trial.

Signature [redacted] Date [redacted]

[redacted], MD
Vice President, Clinical Development
Zealand Pharma A/S

[redacted] [redacted]

[redacted], DVM, PhD
Principal Clinical Pharmacologist
Zealand Pharma A/S

Clinical Trial Protocol
ZP4207-16051

Version number: 2.0
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INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the trial as described. I will conduct this trial in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the trial within the time designated. I will provide copies of this protocol and access to all information furnished by Zealand Pharma A/S to trial personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the trial product and trial procedures. I will let them know that this information is confidential and proprietary to Zealand Pharma A/S and that it may not be further disclosed to third parties. I understand that the trial may be terminated or enrollment suspended at any time by Zealand Pharma A/S, with or without cause, or by me if it becomes necessary to protect the best interests of the trial patients.

I agree to conduct this trial in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and ICH Guidelines for Good Clinical Practices.

[redacted] _____ [redacted] _____

Investigator's Signature Date

[redacted] _____

Investigator's Printed Name

Clinical Trial Protocol
ZP4207-16051

Version number: 2.0
Amendment 1.0
Date: 28 June 2016

SYNOPSIS

TITLE: The iLet Feasibility Trial Testing the iLet, a Fully Integrated Bihormonal Bionic Pancreas with ZP4207

PROTOCOL NUMBER: ZP4207-16051

INVESTIGATIONAL PRODUCT: ZP4207

PHASE: 2

INDICATION: ZP4207 is an anti-hypoglycemic glucagon analog in a ready-to-use liquid formulation which is being studied to improve glycemic control in adults (and children) with type 1 diabetes mellitus (T1DM) as part of a bihormonal bionic pancreas (BP).

OBJECTIVES:

Primary: The primary objective is to conduct a trial testing the safety and tolerability of the iLet when used with ZP4207 in 10 adult (≥18 years of age) patients with T1DM.

Secondary: The secondary objectives are to measure glycemic regulation, including hypoglycemia exposure (percent of time spent with continuous glucose monitor [CGM] glucose <60 mg/dL), evaluate BP device reliability, and to document the satisfaction of patients with the iLet with the goal of optimizing the functionality and user interface of the iLet.

POPULATION: Up to 20 adult (≥18 years of age) patients who already manage their T1DM using continuous subcutaneous (SC) insulin infusion pump therapy can be enrolled. It is expected that up to 10 patients will complete the trial protocol.

TRIAL DESIGN: This trial is a single-center, open-label, randomized cross-over trial. The trial will enroll adult patients with T1DM and will assess the safety and efficacy of the iLet using the glucagon analog ZP4207 versus the iLet using Lilly glucagon. The iLet will also administer insulin (insulin lispro, Lilly Humalog) using the same blood glucose (BG) control algorithm for both treatment arms. The trial will be conducted at a single center, the Massachusetts General Hospital Diabetes Center in Boston, MA.

TRIAL TREATMENT: The trial involves SC administration of insulin lispro (Humalog, Lilly), which is commercially available by prescription and is indicated for patients with T1DM, but not for use in a BP.

The trial also involves SC administration of Lilly glucagon in one iLet arm. Lilly glucagon is commercially available by prescription and is indicated for patients with T1DM in severe hypoglycemia, but not for use in a BP.

The trial also involves SC administration of the glucagon analog ZP4207, 1 mg/mL, in the other iLet arm. ZP4207 will be made available by Zealand Pharma A/S, Denmark as liquid formulation in prefilled syringes of 0.6 mL.

PRIMARY ENDPOINT:
The primary endpoint is the safety and tolerability of ZP4207 and the iLet as assessed by:

- Number and type of adverse events (AEs)
- Clinical laboratory measurements
- Vital signs
- 12-lead electrocardiogram (ECG)
- Local tolerability and infusion site reactions as measured with the Draize scale
- Immunogenicity as measured by anti-drug antibodies
- Pain as measured on a 10 cm visual analog scale (VAS)
- Nausea as measured on a 10 cm VAS

SECONDARY ENDPOINTS:
The secondary endpoints for the iLet and ZP4207 include measurements of BP function as well as glycemic and non-glycemic measurements.

Bionic Pancreas Function
This endpoint data will be generated from the BP data during each treatment visit:

- Average percent insulin dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
    - Average percent glucagon/ZP4207 dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts calculated by the BP algorithm that are successfully issued to the pump by the BP (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts calculated by the BP control algorithm that are successfully issued by the BP
    - Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully issued by the BP
- Average percent of 5-minute steps during which the BP is functioning nominally in all respects based on real-time CGM data (new CGM glucose reading captured, dose calculated, and dose issued to pumps)
- Average percent of 5-minute steps during which the BP is functioning nominally with or without a new CGM glucose reading captured (dose calculated and dose issued to pumps). If a CGM signal is not available, the dose calculated may be based on weight or historical basal rates.
- CGM reliability index, calculated as percent of possible values actually recorded by CGM
- CGM Mean Absolute Relative Difference versus time-stamped BG values from meter download
- List of technical faults associated with the BP including cause and resolution

[redacted]

Glycemic
All of following metrics will be generated from the Dexcom G4 Platinum CGM data during each treatment visit.

- Fraction of time spent within each of the following glucose ranges:
  - <50 mg/dL
  - <60 mg/dL
  - <70 mg/dL
  - 70-120 mg/dL
  - 70-140 mg/dL
  - 70-180 mg/dL
  - >180 mg/dL
  - >250 mg/dL
  - >300 mg/dL
- Number of severe hypoglycemic events (patients unable to self-treat, requiring the assistance of another person)
- Number of episodes of symptomatic hypoglycemia
- Number of carbohydrate interventions for hypoglycemia
- Total grams of carbohydrates taken for hypoglycemia
- Mean CGM glucose

Non-glycemic

- Glucagon/ZP4207 total delivery per kg of body mass
- Insulin total delivery per kg of body mass
- Number of unscheduled infusion set replacements
- Number of unscheduled CGM sensor changes

EVALUATION OF TRIAL DATA: The following variables will be evaluated according to treatment for safety purposes: AEs, local tolerability, laboratory safety assessments, physical examination, vital signs, and 12-lead ECGs.

The analysis of BP function endpoints and glycemic endpoints will be on an intention-to-treat basis. In cases where a treatment arm was not completed (and that arm was not repeated according to protocol criteria), available data from that arm will be used in the data analysis.

The Shapiro-Wilk test will be used to determine the normality of the residuals for each comparison. Summary tables that display descriptive statistics, including percentages, means or medians, and standard deviation and/or ranges, as appropriate, will be provided.

A paired t-test or the Wilcoxon signed rank test for comparison of means with normally or non-normally distributed residuals, respectively, will be used. In a secondary analysis any period effect and any interaction between treatment and period will be looked for, although no such interaction is predicted for the efficacy outcome.

The number of patients and proportions of severe hypoglycemic events, symptomatic hypoglycemia, and carbohydrate interventions due to hypoglycemia with the event counts will be summarized descriptively, and the proportions will be analyzed by a Fisher's exact test if data allow.

[redacted]

Clinical Trial Protocol
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LIST OF FIGURES

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibodies
AE	Adverse event
BG	Blood glucose
BP	Bionic pancreas
BU	Boston University
CFR	Code of Federal Regulations
CGM	Continuous glucose monitor
CRO	Contract research organization
DBR	Database review
DPP-4	Dipeptidyl peptidase-4
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FDA	Food and Drug Administration
FHD	First Human Dose
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HCG	Human chorionic gonadotropin
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IM	Intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
MD	Doctor of Medicine
MedDRA	Medical Dictionary for Regulatory Activities
MGH	Massachusetts General Hospital
MPC	Model-predictive control
PD	Pharmacodynamic
PK	Pharmacokinetic

[redacted]

Abbreviation	Definition
RN	Registered nurse
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SGLT-2	Sodium-glucose co-transporter-2
SIV	Site Initiation Visit
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 diabetes mellitus
TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
ULN	Upper limit of normal
VAS	Visual analog scale

[redacted]

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Background and Rationale

To date, clinical trials conducted by Boston University (BU) and Massachusetts General Hospital (MGH) in patients with type 1 diabetes mellitus (T1DM) have demonstrated the practicality of a wearable automated bionic pancreas (BP) control system for robust glucose regulation using a continuous glucose monitor (CGM) to provide the input to the control system. Despite current technical limitations in CGMs and infusion pumps, the trials by BU/MGH have shown that a bihormonal BP is capable of achieving safe and effective blood glucose (BG) control automatically, with minimal hypoglycemia during 11 continuous days in the face of unrestrained meals and exercise and with trivial patient input (optional announcement of meals).

The BP provides automatic BG regulation and reduces hypoglycemic episodes. Additionally, the system spares the wearer the relentless tasks of carbohydrate counting, frequent BG monitoring, estimating the effects of specific meals and exercise activity on BG levels, and manual drug administration, which are inexact, demanding, aggravating, and require continuous diligence and vigilance. The degree of glycemic control achieved by the BP is predicted to dramatically reduce the deleterious and debilitating complications of T1DM.

In its last tested embodiment, the BP consisted of a Dexcom G4 CGM, and an iPhone that are hardwired together, with the iPhone running the control algorithm and communicating via Bluetooth with 2 Tandem t:slim pumps to dose insulin and glucagon. The connections are repeatedly lost among these 4 components throughout the day, an issue that has the potential to adversely impact BG control, whether due to missed CGM values or missed doses. In addition, the troubleshooting required to repair these recurring disconnections can be burdensome to the user. Integrating these components into a single device would establish seamless connectivity among them, which would eliminate the need for such troubleshooting. This would lead to a smoother device operation with fewer interruptions, which would enhance its user friendliness, optimize its BG control potential, and further improve the quality of life of its users.

The BU Investigators have recently designed, built, and tested a proprietary first-generation of such a fully integrated BP system, referred to as the iLet and the iLet infusion set. The iLet is a dual-chamber infusion system that currently incorporates the Dexcom G4 CGM technology, a custom user interface with touchscreen display, and all of the mathematical dosing algorithms that were tested in and validated using the iPhone-based BP in outpatient studies over the past 3 years. The iLet infusion set provides 2 independent subcutaneous (SC) fluid pathways from the iLet to the patient (1 for insulin and the other for glucagon). One tube connects to the prefilled insulin cartridge and the other tube connects to the fillable (single-use) glucagon cartridge.

In order to provide automatic BG regulation, the iLet has the ability to deliver both insulin and glucagon. However, currently available glucagon formulations have limited stability at room temperature, necessitating frequent changes to the glucagon infusion set. Therefore, the current trial is designed to test the glucagon analog ZP4207 in the iLet, as this peptide analog of human glucagon is provided in a liquid formulation stable at room temperature.

[redacted]

The current trial is a first feasibility trial designed to use the first-generation iLet and iLet infusion set to compare ZP4207 with marketed glucagon (Lilly). The trial is intended to demonstrate the safety and tolerability of ZP4207 in the iLet and the feasibility of achieving comparable autonomous glycemic control. It is not intended to comprehensively demonstrate the definitive efficacy of the iLet in extended, continuous daily use, but rather to demonstrate its functionality and accuracy in a practical, albeit very controlled, clinical setting. The trial is expected to provide practical information that will benefit the design of a next-generation iLet and iLet infusion set and help pave the way for a more comprehensive outpatient home-use Phase 2 trial and ultimately a pivotal trial where comprehensive safety and efficacy through continuous full daily use of the iLet with ZP4207 will be documented.

The data derived from this trial will permit evaluation of the robustness of the iLet as well as the safety and efficacy of ZP4207 when used in conjunction with the iLet. The data obtained will be used to further improve the iLet and will allow BU/MGH to expand to larger outpatient trials using the iLet with ZP4207.

1.2 Bihormonal Bionic Pancreas System

The BP is an autonomous, self-learning system that requires only the patient's weight for initialization, and then autonomously adapts, modestly or dramatically, as needed, to cope with the wide range of insulin requirements of adults, adolescents, and pre-adolescents with T1DM. The BP obviates the need for the patient to know, or even appreciate, their insulin requirements, and renders obsolete any need for patients or caregivers to know carbohydrate-to-insulin ratios, basal rates, or insulin correction factors.

The core technology is a suite of control algorithms that orchestrate the automated dosing of insulin and glucagon to regulate BG levels. An insulin controller orchestrates all SC insulin dosing. At its centerpiece is a model-predictive control (MPC) algorithm, which bases insulin doses on the glucose data and insulin absorption kinetics, compensating for the slow absorption rate of SC insulin analogs (peak time in blood of 30-90 min, clearance in 4-8 hr). This enables the algorithm to refrain from stacking and overdosing insulin. Furthermore, the MPC algorithm automatically adjusts its insulin-dosing aggressiveness continuously and in real-time to different insulin needs between individuals and variable needs within the same individual. Running in parallel with the MPC algorithm is an algorithm that automatically modulates basal insulin delivery over multiple time scales, and another algorithm that automatically adapts insulin doses in response to optional meal announcements. Unlike current insulin pumps and the insulin-only control algorithms, the adaptive basal insulin algorithm obviates the need for the user to set, or even know, his or her “basal-rate profile.” Instead, it is capable of automatically adapting to, and compensating for, changes in an individual's basal insulin need, such as might occur over a period of hours, days, or weeks (e.g., circadian hormonal fluctuations, intercurrent illness, physical activity, or emotional state) or as might occur over a period of months or years due to developmental changes (e.g., hormonal changes that occur during puberty or menopause). The adaptive meal dose controller obviates the need for the user to set, or even know, his or her “carbohydrate-to-insulin ratios,” as it makes automatic adjustments based on dosing history for similar meal announcements made on previous days, and customizes the dose for each individual and for time of day.

[redacted]

The BP also includes a proportional-derivative algorithm governing SC micro-doses of glucagon to help prevent impending hypoglycemia. Glucagon dosing is based on the glucose level and rate of descent. It may occur preemptively even if glucose is above range, and it includes a feedback term to account for the pending effects of recent glucagon doses.

Taken together, these mathematical algorithms provide a universal framework for a glycemic control strategy that requires no quantitative input from, or participation by, the user (besides entering body weight to initialize the system), but which automatically adapts insulin and glucagon dosing to meet the individual needs of each user. Another challenge met is enabling the technology to remain completely autonomous in managing insulin and glucagon delivery even when the CGM is offline. Specifically, when the CGM is offline, the BP invokes the high-resolution “basal rate profile” that it had recently learned and stored when the CGM was online. On the basis of what the system learned and stored about meal announcements when the CGM was online, it is able to respond to meal announcements in the same manner when the CGM is offline. Finally, it automatically responds to user-entered BG values when the CGM is offline by issuing a correction dose of insulin or glucagon based on what it learned about the user's insulin and glucagon needs when the CGM was online. Thus, the BP never relies on, or burdens the user with, the determination of subjective dosing decisions, which inevitably vary in quality and reliability among different users. The BP provides a turnkey solution for people with T1DM that comprehensively manages glycemia across a broad range of individual needs and across a large spectrum of circumstances and challenges to glycemic control.

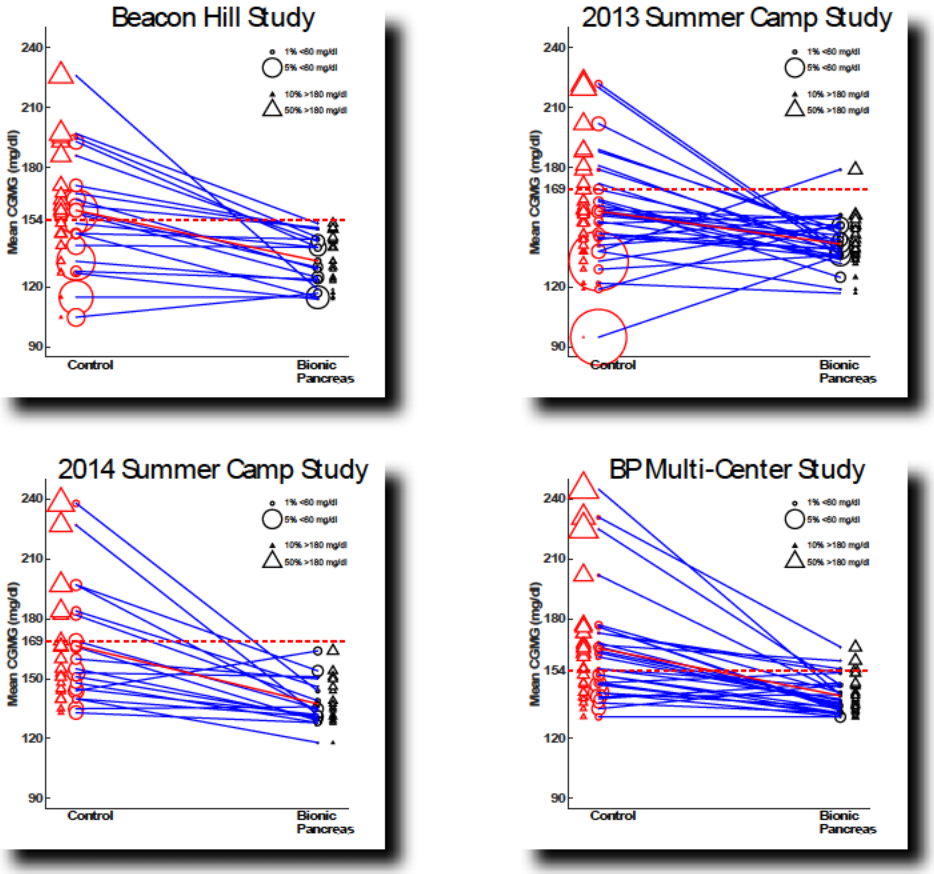
A significant challenge for the use of glucagon in a bihormonal BP is the lack of a commercially available glucagon formation that is stable and well-suited to infusion over several days in a pump reservoir. However, BU/MGH have proceeded with studies using a relatively unstable marketed formulation that must be reconstituted from a lyophilized powder on a daily basis. This allowed BU/MGH to proceed with studies of the bihormonal system while awaiting the production of stable glucagon formulations or stable glucagon analogs.

1.3 Preliminary Studies with the Bihormonal Bionic Pancreas System

The BP hardware platform has evolved over the years from a laptop-driven system, which was used in all inpatient studies to the first truly mobile wearable iPhone-driven platform, which has been used in a number of outpatient studies. Using the iPhone-based BP system, >110 outpatient experiments of 5-11 days in duration in each subject have been conducted (>800 patient days or >2 patient years of data) across subjects ranging in age between 6 and 76 years old and in body mass between 21 and 128 kg. The robust adaptation capabilities of the BP is evident in the fact that the average total daily dose of insulin among these subjects varied by over 13-fold (from 11 to 145 units/day).

In November 2012, Food and Drug Administration (FDA) approval was obtained to conduct the first outpatient study testing the BP in adults 21 years or older with T1DM. This study, referred to as the Beacon Hill Study, followed a random-order cross-over design in which 20 adults with T1DM participated in 5 days on the iPhone-based BP and 5 days of usual care in which they wore a CGM with blinded display and muted alarms. In the BP arm, subjects kept to a 3-square-mile geographic area centered around the Beacon Hill neighborhood in Boston. They ate as they chose at local restaurants, and exercised at will with access to 2 gyms. Analysis was pre-specified to focus on Days 2-5, since glycemic control is more representative of BP performance after most of the adaptation by the BP occurs on Day 1 (Russell, 2014). Results are summarized in Figure 1.

Figure 1. Outpatient Results Summarizing the Distribution of Mean CGM Glucose Levels and Hypoglycemia in the BP and Control Arms



Study	Age (years)	Bionic Pancreas (BP) Mean CGM glucose level (mg/dl)	Bionic Pancreas (BP) % of CGM glucose levels <50 mg/dl (%)	Bionic Pancreas (BP) % of CGM glucose levels 70–180 mg/dl (%)	Control Mean CGM glucose level (mg/dl)	Control % of CGM goucose values <50 mg/dl (%)	Control % of CGM goucose values 70–180 mg/dl (%)	*p* value (BP versus Control) for: Mean CGM glucose level	*p* value (BP versus Control) for: % of CGM glucose values <50 mg/dl	*p* value (BP versus Control) for: % of CGM glucose values 70–180 mg/dl
Beacon Hill (n 20, 5-day experiments)	≥21	133	1.5	80	159	3.7	59	<0.001	0.020	<0.001
2013 Summer Camp (n 32, 5-day experiments)	12–20	142	1.3	76	158	2.2	65	0.004	0.192	<0.001
2014 Summer Camp (n 19, 5-day experiments)	6–11	137	1.2	81	168	2.8	58	0.004	0.001	<0.001
BP Multi Center (n 39, 11-day experiments)	≥18	141	0.6	78	162	1.9	62	<0.001	<0.001	<0.001

Mean CGM glucose levels for each subject under usual care (red circles) are connected with the subject's mean CGM glucose level on the BP (black circles). The diameters of the circles shown are proportional to the percentage of CGM glucose values <60 mg/dL, and the size of the triangle is proportional to the percentage of CGM glucose values >180 mg/dL. The horizontal red dashed line refers to the glucose level corresponding to the American Diabetes Association therapy goal for each age group tested, which corresponds to 154 mg/dL (HbA1c of 7%) for adults and 169 mg/dL (HbA1c of 7.5%) for children. Results are summarized in the table, where the co-primary outcomes (mean CGM glucose level and percentage of CGM glucose values <60 mg/dL) for the BP arm are highlighted in red for each of the 4 studies.
BP = bionic pancreas; CGM = continuous glucose monitoring; HbA1c = hemoglobin A1c.

In April 2013, FDA approval was obtained to conduct the first outpatient study testing the BP in adolescents 12-20 years old with T1DM. This study, referred to as the 2013 Summer Camp Study, followed a random-order cross-over design in which 32 adolescents with T1DM participated in 5 days on the BP and 5 days of supervised camp care in which they wore a CGM with blinded display and muted alarms. Subjects were fully integrated into normal camp activities without restrictions on diet or exercise. The study used the same iPhone-based BP that was used in the Beacon Hill Study. Results are summarized in Figure 1 (Russell, 2014). In April 2014, FDA approval was obtained to conduct the first outpatient study testing the BP in pre-adolescents 6-11 years old with T1DM. This study, referred to as the 2014 Summer Camp Study, was similar in design to the 2013 Summer Camp Study. Results are summarized in Figure 1 (Russell, 2016).

In April 2014, FDA approval was obtained to conduct the first multi-center study, which was also the first home study, to test the BP in adults 18 years or older with T1DM. This study, referred to as the Bionic Pancreas Multi-Center Study, followed a random-order cross-over design in which 39 adults participated in 11 days on the BP and 11 days of usual care. Participants went to work as usual, and lived and slept at home, all without clinical supervision. There were no restrictions placed on diet or exercise. The study included 4 medical centers (10 subjects per center), which included MGH, the University of Massachusetts Medical School, Stanford University, and the University of North Carolina at Chapel Hill. Results are summarized in Figure 1.

All of these studies used marketed glucagon (glucagon for injection, Eli Lilly). Due to its limited stability, Lilly glucagon must be reconstituted immediately before use. Animal studies have previously shown that despite its limited chemical stability, Lilly glucagon maintains its biological activity for up to 7 days in solution. Using this data, an Investigational New Drug (IND) exemption was obtained from the FDA for its use in a pump for up to 27 hours. This allowed these studies to be performed by asking volunteers to reconstitute a new vial of glucagon and fill the glucagon pump at approximately the same time every day. However, marketed Lilly glucagon has no path forward for approval for chronic BP use.

1.4 ZP4207

ZP4207 is a peptide analog of human glucagon that is being developed to treat hypoglycemia in patients with T1DM and type 2 diabetes mellitus. ZP4207 exhibits improved physical and chemical stability in aqueous media and is suitable for liquid formulation. ZP4207 is comprised of 29 amino acids and has 7 amino acid substitutions when compared to native glucagon.

Two clinical Phase 1 trials have been conducted to establish safety and tolerability of ZP4207 after single and multiple dosing to healthy patients and T1DM patients under insulin-induced hypoglycemic conditions.

The First Human Dose (FHD) trial (ZP4207-14013) was finalized in April 2015. The trial was a randomized, double-blinded trial with the objectives to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of ZP4207 as compared to an active comparator. Part 1 included a single ascending dose in healthy volunteers in cohorts of 8. In each cohort, the patients were randomized 3:1 to ZP4207 (n=6) or Novo Nordisk GlucaGen® (n=2). Five cohorts with SC administration (0.01, 0.1, 0.3, 1.0, and 2.0 mg ZP4207 compared to 1 mg GlucaGen) and 3 cohorts with intramuscular (IM) administration (0.3, 1.0, and 2.0 mg ZP4207 compared to 1 mg GlucaGen) were included. Part 2 included 2 sequence groups of

10 hypoglycemic T1DM patients. The patients were treated with fixed single IM doses of 0.7 mg ZP4207 and 1.0 mg GlucaGen in a sequential cross-over design in a randomized treatment order.

The second clinical trial (ZP4207-15007) was a single-center, double-blind, Phase 1b trial investigating the safety and tolerability, PK and PD of ZP4207 following repeated administration in healthy volunteers compared to placebo. It was finalized in July 2015. Each of the 3 cohorts comprised 8 subjects, who received 5 repeated SC doses of ZP4207 or placebo in a 3:1 treatment allocation. The first cohort started with the lowest dose of 0.1 mg. Cohort 2 and 3 continued with 0.3 and 1.0 mg, respectively.

The Phase 1 results did not give rise to specific safety concerns, beyond those related to the pharmacological effect of ZP4207. All adverse events (AEs) recorded in the trials were of mild or moderate severity. The most frequent systemic AE related to treatment with ZP4207 was nausea, which is a known side-effect following administration of glucagon. The most frequent injection site reaction was transient erythema, occurring in all ZP4207, glucagon, and placebo treatment groups, irrespective of dose. No anti-drug antibodies (ADA) incidences were observed.

