Clinical Study Report

A Prospective, Single Center Study to Assess the Performance, Safety, and Patient Reported Outcomes of Insulin Delivery with PaQ® in Patients with Type 2 Diabetes Mellitus

Protocol:	CQR-14002
Investigational Product:	PaQ
Date of Inclusion of First Patient:	06 Feb 2015
Date of Completion of Last Patient:	13 Oct 2015
Indication Studied:	Type 2 Diabetes Mellitus
Methodology:	This was a prospective, single-center, open-label study to evaluate the performance, safety, and patient-reported outcomes during the use of basal bolus insulin delivery with PaQ in patients with type 2 diabetes mellitus who were not previously achieving glycemic targets.
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This study was conducted with Good Clinical Practices (GCP) and applicable regulatory requirements, including the archiving of essential documents.

1 STUDY SYNOPSIS

Title of Study: A Prospective, Single Center Study to Assess the Performance, Safety, and Patient Reported Outcomes of Insulin Delivery with PaQ® in Patients with Type 2 Diabetes Mellitus

Study Center and Principal Investigator: The investigator was Thomas Rudolf Pieber, Medical University of Graz, Division of Endocrinology and Diabetology, Department of Internal Medicine, Auenbruggerplatz 15, A-8036 Graz, Austria.

Introduction: Type 2 diabetes mellitus (T2DM) is a progressive disorder characterized by loss of insulin secretory capacity over time that translates into a need for intensified diabetes therapies. Over time, diet, lifestyle, and oral antidiabetic drugs (OADs) no longer provide adequate blood glucose control, and many patients with T2DM require basal/bolus insulin therapy through multiple daily injections (MDI) However, patient adherence to and persistence with administering MDI therapy is often inadequate. In fact, in the United States, only 57% of patients who use insulin achieve good glycemic control. Barriers to achieving control with MDI include the need for multiple injections, interference of injections with daily activities, injection pain, fear of hypoglycemia and embarrassment.

PaQ insulin delivery device is a small, discreet, wearable device that continuously delivers insulin into the subcutaneous tissue. It is designed to deliver rapid-acting insulin (100 units/mL) for both basal (continuous infusion of insulin at a preset delivery rate for up to 3 days) and bolus insulin (additional insulin administered by the user at mealtime by pushing a "bolus" button). The user is prescribed 1 of 5 preset basal rates. The basal rate of an individual PaQ is set at the time of manufacture and cannot be changed.

This 14-week, open-label, single-center observational study assessed the performance, safety, and patient-reported outcomes (PROs) of CSII therapy with PaQ (referred to internally as PaQ 1.3) in 20 patients with T2DM not achieving individual glycemic targets at study entry with basal-bolus or premixed insulin therapy (with or without OADs and/or GLP-1 based therapy).

Objectives of the Clinical Investigation:

Primary Study Objective

- To evaluate the performance of PaQ, as measured by HbA_{1c}, after 12 weeks of treatment in patients with T2DM who were on basal bolus insulin or premixed insulin therapy taking at least 2 insulin injections per day.

Secondary Study Objectives

1. To evaluate the transition of patients from basal bolus insulin therapy to PaQ as measured by:
   - The number of preset basal doses tried to achieve the desired fasting blood glucose level
   - The number of days taken to identify the preset PaQ basal dose that achieved the desired fasting blood glucose level
2. To evaluate the effect of basal bolus therapy with PaQ over a 12-week period in patients with T2DM on:
   - self-monitored blood glucose (SMBG) readings taken by the patient before and 2 hours after each meal and at bedtime, hereafter referred to as 7-point glucose profile
   - continuous glucose monitoring endpoints of; glucose exposure, glucose variability and percentage of time in target glucose ranges

- the total dose of basal insulin, bolus insulin and combined basal bolus insulin per day (TDD) used on injectable insulin therapy and PaQ
- the patient's body weight measurement at baseline with his or her body weight following PaQ

3. To evaluate the effect of PaQ treatment on Patient Reported Outcomes (PROs) utilizing 3 validated tools:
   - Barriers to Insulin Therapy (BIT) questionnaire
   - Diabetes Treatment Satisfaction (DTSQs) questionnaire
   - Short Form - 36 Health Survey (SF-36).
4. To track the number of PaQ deficiencies (use errors and device malfunctions) that occurred and their association with adverse events (AEs).
5. To evaluate the safety of PaQ as measured by:
   - occurrence and severity of adverse events
   - number and severity of hypoglycemic (SMBG values ≤70 mg/dL) episodes
   - presence and severity of dermal irritation at the PaQ application site, and
   - presence and severity of cannula insertion site infections.

Clinical Trial Methodology: This was a prospective, single center, open-label, uncontrolled study to assess the performance, safety, and PROs of basal bolus insulin delivery with PaQ in basal bolus insulin-using patients with T2DM.

Twenty five (25) patients who were not achieving glycemic targets (screening HbA_{1c} ≥7.0% and ≤11.0%) on an established regimen of basal-bolus insulin therapy ±OADs and/or glucagon-like peptide -1 (GLP-1) agonist were to initiate basal bolus therapy with PaQ using a rapid-acting insulin analog (insulin aspart, NovoRapid®, Novo Nordisk, Copenhagen, DK).

Metformin, thiazolidinediones (TZDs), meglitinides, dipeptidyl peptidase 4 inhibitors, alpha glucosidase inhibitors (AGIs), sodium glucose cotransport 2 (SGLT2) inhibitor and/or GLP-1 agonist if being used at baseline, were continued throughout the study without changing the dose unless medically required.

PaQ devices, each with 1 of 5 distinct basal doses per day administered over a 24-hour time period, were used for insulin delivery during the study; 20 units/day (0.83 units/hr), 24 units/day (1.00 units/hr), 32 units/day (1.33 units/hr), 40 units /day (1.67 units/hr), 50 U units/day (2.08 units/hr).

The PaQ dose chosen for initiation of therapy, as well as initial bolus insulin doses was guided by protocol recommendations. Insulin dose adjustments were subsequently made by the investigative site based on protocol recommendations to safely achieve targets of normal or near-normal glycemic control.

The patient's participation in the study comprised 3 periods as follows:

- **Screening/baseline Period** – This portion of the study was approximately 7 ±2 days. Patients attended the study site (Visit 1) to obtain informed consent and to assess eligibility (screening) for enrollment into the study. During this period, the patient's glycemic control was evaluated while they continued on their current therapy. Providing they met the initial eligibility criteria, they received a home blood glucose meter and paper diary (for documenting self-monitored glucose readings and insulin doses), and were instructed to perform 2 complete 7-point glucose profiles on 2 non-consecutive days prior to starting the PaQ Transition Period at Visit 2 (Day 0).
- **PaQ Transition Period** - During this phase of the study, the patient was switched from his or her current regimen of basal-bolus insulin therapy to basal bolus PaQ therapy. The length of this transition period was dependent upon how long it took to identify a daily PaQ basal dose that

would allow the patient to safely achieve a fasting blood glucose level that met their fasting glycemic target. This period of the study was at least 6 days long (two 3-day wear periods), but might be extended to identify the correct basal dose the patient required for glycemic control. They were evaluated for at least 2 consecutive 3-day wear periods on a given PaQ basal dose to determine whether adequate glycemic control had been obtained before they could proceed to the PaQ Treatment period.

- **PaQ Treatment Period** – This portion of the study was 12 weeks (±2 weeks) in duration. During this period, the patients' glycemic control was managed by PaQ. Patients were seen approximately every 4 weeks, with phone calls occurring 1 week prior to their visit to remind them of their upcoming study visit and to perform and record two 7-point glucose profiles and insulin doses in the study diary within 3 days of their upcoming visit.

Population Studied: Patients with T2DM who had an HbA_{1c} of 7.0% to 11.0%, inclusive, and were on basal bolus or pre-mixed insulin therapy at Screening (Visit 1) were recruited at the single investigative site.

Statistical Analysis: The analyses described in this plan are considered a priori, in that they have been defined prior to database lock. Additional exploratory analyses of data may be conducted, as deemed appropriate.

All individual data were to be listed. The efficacy and safety data were to be further summarized by treatment period. The change from baseline measurements at the end of the study was analyzed using a 2-sided paired t-test for the numeric measurements and a McNemar's test for the categorical measurements with an alpha of 0.10. Data listings, summaries, and analyses were performed by B2S Consulting and/or CeQur under the guidance and approval of CeQur as well as the statistician at B2S Consulting. All analyses and tabulations were performed using SAS® Version 9.3 or higher on a PC platform. Tables and listings were presented in RTF format. Upon completion, all SAS® programs were validated by an independent programmer.

Conclusions:

Patients were able to use PaQ and it worked as it was designed. The concept behind the PaQ insulin delivery device is to provide an alternative mode of insulin delivery that is easy to use, safe and effective. The data from this study support that PaQ's overall performance is achieving this goal:

- Easy to use - The transition from the patients' previous injectable insulin therapy to PaQ was relatively easy; 80% of the patient were able to switch and continue on the first basal rate selected after two 3-day wear periods
- Safe
  - Improved glycemic control was achieved without the occurrence of severe hypoglycemia
  - No use errors were committed that led to patient harm and the adverse events that were seen were predominantly mild and consistent with other body worn CSII devices.
- Effective
  - Clinically meaningful reductions in HbA_{1c} values were seen following 12 weeks of PaQ use
  - Fasting plasma glucose values were significantly improved and demonstrated the performance of the device to deliver a constant basal rate of insulin
  - Seven-point blood glucose data demonstrated the ability of participants to effectively administer meal time insulin and reduce glycemic excursions following meals.
- Improvement in quality of life

  - A trend toward the reduction of barriers to insulin therapy were seen
- Patients were satisfied with the PaQ and had less concerns about hyperglycemia while using PaQ.

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2 INTRODUCTION

2.1 Disease Background and Incidence

Type 2 diabetes mellitus (T2DM) is a progressive disorder characterized by loss of insulin secretory capacity over time that translates into a need for intensified diabetes therapies. Over time, diet, lifestyle, and oral antidiabetic drugs (OADs) no longer provide adequate blood glucose control, and many patients with T2DM require basal/bolus insulin therapy through multiple daily injections (MDI).[1] However, patient adherence to and persistence with administering MDI therapy is often inadequate.[2] In fact, in the United States, only 57% of patients who use insulin achieve good glycemic control.[3] Barriers to achieving control with MDI include the need for multiple injections, interference of injections with daily activities, injection pain, fear of hypoglycemia and embarrassment.[2]

Continuous subcutaneous insulin infusion (CSII) using insulin pumps help patients overcome many of the barriers associated with MDI therapy and might result in higher adherence to therapy. In type 1 diabetes, CSII has demonstrated benefits over MDI therapy, including improved glycemic control, reduced glycemic variability, and improved quality of life (QOL). [4,5,6] However, the complexity of existing pumps often leads to discontinuation of CSII.[7] Consequently, CSII has not been widely used in T2DM due to its complexity and cost.[8] Several studies have assessed the use of CSII in T2DM and have demonstrated improved glycemic control and improved QOL compared to their values at the initiation of CSII therapy.[9,10,11,12,13]

PaQ insulin delivery device is a small, discreet, wearable device that continuously delivers insulin into the subcutaneous tissue. It is designed to deliver rapid-acting insulin (100 units/mL) for both basal (continuous infusion of insulin at a preset delivery rate for up to 3 days) and bolus (additional insulin administered by the user at mealtime by pushing a “bolus” button) insulin. The user is prescribed 1 of 7 preset basal rates. The basal rate of an individual PaQ is set at the time of manufacture and cannot be changed.

The concept behind the PaQ insulin delivery device is to provide an alternative mode of insulin delivery that is easy to use, safe and effective. It is hypothesized that PaQ will overcome many of the barriers of MDI therapy, resulting in better compliance and adherence to therapy, improved patient reported outcomes (PROs - QoL and patient satisfaction), and optimized glycemic control.

This 14-week, open-label, single-center observational study was designed to assess the performance, safety, and patient-reported outcomes (PROs) of CSII therapy with PaQ (referred to internally as PaQ 1.3) in approximately 25 patients with T2DM not achieving glycemic targets at study entry with basal-bolus therapy (with or without OADs and/or GLP-1 based therapy).

3 PAQ - INVESTIGATIONAL DEVICE

PaQ Insulin Delivery Device is intended for continuous subcutaneous infusion of either 16, 20, 24, 32, 40, 50, or 60 units of insulin in one 24-hour time period (delivered at 0.67 to 2.5 IU/hour) for up to 3 days of use, and on-demand bolus dosing in 2-unit increments in adults with diabetes mellitus requiring insulin.

CeQur holds an EC Certificate for CE marking the PaQ Insulin Delivery Device.

3.1 General Product Information

PaQ is a polymer-based, high-accuracy, insulin-delivery device that is composed of an Insulin Reservoir Unit (single-use insulin storage and delivery components) and a Messenger (reusable electronic component) that communicates to the user the battery status (upon connection to the Insulin Reservoir Unit) and insulin status (when worn on the body); specifically, length of time worn, whether the fluid path is blocked, or the device is running out of insulin.

PaQ is assembled (Cannula Placement Device [CPD] attached to Insulin Reservoir Unit that is then attached to the Messenger), filled with rapid-acting insulin, and then applied to the abdomen with a skin adhesive tape by the patient. Using the CPD a soft polymeric cannula is inserted into the subcutaneous tissue by the patient and insulin is delivered from a pressurized elastomeric bladder (reservoir) that provides a constant insulin flow over a 3-day period.

Specific PaQ basal doses are available for delivery of rapid-acting insulin (100 unit/mL concentration) at the following seven pre-set daily basal insulin doses: 16, 20, 24, 32, 40, 50 and 60 units per day. The preset basal dose of an individual PaQ cannot be changed.

Mealtime (bolus) insulin doses are administered in 2-unit increments by pressing a Bolus Button on the side of the device.

The fully assembled device, after filling with insulin and removing the CPD, has dimensions of 51 mm x 74 mm x 17 mm and weighs 33 g, Figure 1.

Figure 1 Fully Assembled and Ready to Use PaQ

3.2 PaQ Components

The PaQ device comprises 2 primary components. These components and their functionality are presented in the text that follows.

3.2.1 Insulin Reservoir Unit

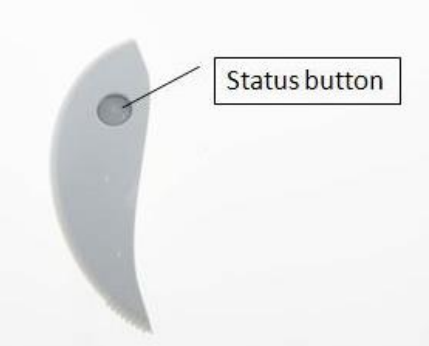
The Insulin Reservoir Unit (Figure 2) is designed to store and deliver insulin for a maximum of 3 days (72 hours). It is a sterile, single-use component that contains the reservoir for insulin storage (capacity = 120 to a maximum of 370 units), a mechanical push button for bolus delivery, the insulin filling port, and the adhesive tape that adheres PaQ to the intended user's abdomen. The Insulin Reservoir Unit is designed to operate with the Messenger, as illustrated in Figure 5.

Figure 2 Insulin Reservoir Unit

3.2.2 Messenger

The Messenger, the reusable component of the PaQ, contains the electronic monitoring system and user interface (Figure 3). The Messenger attaches to the Insulin Reservoir Unit. When these 2 components of the PaQ are attached, the Messenger is activated. Upon initial activation of the device and filling of the reservoir, it requires 1.5 hours for the Messenger to sense insulin flow and detect potential faults, e.g., high pressure indicating an occlusion or low pressure indicating the device is running out of insulin. Thereafter, the unit will perform a safety check of the device every 10 minutes. If a specific issue is detected on 10 consecutive safety checks (e.g., if the insulin in the reservoir is depleted), the Messenger changes status and will deliver this message to the user upon the next press of the Status Button. It also communicates to the user the number of days an Insulin Reservoir Unit has been in use and the battery status of the Messenger at the time of its attachment to the Insulin Reservoir Unit. The user manually checks the PaQ status by pressing the Status Button on the surface of the Messenger (Figure 3).

Figure 3 Messenger

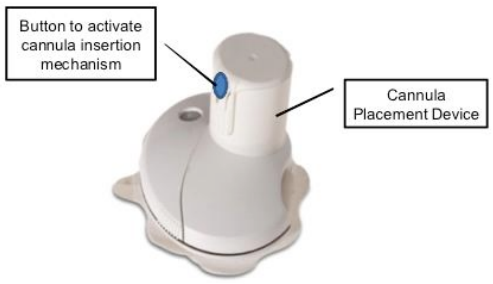


There are 2 additional components that enable the user to prepare and apply PaQ. These components and their functionality are presented in the following sections.

