Prepivotal Evaluation of the Safety and Effectiveness of the Omnipod Horizon™ Automated Glucose Control System in Patients with Type 1 Diabetes

IDE G190267

Version 2.3

November 14, 2019

Insulet Corporation

100 Nagog Park

Acton, MA 01720

PROTOCOL APPROVAL

Prepivotal Evaluation of the Safety and Effectiveness of the Omnipod Horizon™ Automated Glucose Control System in Patients with Type 1 Diabetes

IDE G190267

Version 2.3

November 14, 2019

Trang Ly MBBS FRACP PhD - SVP, Clinical and Medical Director, Insulet Corporation	Date
Bonnie Dumais, RN – Director of Clinical Affairs, Insulet Corporation	Date
Julie Perkins - Senior Director, Quality and Regulatory, Insulet Corporation	Date

INVESTIGATOR STATEMENT

Prepivotal Evaluation of the Safety and Effectiveness of the Omnipod Horizon™ Automated Glucose Control System in Patients with Type 1 Diabetes

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I agree to conduct the above referenced clinical study protocol in accordance with the design and specific provisions as designated in this protocol, the signed agreement with the Sponsor, applicable FDA regulations, and any conditions of approval imposed by an Institutional Review Board (IRB) or Food and Drug Administration (FDA). Modifications to the study protocol are acceptable only in the form of a protocol amendment, except when necessary to protect the safety, rights, or welfare of subjects. I agree to await Institutional Review Board (IRB) and Insulet approval for the protocol, informed consent and documentation to be presented to subjects before initiating the study pursuant to 21 CFR Part 56, to obtain informed consent from subjects prior to their enrollment into the study pursuant to 21 CFR Part 50, to collect and record data as required by this protocol and case report forms, to report non serious and serious adverse events that may occur for any subject participating in this study under my care, to report product complaints for any of the devices utilized in this protocol, and to maintain study related documentation (regulatory documentation) for the period of time required. I agree to supervise all utilization of investigational study devices and to ensure their usage is only in connection with the Study. I agree to provide a Financial Disclosure Statement to Sponsor and will also notify Sponsor if my disclosed financial information changes during the Study and up to one year following the closure of the Study. I have read and understand the contents of this protocol. I agree to follow and abide by the requirements set forth in this document.

I understand the information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to me, which is indicated as privileged or confidential.

_____

Clinical Site Investigator Name (print)

_____ _____

Clinical Site Investigator Signature Date

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PROTOCOL SUMMARY

Protocol title	Prepivotal evaluation of the safety and effectiveness of the Omnipod Horizon™ Automated Glucose Control System in patients with type 1 diabetes
Protocol ID	G190267
Purpose	To evaluate the safety and effectiveness of the Omnipod Horizon™ Automated Glucose Control System in patients with type 1 diabetes.
Design	This study is a single-arm, multi-center, prospective clinical study
Enrollment	Up to 48 subjects will be enrolled in the study in order to obtain a minimum of 36 evaluable subjects. The study will consist of two phases: 1) 14-day standard therapy phase, followed by; 2) 14-day hybrid closed-loop phase Subjects will be enrolled across 6-8 clinical study sites. The 36 evaluable subjects will be comprised of two age cohorts as follows: • 18 subjects aged 6-13.9 years • 18 subjects aged 14-70 years
Indication	The Omnipod Horizon™ Automated Glucose Control System is a single hormone insulin delivery system intended for the management of diabetes in persons requiring insulin. Continuous subcutaneous insulin infusion may be delivered by user-defined settings (manual mode) or automatically adjusted in response to feedback from a continuous glucose monitor (CGM). The Omnipod Horizon™ System can automatically increase insulin delivery based on CGM sensor glucose values and can decrease or suspend delivery of insulin when the glucose value falls below or is predicted to fall below predefined threshold values. The Omnipod HORIZON™ System is interoperable with compatible iCGMs and ACE pumps. The Omnipod Horizon™ System is designed to assist patients with diabetes in achieving glycemic targets set by their health care providers.
Study duration	The study is expected to be completed within 6-months which includes clinical site initiation to completion of all data entry and monitoring procedures.
Investigational devices	The Omnipod Horizon™ Automated Glucose Control System is comprised of the following components: • Omnipod Horizon™ tubeless, insulin delivery alternate controller enabled (ACE) pump (Pod) with the Horizon™ algorithm • Omnipod Horizon™ Personal Diabetes Manager (PDM) which is a Samsung J3 locked down Android device that operates the Omnipod Horizon™ App.
Non-investigational, commercially available devices	• Dexcom G6 - Continuous Glucose Monitoring (CGM) system • Contour® Next One blood glucose meter (Ascensia Diabetes Care, 5 Wood Hollow Road, Parsippany, NJ 07054 USA) • Precision Xtra ketone meter (Abbott Diabetes Care Inc., 1360 South Loop Road, Alameda, CA 94502 USA)

Safety objective	To evaluate the safety of the Omnipod Horizon™ Automated Glucose Control System in patients with type 1 diabetes
Primary safety endpoint	Proportion of subjects with serious device-related adverse events
Secondary safety endpoints	• Proportion of subjects with severe hypoglycemia during hybrid closed-loop • Proportion of subjects with diabetic ketoacidosis (DKA) during hybrid closed-loop
Primary effectiveness objective	To evaluate the effectiveness of the Omnipod Horizon™ Automated Glucose Control System
Primary effectiveness endpoints	Percentage of time in range (70-180 mg/dL) during hybrid closed-loop compared to standard therapy for: • Target blood glucose (BG) challenge days (approximately hybrid closed-loop days 1-9) • Non-challenge days (approximately hybrid closed-loop days 10-14) • Overall (hybrid closed-loop days 1-14)
Secondary effectiveness objective	To evaluate additional glycemic measures of effectiveness of the Omnipod Horizon™ Automated Glucose Control System

Secondary effectiveness endpoints	The secondary objective will be evaluated using the following per subject endpoints:
	• Glucose metrics from system CGM during the hybrid closed-loop phase will be compared to the standard therapy phase during the day, overnight, and overall:
	  • Mean glucose
	  • % of time in range 70-180 mg/dL
	  • % of time in range 70-140 mg/dL
	  • % of time > 180 mg/dL
	  • % of time ≥ 250 mg/dL
	  • % of time ≥ 300 mg/dL
	  • % of time < 70 mg/dL
	  • % of time < 54 mg/dL
	  • Standard deviation
	  • Coefficient of variation
	• Glucose management indicator (GMI) based on overall mean glucose
	• Percentage of time in hybrid closed-loop as proportion of overall device usage time
	• Insulin requirements during the hybrid closed-loop phase will be compared to the standard therapy phase:
	  • Total daily insulin (TDI) (units, units/kg)
	  • Total daily basal insulin (units, units/kg)
	  • Total daily bolus insulin (units, units/kg)

Eligibility criteria	***Inclusion Criteria*** Subjects must meet all of the following criteria to be included in the study: 1. Age at time of consent/assent 6-70 years 2. Subjects aged < 18 years must be living with parent/legal guardian 3. Diagnosed with type 1 diabetes for at least 6 months. Diagnosis is based on investigator's clinical judgment. 4. Deemed appropriate for pump therapy per investigator's assessment taking into account previous history of severe hypoglycemic and hyperglycemic events, and other comorbidities 5. Investigator has confidence that the subject can successfully operate all study devices and is capable of adhering to the protocol 6. Willing to use only the following types of insulin during the study: Humalog, Novolog, Admelog, or Apidra during the study 7. Must be willing to set target glucose between 130-150 mg/dL each for approximately 72-hours on predefined days during the hybrid closed-loop phase 8. Must be willing to extend their participation into the pivotal study if they continue to meet the protocol criteria 9. Willing to wear the system continuously throughout the study 10. A1C <10% at screening visit 11. Must be willing to use the Dexcom App on the Omnipod Horizon™ PDM as the sole source of Dexcom data (with the exception of the Dexcom Follow App) during the hybrid closed-loop phase 12. Subjects scoring ≥ 4 on the Clarke Questionnaire must agree to have an overnight companion, defined as someone who resides in the same home or building as the study subject and who can be available overnight 13. Able to read and speak English fluently 14. Subject must be in an AT&T covered area 15. Willing and able to sign the Informed Consent Form (ICF) and/or has a parent/guardian willing and able to sign the ICF. Assent will be obtained from pediatric and adolescent subjects aged < 18 years per State requirements. ***Exclusion Criteria*** Subjects who meet any of the following criteria will be excluded from the study: 1. A medical condition, which in the opinion of the investigator, would put the subject at an unacceptable safety risk 2. History of severe hypoglycemia (as defined in Section 11.3.3) in the past 6 months 3. History of DKA (as defined in Section 11.3.4) in the past 6 months, unrelated to an intercurrent illness, infusion set failure or initial diagnosis 4. Diagnosed with sickle cell disease 5. Diagnosed with hemophilia or any other bleeding disorders 6. Plans to receive blood transfusion over the course of the study 7. Currently diagnosed with anorexia nervosa or bulimia 8. Acute or chronic kidney disease (e.g. estimated GFR < 45) or currently on hemodialysis 9. History of adrenal insufficiency 10. Has taken oral or injectable steroids within the past 8 weeks or plans to take oral or injectable steroids during the course of the study 11. Unable to tolerate adhesive tape or has any unresolved skin condition in the area of sensor or pump placement 12. Plans to use insulin other than U-100 insulin intended for use in the study device during the course of the study

	13. Use of non-insulin anti-diabetic medication other than metformin (e.g. GLP1 agonist, SGLT2 inhibitor, DPP-4 inhibitor, pramlintide) 14. Current or known history of coronary artery disease that is not stable with medical management, including unstable angina, or angina that prevents moderate exercise despite medical management, or a history of myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting within the previous 12 months. 15. For subjects >50 years old or with diabetes duration >20 years, abnormal electrocardiogram consistent with increased risk of arrhythmia, ischemia, or prolonged QT_c interval (> 450 ms) 16. Thyroid Stimulating Hormone (TSH) is outside of normal range with clinical signs of hypothyroidism or hyperthyroidism 17. Pregnant or lactating, or is a woman of childbearing potential and not on acceptable form of birth control (acceptable includes abstinence, condoms, oral/injectable contraceptives, IUD or implant) 18. Participation in another clinical study using an investigational drug or device within the preceding 30-days or intends to participate during the study period 19. Unable to follow clinical protocol for the duration of the study or is otherwise deemed unacceptable to participate in the study per the investigator's clinical judgment.
Study schedule overview	The study schedule consists of the following two phases: 1) 14-day outpatient standard therapy phase followed by; 2) 14-day hybrid closed-loop phase Following subject screening, enrollment, and device training, subjects will commence the outpatient standard therapy phase of the study. Current Dexcom G6 CGM users may provide data from a 14-day period within the last 30-days. The CGM data meeting the minimum criteria must be the most recent data from the last 30-days. For non-G6 users, subjects will wear a study CGM, in blinded mode, to record glucose measurements over 14-days while subjects manage their diabetes at home per their usual routine and remaining on their current MDI or pump therapy, and sensor, if applicable, for 14-days. After completion of the standard therapy phase, subjects will be trained on the system and transition to the hybrid closed-loop phase initiating treatment with the Omnipod Horizon™ System. For the hybrid closed-loop phase, subjects will be divided into two groups: **Group 1:** 1. N=16 subjects aged 6-70 years will participate in the hybrid closed-loop phase for the first 2-days while in a supervised hotel/rental house environment and then transition to 12-day outpatient environment o N=8 subjects aged 6-13.9 years o N=8 subjects aged 14-70 years **Group 2:** 2. N=20 subjects aged 6-70 years will participate in the hybrid closed-loop phase in a 14-day outpatient environment o N=10 subjects aged 6-13.9 years o N=10 subjects aged 14-70 years

	The first group of subjects (n=16) will commence the hybrid closed-loop phase in the hotel setting. On study day-3, subjects will transition to the outpatient setting for the remaining 12-days. After all subjects from the first group have completed the 2-day hotel phase, the second group of subjects may commence hybrid closed-loop. The second group of subjects (n=20) will use hybrid closed-loop in the outpatient setting for 14-days. All subjects will participate in target glucose challenges during the hybrid closed-loop phase. In total, all subjects will complete 14-days of hybrid closed-loop control, with approximately 72-hours spent at target blood glucoses levels set to 130mg/dL, 140mg/dL and 150mg/dL, respectively. Clinical site staff will receive alerts through a remote monitoring system during the study. After each subject in the prepivotal study has successfully completed 14-days of hybrid-closed loop, they may immediately transition to and enroll in the pivotal study bypassing standard therapy (Phase 1) and continuing with the pivotal hybrid closed-loop phase (Phase 2). Remote monitoring will be discontinued as each subject enrolls in the pivotal study. After 16-subjects from the prepivotal study have completed a minimum of 10-days of hybrid-closed-loop, the Data Safety Monitoring Board (DSMB) will convene and if the system is determined to be safe, the pivotal study may open enrollment to additional subjects for the hybrid closed-loop phase (Phase 2). The standard therapy phase (Phase 1) of the pivotal study may commence in parallel to the prepivotal study.