The observed PD response, in terms of increased plasma glucose, in insulin-induced hypoglycemic patients with T1DM following dosing with 0.7 mg ZP4207 administered IM was similar to that observed following IM dosing with 1.0 mg glucagon (GlucaGen, Novo Nordisk). An increase in plasma glucose of ≥20 mg/dL from hypoglycemic levels was achieved within 30 minutes for all patients.

In terms of PK, ZP4207 had a short half-life and high clearance and dose proportionality for both maximum plasma concentration and area under the concentration-time curve from time 0 to 300 minutes in the dose range 0.1 to 2.0 mg following SC administration. Following IM administration, dose proportionality was shown in the investigated dose range of 0.3 to 2.0 mg. The PK properties of 0.7 mg ZP4207 IM were comparable with those of 1.0 mg glucagon (GlucaGen, Novo Nordisk) with IM administration.

1.5 Risk/Benefit

While the potential risks are minimal, the findings of this trial may reveal information that can substantially improve medical care for persons with diabetes. Therefore, the overall risk/benefit for patients participating in this trial is assessed as acceptable.

Potential Risks and Discomforts

Trial patients will be informed by the Investigator of the potential risks of ZP4207 and other trial-related procedures before they enter the trial.

In this trial, patients with T1DM will be included to test the safety and efficacy of the iLet using ZP4207 versus the iLet using Lilly glucagon. The cross-over design with inclusion of the same T1DM patients into the 2 treatment arms in a randomized order will allow for a direct comparison of the safety and efficacy of the 2 treatments, based on intra-patient variability only.

Patients may experience mild discomfort associated with the insertion of the infusion sets and sensor into the SC tissues. The risk of discomfort due to insertion of infusion sets and sensors is expected to be slightly greater than in their lives outside the trial because more infusion sets will be inserted and a CGM sensor will be inserted. Most patients will use only one infusion set and not all will use a CGM sensor in usual care.

There is a potential risk of hypoglycemia, since recombinant insulin analog will be administered. Due to frequent monitoring of glucose and direct supervision by a registered nurse (RN) or Doctor of Medicine (MD) at all times, the risk of a hypoglycemic episodes leading to significant harm to patients is expected to be substantially lower than their risk during their usual therapy.

There is a risk of hyperglycemia. This risk is expected to be less than the risk during the patients' lives outside of the trial based on data from earlier BP trials and the design of this trial.

Treatment with ZP4207 and marketed glucagon can result in undesired effects or complaints. Undesired effects and complaints such as gastrointestinal side effects including nausea, vomiting, and diarrhea are known side effects of glucagon administration at higher dose levels. The frequency of nausea associated with the administration of 1 mg of glucagon according to the Summary of Product Characteristics (SPC) for Glucagon is described to be between 1/10 and 1/100. The frequency of vomiting is described to be between 1/100 and 1/1000 (Novo Nordisk, 2015). Similar gastrointestinal side effects have also been observed to a limited degree in the 2 clinical trials conducted with ZP4207, again at higher dose levels. The individual doses of ZP4207 and Lilly glucagon delivered by the BP are expected to be significantly lower than doses typically associated with nausea. As with every novel drug substance, new and yet unknown side effects may also occur.

There are limited data available to describe the immunogenic potential of glucagon products available on the market, but the data available indicate that marketed glucagon only has a small immunogenic potential. A Phase 1 trial performed with recombinant human glucagon and animal derived glucagon in 75 healthy patients did not show signs of ADA measured 13 weeks after trial product administration (Eli Lilly, 2005). In the ZP4207 FHD trial, ZP4207-14013, no confirmed anti-ZP4207 or anti-glucagon antibodies were detected in any of the samples. In addition, the 5 sequential administrations of ZP4207, as applied in trial ZP4207-15007, were not associated with the development of antibodies against ZP4207 in the 18 subjects enrolled to receive ZP4207. The optimized formulation of ZP4207, as applied in the present trial is not expected to change the immunogenic potential of the Investigational Medicinal Product (IMP).

In relation to diabetes therapy, development of insulin-antibodies is documented more substantially and route of administration has been shown to influence immunogenic potential of insulins. However, these antibodies against insulin generally do not have an impact on insulin action and are thus not clinically relevant.

In terms of consequence, development of high titer antibodies against ZP4207 could, in theory reduce the activity of endogenous glucagon, which again, in theory could influence hypoglycemic episodes. However, most patients with T1DM do not secrete glucagon normally in response to hypoglycemia, so they would be less likely to be negatively impacted by

anti-glucagon antibodies. Limited suppression of glucagon would, however, not be considered critical, as low glucose levels can also be corrected by other means, including oral intake of glucose and by other endogenous hormones such as oxyntomodulin.

Overall, ZP4207 is judged to be a low-risk molecule, based upon the available clinical data as well as the outcome of the risk-based approach to the immunogenicity assessment made. The present trial will include sampling for measurement of antibodies against ZP4207 prior to first dosing (Visit 3) and at the Follow-up Visit. In line with regulatory guidance documents, these samples will be appropriately analyzed and the results will be included in the overall assessment of the immunogenic potential of ZP4207 after completion of each trial and as the clinical development program advances.

Administration of ZP4207 may be associated with a risk of allergic reactions similar to those observed for other therapeutic peptides or proteins. Patients with known or suspected allergies to the trial products or related products will be excluded from the trial. Mild or moderate allergic reactions may include symptoms of rash, fever, flu-like symptoms, nausea, headache, and myalgia. Acute generalized hypersensitivity reactions are usually very rare but may include symptoms of flushing, sweating, dizziness, change in blood pressure, and difficulties in breathing. The risk of acute hypersensitivity reactions is described to be less than 1/10,000 for native glucagon. No severe acute hypersensitivity reactions have been observed in the 2 clinical trials conducted with ZP4207.

Potential Benefits

Based on experiences from previous trials of the BP and the design of this trial, patients enrolled in the trial may benefit from a reduction in risk of hypoglycemia and hyperglycemia and a better mean glucose compared to their usual diabetes care during their short trial participation.

The data derived from this trial will allow evaluation of safety and tolerability of ZP4207 in the iLet, and the robustness and effectiveness of the new BP control system. The data obtained will be used to further improve the iLet and will allow the expansion to larger outpatient trials using the iLet with ZP4207.

This trial is a necessary step in preparing the BP with ZP4207 to become available to people with T1DM. Wide availability of the BP with ZP4207 could improve the medical care of adults and children with T1DM.

[redacted]

2 TRIAL OBJECTIVES

2.1 Primary Objective

The primary objective is to conduct a trial testing the safety and tolerability of the iLet when used with ZP4207 in 10 adult (≥18 years of age) patients with T1DM.

2.2 Secondary Objectives

The secondary objectives are to measure glycemic regulation, including hypoglycemia exposure (percent of time spent with CGM glucose <60 mg/dL), evaluate BP device reliability, and to document the satisfaction of patients with the iLet with the goal of optimizing the functionality and user interface of the iLet.

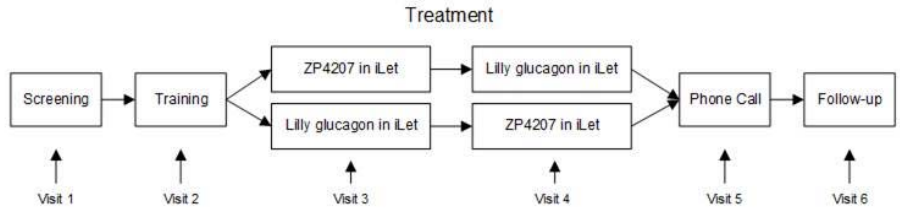
3 TRIAL DESCRIPTION

3.1 Summary of Trial Design

This trial is a single-center, open-label, randomized cross-over trial. The trial will enroll adult patients with T1DM and will assess the safety and efficacy of the iLet using the glucagon analog ZP4207 versus the iLet using Lilly glucagon. The iLet will also administer insulin (insulin lispro, Lilly Humalog) using the same BG control algorithm for both treatment arms. The trial will be conducted at a single center, the MGH Diabetes Center in Boston, MA.

The overall trial design schematic is displayed in Figure 2.

Figure 2. Trial Design Schematic



3.2 Indication

ZP4207 is an anti-hypoglycemic glucagon analog in a ready-to-use liquid formulation which is being studied to improve glycemic control in adults (and children) with T1DM as part of a bihormonal BP.

3.3 Number of Patients

Up to 20 adult patients with T1DM can be enrolled. The upper bound is based on the expectation that some patients will be excluded after the Screening Visit and the possibility that some patients may have to be discontinued before completion (due to, for instance, inter-current illness or patient withdrawal). It is expected that up to 10 patients will complete the trial protocol.

4 SELECTION AND WITHDRAWAL OF PATIENTS

The trial will enroll patients who already manage their T1DM using continuous SC insulin infusion pump therapy. This requirement is imposed because multiple daily injection therapy involves the use of medium-acting or long-acting basal insulin that would require an extended washout period.

4.1 Inclusion Criteria

1. Male and female patients with T1DM for at least 1 year, as defined by the American Diabetes Association
2. Age ≥18 years
3. Diabetes managed using an insulin pump for ≥6 months
4. Prescription medication regimen stable for >1 month (except for medications that will not affect the safety of the trial and are not expected to affect any outcome of the trial, in the judgment of the Investigator)
5. Informed consent obtained before any trial-related activities (trial-related activities are any procedure that would not have been performed during normal management of the patient)
6. Patients in good health according to age (medical history, physical examination, vital signs, 12-lead electrocardiograms [ECGs], laboratory assessments), as judged by the Investigator

4.2 Exclusion Criteria

1. Unable to provide informed consent (e.g., impaired cognition or judgment)
2. Unable to safely comply with trial procedures and reporting requirements (e.g., impairment of vision or dexterity that prevents safe operation of the BP, impaired memory, unable to speak and read English)
3. Participation in another clinical trial of an investigational agent or device concurrently or within 1 month (or 5 half-lives) prior to the Screening Visit
4. Previous exposure to ZP4207
5. Females of childbearing potential who are pregnant (positive urine human chorionic gonadotropin [HCG]), breast feeding, plan to become pregnant in the immediate future, or sexually active without using highly effective contraception methods (highly effective methods are considered those with a failure rate less than 1% undesired pregnancies per year including surgical sterilization, hormonal intrauterine devices [coil], oral hormonal contraceptives, sexual abstinence, or a surgically sterilized partner) or postmenopausal women amenorrheic for less than 1 year with serum follicle-stimulating hormone (FSH) level ≤40 IU/L and not using highly effective contraceptive methods during the trial and until 1 month after last dosing in the trial
6. Male who is sexually active and not surgically sterilized who or whose partner(s) is not using highly effective contraceptive methods (highly effective contraceptive measures include surgical sterilization, hormonal intrauterine devices [coil], oral hormonal contraceptives, each in combination with spermicide-coated condoms), or who is not willing to refrain from sexual intercourse from the first dosing until 1 month after last dosing in the trial
7. Current alcohol abuse (intake averaging >3 drinks daily in last 30 days) or use within the last 6 months of controlled substances without a prescription (other than marijuana)

[redacted]

8. New onset clinically significant illness within 4 weeks prior to screening, as judged by the Investigator
9. Unwilling or unable to refrain on the treatment visits from:
    a. Acetaminophen in any form
    b. Use of drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the trial (use of beta blockers will be allowed as long as the dose is stable and the patient does not meet the criteria for hypoglycemia unawareness while taking that stable dose, but use of benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the Investigator)
10. History of liver disease that is expected to interfere with the anti-hypoglycemia action of glucagon (e.g., liver failure or cirrhosis). Other liver disease (i.e., active hepatitis, steatosis, active biliary disease, any tumor of the liver, hemochromatosis, glycogen storage disease) may exclude the patient if it causes significant compromise to liver function or may do so in an unpredictable fashion.
11. Aspartate aminotransferase >2 × upper limit of normal (ULN), alanine aminotransferase >2 × ULN, or bilirubin >1.5 × ULN on screening laboratories
12. Renal failure on dialysis or estimated glomerular filtration rate <30 mL/min/1.73 m^2 on screening laboratories
13. Hemoglobin <12 gm/dL for men and <11 gm/dL for women
14. Personal history of cystic fibrosis, pancreatitis, pancreatic tumor, or any other pancreatic disease besides T1DM
15. Any known history of coronary artery disease including, but not limited to, history of myocardial infarction, stress test showing ischemia, history of angina, or history of intervention such as coronary artery bypass grafting, percutaneous coronary intervention, or enzymatic lysis of a presumed coronary occlusion)
16. Congestive heart failure with New York Heart Association Functional Classification III or IV
17. History of transient ischemic attack or stroke in the last 12 months
18. Seizure disorder, history of any non-hypoglycemic seizure within the last 2 years, or ongoing treatment with anticonvulsants
19. History of hypoglycemic seizures (grand-mal) or coma in the last 12 months
20. History of pheochromocytoma: fractionated metanephrines will be tested in patients with history increasing the risk for a catecholamine secreting tumor:
    a. Episodic or treatment refractory (requiring 4 or more medications to achieve normotension) hypertension
    b. Paroxysms of tachycardia, pallor, or headache
    c. Personal or family history of MEN 2A, MEN 2B, neurofibromatosis, or von Hippel-Lindau disease
21. History of adrenal disease or tumor
22. Hypertension with systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg despite treatment
23. Untreated or inadequately treated mental illness (indicators would include symptoms such as psychosis, hallucinations, mania, and any psychiatric hospitalization in the last year), or treatment with anti-psychotic medications that are known to affect glucose regulation
24. Electrically powered implants (e.g., cochlear implants, neurostimulators) that might be susceptible to radio frequency interference

25. History of adverse reaction to glucagon (including allergy) besides nausea and vomiting
26. Established history of allergy or severe reaction to adhesive or tape that must be used in the trial
27. Use of oral anti-diabetic medications (e.g., thiazolidinediones, biguanides, sulfonylureas, glitinides, dipeptidyl peptidase-4 [DPP-4] inhibitors, sodium-glucose co-transporter-2 [SGLT-2] inhibitors)
28. Inadequate venous access as determined by trial nurse or physician at time of screening
29. Any factors that, in the opinion of the Investigator, would interfere with trial endpoints or the safe completion of the trial

4.3 Target Population

Patients who meet all of the inclusion and none of the exclusion criteria will be considered as candidates for this trial. Individuals who have previously inquired about participation in BU/MGH trials and have asked to have their contact information kept on file will be contacted. In addition, advertisements for the trial may be posted at the MGH Diabetes Center and other places, and may be distributed in the weekly broadcast e-mail of research studies seeking volunteers. A letter may be sent to adult endocrinologists in the Boston metropolitan as well as selected nearby endocrinologists informing them of the trial and asking them to refer any eligible patients who might be interested. Information will be posted about the trial along with contact information on the BU/MGH website www.bionicpancreas.org and on www.clinicaltrials.gov.

4.4 Withdrawal Criteria

The participation of individual patients will be discontinued if they experience:

- Seizure or unconsciousness associated with hypoglycemia and associated with participation in the trial
- Persistent nausea and vomiting thought to be related to glucagon dosing associated with participation in the trial
- Hospitalization associated with participation in the trial
- Pregnancy
- Diabetic ketoacidosis

If more than 1 patient must be withdrawn from the trial for these reasons, the trial will stop and a vote of the Data and Safety Monitoring Board (DSMB) will be required to restart it. All AEs that are serious and unexpected but related will be reported to the DSMB within 5 working days.

Note that patients may discontinue participation at any time. Patients may be removed from the trial for other reasons, for instance, failure to comply with trial procedures or intercurrent illness that is unrelated to the BP but that precludes safe participation. Discontinuation of participation for these reasons will not contribute to a decision to discontinue the trial.

[redacted]

5 ASSIGNMENT TO TREATMENT GROUPS

This trial is an open-label, randomized cross-over trial. Patients who have completed the Screening Visit and meet all of the inclusion and none of exclusion criteria will be enrolled into the trial. All patients will participate in two 1-day treatment arms in random order (iLet using ZP4207 and iLet using Lilly glucagon) according to a pre-generated randomization scheme. Up to 2 patients may participate in the trial per day. The order of the iLet visits will be randomized in blocks of 2 patients.

6 TRIAL TREATMENT

6.1 Investigational Medicinal Products

Insulin: The trial involves SC administration of insulin lispro *(*Humalog, Lilly*)*, which is commercially available by prescription and is indicated for patients with T1DM, but not for use in a BP.

Glucagon: The trial also involves SC administration of Lilly glucagon in one iLet arm. Lilly glucagon is commercially available by prescription and is indicated for patients with T1DM in severe hypoglycemia, but not for use in a BP.

ZP4207: The trial also involves SC administration of the glucagon analog ZP4207, 1 mg/mL, in the other iLet arm. ZP4207 will be made available by Zealand Pharma A/S, Denmark as liquid formulation in prefilled syringes of 0.6 mL.

6.2 Storage and Drug Accountability of IMPs

All IMPs will be stored and handled in accordance with the Sponsor's instructions and/or the product labelling at the Investigator's site, e.g., refrigerated (+2ºC to +8ºC) and should not be exposed to excessive heat, direct sunlight and never be frozen.

All used, partly used, and unused vials or prefilled syringes must be kept by the Investigator and stored between +2ºC and +8ºC (unused) or at room temperature (partly used and used). Used and unused pre-filled syringes must be stored separately.

The Investigator must ensure the availability of proper storage conditions and record and evaluate the temperature. Temperature of the refrigerator used for drug storage is monitored continuously, an alarm system is established. The Investigator must inform the monitor immediately if any IMP has been stored outside specified conditions (e.g., outside temperature storage). Investigational Medicinal Product that has been stored improperly must not be dispensed to any patient before it has been re-evaluated and approved for further use. The Investigator must take appropriate action to ensure correct storage.

For the IMP, the Investigator must keep an accurate record of all IMPs received and the products used for each patient in a Drug Accountability Record. Storage locations, batch numbers, and expiry dates are also documented in this form.

The drug accountability must be performed in a timely manner by the monitor.

[redacted]

6.3 Dispensing and Return of IMPs

No IMPs may be dispensed to any person not enrolled in the trial.

Upon completion of the trial, the Sponsor will be responsible for destruction or storage of IMPs (used, partially used, or unused). These duties can be delegated to a contract research organization (CRO) and must be documented in the trial files.

6.4 Doses

The iLet can administer isolated insulin-glucagon doses once every 5 minutes. A single automated bolus of insulin will not exceed 3 units per 5-minute dose (30 µl of U-100 insulin) in both systems, and a single meal-priming dose, in response to a meal announcement made by the user, will not exceed 12 units (120 µl of U-100 insulin). A single bolus of glucagon will not exceed 80 µg (80 µl of 1 mg/mL Lilly glucagon or 1 mg/mL ZP4207). In prior studies, typical doses of glucagon were in the range of 0.005-0.04 mg per dose. The iLet is capable of administering as little as ~0.1 µl (0.011 units of U-100 insulin or 0.1 µg of 1 mg/mL ZP4207).

It is expected that the mean total daily doses of glucagon/ZP4207 will be <1.0 mg daily as in previous studies. The mean daily glucagon dose in a previous 11-day outpatient trial was 0.5 mg/day (range 0.2-0.9 mg/day). Currently, single doses of up to 2 mg ZP4207 have been administered in clinical trials. The recommended dose of marketed glucagon for adult patients suffering from severe hypoglycemia is 1 mg as a single injection. Mean glucagon levels in previous inpatient studies have been above the normal fasting range for glucagon only 1% of the time. Therefore, the glucagon exposure of patients is expected to be modest.

6.5 iLet Bionic Pancreas

Infusion set: A novel, dual cannula infusion set has been designed specifically for use with the iLet. Patients will wear dual channel tubing that will be attached to 2 infusion sets with 1 steel cannula each, one for insulin infusion and the other for glucagon infusion. The tubing and infusion sets will have undergone sterilization prior to being delivered in a sealed pouch. The steel cannulae will be inserted in the abdominal SC tissue.

Continuous glucose monitors: One transcutaneous glucose sensor for the Dexcom G4 Platinum (Garcia, 2013) will be inserted in the abdominal SC tissue and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to the sensor and the whole assembly is held to the skin with an adhesive patch and communicates wirelessly with the BP. If the G4 sensor fails for any reason during the trial (loss of CGM signal), it will be replaced promptly.

Bionic Pancreas Control Unit: The iLet is being built according to Class III medical device standards, adheres to a comprehensive and robust quality system, and is fully compliant with International Organization for Standardization (ISO) 13485 standards and document control practices. The iLet is a fully-integrated dual-hormone BP system that integrates the CGM technology (currently the Dexcom G4 Share system) as well as 2 independent motor-drivetrain pumping assemblies, which independently actuate the delivery of insulin and glucagon from pre-filled cartridges that are separately loaded into the iLet housing. Each drivetrain assembly utilizes a lead screw, which is driven by a precision micromotor, a gear case assembly, and a motor controller unit, in a manner similar to what is commonly found in most insulin infusion pumps on the market today. The iLet has dosing accuracy that is comparable to

FDA-approved insulin pumps currently on the market. The iLet has a built-in Bluetooth Low Energy radio that also allows automatic communication with the paired CGM, as well as the Nova StatStrip® Xpress BG meter (Nova Biomedical). The iLet does not contain a cellular nor a WiFi radio, and does not accept input data from another mobile device (e.g., smartphone), other than the paired CGM and BG meter(s).

The mathematical control algorithms (which are the same as those used in the iPhone-based BP), the CGM glucose engine (Dexcom), and the native user interface software, are all interconnected through controller framework software and reside as embedded systems on printed circuit boards contained within the device housing. The touchscreen-enabled, menu-driven user interface and onboard processor provide a comprehensive and standalone platform, which allows the iLet to operate independently of smartphones or other devices and without the need for internet support during routine operation. The graphical user interface of the iLet has the same user options and capabilities of the iPhone BP, including having its home screen password protected and its settings options only accessible to trial staff via a separate password.

6.6 Other Trial Devices

YSI 2300 STAT Plus™ (Yellow Springs Instruments): The YSI 2300 STAT Plus is an FDA-approved glucose analyzer. Blood glucose measurements using the YSI 2300 STAT Plus will be obtained off of the IV line during both treatment visits.

Nova Biomedical StatStrip Xpress Glucose Meter: The Nova StatStrip Xpress glucose meter is an FDA-approved glucose meter that is commercially available. Blood glucose measurements for CGM calibration will be obtained with the Nova StatStrip Xpress during both treatment visits if the YSI 2300 STAT Plus fails and via fingerstick with the Nova StatStrip Xpress during any periods when IV blood samples are not available for any reason or the IV fails.

Exercise Bike: The trial will utilize a stationary exercise bike (ergometer) for the in-clinic exercise at the treatment visits. This bike will be stored at the Diabetes Research Center when not in use.

6.7 Concomitant Medications

6.7.1 Permitted Medications and/or Procedures

Patients may take any over-the-counter medications that they wish during the trial, with the exception of any medication containing acetaminophen as that may cause interference with CGM sensing. All concomitant medications, including over-the-counter medications, should be recorded.

Use of beta blockers will be allowed as long as the dose is stable and the patient does not meet the criteria for hypoglycemia unawareness while taking that stable dose.

If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.

[redacted]

6.7.2 Excluded Medications and/or Procedures

During the trial, patients will not use any recreational drugs or drugs of abuse. The need to take prescription drugs that dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder appropriate decision-making may be grounds for exclusion from the trial or discontinuation of participation, a decision that will be made by the Investigator.

Use of benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the Investigator. Use of oral anti-diabetic medications (e.g., thiazolidinediones, biguanides, sulfonylureas, glitinides, DPP-4 inhibitors, SGLT-2 inhibitors) will also be excluded.

7 TRIAL PROCEDURES

7.1 Informed Consent

After potential patients have had time to review the consent document, and prior to any trial-related activities, they will meet with a trial MD or designee who will explain the trial, answer any questions, and administer informed consent. In the event that a volunteer is a patient of one of the trial MDs, another staff MD or designee will answer questions and administer consent. The patients will be fully informed of their responsibilities and their rights while participating in the trial as well as of the possible risks and potential benefits of participation in the trial. They will have the opportunity to discuss all questions and ample time to consider participation.

Trial-related activities are any procedures that would not have been performed during normal management of the patient. Patients who wish to participate in the trial will be asked to personally date and sign an informed consent form (ICF). Likewise, the Investigator must also personally date and sign the ICF. All patients will be provided with a copy of their own signed and dated ICF.

Trial staff will answer any questions that the patients may have during their participation. They will share any new information in a timely manner that may be relevant to the patient's willingness to continue participating in the trial. The patients may choose to discontinue their participation at any time.

7.2 Screening Visit (Visit 1)

All patients will have a Screening Visit to confirm eligibility. The patient will be interviewed and the electronic Case Report Form (eCRF) will be completed by trial staff to establish whether the patient is eligible.

Once all of the results have been returned, a trial MD will review the eCRF to determine patient eligibility. If a patient is not eligible to continue in the trial, the results of abnormal tests will be reported to the patient and to a health care provider of their choosing.

7.2.1 Data Collected at Screening

- Age, sex, race, and ethnicity
- Date of last menstrual period in female patients

- Medical, surgical, and social history, allergies, and review of systems relevant to inclusion and exclusion criteria, including:
  - Date of diabetes diagnosis
  - Duration of insulin pump use and type of insulin used in pump
  - Type/model of insulin pump
  - Insulin regimen (basal rate, sensitivity factor, and carbohydrate ratio)
  - Average total daily dose of insulin in the last 30 days as available (from pump history)
  - Usage of CGM, if any (type of CGM, days per month worn, usage of data, whether insulin is dosed based on CGM alone, alarm settings)
- Concomitant illness (any illness present at screening)
- Concomitant medications (prescription and non-prescription) and date of last change in medication regimen
- Height, weight, physical examination, and vital signs including body temperature and blood pressure
- 12-lead ECG
- Hemoglobin A1c
- Chemistry and hematology samples (see Appendix B)
- Urine HCG pregnancy test for women of childbearing potential
- FSH level for postmenopausal women amenorrheic for less than 1 year
- Fractionated plasma metanephrines (if indicated by history)

7.3 Training Visit (Visit 2)

A Training Visit will take place before the first treatment visit. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor and trial policies and procedures. Trial staff will verify that the patients have understood the material and are competent to participate safely in the trial. Concomitant medications will also be reviewed.