3.2.3 Cannula Placement Device

The CPD (Figure 4) is a sterile, single-use part that is mounted on the top of the Insulin Reservoir Unit for introduction of the insulin delivery cannula into the subcutaneous tissue. The attachment contains a spring-loaded needle surrounded by a flexible tube (cannula). The user presses the button on the side of the CPD to activate the needle insertion mechanism. The needle penetrates the skin, the cannula inserts, and the needle then retracts back into the CPD. After cannula placement, the CPD is removed and discarded.

Figure 4 Cannula Placement Device



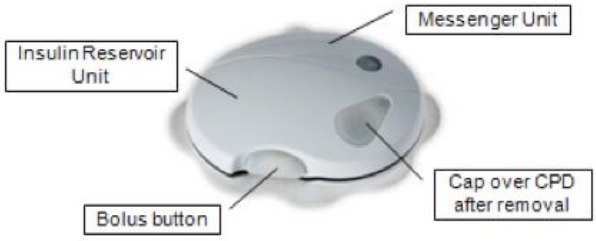
3.2.4 Filling Syringe

A 5-mL syringe is used to draw insulin from an insulin vial and to fill the PaQ reservoir.

3.2.5 Assembled PaQ Device

The PaQ device and its associated components are shown in Figure 5.

Figure 5 Assembled PaQ



3.2.6 Battery Status Messages

Battery status messages are emitted from the Messenger each time the user attaches it to the Insulin Reservoir Unit. While attaching the Messenger to the Insulin Reservoir Unit the user will hold the components in his/her hand, thus allowing the user to see the light when emitted. The following battery status messages are emitted:

- **System OK**: This message is comprised of a single short vibration, a "happy tone," and a green light. This indicates there is ample battery life. The user needs to detect only 1 of the signals to accurately detect the message.
- **3 Days of Battery Power Left:** This message comprises an alert tone and yellow light that repeat 3 times to notify the user that they will need a new Messenger in about 3 days.
- **Replace Messenger:** This message is a continuous vibration (rumble) that will continue until the user disengages the Insulin Reservoir Unit from the Messenger. This signals that the Messenger does not have enough battery power to last for 3 days of use. A new Messenger is required.

3.2.7 Insulin Delivery Messages

Insulin delivery messages will be emitted from the Messenger when the user presses the Status Button on the Messenger. These messages are accompanied by vibrations only, with the exception of the "System OK" message, to allow the messages to be discreet and only detected by the user. The following are the insulin delivery messages:

- **System OK**: This message is comprised of a single short vibration, a "happy tone," and green light. If the insulin is flowing without obstruction and there is an adequate amount of insulin in the PaQ, it is the only message that will be emitted when the user presses the Status Button during the initial 48 hours of use.
- **One Day Left**: This message is 2 short vibrations that will be emitted when the user presses the Status button, after a PaQ device has been worn for 48 hours. It notifies the device user that the insulin is still flowing, but a new Insulin Reservoir Unit will be needed within 24 hours (1 day).
- **Change Insulin Reservoir within 6 hours**: This message is 3 short vibrations that are emitted when the user presses the Status button, after 66 hours (almost 3 days) of PaQ. It notifies the device user that it is time to change the Insulin Reservoir Unit and this should be done within 6 hours.

- **Change Insulin Reservoir Now**: This message is 4 short vibrations that are emitted when the user presses the Status button, after 72 hours of PaQ use to notify the user that the PaQ is running out of insulin and must be changed immediately. This message may also be emitted at any time during PaQ use if the insulin flow path has become occluded. In either case, the PaQ must be changed immediately.

3.2.8 PaQ Functionality

When the fully assembled and filled PaQ is applied to the abdomen and the cannula is inserted, insulin will flow at a constant rate from the insulin reservoir through the basal flow path and be delivered into the subcutaneous tissue. The average basal flow rate of the PaQ device is within ±10% of the intended basal flow rate. Check valves prevent the back flow of insulin through the filling port.

A flow sensor monitors insulin flow to verify that flow is occurring. The flow sensor will alert the Messenger and in turn change the status to "Change Insulin Reservoir Now," if an occlusion is detected or the device is running out of insulin. This status/message will be emitted the next time the user presses the Status Button.

Insulin also flows from the main reservoir into the bolus circuit. When the Bolus Button is pressed, valves open to deliver a bolus of insulin into the subcutaneous tissue. Each press of the button will deliver two units of insulin (±10%).

4 STUDY OBJECTIVES

4.1 Primary Study Objective

To evaluate the performance of PaQ, as measured by HbA_{1c}, after 12 weeks of treatment in patients with T2DM who were on basal bolus insulin therapy taking at least 2 insulin injections per day.

4.2 Secondary Study Objectives

1. To evaluate the transition of patients from basal bolus insulin therapy to PaQ as measured by:
    - The number of preset basal doses tried to achieve the desired fasting blood glucose level
    - The number of days taken to identify the preset PaQ basal dose that achieved the desired fasting blood glucose level
2. To evaluate the effect of basal bolus therapy with PaQ over a 12-week period in patients with T2DM on:
    - self-monitored blood glucose (SMBG) readings taken by the patient before and 2 hours after each meal and at bedtime, hereafter referred to as 7-point glucose profile
    - continuous glucose monitoring endpoints of; glucose exposure, glucose variability and percentage of time in target glucose ranges
    - the total dose of basal insulin, bolus insulin and combined basal bolus insulin per day (TDD) used on injectable insulin therapy and PaQ
    - the patient's body weight measurement at baseline with his or her body weight following PaQ
3. To evaluate the effect of PaQ treatment on Patient Reported Outcomes (PROs) utilizing 3 validated tools:
    - Barriers to Insulin Therapy (BIT) questionnaire
    - Diabetes Treatment Satisfaction (DTSQs) questionnaire
    - Short Form - 36 Health Survey (SF-36).
4. To track the number of PaQ deficiencies (use errors and device malfunctions) that occurred and their association with adverse events (AEs).
5. To evaluate the safety of PaQ as measured by:
    - occurrence and severity of adverse events
    - number and severity of hypoglycemic (SMBG values $\leq$70 mg/dL) episodes
    - presence and severity of dermal irritation at the PaQ application site, and
    - presence and severity of cannula insertion site infections.

5 CLINICAL INVESTIGATION PLAN

5.1 Overall Study Design

This was a prospective, single center, open-label, uncontrolled study to assess the performance, safety, and PROs of basal bolus insulin delivery with PaQ in basal bolus or premixed insulin therapy using patients with T2DM.

Twenty five (25) patients who were not achieving glycemic targets (screening HbA_{1c} ≥7.0% and ≤11.0%) on an established regimen of basal-bolus insulin therapy ±OADs and/or glucagon-like peptide -1 (GLP-1) agonist were to initiate basal bolus therapy with PaQ using a rapid-acting insulin analog (insulin aspart, NovoRapid®, Novo Nordisk, Copenhagen, DK).

Metformin, thiazolidinediones (TZDs), meglitinides, dipeptidyl peptidase 4 inhibitors, alpha glucosidase inhibitors (AGIs), sodium glucose cotransport 2 (SGLT2) inhibitor and/or GLP-1 agonist if being used at baseline, were continued throughout the study without changing the dose unless medically required. Patients who had received sulfonylureas within the last 2 months were not eligible for enrollment.

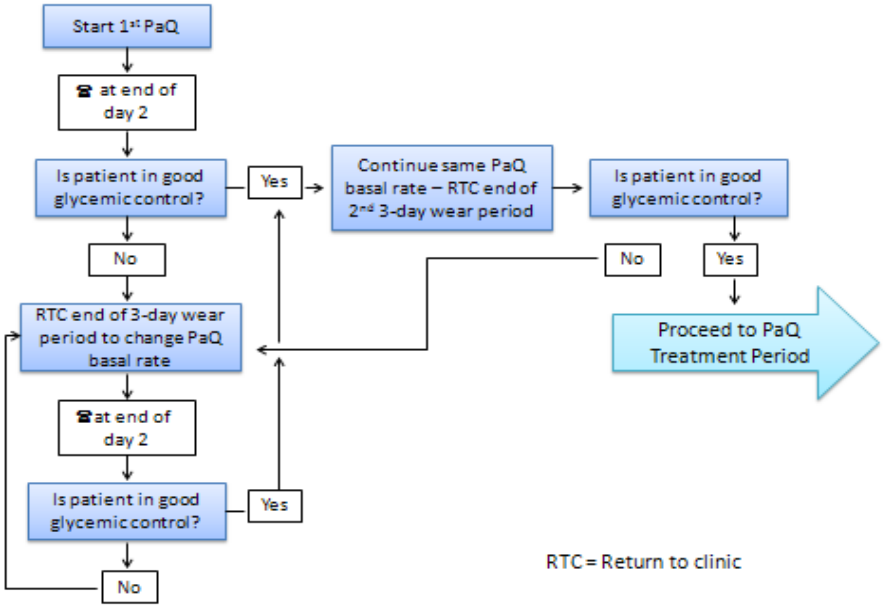
PaQ devices, each with 1 of 5 distinct basal doses per day administered over a 24-hour time period, were used for insulin delivery during the study; 20 units/day (0.83 units/hr), 24 units/day (1.00 units/hr), 32 units/day (1.33 units/hr), 40 units /day (1.67 units/hr), 50 U units/day (2.08 units/hr).

The PaQ dose chosen for initiation of therapy, as well as initial bolus insulin doses was guided by protocol recommendations. Insulin dose adjustments were subsequently made by the investigative site based on protocol recommendations to safely achieve targets of normal or near-normal glycemic control.

The patient's participation in the study comprised 3 periods as follows:

- **Screening/baseline Period** – This portion of the study was approximately 7 ±2 days. Patients attended the study site (Visit 1) to obtain informed consent and to assess eligibility (screening) for enrollment into the study. During this period, the patient's glycemic control was evaluated while they continued on their current therapy. Providing they met the initial eligibility criteria, they received a home blood glucose meter and paper diary (for documenting self-monitored glucose readings and insulin doses), and were instructed to perform 2 complete 7-point glucose profiles on 2 non-consecutive days prior to starting the PaQ Transition Period at Visit 2 (Day 0).
- **PaQ Transition Period** - During this phase of the study, the patient was switched from his or her current regimen of basal-bolus insulin therapy to basal bolus PaQ therapy. The length of this transition period was dependent upon how long it took to identify a daily PaQ basal dose that would allow the patient to safely achieve a fasting blood glucose level that met their fasting glycemic target. This period of the study was at least 6 days long (two 3-day wear periods), but might be extended to identify the correct basal dose the patient required for glycemic control as illustrated in Figure 6. They were evaluated for at least 2 consecutive 3-day wear periods on a given PaQ basal dose to determine whether adequate glycemic control had been obtained before they could proceed to the PaQ Treatment period.

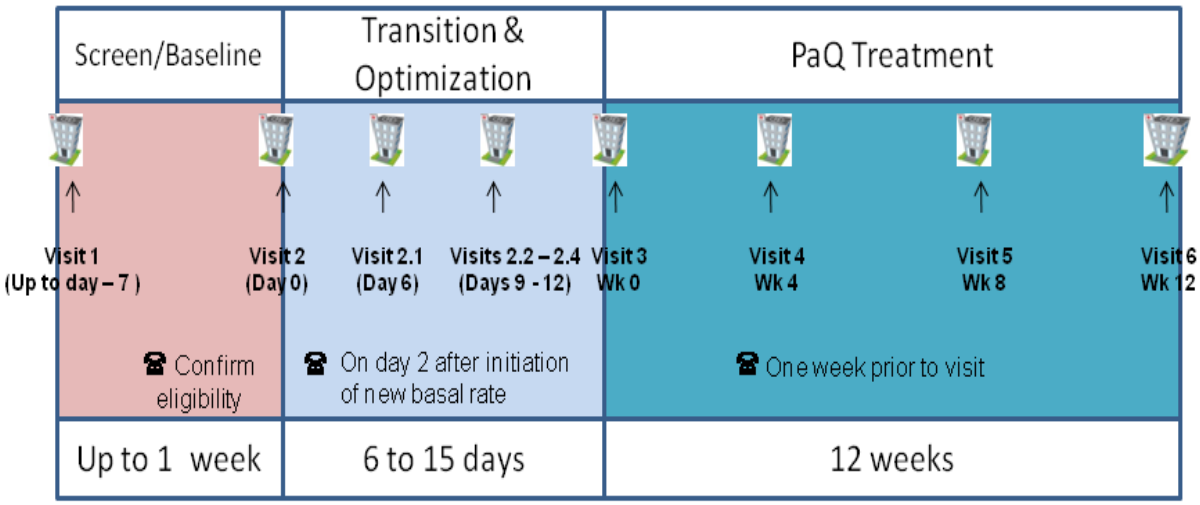
Figure 6 Decision Tree for Identification of Correct PaQ Basal Dose



- **PaQ Treatment Period** – This portion of the study was 12 weeks (±2 weeks) in duration. During this period, the patients' glycemic control was managed by PaQ. Patients were seen approximately every 4 weeks, with phone calls occurring 1 week prior to their visit to remind them of their upcoming study visit and to perform and record two 7-point glucose profiles and insulin doses in the study diary within 3 days of their upcoming visit.

The overall study design and visit structure are illustrated in Figure 7.

Figure 7 Study Design Schematic



5.2 Discussion of Study Design

The overarching objective of this study was to assess the performance, safety, and PROs of CSII therapy with PaQ in a "real world" setting. To achieve these objectives, an uncontrolled, observational study design was appropriate. Endpoints throughout the course of the study were compared with baseline values. The PaQ Treatment Period of 12 weeks allowed assessment of both achievement and maintenance (durability) of glycemic control.

As PaQ is intended for use in patients with T2DM not achieving desired glycemic control on their current insulin regimen (with or without OADs and/or GLP-1 agonists), patients suboptimally controlled on basal bolus insulin therapy were the appropriate population for this study.

Although a therapeutic effect may be partially attributable to the study effect, a positive therapeutic effect demonstrated that the PaQ device was able to provide basal and bolus insulin.

To best isolate the performance/effect of PaQ, confounding variables that could affect a patient's glycemic control and/or safety was controlled through the inclusion/exclusion criteria, patient restrictions, and concomitant medications.

5.3 Study Duration

The total study was expected to last approximately 6 months, including 8 to 10 weeks for enrollment and approximately 14 weeks for the patient's participation in the study.

5.4 Selection of Study Population

Patients with T2DM who had an HbA_{1c} of 7.0% to 11.0%, inclusive, at Screening (Visit 1) were recruited at the single investigative site.

5.4.1 Inclusion Criteria

A patient was eligible for study participation if he or she met the following criteria:

1. Was at least 18 years of age
2. Had a clinical diagnosis of T2DM, as determined by clinical history and medication usage
3. Had an HbA_{1c} ≥7.0% and ≤11.0%
4. Was treated with basal-bolus insulin therapy (at least 2 injections per day) with or without OADs, and/or GLP-1 agonist for at least 3 months and had not had a change (addition or discontinuation of existing drug or change in dose) in his or her OADs for the last 8 weeks
5. Determined by the investigator that insulin requirements to achieve glycemic targets can be met by the insulin capacity of the PaQ device
6. If on concomitant metformin, had serum creatinine <1.5 mg/dL (male) or <1.4 mg/dL (female)
7. If female, and of child-bearing potential, had a negative urine pregnancy test at screening and was using adequate means of contraception as determined by the investigator
8. Was clinically euthyroid as judged by the investigator
9. Was able to understand and sign the required study documents and complied with the clinical investigation plan (CIP) requirements
10. Was deemed capable by the investigator to perform the requirements of the CIP, including use of PaQ and frequent self-monitoring of blood glucose.

5.4.2 Exclusion Criteria

A patient was not eligible for study participation if he or she met any of the following criteria:

1. Was poorly compliant with the currently prescribed diabetes regimen, as determined by the investigator
2. Was poorly compliant with prescribed self-monitoring of blood glucose, as determined by the investigator
3. Was currently taking or has taken sulfonylureas within the last 2 months
4. Had a body mass index (BMI) greater than 40 kg/m^2
5. Had experienced recurrent severe hypoglycemia (>2 episodes) requiring assistance during the past 6 months
6. Had existing dermal irritation/inflammation over the abdominal area that could have interfered with use of PaQ, as determined by the investigator
7. Had known clinically significant hypersensitivity to skin adhesives
8. Was female and if of child-bearing potential, was pregnant, lactating, or planning to become pregnant
9. Was currently being treated with or expected to require or undergo treatment with systemic steroids by oral, intravenous, or intramuscular route (inhaled with low systemic exposure was permitted)

10. Currently abused drugs or alcohol or had a history of abuse that in the investigator's opinion would have caused the individual to be non-compliant
11. Had received any investigational drug within 1 month
12. Had donated blood within 30 days
13. Had any significant medical condition (including current or past history of cardiovascular disease), laboratory findings, or medical history that in the investigator's opinion could affect successful completion of the study and/or personal well-being
14. Was an immediate family member (spouse, parent, child, or sibling) of personnel directly affiliated with the study at the investigative site, or was personally directly affiliated with the study at the investigative site.