GLOSSARY OF ACRONYMS

ACE	Alternate Controller Enabled
ADA	American Diabetes Association
ADE	Adverse Device Effect
AID	Automated Insulin Delivery
AE	Adverse Event
BG	Blood Glucose
BLE	Bluetooth Low Energy
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CRA	Clinical Research Associate
CRO	Contract Research Organization
CV	Curricula Vitae
DD	Device Deficiency
DKA	Diabetic Ketoacidosis
dL	Deciliter
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGV	Estimated Glucose Value
FDA	Food and Drug Administration
GMI	Glucose Management Indicator
HDP	Horizon Data Portal
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IOB	Insulin on Board
IRB	Institutional Review Board
ITT	Intention to Treat
MD	Doctor of Medicine
MDI	Multiple Daily Injections
mg	Milligram
mITT	Modified Intention to Treat
mmol	Millimole
MPC	Model Predictive Control
NGSP	National Glycohemoglobin Standardization Program
PDM	Personal Diabetes Manager
PHI	Protected Health Information
POC	Point of Care
pMPC	Personalized Model Predictive Control
PP	Per Protocol
PTOF	Pump Therapy Order Form
SADE	Serious Adverse Device Effect

SAE	Serious Adverse Event
SMP	Safety Management Plan
TSH	Thyroid Stimulating Hormone
TDI	Total Daily Insulin
UADE	Unanticipated Adverse Device Effect

1 INTRODUCTION

Diabetes is a disorder affecting the normal homeostatic regulation of blood glucose. In type 1 diabetes, insulin insufficiency occurs due to autoimmune destruction of the beta cells in the pancreas resulting in persistently elevated glucose. The long-term effects of elevated blood glucose or hyperglycemia may result in a range of microvascular complications including retinopathy, nephropathy, and neuropathy. Diabetes is the leading cause of blindness, kidney disease, and amputation in the United States.[1]

The risk for long-term complications of diabetes can be reduced, however, by minimizing patient exposure to hyperglycemia and maximizing the time in euglycemia. The landmark Diabetes Control and Complications Trial published in 1993 found that maintenance of near normal glucose levels reduced the risk of long-term microvascular complications. In 2005, the publication of the Epidemiology of Diabetes Interventions and Complications study found that despite the multifactorial etiology of heart disease, intensive insulin therapy in patients with type 1 diabetes was shown to reduce the incidence of nonfatal myocardial infarction, stroke, and death from cardiovascular disease.[2]

Unfortunately, efforts to minimize hyperglycemia and maximize euglycemia are invariably accompanied by episodes of hypoglycemia. Indeed, the justifiable fear of hypoglycemia is often described as the single most significant barrier to improved glucose control in patients with diabetes.[3] A paper by Weinstock et. al. reported on data collected by the T1D Exchange and found an annual incidence of 11.8% of one or more severe hypoglycemic events defined as a seizure or loss of consciousness. The annual incidence of severe hypoglycemic events increased to 18.6% in patients with diabetes duration greater than 40 years.[4]

Two other recent papers have highlighted the effect of acute and chronic complications on the longevity of patients with diabetes. Livingstone et. al. found premature death in a Scottish registry of patients with diabetes of 11 years in males and 13 years in females.[5] Lind et. al. found a twofold increase in mortality in a Swedish registry compared with age-matched non-diabetic cohorts even in patients with recommended levels of glycemic control (A1C < 7.0%).[6]The most recent treatment guidelines from the American Diabetes Association now recommend that adults with type 1 diabetes should aim for target A1C levels of 7.0% and that children and adolescents should aim for target A1C levels of 7.5%.[7] These recommendations are equivalent to a mean blood glucose of 154 mg/dL in adults and 169 mg/dL in children and adolescents compared with mean blood glucose in patients without diabetes of 100 mg/dL or less.[8]

The last 20 years have seen a number of significant improvements in diabetes care, most notably the advent of faster analog insulins, the widespread use of insulin pumps and the introduction of continuous glucose monitoring systems. Despite these advances, diabetes data registries continue to show that the majority of patients are unable to meet recommended glycemic targets with available medication and technology. In the 2012 report from the T1D Exchange Registry, Beck et. al. found the average A1C across all ages greater than 8.0% or, equivalently, greater than 183 mg/dL and only 30% of patients met the ADA target A1C of 7.0% (adults) and 7.5% (children).[9] A more recent paper from the T1D Exchange Registry by Foster et. al. comparing the 2016-2018 cohort with 2010-2012 cohort indicated that among the 9,657

participants that had data in both cohorts and at least 3 years of diabetes duration in 2010-2012, mean HbA1c was higher in the 2016-2018 cohort. The increase in HbA1c over time was predominately seen in adolescents and young adults. The American Diabetes Association (ADA) HbA1c target as of 2018 of < 7.5% for children and adolescents was achieved by only a small percentage of youth < 18 years of age (17%); only 21% of adults achieved the ADA treatment goal of < 7.0%.[10]

The current dilemma of persistent poor diabetes outcomes despite significant improvements in diabetes technology such as modern blood glucose meters, insulin pumps and continuous glucose monitoring systems is summarized in the FDA Guidance Document on Artificial Pancreas Device Systems: "Even with the aid of these devices, maintaining blood glucose concentrations within a suggested optimal range is a daily struggle for people living with diabetes mellitus and the risk of hypoglycemia associated with attempts at improved glycemic control remains an ever-present danger".[11]

Insulet has developed the Omnipod Horizon™ Automated Glucose Control System (hereafter named Omnipod Horizon™ System or Omnipod Horizon™) which is similar in function to the systems described in the FDA guidance document dated November 9, 2012. The system provides automated glucose control at all times, but for optimum performance, requires user input for meal boluses. The commercial system will consist of an Omnipod® tubeless, insulin delivery ACE pump, a Personal Diabetes Manager (PDM), and the Dexcom G6 CGM. The control algorithm will reside on the Pod.

This prepivotal study is designed to evaluate the safety and effectiveness of the Omnipod Horizon™ System while in a more closely supervised environment prior to commencing the pivotal study. Target BG challenges will be conducted to ensure exposure to stressors during the study.

2 OMNIPOD HORIZON™ SYSTEM STUDY DEVICE OVERVIEW

This study will evaluate the safety and effectiveness of the Omnipod Horizon™ System. The Omnipod Horizon™ System is a hybrid closed-loop automated insulin delivery (AID) system developed by Insulet.

2.1 Device Description of the Omnipod Horizon™ System

The Omnipod Horizon™ System intended for commercialization is composed of three primary components as shown in Figure 1.

- Omnipod Horizon™ Controller – Horizon App (PDM) and Algorithm
- Omnipod Horizon™ ACE Pump – Pod
- iCGM – Dexcom G6

The Omnipod Horizon™ System will provide automated insulin delivery when connected to CGM. The system is expected to reduce hypoglycemia without incurring an unacceptable increase in hyperglycemia and mean glucose. The system is also expected to reduce the extent and magnitude of hyperglycemia associated with meals. Optimal post-prandial control requires the user to deliver meal boluses as in current open-loop therapy, but the normal operation of the control algorithm will be expected to

compensate for mismatched meal boluses and prevent prolonged hyperglycemia. The system uses a control-to-target strategy that attempts to achieve and maintain a set target glucose level.

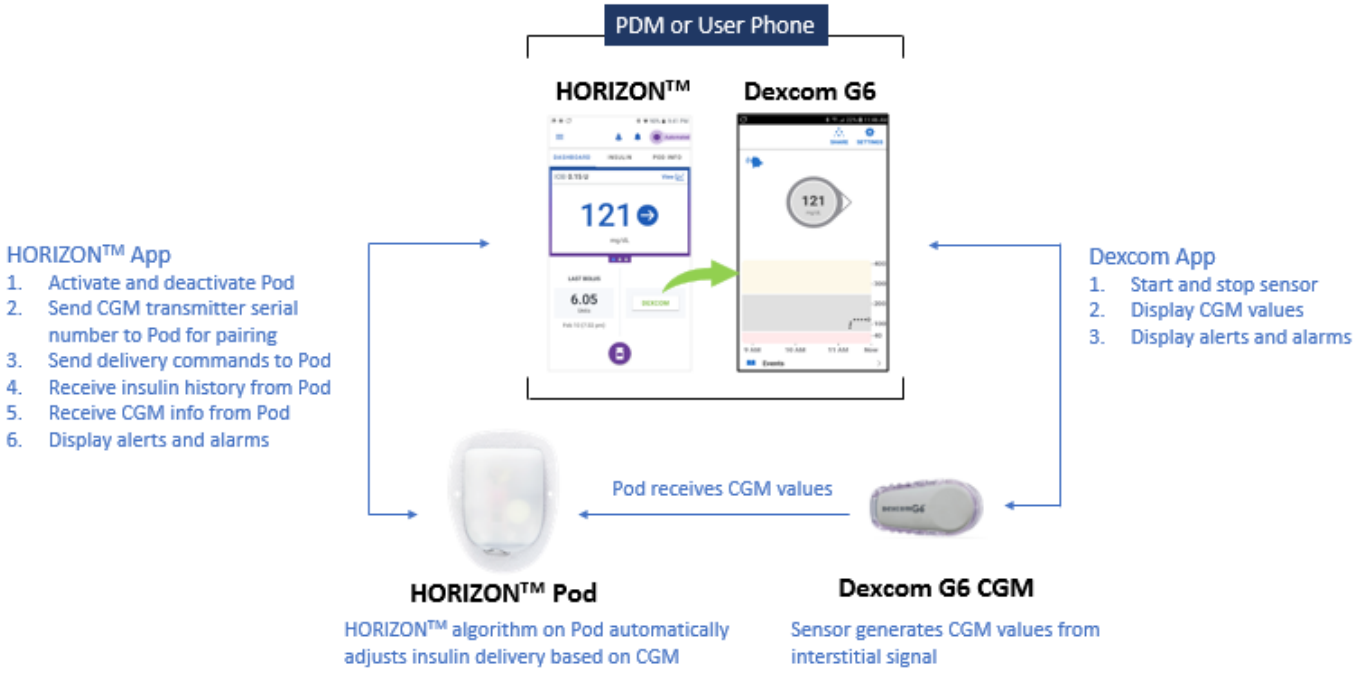

Figure 1: System components of the Omnipod Horizon™ System

2.1.1. Omnipod Horizon™ Controller (App and Algorithm)

The Omnipod Horizon™ Controller is composed of two parts: the Horizon application ("app") and the model predictive control (MPC) algorithm on the Pod. The MPC algorithm provides insulin micro-boluses once every 5 minutes based upon the predicted glucose over a 60-minute prediction horizon. Optimal post-prandial control will require the user to give meal boluses in the same manner as current pump therapy, but normal operation of the MPC algorithm will compensate for missed meal boluses and mitigate prolonged hyperglycemia. The MPC algorithm uses a control-to-target strategy that attempts to achieve and maintain a set target glucose value, thereby reducing the duration of prolonged hyperglycemia and hypoglycemia. The MPC algorithm resides on the Pod (Pump) component of the Omnipod® Horizon System (similar to the DASH ACE pump cleared in K191679, as described further below).

The Omnipod Horizon™ app will be the primary user interface and will be used to start and stop a Pod, program basal and bolus calculator settings for Manual Mode as well as program settings specific for Automated Mode (hybrid closed-loop).

Manual Mode

In Manual Mode, the Horizon™ System will function equivalently to the Omnipod® DASH System, which was first cleared under K180045, most recently under K191679.

This includes delivering insulin at programmed basal rates and bolus amounts with the option to set temporary basal profiles. The Omnipod Horizon™ Controller will also have the ability to function as a sensor augmented pump in Manual Mode, using sensor glucose data provided by the iCGM to populate the bolus calculator.

Automated Mode

In Automated Mode, the system will support the use of multiple target glucose values, currently intended to be 110-150 mg/dL at commercialization, in 10 mg/dL increments. The experience for the user will reflect current setup flows whereby the health care provider assists the user to program basal rates, glucose targets and bolus calculator settings. These in turn will inform the MPC algorithm for insulin dosing parameters. The insulin dosing parameters will be adapted over time based on the total daily insulin (TDI) delivered during each Pod use. A temporary hypoglycemia protection mode (Hypo Protect) may be implemented by the user for various time durations during Automated Mode. With Hypo Protect, the algorithm reduces insulin delivery and is intended for use over temporary durations when insulin sensitivity is expected to be higher, such as during exercise.

The Omnipod Horizon™ System will include two apps on a locked-down smartphone (the Samsung J3), referred to as Personal Diabetes Manager (PDM): the Horizon App and the Dexcom App. The Horizon App, which will have a similar interface to the cleared Omnipod® DASH System (K191679), will allow the use of large text, graphics, and on-screen instructions to prompt the user through set-up processes. It will also be used to program the user's custom basal insulin delivery profile, check the Pod status, initiate bolus doses of insulin, make changes to a patient's insulin delivery profile, handle system alerts and alarms, and enter Automated Mode.

The Dexcom App interface is identical to the current app of the interoperable Dexcom G6 Continuous Glucose Monitoring System (K191450) and will provide CGM data, alerts, and alarms to the user.

The Horizon App and Dexcom App will not directly communicate with one another. Instead, the iCGM transmitter will communicate EGV (estimated glucose values) directly to the Pod. The Dexcom transmitter number must be entered into the Horizon App, and this information is sent to the Pod to allow transmission of EGV. The Pod will pair directly to the transmitter to receive EGV for the algorithm and also sends the EGV back to the Horizon App as shown in Figure 1.

The Omnipod Horizon™ Controller provides the ability to calculate a suggested bolus dose through the use of the bolus calculator. The bolus calculator will have the option for user-selected population of the EGV, which is communicated to the app via the Pod. This suggested bolus calculation feature is provided as a convenience to the user to aid in determining the suggested bolus dose based on ingested carbohydrates, most recent sensor glucose reading (or blood glucose reading if using fingerstick), programmable correction factor, insulin to carbohydrate ratio, target glucose value and insulin on board (IOB). IOB is calculated by the algorithm taking into account any manual bolus and insulin delivered by the algorithm.

As with the cleared Omnipod® DASH System, Insulet will utilize a proprietary encrypted security stack embedded within the Bluetooth Low Energy (BLE) communication

between the Horizon app and Pod. The communication to the iCGM will use Dexcom's communication protocol. The proprietary security stack increases the resilience of the device and improves the ability of the system to be protected in the event of future identification of vulnerabilities in standard communication protocols.

2.1.2. Omnipod Horizon™ ACE Pump

The Pod component of the Omnipod Horizon™ System is similar to the Omnipod® DASH ACE Pump cleared under K191679. Compared to the DASH ACE Pump (K191679), the Horizon™ ACE Pump (Pod) has additional software to optimize communication to accept inputs from the iCGM (initially the Dexcom G6) and the Horizon™ Controller. The insulin delivery mechanism and the patient and fluid contacting components are identical to the DASH Pod.

The Pod is a lightweight, self-adhesive device that the user fills with U-100 rapid-acting insulin and wears directly on their body. The Pod delivers insulin into the user's body through a small flexible tube, called a cannula, based on the commands from the compatible controller. In the Omnipod Horizon™ System, the Pod will house the MPC algorithm and communicate directly with the iCGM and the Horizon App. The algorithm commands the Pod's insulin delivery in the form of micro-boluses based on predicted glucose values. Figure 2 below is a representation of the Pod.