7.4 Treatment Visits (Visit 3 and Visit 4)

- Visit 3 will take place at least 48 hours after screening (Visit 1) and no more than 30 days after screening (Visit 1).
- There will be a 24-hour minimum washout between Visit 3 and Visit 4 and a maximum of 3 weeks between Visit 3 and Visit 4.
- Up to 2 patients may participate per day.
- Each patient will participate in 2 treatment visits: one with the iLet using ZP4207 and one with the iLet using Lilly glucagon in a randomized order.
- The night before the treatment visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be instructed to call if they encounter any difficulty with their CGM.
- Patients will be responsible for their own medications other than insulin during the trial. Any medical advice needed by the patients during their participation that is not directly related to BG control should be obtained from them in their usual manner. Patients may take any over-the-counter medications that they wish during the trial, with the exception of any medication containing acetaminophen as that may cause interference with CGM sensing. If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken

to the MGH walk-in clinic or emergency room, or if necessary call 911.

- During the trial, patients will not use any recreational drugs or drugs of abuse. The need to take prescription drugs that dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder appropriate decision-making may be grounds for exclusion from the trial or discontinuation of participation, a decision that will be made by the Investigator.
- Patients will not tamper with the BP, including changing any settings.
- Patients may not remove the BP during the trial unless the BP failed or they are withdrawing from the trial.
- The exact time of each procedure and assessment will be documented.

7.4.1 Visit Procedures

- Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window.
- Upon arrival to the visit, the patient's weight and vital signs including body temperature and blood pressure will be documented.
- Patient reports of symptoms, any other complaints, and AEs will be reviewed.
- Concomitant medications will be recorded.
- Chemistry and hematology samples will be collected at visit start (see Appendix B).
- ADA samples will be collected before the start of dosing (Visit 3 only).
- A 12-lead ECG will be performed.
- A urine HCG pregnancy test will be performed in female patients of childbearing potential. If the test is positive, the patient will be informed of the result and the visit will be ended.
- Patients will complete a baseline survey about their attitudes and experience with their usual diabetes care.
- An intravenous (IV) catheter will be placed for blood sampling.
- Trial staff will assist the patient to calibrate their CGM, review the trial procedures again and assist with the setup of the BP system, including inserting and priming infusion sets.
- The control algorithm will be initialized only with the patient's weight. Diagnostics will be performed to ensure that the CGM device is appropriately calibrated and that all of the components of the BP systems are in working order.
- The basal rate of the patient's own insulin infusion pump will be changed to be 2-fold higher than weighted mean of the basal rate during the trial period. This is intended to increase the usage of glucagon during the treatment visit.
- The patients will continue to wear their own infusion pump infusing at the temporary 2-fold basal rate throughout the visit until the start of the structured exercise period, in addition to the BP.
- The staff will start the BP as close as possible to a minute divisible by 5 minutes (i.e., on a 5-minute mark). The starting time will be considered Hour 0.
- Additional calibrations will be performed at any of the BG checks throughout the day if the CGM value does not meet the ISO standard (<15 mg/dL difference for BG values <75 mg/dL; <20% absolute difference for BG values >75 mg/dL) at the time of the BG

measurement AND it is a good time to calibrate (the CGM trend arrow is flat and there has been no carbohydrate intake in the last 30 minutes or glucagon boluses in the last 15 minutes).

- Blood samples will be taken from the IV at least hourly and processed for plasma ZP4207/glucagon. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator. The actual time of sampling will be recorded in the eCRF.
- Plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.
- Patients will be asked to rate any nausea and/or infusion site pain on 10 cm visual analog scales (VAS) at the beginning of the visit once the infusion sites have been placed but no drug has yet been administered, then approximately at the top of every hour during the visit, and at the end of the visit. Trial staff will also evaluate their infusion sites to document any erythema or edema at the same times. If moderate or severe pain is reported or swelling or redness occurs at the infusion site, the infusion site will be replaced in a different location. If moderate or severe pain, swelling, or redness continues at the old site for more than 30 minutes after the infusion site is removed, or if moderate or severe pain, swelling, or redness occurs at the new site, all infusion sites will be removed and the patient will be discontinued from the study.
- From the start of closed loop control until approximately Hour 3, the patients will continue to fast.
- Between approximately Hour 3 and Hour 4, patients will be provided with a lunch meal of their choice in the Diabetes Research Center from a menu of choices from nearby restaurants. They will be asked to choose a meal that is a “typical meal” for them. The content of their meal will not be restricted in any way, with the exception that the number of carbohydrates should be in the “typical” range for them at lunch, and that they must eat the same meal at the same time during both visits.
- At approximately 15 minutes before the meal, patients will administer a bolus for the meal with their own insulin pump based on the carbohydrate count for the meal.
- After lunch is completed, the patients will not be allowed any carbohydrate intake (non-caloric drinks will be permitted) until the trial is completed (except as necessary to treat hypoglycemia), to allow the BP to control the post-prandial BG without further interruption.
- Between approximately Hour 6 and Hour 7, the patients will start a period of structured exercise.
- At the start of the exercise period, patients will restore their normal basal insulin profile so that they will not have elevated insulin levels at the end of the study period when they are to transition back to their usual care.
- Patients will exercise on a stationary bike with a heart rate from 120-140 beats per minute for a total of 4,000 heart beats (approximately 30 minutes). Patients will rate their exercise intensity using the Borg scale every 5 minutes, with the target intensity level between 12 and 14. Heart rate will be measured every 5 minutes.

[redacted]

- BG measurements will be obtained off of the IV line every 10 minutes. If BG is <80 mg/dL, BG measurements will be obtained off of the IV line every 5 minutes.
  - Carbohydrates will be given for any BG <50 mg/dL according to the following protocol: Dextrose (g) = BSA (m^2)/[1.7 m^2 (women) or 1.9 m^2 (men)] *15 g.
  - Repeat treatments will be given at 15-minute intervals as long as BG remains <50 mg/dL.
- If there is an interruption in the Dexcom CGM output, trial staff will assist the patient in recovering CGM data streaming. If this requires replacement of the CGM sensor, BGs will be checked every 10 minutes (every 5 minutes if BG is <80 mg/dL) using blood from the IV until the CGM is able to be calibrated again. These BGs will be entered into the BP, which will treat them as CGM values and dose insulin and/or glucagon appropriately.
- If there is a complete failure of the BP operation, patients will take over their own BG control using their personal insulin pump until the BP can be brought back online. If BP control cannot be promptly resumed (e.g., within 30 minutes), the patient may be asked to repeat that trial day once.
- Patients may choose to withdraw from the trial at any time. If they withdraw from the trial, they should alert a provider immediately.
- Just prior to the end of the study visit, vital signs including body temperature and blood pressure will be obtained and a 12-lead ECG will be performed.
- After approximately Hour 8, but not earlier than at least 60 minutes after end of exercise, the BP will be stopped and the patient will continue with their personal insulin pump.
- The maximum amount of blood loss per study visit will be approximately 230 mL. The total blood loss for the entire study will be up to 460 mL.
- Patients will answer questionnaires (see Appendix C).
- Chemistry and hematology samples will be collected at visit end (see Appendix B).
- The BP and glucose meters will be collected and downloaded.
- A trial MD will review the last several hours of insulin and glucagon dosing and assist the patient in resuming their usual diabetes care. They will be instructed to call trial staff with any questions, issues, or concerns.

7.4.2 Data Collected During the Treatment Visits

- CGM glucose every 5 minutes from the Dexcom G4 Platinum CGM
- All BG measurements taken
- Insulin total dose by the BP and the patient's own insulin pump
- Glucagon total dose
- Timing and content of the meal eaten and carbohydrate amount
- Timing of meal announcement and size of meal announced
- Timing and glucose values at calibrations
- Timing and amount of carbohydrates taken for hypoglycemia
- Data from a questionnaire about attitudes and expectations regarding the BP before and after each treatment arm (see Appendix C)
- Time patients were not under BP control for any reason
- List of technical faults associated with the BP including cause and resolution
- ZP4207/glucagon sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.

[redacted]

- Plasma glucose sampling will be collected at least hourly in parallel with ZP4207/glucagon exposure sampling. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
- Nausea and infusion site pain on a VAS at visit start (after insertion and before any drug administration), hourly, and at visit end
- Infusion site reaction according to the Draize scale at visit start (after insertion and before any drug administration), hourly, and at visit end
- Patient reports of symptoms, any other complaints, and AEs
- Vital signs including body temperature and blood pressure (at visit start and visit end) and weight
- Concomitant medications
- Chemistry and hematology samples (see Appendix B) at visit start and visit end
- ADA (Visit 3 only)
- 12-lead ECG at visit start and visit end
- Urine HCG pregnancy test for women of childbearing potential

7.4.3 Response to Hypoglycemia

- Patients are encouraged to check their BG for any symptoms of hypoglycemia.
- Patients will be permitted to take 15 grams of carbohydrates for any BG value <60 mg/dL. Trial staff will ensure proper functioning of the BP, infusion set, and insulin pump, and will encourage the patient to wait for the BP to treat the low blood sugar for as long as they feel comfortable.
- Patients will be required to take 15 grams of carbohydrates for any BG value <50 mg/dL. After treatment of hypoglycemia, a follow-up measurement will be taken 15 minutes later. Repeated measurements will be taken every 15 minutes until the BG is >60 mg/dL. Treatment will be repeated if subsequent BG values are still <50 mg/dL. All carbohydrate treatments for hypoglycemia will be documented by trial staff (amount and time).
- Trial staff will check the infusion site, BP, and insulin pump for normal operation any time hypoglycemia occurs. If there is any suspicion of infusion set malfunction, the site should be replaced. Trial staff will check the BP for any malfunction and correct any problems that are found.
- If no correctable fault is found, but there is doubt regarding the correct function of the BP system, an entirely new backup BP system may be started.
- If a patient experiences a seizure or unconsciousness associated with hypoglycemia, his or her participation in the trial will be discontinued.

7.4.4 Response to Hyperglycemia

- Trial staff will check the infusion site, BP, and insulin pump for normal operation any time BG is >300 mg/dL. If there is any suspicion of infusion set malfunction, the site should be replaced. Trial staff will check the BP for any malfunction and correct any problems that are found. If the BG remains >300 mg/dL for 2 hours despite troubleshooting, blood ketones will be measured. If the blood ketone result is >1.5 mmol/L, the visit will be stopped and rescheduled. The patient will be provided with insulin and a syringe to give an injection based on their correction factor.
- If a patient experiences diabetic ketoacidosis, his or her participation in the trial will be discontinued.

- If no correctable fault is found, but there is doubt regarding the correct function of the BP system, the treatment visit may be stopped and the visit rescheduled.

7.4.5 Response to Nausea/Vomiting

If significant nausea (e.g., that prevents the patient from eating normally) or any vomiting occurs, trial staff will notify the Investigator. Trial staff will assist the patient in troubleshooting, such as checking BG and the calibration of the CGM (excessive glucagon dosing may occur if the CGM is reading lower than the true BG). If a patient experiences persistent nausea and vomiting thought to be related to glucagon dosing, his or her participation in the trial will be discontinued.

7.4.6 Response to Other Medical Needs

If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.

7.4.7 Monitoring of Bionic Pancreas Performance

Bionic pancreas inventors and developers [redacted], [redacted], and/or an engineer trained by them will be readily available by phone for consultation for the trial staff at all times during the course of the trial.

7.4.8 Supervision by Trial Staff

A trial MD will be on call at all times during the course of the trial. An RN or MD will be with the trial patients in the Diabetes Research Center at all times.

7.5 Phone Call (Visit 5)

A phone call will be conducted 7 days ±3 days following the last day of dosing (Visit 4) to review AEs and concomitant medications.

7.6 Follow-up Visit (Visit 6)

Patients will return for a Follow-up Visit 25 days ±4 days following the last day of dosing (Visit 4), for chemistry, hematology, and ADA sampling, and a review of AEs and concomitant medications.

8 ENDPOINTS

8.1 Primary Endpoint

The primary endpoint is the safety and tolerability of ZP4207 and the iLet as assessed by:

- Number and type of AEs
- Clinical laboratory measurements
- Vital signs
- 12-lead ECG
- Local tolerability and infusion site reactions as measured with the Draize scale
- Immunogenicity as measured by ADA
- Pain as measured on a 10 cm VAS
- Nausea as measured on a 10 cm VAS

8.2 Secondary Endpoints

The secondary endpoints for the iLet and ZP4207 include measurements of BP function as well as glycemic and non-glycemic measurements.

8.2.1 Bionic Pancreas Function

This endpoint data will be generated from the BP data during each treatment visit:

- Average percent insulin dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
    - Average percent glucagon/ZP4207 dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts calculated by the BP algorithm that are successfully issued to the pump by the BP (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts calculated by the BP control algorithm that are successfully issued by the BP
    - Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully issued by the BP
- Average percent of 5-minute steps during which the BP is functioning nominally in all respects based on real-time CGM data (new CGM glucose reading captured, dose calculated, and dose issued to pumps)
- Average percent of 5-minute steps during which the BP is functioning nominally with or without a new CGM glucose reading captured (dose calculated and dose issued to pumps). If a CGM signal is not available, the dose calculated may be based on weight or historical basal rates.
- CGM reliability index, calculated as percent of possible values actually recorded by CGM
- CGM Mean Absolute Relative Difference versus time-stamped BG values from meter download
- List of technical faults associated with the BP including cause and resolution

8.2.2 Glycemic

All of following metrics will be generated from the Dexcom G4 Platinum CGM data during each treatment visit.

- Fraction of time spent within each of the following glucose ranges:
    - <50 mg/dL
    - <60 mg/dL
    - <70 mg/dL
    - 70-120 mg/dL
    - 70-140 mg/dL
    - 70-180 mg/dL
    - >180 mg/dL

[redacted]

  - >250 mg/dL
  - >300 mg/dL
- Number of severe hypoglycemic events (patients unable to self-treat, requiring the assistance of another person)
- Number of episodes of symptomatic hypoglycemia
- Number of carbohydrate interventions for hypoglycemia
- Total grams of carbohydrates taken for hypoglycemia
- Mean CGM glucose

8.2.3 Non-glycemic

- Glucagon/ZP4207 total delivery per kg of body mass
- Insulin total delivery per kg of body mass
- Number of unscheduled infusion set replacements
- Number of unscheduled CGM sensor changes

9 LABORATORY ASSESSMENTS

Descriptions of sample handling and sample processing, storage, and shipment at the site will be included in the laboratory manual.

The responsible laboratories are listed in the address list.

9.1 Safety Laboratory Assessments

Chemistry and hematology samples will be collected at specified time points. See Appendix A for the schedule of procedures and Appendix B for a list of clinical laboratory analytes.

9.2 Pharmacodynamic Assessments (Plasma Glucose)

At Visit 3 and Visit 4, plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.

9.3 Exposure Assessments (ZP4207 and Glucagon)

At Visit 3 and Visit 4, ZP4207/glucagon exposure sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator. The actual time of sampling will be recorded in the eCRF.

Bioanalytical Reports will be prepared.

9.4 Anti-drug Antibody Assessments

Blood samples (including back-up samples) for serum anti-ZP4207 and anti-glucagon antibodies will be taken at Visit 3 and the Follow-up Visit 6.

A Bioanalytical Report will be prepared.

[redacted]

10 SAFETY REPORTING

10.1 Adverse Events

An AE is any untoward medical occurrence in a trial patient administered an IMP and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP. Patients should be instructed to report any AE they experience to the Investigator.

Note: This includes events from the first trial-related activity from Visit 3.

AEs for ZP4207 include:

- A clinically significant worsening of a concomitant illness
- A clinical laboratory abnormality which is clinically significant, i.e., any abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example, change of medicine dose or more frequent follow-up due to the abnormality.
- Hypoglycemic episodes
- Injection site reactions

The following should **not** be recorded as AEs, if recorded prior to randomization (on the Screening Form or the eCRF):

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial-related activity from Visit 3.
- Pre-existing conditions found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).

For known (listed) AEs for Glucagon and Humalog, please refer to SPC for Glucagon and Humalog.

10.1.1 Follow-up of Adverse Events

All AEs that are ongoing at the end of the patient's participation in the trial will be followed-up until the event is resolved or reaches a satisfactory outcome as deemed by the Investigator. Follow-up actions for all serious adverse events (SAEs) will be performed according to appropriate clinical care practices and may depend on the nature of the event. These will be determined after internal review and/or Sponsor review. The follow-up information should only include new (updated and/or additional) information that reflects the situation at the time of the Investigator's signature.

Follow-up information on (S)AEs will be updated using the (S)AE Form. If a non-serious event becomes serious during the follow-up, the AE Form and SAE Form must be used and reporting timelines follow those of an SAE.

The Investigator must forward follow-up information on SAEs, and if previously non-serious AEs become SAEs, to the Sponsor.

[redacted]

10.1.2 Precautions

Normal precautions taken for a human trial will be taken during this trial. Qualified and well-trained physicians and medical staff will instruct the patients. During a patient's participation in the trial, the Investigator should ensure that adequate medical care is provided to the patient for any AEs, including clinically significant laboratory values related to the trial. The Investigator should inform the patient when medical care is needed for intercurrent illnesses of which the Investigator becomes aware.

For further information on safety precautions for ZP4207, Lilly glucagon, Lilly Humalog, and the iLet, please refer to the current version of the Investigator's Brochure (IB) for ZP4207 (Zealand Pharma A/S, 2015, or any updates hereof), and the SPC for Glucagon (Eli Lilly, 2012) and Humalog (Eli Lilly, 2015), respectively.

10.1.3 Assessment of Adverse Events by the Investigator

Intensity of an Adverse Event
The maximum intensity (severity) of all AEs must be assessed by the Investigator and documented. Severity should be graded when the AE outcome is known:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

A "severe" reaction does not necessarily deem the AE as "serious," and an SAE may not be "severe" in nature.

Causality Relationship to IMP
Insulin (insulin lispro, Lilly Humalog), glucagon (glucagon for injection, Eli Lilly), and ZP4207 are all regarded as IMP.

The causality of each AE should be assessed by the Investigator according to the following classification:

- Related: Good reason and sufficient documentation to assume a causal relationship.
- Not related: No relationship to trial product can be established.

Outcome of an Adverse Event
The outcome of all AEs must be assessed by the Investigator and documented by his/her staff. The following definitions should be used:

- Recovered/resolved: The patient has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity from Visit 3.
- Recovering/resolving: The condition is improving and the patient is expected to recover from the event. This term is only applicable if the patient has completed the trial.

[redacted]

- Recovered/resolved with sequelae: The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment, or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- Not recovered/not resolved: The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known.
- Fatal: This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as "recovered/resolved," "recovering/resolving," "recovered/resolved with sequelae," or "not recovered/not resolved." An AE with a fatal outcome must be reported as an SAE.
- Unknown: This term is only applicable if the patient is lost to follow-up.

10.2 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Medically important

Medical judgement must be exercised in deciding whether an AE is believed to be "medically important." Medically important events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Suspected Unexpected Serious Adverse Reactions (SUSAR)
A SUSAR is an AE fulfilling one of the criteria of seriousness and being assessed as related to an IMP, the nature or severity of which is not consistent with the applicable reference document (e.g., ZP4207 IB or package leaflet/SPC for an approved product).

Unanticipated Adverse Device Effect (UADE)
A UADE is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

10.3 Adverse Event Reporting – Procedures for Investigators

The Principal Investigator and co-investigators will review any AEs and report any SAEs to the Sponsor as soon as possible and within 24 hours of obtaining knowledge of the event. The Principal Investigator and co-investigators will promptly report AEs to the Partner's Institutional Review Board (IRB) and to the BU IRB (unless oversight is ceded by the BU IRB to the Partners IRB), in accordance with local requirements.

Ed Damiano is the Sponsor of the Investigational Device Exception for the BP and Zealand Pharma A/S is the Sponsor of the IND for ZP4207.

[redacted]

Reports of AEs will be submitted to the FDA in compliance with the terms of the Code of Federal Regulations.

All events meeting the definition of an AE must be collected and reported from the first trial-related activity from Visit 3 until the end of the post-treatment follow-up period. At each contact with the site (visit or telephone, excluding safety visits, where the patient is not seeing the Investigator or staff [e.g., visits to the laboratory], the patient must be asked about AEs. All AEs, either observed by the Investigator or reported by the patient, must be recorded by the Investigator and evaluated.

The Investigator should record the diagnosis, if possible. If no diagnosis can be made, the Investigator should record each sign and symptom as individual AEs.
All AEs must be recorded by the Investigator. One single AE Form must be used per AE from start to resolution. For SAEs, the SAE Form must also be completed.

AE information should include the following:

- Patient identification number on all pages
- Date and time of treatment start
- Date and time of onset and date of outcome
- Date and time of Investigator's first information on the (S)AE
- Seriousness
- Severity
- Causal relationship with IMP ZP4207
- Causal relationship with IMP insulin
- Causal relationship with IMP glucagon
- Causal relationship with medical device
- Causal relationship with procedures
- Interruption or withdrawal of treatment with IMP or medical device and other measures taken
- Outcome

All AEs are coded; details are described in the trial specific Data Management Plan.

The Investigator must report initial information in writing on the SAE Form for all SAEs to the Sponsor's responsible pharmacovigilance unit (here: Lindeq) immediately (within 24 hours) after obtaining knowledge about the event.

Name: [redacted]
Company: Lindeq
Address: Lyskær 8, 2730 Herlev, Denmark
Tel: [redacted]
Fax:
Mobile:
E-mail: drugsafety@lindeq.com

In addition and meeting the same timeline, Investigators must report all SAEs to Zealand Pharma A/S by forwarding the SAE Form electronically within 24 hours of obtaining knowledge of the event to the representatives of Zealand Pharma A/S.

Names: [redacted] and [redacted]
Address: Smedeland 36, DK-2600 Glostrup, Denmark
Tel: [redacted]
E-mails: [redacted]

It is the responsibility of Lindeq to report all SUSARs that occur in this trial to the Competent Authorities and to the Investigators. It is the responsibility of the Investigators to report the SUSARs to the IRBs in accordance with the local requirements in force and the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP). The trial monitor must be informed accordingly.

It is the responsibility of Lindeq to report all serious adverse reactions on insulin lispro and glucagon for injection to the Eli Lilly Pharmacovigilance department within 5 days.

It is the responsibility of the Investigators to report all UADEs to Beta Bionics within 24 hours of the time they are detected. It is the responsibility of the Investigators to report all UADEs to the IRB in accordance with the local requirements in force and the ICH GCP. It is the responsibility of Beta Bionics to report all UADEs to the Competent Authorities.

All device deficiencies should be documented and should be reported to Beta Bionics within 24 hours. Device deficiencies are inadequacies of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

Name: [redacted]
Company: Beta Bionics, Inc.
Address: Business Innovation Center, Photonics Center, 8 Saint Mary's Street, Suite 936
Boston, Massachusetts 02215-2421, United States
Tel: [redacted]
E-mail: [redacted]

10.4 Pregnancy Reporting

Female patients must be instructed to notify the Investigator immediately if they become pregnant or if they suspect to be pregnant during the trial. The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical trial.

Male patients must be instructed to notify the Investigator immediately if their partner becomes pregnant or suspects to be pregnant. The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical trial. During an information meeting at the trial site, the patient's partner will be fully informed by a physician of her participation in capturing the outcome data, and will be asked to provide her written consent.

The Investigator must report all information on pregnancies, including AEs in the patient/patient's partner, the fetus, and newborn infant/ toddler. The pregnancy report must be forwarded to the Sponsor preferably electronically as PDF or by fax.

The Investigator must follow the pregnancy until the pregnancy outcome and the newborn infant(s) until the age of 1 month. The Investigator must collect information on the pregnancy and pregnancy complications as well as the pregnancy outcome including the health of the newborn infant(s) on the pregnancy forms.

The following must be collected:

- Initial information of the pregnancy
- Information on the outcome of the pregnancy, including the health status of the newborn infant(s) at the age of 1 month
- All AEs in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms. It must be clear in the description if the event occurs in the patient/patient's partner, the fetus, or the newborn infant.
- All SAEs in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms following the same timelines as required for other SAEs. It must be clear in the description if the event occurs in the patient/patient's partner, the fetus, or the newborn infant.

The SAEs that must be reported include abnormal outcome – such as congenital anomalies, fetal death, and termination of pregnancy (spontaneous or elective abortion), including any anomalies of the fetus observed at gross examination or during autopsy – as well as other pregnancy complications (ectopic pregnancy) fulfilling the criteria of an SAE.

10.5 Hypoglycemia

Hypoglycemia will be regarded as an AE and will be recorded and documented on an AE Form. For the purposes of AE reporting, the following definitions of hypoglycemia will be used:

- Symptomatic hypoglycemia: an event during which typical symptoms of hypoglycemia are accompanied by a BG concentration ≤70 mg/dL
- Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with a BG concentration ≤50 mg/dL
- Severe hypoglycemia: an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions

10.6 Safety Monitoring

10.6.1 Data and Safety Monitoring Board

An external DSMB will oversee the conduct of the trial, as set forth in the DSMB Charter. Additionally, the DSMB will be informed in the event of any serious and unexpected AEs. The DSMB will be informed if there are any changes to the trial protocol that could significantly impact the safety or scientific validity of the trial. A final DSMB meeting will convene after the completion of the trial.

The participation of individual patients will be discontinued if they experience:

- Seizure or unconsciousness associated with hypoglycemia and associated with participation in the trial
- Persistent nausea and vomiting thought to be related to glucagon dosing associated with participation in the trial
- Hospitalization associated with participation in the trial
- Pregnancy
- Diabetic ketoacidosis

If more than 1 patient must be withdrawn from the trial for these reasons, the trial will stop and a vote of the DSMB will be required to restart it. All AEs that are serious and unexpected but related will be reported to the DSMB within 5 working days.