5.4.3 Patient Withdrawal or Discontinuation

The following events were considered sufficient reasons for a patient to discontinue participation in the study:

- Whenever the patient decided that it was in his or her best interest to discontinue study participation.
- Whenever the investigator or CeQur decided that discontinuing the study was advisable or in the patient's best interest, e.g., the patient did not achieve comparable FBG with PaQ treatment.
- If the patient died due to any cause.

If any treated patient was unable to return to the study center after treatment, efforts were made to obtain complete follow-up information from a local physician. The reason for a patient's failure to return for the necessary follow-up visits or for a patient's discontinuation from the study was determined and recorded on the Conclusion of Patient Participation electronic case report form (eCRF). A clinical investigation deviation form was completed.

5.5 Study Treatment

5.5.1 PaQ Kits and Accountability

PaQ (version 1.3) was provided by CeQur Corporation. The PaQ kits were shipped to the investigational site once ethics committee, competent authority, and contract approvals were obtained. The PaQ device kits contained:

- Two individually packaged disposable Insulin Reservoir Units with filling syringes
- Two individually packaged disposable CPDs
- PaQ quick start guide (QSG) in German language

The instructions for use (IFU, in German language) and reusable Messenger were provided separately from the PaQ device kits.

The device kits were packaged and labelled according to the Insulin Reservoir Unit basal rate. Five basal rates were supplied: 0.83 U/h (20 U/day), 1.0 U/h (24 U/day), 1.33 U/h (32 U/day), 1.67 U/h (40 U/day), and 2.08 U/h (50 U/day). The lot numbers that were used in this study are provided in Appendix 20.1.4.

Device accountability was managed according to the procedure outlined in the CIP (Appendix 20.1.1).

Each Insulin Reservoir Unit and Messenger was labeled with the following information: CE mark, lot number, storage requirements and manufacturer.

5.5.2 Other Study Supplies

Patients were provided with a glucose meter (Life Scan One Touch Ultra manufactured by Life Scan, a Johnson & Johnson Company), glucose test strips, and lancets at Visit 1 (beginning of Screening/Baseline period).

Patients were provided with a rapid acting insulin (insulin aspart [NovoRapid®]) at Visit 2 (Day 1) and as needed throughout the course of the study.

5.5.3 Patient Training

Patients received study-related training, including preparation and application of and bolus dosing with PaQ, by the study site as well as instruction on the messages emitted by the PaQ device. They could also refer to the QSG and/or the IFU for directions on PaQ assembly, filling of the Insulin Reservoir and application. Additionally, they were instructed to call the study site, who had established a 24 hour hot line, if any questions arose during the course of the study pertaining to PaQ or any of the study-related clinical supplies (i.e., blood glucose meter).

Patient education and study-related training was conducted formally at Visit 2. This training included general concepts of basal-bolus insulin therapy, dietary instructions, use of the PaQ, use of the glucose meter, recognition and treatment of hypoglycemia, and study-specific training (including self-monitoring and recording of blood glucose, 7-point glucose profiles, and recording of insulin doses). If commonly performed by the study site, and thought to be appropriate for an individual study patient, the patient was trained on carbohydrate counting for mealtime (bolus) insulin dose determination.

Ongoing patient education and training was expected to occur as needed throughout the duration of the study.

Study training materials were provided to the sites by the sponsor or designee.

5.6 Patient Registration and Numbering

Patients were assigned a number as they were screened for consideration into the study. The numbers were assigned sequentially by the investigative site. The patient was identified on each eCRF by the assigned patient number.

The study site maintained a log of all screened patients. This allowed assessment of the number and characteristics of excluded patients, and the reasons for their exclusion.

The principal investigator maintained a list identifying each patient entered into the trial as part of his or her study files.

5.7 Prior and Concomitant Therapy

When enrolled into the study, patients were instructed to:

- Take no new medications excluded by the protocol
- Not to donate blood for the duration of the study

Patients were not allowed to receive any of the medications listed in the exclusion criteria during the study, and must have observed instructions listed in patient restrictions.

Hyperglycemia and hypoglycemia (if encountered) were to be addressed by appropriate adjustments in the patient's insulin dose, not by modification to the dose of OADs (if applicable).

The sponsor or designee was to be contacted if the investigator is informed of any restriction violations.

5.8 Visit Schedule and Assessments

Table 1 presents a schedule of study procedures at each of the study visits. To allow for flexibility in the scheduling of the visits and to maintain the comparability of the data, visit windows were established for each of the visits defined in the protocol. Please refer to CIP CQR-14002 (Appendix 20.1.1) for further details concerning study procedures.

Table 1 Schedule of Study Procedures

	Screen/ Baseline	Transition ±1 days		PaQ Treatment ±6 days			
Study Visit	**Visit 1**	**Visit 2**	**Visits 2.1 to 2.4**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Study Procedures	**-7 to Day 0**	**Day 0**	**Day 6-15**	**Week 0**	**Week 4**	**Week 8**	**Week 12 or ET**
Informed consent	X						
Blood pressure and heart rate	X	X	X	X	X	X	X
Complete medical history, concurrent medications, demographics	X						
Blood chemistry and hematology	X						X
Urine pregnancy (β-HCG)	X						X
HbA_{1c}	X[a]					X	X
Fasting plasma glucose	X			X	X	X	X
Height	X						
Body weight	X						X
Education, study-related training	X	X					
Dispense glucose meter, strips and diary	X			X		X	
Dispense PaQ		X	X	X	X	X	
Dispense study insulin		X		X	X	X	
Phone calls by study staff		X	X	X	X	X	
Concomitant medications and AE review		X	X	X	X	X	X
Examine PaQ application site		X	X	X	X	X	X
Diary Review - 7-Point SMBG, insulin doses[b]		X	X	X	X	X	X
PRO questionnaires		X					X
Device deficiencies			X	X	X	X	X
Study closeout							X

Abbreviations: AE = adverse event; ET = early termination; PRO = patient reported outcomes; SMBG = self-monitored blood glucose.

a HbA_{1c} - Screening point of care to confirm eligibility and 3mL blood draw for baseline value.

b Patients performed 7-point glucose profiles on 2 nonconsecutive days the week prior to Visits 2, 4, 5 and 6 and daily during the Transition Period. Confirmed glucose values from glucose meter prior to data entry.

5.9 Study Methodology

5.9.1 Insulin Dosing Requirements

Selection of the initial PaQ basal dose and mealtime insulin bolus doses, as well as insulin dose adjustments, were to be made only as directed by the investigator or qualified site personnel.

As a general guidance, insulin dose adjustments were to be made to safely achieve the best glycemic control possible.

The insulin dosing guidance was to be followed for all patients unless the investigator considered it unsafe (due to risk of hypoglycemia or extreme hyperglycemia) based upon an individual patient's clinical information (i.e., current glycemic control, history of hypoglycemia, prestudy insulin doses, oral agents that would have been discontinued at baseline). Basal insulin dose adjustments on the day prior to and/or on the morning of PaQ initiation (Visit 2 [Day 0]) were to be considered for all patients as follows:

- If taking a long-acting basal insulin (insulin glargine or insulin detemir) once per day in the evening, the patient was to reduce his or her dose by 50% the evening prior to Visit 2 (Day 0). If taking an intermediate-acting basal insulin (i.e., NPH), a reduction in the evening dose might not have been necessary, and was up to the discretion of the investigator.
- If taking basal insulin once per day in the morning (long- or intermediate-acting), the patient was to omit his or her morning dose on the day of Visit 2 (Day 0)
- If taking basal insulin twice per day (evening and morning) the patient was to adjust the evening dose as described above the evening prior to and omit his or her morning dose on the day of Visit 2 (Day 0)

No adjustments to bolus (mealtime) insulin doses prior to Visit 2 (Day 0) were to be made.

5.9.1.1 Initial PaQ Basal Dose Selection and Bolus (Mealtime) Dosing Recommendations at Visit 2 (Day 0)

Visit 2 dosing recommendations included the following:

- Select an initial PaQ basal dose that was closest to the patient's current total daily basal dose.
- If the current total daily basal dose was greater than one of the preset PaQ basal doses, then round down to the closest PaQ basal dose; however, if the investigator believed that a different basal rate was needed to reach the preprandial target, then they could have selected a different PaQ basal rate.
- Initial bolus insulin doses using PaQ should have been generally similar to bolus doses being administered by the patient at baseline.
- Alternatively, at the investigator's discretion (based on patient characteristics and the study center's usual practice) patients could have continued or been instructed on carbohydrate counting and dose mealtime insulin based on the meal's carbohydrate content.
- Bolus insulin doses should have been taken immediately before each major meal (breakfast, lunch, and dinner).

5.9.1.2 Glycemic Targets

Efforts were to have been made to safely achieve fasting and preprandial plasma glucose values of 70 to 130 mg/dL and 1.5- to 2-hour postprandial plasma glucose values <140 mg/dL.

At the investigator's discretion, individual patient's goals/targets may have been modified to ensure safe achievement of the best possible glycemic control. These patient-specific targets were to have been documented and entered into the database. Additional detailed information concerning basal and bolus insulin dose adjustments and recommendations, and correction boluses is detailed in the Clinical Investigation Plan, Appendix 20.1.1.

5.9.2 Self-monitoring of Blood Glucose

The sponsor or designee provided glucose meters for patients to self-monitor his or her blood glucose concentrations. A glucose meter that reported values corresponding to laboratory-measured plasma glucose was dispensed at Visit 1 (Screening/baseline); patients were trained in its use at that visit.

Patients were instructed to perform the measurements via finger-stick at the fingertip and not at any alternate site, regardless of possible statements in the packaging information for the glucose meter.

The provided blood glucose meters were to be used exclusively throughout study conduct for self-monitored glucose measurements.

Throughout the study, patients self-monitored and recorded glucose concentrations at least 3 times daily, as directed by the investigator.

Patients were instructed to test and record a self-monitored glucose measurement if they experienced symptoms of hypoglycemia, and to contact the clinic as soon as possible if they experienced an episode of severe hypoglycemia.

Seven-point glucose profiles

Patients were instructed to take glucose measurements within 15 minutes before and 1.5 to 2 hours after the start of each meal and 1 at bedtime.

The patient was reminded to use the study-provided glucose meter for these measurements, and to record the glucose concentration, time of measurement indicated on the meter, and time at which the meal was started in the paper diary.

The study staff confirmed this information by reviewing glucose meter history directly from the meter and/or the meter download at the time of the study site visit.

5.9.3 Patient Diary

The following information was entered into the patient's diary on a daily basis:

- Insulin therapy during screen/baseline period
  - Type administered – basal or bolus
  - Time administered – 24-hour clock
- Dose administered – expressed in numerical value, e.g., 10 units
- SMBG concentrations – time, date and value indicated on the meter expressed in mg/dL

- Meals on days 7-point glucose profiles are performed – Time meal started
- Symptomatic hypoglycemia – symptoms experienced and SMBG concentration

During the CeQur treatment period, the study patients also noted the following information in their diary:

- Date and time a new device was applied to their body
- Date and day the PaQ was removed
- Whether the device was fully adhered to their body, if not, whether it was partially adhered or fell off.

5.9.4 Continuous Glucose Monitoring

Patients were provided with iPro®, a CGM monitoring system manufactured by Medtronic Minimed, Inc. The investigative site applied and removed the iPro devices to and from the study participants according to the manufacturer's directions. The iPro devices were worn by the participants as follows:

- One 6-day (± 1 day) wear period during the screen/baseline period
- Two 6-day (± 1 day) wear periods when starting the PaQ treatment period
- Two 6-day (± 1 day) wear periods after wearing PaQ for 8-weeks

The data from the iPro devices, as well as the participants' SMBG readings, were then uploaded by the clinical site to Medtronic's CareLink iPro web site. Once the data had been uploaded, the CGM readings were then calculated retrospectively.

5.9.5 PaQ Application Site Examination

The following scales were used to assess tape adherence, dermal irritation, and characteristics of the cannula site at the PaQ application site (Table 2).

Table 2 Dermal Irritation, Tape Adherence, and Cannula Assessment Scales

Dermal Irritation			
Blister Formation	**Patient reported Irritation**	**Adherence of Tape to Body**	**Cannula Intact**
0 = none	0 = none	0 = adhered	0 = yes
1 = present	1 = mild	1 = fell off	1 = no
	2 = moderate		
	3 = severe		

If a blister was present or if the patient experienced severe irritation, this was entered as an AE into the database.

The scale used to characterize erythema, edema, ecchymosis, and exudate of the cannula insertion site during examination is summarized in Table 3.

Table 3 Dermal Irritation Scale

Erythema	Edema	Ecchymosis	Exudate
0 = none	0 = none	0 = none	0 = none
1 = mild	1 = mild	1 = small	1 = present
2 = moderate	2 = moderate	2 = moderate	
3 = severe	3 = severe	3 = large	

If symptoms were suggestive of an infection at the cannula insertion site, then infection as an AE was entered into the database.

5.9.6 Patient-reported Outcomes

To assess the patient's Health-Related QoL and treatment satisfaction during the study, 3 validated questionnaires were administered at Visit 2 (Beginning of Transition Period) and again at the end of the study.

The questionnaires administered were the following:

- Barriers to Insulin Treatment Questionnaire[14]
- Diabetes Treatment Satisfaction (DTSQ) questionnaire[15]
- Short Form - 36 Health Survey (SF-36)[16]

Study personnel were trained by the sponsor or the sponsor's designee regarding the appropriate procedures for questionnaire administration.

5.10 Safety

Randomized, controlled trials as well as observational studies have been conducted with CSII devices in patients with T2DM. Data from these studies suggest that the risks associated with the use of CSII devices in this patient population include the following: 1) overdosing that can lead to hypoglycemia; 2) underdosing that can lead to hyperglycemia; 3) potential for infection at the cannula infusion site; and 4) potential risk of dermal irritation due to the adhesive used to attach the device to the patient's abdomen. In addition, device deficiencies, whether they are use errors or device malfunctions, can also be associated with these known risks.

Adverse event surveillance was utilized to monitor the occurrence of hypoglycemia or hyperglycemia, in addition to any new illness, symptom, or clinically significant laboratory abnormality that appeared or worsened during the course of the clinical investigation.

5.10.1 Hypoglycemia

Patients were to be instructed to monitor blood glucose concentrations frequently while using insulin, especially during the initial weeks after intensifying insulin therapy with PaQ.

Patients were instructed to test and record a self-monitored glucose measurement if they experienced symptoms of hypoglycemia, and to contact the study site as soon as possible if they experienced an episode of severe hypoglycemia.

If the investigator determined that a patient experienced an episode of hypoglycemia, the event was documented in the patient's source documentation and on the Hypoglycemia eCRF. If a glucose value at the time of the hypoglycemic episode was available, it was to be included in this documentation. In addition, the events that may have led to the symptomatic hypoglycemic event, (e.g., missed meal, exercise, meal time bolus dose exceeded amount required) were documented and entered into the eCRF.

In this study, hypoglycemia was defined as less than or equal to 70 mg/dL (3.9 mmol/mol) and categorized according to the definitions published by the American Diabetes Association Workgroup on Hypoglycemia.[17] These definitions can be found in Section 15 Abbreviation and Definition of terms. To ensure the timely collection of information related to hypoglycemia, patient diaries were reviewed at each study visit and during each of the phone visits with patients.

5.10.2 Hyperglycemia

Hyperglycemia is a common occurrence in patients with diabetes. It was considered an AE if the patient had high blood glucose levels that were associated with symptoms and required medical intervention or replacement of the PaQ device. Qualified study personnel educated patients regarding hyperglycemia and the appropriate medical action to take if hyperglycemia occurred.

5.10.3 Recording and Reporting of Adverse Events

Patients were carefully monitored during the study for possible AEs. The method used for recording and reporting AEs is detailed in the CIP, Appendix 20.1.1.

The definitions AE, adverse device effect (ADE), serious adverse event (SAE), and serious adverse device effect (SADE), are consistent with ISO 14155 and can be found in Section 15 Abbreviations and Definitions of Terms.

The relation between an AE and PaQ was determined by the investigator on the basis of his or her clinical judgment as either associated, undetermined (unknown), or not related according to the definitions in Section 15 (Abbreviations and Definitions).

The severity of AEs was assessed as mild, moderate, severe, and serious according to the definitions provided in Section 15.

The occurrence of device deficiencies, use errors or malfunctions, and their association with AEs was also monitored. The definitions used for device deficiencies, use errors, and malfunctions are taken directly from ISO 14155 and can be found in Section 15.

Occurrences of dermal irritation were closely monitored by asking the investigative site to look specifically at the PaQ application site for signs of erythema, edema, blister formation, and complaints of irritation. To evaluate the occurrence of infection at the cannula insertion site, the investigator was asked to examine the site specifically for signs of infections, including erythema, edema, ecchymosis, and exudate. The scales used for these examinations are detailed in the previous section.