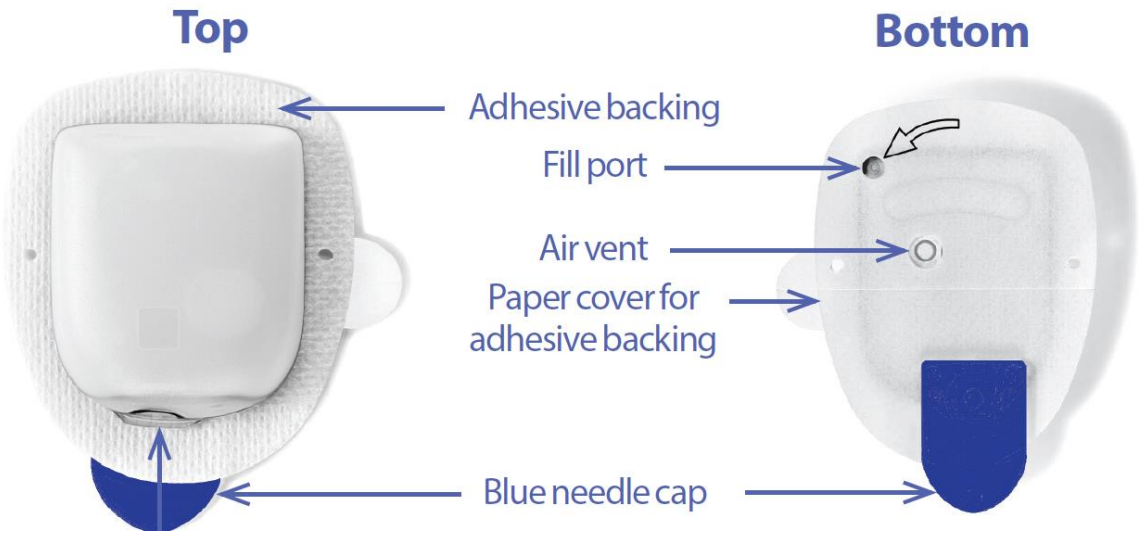

Figure 2: The Pod of the Omnipod Horizon ACE pump

2.1.3. iCGM

The third component of the Omnipod Horizon™ System is the iCGM. The Omnipod Horizon™ System will be interoperable with a compatible iCGM, currently the Dexcom G6 Continuous Glucose Monitoring System (K191450). The Omnipod Horizon™ Pod will communicate with the Dexcom G6 via Bluetooth Low Energy (BLE). Glucose values from the Dexcom transmitter will be sent to the MPC algorithm residing on the Pod and

used in insulin dosing adjustments. The glucose values from the Dexcom transmitter will be sent independently to the Dexcom App on the controller.

3 HORIZON™ DATA PORTAL

Data are securely uploaded from the PDM to Insulet Cloud by cellular connection. Data are then transferred from Insulet Cloud to the Horizon Data Portal (HDP), which is a platform for data review and management. The HDP runs on an Amazon-based web server. The HDP will provide insights including but not limited to: time in range, time at each target BG, automated/manual mode comparisons, and time spent in each mode. Alerts and alarms triggered by the PDM will also be logged in the portal.

Investigators will have access to all uploaded data and be able to view historical trends. During the prepivotal study, the system will provide a means for investigators to monitor live updates of CGM and insulin delivery as well as system alerts and alarms.

3.1 Remote Monitoring

Subjects will be monitored remotely via the HDP alert system during the prepivotal hybrid closed-loop phase to allow for real-time assessment of safety.

Investigators will be alerted via text message to prespecified alerts including:

- No data alert for 60 minutes
- Sensor glucose <55 mg/dL
- Sensor glucose <70 mg/dL for 20 minutes
- Sensor glucose >300 mg/dL for 1 hour

Contact information for site staff will be programmed into the HDP. In the event of an alert, site staff will receive a text message describing the specific alert type and will contact subjects for follow-up.

4 RESULTS FROM FEASIBILITY STUDIES

The Omnipod Horizon™ System has been tested in 194 subjects across IDE G160169, G170012, G170143 yielding approximately 13,000 subject hours of hybrid closed-loop control. The study results were presented in part at ATTD 2017, 2018, ADA 2017, 2018, and 2019, and have also been published in Diabetes Technology and Therapeutics [13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23,29].

5 STUDY SUMMARY

5.1 Study Purpose

The purpose of this study is to assess the safety and effectiveness of the Omnipod Horizon™ System in patients with type 1 diabetes.

5.2 Study Design

This is a single-arm, multi-center, prospective clinical study. Up to 48 subjects aged 6-70 years with type 1 diabetes will be enrolled in the study in order to obtain a minimum of 36 evaluable subjects, 18 evaluable subjects in each age cohort (**Table 1: Cohorts**).

Subjects will be enrolled across 6-8 clinical study sites. Subjects who have previously participated during the feasibility studies may be enrolled in the prepivotal study and will be assigned a new subject identification number.

The study schedule consists of the following two phases:

1) 14-day outpatient standard therapy phase followed by;
2) 14-day hybrid closed-loop phase

Cohorts are defined as shown in Table 1:

Table 1: Cohorts

Cohort	Age Range	N (minimum)
Adults	14-70 years	18
Children	6-13.9 years	18

Following subject screening, enrollment, and device training, subjects will commence the outpatient standard therapy phase of the study.

Current Dexcom G6 CGM users may provide data from a 14-day period within the last 30-days. The CGM data meeting the minimum criteria must be the most recent data from the last 30-days. For non-G6 users, subjects will wear a study CGM, in blinded mode, to record glucose measurements over 14-days while subjects manage their diabetes at home per their usual routine while wearing a study CGM while remaining on their current MDI or pump therapy, and sensor, if applicable, for 14-days.

After completion of the standard therapy phase, subjects will be trained on the system and transition to the hybrid closed-loop phase initiating treatment with the Omnipod Horizon™ System.

Clinical site staff will receive alerts through a remote monitoring system during the hybrid closed-loop phase.

For the hybrid closed-loop phase, subjects will be divided into two groups:

Group 1:

1. N=16 subjects aged 6-70 years will participate in the hybrid closed-loop phase for the first 2-days while in a supervised hotel/rental house environment and then transition to 12-day outpatient environment
    - N=8 subjects aged 6-13.9 years
    - N=8 subjects aged 14-70 years

Group 2:

2. N=20 subjects aged 6-70 years will participate in the hybrid closed-loop phase in a remotely monitored 14-day outpatient environment
    - N=10 subjects aged 6-13.9 years
    - N=10 subjects aged 14-70 years

The first group of subjects (n=16) will commence the hybrid closed-loop phase in the hotel setting. On study day 3, subjects will transition to the outpatient setting for the remaining 12-days. After all subjects from the first group have completed the 2-day hotel phase, the second group of subjects may commence hybrid closed-loop. The second group of subjects (n=20) will use hybrid closed-loop in the outpatient setting for 14-days. It is anticipated that Group 1 will solely consist of existing Dexcom G6 users (those who were using the Dexcom G6 at the time of screening), while Group 2 will include some existing Dexcom G6 users and some non-Dexcom G6 users. Therefore, the primary safety and primary effectiveness endpoints will also be presented by Dexcom G6 use (users and non-users).

All subjects will participate in target BG challenges during the hybrid closed-loop phase. In total, all subjects will complete 14-days of closed-loop control, with approximately 72-hours spent at target blood glucose levels set to 130mg/dL, 140mg/dL and 150mg/dL, respectively.

After each subject in the prepivotal study has successfully completed 14-days of hybrid-closed-loop, they may immediately transition to and enroll in the pivotal study bypassing standard therapy (Phase 1) and continuing with the pivotal hybrid closed-loop phase (Phase 2). Remote monitoring will be discontinued as each subject enrolls in the pivotal study.

After 16-subjects from the prepivotal study have completed a minimum of 10-days on hybrid-closed-loop, the Data Safety Monitoring Board (DSMB) will convene and if the system is determined to be safe, the pivotal study may open enrollment to additional subjects for the hybrid closed-loop phase (Phase 2).

The standard therapy phase (Phase 1) of the pivotal study may commence in parallel to the prepivotal study. Figure 3 is a representation of the prepivotal transition into pivotal.

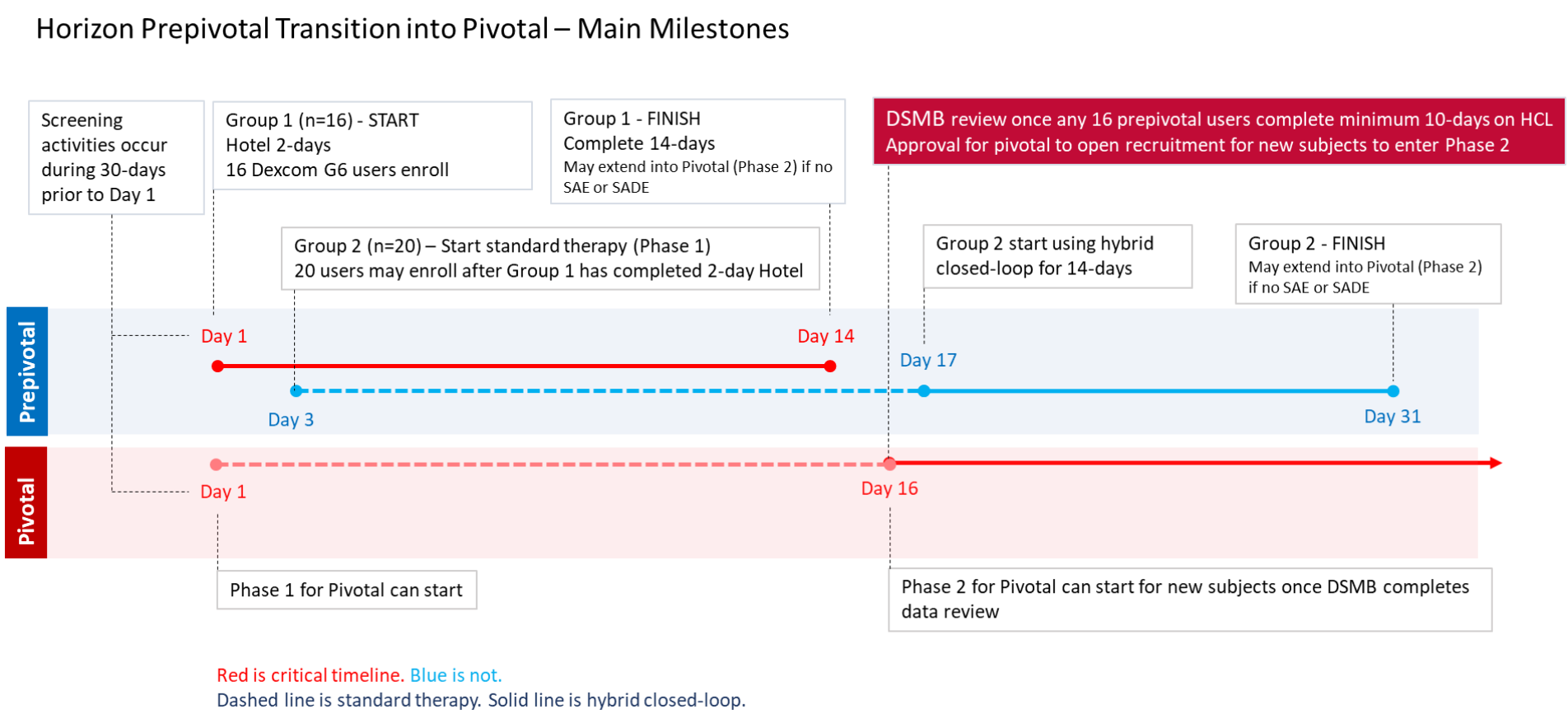

Figure 3: Horizon Prepivotal Transition into Pivotal

Table 2: Schedule of Assessments

Assessment Schedule	Screening	ST1	ST2	Hybrid Closed-Loop (HCL)								EW[a]
	Phase 1			Phase 2								
Visit Number	1	2	3	4	5	6	7	8	9	10	UV[b]	
Study Day/Visit Window	-30d to HCL start	-14d to HCL start	-1d to HCL start	1	2	3	4 +1d	7 ±1d	10 ±1d	14 +2d	N/A	
Group 1[i]: 2-day Hotel + 12-days Outpatient Hotel (H), Telephone (T) or Office (O) Visit	O	O	O	H	H	H	T/O[f]	T/O[f]	T/O[f]	T/O[f]	T/O[f]	O
Group 2[i]: 14-days Outpatient Hotel (H), Telephone (T) or Office (O) Visit	O	O	O	O	T/O[f]	T/O[f]	T/O[f]	T/O[f]	T/O[f]	T/O[f]	T/O[f]	O
Laboratory Assessments												
A1C	X											
TSH	X											
Creatinine Level	X											
Pregnancy Test	X			X								
Clinical Assessments												
Informed Consent	X											
Confirm Eligibility	X											
Medical History (including demographics)	X											
Concomitant medications	X	X[e]		X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
Average total daily insulin (~ 7 days)		X		X								
Average total basal insulin (~ 7 days)		X		X								
Average total bolus insulin (~ 7 days)		X		X								
Pump settings/MDI dosing		X		X								

Assessment Schedule	Screening	ST1	ST2	Hybrid Closed-Loop (HCL)								EW[a]
	Phase 1			Phase 2								
Visit Number	1	2	3	4	5	6	7	8	9	10	UV[b]	
Study Day/Visit Window	-30d to HCL start	-14d to HCL start	-1d to HCL start	1	2	3	4 +1d	7 ±1d	10 ±1d	14 +2d	N/A	
Height	X									X		X
Weight	X									X		X
Vital signs	X									X	X	X
Electrocardiogram[c] (if applicable)	X											
Adverse events				X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
Questionnaires												
See Table 3 for specific questionnaires	X	X								X		X
Study Devices												
Training on Glucagon administration and information on treatment of hypo/hyperglycemia		X										
Remote monitoring initiation/discontinuation				X						X		X
Study device training		X[g]		X[h]								
Dispense/Return BG/Ketone meter, and CGM		X								X[d]		X
QC testing of BG/Ketone meter by site		X										
CGM sensor placement (as needed throughout)		X										
Assess CGM usage and data criteria has been met	X[j]		X									
Dispense/Return Horizon System				X						X[d]		X
Complaints/device deficiencies				X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
Device uploads/Data review				X	X	X	X	X	X	X	X	X

Abbreviations: S=Screening; ST1=Standard Therapy Day One; ST2=Standard Therapy Day Two; HCL=Hybrid Closed-loop; EW=Early Withdrawal; QC=Quality Control Testing; Hotel/Rental House=HRH; UV=Unscheduled Visit

[a]Early withdrawal visit will only be conducted for any subjects that started but did not complete the full study to include standard therapy and the hybrid closed-loop phase.