[redacted]

Note that patients may discontinue participation at any time. Patients may be removed from the trial for other reasons, for instance, failure to comply with trial procedures or intercurrent illness that is unrelated to the BP but that precludes safe participation. Discontinuation of participation for these reasons will not contribute to a decision to discontinue the trial.

10.6.2 Zealand Pharma Safety Committee

The internal Zealand Pharma Safety Committee is constituted to perform ongoing safety surveillance of clinical trials within ZP4207, including this trial.

If safety signals are observed either based on reported SAEs, periodic review of laboratory parameters, planned review of all AEs reported between the safety committee meetings, or on notification of significant findings, the Safety Committee will take appropriate measures to safeguard the patients.

11 STATISTICS

11.1 Analysis Populations

The following analysis sets are defined in accordance with the ICH-E9 guidance:

The Full Analysis Set is based on the intention-to-treat principle and includes all randomized patients. In exceptional cases, patients from the Full Analysis Set may be excluded (will be decided in the database review [DBR] meeting). In such cases, the exclusion will be justified and documented. Patients will contribute to the evaluation “as randomized.”

The Per-Protocol Set includes all patients of the Full Analysis Set who completed the trial without any major protocol violations. Patients in the Per-Protocol Set will contribute to the evaluation “as treated.” This analysis will only be used if it is different than the Full Analysis Set.

The Safety Analysis Set includes all patients receiving at least 1 dose of the IMP. Patients in the Safety Analysis Set will contribute to the evaluation “as treated.”

Analyses of efficacy endpoints will be based on the Full Analysis Set (and the Per-Protocol Set if necessary). This decision will be made in the DBR meeting. The analysis of the safety endpoints will be based on the Safety Analysis Set.

Before data are released for statistical analysis, a blinded review of all data will take place to identify protocol deviations that may potentially affect the results. At this time, it will be determined if patients and/or data should be excluded from the analysis. Furthermore, outliers will be identified by data review according to ICH-E9.

Obviously erroneous data points may be excluded from the analyses or re-analyzed (e.g., serum concentrations). The decision to re-analyze or exclude data points from the statistical analysis is the joint responsibility of the Sponsor, the Principal Investigator, and the Trial Statistician.

The patients or observations to be excluded and the reason for their exclusion will be documented and signed by those responsible prior to database release. The documentation

[redacted]

will be stored together with the remaining trial documentation. The patients and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

11.2 Statistical Methods

Medpace will be responsible for the statistical analysis. The statistical planning and conduct of analyses of the data from this trial will follow the principles defined in relevant ICH guidelines and Medpace's biostatistical standard operating procedures (SOPs). A general description of the statistical methods to be used is given in this section, specific details will be provided in the Statistical Analysis Plan (SAP), which will be prepared before database lock. All statistical analyses will be performed using SAS® (SAS Institute Inc., Cary, North Carolina, USA), version 9.4 or later.

11.2.1 Analysis of Safety

The following variables will be evaluated according to treatment for safety purposes:

Adverse Events
All AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Individual AEs will be presented in a listing including relationship to trial product/device, severity, and treatment period at onset. If more than 20 treatment-emergent AEs (AEs with onset after [first] dosing at Visit 3 until the Follow-up Visit 6) are registered, a summary table including number of AEs, number of patients with at least 1 AE, and percentage of exposed patients with at least 1 AE will be made by system organ class and treatment period at onset.

Local Tolerability
Local tolerability at the injection site will be summarized using descriptive statistics as appropriate.

Laboratory Safety Assessments
Laboratory assessments will be summarized. A listing of abnormal values will be provided.

Physical Examination
A frequency table will show the number and percentage of physical examination results.

Vital Signs
Vital signs will be summarized using descriptive statistics.

12-lead ECG
The Investigator's evaluations of 12-lead ECGs will be summarized and abnormal individual evaluations will be listed together with the Investigator's comments. Changes in 12-lead ECG between measurements will be recorded as AEs if the Investigator judges them to be clinically significant.

11.2.2 Analysis of Efficacy

The analysis of BP function endpoints and glycemic endpoints will be on an intention-to-treat basis. In cases where a treatment arm was not completed (and that arm was not repeated according to protocol criteria), available data from that arm will be used in the data analysis.

[redacted]

The Shapiro-Wilk test will be used to determine the normality of the residuals for each comparison. Summary tables that display descriptive statistics, including percentages, means or medians, and standard deviation and/or ranges, as appropriate, will be provided.
A paired t-test or the Wilcoxon signed rank test for comparison of means with normally or non-normally distributed residuals, respectively, will be used. In a secondary analysis, any period effect and any interaction between treatment and period will be looked for, although no such interaction is predicted for the efficacy outcome. Further details will be included in the SAP.

The number of patients and proportions of severe hypoglycemic events, symptomatic hypoglycemia, and carbohydrate interventions due to hypoglycemia with the event counts will be summarized descriptively, and the proportions will be analyzed by a Fisher's exact test if data allow.

11.2.3 Interim Analysis

No interim analysis is planned.

11.2.4 Sample Size Determination

No formal sample size calculations were made. It is expected that between 10 and 12 patients will be randomized in the trial. The sample size is based on a clinical rather than statistical rationale. The sample size is considered adequate to address the primary trial objective of exploring the safety of ZP4207 when used in the iLet and with reference to Lilly glucagon used in the iLet.

12 DATA MANAGEMENT AND RECORD KEEPING

Data Management is the responsibility of Medpace. The complete Data Management process will be described in detail and agreed on in the Data Management Plan for this trial.

12.1 Data Handling

Case Report Forms
Electronic Case Report Forms will be used in this trial. The Data Management Department of Medpace will provide the eCRFs. All further information regarding the eCRFs and the data flow will be described and agreed on in the Data Management Plan.

Device-Related Data
During the trial, CGM data, calibration data, insulin dosing data, and glucagon dosing data will be automatically stored in the BP device (from which it will be downloaded at intervals), combined in a single database that will be compared against the primary data files for integrity, and ultimately transferred to Medpace.

12.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

12.3 Data Entry

Data must be recorded using the electronic data capture (EDC) system as the trial is in progress. The patient questionnaires will be transcribed into the EDC system by site personnel. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct trial data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

12.4 Medical Information Coding

Adverse events and medical history will be coded using the latest version of MedDRA. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary.

12.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

12.6 Record Keeping

Medpace will be responsible for hosting the TMF. Records of patients, source documents, monitoring visit logs, eCRFs, inventory of trial product, regulatory documents, and other Sponsor correspondence pertaining to the trial must be kept in the appropriate trial files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the evaluation and reconstruction of the clinical trial. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Trial Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

13 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

13.1 Ethical Conduct of the Trial

The trial will be conducted according to Medpace, MGH, and/or the Sponsor's written instructions (SOPs, working instructions, or process descriptions). Content and definitions of the written instructions are based on the Declaration of Helsinki and the ICH GCP.

13.2 Institutional Review Board

Written favorable opinion must be obtained from the responsible IRB prior to commencement of the trial. Clinical trial submission and reporting requirements before, during, and after completion of the trial will be performed in accordance with national law and local regulations.

[redacted]

All amendments that affect patient safety or the trial integrity (substantial amendments) must not be implemented before favorable opinion has been obtained, unless necessary to eliminate hazards to the patients. Non-substantial amendments do not require favorable opinion by the IRB, but the respective IRB will be notified according to local requirements.

The Sponsor and Investigator must approve any amendment in writing before its implementation.

The Sponsor must maintain an accurate and complete record of all submissions made to the IRB. The records should be filed in the Sponsor's Trial Master File (TMF).

13.3 Informed Consent

In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirement(s) and adhere to the ICH GCP guideline and the requirements in the Declaration of Helsinki.

Prior to any trial-related activity, the Investigator must give the patient oral and written information in a form that the patient can read and understand about all aspects of the trial that are relevant to the patient's decision to participate. The patient will be given ample time to decide whether or not to participate in the trial.

The patient must be informed that his/her personal trial-related data will be used in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by authorized monitors or Clinical Quality Assurance auditors appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

A voluntary, personally signed and dated ICF must be obtained from the patient prior to any trial-related activity. The ICF must also be signed and dated by the physician or designee who conducted the informed consent procedure. A signed copy of the ICF and any additional patient information must be given to each patient.

The responsibility for taking informed consent must remain with that of a research physician or designee. If information becomes available that may be relevant to the patient's willingness to continue participating in the trial, the Investigator must inform the patient in a timely manner, and a revised written informed consent must be obtained.

Should a protocol amendment become necessary, the ICF may need to be revised to reflect the changes to the protocol. It is the responsibility of the Sponsor to ensure that an amended consent form is reviewed and has received favorable opinion from IRB, and the Investigator must ensure that the amended consent form is signed by all patients subsequently entered into the trial and those currently in the trial, if affected by the amendment.

13.4 Trial Monitoring Requirements

The monitoring procedures for this trial are described in detail in the Monitoring Manual. The objectives of the monitoring procedures are to ensure that (i) the safety and rights of the trial patients are respected, (ii) that accurate, valid, and complete data are collected, and (iii) that

[redacted]

the trial is conducted in accordance with the trial protocol, the principles of GCP, and local legislation, including drug accountability.

The monitor must be given direct access to the investigational site files and source documents (original documents, data, and records). Direct access includes permission to examine, analyze, verify, and reproduce any record(s) and report(s) that are important to evaluation of the clinical trial.

Key tasks of the monitor include verifying the presence of informed consent, the adherence to the inclusion/exclusion criteria, the documentation of SAEs, and the recording of all safety and efficacy variables. The monitor will also confirm the completeness of patient records, the adherence to the protocol, ICH GCP, and the progress in patient enrollment and perform drug accountability.

Because no information that could reveal the identity of patients may ever be removed from the trial site, the monitor will visit the site at regular intervals to perform these monitoring tasks. Other contact between the Investigator and monitors will be maintained as required through telephone calls and e-mail. The Investigator and/or key members of staff involved in the trial must be available to assist the monitors during all visits.

Site Initiation Visit
During the Site Initiation Visit (SIV) the CRO, Sponsor, and/or monitors will go through information on the IMP, the protocol, the eCRFs, and other key aspects of the trial with the Investigator and the key members of staff involved in the trial. The topics of the SIV are documented in a SIV report made available to the Investigator. Documentation on the SIV (e.g., power point presentation) should be filed by both Investigator and Sponsor.

13.5 Disclosure of Data

Data generated by this trial must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the trial is confidential and disclosure to third parties other than those noted above is prohibited.

13.6 Retention of Records

Massachusetts General Hospital will maintain the patient's medical file according to local regulations. MGH will archive the documentation pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. MGH should not destroy any documents without prior permission from the Sponsor.

The documentation includes all the raw data generated during the clinical trial, the investigational site files, and a copy of the clinical trial report. The documents will be retained for a period of at least 15 years at archives by MGH, or its sub-contractor. After this period, the Sponsor will be contacted and their advice sought on the return or further retention of the trial records.

[redacted]

The Sponsor will maintain the documentation pertaining to the trial in accordance with national regulations.

13.7 Publication Policy

The Principal Investigator of the trial will review and sign the clinical trial report. A summary of the final clinical trial report will be submitted to the IRB and Competent Authority.

According to the Declaration of Helsinki Investigators and Sponsors "have ethical obligations with regard to the publication and dissemination of the results of research." The trial design and results may be published as one or more original research manuscripts/abstracts and presented at a scientific meeting. The Investigator and Sponsor reserve the right to review any proposed presentation of the results of this trial before they are submitted for publication. Authorship on any publication(s) resulting from this clinical trial will be assigned according to the recommendations of the International Committee of Medicinal Journal Editors.

Participating patients will not be identified by name in any published reports about the clinical trial.
The Sponsor is responsible for trial registration at ClinicalTrials.gov (www.clinicaltrials.gov) according to the requirements from the FDA.

13.8 Legal Aspects

An implicit or explicit approval must be obtained from the Competent Authority prior to commencement of the trial. Clinical trial submission and reporting requirements before, during, and after completion of the trial will be performed in accordance with national law and local regulations.

An implicit or explicit approval will also be mandatory before implementation of substantial changes. Non-substantial amendments do not require approval from the Competent Authority but will be notified according to local requirements.

The Sponsor and Investigator must approve the amendment in writing before its implementation.

The Sponsor must maintain an accurate and complete record of all submissions made to the Competent Authority. The records should be filed in the Sponsor's TMF.

Audits and Inspections
In the event of an audit, representatives of the Sponsor or designee, or national and international regulatory authorities may request access to all trial records for inspection and copying. Such access must be stated in the ICF signed by the patient.

13.9 Sponsor Discontinuation Criteria

The Sponsor, Investigator, or a pertinent regulatory authority may decide to stop the trial or part of the trial at any time but agreement on procedures to be followed must be obtained.
Conditions that may warrant termination of the clinical trial include, but are not limited to:

- Safety or administrative reasons
- The discovery of an unexpected, relevant, or unacceptable risk to the patients enrolled in the clinical trial

[redacted]

- A decision of the Sponsor to suspend or discontinue investigation of the IMP

If the trial is prematurely terminated or suspended, the Investigator should promptly inform the patients and assure appropriate therapy and follow-up. Furthermore, the Sponsor should promptly inform the IRB and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.
If after the termination of the trial the risk/benefit analysis has changed, the new evaluation should be provided to the IRB in case it will have an impact on the planned follow-up of the patients who have participated in the trial. Necessary actions needed to protect the patients should be described.

13.10 Patient Compensation

Financial compensation will be provided to all patients who complete the Screening Visit. Patients will be paid $25 for completing the Screening Visit whether or not they are eligible to participate in the trial. Patients will be compensated $25 for completing the Training Visit. Patients will be compensated $100 for completing each of the 2 treatment visits, $25 for completing the phone call, and $25 for completing the Follow-up Visit. Thus, the total compensation for a patient who completes the trial would be $300. Patients who are unable to complete the trial or choose to stop participation will receive prorated compensation for each visit. In addition to the monetary compensation, the cost of the patients' lunch meals during their participation in the trial, as well as the patients' parking at each visit, will be covered by trial funds.

14 TRIAL ADMINISTRATIVE INFORMATION

14.1 Protocol Amendments

Any amendments to the trial protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

14.2 Address List

14.2.1 Sponsor

Zealand Pharma A/S
Smedeland 36
DK-2600 Glostrup (Copenhagen)
Denmark
Telephone: +45 88 77 36 00
Facsimile: +45 88 77 38 98

[redacted]

14.2.2 Supplier of Device

[redacted], PhD
Beta Bionics, Inc.
Business Innovation Center, Photonics Center
8 Saint Mary's Street, Suite 936
Boston, Massachusetts 02215-2421
United States
Tel: [redacted]

14.2.3 Principal Investigator (Site)

Steven J. Russell, M.D., Ph.D.
MGH Diabetes Center
50 Staniford Street Suite 301
Boston, Massachusetts 02114
Telephone: [redacted]
Facsimile: [redacted]

14.2.4 Contract Research Organization (Including Monitoring)

Medpace, Inc.
5375 Medpace Way
Cincinnati, Ohio 45227
Telephone: +1-513-579-9911
Facsimile: +1-513-579-0444

14.2.5 Medical Monitoring

Medpace Clinical Safety
5375 Medpace Way
Cincinnati, OH 45227
United States
Telephone: +1-800-730-5779, ext. 2999 or +1-513-579-9911, ext. 2999
Facsimile: +1-866-336-5320 or +1-513-579-0444
medpace-safetynotification@medpace.com

14.2.6 Pharmacovigilance

Lindeq
Lyskær 8
2730 Herlev
Denmark
Telephone: [redacted]
Facsimile:
Mobile:
E-mail: drugsafety@lindeq.com

14.2.7 Central Laboratory (Safety Laboratory and Plasma Glucose)

Medpace Reference Laboratories, LLC
5365 Medpace Way
Cincinnati, OH 45227
United States
Telephone: +1-513-366-3270
Facsimile: +1-513-366-3273

14.2.8 Special Laboratory (ZP4207 Exposure and ADA Analyses)

Unilabs – York Bioanalytical Solutions
[redacted]
Cedar House
Northminster Business Park
Upper Poppleton
York YO26 6QR
Great Britain
Telephone: [redacted]
Facsimile: [redacted]

14.2.9 Special Laboratory (Glucagon Exposure)

MLM Medical Labs GmbH
Dr. [redacted]
Dohrweg 63
D-41066 Mönchengladbach
Germany
Telephone: [redacted]
Facsimile: [redacted]

15 REFERENCES

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7. Summary of Product Characteristics. Glucagon for Injection. Indianapolis, IN, USA; Eli Lilly and Company:2012.
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9. ICH Harmonised Tripartite Guideline. Statistical Principles for Clinical Trials E9. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf. 5 February 1998.
10. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R1). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf. 10 June 1996.

[redacted]

Clinical Trial Protocol
ZP4207-16051

Version number: 2.0
Amendment 1.0
Date: 28 June 2016

APPENDIX A: SCHEDULE OF PROCEDURES

Trial Visit	Visit 1 [1] Screening	Visit 2 Training	Visit 3 [2] [3] [4] [5] (1st Treatment Visit)	Visit 4 [2] [3] [5] (2nd Treatment Visit)	Visit 5 Phone Call [6]	Visit 6 Follow-Up [7]
Informed consent	X					
Assess/confirm elig bility	X	X				
Demographics	X					
Medical, surgical, and social history; allergies	X					
Concomitant illness	X					
Concomitant medications	X	X	X	X	X	X
Height, weight, physical examination, and vital signs including body temperature and blood pressure [8]	X		X [9]	X [9]		
12-lead ECG	X		X [10]	X [10]		
Urine HCG pregnancy test and menstrual history [11]	X		X	X		
FSH [12]	X					
Screening labs – HbA1c, optional fractionated metanephrines [13]	X					
Safety lab sampling including chemistry and hematology	X		X [10]	X [10]		X
Training on devices [14]		X				
Monitored BP use			X	X		
Plasma glucose sampling [15]			X	X		
ZP4207/glucagon exposure sampling [16]			X	X		
Nausea and infusion site pain VAS and infusion site reaction Draize scale (visit start [17], hourly, & visit end)			X	X		

[redacted]

Clinical Trial Protocol
ZP4207-16051

Version number: 2.0
Amendment 1.0
Date: 28 June 2016

Trial Visit	Visit 1 [1] Screening	Visit 2 Training	Visit 3 [2] [3] [4] [5] (1st Treatment Visit)	Visit 4 [2] [3] [5] (2nd Treatment Visit)	Visit 5 Phone Call [6]	Visit 6 Follow-Up [7]
Standardized lunch [18]			X	X		
In-clinic exercise [19]			X	X		
Questionnaires (pre & post BP)			X	X		
ADA			X [20]			X
Adverse event review			X	X	X	X

1. Once the patient has been enrolled and eligibility has been established, the order of the iLet visits will be randomized in blocks of 2 patients.
2. Each patient will participate in 2 treatment visits: one with the iLet using ZP4207 and one with the iLet using Lilly glucagon in a randomized order. Up to 2 patients may participate in the trial per day.
3. The night before the visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12 00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window.
4. Visit 3 will take place at least 48 hours after screening (Visit 1) and no more than 30 days after screening (Visit 1).
5. There will be a 24-hour minimum washout between Visit 3 and Visit 4 and a maximum of 3 weeks between Visit 3 and Visit 4.
6. Visit 5 will take place 7 days ±3 days from Visit 4.
7. Visit 6 will take place 25 days ±4 days from Visit 4.
8. Height and physical examination will be measured at Visit 1 only.
9. Vital signs including body temperature and blood pressure will be obtained at visit start and visit end.
10. At visit start and visit end.
11. Urine HCG pregnancy test only for women of childbearing potential. The date of the last menstrual period in female patients will be obtained at Visit 1 only.
12. Test for FSH level only for postmenopausal women amenorrheic for less than 1 year.
13. If indicated by history.
14. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor and trial policies and procedures.
15. Collected at least hourly. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
16. Collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.
17. Once the infusion sites have been placed but no drug has yet been administered.
18. Between approximately Hour 3 and Hour 4.
19. Between approximately Hour 6 and Hour 7.
20. Before the start of dosing.

ADA = anti-drug antibodies; BG = blood glucose; BP = bionic pancreas; CGM = continuous glucose monitor; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HCG = human chorionic gonadotropin; VAS = visual analog scale.

[redacted]

APPENDIX B: CLINICAL LABORATORY ANALYTES

Chemistry

Alanine aminotransferase	Aspartate aminotransferase
Alkaline phosphatase	Total protein
Albumin	Total and direct bilirubin
Gamma-glutamyl transferase	Glucose
Creatinine	Estimated glomerular filtration rate
Blood urea nitrogen	Uric acid
Bicarbonate	Sodium
Potassium	Calcium
Chloride	Phosphorus

Hematology

Hemoglobin	Hematocrit
Red blood cell count	White blood cell count and differential
Platelets	Mean corpuscular volume
Mean corpuscular hemoglobin	Mean corpuscular hemoglobin concentration

Pregnancy Test
A urine HCG pregnancy test will be performed at screening, Visit 3, and Visit 4 only for women of childbearing potential.

Anti-drug Antibody Assessments
Blood samples (including back-up samples) for serum anti-ZP4207 and anti-glucagon antibodies will be taken prior to first dosing (Visit 3) and at the Follow-up Visit (Visit 6).

ZP4207/Glucagon Exposure Sampling
At Visit 3 and Visit 4, ZP4207/glucagon exposure sampling will be collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.

Screening Visit Only
Test for FSH level only for postmenopausal women amenorrheic for less than 1 year
Optional fractionated plasma metanephrines (if indicated by history)
Hemoglobin A1c

[redacted]

APPENDIX C: BRIEF DESCRIPTION OF QUESTIONNAIRES

Diabetes Treatment Satisfaction Questionnaire - Status (DTSQs)
The DTSQs measures patient satisfaction with diabetes treatment. It consists of a 6 item scale for assessing treatment satisfaction and two additional items assessing perceived frequency of hyperglycemia and hypoglycemia. The DTSQs is meant for adults and older children. Dr. Clare Bradley has produced a version that is appropriate for bionic pancreas studies for this use, along with a version for younger children. It is administered before the intervention. The DTSQs is valid and reliable. Administration time is less than 5 minutes.

Diabetes Treatment Satisfaction Questionnaire – Change (DTSQc)
Although the DTSQ is responsive to treatment changes, ceiling effects are often seen with this instrument, where maximum or close-to-maximum scores at baseline provide little opportunity for registering improvement. The DTSQc contains the same items as the DTSQs version but asks patients to consider their satisfaction with their current treatment compared with their previous treatment. The DTSQc is meant for adults and older children. Dr. Clare Bradley has produced a version that is appropriate for bionic pancreas studies for our use, along with a version for younger children. It is administered during and at the end of the intervention. The DTSQc is valid and reliable. Administration time is less than 5 minutes.

T1-Diabetes Distress Scale (T1-DDS)
The T1-DDS is a 28-item survey that assesses seven sources of diabetes distress for type 1 adults. It captures feelings of powerlessness; management distress; hypoglycemia distress; negative social perceptions by others; eating distress; physician (health care) distress; and friend/family distress. Items are scored on a 6-point scale from not a problem to a very serious problem. It is administered before, during, and at the end of the intervention. The scale is valid and reliable, and has been shown to be sensitive to change over time. Administration time is 5 minutes.

Problem Areas in Diabetes Survey (PAID)
There are three versions of the PAID: Teen (PAID-T), Parent (PAID-P), and Child (PAID-C) versions. This measure of diabetes-specific emotional distress in youth with diabetes and their parents is 26 items. A total score is generated. It is administered before, during, and at the end of the intervention. The PAID-T and PAID-P are valid and reliable. Psychometric analysis of the PAID-C is in progress. Administration time is 5 minutes.

Hypoglycemia Fear Survey (HFS)
There are three versions of the HFS, Adult (HFS), Youth (HFS-Y) and Parent (HFS-P). The HFS measures several dimensions of fear of hypoglycemia among adults with type 1 diabetes. It consists of 23 items and produces two sub-scale scores; a Behavior sub-scale that measures behaviors involved in avoidance and/or over-treatment of hypoglycemia and a Worry sub-scale that measures anxiety and fear surrounding hypoglycemia. The HFS-Y consists of 25 items and the HFS-P consists of 26 items; both produce sub-scale scores similar to the Adult HFS. It is administered before, during, and at the end of the intervention. All versions of the HFS are valid and reliable. Administration time is 5-10 minutes.

[redacted]

Impact of Daily Diabetes Demands (IDDD)
There are four versions of the IDDD; Adult (IDDD-A), Youth (IDDD-Y), Parent (IDDD-P), and Significant Other (IDDD-SO). This instrument measures the burden related to the demands of the daily diabetes regimen and is 22 items. A total score is generated. It is administered before, during, and at the end of the intervention. Psychometric analysis of the IDDD-Y is in progress using the data from the second Bionic Pancreas Camp Study in pre-adolescent children, and of the IDDD-A is in progress using data from the Bionic Pancreas Multicenter Study in adults. Administration time is 5 minutes.

Bionic Pancreas User Opinion Survey (BPUOS)
There are four versions of the BPUOS; Adult (BPUOS-A), Youth (BPUOS-Y), Parent (BPUOS-P), and Significant Other (BPUOS-SO). This measure assessing both the benefits from, and difficulties with, use of the bionic pancreas, and consists of 38 items. A total score is generated. It is administered during and at the end of the intervention. Psychometric analysis of the BPUOS-Y is in progress using the data from the second Bionic Pancreas Camp Study in pre-adolescent children, and of the BPUOS -A is in progress using data from the Bionic Pancreas Multicenter Study in adults. Administration time is 10 minutes.