6 CHANGES IN STUDY CONDUCT

The original CIP (dated 11 September 2014) was revised twice. A summary of the changes made for each revision are outlined as follows.

- Revision Number 2 – 30 October 2014
    - Per the ethics committee's request, "observational" was deleted from the title of the protocol
    - In the sample size section, CI limits were revised from 0.403 to 0.376.
- Revision Number 3 – 25 March 2015
    - Added continuous glucose monitoring (CGM) as a secondary study objective.
        - Included in the procedures section that the CGM device (iPro, Medtronic Minimed. Inc.) would be worn for: 1) one 6-day (± 1 day) wear period during the screen/baseline period, 2) two 6-day (± 1 day) wear periods when starting the PaQ treatment period and 3) two 6-day (± 1 day) wear periods beginning at Week 8 during the PaQ treatment period
        - Included in the statistical section the CGM endpoints that were to be evaluated
        - Added to the statistical section that approximately 10 enrolled patients would wear the CGM device
    - Added language that allowed study participants to be able to discontinue the use of PaQ for up to 7 days to allow for elective medical procedures.

Twenty rather than 25 patients were enrolled into the study due to a limitation of PaQ devices. This resulted in 5 rather than 10 enrolled patients wearing the CGM device.

Patient-specific glycemic targets were not entered into the database as written in the protocol. This was an error; the text should have been deleted. While there were guidelines for glycemic targets, there was no study objective to assess patients' ability to reach glycemic targets while on study.

The original statistical analysis plan was conducted as described. Three additional secondary endpoint analyses that had not been specified in Section 4.2 were performed: 1) change in HbA1c from baseline at Week 8; 2) change in bolus injection frequency per day from baseline at Week 4, Week 8 and Week 12; and 3) number of patients with hypoglycemia episodes with blood glucose values ≤ 56 mg/dL.

There were no changes to the device design or functionality during the course of the study.

7 DATA MANAGEMENT

Steps to assure the accuracy and reliability of data included the selection of qualified investigators and appropriate study sites, review of CIP procedures with the investigator and associated personnel prior to the study, and periodic monitoring visits by a CeQur monitor or designee who reviewed data for accuracy and completeness during and after on-site monitoring visits. Any discrepancies were resolved with the investigator or designee as appropriate.

7.1 Case Report Forms

The eCRFs contained confidential material. Specific instructions to complete the eCRFs were provided to the investigator and other site personnel as appropriate.

7.2 Monitoring Procedures

Monitors conducted site visits to the study facilities to monitor the study. During these visits the clinical research associate (CRA) verified the data entered into the eCRFs against hospital or other source documents to ensure its accuracy and completeness as well as ensure compliance to the CIP and GCP.

8 STATISTICAL METHODS AND ANALYSIS

All study endpoint data analysis was performed by B2S Consulting and/or CeQur with the exception of the statistical analysis of the CGM glycemic control variables, which was performed by Joanneum Research, Graz, Austria. The endpoints for the analysis were based on the Bergenstal et al publication, "Recommendations for standardizing glucose reporting and analysis to optimize clinical decision making in diabetes".[18] A copy of CeQur's SAP, as well as a copy of the SAP for the CGM analysis, is provided in Appendix 20.4.1. A summary of the CeQur SAP, excluding the CGM SAP, is presented in the following sections.

8.1 Analysis Populations

The intent-to-treat (ITT) population consisted of all patients who received at least 1 dose of insulin with PaQ

The evaluable population consisted of all ITT patients who completed the study procedures through Week 12, respectively, without major protocol deviations as defined in the SAP.

The ITT population was to be used for all safety analyses. Efficacy and PRO analyses were summarized for both ITT and evaluable populations. Patient disposition summary was produced for all patients enrolled.

8.2 Study Endpoints

The endpoints that were analyzed for the primary and secondary study objectives have previously been listed in Section 4 Study Objectives. Three additional secondary endpoint analyses that had not been specified in Section 4 are the following: 1) change in HbA1c from baseline at Week 8, 2) change in bolus injection frequency per day from baseline at Week 4, Week 8 and Week 12, and 3) number of patients with hypoglycemia episodes with blood glucose values ≤ 56 mg/dL.

8.3 Sample Size and Power

A sufficient number of individuals were to be screened to enroll at least 25 patients. The premature withdrawal rate was assumed to be approximately 15%. Therefore, approximately 21 patients were expected to complete treatment through Week 12. This sample size was considered to be sufficient to evaluate the effectiveness and safety of PaQ in this study. The purpose of this study was to estimate the change in HbA_{1c} from baseline after 12 weeks of therapy. A sample size of 21 patients produced a 2-sided 90% confidence interval with a distance from the HbA_{1c} mean change from baseline to the CI limits that was less than or equal to 0.376 assuming a standard deviation of 1.0.

8.4 Statistical Methods

8.4.1 General Considerations

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock. Additional exploratory analyses of data may be conducted, as deemed appropriate.

All individual data were to be listed. The efficacy and safety data were to be further summarized by treatment period. The change from baseline measurements at the end of the study was analyzed using a 2-sided paired t-test for the numeric measurements and a McNemar's test for the categorical measurements with an alpha of 0.10. Data listings, summaries, and analyses were performed by B2S

Consulting and/or CeQur under the guidance and approval of CeQur as well as the statistician at B2S Consulting. All analyses and tabulations were performed using SAS® Version 9.3 or higher on a PC platform. Tables and listings were presented in RTF format. Upon completion, all SAS® programs were validated by an independent programmer.

8.4.2 Patient Disposition

Frequency counts and percentages of all patients enrolled, initiating the use of PaQ, completing, and/or discontinuing from the study were presented. The reasons for discontinuation from the study were summarized.

Major protocol deviations included, but were not limited to:

- Patients with missing or invalid consent (legal representative needs to sign, but signature was not obtained)
- Protocol-specified insulin (insulin asparte) not used, other insulin used (risk of either a hypoglycemic or a hyperglycemic episode)
- Patients who did not satisfy the inclusion and exclusion criteria
- Prohibited concomitant medication (considered a violation if the prohibited medication had the potential to influence insulin metabolism or skin reaction) was used

Protocol deviations and violations were documented as they were noted by the CRA in monitoring trip reports and entered into the database.

8.4.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics were summarized for the ITT population. The categorical variables were summarized using frequencies and percentages and the continuous measures were summarized using means, SDs, sample sizes, and possibly other descriptive statistic measures.

The demographic and baseline characteristics included:

- Age, gender, race
- Height, weight, BMI
- Duration of diabetes
- HbA_{1c} at baseline
- Diabetes-related conditions
- Total daily insulin dose
- Basal insulin dose
- Bolus insulin dose
- Total injections per day

8.4.4 Medical and Surgical History

Medical and surgical histories were listed by patient. A summary of concurrent medical conditions and concomitant medications taken in greater than 20% of the patients at study start was provided.

8.4.5 Prior and Concomitant Medications

Verbatim terms on case report forms were coded using the World Health Organization Drug Dictionary. A summary table and listing of the concomitant medications was provided.

8.4.6 Efficacy Analyses

8.4.6.1 Primary Variable Change in HbA_{1c} from Baseline at Week 12

The HbA_{1c} measurements at each visit was presented and summarized and a simple t-test were performed comparing the change in HbA_{1c} to baseline. All reports of HbA_{1c} were in International Federation of Clinical Chemistry (IFCC) mmol/mol). The conversion to Diabetes Control and Complications Trial (DCCT) units was the following:

- DCCT HbA_{1c} (%) = 2.15 + (IFCC HbA_{1c} (mmol/mol)/10.929)

This analysis was performed for both the ITT and evaluable populations.

8.4.6.2 Seven-point Blood Glucose Profile

A summary and analysis comparing the blood glucose (BG) profile measurements to baseline was performed for the following measurements:

- Mean daily blood glucose (MDBG) using the 7-point SMBG measurements
- Each time point separately
- Mean of the pre-meal BG values
- Mean of the 2-hour post-meal BG values
- Glycemic excursion = 2 hour postprandial BG minus preprandial BG value at each meal
- Mean of the glycemic excursion values of all meals
- Glucose variability (SD, M-value, MAGE and coefficient of variation [CV])[19]

Mean daily blood glucose was defined as the mean daily blood glucose obtained from the 7-point blood glucose (morning fasting, 2-hour postprandial breakfast, preprandial lunch, 2-hour postprandial lunch, preprandial dinner, 2-hour postprandial dinner, and bedtime) averaged over 2 days within each visit.

The glucose variability calculations included the following:

- The SD was the simple standard deviation of the daily BG measurements.
- The M value = Sum {|10*log(BG/90)|^3}/(Number of BG Values) for BG measured in mg/dL.
- MAGE was calculated by taking the arithmetic mean of blood glucose increases or decreases when both ascending and descending variations exceeds 1 standard deviation of the 7-point daily blood glucose values.
- Coefficient of variation was 100 x the SD divided by the mean BG.

Glucose variability measurements were also estimated within each day and then averaged.

Each of these measurements was summarized by visit and the comparisons to baseline using the same model as was used for the analysis of the primary efficacy measurement.

8.4.6.3 Transition from Basal Bolus Insulin Therapy to PaQ

The number of preset basal doses tried to achieve the desired fasting blood glucose level, and the number of days taken to identify the preset PaQ basal dose that achieved the desired fasting blood glucose level was listed and summarized.

In addition, the number of times patients injected bolus insulin per day during baseline on his or her current therapy was compared to that when wearing PaQ.

8.4.6.4 Body Weight

Body weight and BMI was listed by patient and visit and summarized by visit and the comparisons to baseline used the same model as was used for the analysis of the primary efficacy measurement.

8.4.6.5 Patient-reported Outcomes

The PROs included the following:

- BIT questionnaire
- DTSQs questionnaire
- SF-36

Each of these PROs was listed by individual item, total score and relevant sub scores. The total and sub scores were summarized by visit, and comparisons to baseline used the same model as was used for the analysis of the primary efficacy measurement.

8.4.6.6 PaQ Application Site Examination

Summaries of dermal irritation included presence or absence of blister formations, and severity of irritation (none, mild, moderate, or severe). Adherence of tape to body (adhered, fell off), and cannula intact (yes, no) were summarized.

Summaries of Cannula Insertion Site Examination included:

- Erythema (none, mild, moderate, or severe)
- Edema (none, mild, moderate, or severe)
- Ecchymosis (none, mild, moderate, or severe)
- Exudate (none, present)

8.4.7 Safety Analyses

8.4.7.1 Exposure

PaQ use was summarized using the total number of days the device was used. Duration of use was defined as the number of days between visits +1 day for visits that the patient was assigned this device.

8.4.7.2 Adverse Events

All AEs including serious AEs (SAEs) were listed. All AE summaries were restricted to treatment-emergent AEs (TEAEs); these were defined as AEs that occurred after initiation of use of PaQ and existing AEs that worsened during the study. Verbatim terms on case report forms were mapped to preferred terms (PTs) and system organ classes (SOCs) using the MedDRA dictionary.

Each AE summary was displayed. Summaries that were displayed by SOC and PTs were presented by descending order of incidence within each SOC.

Adverse events that were related to the device were summarized separately.

8.4.7.3 Insulin Insertion Site Reaction Assessments

Listings and summaries of insulin insertion site reaction assessments were presented for each of the 4 questions.

8.4.7.4 Weight

Weights were listed and summarized using descriptive statistics at baseline and at Week 12 (end of study). Changes from baseline were also summarized.

8.4.7.5 Hypoglycemic Episodes

A listing of individual hypoglycemic episodes, severe hypoglycemic episodes (requiring third party assistance), symptomatic and asymptomatic hypoglycemia, by patient was produced along with a listing of the adjusted rate of hypoglycemia per 30 days for each visit. The incidence of hypoglycemic episodes was summarized by frequencies and percentages for each visit. The similar incidence summary of severe hypoglycemic episodes was also produced.

The rate of all hypoglycemic episodes adjusted for 30-day intervals was summarized by visit.

8.4.7.6 Laboratory Assessments

A summary and analysis was performed for the chemistry and hematology laboratory measurements. Each of these laboratory measurements was summarized by visit and the comparisons to baseline used the same model as was used for the analysis of the primary efficacy measurement. Multiple measurements for a patient within a visit were averaged.

8.4.8 Subgroup Analyses

No subgroup summaries or analyses were planned.

9 STUDY PATIENTS

9.1 Disposition of Patients

Table 4 presents patient disposition for the study. A total of 20 patients (100%) were enrolled, 3 patients (15.0%) withdrew after start of treatment, and 17 patients (85.0%) completed the study.

Table 4 Patient Disposition (All Patients)

Patients	Total N = 20 N (%)
Enrolled	20 (100.0)
Treated	20 (100.0)
Withdrawn after start of treatment	3 (15.0)
Completed study	17 (85.0)

Abbreviation: N = number.
Source: Table T01 in Appendix 20.4.1. A by-patient listing of study completion status and discontinued patients is available in Listing L01.

Patient 01-010 withdrew from the study due to personal reasons (his relative died). Patient 01-013 withdrew consent and ended participation in the study due to device reasons (he frequently knocked the device off his body during construction work). Patient 01-014 was discontinued from the study since she/he was in violation of Exclusion Criterion 11 prohibiting participation by patients who had received investigational drugs within 1 month of entry into CeQur study 14002.

9.2 Analysis Populations

Table 5 summarizes the 2 planned analysis populations. The intent-to-treat population consisted of all patients who received at least one dose of insulin with PaQ. The evaluable population included patients who did not have any major protocol violations and completed the study through the 12-week PaQ treatment period. The results from the ITT population were used for the presentation of the safety and PRO data. The results from the Evaluable population were used for the presentation of the efficacy data, e.g., HbA1c, fasting blood glucose, and 7-point profile, with reference to the results of the ITT population in Appendix 20.4.1.

Table 5 Summary of Analysis Sets

Populations	Total N = 15 N (%)
ITT Population	20 (100.0)
Evaluable Patients Population	17 (85.0)

Abbreviations: ITT = intent=to-treat; N = number.
The ITT population consisted of all patients who received at least 1 dose of insulin with PaQ
Source: Table T01.1 (Appendix 20.4.1)

9.3 Baseline Demographic and Background Characteristics

Table 6 presents a summary of the Baseline demographic characteristics of the ITT population. The population was white and predominantly male (17 patients, 85%). The mean age of the patients was 62.7 years, and they ranged in age from 46.7 to 73.0 years. Their mean (SD) weight was 100.0 (10.6) kg and mean (SD) BMI was 32.2 (3.7) kg/m^2. The mean (SD) duration of diabetes was 15.2 (6.6) years. At the Baseline visit, the mean (SD) HbA_{1c} was 8.6 (1.1) % / 70.2 (12.3) mmol/mol; range 7.2% / 55 mmol/mol to 11.0% / 97 mmol/mol. Eleven (55.0%) of the 20 patients had peripheral neuropathy, 4 patients (20.0%) had retinopathy, and 5 (25.0%) had nephropathy. Mean (SD) serum creatinine in the group was 1.1 mg/dL, and values ranged from 0.6 to 2.4 mg/dL. The mean (SD) total daily dose (TDD) of insulin at Baseline was 59.7 (22.3) U, which was evenly distributed between the participants' basal and bolus insulin, 29.2 (10.4) U and 30.4 U (17.7), respectively. The mean (SD) number of insulin injections administered per day was 4.3 (1.5), and ranged from 1 to 9. Note the eligibility criteria required participants to be on at least 2 injections per day, which was met. However, 1 patient took only 1 of their 2 injections of pre-mixed insulin on a given day during the Baseline period; hence, the minimum injection was 1.

Table 6 Demographic and Baseline Characteristics (ITT Population)

Value Statistic	Total N = 20	
Age (years)		
Mean (SD)	62.7 (7.0)	
Min, max	46.7, 73.0	
Sex – n (%)		
Female	3 (15.0%)	
Male	17 (85.0%)	
Race – n (%)		
White	20 (100.0%)	
Weight (kg)		
Mean (SD)	100.0 (10.6)	
Min, max	85.0, 120.0	
BMI (kg/m^2)		
Mean (SD)	32.2 (3.7)	
Min, max	26.5, 39.7	
Duration of diabetes (years)		
Mean (SD)	15.2 (6.6)	
Min, max	4.0, 26.0	
HbA_{1c} (%)	(%)	mmol/mol
Mean (SD)	8.6 (1.1)	70.2 (12.3)
Min, max	7.2,11.0	55.0, 97.0
Diabetes-related conditions		
Peripheral neuropathy	11 (55.0%)	
Retinopathy	4 (20.0%)	
Nephropathy	5 (25.0%)	
Serum creatinine (mg/dL)		
Mean (SD)	1.1 (0.4)	
Min, max	0.6, 2.4	
Daily insulin dose (Units)		
Basal Insulin (Mean [SD])	29.2 (10.4)	
Bolus Insulin (Mean [SD])	30.4 (17.7)	
Total Insulin (Mean [SD])	59.7 (22.3)	
Total injections per day		
Mean (SD)	4.3 (1.5)	
Min, max	1.0, 9.0	

Abbreviations: BMI = body mass index; $HbA_{1c,}$ glycosylated hemoglobin; max = maximum; min = minimum; N = number in population; SD = standard deviation.
Source: Table T02 (Appendix 20.4.1)

The most common medical conditions present in >20% of the patients at the time of enrollment are summarized in Table 7. These medical conditions are consistent with those commonly observed in patients with T2DM. The most common conditions reported were hypertension (85.0%), hyperlipidemia (60.0%), obesity (30.0%) and diabetic neuropathy (25.0%).