[b]Unscheduled visits will serve as extra study visits, if needed

[c]Electrocardiogram required for subjects >50 years old or with diabetes duration >20 years

[d]Collect only if subject is not extending their participation into the pivotal study

[e]Documentation only applicable if there are changes from previous assessment

[f]Visits identified as "T/O" can either be conducted in person at the clinical site or over the telephone. Visits identified as "O" can only be conducted in person at the clinical site

[g]Study device training for the CGM, blood glucose and ketone meters

[h]Study device training for the Omnipod Horizon™ System

[i]Subjects deemed exempt from wearing the study CGM for 14-days will be eligible to immediately commence the hybrid closed-loop phase and may skip visit ST2

[j]Assessment of CGM criteria during screening applies to current Dexcom G6 users only

Table 3: Questionnaires

Visit	Age Groups				
	Adult	**Teen (ages 12-18)**	**Caregiver-Teen (ages 12-18)**	**Pediatric (ages 8-11.9)**	**Caregiver-Pediatric (ages 6-11.9)**
Screening	Clarke	Clarke	n/a	n/a	Clarke
Visit 2	WHO-5 EQ-5D T1DDS DTSQs Hypoglycemia Confidence Scale HABS PSQI IDSS (T1) SUS	WHO-5 EQ-5D PAID-Teen Hypoglycemia Confidence Scale PSQI SUS	WHO-5 P-PAID-Teen Hypoglycemia Confidence Scale PSQI DTSQs IDSS (T1)	EQ-5D-Y PAID-Child	WHO-5 P-PAID-Child Hypoglycemia Confidence Scale PSQI DTSQs IDSS (T1) SUS
Final Visit/Early Withdrawal	WHO-5 EQ-5D T1DDS DTSQc Hypoglycemia Confidence Scale HABS PSQI IDSS (T1) SUS INSPIRE-Adult Clarke HF Questionnaire	WHO-5 EQ-5D PAID-Teen Hypoglycemia Confidence Scale PSQI SUS INSPIRE-Youth Clarke HF Questionnaire	WHO-5 P-PAID-Teen Hypoglycemia Confidence Scale PSQI DTSQc IDSS (T1) INSPIRE-Parent	EQ-5D-Y PAID-Child INSPIRE-Youth	WHO-5 P-PAID-Child Hypoglycemia Confidence Scale PSQI DTSQc IDSS (T1) SUS INSPIRE-Parent Clarke HF Questionnaire

6 OBJECTIVES AND ENDPOINTS

6.1 Safety Objective

The safety objective of this study is to evaluate the safety of the Omnipod Horizon™ System in patients with type 1 diabetes.

6.1.1 Primary Safety Endpoint

Proportion of subjects with serious device-related adverse events.

6.1.2 Secondary Safety Endpoints

- Proportion of subjects with severe hypoglycemia during hybrid closed-loop
- Proportion of subjects with diabetic ketoacidosis (DKA) during hybrid closed-loop

6.2 Primary Effectiveness Objective

The primary effectiveness objective of this study is to evaluate the effectiveness of the Omnipod Horizon™ System.

6.2.1 Primary Effectiveness Endpoint

Percentage of time in range (70-180 mg/dL) during hybrid closed-loop compared to standard therapy for:

- Target BG challenge days (approximately hybrid closed-loop days 1-9)
- Non-challenge days (approximately hybrid closed-loop days 10-14)
- Overall (hybrid closed-loop days 1-14)

6.3 Secondary Effectiveness Objective

To evaluate additional glycemic measures of effectiveness of the Omnipod Horizon™ System in patients with type 1 diabetes.

6.3.1 Secondary Effectiveness Endpoints

The secondary objective will be evaluated using the following per subject endpoints:

- Glucose metrics from system CGM during the hybrid closed-loop phase will be compared to the standard therapy phase during the day, overnight, and overall:
    - Mean glucose
    - % of time in range 70-180 mg/dL
    - % of time in range 70-140 mg/dL
    - % of time > 180 mg/dL

- % of time ≥ 250 mg/dL
- % of time ≥ 300 mg/dL
- % of time < 70 mg/dL
- % of time < 54 mg/dL
- Standard deviation
- Coefficient of variation

- GMI based on overall mean glucose
- Percentage of time in hybrid closed-loop as proportion of overall device usage time
- Insulin requirements during the hybrid closed-loop phase will be compared to the standard therapy phase:

    - Total daily insulin (TDI) (units, units/kg)
    - Total daily basal insulin (units, units/kg)
    - Total daily bolus insulin (units, units/kg)

7 SCREENING AND ELIGIBILITY

Potential subjects for this study will include individuals who have been diagnosed with type 1 diabetes for at least 6 months and are appropriate for pump therapy per investigator's assessment. Potential subjects will be selected at each clinical study site and screened accordingly. Clinical study sites will be advised to:

- Recruit subjects using insulin aspart, lispro, and glulisine also known as Humalog, Novolog, Admelog, and Apidra
- Recruit at least 20% of subjects using MDI

Every effort will be made to establish eligibility of the patient prior to enrollment. Only patients who appear to meet all eligibility criteria will be enrolled in the study. Subject eligibility will be confirmed by study staff during a screening visit at the clinical site. Blood draws will be collected as required to demonstrate study eligibility as noted below. Laboratory results within the last 6 months, with the exception of A1C, may also be used if available.

Subjects that have participated in the prepivotal study may be eligible to extend their participation into the pivotal study.

7.1 Visit 1

Visit 1 will be conducted in person at the clinical study site. This visit will assess eligibility and will include:

- Signing of informed consent/assent
- Review of inclusion/exclusion criteria
- Screening assessments performed following Table 2: Schedule of Assessments
- Enrollment

Informed Consent/Assent

Subjects who appear to meet the eligibility criteria will be asked to sign an Informed Consent Form (ICF) approved by each respective Institutional Review Board (IRB) for participation in the study. A parent/guardian must sign the ICF for subjects <18 years of age. Assent will also be obtained from subjects aged <18 years per State requirements. Failure to provide informed consent/assent will render the subject ineligible for the study.

Subjects must also have a signed HIPAA (Health Insurance Portability and Accountability Act) release of protected health information (PHI). The release may be a stand-alone document or part of the informed consent.

After informed consent/assent is obtained, a subject identification number will be issued to uniquely identify each subject. The unique identifier will be used to identify the subject throughout the study and will be used for all source documents and electronic Case Report Forms (eCRFs). Subjects will retain the same subject identification number if they continue in the pivotal study.

Inclusion Criteria

Subjects must meet all of the following criteria in order to be enrolled in the study:

1. Age at time of consent 6-70 years
2. Subjects aged < 18 years must be living with parent/legal guardian
3. Diagnosed with type 1 diabetes for at least 6 months. Diagnosis is based on investigator's clinical judgment
4. Deemed appropriate for pump therapy per investigators assessment taking into account previous history of severe hypoglycemic and hyperglycemic events, and other comorbidities
5. Investigator has confidence that the subject can successfully operate all study devices and is capable of adhering to the protocol
6. Willing to use only Humalog, Novolog, Admelog or Apidra during the study
7. Must be willing to set target glucose between 130-150 mg/dL each for approximately 72-hours on predefined days during the hybrid closed-loop phase
8. Must be willing to extend their participation into the pivotal study if they continue to meet the protocol criteria
9. Willing to wear the system continuously throughout the study
10. A1C <10% at screening visit
11. Must be willing to use the Dexcom App on the Omnipod Horizon PDM as the sole source of Dexcom data (with the exception of the Dexcom Follow App) during the hybrid closed-loop phase
12. Subjects scoring ≥ 4 on the Clarke Questionnaire must agree to have an overnight companion, defined as someone who resides in the same home or building as the study subject and who can be available overnight
13. Able to read and speak English fluently
14. Subject must be in an AT&T covered area
15. Willing and able to sign the Informed Consent Form (ICF) and/or has a parent/guardian willing and able to sign the ICF. Assent will be obtained from

subjects aged < 18 years per State requirements.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. A medical condition, which in the opinion of the investigator, would put the subject at an unacceptable safety risk
2. History of severe hypoglycemia (as defined in Section 11.3.3) in the past 6 months
3. History of Diabetic Ketoacidosis (DKA) (as defined in Section 11.3.4) in the past 6 months, unrelated to an intercurrent illness, infusion set failure or initial diagnosis
4. Diagnosed with sickle cell disease
5. Diagnosed with hemophilia or any other bleeding disorders
6. Plans to receive blood transfusion over the course of the study
7. Currently diagnosed with anorexia nervosa or bulimia
8. Acute or chronic kidney disease (e.g. estimated GFR < 45) or currently on hemodialysis
9. History of adrenal insufficiency
10. Has taken oral or injectable steroids within the past 8 weeks or plans to take oral or injectable steroids during the course of the study
11. Unable to tolerate adhesive tape or has any unresolved skin condition in the area of sensor or pump placement
12. Use of insulin other than U-100 insulin intended for use in the pump
13. Use of non-insulin anti-diabetic medication other than metformin (e.g. GLP1 agonist, SGLT2 inhibitor, DPP-4 inhibitor, pramlintide)
14. Current or known history of coronary artery disease that is not stable with medical management, including unstable angina, or angina that prevents moderate exercise despite medical management, or a history of myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting within the previous 12 months.
15. For subjects > 50 years old or with diabetes duration > 20 years, abnormal electrocardiogram consistent with increased risk of arrhythmia, ischemia, or prolonged QT_c interval (> 450 ms)
16. Thyroid Stimulating Hormone (TSH) is outside of normal range with clinical signs of hypothyroidism or hyperthyroidism
17. Pregnant or lactating, or is a woman of childbearing potential and not on acceptable form of birth control (acceptable includes abstinence, condoms, oral/injectable contraceptives, IUD or implant)
18. Participation in another clinical study using an investigational drug or device within the preceding 30-days or intends to participate during the study period
19. Unable to follow clinical protocol for the duration of the study or is otherwise deemed unacceptable to participate in the study per the investigator's clinical judgment

Screening Assessments

Subjects who have signed the informed consent and appear to meet the eligibility criteria will continue to the screening assessments which will be performed at the clinical study site.

Screening assessments must be completed within 30-days prior to the start date of the hybrid closed-loop phase (assessments do not need to be completed on the same day) and include the following:

- Medical history (including prior and current medical conditions and surgical history)
- Demographics (age, gender, race)
- A1C*
- Thyroid Stimulating Hormone (TSH) level (local laboratory)
- Creatinine level (local laboratory)
- Pregnancy test for women of childbearing potential
- Review of concomitant medications
- Height
- Weight
- Assessment of vital signs
- Electrocardiogram (if applicable, see exclusion criteria 15)
- Questionnaire (Table 3: Questionnaires):
  - Clarke
    - Used to assess impaired awareness of hypoglycemia
- For Dexcom G6 users, assessment of whether subjects have met the CGM usage and data criteria to participate in an abbreviated standard therapy phase (Visit 2 only) per Table 2: Schedule of Assessments
  - At least 80% CGM use (11.2-days) during any consecutive 14-days in the past 30-days and
  - ≥ 2,016 CGM values during the 14-days

*Clinical sites will send the blood specimens for A1C to a NGSP (National Glycohemoglobin Standardization Program) certified central laboratory. A point of care (POC) A1C may be used to determine eligibility.

The Clarke Questionnaire will be administered during the screening visit. Subjects scoring ≥ 4 on the Clarke Questionnaire will require an overnight companion during the hybrid closed-loop phase A companion is defined as someone who resides in the same home or building as the study subject and who can be available overnight.

Enrollment

Subjects who meet all eligibility criteria and have completed all screening assessments will continue to enrollment. A subject is enrolled in the study upon placement of the first study CGM. Subjects that do not meet the eligibility criteria will not continue in the study and will be considered screen failures.

If for any reason a subject is no longer eligible for the study after the standard therapy phase has commenced but prior to the commencement of the hybrid closed-loop phase, the subject will not continue in the prepivotal study. No additional study assessments will be required. The reason for study exit will be clearly documented.

8 STANDARD THERAPY - PHASE 1

The standard therapy phase will commence after all standard therapy assessments are completed per **Visit 2** – see Table 2: Schedule of Assessments.

During the standard therapy phase, subjects will be asked to perform the following:

- Manage their diabetes at home per their usual routine
- Administer meal boluses per their usual dosing routine
- Change their sensor if a sensor fails, or as needed
- Calibrate their CGM, if required, per the manufacturer's instructions
- Monitor their capillary blood glucose (BG) per usual routine
- Give meal boluses. The timing of the bolus delivery will be per each subject's typical dosing routine.

Extending standard therapy past 14-days will not constitute a protocol deviation unless standard therapy extends past 30-days. If subjects extend beyond the 14-days, the most recent 14-days of data will be used in the endpoint analysis if the data meets the criteria defined for CGM use and data availability. If a subject enrolls into the pivotal study, data collected in the standard therapy phase will be used in the endpoint analyses for the pivotal study as the subject will not be required to repeat the standard therapy phase as part of the pivotal study.

The standard therapy phase will be customized depending on the following subject profile:

- Current Dexcom G6 users
- Non-G6 users
- Pump Naïve users

Current Dexcom G6 Users

Current Dexcom G6 users will be required to participate in the assessments required as part of standard therapy but may be exempt from wearing the study CGM for 14-days if the following criteria are met:

- Willing to provide 14-days of CGM data from the past 30-days
- Meet the success criteria of 80% CGM use during any consecutive 14-days in the past 30-days
- Must have ≥ 2,016 CGM values during the 14-days

If exemption criteria are not met, subjects may choose to continue to collect data until they meet the criteria or will be required to participate in the entire 14-day standard therapy phase consistent with the requirements for non-G6 users.

Subjects deemed exempt from wearing the study CGM for 14-days will be eligible to immediately commence the hybrid closed-loop phase.

Non-G6 Users

All non-G6 users will be required to participate in the entire 14-day standard therapy phase. At the commencement of the standard therapy phase, subjects will be dispensed a CGM receiver that will be blinded and all user settable CGM alerts will be turned off. The device will record continuous glucose information over the 14-day period.