[redacted]

Clinical Trial Protocol
ZP4207-16051

Version number: 1.0
Date: 03 May 2016

CLINICAL TRIAL PROTOCOL

The iLet Feasibility Trial Testing the iLet, a Fully Integrated Bihormonal Bionic Pancreas with ZP4207

Investigational Product: ZP4207
Protocol Number: ZP4207-16051
Phase: 2

Principal Investigator:
Steven J. Russell, MD, PhD[1]

Co-Investigator:
[redacted], MD[1]

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SIGNATURE PAGE

TRIAL TITLE: The iLet Feasibility Trial Testing the iLet, a Fully Integrated Bihormonal Bionic Pancreas with ZP4207

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the trial.

Signature [redacted] Date [redacted]

Ulrik Mouritzen, MD [redacted]
Vice President, Clinical Development
Zealand Pharma A/S

[redacted] Date [redacted]

[redacted] DVM, PhD
Principal Clinical Pharmacologist
Zealand Pharma A/S

Clinical Trial Protocol
ZP4207-16051

Version number: 1.0
Date: 03 May 2016

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the trial as described. I will conduct this trial in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the trial within the time designated. I will provide copies of this protocol and access to all information furnished by Zealand Pharma A/S to trial personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the trial product and trial procedures. I will let them know that this information is confidential and proprietary to Zealand Pharma A/S and that it may not be further disclosed to third parties. I understand that the trial may be terminated or enrollment suspended at any time by Zealand Pharma A/S, with or without cause, or by me if it becomes necessary to protect the best interests of the trial patients.

I agree to conduct this trial in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and ICH Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

Clinical Trial Protocol
ZP4207-16051

Version number: 1.0
Date: 03 May 2016

SYNOPSIS

TITLE: The iLet Feasibility Trial Testing the iLet, a Fully Integrated Bihormonal Bionic Pancreas with ZP4207

PROTOCOL NUMBER: ZP4207-16051

INVESTIGATIONAL PRODUCT: ZP4207

PHASE: 2

INDICATION: ZP4207 is an anti-hypoglycemic glucagon analog in a ready-to-use liquid formulation which is being studied to improve glycemic control in adults (and children) with type 1 diabetes mellitus (T1DM) as part of a bihormonal bionic pancreas (BP).

OBJECTIVES:

Primary: The primary objective is to conduct a trial testing the safety and tolerability of the iLet when used with ZP4207 in 10 adult (≥18 years of age) patients with T1DM.

Secondary: The secondary objectives are to measure glycemic regulation, including hypoglycemia exposure (percent of time spent with continuous glucose monitor [CGM] glucose <60 mg/dL), evaluate BP device reliability, and to document the satisfaction of patients with the iLet with the goal of optimizing the functionality and user interface of the iLet.

POPULATION: Up to 20 adult (≥18 years of age) patients who already manage their T1DM using continuous subcutaneous (SC) insulin infusion pump therapy can be enrolled.

TRIAL DESIGN: This trial is a single-center, open-label, randomized cross-over trial. The trial will enroll adult patients with T1DM and will assess the safety and efficacy of the iLet using the glucagon analog ZP4207 versus the iLet using Lilly glucagon. The iLet will also administer insulin (insulin lispro, Lilly Humalog) using the same blood glucose (BG) control algorithm for both treatment arms. The trial will be conducted at a single center, the Massachusetts General Hospital Diabetes Center in Boston, MA.

TRIAL TREATMENT: The trial involves SC administration of insulin lispro (Humalog, Lilly), which is commercially available by prescription and is indicated for patients with T1DM, but not for use in a BP.

The trial also involves SC administration of Lilly glucagon in one iLet arm. Lilly glucagon is commercially available by prescription and is indicated for patients with T1DM in severe hypoglycemia, but not for use in a BP.

The trial also involves SC administration of the glucagon analog ZP4207, 1 mg/mL, in the other iLet arm. ZP4207 will be made available by Zealand Pharma A/S, Denmark as liquid formulation in prefilled syringes of 0.6 mL.

[redacted]

PRIMARY ENDPOINT:
The primary endpoint is the safety and tolerability of ZP4207 and the iLet as assessed by:

- Number and type of adverse events (AEs)
- Clinical laboratory measurements
- Vital signs
- 12-lead electrocardiogram (ECG)
- Local tolerability and infusion site reactions as measured with the Draize scale
- Immunogenicity as measured by anti-drug antibodies
- Pain as measured on a 10 cm visual analog scale (VAS)
- Nausea as measured on a 10 cm VAS

SECONDARY ENDPOINTS:
The secondary endpoints for the iLet and ZP4207 include measurements of BP function as well as glycemic and non-glycemic measurements.

Bionic Pancreas Function
This endpoint data will be generated from the BP data during each treatment visit:

- Average percent insulin dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
    - Average percent glucagon/ZP4207 dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts calculated by the BP algorithm that are successfully issued to the pump by the BP (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts calculated by the BP control algorithm that are successfully issued by the BP
    - Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully issued by the BP
- Average percent of 5-minute steps during which the BP is functioning nominally in all respects based on real-time CGM data (new CGM glucose reading captured, dose calculated, and dose issued to pumps)
- Average percent of 5-minute steps during which the BP is functioning nominally with or without a new CGM glucose reading captured (dose calculated and dose issued to pumps). If a CGM signal is not available, the dose calculated may be based on weight or historical basal rates.
- CGM reliability index, calculated as percent of possible values actually recorded by CGM
- CGM Mean Absolute Relative Difference versus time-stamped BG values from meter download
- List of technical faults associated with the BP including cause and resolution

[redacted]

Glycemic
All of following metrics will be generated from the Dexcom G4 Platinum CGM data during each treatment visit.

- Fraction of time spent within each of the following glucose ranges:
  - <50 mg/dL
  - <60 mg/dL
  - <70 mg/dL
  - 70-120 mg/dL
  - 70-140 mg/dL
  - 70-180 mg/dL
  - >180 mg/dL
  - >250 mg/dL
  - >300 mg/dL
- Number of severe hypoglycemic events (patients unable to self-treat, requiring the assistance of another person)
- Number of episodes of symptomatic hypoglycemia
- Number of carbohydrate interventions for hypoglycemia
- Total grams of carbohydrates taken for hypoglycemia
- Mean CGM glucose

Non-glycemic

- Glucagon/ZP4207 total delivery per kg of body mass
- Insulin total delivery per kg of body mass
- Number of unscheduled infusion set replacements
- Number of unscheduled CGM sensor changes

EVALUATION OF TRIAL DATA: The following variables will be evaluated according to treatment for safety purposes: AEs, local tolerability, laboratory safety assessments, physical examination, vital signs, and 12-lead ECGs.

The analysis of BP function endpoints and glycemic endpoints will be on an intention-to-treat basis. In cases where a treatment arm was not completed (and that arm was not repeated according to protocol criteria), available data from that arm will be used in the data analysis.

The Shapiro-Wilk test will be used to determine the normality of the residuals for each comparison. Summary tables that display descriptive statistics, including percentages, means or medians, and standard deviation and/or ranges, as appropriate, will be provided.

A paired t-test or the Wilcoxon signed rank test for comparison of means with normally or non-normally distributed residuals, respectively, will be used. In a secondary analysis any period effect and any interaction between treatment and period will be looked for, although no such interaction is predicted for the efficacy outcome.

The number of patients and proportions of severe hypoglycemic events, symptomatic hypoglycemia, and carbohydrate interventions due to hypoglycemia with the event counts will be summarized descriptively, and the proportions will be analyzed by a Fisher's exact test if data allow.

[redacted]

Clinical Trial Protocol
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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibodies
AE	Adverse event
BG	Blood glucose
BP	Bionic pancreas
BU	Boston University
CFR	Code of Federal Regulations
CGM	Continuous glucose monitor
CRO	Contract research organization
DBR	Database review
DPP-4	Dipeptidyl peptidase-4
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FDA	Food and Drug Administration
FHD	First Human Dose
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HCG	Human chorionic gonadotropin
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IM	Intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
MD	Doctor of Medicine
MedDRA	Medical Dictionary for Regulatory Activities
MGH	Massachusetts General Hospital
MPC	Model-predictive control
PD	Pharmacodynamic
PK	Pharmacokinetic

[redacted]

Abbreviation	Definition
RN	Registered nurse
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SGLT-2	Sodium-glucose co-transporter-2
SIV	Site Initiation Visit
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 diabetes mellitus
TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
ULN	Upper limit of normal
VAS	Visual analog scale

[redacted]

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Background and Rationale

To date, clinical trials conducted by Boston University (BU) and Massachusetts General Hospital (MGH) in patients with type 1 diabetes mellitus (T1DM) have demonstrated the practicality of a wearable automated bionic pancreas (BP) control system for robust glucose regulation using a continuous glucose monitor (CGM) to provide the input to the control system. Despite current technical limitations in CGMs and infusion pumps, the trials by BU/MGH have shown that a bihormonal BP is capable of achieving safe and effective blood glucose (BG) control automatically, with minimal hypoglycemia during 11 continuous days in the face of unrestrained meals and exercise and with trivial patient input (optional announcement of meals).

The BP provides automatic BG regulation and reduces hypoglycemic episodes. Additionally, the system spares the wearer the relentless tasks of carbohydrate counting, frequent BG monitoring, estimating the effects of specific meals and exercise activity on BG levels, and manual drug administration, which are inexact, demanding, aggravating, and require continuous diligence and vigilance. The degree of glycemic control achieved by the BP is predicted to dramatically reduce the deleterious and debilitating complications of T1DM.

In its last tested embodiment, the BP consisted of a Dexcom G4 CGM, and an iPhone that are hardwired together, with the iPhone running the control algorithm and communicating via Bluetooth with 2 Tandem t:slim pumps to dose insulin and glucagon. The connections are repeatedly lost among these 4 components throughout the day, an issue that has the potential to adversely impact BG control, whether due to missed CGM values or missed doses. In addition, the troubleshooting required to repair these recurring disconnections can be burdensome to the user. Integrating these components into a single device would establish seamless connectivity among them, which would eliminate the need for such troubleshooting. This would lead to a smoother device operation with fewer interruptions, which would enhance its user friendliness, optimize its BG control potential, and further improve the quality of life of its users.

The BU Investigators have recently designed, built, and tested a proprietary first-generation of such a fully integrated BP system, referred to as the iLet and the iLet infusion set. The iLet is a dual-chamber infusion system that currently incorporates the Dexcom G4 CGM technology, a custom user interface with touchscreen display, and all of the mathematical dosing algorithms that were tested in and validated using the iPhone-based BP in outpatient studies over the past 3 years. The iLet infusion set provides 2 independent subcutaneous (SC) fluid pathways from the iLet to the patient (1 for insulin and the other for glucagon). One tube connects to the prefilled insulin cartridge and the other tube connects to the fillable (single-use) glucagon cartridge.

In order to provide automatic BG regulation, the iLet has the ability to deliver both insulin and glucagon. However, currently available glucagon formulations have limited stability at room temperature, necessitating frequent changes to the glucagon infusion set. Therefore, the current trial is designed to test the glucagon analog ZP4207 in the iLet, as this peptide analog of human glucagon is provided in a liquid formulation stable at room temperature.

[redacted]

The current trial is a first feasibility trial designed to use the first-generation iLet and iLet infusion set to compare ZP4207 with marketed glucagon (Lilly). The trial is intended to demonstrate the safety and tolerability of ZP4207 in the iLet and the feasibility of achieving comparable autonomous glycemic control. It is not intended to comprehensively demonstrate the definitive efficacy of the iLet in extended, continuous daily use, but rather to demonstrate its functionality and accuracy in a practical, albeit very controlled, clinical setting. The trial is expected to provide practical information that will benefit the design of a next-generation iLet and iLet infusion set and help pave the way for a more comprehensive outpatient home-use Phase 2 trial and ultimately a pivotal trial where comprehensive safety and efficacy through continuous full daily use of the iLet with ZP4207 will be documented.

The data derived from this trial will permit evaluation of the robustness of the iLet as well as the safety and efficacy of ZP4207 when used in conjunction with the iLet. The data obtained will be used to further improve the iLet and will allow BU/MGH to expand to larger outpatient trials using the iLet with ZP4207.

1.2 Bihormonal Bionic Pancreas System

The BP is an autonomous, self-learning system that requires only the patient's weight for initialization, and then autonomously adapts, modestly or dramatically, as needed, to cope with the wide range of insulin requirements of adults, adolescents, and pre-adolescents with T1DM. The BP obviates the need for the patient to know, or even appreciate, their insulin requirements, and renders obsolete any need for patients or caregivers to know carbohydrate-to-insulin ratios, basal rates, or insulin correction factors.

The core technology is a suite of control algorithms that orchestrate the automated dosing of insulin and glucagon to regulate BG levels. An insulin controller orchestrates all SC insulin dosing. At its centerpiece is a model-predictive control (MPC) algorithm, which bases insulin doses on the glucose data and insulin absorption kinetics, compensating for the slow absorption rate of SC insulin analogs (peak time in blood of 30-90 min, clearance in 4-8 hr). This enables the algorithm to refrain from stacking and overdosing insulin. Furthermore, the MPC algorithm automatically adjusts its insulin-dosing aggressiveness continuously and in real-time to different insulin needs between individuals and variable needs within the same individual. Running in parallel with the MPC algorithm is an algorithm that automatically modulates basal insulin delivery over multiple time scales, and another algorithm that automatically adapts insulin doses in response to optional meal announcements. Unlike current insulin pumps and the insulin-only control algorithms, the adaptive basal insulin algorithm obviates the need for the user to set, or even know, his or her “basal-rate profile.” Instead, it is capable of automatically adapting to, and compensating for, changes in an individual's basal insulin need, such as might occur over a period of hours, days, or weeks (e.g., circadian hormonal fluctuations, intercurrent illness, physical activity, or emotional state) or as might occur over a period of months or years due to developmental changes (e.g., hormonal changes that occur during puberty or menopause). The adaptive meal dose controller obviates the need for the user to set, or even know, his or her “carbohydrate-to-insulin ratios,” as it makes automatic adjustments based on dosing history for similar meal announcements made on previous days, and customizes the dose for each individual and for time of day.

The BP also includes a proportional-derivative algorithm governing SC micro-doses of glucagon to help prevent impending hypoglycemia. Glucagon dosing is based on the glucose

[redacted]

level and rate of descent. It may occur preemptively even if glucose is above range, and it includes a feedback term to account for the pending effects of recent glucagon doses.

Taken together, these mathematical algorithms provide a universal framework for a glycemic control strategy that requires no quantitative input from, or participation by, the user (besides entering body weight to initialize the system), but which automatically adapts insulin and glucagon dosing to meet the individual needs of each user. Another challenge met is enabling the technology to remain completely autonomous in managing insulin and glucagon delivery even when the CGM is offline. Specifically, when the CGM is offline, the BP invokes the high-resolution “basal rate profile” that it had recently learned and stored when the CGM was online. On the basis of what the system learned and stored about meal announcements when the CGM was online, it is able to respond to meal announcements in the same manner when the CGM is offline. Finally, it automatically responds to user-entered BG values when the CGM is offline by issuing a correction dose of insulin or glucagon based on what it learned about the user's insulin and glucagon needs when the CGM was online. Thus, the BP never relies on, or burdens the user with, the determination of subjective dosing decisions, which inevitably vary in quality and reliability among different users. The BP provides a turnkey solution for people with T1DM that comprehensively manages glycemia across a broad range of individual needs and across a large spectrum of circumstances and challenges to glycemic control.

A significant challenge for the use of glucagon in a bihormonal BP is the lack of a commercially available glucagon formation that is stable and well-suited to infusion over several days in a pump reservoir. However, BU/MGH have proceeded with studies using a relatively unstable marketed formulation that must be reconstituted from a lyophilized powder on a daily basis. This allowed BU/MGH to proceed with studies of the bihormonal system while awaiting the production of stable glucagon formulations or stable glucagon analogs.

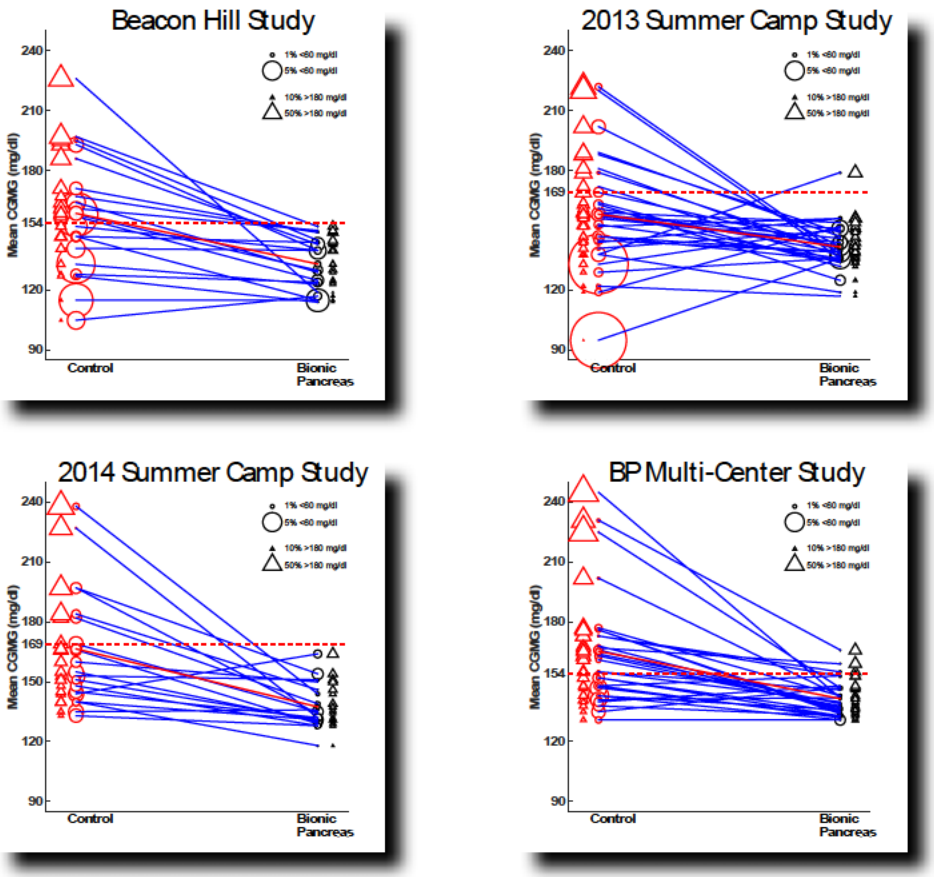
1.3 Preliminary Studies with the Bihormonal Bionic Pancreas System

The BP hardware platform has evolved over the years from a laptop-driven system, which was used in all inpatient studies to the first truly mobile wearable iPhone-driven platform, which has been used in a number of outpatient studies. Using the iPhone-based BP system, >110 outpatient experiments of 5-11 days in duration in each subject have been conducted (>800 patient days or >2 patient years of data) across subjects ranging in age between 6 and 76 years old and in body mass between 21 and 128 kg. The robust adaptation capabilities of the BP is evident in the fact that the average total daily dose of insulin among these subjects varied by over 13-fold (from 11 to 145 units/day).

In November 2012, Food and Drug Administration (FDA) approval was obtained to conduct the first outpatient study testing the BP in adults 21 years or older with T1DM. This study, referred to as the Beacon Hill Study, followed a random-order cross-over design in which 20 adults with T1DM participated in 5 days on the iPhone-based BP and 5 days of usual care in which they wore a CGM with blinded display and muted alarms. In the BP arm, subjects kept to a 3-square-mile geographic area centered around the Beacon Hill neighborhood in Boston. They ate as they chose at local restaurants, and exercised at will with access to 2 gyms. Analysis was pre-specified to focus on Days 2-5, since glycemic control is more representative of BP performance after most of the adaptation by the BP occurs on Day 1 (Russell, 2014). Results are summarized in Figure 1.

[redacted]

Figure 1. Outpatient Results Summarizing the Distribution of Mean CGM Glucose Levels and Hypoglycemia in the BP and Control Arms



Study	Age (years)	Bionic Pancreas (BP) Mean CGM glucose level (mg/dl)	Bionic Pancreas (BP) % of CGM glucose levels <50 mg/dl (%)	Bionic Pancreas (BP) % of CGM glucose levels 70–180 mg/dl (%)	Control Mean CGM glucose level (mg/dl)	Control % of CGM goucose valuss <50 mg/dl (%)	Control % of CGM goucose valuss 70–180 mg/dl (%)	*p* value (BP versus Control) for: Mean CGM glucose level	*p* value (BP versus Control) for: % of CGM glucose values <50 mg/dl	*p* value (BP versus Control) for: % of CGM glucose values 70–180 mg/dl
Beacon Hill (n 20, 5-day experiments)	≥21	133	1.5	80	159	3.7	59	<0.001	0.020	<0.001
2013 Summer Camp (n 32, 5-day experiments)	12–20	142	1.3	76	158	2.2	65	0.004	0.192	<0.001
2014 Summer Camp (n 19, 5-day experiments)	6–11	137	1.2	81	168	2.8	58	0.004	0.001	<0.001
BP Multi Center (n 39, 11-day experiments)	≥18	141	0.6	78	162	1.9	62	<0.001	<0.001	<0.001

Mean CGM glucose levels for each subject under usual care (red circles) are connected with the subject's mean CGM glucose level on the BP (black circles). The diameters of the circles shown are proportional to the percentage of CGM glucose values <60 mg/dL, and the size of the triangle is proportional to the percentage of CGM glucose values >180 mg/dL. The horizontal red dashed line refers to the glucose level corresponding to the American Diabetes Association therapy goal for each age group tested, which corresponds to 154 mg/dL (HbA1c of 7%) for adults and 169 mg/dL (HbA1c of 7.5%) for children. Results are summarized in the table, where the co-primary outcomes (mean CGM glucose level and percentage of CGM glucose values <60 mg/dL) for the BP arm are highlighted in red for each of the 4 studies.
BP = bionic pancreas; CGM = continuous glucose monitoring; HbA1c = hemoglobin A1c.

In April 2013, FDA approval was obtained to conduct the first outpatient study testing the BP in adolescents 12-20 years old with T1DM. This study, referred to as the 2013 Summer Camp Study, followed a random-order cross-over design in which 32 adolescents with T1DM participated in 5 days on the BP and 5 days of supervised camp care in which they wore a CGM with blinded display and muted alarms. Subjects were fully integrated into normal camp activities without restrictions on diet or exercise. The study used the same iPhone-based BP that was used in the Beacon Hill Study. Results are summarized in Figure 1 (Russell, 2014). In April 2014, FDA approval was obtained to conduct the first outpatient study testing the BP in pre-adolescents 6-11 years old with T1DM. This study, referred to as the 2014 Summer Camp Study, was similar in design to the 2013 Summer Camp Study. Results are summarized in Figure 1 (Russell, 2016).

In April 2014, FDA approval was obtained to conduct the first multi-center study, which was also the first home study, to test the BP in adults 18 years or older with T1DM. This study, referred to as the Bionic Pancreas Multi-Center Study, followed a random-order cross-over design in which 39 adults participated in 11 days on the BP and 11 days of usual care. Participants went to work as usual, and lived and slept at home, all without clinical supervision. There were no restrictions placed on diet or exercise. The study included 4 medical centers (10 subjects per center), which included MGH, the University of Massachusetts Medical School, Stanford University, and the University of North Carolina at Chapel Hill. Results are summarized in Figure 1.

All of these studies used marketed glucagon (glucagon for injection, Eli Lilly). Due to its limited stability, Lilly glucagon must be reconstituted immediately before use. Animal studies have previously shown that despite its limited chemical stability, Lilly glucagon maintains its biological activity for up to 7 days in solution. Using this data, an Investigational New Drug (IND) exemption was obtained from the FDA for its use in a pump for up to 27 hours. This allowed these studies to be performed by asking volunteers to reconstitute a new vial of glucagon and fill the glucagon pump at approximately the same time every day. However, marketed Lilly glucagon has no path forward for approval for chronic BP use.

1.4 ZP4207

ZP4207 is a peptide analog of human glucagon that is being developed to treat hypoglycemia in patients with T1DM and type 2 diabetes mellitus. ZP4207 exhibits improved physical and chemical stability in aqueous media and is suitable for liquid formulation. ZP4207 is comprised of 29 amino acids and has 7 amino acid substitutions when compared to native glucagon.

Two clinical Phase 1 trials have been conducted to establish safety and tolerability of ZP4207 after single and multiple dosing to healthy patients and T1DM patients under insulin-induced hypoglycemic conditions.

The First Human Dose (FHD) trial (ZP4207-14013) was finalized in April 2015. The trial was a randomized, double-blinded trial with the objectives to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of ZP4207 as compared to an active comparator. Part 1 included a single ascending dose in healthy volunteers in cohorts of 8. In each cohort, the patients were randomized 3:1 to ZP4207 (n=6) or Novo Nordisk GlucaGen® (n=2). Five cohorts with SC administration (0.01, 0.1, 0.3, 1.0, and 2.0 mg ZP4207 compared to 1 mg GlucaGen) and 3 cohorts with intramuscular (IM) administration (0.3, 1.0, and 2.0 mg ZP4207 compared to 1 mg GlucaGen) were included. Part 2 included 2 sequence groups of

[redacted]

10 hypoglycemic T1DM patients. The patients were treated with fixed single IM doses of 0.7 mg ZP4207 and 1.0 mg GlucaGen in a sequential cross-over design in a randomized treatment order.

The second clinical trial (ZP4207-15007) was a single-center, double-blind, Phase 1b trial investigating the safety and tolerability, PK and PD of ZP4207 following repeated administration in healthy volunteers compared to placebo. It was finalized in July 2015. Each of the 3 cohorts comprised 8 subjects, who received 5 repeated SC doses of ZP4207 or placebo in a 3:1 treatment allocation. The first cohort started with the lowest dose of 0.1 mg. Cohort 2 and 3 continued with 0.3 and 1.0 mg, respectively.