Table 7 Medical Conditions Present in >20% of Patients at Baseline (ITT Population)

System Organ Class Preferred Term	Patients N (%)
Vascular disorders	**17 (85.0)**
Hypertension	17 (85.0)
Metabolism and nutrition disorders	**17 (85.0)**
Hyperlipidemia	12 (60.0)
Obesity	6 (30.0)
Nervous system disorders	**12 (60.0)**
Diabetic neuropathy	5 (25.0)
Polyneuropathy	4 (20.0)
Cardiac disorders	**7 (35.0)**
Coronary artery disease	4 (20.0)
Immune system disorders	**5 (25.0)**
Drug hypersensitivity	4 (20.0)
Infections and infestations	**5 (25.0)**
Osteomyelitis	4 (20.0)
Eye disorders	**4 (20.0)**
Diabetic retinopathy	4 (20.0)

Abbreviations: PT = preferred term; SOC = system organ class.
Source: Table T03.1 (Appendix 20.4.1). Listing L02 in Appendix 20.4.1 provides a by-patient listing of past and concurrent medical conditions in the study population.

The medications used in ≥20% of the patients at the time of enrolment are summarized in Table 8. All 20 patients (100%) used at least 1 concomitant medication. The most commonly used medications are reflective of the patients' underlying conditions at the time of enrolment; insulin for injection (100%), HMG COA reductase inhibitors (55%) and fibrates for hyperlipidemia (20%), biguanides (metformin) (50%) and DPP-4 inhibitors (26.7%) for blood glucose management, platelet aggregation inhibitors for thrombosis prophylaxis (45%), beta blockers (40%) and ACE inhibitors (20%) for hypertension.

Table 8 Concomitant Medication Usage in ≥20% of Patients at Baseline (ITT Population)

Concomitant Medications	Patients N (%)
Insulins and analogs for injection, fast-acting	20 (100.0)
Insulins and analogs for injection, long-acting	12 (60.0)
Insulins and analogs for injection, interim-acting	10 (50.0)
HMG COA reductase inhibitors	11 (55.0)
Biguanides	10 (50.0)
Platelet aggregation inhibitors	9 (45.0)
Beta blocking agents, selective	8 (40.0)
Proton pump inhibitors	7 (35.0)
DPP-4 inhibitors	5 (25.0)
ACE inhibitors, plain	4 (20.0)
Fibrates	4 (20.0)

Abbreviations: ACE = angiotensin-converting enzyme; DPP-4 = Dipeptidyl peptidase 4; HMG-COA = 3-hydroxy-3methylglutaryl-coenzyme;
Source: Table T04 in Appendix 20.4.1.
A complete by-patient listing of concomitant medications is available in Listing L18 in Appendix 20.4.1

10 TRANSITION FROM INJECTABLE INSULIN THERAPY TO PAQ

During this phase of the study, the patient was switched from his/her current regimen of insulin therapy to PaQ. The length of this transition period was dependent upon how long it took to identify a PaQ basal rate that allowed the patient to safely achieve a fasting blood glucose level that met the fasting glycemic target.

This period of the study was at least 6 days long (two 3-day wear periods), but may have been extended to identify the correct basal dose/rate the patient required for glycemic control. Patients were evaluated for at least 2 consecutive 3-day wear periods on the same PaQ basal dose to determine that adequate glycemic control had been obtained before advancing to the PaQ Treatment period.

10.1 PaQ Use During the Transition Period

The length of the PaQ transition period is presented in Table 9. The mean number of days taken to identify their correct PaQ basal rate was 8.5 (5.1) days and the mode was 6.0 days. One patient's (01-002) transition period was 24 days; this was secondary to scheduling difficulties (which resulted in a minor protocol deviation; visits are to occur every 6 days±1day, he was seen outside of this visit window) as well as requiring 2 changes to his basal rate.

Table 9 Number of Days Taken to Transition to PaQ (ITT Population)

	Total Patients **N=20**
Length of Transition (days)	
Mean (SD)	8.5 (5.1)
95% CI	6.0, 10.9
Median	6.0
Mode	6.0
Min, max	6.0, 24

Abbreviations: N = number of population; max = maximum; min = minimum; SD = standard deviation. Source: Table T22 in Appendix 20.4.1

10.2 PaQ Basal Rates Initiated and Changed During the Transition Period

Table 10 presents a summary of the PaQ basal rates initiated and changed during the Transition Period. Most patients (80%) experienced no change to their initial basal rate, two required one increase and two others required two increases in their basal rate to achieve their fasting blood glucose target. A reduction in basal rate was not necessary in any patient. At the end of the transition period, 30% and 35% of the patients were receiving PaQ 32 or PaQ 40 U/day basal rates.

Table 10 PaQ Basal Rates Initiated and Changed During Transition (ITT Population)

Basal Rate at Baseline: Visit 2	Basal Rate at End of Transition Period						Change to basal rate			
	Total N (%)	20 U/day N (%)	24 U/day N (%)	32 U/day N (%)	40 U/day N (%)	50 U/day N (%)	0	1	2	>2
20 U/day	3 (15.0)	3 (15.0)	0	0	0	0	3	0	0	0
24 U/day	4 (20.0)	0	1 (5.0)	1 (5.0)	2 (10.3)	0	1	1	2	0
32 U/day	5 (25.0)	0	0	5 (25.0)	0	0	5	0	0	0
40 U/day	6 (30.0)	0	0	0	5 (25.0)	1 (5.0)	5	1	0	0
50 U/day	2 (10.0)	0	0	0	0	2 (10.0)	2	0	0	0
Total	20 (100.0)	3 (15.0)	0	6 (30.0)	7 (35.0)	3 (15.0)	16	2	2	0

Abbreviations: U = units
Source: Table T14 in Appendix 20.4.1

11 EFFECTIVENESS

11.1 Primary Study Endpoint - HbA_{1c} Change from Baseline

The primary efficacy endpoint for this study was the change in HbA_{1c} (obtained from venous blood) from baseline at Week 12. A secondary endpoint was this same assessment, but at Week 8. Table 11 presents a summary of HbA_{1c} values at Baseline, Week 8 and Week 12 and the change from Baseline for each of these time points for the Evaluable population. A statistically significant reduction in the mean (SD) HbA_{1c} of -1.37% (0.87), P <0.0001, was seen from the Baseline value of 8.5 (1.18) to 7.13 (0.62) at Week 12. The Week-8 values also show a statistically significant reduction with a mean (SD) reduction of -1.25 (0.87), P=0.0001.

Table 11 Summary of HbA_{1c} (%) by Week (Evaluable Population)

	Baseline	PaQ Week	
		8	12
N	17	17	17
Mean (SD)	8.50 (1.18)	7.25 (0.64)	7.13 (0.62)
Median	8.19	7.00	7.18
SE	0.29	0.16	0.15
Change from Baseline			
N		17	17
Mean (SD)		-1.25 (0.87)	-1.37 (0.87)
Median		-1.01	-1.10
SE		0.21	0.21
t test		P≤0.0001	P≤0.0001
Sign rank test		P≤0.0001	P≤0.0001

Abbreviations: N = number in population; SD = standard deviation; SE = standard error.
Source: Table T05.1A in Appendix 20.4.1

A statistically significant reduction was also seen in the ITT population, (Appendix 20.4.1, Table T05A). A mean (SD) reduction of -1.33 (0.85), *P* <.0001 was seen from the Baseline value of 8.57 (1.12) to Week-12 value of 7.25 (0.64). Likewise, a reduction of -1.25 (1.01) was seen from the Week-8 value of 7.25 (0.64), *P* <.0001.

These results in IFCC HbA_{1c} (mmol/mol) for the Evaluable and ITT populations are available in Appendix 20.4.1, Tables T051.B Evaluable Population and T05B ITT Population.

A by-patient listing of HbA_{1c} and FBG values across all study visits is available in Listing L04 in Appendix 20.4.1

11.2 Secondary Study Endpoints

11.2.1 Fasting Plasma Glucose Change from Baseline

A summary of fasting plasma glucose values, obtained via venipuncture, across study visits is presented for the Evaluable population in Table 12. The mean (SD) fasting plasma glucose value at Baseline was 173.00 mg/dL (52.36) and declined by Week 8 to a low value of 134.41 mg/dL (31.46), rising slightly at Week 12 to 143.24 mg/dL (45.45). The changes from Baseline were statistically significant at Week 4 (*P*=0.0138), Week 8 (*P*=0.0317), and Week 12 (*P*=0.0366).

Table 12 Summary Fasting Plasma Glucose (mg/dL) (Evaluable Population)

		PaQ Transition	Weeks on PaQ		
	Baseline	**6-15 Days**	**4**	**8**	**12**
N	17	16	17	17	17
Mean (SD)	173.00 (52.36)	160.00 (46.28)	144.88 (52.55)	134.41 (31.46)	143.24 (45.45)
Median	169.00	172.50	126.00	137.00	155.00
SE	12.70	11.57	12.75	7.63	11.02
Change from Baseline					
N		16	17	17	17
Mean (SD)		-13.25 (43.03)	-28.12 (40.14)	-38.59 (51.30)	-29.67 (53.80)
Median		-19.00	-29.00	-36.00	-45.00
SE		10.76	9.74	12.44	13.05
t-test		*P*=0.2370	*P* =0.0107	*P* =0.0069	*P* =0.0366
Sign Rank test		*P* =0.1794	*P* =0.0194	*P* =0.0052	*P* =0.0387

Abbreviations: N = number in population; SD = standard deviation; SE = standard error.
Source: Table T06.1 in Appendix 20.4.1

A statistically significant reduction was also seen in the ITT population, (Appendix 20.4.1, Table T06). Like the Evaluable population data set, statistically significant reductions from Baseline values were seen at Week 4, -26.28 (39.72) (*P*=0.0121); Week 8, -38.59 (51.30) *P*=0.0069; and Week 12, -28.90 (54.66) *P*=0.0289.

Fasting blood glucose values are presented by patient in Listing L04 in Appendix 20.4.1.

11.2.2 7-point Blood Glucose Profiles Change from Baseline

Table 13 presents a summary of the 7-point blood glucose profile, comparing values from Baseline to PaQ Week 12 for the Evaluable population. At Week 12 statistically significant reductions were seen across all 7 time points in the comparison to the Baseline mean blood glucose values: fasting -37.29 (*P*=0.005), post-breakfast -42.73 (*P*=0.005), pre-lunch -33.06 (*P*=0.021), post-lunch -44.23 (*P*=0.003), pre-dinner -32.15 (*P*=0.023), post-dinner -64.07 (*P*=0.001), and bedtime -51.33 (*P*=0.003).

Table 13 Seven-Point Blood Glucose (mg/dL) Profile - Evaluable Population

		Fasting	Post-Breakfast	Pre-Lunch	Post-Lunch	Pre-Dinner	Post-Dinner	Bedtime
Baseline	N	17	17	17	16	17	16	16
	Mean	189.91	230.88	186.50	205.19	193.56	220.22	211.34
	SD	45.86	52.88	46.23	45.41	55.14	60.88	63.62
Week 12	N	17	15	17	16	17	16	16
	Mean	152.62	184.27	153.44	159.00	161.41	156.91	162.38
	SD	38.88	52.82	46.66	52.97	37.30	33.50	41.38
Change	N	17	15	17	15	17	15	15
	Mean	-37.29	-42.73	-33.06	-44.23	-32.15	-64.07	-51.33
	SD	47.61	50.46	53.09	48.50	52.88	62.16	55.33
	P value	0.005	0.005	0.021	0.003	0.023	0.001	0.003

Abbreviations: N = number in population; SD = standard deviation.
Source: Table T08.1 in Appendix 20.4.1

A statistically significant reduction was also seen in the ITT population, (Appendix 20.4.1, Table T08). Like the Evaluable population data set, statistically significant reductions from Baseline values were seen at all 7 time points at Week 12: fasting -37.29 (*P*=0.005), post-breakfast -42.73 (*P*=0.005), pre-lunch -33.06 (*P*=0.021), post lunch -44.23 (*P*=0.003), pre-dinner -32.15 (*P*=0.023), post-dinner -64.07 (*P*=0.001), and bedtime -51.33 (*P*=0.003).

A summary of blood glucose excursions derived from the 7-point blood glucose profile for the Evaluable population is presented in Table 14. Statistically significant reductions compared to Baseline were seen at Week 12 for the following parameters: mean daily blood glucose (MDBG) -45.87 (*P* <0.001), mean pre-meal -36.25 (*P*=0.003), mean post-meal -49.23 (*P* <0.001), excursion dinner -28.43 *P*=0.035, SD -14.93 (*P* =0.002) and M-value -31.68 (*P*<0.001).

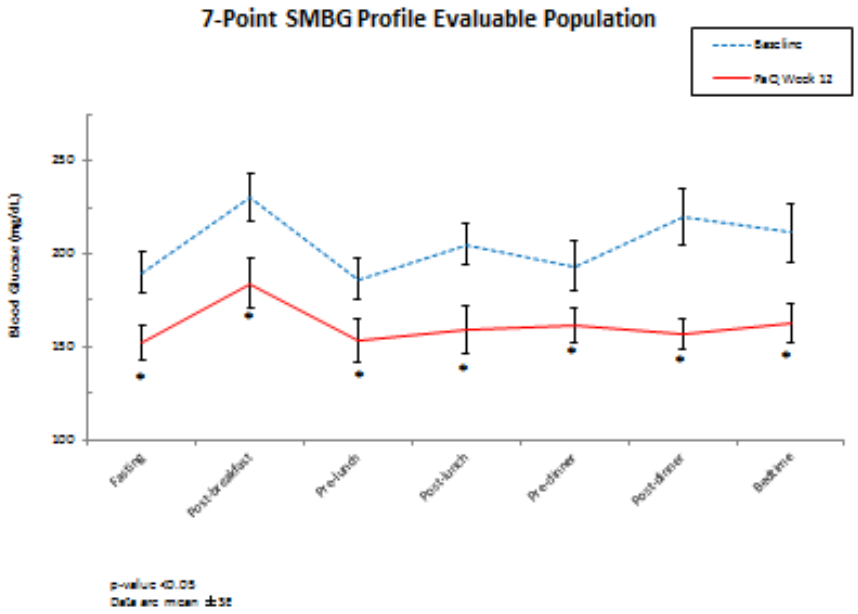
Table 14 Seven-Point Blood Glucose (mg/dL) Excursions (Evaluable Population)

	MDBG	Mean Pre Meal	Mean Post Meal	Excur Breakfast	Excur Lunch	Excur Dinner	Mean Excurs	SD	M-value	CV
Baseline										
N	17	17	17	17	16	16	17	17	17	17
Mean	203.68	191.72	218.03	40.15	16.19	23.66	27.23	50.06	56.36	24.58
SD	38.29	38.53	44.24	52.32	30.46	34.06	27.98	16.38	30.32	6.32
Week 12										
N	17	17	16	15	16	16	16	17	17	17
Mean	160.81	155.46	166.41	30.10	3.63	-3.44	10.92	35.13	24.68	22.19
SD	33.00	35.29	39.00	30.93	32.63	31.29	21.08	11.41	18.92	6.34
Change from Baseline										
N	17	17	16	15	15	15	16	17	17	17
Mean	-42.87	-36.25	-49.23	-16.33	-9.70	-28.43	-16.30	-14.93	-31.68	-2.39
SD	35.23	42.42	37.88	38.27	47.15	47.17	36.34	17.16	26.45	7.61
P value	<.001	0.003	<.001	0.121	0.439	0.035	0.093	0.002	<.001	0.213

Abbreviations: CV = coefficient of variation; Excur = excursion; MDBG = mean daily blood glucose; N = number in population; SD = standard deviation.
Source: Table T08 (Excursions) in Appendix 20.4.1

A similar analysis of the ITT population is presented in Table 08 7-Point Blood Glucose (mg/dL) Profile – Excursions in Appendix 20.4.1. These data are consistent with the Evaluable population. Statistically significant reductions compared to baseline were seen at Week 12 for the following parameters; mean daily blood glucose (MDBG) -42.87 (P<0.001), mean pre meal -36.25 (P=0.003), mean post meal -49.23 (P<0.001), excursion dinner -28.4 P=0.035, SD -14.93 (P=0.002), and M-value -31.68 (P<0.001). A graphic representation of the 7-point self-monitored blood glucose values for Baseline contrasted with Week 12 on PaQ is presented in Figure 8. The profile for Week 12 compared with that for the Baseline period reflects lower and more stable serum glucose values across the time points; the reduction in serum glucose was significant at the time points designated with an asterisk (P<0.05).