Pump Naïve Users

Subjects who are naïve to pump therapy will have the opportunity to participate in a saline trial during the standard therapy phase. A saline trial consists of wearing a cleared Omnipod® DASH System with the Pod filled with saline to simulate pump therapy. This would enable subjects to familiarize themselves with the basic concepts of basal and bolus insulin delivery as well as provide the experience of wearing an on-body device prior to their participation in the hybrid closed-loop phase, if they choose to do so. This is optional and not required.

8.1 Visit 2

Visit 2 represents the commencement of the standard therapy phase. All scheduled assessments will be performed according to Table 2: Schedule of Assessments. This visit will include:

- Review of concomitant medications
- Average total daily insulin (approximately over the past 7 days)
- Average total daily basal insulin (approximately over the past 7 days)
- Average total daily bolus insulin (approximately over the past 7 days)
- Review pump settings/MDI dosing
- Completion of questionnaires (see Table 3: Questionnaires for specific requirements by age group):
  - WHO-5
    - Used to measure current mental well-being
  - EQ-5D
    - Used to measure quality of life
  - T1DDS
    - Used to measure four critical dimensions of distress
  - DTSQs
    - Used to measure satisfaction with diabetes treatment regimens
  - Hypoglycemia Confidence Scale
    - Used to measure hypoglycemia unawareness, hypoglycemia frequency, severity and impact
  - HABS
    - Used to measure critical dimensions of hypoglycemia related concerns and confidence
  - PSQI
    - Used to measure sleep disturbance and usual sleep habits
  - IDSS (T1)
    - Used to measure patient satisfaction with their devices and impact on quality of life
  - SUS

    - Used to measure usability of a system
  - PAID-(Teen, Child)
    - Measures diabetes-related burden
- Training on Glucagon administration and information on treatment of hypo/hyperglycemia
  - All subjects are required to have access to glucagon and receive training on how to deliver the medication
- Study device training per manufacturer's instructions (CGM - blinded, BG, and ketone meters)
- Dispensing of CGM (blinded for non-G6 users), BG, and ketone meter
- QC testing of BG and ketone meter
  - Must pass as least one level of quality control testing prior to dispensing
- CGM sensor placement (if applicable)
  - Approved anatomical locations for CGM sensor placement will be reinforced as well as the importance of using approved locations

During this visit, subjects will be dispensed the following supplies:

- Dexcom transmitter
- Dexcom receiver
- Dexcom sensors
- Contour® Next One blood glucose meter
- Contour® Next One blood glucose meter test strips
- Contour® Next One blood glucose meter control solution
- Lancets
- Precision Xtra blood ketone meter
- Precision Xtra blood ketone meter test strips
- Precision Xtra blood ketone meter control solution

Subjects will be provided, by the site, information regarding treatment of hypoglycemia and hyperglycemia including sick day management and emergency management of severe hypoglycemia and diabetic ketoacidosis. Subjects will be given contact information for study personnel and product support.

If a subject is on MDI, the investigator will advise the subject on the treatment regimen to reduce insulin depending on the insulin action profile of injected doses prior to the commencement of the hybrid closed-loop phase. MDI subjects will be required to keep a log to record daily doses of insulin during the standard therapy phase.

8.2 Visit 3

Visit 3 will be conducted in person at the clinical study site one (1) day prior to the start of the hybrid closed-loop phase. All scheduled assessments will be performed according to Table 2: Schedule of Assessments. This visit will include assessment of whether subjects have met the CGM usage and data criteria.

Prior to the commencement of the hybrid closed-loop phase, subjects must meet the following criteria:

- At least 80% CGM use (11.2-days) during any consecutive 14-days in the past 30-days and
- ≥ 2,016 CGM values during the 14-days

If the CGM criteria is not met, the standard therapy phase may be extended, per investigator discretion, or the subject may be withdrawn from the study. At the conclusion of the standard therapy phase, if the investigator determines that there have been no safety concerns, the subject will continue to the hybrid closed-loop phase. If the investigator determines that it is unsafe for the subject to continue into the hybrid closed-loop phase, the subject will not be allowed to continue in the second phase of the study, and the reason for study exit will be documented.

9 HYBRID CLOSED-LOOP - PHASE 2

The hybrid closed-loop phase will commence at **Visit 4** upon the conclusion of the standard therapy phase and after all assessments are performed according to Table 2: Schedule of Assessments.

During the hybrid closed-loop phase, subjects will be asked to do the following:

- Adjust pump and CGM parameters to optimize their insulin therapy in collaboration with the recommendations from the clinical study staff
- Follow their pre-exercise management such as insulin reduction for meal boluses, consumption of snacks, or adjusting their insulin delivery settings
- Treat themselves per their usual routine if they become hypoglycemic or hyperglycemic or have symptoms of either at any time during the study
- Consume meals and snacks of their own choosing. Subjects will be encouraged to estimate the grams of carbohydrates for each meal or snack per their usual routine. The estimate should be entered into the meal bolus calculator.
- Administer meal boluses per their usual dosing routine
- Participate in target BG challenges as specified
- Change their CGM per manufacturer's instructions or sooner if necessary
- Change the Pod at least once every 72 hours
- Complete questionnaires (Table 3: Questionnaires)

Subjects will have scheduled follow-up visits according to Table 2: Schedule of Assessments and complete questionnaires according to Table 3: Questionnaires. Visits will be conducted either in the hotel/rental house environment, in person at the clinical study site or over the telephone. Subjects may also choose to use email or text as a substitute for their scheduled telephone visit.

The duration of the hybrid closed-loop phase will last 14-days.

9.1 Target BG Challenges

All subjects will take part in the target blood glucose (BG) challenges (Table 4: Target BG Challenges). Following the commencement of the hybrid closed-loop phase, subjects will be required to set their target BG to 130 mg/dL for approximately 72 hours for days 1-3, 140 mg/dL for days 4-6, and 150 mg/dL for

day 7-9 according to Table 4: Target BG Challenges. Upon completion of the 3 target BG challenges (130 mg/dL, 140 mg/dL, and 150 mg/dL), subjects may choose their desired target BG between 110-150 mg/dL for the remainder of the 5-days of the hybrid closed-loop phase.

Table 4: Target BG Challenges

	Days									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10-14**
Target BG	130 mg/dL			140 mg/dL			150 mg/dL			110-150 mg/dL

These settings will be reviewed by clinical staff at scheduled visits and through the remote monitoring system to ensure the requirements are met. If the requirements have not been met, clinical staff may request the subject adjust their setpoint until the requirements are met unless there are safety concerns.

9.2 Hotel/Rental House Environment

The subset of subjects participating in the hotel/rental house environment will be encouraged to eat meals of their own choosing, unrestricted in carbohydrates, and to engage in moderate intensity exercise for a minimum of 1 hour per day.

Moderate intensity exercise is defined using the CDC guidelines[12]:

Table 5: CDC Guidelines[12] for Moderate Intensity Exercise

	Children and Adolescents	**Adults**	**Older Adults**
Moderate Intensity Activities	Brisk walking Bicycling Hiking Catching/throwing	Walking/jogging 2.5 miles per hour Bicycling Aerobics	Walking/hiking Jogging Bicycling Aerobics

9.3 Visit 4

Visit 4 represents the commencement of the hybrid closed-loop phase. For subjects in Group 1, this visit will be conducted at the hotel/rental house. For subjects in Group 2 this visit will be conducted at the clinical study site. All scheduled assessments will be performed according to Table 2: Schedule of Assessments. This visit will include:

- Pregnancy test for women of childbearing potential
- Review of concomitant medications
- Average total daily insulin (approximately over the past 7 days)
- Average total daily basal insulin (approximately over the past 7 days)
- Average total daily bolus insulin (approximately over the past 7 days)

- Pump settings/MDI dosing
- Assessment of AEs
- Remote monitoring initiation
- Omnipod Horizon™ System device training conducted by trained clinical site staff
  - Subjects will be trained on operating Omnipod Horizon™ in both Manual and Automated Modes.
  - This will include first time device set-up with entry of basal profile, bolus calculator settings with insulin:carbohydrate ratio, target glucose and correction factor.
  - The Pod will be filled with the subject's own U-100 rapid-acting insulin and placed on body. Subjects will also be trained on use of Dexcom G6 CGM, regardless of previous experience, setting up low (recommended to be 70 mg/dL or higher) and high glucose alerts (recommended to be 300 mg/dL or lower) and entering transmitter serial number into the Horizon App.
  - In addition, Omnipod Horizon™ has a novel bolus calculator feature that incorporates both the CGM value and trend into the suggested bolus amount. In general, if the CGM values are trending up or down, the calculator will add or subtract insulin from the suggested bolus amount to help keep BGs within target range.
- Dispense Omnipod Horizon™ System
- Complaints/device deficiencies for CGM, BG and ketone meter
- Device uploads for CGM, BG and ketone meter
- Data review by clinician
- Removal of the subject's personal insulin pump (if applicable)
  - Prior to commencing hybrid closed-loop, the subject's personal insulin pump will be removed, if applicable. Investigators may use the Insulet-provided Patient Therapy Order Form (PTOF) as a guide to transition subjects from MDI to pump therapy (Appendix).

At the conclusion of the training and completion of assessments, each subject will initiate their treatment marking their commencement of the hybrid closed-loop phase.

9.4 Visit 5

Visit 5 will be conducted in the hotel/rental house for subjects in Group 1, and over the telephone for subjects in Group 2. All scheduled assessments will be performed according to Table 2: Schedule of Assessments. This visit will include:

- Review of concomitant medications
- Assessment of AEs since last visit
- Complaints/device deficiencies such as occlusion alarms and system hazard alarms since last visit
- Device uploads for BG and ketone meter
- Data review by clinician

9.5 Visit 6

Visit 6 will be conducted in the hotel/rental house for subjects in Group 1, and over the telephone for subjects in Group 2. All scheduled assessments will be performed according to Table 2: Schedule of Assessments. This visit will include:

- Review of concomitant medications
- Assessments of AEs since last visit
- Complaints/device deficiencies such as occlusion alarms and system hazard alarms since last visit
- Device uploads for BG and ketone meter
- Data review by clinician

Subjects in Group 1 will be discharged home on study day 3 (Visit 6).

During each visit, subjects will be reminded to set the appropriate target BG on the appropriate day as applicable.

9.6 Visits 7, 8 and 9

Visits 7 through Visit 9 will be conducted over the telephone. All scheduled assessments will be performed according to Table 2: Schedule of Assessments. These visits will include:

- Review of concomitant medications
- Assessment of AEs since last visit
- Complaints/device deficiencies such as occlusion alarms and system hazard alarms since last visit
- Device uploads for BG and ketone meter (if visit is conducted at the clinical study site)
- Data review by clinician
- Ensuring at least 72 hours of data collected at designated target BG levels per Table 4 – Target BG Challenges.

During each visit, subjects will be reminded to set the appropriate target BG on the appropriate day as applicable.

9.7 Visit 10 (End of Study)

Visit 10 will be conducted in person at the clinical study site. All scheduled assessments will be performed according to Table 2: Schedule of Assessments. If the subject has not experienced any serious adverse events, and continue to meet eligibility requirements, the subject will be deemed eligible to participate in the pivotal study. This visit will conclude their participation in the prepivotal study. This visit will include:

- Review of concomitant medications
- Height
- Weight

- Assessment of vital signs
- Assessment of AEs since last visit
- Completion of questionnaires (see Table 3: Questionnaires for specific requirements by age group) :
  - WHO-5
  - EQ-5D
  - T1DDS
  - DTSQc
  - Hypoglycemia Confidence Scale
  - HABS
  - PSQI
  - IDSS (T1)
  - SUS
  - PAID-(Teen, Child)
  - INSPIRE-(Adult, Youth, Parent)
    - Used to measure a caregiver's experience of the support they receive
  - Clarke
  - Human Factors (HF) Questionnaire
    - Measures trust in the Horizon™ System
- Discontinuation of remote monitoring
- Return study devices (Omnipod Horizon™ System, CGM, BG and ketone meters if not extending into pivotal study)
- Complaints/device deficiencies such as occlusion alarms and system hazard alarms since last visit
- Device uploads for BG and ketone meter
- Data review by clinician

For subjects not extending their participation into the pivotal study, they will return their study devices to the site and their participation in the study will end.

9.8 Unscheduled Visits

Aside from scheduled visits, subjects may require an unscheduled visit either by telephone or in person at the clinical study site. All scheduled assessments will be performed according to Table 2: Schedule of Assessments. This visit will include, at a minimum:

- Review of concomitant medications
- Assessment of vital signs (if visit is conducted at the clinical study site)
- Assessment of AEs since last visit
- Complaints/device deficiencies such as occlusion alarms and system hazard alarms since last visit
- Device uploads for BG and ketone meter (if visit is conducted at the clinical study site)
- Data review by clinician

Additional assessments may be warranted at the discretion of the investigator.

Instructions will be given to subjects on how to contact clinical study staff 24 hours per day to report any study related problems. Subjects will be encouraged to call the clinical study site at any time with any concerns.

9.9 Early Withdrawal

Any subject may withdraw early from the study at any time for any reason. Upon withdrawal, assessments will be performed following the Table 2: Schedule of Assessments. The investigator may also terminate a subject's participation in the study if it is in the best interest of the subject or if the Sponsor or local regulatory agency (e.g., FDA) terminates the study.

The Early Withdrawal visit will include:

- Review of concomitant medications
- Height
- Weight
- Assessment of vital signs
- Assessment of AEs since last visit
- Completion of questionnaires (see Table 3: Questionnaires for specific requirements by age group):
  - WHO-5
  - EQ-5D
  - T1DDS
  - DTSQc
  - Hypoglycemia Confidence Scale
  - HABS
  - PSQI
  - IDSS (T1)
  - SUS
  - PAID-(Teen, Child)
  - INSPIRE-(Adult, Youth, Parent)
  - Clarke
  - Human Factors (HF) Questionnaire
- Discontinuation of remote monitoring
- Return all study devices
- Complaints/device deficiencies such as occlusion alarms and system hazard alarms since last visit
- Device uploads for BG and ketone meter
- Data review by clinician

The reasons for withdrawal will be recorded, and the subject's participation in the study will end.