The Phase 1 results did not give rise to specific safety concerns, beyond those related to the pharmacological effect of ZP4207. All adverse events (AEs) recorded in the trials were of mild or moderate severity. The most frequent systemic AE related to treatment with ZP4207 was nausea, which is a known side-effect following administration of glucagon. The most frequent injection site reaction was transient erythema, occurring in all ZP4207, glucagon, and placebo treatment groups, irrespective of dose. No anti-drug antibodies (ADA) incidences were observed.

The observed PD response, in terms of increased plasma glucose, in insulin-induced hypoglycemic patients with T1DM following dosing with 0.7 mg ZP4207 administered IM was similar to that observed following IM dosing with 1.0 mg glucagon (GlucaGen, Novo Nordisk). An increase in plasma glucose of ≥20 mg/dL from hypoglycemic levels was achieved within 30 minutes for all patients.

In terms of PK, ZP4207 had a short half-life and high clearance and dose proportionality for both maximum plasma concentration and area under the concentration-time curve from time 0 to 300 minutes in the dose range 0.1 to 2.0 mg following SC administration. Following IM administration, dose proportionality was shown in the investigated dose range of 0.3 to 2.0 mg. The PK properties of 0.7 mg ZP4207 IM were comparable with those of 1.0 mg glucagon (GlucaGen, Novo Nordisk) with IM administration.

1.5 Risk/Benefit

While the potential risks are minimal, the findings of this trial may reveal information that can substantially improve medical care for persons with diabetes. Therefore, the overall risk/benefit for patients participating in this trial is assessed as acceptable.

Potential Risks and Discomforts

Trial patients will be informed by the Investigator of the potential risks of ZP4207 and other trial-related procedures before they enter the trial.

In this trial, patients with T1DM will be included to test the safety and efficacy of the iLet using ZP4207 versus the iLet using Lilly glucagon. The cross-over design with inclusion of the same T1DM patients into the 2 treatment arms in a randomized order will allow for a direct comparison of the safety and efficacy of the 2 treatments, based on intra-patient variability only.

[redacted]

Patients may experience mild discomfort associated with the insertion of the infusion sets and sensor into the SC tissues. The risk of discomfort due to insertion of infusion sets and sensors is expected to be slightly greater than in their lives outside the trial because more infusion sets will be inserted and a CGM sensor will be inserted. Most patients will use only one infusion set and not all will use a CGM sensor in usual care.

There is a potential risk of hypoglycemia, since recombinant insulin analog will be administered. Due to frequent monitoring of glucose and direct supervision by a registered nurse (RN) or Doctor of Medicine (MD) at all times, the risk of a hypoglycemic episodes leading to significant harm to patients is expected to be substantially lower than their risk during their usual therapy.

There is a risk of hyperglycemia. This risk is expected to be less than the risk during the patients' lives outside of the trial based on data from earlier BP trials and the design of this trial.

Treatment with ZP4207 and marketed glucagon can result in undesired effects or complaints. Undesired effects and complaints such as gastrointestinal side effects including nausea, vomiting, and diarrhea are known side effects of glucagon administration at higher dose levels. The frequency of nausea associated with the administration of 1 mg of glucagon according to the Summary of Product Characteristics (SPC) for Glucagon is described to be between 1/10 and 1/100. The frequency of vomiting is described to be between 1/100 and 1/1000 (Novo Nordisk, 2015). Similar gastrointestinal side effects have also been observed to a limited degree in the 2 clinical trials conducted with ZP4207, again at higher dose levels. The individual doses of ZP4207 and Lilly glucagon delivered by the BP are expected to be significantly lower than doses typically associated with nausea. As with every novel drug substance, new and yet unknown side effects may also occur.

There are limited data available to describe the immunogenic potential of glucagon products available on the market, but the data available indicate that marketed glucagon only has a small immunogenic potential. A Phase 1 trial performed with recombinant human glucagon and animal derived glucagon in 75 healthy patients did not show signs of ADA measured 13 weeks after trial product administration (Eli Lilly, 2005). In the ZP4207 FHD trial, ZP4207-14013, no confirmed anti-ZP4207 or anti-glucagon antibodies were detected in any of the samples. In addition, the 5 sequential administrations of ZP4207, as applied in trial ZP4207-15007, were not associated with the development of antibodies against ZP4207 in the 18 subjects enrolled to receive ZP4207. The optimized formulation of ZP4207, as applied in the present trial is not expected to change the immunogenic potential of the Investigational Medicinal Product (IMP).

In relation to diabetes therapy, development of insulin-antibodies is documented more substantially and route of administration has been shown to influence immunogenic potential of insulins. However, these antibodies against insulin generally do not have an impact on insulin action and are thus not clinically relevant.

In terms of consequence, development of high titer antibodies against ZP4207 could, in theory reduce the activity of endogenous glucagon, which again, in theory could influence hypoglycemic episodes. However, most patients with T1DM do not secrete glucagon normally in response to hypoglycemia, so they would be less likely to be negatively impacted by

[redacted]

anti-glucagon antibodies. Limited suppression of glucagon would, however, not be considered critical, as low glucose levels can also be corrected by other means, including oral intake of glucose and by other endogenous hormones such as oxyntomodulin.

Overall, ZP4207 is judged to be a low-risk molecule, based upon the available clinical data as well as the outcome of the risk-based approach to the immunogenicity assessment made. The present trial will include sampling for measurement of antibodies against ZP4207 prior to first dosing (Visit 3) and at the Follow-up Visit. In line with regulatory guidance documents, these samples will be appropriately analyzed and the results will be included in the overall assessment of the immunogenic potential of ZP4207 after completion of each trial and as the clinical development program advances.

Administration of ZP4207 may be associated with a risk of allergic reactions similar to those observed for other therapeutic peptides or proteins. Patients with known or suspected allergies to the trial products or related products will be excluded from the trial. Mild or moderate allergic reactions may include symptoms of rash, fever, flu-like symptoms, nausea, headache, and myalgia. Acute generalized hypersensitivity reactions are usually very rare but may include symptoms of flushing, sweating, dizziness, change in blood pressure, and difficulties in breathing. The risk of acute hypersensitivity reactions is described to be less than 1/10,000 for native glucagon. No severe acute hypersensitivity reactions have been observed in the 2 clinical trials conducted with ZP4207.

Potential Benefits

Based on experiences from previous trials of the BP and the design of this trial, patients enrolled in the trial may benefit from a reduction in risk of hypoglycemia and hyperglycemia and a better mean glucose compared to their usual diabetes care during their short trial participation.

The data derived from this trial will allow evaluation of safety and tolerability of ZP4207 in the iLet, and the robustness and effectiveness of the new BP control system. The data obtained will be used to further improve the iLet and will allow the expansion to larger outpatient trials using the iLet with ZP4207.

This trial is a necessary step in preparing the BP with ZP4207 to become available to people with T1DM. Wide availability of the BP with ZP4207 could improve the medical care of adults and children with T1DM.

2 TRIAL OBJECTIVES

2.1 Primary Objective

The primary objective is to conduct a trial testing the safety and tolerability of the iLet when used with ZP4207 in 10 adult (≥18 years of age) patients with T1DM.

2.2 Secondary Objectives

The secondary objectives are to measure glycemic regulation, including hypoglycemia exposure (percent of time spent with CGM glucose <60 mg/dL), evaluate BP device reliability,

[redacted]

and to document the satisfaction of patients with the iLet with the goal of optimizing the functionality and user interface of the iLet.

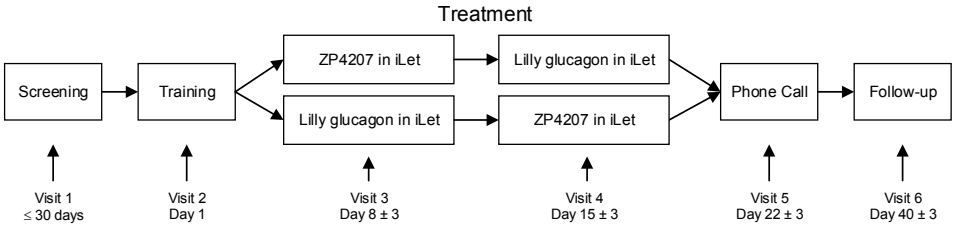
3 TRIAL DESCRIPTION

3.1 Summary of Trial Design

This trial is a single-center, open-label, randomized cross-over trial. The trial will enroll adult patients with T1DM and will assess the safety and efficacy of the iLet using the glucagon analog ZP4207 versus the iLet using Lilly glucagon. The iLet will also administer insulin (insulin lispro, Lilly Humalog) using the same BG control algorithm for both treatment arms. The trial will be conducted at a single center, the MGH Diabetes Center in Boston, MA.

The overall trial design schematic is displayed in Figure 2.

Figure 2. Trial Design Schematic



3.2 Indication

ZP4207 is an anti-hypoglycemic glucagon analog in a ready-to-use liquid formulation which is being studied to improve glycemic control in adults (and children) with T1DM as part of a bihormonal BP.

3.3 Number of Patients

Up to 20 adult patients with T1DM can be enrolled. The upper bound is based on the expectation that some patients will be excluded after the Screening Visit and the possibility that some patients may have to be discontinued before completion (due to, for instance, inter-current illness or patient withdrawal). Eligible patients will be randomized until 10 patients have completed the trial protocol. It is expected that between 10 and 12 patients will be randomized.

4 SELECTION AND WITHDRAWAL OF PATIENTS

The trial will enroll patients who already manage their T1DM using continuous SC insulin infusion pump therapy. This requirement is imposed because multiple daily injection therapy involves the use of medium-acting or long-acting basal insulin that would require an extended washout period.

4.1 Inclusion Criteria

1. Male and female patients with T1DM for at least 1 year, as defined by the American Diabetes Association
2. Age ≥18 years
3. Diabetes managed using an insulin pump for ≥6 months
4. Prescription medication regimen stable for >1 month (except for medications that will not affect the safety of the trial and are not expected to affect any outcome of the trial, in the judgment of the Investigator)
5. Informed consent obtained before any trial-related activities (trial-related activities are any procedure that would not have been performed during normal management of the patient)
6. Patients in good health according to age (medical history, physical examination, vital signs, 12-lead electrocardiograms [ECGs], laboratory assessments), as judged by the Investigator

4.2 Exclusion Criteria

1. Unable to provide informed consent (e.g., impaired cognition or judgment)
2. Unable to safely comply with trial procedures and reporting requirements (e.g., impairment of vision or dexterity that prevents safe operation of the BP, impaired memory, unable to speak and read English)
3. Participation in another clinical trial of an investigational agent or device concurrently or within 1 month (or 5 half-lives) prior to the Screening Visit
4. Previous exposure to ZP4207
5. Females of childbearing potential who are pregnant (positive urine human chorionic gonadotropin [HCG]), breast feeding, plan to become pregnant in the immediate future, or sexually active without using highly effective contraception methods (highly effective methods are considered those with a failure rate less than 1% undesired pregnancies per year including surgical sterilization, hormonal intrauterine devices [coil], oral hormonal contraceptives, sexual abstinence, or a surgically sterilized partner) or postmenopausal women amenorrheic for less than 1 year with serum follicle-stimulating hormone (FSH) level ≤40 IU/L and not using highly effective contraceptive methods during the trial and until 1 month after last dosing in the trial
6. Male who is sexually active and not surgically sterilized who or whose partner(s) is not using highly effective contraceptive methods (highly effective contraceptive measures include surgical sterilization, hormonal intrauterine devices [coil], oral hormonal contraceptives, each in combination with spermicide-coated condoms), or who is not willing to refrain from sexual intercourse from the first dosing until 1 month after last dosing in the trial
7. Current alcohol abuse (intake averaging >3 drinks daily in last 30 days) or use within the last 6 months of controlled substances without a prescription (other than marijuana)
8. New onset clinically significant illness within 4 weeks prior to screening, as judged by the Investigator
9. Unwilling or unable to refrain on the treatment visits from:
    a. Acetaminophen in any form
    b. Use of drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the trial (use of beta blockers will be allowed as long as the dose is stable and the patient does not meet the criteria for hypoglycemia unawareness while

[redacted]

taking that stable dose, but use of benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the Investigator)

10. History of liver disease that is expected to interfere with the anti-hypoglycemia action of glucagon (e.g., liver failure or cirrhosis). Other liver disease (i.e., active hepatitis, steatosis, active biliary disease, any tumor of the liver, hemochromatosis, glycogen storage disease) may exclude the patient if it causes significant compromise to liver function or may do so in an unpredictable fashion.
11. Aspartate aminotransferase >2 × upper limit of normal (ULN), alanine aminotransferase >2 × ULN, or bilirubin >1.5 × ULN on screening laboratories
12. Renal failure on dialysis or estimated glomerular filtration rate <30 mL/min/1.73 m^2 on screening laboratories
13. Hemoglobin <12 gm/dL for men and <11 gm/dL for women
14. Personal history of cystic fibrosis, pancreatitis, pancreatic tumor, or any other pancreatic disease besides T1DM
15. Any known history of coronary artery disease including, but not limited to, history of myocardial infarction, stress test showing ischemia, history of angina, or history of intervention such as coronary artery bypass grafting, percutaneous coronary intervention, or enzymatic lysis of a presumed coronary occlusion)
16. Congestive heart failure with New York Heart Association Functional Classification III or IV
17. History of transient ischemic attack or stroke in the last 12 months
18. Seizure disorder, history of any non-hypoglycemic seizure within the last 2 years, or ongoing treatment with anticonvulsants
19. History of hypoglycemic seizures (grand-mal) or coma in the last 12 months
20. History of pheochromocytoma: fractionated metanephrines will be tested in patients with history increasing the risk for a catecholamine secreting tumor:
    a. Episodic or treatment refractory (requiring 4 or more medications to achieve normotension) hypertension
    b. Paroxysms of tachycardia, pallor, or headache
    c. Personal or family history of MEN 2A, MEN 2B, neurofibromatosis, or von Hippel-Lindau disease
21. History of adrenal disease or tumor
22. Hypertension with systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg despite treatment
23. Untreated or inadequately treated mental illness (indicators would include symptoms such as psychosis, hallucinations, mania, and any psychiatric hospitalization in the last year), or treatment with anti-psychotic medications that are known to affect glucose regulation
24. Electrically powered implants (e.g., cochlear implants, neurostimulators) that might be susceptible to radio frequency interference
25. History of adverse reaction to glucagon (including allergy) besides nausea and vomiting
26. Established history of allergy or severe reaction to adhesive or tape that must be used in the trial
27. Use of oral anti-diabetic medications (e.g., thiazolidinediones, biguanides, sulfonylureas, glitinides, dipeptidyl peptidase-4 [DPP-4] inhibitors, sodium-glucose co-transporter-2 [SGLT-2] inhibitors)
28. Inadequate venous access as determined by trial nurse or physician at time of screening

[redacted]

29. Any factors that, in the opinion of the Investigator, would interfere with trial endpoints or the safe completion of the trial

4.3 Target Population

Patients who meet all of the inclusion and none of the exclusion criteria will be considered as candidates for this trial. Individuals who have previously inquired about participation in BU/MGH trials and have asked to have their contact information kept on file will be contacted. In addition, advertisements for the trial may be posted at the MGH Diabetes Center and other places, and may be distributed in the weekly broadcast e-mail of research studies seeking volunteers. A letter may be sent to adult endocrinologists in the Boston metropolitan as well as selected nearby endocrinologists informing them of the trial and asking them to refer any eligible patients who might be interested. Information will be posted about the trial along with contact information on the BU/MGH website www.bionicpancreas.org and on www.clinicaltrials.gov.

4.4 Withdrawal Criteria

The participation of individual patients will be discontinued if they experience:

- Seizure or unconsciousness associated with hypoglycemia and associated with participation in the trial
- Persistent nausea and vomiting thought to be related to glucagon dosing associated with participation in the trial
- Hospitalization associated with participation in the trial
- Pregnancy

If more than 1 patient must be withdrawn from the trial for these reasons, the trial will stop and a vote of the Data and Safety Monitoring Board (DSMB) will be required to restart it. All AEs that are serious and unexpected but related will be reported to the DSMB within 5 working days.

Note that patients may discontinue participation at any time. Patients may be removed from the trial for other reasons, for instance, failure to comply with trial procedures or intercurrent illness that is unrelated to the BP but that precludes safe participation. Discontinuation of participation for these reasons will not contribute to a decision to discontinue the trial.

5 ASSIGNMENT TO TREATMENT GROUPS

This trial is an open-label, randomized cross-over trial. Patients who have completed the Screening Visit and meet all of the inclusion and none of exclusion criteria will be enrolled into the trial. All patients will participate in two 1-day treatment arms in random order (iLet using ZP4207 and iLet using Lilly glucagon) according to a pre-generated randomization scheme. Up to 2 patients can participate in the trial per day. The order of the iLet visits will be randomized in blocks of 2 patients.

[redacted]

6 TRIAL TREATMENT

6.1 Investigational Medicinal Products

Insulin: The trial involves SC administration of insulin lispro *(*Humalog, Lilly*)*, which is commercially available by prescription and is indicated for patients with T1DM, but not for use in a BP.

Glucagon: The trial also involves SC administration of Lilly glucagon in one iLet arm. Lilly glucagon is commercially available by prescription and is indicated for patients with T1DM in severe hypoglycemia, but not for use in a BP.

ZP4207: The trial also involves SC administration of the glucagon analog ZP4207, 1 mg/mL, in the other iLet arm. ZP4207 will be made available by Zealand Pharma A/S, Denmark as liquid formulation in prefilled syringes of 0.6 mL.

6.2 Storage and Drug Accountability of IMPs

All IMPs will be stored and handled in accordance with the Sponsor's instructions and/or the product labelling at the Investigator's site, e.g., refrigerated (+2ºC to +8ºC) and should not be exposed to excessive heat, direct sunlight and never be frozen.

All used, partly used, and unused vials or prefilled syringes must be kept by the Investigator and stored between +2ºC and +8ºC (unused) or at room temperature (partly used and used). Used and unused pre-filled syringes must be stored separately.

The Investigator must ensure the availability of proper storage conditions and record and evaluate the temperature. Temperature of the refrigerator used for drug storage is monitored continuously, an alarm system is established. The Investigator must inform the monitor immediately if any IMP has been stored outside specified conditions (e.g., outside temperature storage). Investigational Medicinal Product that has been stored improperly must not be dispensed to any patient before it has been re-evaluated and approved for further use. The Investigator must take appropriate action to ensure correct storage.

For the IMP, the Investigator must keep an accurate record of all IMPs received and the products used for each patient in a Drug Accountability Record. Storage locations, batch numbers, and expiry dates are also documented in this form.

The drug accountability must be performed in a timely manner by the monitor.

6.3 Dispensing and Return of IMPs

No IMPs may be dispensed to any person not enrolled in the trial.

Upon completion of the trial, the Sponsor will be responsible for destruction or storage of IMPs (used, partially used, or unused). These duties can be delegated to a contract research organization (CRO) and must be documented in the trial files.

[redacted]

6.4 Doses

The iLet can administer isolated insulin-glucagon doses once every 5 minutes. A single automated bolus of insulin will not exceed 3 units per 5-minute dose (30 µl of U-100 insulin) in both systems, and a single meal-priming dose, in response to a meal announcement made by the user, will not exceed 12 units (120 µl of U-100 insulin). A single bolus of glucagon will not exceed 80 µg (80 µl of 1 mg/mL Lilly glucagon or 1 mg/mL ZP4207). In prior studies, typical doses of glucagon were in the range of 0.005-0.04 mg per dose. The iLet is capable of administering as little as ~0.1 µl (0.011 units of U-100 insulin or 0.1 µg of 1 mg/mL ZP4207).

It is expected that the mean total daily doses of glucagon/ZP4207 will be <1.0 mg daily as in previous studies. The mean daily glucagon dose in a previous 11-day outpatient trial was 0.5 mg/day (range 0.2-0.9 mg/day). Currently, single doses of up to 2 mg ZP4207 have been administered in clinical trials. The recommended dose of marketed glucagon for adult patients suffering from severe hypoglycemia is 1 mg as a single injection. Mean glucagon levels in previous inpatient studies have been above the normal fasting range for glucagon only 1% of the time. Therefore, the glucagon exposure of patients is expected to be modest.

6.5 iLet Bionic Pancreas

Infusion set: A novel, dual cannula infusion set has been designed specifically for use with the iLet. Patients will wear dual channel tubing that will be attached to 2 infusion sets with one steel cannula each, one for insulin infusion and the other for glucagon infusion. The tubing and infusion sets will have undergone sterilization prior to being delivered in a sealed pouch. The steel cannulae will be inserted in the abdominal SC tissue.

Continuous glucose monitors: One transcutaneous glucose sensor for the Dexcom G4 Platinum (Garcia, 2013) will be inserted in the abdominal SC tissue and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to the sensor and the whole assembly is held to the skin with an adhesive patch and communicates wirelessly with the BP. If the G4 sensor fails for any reason during the trial (loss of CGM signal), it will be replaced promptly.

Bionic Pancreas Control Unit: The iLet is being built according to Class III medical device standards, adheres to a comprehensive and robust quality system, and is fully compliant with International Organization for Standardization (ISO) 13485 standards and document control practices. The iLet is a fully-integrated dual-hormone BP system that integrates the CGM technology (currently the Dexcom G4 Share system) as well as 2 independent motor-drivetrain pumping assemblies, which independently actuate the delivery of insulin and glucagon from pre-filled cartridges that are separately loaded into the iLet housing. Each drivetrain assembly utilizes a lead screw, which is driven by a precision micromotor, a gear case assembly, and a motor controller unit, in a manner similar to what is commonly found in most insulin infusion pumps on the market today. The iLet has dosing accuracy that is comparable to FDA-approved insulin pumps currently on the market. The iLet has a built-in Bluetooth Low Energy radio that also allows automatic communication with the paired CGM, as well as the Nova StatStrip® Xpress BG meter (Nova Biomedical). The iLet does not contain a cellular nor a WiFi radio, and does not accept input data from another mobile device (e.g., smartphone), other than the paired CGM and BG meter(s).

[redacted]

The mathematical control algorithms (which are the same as those used in the iPhone-based BP), the CGM glucose engine (Dexcom), and the native user interface software, are all interconnected through controller framework software and reside as embedded systems on printed circuit boards contained within the device housing. The touchscreen-enabled, menu-driven user interface and onboard processor provide a comprehensive and standalone platform, which allows the iLet to operate independently of smartphones or other devices and without the need for internet support during routine operation. The graphical user interface of the iLet has the same user options and capabilities of the iPhone BP, including having its home screen password protected and its settings options only accessible to trial staff via a separate password.

6.6 Other Trial Devices

YSI 2300 STAT Plus™ (Yellow Springs Instruments): The YSI 2300 STAT Plus is an FDA-approved glucose analyzer. Blood glucose measurements using the YSI 2300 STAT Plus will be obtained off of the IV line during both treatment visits.

Nova Biomedical StatStrip Xpress Glucose Meter: The Nova StatStrip Xpress glucose meter is an FDA-approved glucose meter that is commercially available. Blood glucose measurements for CGM calibration will be obtained with the Nova StatStrip Xpress during both treatment visits if the YSI 2300 STAT Plus fails and via fingerstick with the Nova StatStrip Xpress during any periods when IV blood samples are not available for any reason or the IV fails.

Exercise Bike: The trial will utilize a stationary exercise bike (ergometer) for the in-clinic exercise at the treatment visits. This bike will be stored at the Diabetes Research Center when not in use.

6.7 Concomitant Medications

6.7.1 Permitted Medications and/or Procedures

Patients may take any over-the-counter medications that they wish during the trial, with the exception of any medication containing acetaminophen as that may cause interference with CGM sensing. All concomitant medications, including over-the-counter medications, should be recorded.

Use of beta blockers will be allowed as long as the dose is stable and the patient does not meet the criteria for hypoglycemia unawareness while taking that stable dose.

If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.

6.7.2 Excluded Medications and/or Procedures

During the trial, patients will not use any recreational drugs or drugs of abuse. The need to take prescription drugs that dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder appropriate decision-making may be grounds for exclusion from the trial or discontinuation of participation, a decision that will be made by the Investigator.

[redacted]

Use of benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the Investigator. Use of oral anti-diabetic medications (e.g., thiazolidinediones, biguanides, sulfonylureas, glitinides, DPP-4 inhibitors, SGLT-2 inhibitors) will also be excluded.

7 TRIAL PROCEDURES

7.1 Informed Consent

After potential patients have had time to review the consent document, and prior to any trial-related activities, they will meet with a trial MD or designee who will explain the trial, answer any questions, and administer informed consent. In the event that a volunteer is a patient of one of the trial MDs, another staff MD or designee will answer questions and administer consent. The patients will be fully informed of their responsibilities and their rights while participating in the trial as well as of the possible risks and potential benefits of participation in the trial. They will have the opportunity to discuss all questions and ample time to consider participation.

Trial-related activities are any procedures that would not have been performed during normal management of the patient. Patients who wish to participate in the trial will be asked to personally date and sign an informed consent form (ICF). Likewise, the Investigator must also personally date and sign the ICF. All patients will be provided with a copy of their own signed and dated ICF.

Trial staff will answer any questions that the patients may have during their participation. They will share any new information in a timely manner that may be relevant to the patient's willingness to continue participating in the trial. The patients may choose to discontinue their participation at any time.

7.2 Screening Visit (Visit 1, up to 30 days prior to Visit 2)

All patients will have a screening visit to confirm eligibility. The patient will be interviewed and the electronic Case Report Form (eCRF) will be completed by trial staff to establish whether the patient is eligible.

Once all of the results have been returned, a trial MD will review the eCRF to determine patient eligibility. If a patient is not eligible to continue in the trial, the results of abnormal tests will be reported to the patient and to a health care provider of their choosing.