Figure 8 Graph of 7-Point Self-Monitored Blood Glucose Profile Evaluable Population



Source: Tables T08.1A-G in Appendix 20.4.1

11.2.3 Continuous Glucose Monitoring

The data acquired from the last 5 patients on study, utilizing the iPro CGM system, are summarized below.

11.2.3.1 Time in Target Range

Utilizing the "time in target 70 – 180 mg/dL" endpoint, four of the five participants demonstrated an increase in their glycemic control by having a greater proportion of time in target as summarized in Table 15 below.

Table 15 Percent (%) Time in Target Range 70 to 180 mg/dL

Patient	Baseline	After Transition	Week 8 on PaQ
01-019	59.66	68.90	78.31
01-020	53.17	67.52	54.51
01-021	58.74	90.17	80.60
01-022	58.53	57.29	70.92
01-023	30.26	57.12	65.37

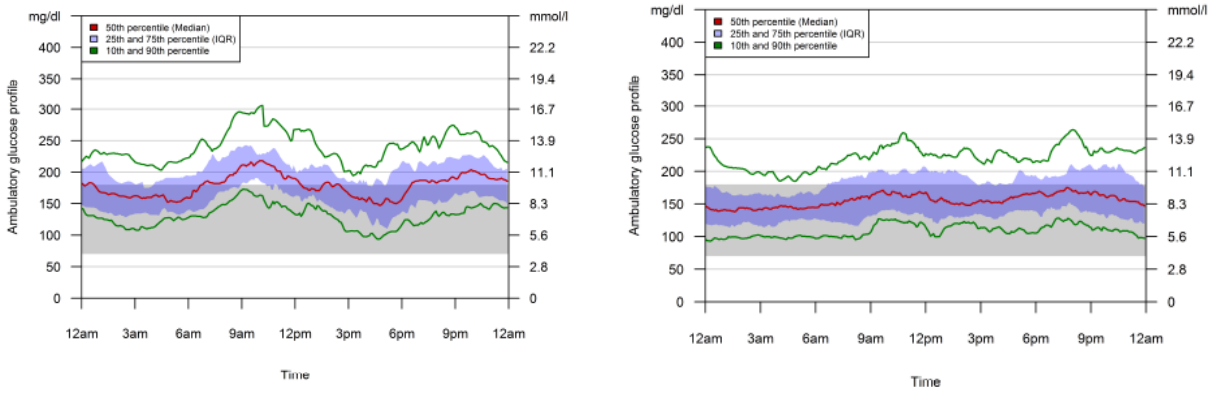
Source: External report Joanneum Research in Appendix 20.4.2

For the combined data set, the percentage of time that the patients' glucose values were in the target range of 70-180 mg/dL (3.9-10 mmol/L) increased from 50.8% at Baseline to 68.6% (P<0.001) and 70.4%

(*P*<0.001) immediately following the PaQ Transition Period and at Week 8 of PaQ, respectively. These results are both clinically and statistically significant. Modal days representing the 1-week Baseline period and the 2-week Wear period after 8 weeks on PaQ are presented in Figure 9 below.

Figure 9 Percentage of Time in Target Range of 70 to 180 mg/dL

Baseline – 50.8% After 8-week on PaQ – 70.4%



Source: External report Joanneum Research in Appendix 20.4.2

Glucose values >180 mg/dL (10 mmol/L), >250 mg/dL (13.9 mmol/L), and >400 mg/dL (22.2 mmol/L)

- The percentage of time that the patients' glucose values were >180 mg/dL (10 mmol/L) decreased from 48.9% at Baseline to 30.1% (*P*<0.001) and 29.2% (*P*<0.001) during the PaQ transition period and at Week 8 of the PaQ, respectively.
- The percentage of time that the patients' glucose values were >250 mg/dL (13.9 mmol/L) decreased from 8.91% at Baseline to 4.01% (*P*<0.001) and 4.02% (*P*<0.001) during the PaQ transition period and at Week 8 of the PaQ, respectively.
- There were no glucose values during the study that were >400 mg/dL

11.2.3.2 Glucose Exposure and Variability

The other endpoints that were evaluated from the CGM readings are summarized in Table 16. A significant difference from Baseline at Week 8 of PaQ was seen for several of the parameters. The mean (SD) glucose of all readings from Baseline to Week 8 on PaQ had a significant decrease from 181 (17) mg/dL to 161 mg/dL (14), *P*= 0.041. A trend toward a significant reduction in the mean glucose values was seen during the day (07:00 to 21:59), *P*=0.075 and a significant decrease was seen in the mean (SD) glucose readings taken overnight (between 22:00 and 06:59); from 170 (25) to 151 (19), *P*=0.046. Likewise the mean glucose readings taken 0 to 2 hours before breakfast had a significant decrease from 162 (18) mg/dL to 134 (22) mg/dL, *P*=0.028. The endpoints for glycemic variability (SD, IQR and mean rate of change in glucose per hour) while decreased from baseline were not statistically significant.

Table 16 Continuous Glucose Monitoring Data

	Baseline (n=5)	8th week PaQ (n=5)	*P* value
Glucose exposure			
Glucose readings (overall)	181.06 (17.21)	161.028 (13.64)	0.041
Glucose readings (07:00 – 21:59)	187.75 (18.47)	166.97 (10.20)	0.075
Glucose readings (22:00 - 06:59)	169.71 (25.55)	151.46 (19.35)	0.046
Glucose readings 0-2 hours before breakfast	161.92 (17.83)	134.27 (22.32)	0.028
Glucose reading 2 to 4 hours after meals	193.64 (18.68)	173.44 (20.12)	0.201
Glucose variability			
Rate of change in glucose/hour (overall)	16.56 (4.17)	11.63 (1.9)	0.061
Rate of change in glucose/hour (07:00-21:59)	18.50 (5.26)	13.19 (2.10)	0.058
Rate of change in glucose/hour (00:00-05:59)	12.36 (3.17)	8.07 (3.79)	0.174

Source: External report Joanneum Research in Appendix 20.4.2

11.2.4 Insulin Dose (Basal, Bolus and Total) Change from Baseline

Table 17 provides a summary of the daily basal insulin dose used throughout the study. The participants' mean basal dose per day had a statistically significant increase of 6.1 (8.7) U/day *P*=0.0054, from baseline values at the end of the PaQ transition phase. The basal dose/rate established during the transition phase remained constant throughout the 12-week PaQ treatment period.

Table 17 Total Basal Dose (U) Per Day – Change from Baseline (ITT Population)

	Baseline	PaQ Transition	Weeks on PaQ		
		6 to 15 Days	4	8	12
N	20	20	17	17	17
Mean (SD)	29.2 (10.4)	35.3 (9.5)	34.9 (10.1)	34.9 (10.1)	34.9 (10.1)
Median	29.3	36.0	32.0	32.0	32.0
SE	2.3	2.1	2.5	2.5	2.5
Change from Baseline					
N		20	17	17	17
Mean (SD)		6.1 (8.7)	6.9 (8.8)	6.9 (8.8)	6.9 (8.8)
Median		4.9	4.7	4.7	4.7
SE		1.9	2.1	2.1	2.1
t test		*P*=0.0054	*P*=0.0049	*P*=0.0049	*P*=0.0049
Sign rank test		*P*=0.0039	*P*=0.0031	*P*=0.0031	*P*=0.0031

Abbreviations: N = number in population; SD = standard deviation; SE = standard error.
Source: Table T10B (Appendix 20.4.1)

A similar summary of this analysis in the Evaluable population is presented in Table 10.1B in Appendix 20.4.1. Significant increases in the change from Baseline to the Transition Period (*P*=0.0049), Week 4 (*P*=0.0049), Week 8 (*P*=0.0049) and PaQ Week 12 (*P*=0.0049) were also noted in this population.

Bolus insulin doses per day (Table 18) were similar to Baseline during PaQ transition, Week 4, Week 8 and Week 12.

Table 18 Total Bolus Dose (U) Per Day – Change from Baseline (ITT Population)

	Baseline	PaQ Transition	Weeks on PaQ		
		6 to 15 Days	4	8	12
N	20	20	17	17	17
Mean (SD)	30.4 (17.7)	28.9 (16.5)	27.9 (11.2)	34.0 (20.5)	38.3 (27.4)
Median	24.5	28.3	29.0	35.0	41.0
SE	4.0	3.7	2.7	5.0	6.7
Change from Baseline					
N		20	17	17	17
Mean (SD)		-1.5 (12.5)	-2.9 (12.6)	3.1 (13.4)	7.4 (18.9)
Median		-0.8	-2.7	-3.3	2.7
SE		2.8	3.0	3.2	4.6
t test		*P*=0.5858	*P*=0.3474	*P*=0.3480	*P*=0.1264
Sign rank test		*P*=0.6477	*P*=0.2842	*P*=0.7467	*P*=0.3060

Abbreviations: N = number in population; SD = standard deviation; SE = standard error.
Source: Table T10A (Appendix 20.4.1)

A similar summary of this analysis in the Evaluable population is presented in Table 10.1A in Appendix 20.4.1. Similar to the ITT population, bolus insulin doses per day were similar to baseline during the PaQ transition, Week 4, Week 8 and at Week 12.

A summary of the number of bolus doses administered per day during the study is presented in Table 19. The number of bolus doses administered per day was significantly increased from Baseline during the Transition Period (*P*=0.0198) and at Week 12 (*P*=0.0504). At Week 12, the mean (SD) number of bolus dose per day increased from 3.0 (0.8) at Baseline to 3.8 (1.3), a mean (SD) increase of 0.8 (1.5) doses.

Table 19 Number of Bolus Doses Per Day – Change from Baseline (ITT Population)

		PaQ Transition	Weeks on PaQ		
Statistic	**Baseline**	**6 to 15 days**	**Week 4**	**Week 8**	**Week 12**
N	20	20	17	17	17
Mean (SD)	3.0 (0.8)	3.6 (1.0)	3.4 (1.0)	3.6 (1.3)	3.8 (1.3)
Median	2.9	3.2	3.5	3.0	3.5
SE	0.2	0.2	0.2	0.3	0.3
Change from Baseline					
N		20	17	17	17
Mean (SD)		0.6 (1.1)	0.3 (1.4)	0.6 (1.3)	0.8 (1.5)
Median		0.5	0.3	0.6	0.3
SE		0.2	0.3	0.3	0.4
t-test		*P*=0.0198	*P*=0.3360	*P*=0.0899	*P*=0.0504
Sign rank test		*P*=0.0361	*P*=0.2684	*P*=0.1116	*P*=0.0731

Abbreviations: n = number in population; SD = standard deviation; SE = standard error.
Source: Table T09 in Appendix 20.4.1

A similar summary of this analysis in the Evaluable population is presented in Table 9.1 in Appendix 20.4.1. Similar to the ITT population, the number of bolus doses administered per day was significantly increased from Baseline during the Transition Period (*P*=0.0179) and at Week 12 (*P*=0.0504). At Week 12, the mean (SD) number of bolus dose administered per day increased from 3.0 injections (0.8) at Baseline to 3.8 injections (1.3), a mean (SD) increase of 0.8 (1.5) injections.

The total daily dose (TDD) of insulin administered per day is summarized in Table 20. There was a statistically significant increase at Weeks 8 and 12 from Baseline values; *P*=0.0134 and *P*=0.0109, respectively). Mean (SD) TDD increased 14.3 (20.5) U from 59.7 U (22.3) at Baseline to 73.2 U (34.9) at Week 12.

Table 20 Total Daily Dose (U) – Change from baseline (ITT Population)

	Baseline	PaQ Transition	Weeks on PaQ		
		6 to 15 Days	4	8	12
N	20	20	17	17	17
Mean (SD)	59.7 (22.3)	64.2 (23.1)	62.9 (19.8)	69.0 (28.8)	73.2 (34.9)
Median	58.8	65.1	68.0	75.0	82.0
SE	5.0	5.2	4.8	7.0	8.5
Change from Baseline					
N		20	17	17	17
Mean (SD)		4.5 (12.5)	4.0 (10.4)	10.1 (14.9)	14.3 (20.5)
Median		4.3	1.4	5.9	8.1
SE		2.8	2.5	3.6	5.0
t test		*P*=0.1228	*P*=0.1353	*P*=0.0134	*P*=0.0109
Sign rank test		*P*=0.1769	*P*=0.2069	*P*=0.0093	*P*=0.0110

Abbreviations: N = number in population; SD = standard deviation; SE = standard error.
Source: Table T10C in Appendix 20.4.1

A similar summary of this analysis in the Evaluable population is presented in Table 10.1 in Appendix 20.4.1. Significant increases in the change from Baseline to the Transition Period (*P*=0.0818), Week 8 (P=0.0134) and PaQ Week 12 (*P*=0.0109) were also noted in this population.

11.2.5 Body Weight Change from Baseline

The change in body weight from baseline values at Week 12 for the Evaluable population is presented in Table 21. The mean (SD) increase in body weight was 1.3 kg (4.1). This change was not statistically significant.

Table 21 Summary of Weight (kg) Change from Baseline (Evaluable Population)

Weight (kg)		
Statistic	**Baseline**	**PaQ Week 12**
N	17	16
Mean (SD)	98.6 (8.6)	100.7 (10.0)
Median	99.0	99.9
SE	2.1	2.5
Change from Baseline		
N		16
Mean (SD)		1.3 (4.1)
Median		-0.5
SE		1.0
t test		*P*=0.2096
Sign rank test		*P*=0.5520

Abbreviations: N = number in population; SD = standard deviation; SE = standard error.
Source: Table T07.1A in Appendix 20.4.1

12 PATIENT REPORTED OUTCOMES

12.1 Barriers to Insulin Treatment

Summary statistics for the results of the BIT questionnaire for the ITT population are presented in Table 22. This questionnaire assessed changes from baseline in patient's fears, concerns, and perceptions with his or her insulin therapy. A moderate reduction (mean [SD] change from baseline of -4.50 [11.596], *P*=0.0989) in perceived barriers to insulin therapy was seen in the overall total score. In particular, the questionnaire reflected a change from baseline perceptions in patients' feeling toward "stigmatization by insulin injections", (-1.66 [4.285, *P*=0.1113]). A similar analysis was performed for the Evaluable Population and is available in Appendix 20.4.1, Table T11.1.

Table 22 Summary of BIT Questionnaire – Change from Baseline to End of Study – ITT Population

BIT	Mean Change	SD	Std Diff d	Lower CL	Upper CL	SE	Student's t	*P*-value
Score (Total)	-4.50	11.596	-0.39	-9.93	0.93	2.593	-1.735	0.0989
Scale 1: 'Fear of injections and self-testing'	0.30	4.131	0.07	-1.63	2.23	0.924	0.325	0.7489
1. I am afraid of the pain when injecting insulin.	0.05	2.481	0.02	-1.11	1.21	0.555	0.090	0.9291
2. Besides the pain, I am just afraid of injections.	0.15	1.040	0.14	-0.34	0.64	0.233	0.645	0.5266
3. I am afraid of the pain during regular blood-sugar checks.	0.10	1.651	0.06	-0.67	0.87	0.369	0.271	0.7894
Scale 2: 'Expectations regarding positive insulin-related outcomes'	-1.35	7.429	-0.18	-4.83	2.13	1.661	-0.813	0.4265
4. Insulin works better than pills.*	-0.50	2.911	-0.17	-1.86	0.86	0.651	-0.768	0.4518
5. People who get insulin feel better.*	-0.20	2.783	-0.07	-1.50	1.10	0.622	-0.321	0.7515
6. Insulin can reliably prevent long-term complications due to diabetes.*	-0.65	2.412	-0.27	-1.78	0.48	0.539	-1.205	0.2430
Scale 3: 'Expected hardship from insulin therapy'	-1.05	6.337	-0.17	-4.02	1.92	1.417	-0.741	0.4677
7. I just don't have enough time for regular doses of insulin.	0.05	2.373	0.02	-1.06	1.16	0.531	0.094	0.9259
8. I can't pay as close attention to my diet as insulin treatment requires.	-1.10	2.845	-0.39	-2.43	0.23	0.636	-1.729	0.1000
9. I can't organize my day as carefully as insulin treatment requires.	0.00	2.847	0.00	-1.33	1.33	0.637	0.000	1.0000
Scale 4: 'Stigmatization by insulin injections'	-1.60	4.285	-0.37	-3.61	0.41	0.958	-1.670	0.1113
10. Injections in public are embarrassing to me. Pills are more discreet.	-0.35	3.281	-0.11	-1.89	1.19	0.734	-0.477	0.6388
11. Regular insulin treatment causes feelings of dependence.	-0.95	2.743	-0.35	-2.23	0.33	0.613	-1.549	0.1379
12. When people inject insulin, it makes them feel like drug addicts.	-0.30	1.218	-0.25	-0.87	0.27	0.272	-1.101	0.2845
Scale 5: 'Fear of hypoglycemia'	-0.80	6.518	-0.12	-3.85	2.25	1.457	-0.549	0.5895
13. An insulin overdose can lead to hypoglycemia. I am afraid of the unpleasant accompanying symptoms.	-0.20	4.336	-0.05	-2.23	1.83	0.970	-0.206	0.8388
14. An insulin overdose can lead to hypoglycemia. I have concerns about possible permanent damage to my health.	-0.60	3.152	-0.19	-2.08	0.88	0.705	-0.851	0.4052

Abbreviations: CL = confidence limit; SD = standard deviation; SE = standard error; Std. Diff = standard deviation divided by the mean, called the Standardized Difference, or d.
Source: Table T11 in Appendix 20.4.1.