In the event of a subject's death during the study, the subject's participation will be considered terminated and the date of death will be used as the date of study exit.

9.10 Lost to Follow-up

Every effort will be made to contact a subject in the event of a missed scheduled visit. A subject will be considered lost to follow-up if they are inaccessible by two or more different methods of contact and fail to show up for two scheduled visits. The site will document each attempt made to contact the subject and specify the reason for early withdrawal as lost to follow-up.

10 SPONSOR REPRESENTATIVES

One or more representatives of the Sponsor may be present at the hybrid closed-loop clinical study site visits under supervision of the investigator.

11 SAFETY

11.1 Types of Known Risks and Benefits

There are known risks and benefits. Most of the risks are not unique to the study and are typical for patients using insulin pumps, CGM, and BG meters.

The known risks are as follows:

- Hypoglycemia and/or hyperglycemia as a result of change in diet, activity, diabetes management or insulin regimen during the study.
- Hypoglycemia, hyperglycemia, diabetic ketoacidosis, seizure, coma or death related to insulin administration, pump use or misuse, or Horizon™ System use or misuse.
- Use of the Pod (Omnipod® tubeless, insulin delivery pump) - Because the Pod uses only rapid-acting insulin, users are at increased risk for developing hyperglycemia if insulin delivery is interrupted. If it is untreated, prolonged hyperglycemia can quickly lead to diabetic ketoacidosis (DKA). DKA can cause symptoms such as breathing difficulties, shock, coma, or death. Further, occlusions can interrupt insulin delivery and lead to hyperglycemia or DKA. Other potential risks associated with using the Pod are:
    - Anaphylaxis (allergic shock)
    - Bruising at the Pod site
    - Bleeding at the Pod site
    - Erythema (redness at the Pod site)
    - Excoriation (raw skin at Pod site)
    - Pruritus (itching)
    - Induration (hardening of the skin at the Pod site)
    - Infection (can include heat, redness, swelling, pain, and drainage)
    - Inflammation (redness, swelling)
    - Skin reaction to adhesive at the Pod site
    - Papule (small, solid raised area on the skin similar to a pimple)
    - Pain or discomfort

- Ulceration (skin sores)
- Vesicles (blisters)

- Use of the CGM - risk of bruising, infection, pain and/or bleeding at the site of insertion, and skin site reaction to adhesive.

- On rare occasions, the CGM sensor may break and leave a small portion of the sensor under the skin that may cause redness, swelling, or pain at the insertion site, and may require surgical removal.

- Blood sampling with fingerstick - minor discomfort and risk of infection at site of fingerstick.

There are several potential benefits from this study. The Omnipod Horizon™ System is designed to provide automated glucose control. The system is expected to reduce hypoglycemia without incurring an unacceptable increase in hyperglycemia and mean glucose. The system is also expected to reduce the extent and magnitude of hyperglycemia associated with meals. The Omnipod Horizon™ System uses a control-to-target strategy that attempts to achieve and maintain a set target glucose level.

11.2 Hypoglycemia/Hyperglycemia

Subjects will be asked to treat per their usual routine if they suspect either hypoglycemia or hyperglycemia, either by confirmation of hypoglycemia with a fingerstick BG, symptoms, or perceived risk.

Subjects will be encouraged to manage their hyperglycemia per their usual routine. This includes checking for ketones using the study-approved ketone meter and administering a correction bolus if needed.

In the event of unexplained hyperglycemia, where the CGM is >300mg/dL for 1h or >250 mg/dL for 2h, blood glucose (measured with BG meter) and ketones should be checked. If BG is ≥300 mg/dL and ketones are >1.0 mmol/L, an occlusion or dislodged cannula should be suspected. The Pod should be removed, and the subject will be instructed to replace the Pod. Subjects should contact the clinical site for further instructions to determine whether an additional injection of insulin is required. This prolonged hyperglycemic event, defined as meter BG ≥300 mg/dL and ketones >1.0 mmol/L, will be recorded as an adverse event and cause may be attributed to suspected occlusion if the cannula is in situ or dislodged cannula if it has been pulled out. Pods will be requested to be returned to Insulet for analysis. An Adverse Event form will be completed per the Reportable Adverse Events section below.

11.3 Adverse Events

11.3.1 Definitions

Adverse Event (AE): is defined as any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1: This includes events related to the investigational medical device or the comparator.[28]

NOTE 2: This definition includes events related to the procedures involved (any procedure in the clinical investigation plan).[28]

Serious Adverse Event (SAE): Any untoward medical occurrence that:

- Led to death
- Led to serious deterioration in the health of the subject, that either resulted in:
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - in-patient or prolonged hospitalization, or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

  NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.[28]

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect 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 investigational plan 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 participants. [28]

Adverse Device Effect (ADE): An adverse device effect is an adverse event related to the use of an investigational medical device. [28]

NOTE 1: This definition includes any adverse event resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.[28]

NOTE 2: This definition includes any event resulting from user error or from intentional misuse of the investigational medical device.[28]

Serious Adverse Device Effect (SADE): A serious adverse device effect is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. [28]

Device Deficiency (DD): A device deficiency is defined as a device related complaint or malfunction or any inadequacy of a device with respect to its identity, quality, durability, reliability, safety or performance and includes misuse or use errors and inadequate labeling. A device deficiency is something that happens to a device or is related to device performance, whereas an adverse event happens to a participant. A device deficiency may occur independently from an AE, or

along with an AE. An AE may occur without a device deficiency or there may be an AE related to a device deficiency.

Note: for reporting purposes, sites will not be asked to distinguish between device complaints and malfunctions.

For any event where there is suspicion that the study device is involved, the Sponsor will request that the investigator return the device for evaluation.

All device complaints or malfunctions involving any investigational component of the Omnipod Horizon™ System used in the study will be reported to the Sponsor within 5 business days of knowledge of the deficiency and documented on an appropriate eCRF. All study product associated with a reported device deficiency (PDM, Pod, and CGM) should be retained at the clinical site and returned to the Sponsor or CGM manufacturer for investigation and analysis.

11.3.2 Reportable Adverse Events

Adverse events will be assessed on an ongoing basis throughout the study. Adverse event reporting will begin at the start time of the standard therapy phase (i.e., insertion of the CGM sensor) and continue through the hybrid closed-loop phase until the subject's participation has ended. All adverse events must be followed until resolution, or until the AE has stabilized, or until the study has been completed.

Pre-existing medical conditions or symptoms observed prior to the start time of the standard therapy phase will not be recorded as an AE and should be collected in the subject's medical history. In the event there is a change (i.e., worsening) in the pre-existing medical condition or symptoms after enrollment meeting the criteria of a reportable adverse event, then an AE must be reported.

For this protocol, a reportable adverse event includes any untoward medical occurrence that meets one of the following criteria:

1. An SAE
2. An ADE unless excluded from reporting in Hypoglycemic Events and Hyperglycemic/Ketotic Events sections below
3. An AE occurring in association with a study procedure
4. An AE not related to a study device issue which leads to temporary or permanent discontinuation of the study device
5. An AE that affects the participant's ability to complete any study procedures
6. An AE for which a visit is made to a hospital emergency department
7. Hypoglycemic Events as defined below
8. Hyperglycemic/Ketotic Events as defined below.

Skin reactions from sensor or pod placement are only reportable if severe and/or required treatment.

For the purpose of this protocol, mild symptoms of hypoglycemia and hyperglycemia (i.e., clinically non-significant) or blood glucose values out of the normal range (whether or not they resulted in delayed meals or correction boluses) will not be reported as AEs unless determined to meet the reportable criteria in the Hypoglycemic Events and Hyperglycemic/Ketotic Events sections below.

All reportable AEs—whether volunteered by the participant, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means—will be reported on an AE eCRF.

11.3.3 Hypoglycemic Events

Hypoglycemia is only reportable as an adverse event when one of the following criteria is met:

- Severe Hypoglycemia: The event required assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions.[25] This means that the participant was impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/her needs, was incoherent, disoriented, and/or combative, or experienced seizure or loss of consciousness. These episodes may be associated with sufficient neuroglycopenia to induce seizure or loss of consciousness. If plasma glucose measurements are not available during such an event, 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.
- Hypoglycemia resulting in an SAE that may not otherwise meet the definition of Severe Hypoglycemia defined above.

When a hypoglycemic event meets the above reporting requirements, an Adverse Event Form should be completed. A severe hypoglycemia event should be considered a serious adverse event and follow the SAE reporting requirements.

11.3.4 Hyperglycemic/Ketotic Events

Hyperglycemia is only reportable as an adverse event when any one of the following criteria is met:

- The event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT)[24] and described below
- Evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis, or the participant contacted the site and received guidance on how to manage the hyperglycemia/ketosis
- Prolonged hyperglycemia: defined as meter BG ≥300 mg/dL and ketones >1.0 mmol/L
- Hyperglycemia resulting in an SAE that may not otherwise meet the above criteria

Hyperglycemic events are classified as DKA[24] if all of the following are present:

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones >1.5 mmol/L or large/moderate urine ketones;
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15; and
- Treatment provided in a health care facility

When a hyperglycemia/ketotic event meets the above reporting requirements, Adverse Event Form should be completed.

Events meeting DKA criteria should be considered a serious adverse event and follow the SAE reporting requirements. Hyperglycemia events not meeting criteria for DKA generally will not be considered as serious adverse events unless one of the SAE criteria above is met.

11.3.5 Relationship of Adverse Event to Investigational Device

The investigator will be responsible for making a determination on the causal relationship of the AE. Specifically, the investigator will report whether the AE was related to study procedures and/or related to the investigational device.

To ensure consistency of adverse event causality assessments, investigators should apply the following general guideline when determining whether an adverse event is related:

The causal relationship to the study procedures and the investigational device for each adverse event will be rated as follows:

- Unrelated: The event is not related to the procedures or the investigational device.

- Possibly Related: The temporal sequence is such that the relationship is not unlikely or there is no contradicting evidence that can reasonably explain the subject's condition. There is a possibility of any relation between the event and the procedures or the investigational device.

- Related: The temporal sequence is relevant or the event abates upon completion of the procedure/ investigational device, or the event cannot be reasonably explained by the subject's condition or comorbidities. The event is related or most likely associated with the procedures or the investigational device.

11.3.6 Severity (Intensity) of Adverse Events

The severity (intensity) of an adverse event will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. A severity assessment is a clinical determination of the intensity of an event. Thus, a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

- MILD: Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.

- MODERATE: Usually causes a low level of inconvenience, discomfort or concern to the participant and may interfere with daily activities but is usually ameliorated by simple therapeutic measures and participant is able to continue in study.
- SEVERE: Interrupts a participant's usual daily activities, causes severe discomfort, may cause discontinuation of study device, and generally requires systemic drug therapy or other treatment.

11.3.7 Outcome of Adverse Events

The outcome of each reportable adverse event will be classified by the investigator as follows:

- RECOVERED/RESOLVED - The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RECOVERED/RESOLVED WITH SEQUELAE - The event persisted and had stabilized without further anticipated change in the event status. Record the AE/SAE stop date.
- FATAL - A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.
- NOT RECOVERED/NOT RESOLVED (ONGOING) - An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.
  - An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE or until participant completes the study.
  - The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.
- UNKNOWN - An unknown outcome is defined as an inability to access the participant or the participant's records to determine the outcome (for example, a participant that was lost to follow-up).

If any UADEs are ongoing when a participant completes the study (or withdraws), the subject will continue to be followed until the event resolves or has no prospect of improvement or change, even after the participant has completed all applicable study visits/contacts, unless that subject has withdrawn their consent. For all other reportable adverse events, data collection will end at the time the participant completes the study. Note: Participants should continue to receive appropriate medical care for an adverse event after their participation in the study ends.

11.4 Reportable Device Issues

Device complaints and malfunctions will be reported except in the following circumstances. These occurrences are expected and will not be reported on a Device Deficiency Form:

- CGM sensor or Pod lasting fewer days than expected per manufacturer
- CGM tape or Pod adherence issues

- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- Intermittent device component disconnections/communication failures not requiring system replacement or workaround/resolution not specified in user guide/manual.
- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting

11.5 Timing of Event Reporting

SAEs possibly related or related to a study device or study procedures and UADEs must be reported to the Sponsor/CRO within 2 business days of the site becoming aware of the event. This can occur via phone or email, or by completion of the AE eCRF. If the form is not initially completed, it should be completed as soon as possible after there is sufficient information to evaluate the event. All other reportable AEs should be submitted by completion of the AE eCRF within 5 business days of the site becoming aware of the event.

Each principal investigator is responsible for reporting adverse events required by this protocol and abiding by any other reporting requirements specific to his/her Institutional Review Board or Ethics Committee.

Upon receipt of a UADE report, the Sponsor will investigate the UADE and if indicated, report the results of the investigation to all participating investigators, overseeing IRBs, and the FDA within 10 business days of the Sponsor becoming aware of the UADE per 21CFR 812.46(b). Copies of the associated reports and correspondence with the investigators, regulatory authorities, and Sponsor must be retained with study records.

The Medical Monitor must notify the DSMB of any UADEs and determine if the UADE presents an unreasonable risk to participants. If so, the Sponsor must ensure that all investigations, or parts of investigations presenting that risk, are terminated as soon as possible but no later than 5 working days after the Medical Monitor makes this determination and no later than 15 working days after first receipt notice of the UADE.

Device deficiencies will be handled by the Sponsor or designee as described below. In the case of a Dexcom CGM transmitter or sensor device malfunction, information should be forwarded to Dexcom by the site personnel, to be handled by Dexcom's complaint management system.

If the subject is hospitalized because of or during the course of an SAE, then a copy of the hospital discharge summary must be requested for inclusion with the SAE documentation. In case of death, the investigator must make every effort to obtain a copy of the death certificate to submit to the Sponsor. When submitting copies of documentation, all subject identifying information must be redacted and only the unique subject number will be used to label the forms for identification purposes.

For any event where there is suspicion that the study device is involved, the investigator will return the device for evaluation when possible.

11.6 Safety Oversight

The study Medical Monitor will review all adverse events that are reported during the study. SAEs will typically be reviewed within 24-hours of reporting. Other AEs will typically be reviewed approximately weekly.