7.2.1 Data Collected at Screening

- Age, sex, race, and ethnicity
- Date of last menstrual period in female patients
- Medical, surgical, and social history, allergies, and review of systems relevant to inclusion and exclusion criteria, including:
  - Date of diabetes diagnosis
  - Duration of insulin pump use and type of insulin used in pump
  - Type/model of insulin pump
  - Insulin regimen (basal rate, sensitivity factor, and carbohydrate ratio)
  - Average total daily dose of insulin in the last 30 days as available (from pump history)

  - Usage of CGM, if any (type of CGM, days per month worn, usage of data, whether insulin is dosed based on CGM alone, alarm settings)
- Concomitant illness (any illness present at screening)
- Concomitant medications (prescription and non-prescription) and date of last change in medication regimen
- Height, weight, physical examination, and vital signs including body temperature and blood pressure
- 12-lead ECG
- Hemoglobin A1c
- Chemistry and hematology samples (see Appendix B)
- Urine HCG pregnancy test for women of childbearing potential
- FSH level for postmenopausal women amenorrheic for less than 1 year
- Fractionated plasma metanephrines (if indicated by history)

7.3 Training Visit (Visit 2) (Day 1)

A training visit will take place before the first treatment visit. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor and trial policies and procedures. Trial staff will verify that the patients have understood the material and are competent to participate safely in the trial. Concomitant medications will also be reviewed.

7.4 Treatment Visits (Visit 3 [Day 8 ±3] and Visit 4 [Day 15 ±3])

- Up to 2 patients may participate per day.
- Each patient will participate in 2 treatment visits: one with the iLet using ZP4207 and one with the iLet using Lilly glucagon in a randomized order.
- The night before the treatment visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be instructed to call if they encounter any difficulty with their CGM.
- Patients will be responsible for their own medications other than insulin during the trial. Any medical advice needed by the patients during their participation that is not directly related to BG control should be obtained from them in their usual manner. Patients may take any over-the-counter medications that they wish during the trial, with the exception of any medication containing acetaminophen as that may cause interference with CGM sensing. If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.
- During the trial, patients will not use any recreational drugs or drugs of abuse. The need to take prescription drugs that dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder appropriate decision-making may be grounds for exclusion from the trial or discontinuation of participation, a decision that will be made by the Investigator.
- Patients will not tamper with the BP, including changing any settings.
- Patients may not remove the BP during the trial unless the BP failed or they are withdrawing from the trial.
- The exact time of each procedure and assessment will be documented.

[redacted]

7.4.1 Visit Procedures

- Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window.
- Upon arrival to the visit, the patient's weight and vital signs including body temperature will be documented.
- Patient reports of symptoms, any other complaints, and AEs will be reviewed.
- Concomitant medications will be recorded.
- Chemistry and hematology samples will be collected at visit start (see Appendix B).
- ADA samples will be collected before the start of dosing (Visit 3 only).
- A 12-lead ECG will be performed.
- A urine HCG pregnancy test will be performed in female patients of childbearing potential. If the test is positive, the patient will be informed of the result and the visit will be ended.
- Patients will complete a baseline survey about their attitudes and experience with their usual diabetes care.
- An intravenous (IV) catheter will be placed for blood sampling.
- Trial staff will assist the patient to calibrate their CGM, review the trial procedures again and assist with the setup of the BP system, including inserting and priming infusion sets.
- The control algorithm will be initialized only with the patient's weight. Diagnostics will be performed to ensure that the CGM device is appropriately calibrated and that all of the components of the BP systems are in working order.
- The basal rate of the patient's own insulin infusion pump will be changed to be 2-fold higher than weighted mean of the basal rate during the trial period. This is intended to increase the usage of glucagon during the treatment visit.
- The patients will continue to wear their own infusion pump infusing at the temporary 2-fold basal rate throughout the visit until the start of the structured exercise period, in addition to the BP.
- The staff will start the BP as close as possible to a minute divisible by 5 minutes (i.e., on a 5-minute mark). The starting time will be considered Hour 0.
- Additional calibrations will be performed at any of the BG checks throughout the day if the CGM value does not meet the ISO standard (<15 mg/dL difference for BG values <75 mg/dL; <20% absolute difference for BG values >75 mg/dL) at the time of the BG measurement AND it is a good time to calibrate (the CGM trend arrow is flat and there has been no carbohydrate intake in the last 30 minutes or glucagon boluses in the last 15 minutes).
- Blood samples will be taken from the IV at least hourly and processed for plasma ZP4207/glucagon. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.
- Plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. If BG is <100 mg/dL, then sampling will be every 20 minutes.

[redacted]

If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.

- Patients will be asked to rate any nausea and/or infusion site pain on 10 cm visual analog scales (VAS) at the beginning of the visit once the infusion sites have been placed but no drug has yet been administered, then approximately at the top of every hour during the visit, and at the end of the visit. Trial staff will also evaluate their infusion sites to document any erythema or edema at the same times. If moderate or severe pain is reported or swelling or redness occurs at the infusion site, the infusion site will be replaced in a different location. If moderate or severe pain, swelling, or redness continues at the old site for more than 30 minutes after the infusion site is removed, or if moderate or severe pain, swelling, or redness occurs at the new site, all infusion sites will be removed and the patient will be discontinued from the study.
- From the start of closed loop control until approximately Hour 3, the patients will continue to fast.
- Between approximately Hour 3 and Hour 4, patients will be provided with a lunch meal of their choice in the Diabetes Research Center from a menu of choices from nearby restaurants. They will be asked to choose a meal that is a “typical meal” for them. The content of their meal will not be restricted in any way, with the exception that the number of carbohydrates should be in the “typical” range for them at lunch, and that they must eat the same meal at the same time during both visits.
- At approximately 15 minutes before the meal, patients will administer a bolus for the meal with their own insulin pump based on the carbohydrate count for the meal.
- After lunch is completed, the patients will not be allowed any carbohydrate intake (non-caloric drinks will be permitted) until the trial is completed (except as necessary to treat hypoglycemia), to allow the BP to control the post-prandial BG without further interruption.
- Between approximately Hour 6 and Hour 7, the patients will start a period of structured exercise.
- At the start of the exercise period, patients will restore their normal basal insulin profile so that they will not have elevated insulin levels at the end of the study period when they are to transition back to their usual care.
- Patients will exercise on a stationary bike with a heart rate from 120-140 beats per minute for a total of 4,000 heart beats (approximately 30 minutes). Patients will rate their exercise intensity using the Borg scale every 5 minutes, with the target intensity level between 12 and 14. Heart rate will be measured every 5 minutes.
- BG measurements will be obtained off of the IV line every 10 minutes. If BG is <80 mg/dL, BG measurements will be obtained off of the IV line every 5 minutes.
    - Carbohydrates will be given for any BG <50 mg/dL according to the following protocol: Dextrose (g) = BSA (m^2)/[1.7 m^2 (women) or 1.9 m^2 (men)] *15 g.
    - Repeat treatments will be given at 15-minute intervals as long as BG remains <50 mg/dL.
- If there is an interruption in the Dexcom CGM output, trial staff will assist the patient in recovering CGM data streaming. If this requires replacement of the CGM sensor, BGs will be checked every 10 minutes (every 5 minutes if BG is <80 mg/dL) using blood from the IV until the CGM is able to be calibrated again. These BGs will be entered into the BP, which will treat them as CGM values and dose insulin and/or glucagon appropriately.

[redacted]

- If there is a complete failure of the BP operation, patients will take over their own BG control using their personal insulin pump until the BP can be brought back online. If BP control cannot be promptly resumed (e.g., within 30 minutes), the patient may be asked to repeat that trial day once.
- Patients may choose to withdraw from the trial at any time. If they withdraw from the trial, they should alert a provider immediately.
- Just prior to the end of the study visit, vital signs including body temperature will be obtained and a 12-lead ECG will be performed.
- After approximately Hour 8, but not earlier than at least 60 minutes after end of exercise, the BP will be stopped and the patient will continue with their personal insulin pump.
- Patients will answer questionnaires (see Appendix C).
- Chemistry and hematology samples will be collected at visit end (see Appendix B).
- The BP and glucose meters will be collected and downloaded.
- A trial MD will review the last several hours of insulin and glucagon dosing and assist the patient in resuming their usual diabetes care. They will be instructed to call trial staff with any questions, issues, or concerns.

7.4.2 Data Collected During the Treatment Visits

- CGM glucose every 5 minutes from the Dexcom G4 Platinum CGM
- All BG measurements taken
- Insulin total dose by the BP and the patient's own insulin pump
- Glucagon total dose
- Timing and content of the meal eaten and carbohydrate amount
- Timing of meal announcement and size of meal announced
- Timing and glucose values at calibrations
- Timing and amount of carbohydrates taken for hypoglycemia
- Data from a questionnaire about attitudes and expectations regarding the BP before the trial and after each treatment arm (see Appendix C)
- Time patients were not under BP control for any reason
- List of technical faults associated with the BP including cause and resolution
- ZP4207/glucagon sampling collected at least hourly. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
- Plasma glucose sampling will be collected at least hourly in parallel with ZP4207/glucagon exposure sampling. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
- Nausea and infusion site pain on a VAS at visit start (after insertion and before any drug administration), hourly, and at visit end
- Infusion site reaction according to the Draize scale at visit start (after insertion and before any drug administration), hourly, and at visit end
- Patient reports of symptoms, any other complaints, and AEs
- Vital signs including body temperature (at visit start and visit end) and weight
- Concomitant medications
- Chemistry and hematology samples (see Appendix B) at visit start and visit end
- ADA (Visit 3 only)

[redacted]

- 12-lead ECG at visit start and visit end
- Urine HCG pregnancy test for women of childbearing potential

7.4.3 Response to Hypoglycemia

- Patients are encouraged to check their BG for any symptoms of hypoglycemia.
- Patients will be permitted to take 15 grams of carbohydrates for any BG value <60 mg/dL. Trial staff will ensure proper functioning of the BP, infusion set, and insulin pump, and will encourage the patient to wait for the BP to treat the low blood sugar for as long as they feel comfortable.
- Patients will be required to take 15 grams of carbohydrates for any BG value <50 mg/dL. After treatment of hypoglycemia, a follow-up measurement will be taken 15 minutes later. Repeated measurements will be taken every 15 minutes until the BG is >60 mg/dL. Treatment will be repeated if subsequent BG values are still <50 mg/dL. All carbohydrate treatments for hypoglycemia will be documented by trial staff (amount and time).
- Trial staff will check the infusion site, BP, and insulin pump for normal operation any time hypoglycemia occurs. If there is any suspicion of infusion set malfunction, the site should be replaced. Trial staff will check the BP for any malfunction and correct any problems that are found.
- If no correctable fault is found, but there is doubt regarding the correct function of the BP system, an entirely new backup BP system may be started.
- If a patient experiences a seizure or unconsciousness associated with hypoglycemia, his or her participation in the trial will be discontinued.

7.4.4 Response to Hyperglycemia

- Trial staff will check the infusion site, BP, and insulin pump for normal operation any time BG is >300 mg/dL. If there is any suspicion of infusion set malfunction, the site should be replaced. Trial staff will check the BP for any malfunction and correct any problems that are found.
- If no correctable fault is found, but there is doubt regarding the correct function of the BP system, the treatment visit may be stopped and the visit rescheduled.

7.4.5 Response to Nausea/Vomiting

If significant nausea (e.g., that prevents the patient from eating normally) or any vomiting occurs, trial staff will notify the Investigator. Trial staff will assist the patient in troubleshooting, such as checking BG and the calibration of the CGM (excessive glucagon dosing may occur if the CGM is reading lower than the true BG). If a patient experiences persistent nausea and vomiting thought to be related to glucagon dosing, his or her participation in the trial will be discontinued.

7.4.6 Response to Other Medical Needs

If patients experience urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they will be taken to the MGH walk-in clinic or emergency room, or if necessary call 911.

[redacted]

7.4.7 Monitoring of Bionic Pancreas Performance

Bionic pancreas inventors and developers [redacted], [redacted], and/or an engineer trained by them will be readily available by phone for consultation for the trial staff at all times during the course of the trial.

7.4.8 Supervision by Trial Staff

A trial MD will be on call at all times during the course of the trial. An RN or MD will be with the trial patients in the Diabetes Research Center at all times.

7.5 Phone Call (Visit 5) (Day 22 ±3)

A phone call will be conducted 1 week following the last day of dosing (Visit 4) to review AEs and concomitant medications.

7.6 Follow-up Visit (Visit 6) (Day 40 ±3)

Three to 4 weeks following the last day of dosing (Visit 4), patients will return for a Follow-up Visit for chemistry, hematology, and ADA sampling, and a review of AEs and concomitant medications.

8 ENDPOINTS

8.1 Primary Endpoint

The primary endpoint is the safety and tolerability of ZP4207 and the iLet as assessed by:

- Number and type of AEs
- Clinical laboratory measurements
- Vital signs
- 12-lead ECG
- Local tolerability and infusion site reactions as measured with the Draize scale
- Immunogenicity as measured by ADA
- Pain as measured on a 10 cm VAS
- Nausea as measured on a 10 cm VAS

8.2 Secondary Endpoints

The secondary endpoints for the iLet and ZP4207 include measurements of BP function as well as glycemic and non-glycemic measurements.

8.2.1 Bionic Pancreas Function

This endpoint data will be generated from the BP data during each treatment visit:

- Average percent insulin dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump (calculated doses are not issued unless the pump is accessible and its delivery channel is available)

  - Average percent insulin dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
  - Average percent glucagon/ZP4207 dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts calculated by the BP algorithm that are successfully issued to the pump by the BP (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
  - Average percent insulin dose amounts calculated by the BP control algorithm that are successfully issued by the BP
  - Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully issued by the BP
- Average percent of 5-minute steps during which the BP is functioning nominally in all respects based on real-time CGM data (new CGM glucose reading captured, dose calculated, and dose issued to pumps)
- Average percent of 5-minute steps during which the BP is functioning nominally with or without a new CGM glucose reading captured (dose calculated and dose issued to pumps). If a CGM signal is not available, the dose calculated may be based on weight or historical basal rates.
- CGM reliability index, calculated as percent of possible values actually recorded by CGM
- CGM Mean Absolute Relative Difference versus time-stamped BG values from meter download
- List of technical faults associated with the BP including cause and resolution

8.2.2 Glycemic

All of following metrics will be generated from the Dexcom G4 Platinum CGM data during each treatment visit.

- Fraction of time spent within each of the following glucose ranges:
  - <50 mg/dL
  - <60 mg/dL
  - <70 mg/dL
  - 70-120 mg/dL
  - 70-140 mg/dL
  - 70-180 mg/dL
  - >180 mg/dL
  - >250 mg/dL
  - >300 mg/dL
- Number of severe hypoglycemic events (patients unable to self-treat, requiring the assistance of another person)
- Number of episodes of symptomatic hypoglycemia
- Number of carbohydrate interventions for hypoglycemia
- Total grams of carbohydrates taken for hypoglycemia
- Mean CGM glucose

8.2.3 Non-glycemic

- Glucagon/ZP4207 total delivery per kg of body mass
- Insulin total delivery per kg of body mass

[redacted]

- Number of unscheduled infusion set replacements
- Number of unscheduled CGM sensor changes

9 LABORATORY ASSESSMENTS

Descriptions of sample handling and sample processing, storage, and shipment at the site will be included in the laboratory manual.

The responsible laboratories are listed in the address list.

9.1 Safety Laboratory Assessments

Chemistry and hematology samples will be collected at specified time points. See Appendix A for the schedule of procedures and Appendix B for a list of clinical laboratory analytes.

9.2 Pharmacodynamic Assessments (Plasma Glucose)

At Visit 3 and Visit 4, plasma glucose samples will be taken from the IV at least hourly in parallel with ZP4207/glucagon exposure sampling and measured using the YSI 2300 STAT Plus. If the YSI 2300 STAT Plus and/or IV fails, the Nova StatStrip Xpress will be used for glucose measurements. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.

9.3 Exposure Assessments (ZP4207 and Glucagon)

At Visit 3 and Visit 4, ZP4207/glucagon exposure sampling will be collected at least hourly. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes. The actual time of sampling will be recorded in the eCRF.

Bioanalytical Reports will be prepared.

9.4 Anti-drug Antibody Assessments

Blood samples (including back-up samples) for serum anti-ZP4207 and anti-glucagon antibodies will be taken at specified time points; see Appendix A.

A Bioanalytical Report will be prepared.

10 SAFETY REPORTING

10.1 Adverse Events

An AE is any untoward medical occurrence in a trial patient administered an IMP and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP. Patients should be instructed to report any AE they experience to the Investigator.

Note: This includes events from the first trial-related activity from Visit 3.

[redacted]

AEs for ZP4207 include:

- A clinically significant worsening of a concomitant illness
- A clinical laboratory abnormality which is clinically significant, i.e., any abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example, change of medicine dose or more frequent follow-up due to the abnormality.
- Hypoglycemic episodes
- Injection site reactions

The following should **not** be recorded as AEs, if recorded prior to randomization (on the Screening Form or the eCRF):

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial-related activity from Visit 3.
- Pre-existing conditions found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).

For known (listed) AEs for Glucagon and Humalog, please refer to SPC for Glucagon and Humalog.

10.1.1 Follow-up of Adverse Events

All AEs that are ongoing at the end of the patient's participation in the trial will be followed-up until the event is resolved or reaches a satisfactory outcome as deemed by the Investigator. Follow-up actions for all serious adverse events (SAEs) will be performed according to appropriate clinical care practices and may depend on the nature of the event. These will be determined after internal review and/or Sponsor review. The follow-up information should only include new (updated and/or additional) information that reflects the situation at the time of the Investigator's signature.

Follow-up information on (S)AEs will be updated using the (S)AE Form. If a non-serious event becomes serious during the follow-up, the AE Form and SAE Form must be used and reporting timelines follow those of an SAE.

The Investigator must forward follow-up information on SAEs, and if previously non-serious AEs become SAEs, to the Sponsor.

10.1.2 Precautions

Normal precautions taken for a human trial will be taken during this trial. Qualified and well-trained physicians and medical staff will instruct the patients. During a patient's participation in the trial, the Investigator should ensure that adequate medical care is provided to the patient for any AEs, including clinically significant laboratory values related to the trial. The Investigator should inform the patient when medical care is needed for intercurrent illnesses of which the Investigator becomes aware.

For further information on safety precautions for ZP4207, Lilly glucagon, Lilly Humalog, and the iLet, please refer to the current version of the Investigator's Brochure (IB) for ZP4207 (Zealand Pharma A/S, 2015, or any updates hereof), and the SPC for Glucagon (Eli Lilly, 2012) and Humalog (Eli Lilly, 2015), respectively.

[redacted]

10.1.3 Assessment of Adverse Events by the Investigator

Intensity of an Adverse Event
The maximum intensity (severity) of all AEs must be assessed by the Investigator and documented. Severity should be graded when the AE outcome is known:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

A “severe” reaction does not necessarily deem the AE as “serious,” and an SAE may not be “severe” in nature.

Causality Relationship to IMP
Insulin (insulin lispro, Lilly Humalog), glucagon (glucagon for injection, Eli Lilly), and ZP4207 are all regarded as IMP.

The causality of each AE should be assessed by the Investigator according to the following classification:

- Related: Good reason and sufficient documentation to assume a causal relationship.
- Not related: No relationship to trial product can be established.

Outcome of an Adverse Event
The outcome of all AEs must be assessed by the Investigator and documented by his/her staff. The following definitions should be used:

- Recovered/resolved: The patient has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity from Visit 3.
- Recovering/resolving: The condition is improving and the patient is expected to recover from the event. This term is only applicable if the patient has completed the trial.
- Recovered/resolved with sequelae: The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment, or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- Not recovered/not resolved: The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known.
- Fatal: This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as “recovered/resolved,” “recovering/resolving,” “recovered/resolved with sequelae,” or “not recovered/not resolved.” An AE with a fatal outcome must be reported as an SAE.
- Unknown: This term is only applicable if the patient is lost to follow-up.

[redacted]

10.2 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Medically important

Medical judgement must be exercised in deciding whether an AE is believed to be "medically important." Medically important events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Suspected Unexpected Serious Adverse Reactions (SUSAR)
A SUSAR is an AE fulfilling one of the criteria of seriousness and being assessed as related to an IMP, the nature or severity of which is not consistent with the applicable reference document (e.g., ZP4207 IB or package leaflet/SPC for an approved product).

Unanticipated Adverse Device Effect (UADE)
A UADE is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

10.3 Adverse Event Reporting – Procedures for Investigators

The Principal Investigator and co-investigators will review any AEs and report any SAEs to the Sponsor as soon as possible and within 24 hours of obtaining knowledge of the event. The Principal Investigator and co-investigators will promptly report AEs to the Partner's Institutional Review Board (IRB) and to the BU IRB (unless oversight is ceded by the BU IRB to the Partners IRB), in accordance with local requirements.

Ed Damiano is the Sponsor of the Investigational Device Exception for the BP and Zealand Pharma A/S is the Sponsor of the IND for ZP4207.

Reports of AEs will be submitted to the FDA in compliance with the terms of the Code of Federal Regulations.

All events meeting the definition of an AE must be collected and reported from the first trial-related activity from Visit 3 until the end of the post-treatment follow-up period. At each contact with the site (visit or telephone, excluding safety visits, where the patient is not seeing the Investigator or staff [e.g., visits to the laboratory], the patient must be asked about AEs. All AEs, either observed by the Investigator or reported by the patient, must be recorded by the Investigator and evaluated.

The Investigator should record the diagnosis, if possible. If no diagnosis can be made, the Investigator should record each sign and symptom as individual AEs.

[redacted]

All AEs must be recorded by the Investigator. One single AE Form must be used per AE from start to resolution. For SAEs, the SAE Form must also be completed.

AE information should include the following:

- Patient identification number on all pages
- Date and time of treatment start
- Date and time of onset and date of outcome
- Date and time of Investigator's first information on the (S)AE
- Seriousness
- Severity
- Causal relationship with IMP ZP4207
- Causal relationship with IMP insulin
- Causal relationship with IMP glucagon
- Causal relationship with medical device
- Causal relationship with procedures
- Interruption or withdrawal of treatment with IMP or medical device and other measures taken
- Outcome

All AEs are coded; details are described in the trial specific Data Management Plan.

The Investigator must report initial information in writing on the SAE Form for all SAEs to the Sponsor's responsible pharmacovigilance unit (here: Lindeq) immediately (within 24 hours) after obtaining knowledge about the event.

Name: [redacted]
Company: Lindeq
Address: Lyskær 8, 2730 Herlev, Denmark
Tel: [redacted]
Fax:
Mobile:
E-mail: drugsafety@lindeq.com

In addition and meeting the same timeline, Investigators must report all SAEs to Zealand Pharma A/S by forwarding the SAE Form electronically within 24 hours of obtaining knowledge of the event to the representatives of Zealand Pharma A/S.

Names: [redacted] and [redacted]
Address: Smedeland 36, DK-2600 Glostrup, Denmark
Tel: [redacted] / [redacted]
E-mails: [redacted] / [redacted]

It is the responsibility of Lindeq to report all SUSARs that occur in this trial to the Competent Authorities and to the Investigators. It is the responsibility of the Investigators to report the SUSARs to the IRBs in accordance with the local requirements in force and the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP). The trial monitor must be informed accordingly.

It is the responsibility of Lindeq to report all serious adverse reactions on insulin lispro and glucagon for injection to the Eli Lilly Pharmacovigilance department within 5 days.

It is the responsibility of the Investigators to report all UADEs to Beta Bionics within 24 hours of the time they are detected. It is the responsibility of the Investigators to report all UADEs to the IRB in accordance with the local requirements in force and the ICH GCP. It is the responsibility of Beta Bionics to report all UADEs to the Competent Authorities.

All device deficiencies should be documented and should be reported to Beta Bionics within 24 hours. Device deficiencies are inadequacies of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

Name: [redacted]
Company: Beta Bionics, Inc.
Address: Business Innovation Center, Photonics Center, 8 Saint Mary's Street, Suite 936 Boston, Massachusetts 02215-2421, United States
Tel: [redacted]
E-mail: [redacted]

10.4 Pregnancy Reporting

Female patients must be instructed to notify the Investigator immediately if they become pregnant or if they suspect to be pregnant during the trial. The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical trial.

Male patients must be instructed to notify the Investigator immediately if their partner becomes pregnant or suspects to be pregnant. The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical trial. During an information meeting at the trial site, the patient's partner will be fully informed by a physician of her participation in capturing the outcome data, and will be asked to provide her written consent.

The Investigator must report all information on pregnancies, including AEs in the patient/patient's partner, the fetus, and newborn infant/ toddler. The pregnancy report must be forwarded to the Sponsor preferably electronically as PDF or by fax.

The Investigator must follow the pregnancy until the pregnancy outcome and the newborn infant(s) until the age of 1 month. The Investigator must collect information on the pregnancy and pregnancy complications as well as the pregnancy outcome including the health of the newborn infant(s) on the pregnancy forms.

The following must be collected:

- Initial information of the pregnancy
- Information on the outcome of the pregnancy, including the health status of the newborn infant(s) at the age of 1 month
- All AEs in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms. It must be clear in the description if the event occurs in the patient/patient's partner, the fetus, or the newborn infant.

- All SAEs in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms following the same timelines as required for other SAEs. It must be clear in the description if the event occurs in the patient/patient's partner, the fetus, or the newborn infant.

The SAEs that must be reported include abnormal outcome – such as congenital anomalies, fetal death, and termination of pregnancy (spontaneous or elective abortion), including any anomalies of the fetus observed at gross examination or during autopsy – as well as other pregnancy complications (ectopic pregnancy) fulfilling the criteria of an SAE.

10.5 Hypoglycemia

Hypoglycemia will be regarded as an AE and will be recorded and documented on an AE Form. For the purposes of AE reporting, the following definitions of hypoglycemia will be used:

- Symptomatic hypoglycemia: an event during which typical symptoms of hypoglycemia are accompanied by a BG concentration ≤70 mg/dL
- Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with a BG concentration ≤50 mg/dL
- Severe hypoglycemia: an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions

10.6 Safety Monitoring

10.6.1 Data and Safety Monitoring Board

An external DSMB will oversee the conduct of the trial, as set forth in the DSMB Charter. Additionally, the DSMB will be informed in the event of any serious and unexpected AEs. The DSMB will be informed if there are any changes to the trial protocol that could significantly impact the safety or scientific validity of the trial. A final DSMB meeting will convene after the completion of the trial.