Listing Table L10 in Appendix 20.4.1 provides a by-patient summary of patients' responses to individual questions in the questionnaire.

12.2 Diabetes Treatment Satisfaction Questionnaire

A summary of the responses in the DTSQ for the ITT population is presented in Table 23. The mean (SD) change from Baseline in the DTSQ total score increased 3.0 (6.3), *P*=0.0475 at the end of the PaQ 12-

week treatment period. The changes in the total score are a reflection of higher satisfaction scores given to the following questions:

- How satisfied would you be to continue with your present form of treatment
- How flexible have you been finding your treatment to be
- How convenient have you been finding your treatment to be
- Would you recommend this form of treatment to someone else with your kind of diabetes?

The hyperglycemia score at Week 12 was statistically significant with a mean (SD) reduction of -2.10 (2.8), *P*=0.0041. The hypoglycemia score, while also reduced, was not statistically different from baseline values. A similar analysis was performed for the Evaluable Population and is available in Appendix 20.4.1, Table 12.1.

Table 23 Summary of DTSQ – Change from Baseline - ITT Population

DTSQ Parameter	N	Baseline Mean	Endpoint Mean	Mean Change	SD	Lower CL Change	Upper CL Change	SE	Student's t	p-value
Hypoglycemia Score	20	1.75	1.25	-0.50	2.460	-1.65	0.65	0.550	-0.909	0.3748
Hyperglycemia Score	20	3.95	1.85	-2.10	2.882	-3.45	-0.75	0.644	-3.259	0.0041
DTSQ Total Score	20	30.25	33.25	3.00	6.333	0.04	5.96	1.416	2.119	0.0475

Source: T12 in Appendix 20.4.1.

Listing Table L11 in Appendix 20.4.1 provides a by-patient summary of the patients' responses to individual questions in the DTSQ questionnaire.

12.3 Short Form – 36 Health Survey

Table 24 summarizes the change from Baseline at the end of the study for the SF-36 questionnaire for the ITT population. The only parameter with a notable change from Baseline was the Mental Health score, which had a mean (SD) increase of 5.50 (14.681), *P*=0.1102 from the baseline value. A similar analysis was performed for the Evaluable Population and is available in Appendix 20.4.1, Table 13.1.

Table 24 Short Form-36 Health Survey Change from Baseline - ITT Population

SF36 Parameter	N	Baseline Mean	Endpoint Mean	Mean Change	SD	Lower CL Change	Upper CL Change	SE	Student's t	*P*-value
Physical Component Summary	20	45.36	45.18	-0.18	4.567	-2.32	1.95	1.021	-0.179	0.8600
Mental Component Summary	20	53.03	54.39	1.36	7.789	-2.29	5.01	1.742	0.781	0.4445
Physical Health	20	69.75	71.75	2.00	16.496	-5.72	9.72	3.689	0.542	0.5940
Role Physical	20	67.50	65.31	-2.19	17.940	-10.58	6.21	4.012	-0.545	0.5919
Bodily Pain	20	63.95	64.05	0.10	27.176	-12.62	12.82	6.077	0.016	0.9870
General Health	20	60.25	62.60	2.35	14.805	-4.58	9.28	3.310	0.710	0.4864
Vitality	20	61.56	64.69	3.13	14.693	-3.75	10.00	3.285	0.951	0.3535
Social Functioning	20	89.38	88.13	-1.25	23.613	-12.30	9.80	5.280	-0.237	0.8154
Role Emotional	20	80.42	79.58	-0.83	19.478	-9.95	8.28	4.355	-0.191	0.8502
Mental Health	20	76.50	82.00	5.50	14.681	-1.37	12.37	3.283	1.675	0.1102

Source: Table T13 in Appendix 20.4.1.
Listing Table L16 in Appendix 20.4.1 provides a by-patient summary of the patients' responses to individual questions in the DTSQ questionnaire

13 SAFETY

To facilitate the review of AEs and device deficiency findings, this safety section is organized as follows:

- Brief summary of AEs
- Patients with AE by system organ class, preferred term and severity
- Serious AEs
- Device related TEAEs
- Hypoglycemia (BG values ≤ 70 mg/dL)
- PaQ use
- Device deficiencies

13.1 Brief Summary of Adverse Events

No patient discontinued from PaQ treatment because of a treatment-emergent adverse event (TEAE), and no deaths were reported during the study. Six SAEs were reported, including events of adenocarcinoma, coronary artery disease, penis carcinoma, kidney failure (2 cases), and bee sting; none of these was considered by the investigator to be related to PaQ use. There were 4 TEAEs of moderate intensity; of those 4 events, 3 were not related to PaQ use; 1 event (cannula site reaction) was associated with the device. There were 12 mild TEAEs reported in 8 patients. Other than TEAEs of dermal irritation or cannula site reaction, none was related to PaQ use.

The largest number of TEAEs was reported in the general disorders and administration site conditions, and these included 1 TEAE of dermal irritation and 5 TEAEs of cannula site reaction.

13.2 Patients with Adverse Events by System Organ Class, Preferred Term and Severity

Table 25 presents a summary of TEAEs reported during the conduct of the study by system organ class (SOC), preferred term (PT) and severity. Fourteen patients (70%) experienced a TEAE; six (20%) were mild, 3 (15%) were moderate and 5 (25%) were severe. The largest number of these was reported in the SOC “general disorders and administrative site conditions” and they were mild to moderate in severity; 5 patients (25%) had catheter site-related reactions and 1 patient (5%) had mild application site irritation. The next largest category of TEAEs was “infections and infestations”, in which 2 patients (10%) experienced mild to moderate nasopharyngitis and 1 (5%) patient experienced tonsillitis. Two patients (10%) experienced renal failure (both of which had renal disorders as an underlying condition upon enrollment [patients 01-011 and 01-020]) and 2 patients had diabetic foot problems. The 5 severe AEs were SAEs unrelated to the study device; they are discussed in Section 13.3.

Table 25 Number of Patients (%) with TEAE by SOC, PT and Maximum Severity

System Organ Class Preferred Term	Maximum Severity Mild n (%)	Moderate n (%)	Severe n (%)	Total (N=20) n (%)
Patients with a Treatment-Emergent Adverse Event	7 (35.0%)	3 (15.0%)	5 (25.0%)	15 (75.0%)
Cardiac disorders	0 (0.0%)	0 (0.0%)	1 (5.0%)	1 (5.0%)
Coronary artery disease	0 (0.0%)	0 (0.0%)	1 (5.0%)	1 (5.0%)
General disorders and administration site conditions	5 (25.0%)	1 (5.0%)	0 (0.0%)	6 (30.0%)
Catheter site related reaction	5 (25.0%)	1 (5.0%)	0 (0.0%)	6 (30.0%)
Application site irritation	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
Infections and infestations	2 (10.0%)	1 (5.0%)	0 (0.0%)	3 (15.0%)
Nasopharyngitis	1 (5.0%)	1 (5.0%)	0 (0.0%)	2 (10.0%)
Tonsillitis	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
Injury, poisoning and procedural complications	1 (5.0%)	0 (0.0%)	1 (5.0%)	2 (10.0%)
Arthropod sting	0 (0.0%)	0 (0.0%)	1 (5.0%)	1 (5.0%)
Limb injury	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
Metabolism and nutrition disorders	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
Hyperglycaemia	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
Musculoskeletal and connective tissue disorders	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
Arthralgia	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0%)	0 (0.0%)	1 (5.0%)	1 (5.0%)
Prostate cancer	0 (0.0%)	0 (0.0%)	1 (5.0%)	1 (5.0%)
Renal and urinary disorders	0 (0.0%)	0 (0.0%)	2 (10.0%)	2 (10.0%)
Renal failure	0 (0.0%)	0 (0.0%)	2 (10.0%)	2 (10.0%)
Respiratory, thoracic and mediastinal disorders	0 (0.0%)	1 (5.0%)	0 (0.0%)	1 (5.0%)
Cough	0 (0.0%)	1 (5.0%)	0 (0.0%)	1 (5.0%)
Skin and subcutaneous tissue disorders	1 (5.0%)	1 (5.0%)	0 (0.0%)	2 (10.0%)
Diabetic foot	1 (5.0%)	1 (5.0%)	0 (0.0%)	2 (10.0%)
Surgical and medical procedures	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
Surgery	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
Vascular disorders	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
Venous thrombosis limb	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)

Abbreviations: PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event
Source: Table T16 in Appendix 20.4.1

13.3 Deaths and Serious Adverse Events

Five patients had 6 SAEs that were unrelated to the study device. Patient 01-003, a 67-year-old male, was diagnosed with prostate adenocarcinoma on 26 March 2015 by punch biopsy. A prostatectomy was planned and the condition remains unresolved. Participant 01-007, a 73-year-old female, had a coronary angiography on 08 Apr 2015, which showed coronary artery disease in 2 vessels. The vessels were

successfully dilated and drug-eluting stents were placed. The patient was discharged from the hospital after 3 days. The condition is now considered resolved. Participant 01-010, a 62-year-old male, was diagnosed with penis carcinoma on 23 March 2015. The cancer was treated by radical circumcision. The condition is considered not resolved. Participant 01-011, a 64-year-old male, was hospitalized to the nephrology department on 20 May 2015 due to acute worsening of his renal function. This was diagnosed during the patient's routine visit in the nephrology outpatient department due to the known nephropathy. Participant 01-013, a 55-year-old male, was stung by a bee on 13 April 2015. He went to the emergency room for treatment because he had a history of allergic reactions to bee stings. The participant was treated, discharged and has recovered. Participant 01-020 is a 46-year-old male who underwent a vitrectomy and silicone oil injection of the right eye April 2015 to treat a known diabetic maculopathy. The participant enrolled into the study on 08 June and started to use PaQ on 19 Jun 2015. The patient underwent a planned hospitalization from 20-23 Jul 2015 for the surgical removal of the silicone oil from his eye and treatment with Tobradex eye ointment and Betnesol N eye drops. The participant recovered after 3 days. This same participant attended his final study visit on 22 Sep 2015 at which time final laboratory work was were drawn per the clinical investigational plan. The laboratory results from the lab work revealed he was experiencing chronic kidney failure. This participant has had a history of diabetic nephropathy at the time of enrolment. The patient was advised to go to the hospital for treatment. Listing L24 in Appendix 20.4.1 provides additional details.

13.4 Device-related Treatment-emergent Adverse Events

Table 26 summarizes the device-related TEAEs that were reported during the study. There were 6 device-related TEAEs reported. Five patients with mild to moderate cannula site related reactions, 1 with mild application site irritation and 1 patient with mild hyperglycemia. Three of the 5 cannula sites reactions received local treatment; 1 patient received Lavasorb wound irrigation and 2 patients received topical betaisodona wound gel (povidone iodine and iodine). All reactions resolved following treatment. The patient with application site irritation of 9 days' duration received Lavasorb twice daily, which resolved. Participant 01-020 inadvertently wore a PaQ device for a full 3-day wear period without the cannula being inserted into the subcutaneous tissue. He discovered this upon removal of the device when he did not see the cannula coming out of his skin. He then flipped the device over and noted that the "red dot" which confirms cannula placement was not present. He stated that he had not checked for the "red dot" (as instructed in the PaQ QSG) following the deployment of the cannula insertion device. A new PaQ was placed and the participant's hyperglycemia resolved.

Table 26 Device-Related TEAEs

System Order Class Preferred Term	Severity			Total (N=20)
	Mild	Moderate	Severe	
Patients with a Treatment-Emergent Adverse Event	6 (30.0%)	1 (5.0%)	0 (0.0%)	7 (35.0%)
General disorders and administration site conditions	5 (25.0%)	1 (5.0%)	0 (0.0%)	6 (30.0%)
Catheter site related reaction	5 (25.0%)	1 (5.0%)	0 (0.0%)	6 (30.0%)
Application site irritation	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
Metabolism and nutrition disorders	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
Hyperglycaemia	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)

Source: Table T17 in Appendix 20.4.1. Listing L18 and Listing L19 in Appendix 20.4.1 provide by-patient listings of concomitant medications and TEAEs, respectively.

13.5 Hypoglycemia (Blood Glucose Values ≤ 70 mg/dL)

13.5.1 Patient with Self-Monitored Blood Glucose Values ≤ 70 mg/dL

The number of patients with hypoglycemic episodes (blood glucose ≤ 70 mg/dL) and the corresponding BG levels (mg/dL) during these episodes is summarized in Table 27. No patients experienced severe hypoglycemia. Fifteen patients experienced non-severe episodes of hypoglycemia; : 10 symptomatic and 12 asymptomatic. The mean (SD) blood glucose level during all episodes was 63.8 (5.37) ranging from 46 to 70 mg/dL. There was no difference in the mean (SD) BG value during symptomatic compared to asymptomatic episodes; 63.3 mg/dL (5.41) and 64.4 mg/dL (5.34), respectively. An analysis of the number of patients with BG < 56 mg/dL was also conducted. This analysis revealed 5 patients (25%) who experienced BG<56 mg/dL: 2 patients with symptoms and 3 patients without (Table 20.1, Appendix 20.4.1). All events resolved: 1 with no action taken, 3 with the ingestion of food, and 1 with glucose tablets.

Table 27 Number of Patients with Hypoglycemia Episodes (SMBG ≤ 70 mg/dL) Corresponding BG (mg/dL) Levels During the Episodes for ITT Population

			Blood Glucose (mg/dL) Statistics						
Episode Type	Patients with Episodes N=20	No. of Episodes	Mean	SD	Min	25th PCTL	50th PCTL	75th PCTL	Max
Patients with Hypo	15	81	63.8	5.37	46.0	61.0	65.0	68.0	70.0
Severe	0	0	-	-	-	-	-	-	-
Symptomatic	10	43	63.3	5.41	46.0	61.0	64.0	68.0	70.0
Asymptomatic	12	38	64.4	5.34	51.0	62.0	66.0	69.0	70.0

Abbreviations: Hypo = hypoglycemic episode; N = number in population; Max = maximum; Min = minimum; PCTL = percentile.
Source: Table T24 in Appendix 20.4.1

The by-patient listing of hypoglycemic episodes, including time relative to visits, symptom and circumstance status, treatment, and resolution is available in Listing L20 in Appendix 20.4.1

13.5.2 Rate of BG episodes ≤ 70 mg/dL

The rate of hypoglycemic episodes (BG ≤ 70 mg/dL) per month is presented in Table T21 in Appendix 20.4.1. During the 1-week Baseline Period, the mean (SD) rate of hypoglycemic episodes was 0.4 (1.55) and the rate of hypoglycemic episodes during the entire PaQ treatment period (approximately 14 weeks) was 1.1. Given the disparity in the time of the Baseline and PaQ Treatment periods, statistical testing for significance would not be meaningful and as a result was not performed.

13.5.3 Continuous Glucose Monitoring - Glucose values < 70, <60, <50 mg/dL

Continuous glucose monitoring (CGM) was performed with the last 5 study participants. These participants wore an iPro CGM device for one 6-day period during Baseline, and for 2 consecutive 6-day wear periods immediately following transition and at the end of 8 weeks on PaQ. The percentages of time of the readings < 70, < 60 and < 50 mg/dL were calculated.

- **Glucose values < 70 mg/dL** - The percentage of time that the patients' glucose values were < 70 mg/dL (3.9 mmol/L) increased from 0.24% at Baseline to 1.34% (P<0.001) immediately following the PaQ transition period and then decreased back to Baseline levels, 0.38% (P<0.085) at Week 8 of the PaQ.
- **Glucose values < 60 mg/dL** - The percentage of time that the patients' glucose values were < 60 mg/dL (3.9 mmol/L) increased from 0.07% at Baseline to 0.9% (P<0.001) immediately following the PaQ transition period and then decreased back to Baseline levels, 0% (P<0.001) in favor of PaQ, at Week 8 of the PaQ.
- **Glucose values < 50 mg/dL** - The percentage of time that the patients' glucose values were < 50 mg/dL (2.8 mmol/L) increased from 0.0% at Baseline to 0.55% (P<0.001) immediately following the PaQ transition period, but decreased to 0% (P=1.00) at Week 8 of the PaQ.