A Data and Safety Monitoring Board (DSMB) will be informed of all cases of severe hypoglycemia and diabetic ketoacidosis irrespective of device relationship and all UADEs during the study and will review compiled safety data at periodic intervals. The DSMB also will be informed of any SADEs and ADEs not meeting criteria for a UADE if the Medical Monitor requests the DSMB review. The DSMB can request modifications to the study protocol or suspension or outright stoppage of the study if deemed necessary based on the totality of safety data available. Details regarding DSMB review will be documented in a separate DSMB Charter.

11.7 Stopping Criteria

11.7.1 Participant Discontinuation of Study Participation

In the case of a UADE, use of the study device will be suspended while the problem is diagnosed. After assessment of the problem and any correction, use of the study device will not be restarted until approval is received from the IRB, DSMB, and FDA.

Use of the study device by a participant will be discontinued if any of the following occur:

- The investigator believes it is unsafe for the participant to continue on the intervention. This could be due to the development of a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety.
- The participant requests that the treatment be stopped
- Participant pregnancy
- Two distinct episodes of DKA as defined above
- Two distinct severe hypoglycemia events as defined above
- One episode of DKA and one severe hypoglycemia event as defined above

An additional requirement for continued study device use following a single DKA or severe hypoglycemia event will be that (1) the site investigator believes that the event is explainable, unlikely to recur, and that it is safe for the participant to continue to use the system and (2) the Medical Monitor concurs. If the Medical Monitor determines that the occurrence of the event indicates that it is not safe for the participant to continue to use the system, use will be discontinued, and the subject will be withdrawn from the study.

11.7.2 Criteria for Suspending or Stopping Overall Study

Stopping criteria for the entire study will be determined by an independent DSMB, who will assess the specific event rates for DKA and severe hypoglycemia from

the study at specific timepoints relative to published rates from large, population-based datasets.

In consideration of adverse events rates occurring in this proposed the rates will be assessed relative to published rates from Foster et. al.[10] and Miller et. al.[26] to determine whether severe hypoglycemia or diabetic ketoacidosis are within expected rates during this study. **Table 6: T1D Exchange Rates of Severe Hypoglycemia and Diabetic Ketoacidosis[10,26]** provides a summary of these published rates.

Table 6: T1D Exchange Rates of Severe Hypoglycemia and Diabetic Ketoacidosis[10,26]

Adverse Event	Frequency of subjects to experience ≥ 1 event extrapolated from T1DX registry 2016-2018, 2013-2014
Severe hypoglycemia (loss of consciousness or seizure)	4-5% < 18 years 7% ≥ 18 years
Diabetic ketoacidosis (overnight hospitalization)	3-4% < 18 years 2-3% ≥ 18 years

For unanticipated adverse device effects (UADEs), the DSMB will determine whether the study should proceed or not based upon risk of additional serious adverse events and the underlying root cause analysis of the UADE.

Study activities could be similarly suspended if the manufacturer of any component of the investigational study device requires stoppage of device use for safety reasons (e.g. product recall).

The affected study activities may resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension.

The study Medical Monitor will review all adverse events that are reported during the study, and the DSMB will review all cases of severe hypoglycemia, DKA and UADEs as well as compiled safety data at periodic intervals. The Medical Monitor and/or DSMB may recommend suspension of study activities or stoppage of the study to the Sponsor if deemed necessary based on the totality of safety data available.

11.8 Data Safety Monitoring Board (DSMB)

The DSMB will be established prior to the first enrollment and consist, at a minimum, of two physicians and one statistician independent from the Sponsor and study. The physicians will have relevant therapeutic and medical expertise. The DSMB will determine the stopping criteria for the entire study and review Severe Hypoglycemia and DKA as well as compiled safety data at periodic intervals to determine if the stopping rules apply. Compiled safety data may include listings of protocol deviations, device deficiencies, subject terminations, and subject withdrawals. In addition, the DSMB members will be notified upon the occurrence of any UADEs to determine whether the study should proceed or not

based upon risk and may request an ad hoc meeting to discuss. At minimum, the DSMB will conduct reviews after 16 subjects from the prepivotal study have completed a minimum of 10-days of hybrid closed-loop and at the conclusion of the prepivotal study. Further reviews will occur during the pivotal study, as defined, in the pivotal study protocol. Additional reviews during the study may be conducted at any time based on the request of the DSMB, Sponsor or Medical Monitor. At the conclusion of each meeting, the DSMB will make a recommendation to the Sponsor concerning the continuation, modification, and/or termination, of the study and/or a statement regarding their overall assessment of device safety and continuation of the pivotal study. The final decision regarding the continuation, modification or termination of the study will reside with the Sponsor. Responsibilities, qualifications, membership and committee procedures, including the final stopping rules, will be outlined in the DSMB Charter.

11.9 Medical Monitor

An independent Medical Monitor will be responsible for individual and timely review of adverse events as defined below. The Medical Monitor will be a physician with relevant therapeutic and medical expertise that is not participating as an Investigator in the study and does not have a financial, scientific, or other conflict of interest with the clinical study.

Specific responsibilities of the Medical Monitor include:

- Review of all adverse events reported during the study
- Review all serious study procedure-related and/or investigational device-related adverse events to determine if the adverse event warrants consideration as a UADE and facilitate the reporting of UADEs if applicable
- Adjudicate the following(a) all SAEs; (b) any events of Diabetic Ketoacidosis or Severe Hypoglycemia; (c) all AEs reported by the site as related or possibly related to the investigational device; and/or (d) any additional events as requested by the Sponsor or DSMB.
- The specified events will be adjudicated to determine:
    - event relatedness to the study procedures and/or the investigational device
    - event categorization and assess seriousness and severity
    - whether an adverse event is anticipated or unanticipated

The adjudication decision of the Medical Monitor will be used for the final classification of events, including relatedness to the study procedures and/or the investigational device, for the determination of safety endpoints and for all regulatory reports, product labeling, and publications or presentations.

The Medical Monitor's roles and responsibilities are described in the Safety Management Plan (SMP).

12 STATISTICAL CONSIDERATIONS

12.1 Objectives and Endpoints

12.1.1 Safety Objective

The safety objective of the study is to evaluate the safety of the Omnipod Horizon™ System in patients with type 1 diabetes.

12.1.1.1 Primary Safety Endpoint

Proportion of subjects with serious device-related adverse events.

12.1.1.1 Secondary Safety Endpoints

- Proportion of subjects with severe hypoglycemia during hybrid closed-loop
- Proportion of subjects with diabetic ketoacidosis (DKA) during hybrid closed-loop

12.1.2 Primary Effectiveness Objective

The primary effectiveness objective of this study is to evaluate the effectiveness of the Omnipod Horizon™ System

12.1.2.1 Primary Effectiveness Endpoints

The primary effectiveness objective will be evaluated by comparing the percentage of time in range (70-180 mg/dL) during hybrid closed-loop compared to the standard therapy for:

- Target BG challenge days (approximately hybrid closed-loop days 1-9)
- Non-challenge days (approximately hybrid closed-loop days 10-14)
- Overall (hybrid closed-loop days 1-14)

12.1.3 Secondary Effectiveness Objective

The secondary objective of the study is to evaluate additional glycemic measures of effectiveness of the Omnipod Horizon™ System.

12.1.4 Secondary Effectiveness Endpoints

The secondary objective will be evaluated using the following per subject endpoints:

- Glucose metrics from system CGM during the hybrid closed-loop phase will be compared to the standard therapy phase during the day, overnight, and overall:
    - Mean glucose

- % of time in range 70-180 mg/dL
- % of time in range 70-140 mg/dL
- % of time > 180 mg/dL
- % of time ≥ 250 mg/dL
- % of time ≥ 300 mg/dL
- % of time < 70 mg/dL
- % of time < 54 mg/dL
- Standard deviation
- Coefficient of variation

- GMI based on overall mean glucose
- Percentage of time in hybrid closed-loop as proportion of overall device usage time
- Insulin requirements during the hybrid closed-loop phase will be compared to the standard therapy phase:

  - Total daily insulin (TDI) (units, units/kg)
  - Total daily basal insulin (units, units/kg)
  - Total daily bolus insulin (units, units/kg)

12.2 Sample Size

This is a single-arm, multi-center, prospective study. The sample size is not hypothesis-driven and was chosen to provide adequate information on the device's safety and performance.

12.3 Analysis Sets

The following analysis sets are planned for the study:

12.3.1 ITT (Intention to Treat) Analysis Set

The ITT analysis set includes all subjects that are enrolled in the study. All safety analyses (other than primary analysis of primary safety endpoints) will be based on the ITT analysis set.

12.3.2 mITT (modified Intention to Treat) Analysis Set

The modified Intention to Treat (mITT) analysis set is a subset of the ITT analysis set. The mITT analysis set will consist of subjects who have entered the hybrid closed-loop phase of the study successfully. The mITT analysis set will be used as the primary analysis for the primary and secondary endpoints and other clinical outcome data.

12.3.3 PP (Per-Protocol) Analysis Set

The Per-Protocol (PP) analysis set is a subset of the mITT analysis set. Subjects will be included in the PP analysis set if they have a minimum of 80% system use during the hybrid closed-loop phase inclusive of Manual and Automated Modes over a duration of 14-days and have completed the study without major protocol

deviations. The PP analysis set will be used as supportive analysis for the effectiveness endpoints. The following will be considered major protocol deviations:

- Major inclusion/exclusion criterion deviation
- Significant protocol non-compliance that may confound the study objective data (e.g., use of prohibited medications)

The list of subjects excluded from the PP analysis set will be determined prior to analysis. If the PP analysis set does not differ from the mITT analysis set, separate analyses will not be presented.

12.4 Analysis of Primary and Secondary Effectiveness Endpoints

Summary statistics will be presented by age cohort for all endpoints, stratified by time points of interest (e.g., day vs. night, overall). The effectiveness endpoints will be summarized for modified Intention to Treat (mITT) and Per Protocol (PP) analysis sets. If the PP analysis set does not differ from the mITT analysis set, separate analyses will not be presented. The data may be stratified by phase of the study, where the data collected in the standard therapy phase of the study (after adjustment of parameters, if necessary) will be compared to the data collected in the hybrid closed-loop phase of the study. The primary effectiveness endpoint will also by presented by existing Dexcom G6 use at the time of screening (users and non-users).

The primary effectiveness endpoint and the secondary effectiveness endpoints that summarize time in specific glycemic ranges will be calculated from device data outputs as follows:

$$100 \times \frac{\#\ of\ CGM\ records\ in\ range}{\#\ of\ evaluable\ CGM\ records} = TIR\%$$

All statistical comparisons will be conducted at a two-side significance level of 5%. Since the results of endpoint analyses are not used to support clinical claims, no adjustment for multiplicity will be included. Data from all sites will be pooled for all analyses; no separate analyses by site or formal testing of poolability will be performed.

12.5 Additional Data Analyses

Following the upload of controller data into the database, the data will be made available to Sponsor representatives for periodic reviews. Reviews of the controller data will be conducted to identify any anomalies and to confirm the algorithm appears to be functioning as expected. These reviews, including any findings, will be documented. Unless potential safety concerns are identified, the results of such reviews will not be shared with study sites or subjects and thus, will not impact study outcomes. Should a potential safety concern be identified, sites may be notified as appropriate to ensure subject safety and measures may be taken to address the issue such as, but not limited to, changes to the protocol and/or device. Any resulting device deficiencies will be reported, if applicable. A

brief summary of the controller data reviews will be included in the final clinical study report.

12.6 Safety Analyses

12.6.1 Evaluation of Adverse Events

All adverse events reported over the course of the study will be summarized and tabulated by study phase (standard therapy or hybrid closed-loop), event category, seriousness, severity, and relationship to the study and the investigational device. For the purposes of summarization, an event will be considered “Related” if the relationship was deemed as “Possibly Related” or “Related”. In cases where the same event is reported more than once per subject, the event will only be counted once in the incidence table(s).

Adverse events leading to death or to discontinuation from the study will be listed separately. A listing of all adverse events will be provided. The primary safety endpoint will also be presented by existing Dexcom G6 use at the time of screening (users and non-users).

12.6.2 Evaluation of Device Deficiencies

Device deficiencies will be tabulated and listed in a manner similar to the methods described for adverse events. Any device deficiency leading to an AE or to study termination will be listed separately.

12.7 Baseline Characteristics

The distribution of each baseline characteristic or demographic parameter of interest (such as age, gender, medical history, etc.) will be presented. Data on all enrolled subjects will be presented. Continuous variables will be summarized using count, mean, median, standard deviation, and range. Categorical variables will be summarized using counts and percentages.

12.8 General Statistical Methods

Standard statistical methods will be employed to analyze all data. All data collected in this study will be documented using summary tables and subject data listings. Unless otherwise noted, all p-values will be considered significant at a two-sided significance level of 5%. Continuous variables will be summarized using descriptive statistics, including count, mean, median, standard deviation (SD), minimum and maximum. Where appropriate, 95% two-sided confidence intervals for the means or medians will be presented. If the observed data are found not to follow a normal distribution, appropriate non-parametric methods may be employed. Categorical variables will be summarized by frequencies and percentages. Unless explicitly stated otherwise, percentages will utilize a denominator corresponding to the number of unique subjects.

12.9 Missing Data

All practical monitoring and follow-up steps will be taken to ensure complete and accurate data collection. It is anticipated that the rate of missing data would be very low due to the limited duration of the study. All analyses will be based on available data only; no imputation for missing data is planned.

12.10 Statistical Software

The statistical software package SAS® 9.4 or later will be used for all the data derivations, summarization, data listings and statistical analyses. Additional software such as Splus or R may be used for graphics or validation as appropriate.

13 DATA HANDLING AND QUALITY ASSURANCE

Data in this study will be collected on Electronic Case Report Forms as well as via electronic device outputs.

13.1 Electronic Case Report Forms (eCRFs)

Study data are collected through a combination of subject electronic CRFs (eCRFs) and electronic device data files. eCRF Data will be recorded in a 21 CFR Part 11 compliant database that will reside on a central server accessible via the Internet.

Electronic data files contain the primary source data for study devices. When data are directly collected in the eCRFs, this will be considered source data. When data is not directly collected in the eCRFs, electronic or paper documents containing source data that is transcribed into the eCRF are the source.

The investigator is responsible for the accuracy and completeness of data reported on the eCRFs. Each set of subject eCRFs must be reviewed and signed by the investigator in the EDC system. The investigator also agrees to maintain accurate source documentation supporting the data. When pertinent supportive information is available for data entered directly into the eCRFs, this supporting documentation will also be maintained. Source documents may include chart notes, laboratory reports, images, study specific source worksheets, eCRFs, device data files, etc.