The participation of individual patients will be discontinued if they experience:

- Seizure or unconsciousness associated with hypoglycemia and associated with participation in the trial
- Persistent nausea and vomiting thought to be related to glucagon dosing associated with participation in the trial
- Hospitalization associated with participation in the trial
- Pregnancy

If more than 1 patient must be withdrawn from the trial for these reasons, the trial will stop and a vote of the DSMB will be required to restart it. All AEs that are serious and unexpected but related will be reported to the DSMB within 5 working days.

Note that patients may discontinue participation at any time. Patients may be removed from the trial for other reasons, for instance, failure to comply with trial procedures or intercurrent illness that is unrelated to the BP but that precludes safe participation. Discontinuation of participation for these reasons will not contribute to a decision to discontinue the trial.

[redacted]

10.6.2 Zealand Pharma Safety Committee

The internal Zealand Pharma Safety Committee is constituted to perform ongoing safety surveillance of clinical trials within ZP4207, including this trial.

If safety signals are observed either based on reported SAEs, periodic review of laboratory parameters, planned review of all AEs reported between the safety committee meetings, or on notification of significant findings, the Safety Committee will take appropriate measures to safeguard the patients.

11 STATISTICS

11.1 Analysis Populations

The following analysis sets are defined in accordance with the ICH-E9 guidance:

The Full Analysis Set is based on the intention-to-treat principle and includes all randomized patients. In exceptional cases, patients from the Full Analysis Set may be excluded (will be decided in the database review [DBR] meeting). In such cases, the exclusion will be justified and documented. Patients will contribute to the evaluation “as randomized.”

The Per-Protocol Set includes all patients of the Full Analysis Set who completed the trial without any major protocol violations. Patients in the Per-Protocol Set will contribute to the evaluation “as treated.” This analysis will only be used if it is different than the Full Analysis Set.

The Safety Analysis Set includes all patients receiving at least 1 dose of the IMP. Patients in the Safety Analysis Set will contribute to the evaluation “as treated.”

Analyses of efficacy endpoints will be based on the Full Analysis Set (and the Per-Protocol Set if necessary). This decision will be made in the DBR meeting. The analysis of the safety endpoints will be based on the Safety Analysis Set.

Before data are released for statistical analysis, a blinded review of all data will take place to identify protocol deviations that may potentially affect the results. At this time, it will be determined if patients and/or data should be excluded from the analysis. Furthermore, outliers will be identified by data review according to ICH-E9.

Obviously erroneous data points may be excluded from the analyses or re-analyzed (e.g., serum concentrations). The decision to re-analyze or exclude data points from the statistical analysis is the joint responsibility of the Sponsor, the Principal Investigator, and the Trial Statistician.

The patients or observations to be excluded and the reason for their exclusion will be documented and signed by those responsible prior to database release. The documentation will be stored together with the remaining trial documentation. The patients and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

11.2 Statistical Methods

Medpace will be responsible for the statistical analysis. The statistical planning and conduct of analyses of the data from this trial will follow the principles defined in relevant ICH guidelines and Medpace's biostatistical standard operating procedures (SOPs). A general description of the statistical methods to be used is given in this section, specific details will be provided in the Statistical Analysis Plan (SAP), which will be prepared before database lock. All statistical analyses will be performed using SAS® (SAS Institute Inc., Cary, North Carolina, USA), version 9.4 or later.

11.2.1 Analysis of Safety

The following variables will be evaluated according to treatment for safety purposes:

Adverse Events
All AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Individual AEs will be presented in a listing including relationship to trial product/device, severity, and treatment period at onset. If more than 20 treatment-emergent AEs (AEs with onset after [first] dosing at Visit 3 until the follow-up Visit 6) are registered, a summary table including number of AEs, number of patients with at least 1 AE, and percentage of exposed patients with at least 1 AE will be made by system organ class and treatment period at onset.

Local Tolerability
Local tolerability at the injection site will be summarized using descriptive statistics as appropriate.

Laboratory Safety Assessments
Laboratory assessments will be summarized. A listing of abnormal values will be provided.

Physical Examination
A frequency table will show the number and percentage of physical examination results.

Vital Signs
Vital signs will be summarized using descriptive statistics.

12-lead ECG
The Investigator's evaluations of 12-lead ECGs will be summarized and abnormal individual evaluations will be listed together with the Investigator's comments. Changes in 12-lead ECG between measurements will be recorded as AEs if the Investigator judges them to be clinically significant.

11.2.2 Analysis of Efficacy

The analysis of BP function endpoints and glycemic endpoints will be on an intention-to-treat basis. In cases where a treatment arm was not completed (and that arm was not repeated according to protocol criteria), available data from that arm will be used in the data analysis.

The Shapiro-Wilk test will be used to determine the normality of the residuals for each comparison. Summary tables that display descriptive statistics, including percentages, means or medians, and standard deviation and/or ranges, as appropriate, will be provided.

[redacted]

A paired t-test or the Wilcoxon signed rank test for comparison of means with normally or non-normally distributed residuals, respectively, will be used. In a secondary analysis, any period effect and any interaction between treatment and period will be looked for, although no such interaction is predicted for the efficacy outcome. Further details will be included in the SAP.

The number of patients and proportions of severe hypoglycemic events, symptomatic hypoglycemia, and carbohydrate interventions due to hypoglycemia with the event counts will be summarized descriptively, and the proportions will be analyzed by a Fisher's exact test if data allow.

11.2.3 Interim Analysis

No interim analysis is planned.

11.2.4 Sample Size Determination

No formal sample size calculations were made. It is expected that between 10 and 12 patients will be randomized in the trial. The sample size is based on a clinical rather than statistical rationale. The sample size is considered adequate to address the primary trial objective of exploring the safety of ZP4207 when used in the iLet and with reference to Lilly glucagon used in the iLet.

12 DATA MANAGEMENT AND RECORD KEEPING

Data Management is the responsibility of Medpace. The complete Data Management process will be described in detail and agreed on in the Data Management Plan for this trial.

12.1 Data Handling

Case Report Forms
Electronic Case Report Forms will be used in this trial. The Data Management Department of Medpace will provide the eCRFs. All further information regarding the eCRFs and the data flow will be described and agreed on in the Data Management Plan.

Device-Related Data
During the trial, CGM data, calibration data, insulin dosing data, and glucagon dosing data will be automatically stored in the BP device (from which it will be downloaded at intervals), combined in a single database that will be compared against the primary data files for integrity, and ultimately transferred to Medpace.

12.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

12.3 Data Entry

Data must be recorded using the electronic data capture (EDC) system as the trial is in progress. The patient questionnaires will be transcribed into the EDC system by site personnel. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct trial data. These procedures must comply with

Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

12.4 Medical Information Coding

Adverse events and medical history will be coded using the latest version of MedDRA. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary.

12.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

12.6 Record Keeping

Medpace will be responsible for hosting the TMF. Records of patients, source documents, monitoring visit logs, eCRFs, inventory of trial product, regulatory documents, and other Sponsor correspondence pertaining to the trial must be kept in the appropriate trial files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the evaluation and reconstruction of the clinical trial. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Trial Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

13 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

13.1 Ethical Conduct of the Trial

The trial will be conducted according to Medpace, MGH, and/or the Sponsor's written instructions (SOPs, working instructions, or process descriptions). Content and definitions of the written instructions are based on the Declaration of Helsinki and the ICH GCP.

13.2 Institutional Review Board

Written favorable opinion must be obtained from the responsible IRB prior to commencement of the trial. Clinical trial submission and reporting requirements before, during, and after completion of the trial will be performed in accordance with national law and local regulations.

All amendments that affect patient safety or the trial integrity (substantial amendments) must not be implemented before favorable opinion has been obtained, unless necessary to eliminate hazards to the patients. Non-substantial amendments do not require favorable opinion by the IRB, but the respective IRB will be notified according to local requirements.

The Sponsor and Investigator must approve any amendment in writing before its implementation.

[redacted]

The Sponsor must maintain an accurate and complete record of all submissions made to the IRB. The records should be filed in the Sponsor's Trial Master File (TMF).

13.3 Informed Consent

In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirement(s) and adhere to the ICH GCP guideline and the requirements in the Declaration of Helsinki.
Prior to any trial-related activity, the Investigator must give the patient oral and written information in a form that the patient can read and understand about all aspects of the trial that are relevant to the patient's decision to participate. The patient will be given ample time to decide whether or not to participate in the trial.

The patient must be informed that his/her personal trial-related data will be used in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by authorized monitors or Clinical Quality Assurance auditors appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

A voluntary, personally signed and dated ICF must be obtained from the patient prior to any trial-related activity. The ICF must also be signed and dated by the physician or designee who conducted the informed consent procedure. A signed copy of the ICF and any additional patient information must be given to each patient.

The responsibility for taking informed consent must remain with that of a research physician or designee. If information becomes available that may be relevant to the patient's willingness to continue participating in the trial, the Investigator must inform the patient in a timely manner, and a revised written informed consent must be obtained.

Should a protocol amendment become necessary, the ICF may need to be revised to reflect the changes to the protocol. It is the responsibility of the Sponsor to ensure that an amended consent form is reviewed and has received favorable opinion from IRB, and the Investigator must ensure that the amended consent form is signed by all patients subsequently entered into the trial and those currently in the trial, if affected by the amendment.

13.4 Trial Monitoring Requirements

The monitoring procedures for this trial are described in detail in the Monitoring Manual. The objectives of the monitoring procedures are to ensure that (i) the safety and rights of the trial patients are respected, (ii) that accurate, valid, and complete data are collected, and (iii) that the trial is conducted in accordance with the trial protocol, the principles of GCP, and local legislation, including drug accountability.

The monitor must be given direct access to the investigational site files and source documents (original documents, data, and records). Direct access includes permission to examine, analyze, verify, and reproduce any record(s) and report(s) that are important to evaluation of the clinical trial.

Key tasks of the monitor include verifying the presence of informed consent, the adherence to the inclusion/exclusion criteria, the documentation of SAEs, and the recording of all safety and efficacy variables. The monitor will also confirm the completeness of patient records, the adherence to the protocol, ICH GCP, and the progress in patient enrollment and perform drug accountability.

Because no information that could reveal the identity of patients may ever be removed from the trial site, the monitor will visit the site at regular intervals to perform these monitoring tasks. Other contact between the Investigator and monitors will be maintained as required through telephone calls and e-mail. The Investigator and/or key members of staff involved in the trial must be available to assist the monitors during all visits.

Site Initiation Visit
During the Site Initiation Visit (SIV) the CRO, Sponsor, and/or monitors will go through information on the IMP, the protocol, the eCRFs, and other key aspects of the trial with the Investigator and the key members of staff involved in the trial. The topics of the SIV are documented in a SIV report made available to the Investigator. Documentation on the SIV (e.g., power point presentation) should be filed by both Investigator and Sponsor.

13.5 Disclosure of Data

Data generated by this trial must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the trial is confidential and disclosure to third parties other than those noted above is prohibited.

13.6 Retention of Records

Massachusetts General Hospital will maintain the patient's medical file according to local regulations. MGH will archive the documentation pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. MGH should not destroy any documents without prior permission from the Sponsor.

The documentation includes all the raw data generated during the clinical trial, the investigational site files, and a copy of the clinical trial report. The documents will be retained for a period of at least 15 years at archives by MGH, or its sub-contractor. After this period, the Sponsor will be contacted and their advice sought on the return or further retention of the trial records.

The Sponsor will maintain the documentation pertaining to the trial in accordance with national regulations.

13.7 Publication Policy

The Principal Investigator of the trial will review and sign the clinical trial report. A summary of the final clinical trial report will be submitted to the IRB and Competent Authority.

[redacted]

According to the Declaration of Helsinki Investigators and Sponsors "have ethical obligations with regard to the publication and dissemination of the results of research." The trial design and results may be published as one or more original research manuscripts/abstracts and presented at a scientific meeting. The Investigator and Sponsor reserve the right to review any proposed presentation of the results of this trial before they are submitted for publication. Authorship on any publication(s) resulting from this clinical trial will be assigned according to the recommendations of the International Committee of Medicinal Journal Editors.

Participating patients will not be identified by name in any published reports about the clinical trial.
The Sponsor is responsible for trial registration at ClinicalTrials.gov (www.clinicaltrials.gov) according to the requirements from the FDA.

13.8 Legal Aspects

An implicit or explicit approval must be obtained from the Competent Authority prior to commencement of the trial. Clinical trial submission and reporting requirements before, during, and after completion of the trial will be performed in accordance with national law and local regulations.

An implicit or explicit approval will also be mandatory before implementation of substantial changes. Non-substantial amendments do not require approval from the Competent Authority but will be notified according to local requirements.

The Sponsor and Investigator must approve the amendment in writing before its implementation.

The Sponsor must maintain an accurate and complete record of all submissions made to the Competent Authority. The records should be filed in the Sponsor's TMF.

Audits and Inspections
In the event of an audit, representatives of the Sponsor or designee, or national and international regulatory authorities may request access to all trial records for inspection and copying. Such access must be stated in the ICF signed by the patient.

13.9 Sponsor Discontinuation Criteria

The Sponsor, Investigator, or a pertinent regulatory authority may decide to stop the trial or part of the trial at any time but agreement on procedures to be followed must be obtained.

Conditions that may warrant termination of the clinical trial include, but are not limited to:

- Safety or administrative reasons
- The discovery of an unexpected, relevant, or unacceptable risk to the patients enrolled in the clinical trial
- A decision of the Sponsor to suspend or discontinue investigation of the IMP

If the trial is prematurely terminated or suspended, the Investigator should promptly inform the patients and assure appropriate therapy and follow-up. Furthermore, the Sponsor should promptly inform the IRB and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

If after the termination of the trial the risk/benefit analysis has changed, the new evaluation should be provided to the IRB in case it will have an impact on the planned follow-up of the patients who have participated in the trial. Necessary actions needed to protect the patients should be described.

13.10 Patient Compensation

Financial compensation will be provided to all patients who complete the Screening Visit. Patients will be paid $25 for completing the Screening Visit whether or not they are eligible to participate in the trial. Patients will be compensated $25 for completing the Training Visit. Patients will be compensated $100 for completing each of the 2 treatment visits, $25 for completing the phone call, and $25 for completing the Follow-Up Visit. Thus, the total compensation for a patient who completes the trial would be $300. Patients who are unable to complete the trial or choose to stop participation will receive prorated compensation for each visit. In addition to the monetary compensation, the cost of the patients' lunch meals during their participation in the trial, as well as the patients' parking at each visit, will be covered by trial funds.

14 TRIAL ADMINISTRATIVE INFORMATION

14.1 Protocol Amendments

Any amendments to the trial protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

14.2 Address List

14.2.1 Sponsor

Zealand Pharma A/S
Smedeland 36
DK-2600 Glostrup (Copenhagen)
Denmark
Telephone: +45 88 77 36 00
Facsimile: +45 88 77 38 98

14.2.2 Supplier of Device

[redacted], PhD
Beta Bionics, Inc.
Business Innovation Center, Photonics Center
8 Saint Mary's Street, Suite 936
Boston, Massachusetts 02215-2421
United States
Tel: [redacted]

14.2.3 Principal Investigator (Site)

Steven J. Russell, M.D., Ph.D.
MGH Diabetes Center
50 Staniford Street Suite 301
Boston, Massachusetts 02114
Telephone: [redacted]
Facsimile: [redacted]

14.2.4 Contract Research Organization (Including Monitoring)

Medpace, Inc.
5375 Medpace Way
Cincinnati, Ohio 45227
Telephone: +1-513-579-9911
Facsimile: +1-513-579-0444

14.2.5 Medical Monitoring

Medpace Clinical Safety
5375 Medpace Way
Cincinnati, OH 45227
United States
Telephone: +1-800-730-5779, ext. 2999 or +1-513-579-9911, ext. 2999
Facsimile: +1-866-336-5320 or +1-513-579-0444
medpace-safetynotification@medpace.com

14.2.6 Pharmacovigilance

Lindeq
Lyskær 8
2730 Herlev
Denmark
Telephone:
Facsimile:
Mobile:
E-mail: drugsafety@lindeq.com

14.2.7 Central Laboratory (Safety Laboratory and Plasma Glucose)

Medpace Reference Laboratories, LLC
5365 Medpace Way
Cincinnati, OH 45227
United States
Telephone: +1-513-366-3270
Facsimile: +1-513-366-3273

[redacted]

14.2.8 Special Laboratory (ZP4207 Exposure and ADA Analyses)

Unilabs – York Bioanalytical Solutions
[redacted]
Cedar House
Northminster Business Park
Upper Poppleton
York YO26 6QR
Great Britain
Telephone: [redacted]
Facsimile: [redacted]

14.2.9 Special Laboratory (Glucagon Exposure)

MLM Medical Labs GmbH
Dr. [redacted]
Dohrweg 63
D-41066 Mönchengladbach
Germany
Telephone: [redacted]
Facsimile: [redacted]

15 REFERENCES

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[redacted]

APPENDIX A: SCHEDULE OF PROCEDURES

Trial Visit	**Visit 1 [1] Screening**	**Visit 2 Training**	**Visit 3 [2] [3] Treatment**	**Visit 4 [2] [3] Treatment**	**Visit 5 Phone Call**	**Visit 6 Follow-Up**
Trial Day	**Up to 30 days prior to Visit 2**	**Day 1**	**Day 8 (±3 days)**	**Day 15 (±3 days)**	**Day 22 (±3 days)**	**Day 40 (±3 days)**
Informed consent	X					
Assess/confirm elig bility	X	X				
Demographics	X					
Medical, surgical, and social history; allergies	X					
Concomitant illness	X					
Concomitant medications	X	X	X	X	X	X
Height, weight, physical examination, and vital signs including body temperature and blood pressure [4]	X		X [5]	X [5]		
12-lead ECG	X		X [6]	X [6]		
Urine HCG pregnancy test and menstrual history [7]	X		X	X		
FSH [8]	X					
Screening labs – HbA1c, optional fractionated metanephrines [9]	X					
Safety lab sampling including chemistry and hematology	X		X [6]	X [6]		X
Training on devices [10]		X				
Monitored BP use			X	X		
Plasma glucose sampling [11]			X	X		
ZP4207/glucagon exposure sampling [12]			X	X		
Nausea and infusion site pain VAS and infusion site reaction Draize scale (visit start [11], hourly, & visit end)			X	X		
Standardized lunch [13]			X	X		

Clinical Trial Protocol
ZP4207-16051

Version number: 1.0
Date: 03 May 2016

Trial Visit	Visit 1 [1] Screening	Visit 2 Training	Visit 3 [2] [3] Treatment	Visit 4 [2] [3] Treatment	Visit 5 Phone Call	Visit 6 Follow-Up
Trial Day	**Up to 30 days prior to Visit 2**	**Day 1**	**Day 8 (±3 days)**	**Day 15 (±3 days)**	**Day 22 (±3 days)**	**Day 40 (±3 days)**
In-clinic exercise [14]			X	X		
Questionnaires (pre & post BP)			X	X		
ADA			X [15]			X
Adverse event review			X	X	X	X

1. Once the patient has been enrolled and eligibility has been established, the order of the iLet visits will be randomized in blocks of 2 patients.
2. Each patient will participate in 2 treatment visits: one with the iLet using ZP4207 and one with the iLet using Lilly glucagon in a randomized order. Up to 2 patients can participate in the trial per day.
3. The night before the visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12 00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window.
4. Height, blood pressure, and physical examination will be measured at Visit 1 only.
5. Vital signs including body temperature will be obtained at visit start and visit end.
6. At visit start and visit end.
7. Urine HCG pregnancy test only for women of childbearing potential. The date of the last menstrual period in female patients will be obtained at Visit 1 only.
8. Test for FSH level only for postmenopausal women amenorrheic for less than 1 year.
9. If indicated by history.
10. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor and trial policies and procedures.
11. Collected at least hourly. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
12. Once the infusion sites have been placed but no drug has yet been administered.
13. Between approximately Hour 3 and Hour 4.
14. Between approximately Hour 6 and Hour 7.
15. Before the start of dosing.

ADA = anti-drug antibodies; BG = blood glucose; BP = bionic pancreas; CGM = continuous glucose monitor; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HCG = human chorionic gonadotropin; VAS = visual analog scale.

[redacted]

APPENDIX B: CLINICAL LABORATORY ANALYTES

Chemistry

Alanine aminotransferase	Aspartate aminotransferase
Alkaline phosphatase	Total protein
Albumin	Total and direct bilirubin
Gamma-glutamyl transferase	Glucose
Creatinine	Estimated glomerular filtration rate
Blood urea nitrogen	Uric acid
Bicarbonate	Sodium
Potassium	Calcium
Chloride	Phosphorus

Hematology

Hemoglobin	Hematocrit
Red blood cell count	White blood cell count and differential
Platelets	Mean corpuscular volume
Mean corpuscular hemoglobin	Mean corpuscular hemoglobin concentration

Pregnancy Test
A urine HCG pregnancy test will be performed at screening, Visit 3, and Visit 4 only for women of childbearing potential.

Anti-drug Antibody Assessments
Blood samples (including back-up samples) for serum anti-ZP4207 and anti-glucagon antibodies will be taken prior to first dosing (Visit 3) and at the Follow-up Visit (Visit 6).

ZP4207/Glucagon Exposure Sampling
At Visit 3 and Visit 4, ZP4207/glucagon exposure sampling will be collected at least hourly. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.

Screening Visit Only
Test for FSH level only for postmenopausal women amenorrheic for less than 1 year
Optional fractionated plasma metanephrines (if indicated by history)
Hemoglobin A1c

[redacted]

APPENDIX C: BRIEF DESCRIPTION OF QUESTIONNAIRES

Diabetes Treatment Satisfaction Questionnaire - Status (DTSQs)
The DTSQs measures patient satisfaction with diabetes treatment. It consists of a 6 item scale for assessing treatment satisfaction and two additional items assessing perceived frequency of hyperglycemia and hypoglycemia. The DTSQs is meant for adults and older children. Dr. Clare Bradley has produced a version that is appropriate for bionic pancreas studies for this use, along with a version for younger children. It is administered before the intervention. The DTSQs is valid and reliable. Administration time is less than 5 minutes.

Diabetes Treatment Satisfaction Questionnaire – Change (DTSQc)
Although the DTSQ is responsive to treatment changes, ceiling effects are often seen with this instrument, where maximum or close-to-maximum scores at baseline provide little opportunity for registering improvement. The DTSQc contains the same items as the DTSQs version but asks patients to consider their satisfaction with their current treatment compared with their previous treatment. The DTSQc is meant for adults and older children. Dr. Clare Bradley has produced a version that is appropriate for bionic pancreas studies for our use, along with a version for younger children. It is administered during and at the end of the intervention. The DTSQc is valid and reliable. Administration time is less than 5 minutes.

T1-Diabetes Distress Scale (T1-DDS)
The T1-DDS is a 28-item survey that assesses seven sources of diabetes distress for type 1 adults. It captures feelings of powerlessness; management distress; hypoglycemia distress; negative social perceptions by others; eating distress; physician (health care) distress; and friend/family distress. Items are scored on a 6-point scale from not a problem to a very serious problem. It is administered before, during, and at the end of the intervention. The scale is valid and reliable, and has been shown to be sensitive to change over time. Administration time is 5 minutes.

Problem Areas in Diabetes Survey (PAID)
There are three versions of the PAID: Teen (PAID-T), Parent (PAID-P), and Child (PAID-C) versions. This measure of diabetes-specific emotional distress in youth with diabetes and their parents is 26 items. A total score is generated. It is administered before, during, and at the end of the intervention. The PAID-T and PAID-P are valid and reliable. Psychometric analysis of the PAID-C is in progress. Administration time is 5 minutes.

Hypoglycemia Fear Survey (HFS)
There are three versions of the HFS, Adult (HFS), Youth (HFS-Y) and Parent (HFS-P). The HFS measures several dimensions of fear of hypoglycemia among adults with type 1 diabetes. It consists of 23 items and produces two sub-scale scores; a Behavior sub-scale that measures behaviors involved in avoidance and/or over-treatment of hypoglycemia and a Worry sub-scale that measures anxiety and fear surrounding hypoglycemia. The HFS-Y consists of 25 items and the HFS-P consists of 26 items; both produce sub-scale scores similar to the Adult HFS. It is administered before, during, and at the end of the intervention. All versions of the HFS are valid and reliable. Administration time is 5-10 minutes.

[redacted]

Impact of Daily Diabetes Demands (IDDD)
There are four versions of the IDDD; Adult (IDDD-A), Youth (IDDD-Y), Parent (IDDD-P), and Significant Other (IDDD-SO). This instrument measures the burden related to the demands of the daily diabetes regimen and is 22 items. A total score is generated. It is administered before, during, and at the end of the intervention. Psychometric analysis of the IDDD-Y is in progress using the data from the second Bionic Pancreas Camp Study in pre-adolescent children, and of the IDDD-A is in progress using data from the Bionic Pancreas Multicenter Study in adults. Administration time is 5 minutes.

Bionic Pancreas User Opinion Survey (BPUOS)
There are four versions of the BPUOS; Adult (BPUOS-A), Youth (BPUOS-Y), Parent (BPUOS-P), and Significant Other (BPUOS-SO). This measure assessing both the benefits from, and difficulties with, use of the bionic pancreas, and consists of 38 items. A total score is generated. It is administered during and at the end of the intervention. Psychometric analysis of the BPUOS-Y is in progress using the data from the second Bionic Pancreas Camp Study in pre-adolescent children, and of the BPUOS -A is in progress using data from the Bionic Pancreas Multicenter Study in adults. Administration time is 10 minutes.

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