The increase seen in the percent of time < 70 mg/dL from Baseline to the period immediately following PaQ transition, while statistically significant, is not clinically relevant. Further, once the patients moved away from the transition period, there is no difference in these values between Baseline and Week 8 of PaQ treatment, External report Joanneum Research, Appendix 20.4.2.

13.6 PaQ Use

A summary of the number of PaQs worn and the total number of days of PaQ use during the study is presented in Table 28. On average (SD) patients wore 32.5 (8.9) devices over a period of 86 (24) days. For the study as a whole, 650 devices were applied and used for 1726 days.

Table 28 Summary of PaQ Use (ITT Population)

		PaQ Usage Statistics							
PaQ Variable	Number of Patients	Mean	SD	Min	25th PCTL	50th PCTL	75th PCTL	Max	Total Count
PaQ Count	20	32.5	8.94	4.0	32.0	33.5	37.5	42.0	650
Days of PaQ Use	20	86.3	23.74	10.0	88.5	93.5	95.5	109.0	1726

Abbreviations: max = maximum; min = minimum; PCTL = percentile; SD = standard deviation.
Source: Table T15 in Appendix 20.4.1.
Table T15.1 in Appendix 20.4.1 present descriptive statistics for PaQ use in the Evaluable population.

A by-patient listing of patient device wear times is provided in Listing L23 in Appendix 20.4.1

13.7 Device Deficiencies

A summary of the device deficiencies identified by the participants during the conduct of the study is presented in Table 29. In total, 666 devices were prepared for use of which 650 were put on and used. Of those prepared for use, 146 (22%) device deficiencies were identified; 21 (14%) were determined to be use errors and 125 (86%) were malfunctions.

Two of the device deficiencies led to AEs. One of the AEs was secondary to a use error in which the user failed to check for the "red dot", which confirms cannula deployment, and wore the device for 3 days. At the end of the 3-day wear period, he discovered that the cannula had not been deployed and the "red dot"

was not present. This led to hyperglycemia during the wear period. The second AE was secondary to a kinked cannula rubbing on the surface of the user's skin, which led to skin irritation.

There were no device deficiencies that could have led to a SAE if no intervention had been made.

Per the protocol, "4 buzzes emitted earlier than 72 hours" was to be categorized as a device deficiency and reported by the site as such in the Case Report form. As a result, the majority of the device deficiencies reported by the site (80/146, 55%) were in the category of "4 buzzes emitted earlier than 72 hours". The Messenger will emit 4 buzzes when the Messenger button is pressed to convey that 72 hours have passed, the PaQ is out of insulin or the fluid path is clogged. In retrospect, after analysis of all the data received, these should have been categorized as observations because "4-buzz emitted earlier than 72 hours" is a design feature of the messenger and the data reported demonstrates that it worked as designed. Regardless of the cause, the 4 buzzes signal the user that they should change the device. In this study, patients recognized the 4-buzz signal and responded as instructed per the QSG, i.e., they removed and replaced the device. Investigations were performed on the reservoirs that had given the 4 buzzes prior to 72 hours. The results of these investigations showed that 4 devices had an occlusion in flow path or had run out of insulin. The reason for the other cases could not be determined.

The second highest number of deficiencies (33/146, 23%) pertained to the adherence of the device to the skin. Approximately 5% of the devices that were prepared and attached to the user's abdomen had adherence issues that interfered with the flow of insulin into the subcutaneous space. Seventeen became non-adherent and came off of the user's skin, 3 in which the cannula had dislodged and become kinked, and 13 instances of the device getting knocked off the user's body, e.g., got caught on the shower door.

Table 29 Summary of Site Reported Device Deficiencies (ITT Population)

Deficiency	Use Error	Malfunction	Lead to AE	Adverse Event
CPD - 6				
CPD button inadvertently pressed before or during connection	1	0	0	
Did not fit into right position during assembly	0	1	0	
Activation button broke	0	1	0	
Activation button could not be pressed	0	1	0	
Cannula not deployed and device worn	2	0	1	Hyperglycemia
Filling - 12				
Could not fill - syringe was too hard to push	0	8	0	
Syringe was hard to push, filled device	0	1	0	
Subject forgot to prime	2	0	0	
Forgot to fill, removed and filled new device	1	0	0	
Messenger - 87				
4 "buzzes" emitted earlier than 72 hours[b]	1	79		
2, 3, "buzzes" emitted earlier than anticipated		2		
Emitted constant rumble	0	2	0	
Messenger fell off	0	1	0	
Emitted yellow light - low charge	0	1	0	
One "leg" of the Messenger broke	0	2	0	
Adherence - 33				
Adhesive tape became non-adherent	1	16		
Cannula kinked	0	3	1	Skin reaction at cannula site
Device knocked off	13	0	0	
Bolus Button - 4				
Could not press bolus button	0	3	0	
No force when pressing button	0	1	0	
Other - 3				
Pain after cannula insertion and with dosing	0	1	0	
Subject didn't record details of deficiency	0	2	0	
Total	**21**	**125**	**2[a]**	

Source: Listing L19 in Appendix 20.4.1.

[a] Please note a device deficiency for a device worn by patient 01-017 from 24-27 May was associated with an AE of dermal irritation at the PaQ application site. However, Listing 24 Adverse events, lists an application site irritation 27 May-06 Jun that was mild, associated with the PaQ, but without a device deficiency or use error for this same patient. Hence it is not include in this table as a device deficiency that led to an AE.

[b] This observation is not a deficiency, refer to the discussion in 13.7 above.

13.8 Additional Safety-related Data

By-patient listings of serum biochemistry parameters and hematology profile values are presented in Listing L06 and Listing L07 (Appendix 20.4.1), respectively. Several high values were noted in creatinine and blood urea nitrogen (BUN), alanine aminotransferase, aspartate aminotransferase, potassium, and bicarbonate. However, these values were generally similar at both Baseline and Visit 6. No elevated laboratory value was reported as a TEAE.

14 DISCUSSION AND OVERALL CONCLUSIONS

14.1 Discussion

This study was designed to mimic the clinical setting, i.e., when a patient with T2D on 2 or more injections of insulin per day presents to the clinic and is in poor glycemic control. Following a very limited baseline period (if any) to assess their level of glycemic control, they would be transitioned from their injectable insulin to PaQ. In this study 80% of these types of patients were able to transition from their injectable insulin and optimize their insulin therapy after two 3-day PaQ wear periods with the initial basal rate selected.

The switch from injectable insulin therapy to, and optimization with PaQ led to a statistically significant reduction in patients' mean HbA_{1c} from 8.5 at baseline to 7.1 % at the end of the PaQ 12-week treatment period [-1. 37% (0.87); ($P \leq 0.0001$)]. The reduction seen in the HbA_{1c} can be attributed to both a reduction in the patients' fasting BG levels as well as their pre and post prandial blood glucose levels. Not only were BG values closer to their glycemic targets, but the excursions from these targets pre and post meals was significantly reduced (-36.25 (42.42) $P=0.003$, -49.23 (37.88), $P<0.001$), respectively. The 7-point profile graph depicts blood glucose values that were lower and more stable during the day compared to their Baseline values.

The significant change from Baseline seen in the patients' basal dose following PaQ transition was a reflection of the investigators' optimization of the patients' insulin therapy. Interestingly, the patients' trend toward an increase in daily bolus dose was not seen until the last 8 weeks of the study. During PaQ transition and at Week 4 participants were administering the same or slightly less U of meal-time insulin per day than they had on their baseline therapy. However, a notable increase in the daily bolus dose was seen at Week 8 and then again at Week 12. This increase was not due to more insulin being taken at each dose administration, but rather an increase in the number of bolus dose(s) administered per day (3 injections versus 3.8 injections per day). This is an interesting finding, given one of the barriers to injectable insulin therapy is "missed" doses due to pain and/or embarrassment.

Often times optimization of insulin therapy can result in hypoglycemia.[20] In addition, people who have chronically elevated BG levels, such as people with T2D, are known to experience hypoglycemia symptoms even when blood glucose values are actually normal.[20] Thus, it is not surprising that 50% of the participants in this study experienced symptomatic hypoglycemia since their TDD of insulin had been increased and their blood glucose levels were brought closer to normal values.

While this study used the American Diabetes Association (ADA) hypoglycemia working group definition of BG values ≤ 70 mg/dL, an exploratory analysis was done to tabulate BG values < 56 mg/dL as this value with symptoms is recognized as having greater clinical significance. In this study 5 of the patients experienced BG values < 56 mg/dL, 2 with symptoms and 3 without, all of which resolved, and none had severe hypoglycemia requiring third party assistance. Given the reduction of HbA1c seen one would have expected a greater magnitude of hypoglycemia which was not seen. The CGM analysis revealed no statistical difference between glucose values < 70 mg/dL at Baseline and after 8 weeks on PaQ.

The results from the 2 PRO questionnaires, BIT and DTSQ, were seen as positive, given the small sample size of the study. The statistically significant change in the hyperglycemia score in the DTSQ questionnaire [-2.10 (2.9); $P=0.0041$] correlated with the reduction seen in HbA_{1c}. The statistically significant change in the total score reflected the participants' satisfaction with the PaQ device.

The device-related adverse events (cannula site reactions, dermal irritation and hyperglycemia) were predominantly mild and to be expected with a body-worn CSII device.

The device deficiencies seen in this study were not unexpected and while inconvenient, they did not lead to harm.

14.2 Conclusions

Patients were able to use PaQ and it worked as it was designed. The concept behind the PaQ insulin delivery device is to provide an alternative mode of insulin delivery that is easy to use, safe and effective. The data from this study support that PaQ's overall performance is achieving this goal:

- Easy to use - The transition from the patients' previous injectable insulin therapy to PaQ was relatively easy; 80% of the patients were able to switch and continue on the first basal rate selected after two 3-day wear periods
- Safe
  - Improved glycemic control was achieved without the occurrence of severe hypoglycemia
  - No use errors were committed that led to patient harm and the adverse events that were seen were predominantly mild and consistent with other body-worn CSII devices.
- Effective
  - Clinically meaningful reductions in HbA_{1c} values were seen following 12 weeks of PaQ use
  - Fasting plasma glucose values were significantly improved and demonstrated the performance of the device to deliver a constant basal rate of insulin
  - Seven-point blood glucose data demonstrated the ability of participants to effectively administer meal-time insulin and reduce glycemic excursions following meals.
- Improvement in quality of life
  - A trend toward the reduction of barriers to insulin therapy was seen
  - Patients were satisfied with the PaQ and had fewer concerns about hyperglycemia while using PaQ (as compared to their injectable insulin therapy).

15 LISTS OF ABBREVIATIONS AND TERMS

Abbreviation	Term/Definition
ADE	Adverse Device Effect
AE	Adverse Event
BG	Blood Glucose
BIT	Barriers to Insulin Treatment
BMI	Body Mass Index
CGM	Continuous glucose monitoring
CI	Confidence Interval
CIP	Clinical Investigation Plan
CPD	Cannula Placement Device
CSII	Continuous Subcutaneous Insulin Infusion
DCCT	Diabetes Control and Complications Trial
eCRF	Electronic Case Report Form
FBG	Fasting Blood Glucose
GCP	Good Clinical Practices
HbA_{1c}	Glycosylated Hemoglobin, Hemoglobin A_{1c}
IFCC	International Federation of Clinical Chemistry
IFU	Instructions For Use
ISO	International Standard Organization
ITT	Intent to Treat
MDI	Multiple Daily Injections of Insulin
OADs	Oral Antidiabetic Drugs
PaQ	Name for CeQur Insulin Delivery Device, investigational device being studied in this protocol
QOL	Quality Of Life
QSG	Quick Start Guide
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SD	Standard Deviation
SMBG	Self-Monitored Blood Glucose
SOC	System Organ Class
SOP	Standard Operating Procedure
T2DM	Type 2 Diabetes Mellitus
TDD	Total Daily Dose

Abbreviation	Term/Definition
Adverse Event (AE)	An AE is defined as any illness, sign, symptom or clinically significant laboratory abnormality that has appeared or worsened during the course of the clinical trial, regardless of causal relationship to the device under study.
Adverse Device Effects (ADE)	An ADE is defined as any untoward and unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in instructions for use or deployment of the device. This definition also includes any event that is a result of user error.
Serious Adverse Event (SAE)	An SAE is defined as any adverse event that meets one or more of the following criteria: 1. Leads to death 2. Leads to serious deterioration in the health of a patient that a. Results in a life-threatening (immediate risk of death) illness or injury, b. Results in a permanent impairment of a body structure or a body function, c. Requires in-patient hospitalization or prolongation of existing hospitalization, d. Results in medical or surgical intervention to prevent permanent impairment to a body structure or body function 3. Leads to fetal distress, fetal death, or a congenital abnormality or birth defect.
Serious Adverse Device Effects (SADE)	A serious adverse device effect is defined as an ADE that results in any of the consequences characteristic of an SAE or that may lead to any of these consequences if suitable action is not taken or intervention is not performed or if circumstances are less opportune.
Unanticipated Adverse Device Event (UADE)	An unanticipated ADE is defined as any SADE on health or safety or 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 CIP or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.
Associated adverse event	There was a reasonable possibility that the AE might have been caused by the test article. This term applied to an AE as follows: – Reasonable temporal sequence from administration of the test article

Abbreviation	Term/Definition
	– Known response pattern to the test article.
Undetermined (unknown) association with adverse event	Sufficient information was not available at the time of the event to determine its causality.
Not related to the adverse event	An AE for which sufficient information existed to indicate that the etiology was unrelated to the test article. One or more of the following variables applied: – The AE did not follow a reasonable temporal sequence following administration of the test article; – The AE was readily explained by the patient's clinical state or other therapies.
Device deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance NOTE - Device deficiencies include malfunctions, use errors, and inadequate labeling.
Severe **hypoglycemia**	An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.[23]
Documented symptomatic **hypoglycemia**	An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L).[23]
Asymptomatic **hypoglycemia**	An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L). Since the glycemic threshold for activation of glucagon and epinephrine secretion as glucose levels decline is normally 65 to 70 mg/dL (3.6 to 3.9 mmol/L) and since antecedent plasma glucose concentrations of less than or equal to 70 mg/dL (3.9 mmol/L) reduce sympathoadrenal responses to subsequent hypoglycemia, this criterion sets the lower limit for the variation in plasma glucose in nondiabetic, nonpregnant individuals as the conservative lower limit for individuals with diabetes.[23]
Malfunction	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP

16 ETHICS

16.1 Ethical Conduct of the Study

This study was performed in accordance with standard operating procedures (SOPs) of CeQur and the clinical research organization, Premier Research Group Limited, operating at the time of the study. These SOPs were designed to ensure adherence to GCP and ensure the protection of the patients, as required by the following directives in operation at the time:

- Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Patients).
- Directive 93/42/EEC: The Rules Governing Medical Devices Directive 90/385/EEC: The rules Governing Implantable Medical Devices
- European Norm ISO 14155 parts 1 and 2: Clinical Investigations of Medical Devices in human patients: General requirements and Clinical Investigation Plan requirements
- USA 21 Code of Federal Regulations dealing with clinical studies for medical devices parts 812, 50 and 56 concerning IDE, Informed Consent and Institutional Review Board approval
- Japanese International Conference on Harmonization

16.2 Ethics Committee

The protocol and protocol amendments were reviewed and approved by an Independent Ethics Committee (listed in Appendix 20.2.2) and the Competent Authority before the study began.

16.3 Patient Informed Consent

Written informed consent was obtained from all patients at the time of their screening visit. Representative written information for the patient and a sample of patient consent form is provided in Appendix 20.1.2.

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18 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The following individuals conducted the study and formed the study's administrative structure.

Principal Investigators

Site	Principal Investigator	Site address
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19 APPROVAL SIGNATURES AND REVISION HISTORY

Revision History

No	Date	File	Author	

Signatures of the Authors of the Report:

Name/Title	Affiliation	Date	Signature
Kathleen Grugan, MSN, RN Principal Medical Writer	Premier Research		
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Signature of the Principal Investigator:

Name/Title	Affiliation	Date	Signature
Thomas Pieber, MD	Medical University of Graz		

20 APPENDICES

20.1 APPENDIX 1: Study Information

20.1.1 Clinical Investigational Plan Revision 3

20.1.2 Information for Patients and Sample Consent Form

- PaQ Quick Start Guide
- PaQ Instruction for Use Manual
- Informed Consent Form

20.1.3 Sample Case Report Form

20.1.4 Lot Numbers Used

20.2 APPENDIX 2: Study Center Information

20.2.1 Investigators' Curricula Vitae

20.2.2 Independent Ethics Committee Approval

20.3 APPENDIX 3: Standardization and Quality Assurance

20.3.1 Laboratory Certificates

20.3.2 Final Data Management Plan

20.4 APPENDIX 4: Statistics

20.4.1 Statistical Methods and Analysis Outputs

- Final SAP
- Final tables
- Final listing

20.4.2 Joanneum Research – CGM

- Final SAP for CGM analysis
- Final CGM Statistical Report