13.2 Electronic Device Outputs

13.2.1 PDM Data

This study will utilize insulin delivery data from the PDM device. All insulin delivery data and all CGM readings from the hybrid closed-loop phase will be stored on the PDM and exported to Insulet Cloud. Data will be saved in a compatible format that will be extractable for statistical analysis purposes. Data from the hybrid closed-loop phase will be uploaded to the database and used for analysis.

13.2.2 CGM Data

This study will utilize CGM measurements from the CGM device. All CGM readings from the hybrid closed-loop phase will be stored on the controller. CGM data will be saved in a compatible format that will be extractable for statistical analysis purposes. CGM data from the standard therapy phase will be uploaded to the database and used for comparative analysis.

13.2.3 BG and Ketone Meter Data

This study will also utilize measurements from a BG and ketone meter. BG fingerstick measurements will recorded in a compatible format that will be extractable for statistical analysis purposes. Ketone meter data, in any format, will be uploaded to the database.

13.3 Subject Identifiers

All data used in the analysis and reporting of the study will be without identifiable reference to the subject. Only the unique subject number will be used to identify subject data submitted to the Sponsor, and only the investigating clinical site will be able to link the unique subject ID to the subject's name.

13.4 Monitoring Responsibilities

This study will be monitored for compliance with the protocol and applicable regulatory requirements. A study specific monitoring plan will specify the minimum frequency, scope, and general conduct of monitoring visits as well as identify any relevant study-specific monitoring responsibilities.

Monitors for this study will be qualified by education, experience and training. The monitor will report to the Sponsor any non-compliance with the protocol, applicable regulations, or any conditions imposed by the IRB or local regulatory authority. If compliance cannot be secured, device shipments to the Investigator may be discontinued and the Investigator's participation in the study terminated.

Investigators and clinical site coordinators are expected to make source files and other records and reports available to the monitors as required.

13.5 Inspection of Records

The Sponsor or its designee may perform quality assurance site and study file audits. Investigators and institutions involved in the study will permit trial-related monitoring, audits, IRB review, and regulatory inspection by providing direct access to all study records. In the event of an audit or inspection, the investigator agrees to allow the Sponsor, representatives of the Sponsor, the FDA, or other regulatory authorities access to all study records.

The investigator should promptly notify the Sponsor of any study inspections scheduled by the regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

13.6 Study Record Retention

Records and reports must remain on file at the investigational site for a minimum of two years after the later of either the completion/termination of the study or the date of market approval for the indication being studied. They may be discarded only upon approval from the Sponsor. The Principal Investigator must contact the Sponsor before destroying any records and reports pertaining to the study to ensure that they no longer need to be retained. In addition, the Sponsor must be contacted if the investigator plans to leave the investigational site to ensure that arrangements for a new investigator or records transfer are made prior to investigator departure.

13.7 Device Accountability

Investigators will be responsible for investigational device accountability, reconciliation and records maintenance throughout the course of the investigation. Accountability records will include receipt, use and final disposition of investigational product.

Study devices must be stored according to the conditions set forth for the device on the label in a controlled, locked area. All device shipment records (packing lists, etc.) must be maintained at the clinical site.

The study monitor will verify accountability of the study devices during routine monitoring visits to the clinical site.

14 STUDY ETHICS AND CONDUCT

14.1 Role of the Sponsor

As the Sponsor of this clinical study, Insulet has the overall responsibility for the conduct of the study, including assurance that the study meets the requirements of the appropriate regulatory bodies. In this study, the Sponsor will have certain direct responsibilities and may delegate certain study tasks to the Contract Research Organization (CRO).

14.2 Ethical Conduct of the Study

The investigation will be conducted according to the applicable FDA regulations (21CFR 812, 56, 54, 50). The investigator will conduct all aspects of this study in accordance with all state, and local laws or regulations.

14.3 Institutional Review Board (IRB)

Federal regulations (21 CFR 812) require that approval be obtained from an IRB prior to participation of subjects in research studies. Prior to subject enrollment, a signed copy of the IRB approval letter must be submitted to the Sponsor. In addition, the protocol, informed consent, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to the subject must be approved by the IRB. Documentation of all IRB approvals

will be maintained by the clinical site and will be available for review by the Sponsor or its designee.

All IRB approvals should be signed by the IRB chairperson or designee and must identify the IRB by name and address, the clinical protocol by title and/or protocol number, and the date approval was granted.

The Investigator is responsible for submitting and obtaining initial and continuing review of the trial at intervals not exceeding 1 year or as otherwise directed by the IRB. The investigator must supply the Sponsor, or its designee written documentation of continued review of the study.

14.4 Informed Consent

A written informed consent in compliance with 21 CFR 50 shall be obtained from each subject prior to participating in the study or performing any unusual or non-routine procedure that involves risk to the subject. An informed consent form (ICF) template will be provided by the Sponsor or designee to investigative clinical sites. If any institution-specific modifications to study-related procedures are proposed or made by the clinical site, the consent must be reviewed by the Sponsor prior to IRB submission. Once reviewed, the consent will be submitted by the investigator to their IRB for review and approval prior to the start of the study.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator or designee is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing the ICF.

The investigator or designee shall provide a copy of the signed ICF to the subject. The original form shall be maintained in the subject binder at the clinical site.

14.5 Confidentiality

All information and data sent to the Sponsor concerning study subjects or their participation in this trial will be considered confidential. Only authorized personnel will have access to these confidential files. All records will be kept in secure storage areas and on password-protected computers.

This includes, but is not limited to the following:

- Subjects will be identified on all eCRFs by a unique subject ID
- eCRFs are confidential documents and will only be available to the Sponsor (including delegates, such as CRAs), DSMB, Medical Monitor, CRO, the investigator and study staff, and if requested, to the IRB or regulatory authorities. The investigator will maintain, as part of the investigation file, a list identifying all subjects entered into the study.

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. Clinical

information will not be released without the written permission of the subject, except as necessary for monitoring and auditing by the Sponsor, its designee, the FDA, or the IRB.

The investigator and all clinical site staff involved in this study may not disclose (or use for any purpose other than performance of the study), any data, record, or other unpublished confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

14.6 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent immediate hazard to the subject, must be reviewed and approved by the Sponsor. The protocol amendment(s) must be signed by the investigator and approved by the IRB before implementation. The protocol amendment(s) will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

Substantial changes will require approval from the Sponsor, FDA, and IRB prior to implementation.

14.7 Protocol Deviations

The investigator will not deviate from the protocol without prior written approval from the Sponsor except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the subject's risk or affect the validity of the trial. In medical emergencies, prior approval for protocol deviations will not be required, but the Sponsor must be notified within 2 working days of the incident. Periodic monitoring of protocol compliance will be performed for each clinical site. The Sponsor has the right to suspend enrollment at clinical sites deemed to have excessive protocol compliance issues.

All deviations related to study inclusion or exclusion criteria, conduct of the study, subject management or subject assessment must be appropriately documented and reported. Other protocol deviations to be considered include non-adherence to the protocol that results in a significant additional risk to the subject, or non-adherence to FDA regulations.

The investigator must document and explain any protocol deviation in the subject's source documentation. The IRB should be notified of all protocol deviations in a timely manner. Protocol deviations should be reported to the IRB periodically, according to their requirements. Deviations will also be reviewed by the monitor during clinical site visits and those observations may be discussed with the investigator.

The Sponsor will evaluate circumstances where the investigator deviates from the study protocol and will retain the right to remove either the investigator or the investigational clinical site from the study.

14.8 Study Reporting Requirements

By participating in this study, the investigator agrees to submit SAE reports according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his/her IRB as appropriate.

Upon completion or termination of the study, the principal investigator (PI) must submit a final written report to the Sponsor and IRB. The report must be submitted within 3 months (90 days) of completion or termination of the trial.

The Sponsor will submit all reports required by the appropriate regulatory authorities, including unanticipated adverse device effects, withdrawal of IRB approval, list of current investigators, annual progress reports, recall information, final reports and protocol deviations.

14.9 Selection of Investigators

The Sponsor will select qualified investigators, ship devices only to participating investigators, obtain a signed Investigator's Agreement and provide all investigators with the information and training necessary to conduct the study.

14.9.1 Financial Disclosure

Investigators and sub-investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must notify the Sponsor promptly of any relevant changes that occur during the course of the study, at the completion of the study, and 1 year following the completion of the study.

14.9.2 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with 21 CFR 812 by providing the following essential documents, including but not limited to:

- An investigator-signed Investigator Agreement page of the protocol
- An IRB approved informed consent, samples of clinical site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject
- IRB approval of the investigator, protocol, and acknowledgement of the user guide
- Curricula vitae (CV) for the PI and each investigator participating in the study. Current licensure must be noted on the CV or a copy of the license provided. CVs must be signed and dated by the investigators within 1 year of study start-up, indicating that they are accurate and current.
- Financial disclosure information (as stated above) and a commitment to promptly update this information if any relevant changes occur

- Laboratory certifications and normal ranges for any local laboratories used by the clinical site.

14.10 Clinical Site Training

The training of appropriate clinical site personnel will be the responsibility of the Sponsor or its designee. To ensure proper device usage, uniform data collection, and protocol compliance, the Sponsor or designee will present formal training sessions to relevant clinical study site personnel. Clinical study personnel trained by the Sponsor may also train additional clinical study personnel at their site. The Sponsor reserves the right to enforce retraining for clinical sites who have demonstrated study or procedure compliance issues. Protocol-specific training will occur for all research personnel and key ancillary staff who will be involved in subject care.

14.11 Device Use

The Omnipod Horizon™ System consists of the following primary components: an Omnipod Horizon™ Pod, Omnipod Horizon™ Controller, and the iCGM.

The Pod and PDM are intended for single use only.

The Dexcom G6 CGM sensor (the component of the system that enters the skin) and the Dexcom G6 CGM transmitter (the component of the system that attaches to the sensor to transmit the signal) will both be single use only in this study. The Dexcom G6 CGM receiver will all be single use only in this study.

Study blood glucose meters and ketone meters will not be cleaned or reused by subjects. A new meter will be used for each subject.

14.12 Device Returns

Any unused or damaged investigational devices or investigational devices related to a suspected deficiency or adverse event must be returned to the study Sponsor. To initiate the return, the clinical site will contact the Sponsor representative and provide the following information:

- Part number/Lot number
- Quantities
- Tracking number

14.13 Policy for Publication and Presentation of Data

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the study Sponsor, Insulet.

14.14 Sponsor or Regulatory Agency Termination of the Study

Although the Sponsor intends to complete the study, the Sponsor reserves the right to stop the study at any time for clinical or administrative reasons, or if required by the local regulatory authority, with suitable written notice to the investigators and regulatory authorities as appropriate.

Similarly, investigators may withdraw from the study by providing written notification to the Sponsor within 30 days of intent to withdraw. However, the Sponsor and investigators will be bound by their obligation to complete the follow-up of subjects already enrolled in the trial. Subjects must be followed according to the clinical protocol and information obtained during subject follow-up shall be reported on the eCRF.

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APPENDIX

OMNIPOD HORIZON™ AUTOMATED GLUCOSE CONTROL SYSTEM PUMP THERAPY ORDER FORM

Investigator Site Use Only. Confidential: Protected Health Information

Subject Name_____ Date _____/_____/_____

Subject DOB_____ Subject Weight _____ Subject ID# _____

Standard Therapy Regimen_____ = _____ units Total Daily Dose (Pre-Pump)

Dosing Calculation Section (optional)

Total Daily Dose (TDD) for pump calculations	
Pre-Pump TDD _____ units	**Weight-based** _____ kg OR _____ lbs.
Pre-Pump TDD x 0.75 = Pump TDD _____ (Pre-Pump TDD) units/day x 0.75 = _____ (Pump TDD) units	**Weight kg x 0.5** or **lbs x 0.23** _____ kg x 0.5 = _____ (Pump TDD) units OR _____ lbs. x 0.23 = _____ (Pump TDD) units
If Pre-Pump TDD and Weight-based are compared consider the following:	☐ Average value of Pre-Pump and weight based methods ☐ Hypoglycemic patients – use more conservative lower value ☐ Hyperglycemic patients, elevated A1C – use higher value
Pump TDD = _____ units	
Basal Rate	
Total Daily Basal *(Pump TDD x 50% = Total Daily Basal)*	_____ (Pump TDD) units/day x 0.5 = _____ (Total Daily Basal) units
Initial Basal Rate *(Total Daily Basal / 24 hours = Initial Basal Rate)*	_____ (Total Daily Basal) units/24 hours = _____ (Initial Basal Rate) U/hr
Bolus Settings	
Insulin to Carb Ratio *(450/TDD = Insulin to Carb Ratio)*	450/_____ (TDD) units/day = _____ (Insulin to Carb Ratio) grams/unit
Correction Factor *(1700/Pump TDD = Correction Factor)*	1700/_____ (Pump TDD) units/day = _____ (Correction Factor) mg/dL/unit

Initial Pump Settings (required) ☐ **Transfer Pump Settings**			
Basal			
Max Basal Rate		_____ U/hr	
Basal 1	Time Segment 12:00 am - _____ _____ - _____ _____ - _____ _____ - _____	_____ U/hr _____ U/hr _____ U/hr _____ U/hr	
Temporary Basal Rate		☐ On ☐ Off	
Bolus			
Target BG & Correct Above	Time Segment 12:00 am - _____ _____ - _____ _____ - _____ _____ - _____	Target _____ mg/dL _____ mg/dL _____ mg/dL _____ mg/dL	Correct Above _____ mg/dL _____ mg/dL _____ mg/dL _____ mg/dL
Insulin to Carb (IC) Ratio	Time Segment 12:00 am - _____ _____ - _____ _____ - _____ _____ - _____	1 unit of insulin covers _____ g _____ g _____ g _____ g	
Correction Factor	Time Segment 12:00 am - _____ _____ - _____ _____ - _____ _____ - _____	1 unit of insulin decreases BG by _____ mg/dL _____ mg/dL _____ mg/dL _____ mg/dL	
Duration of Insulin Action		_____ hours	
Maximum Bolus		_____ units	
Extended Bolus		☐ On ☐ Off	

Physician Name _____ Signature _____ Date _____

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