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

IDE G190270

Version 5.0

November 12, 2020

Insulet Corporation

100 Nagog Park

Acton, MA 01720

PROTOCOL APPROVAL

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Version 5.0

November 12, 2020

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

INVESTIGATOR STATEMENT

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

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November 12, 2020

Version 5

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	Evaluating the safety and effectiveness of the Omnipod Horizon™ Automated Glucose Control System in patients with type 1 diabetes
Protocol ID	G190270
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	A total of up to 240 subjects will be enrolled in the study in order to obtain a minimum of 200 evaluable subjects. The study will consist of three phases: 1) 14-day standard therapy outpatient phase (Phase 1) 2) 13-week outpatient hybrid closed-loop phase (Phase 2) • Phase 2 excludes periods due to a study pause 3) 12-month hybrid-closed-loop extension phase (Phase 3) Subjects will be enrolled across 12-20 clinical study sites. The 200 evaluable subjects will be comprised of two age cohorts of 100 subjects each as follows: • 100 subjects aged 6-13.9 years • 100 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 30-months which includes clinical site initiation to completion of Phase 3 and all data entry and monitoring procedures. The sponsor intends to submit results from Phase 2 for marketing clearance after data collection for Phase 2 is complete. The results from Phase 3 will be submitted separately.
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. • Dexcom G6 - Continuous Glucose Monitoring (CGM) system
Non-investigational, commercially available devices	• 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)
Primary safety objective	To evaluate the safety of the Omnipod Horizon™ Automated Glucose Control System in patients with type 1 diabetes
Primary safety endpoints	The primary safety objective will be evaluated by summarizing the following events during Phase 2, and separately during Phase 3: • Incidence rate of severe hypoglycemia (events per person months) • Incidence rate of diabetic ketoacidosis (DKA) (events per person months)
Primary effectiveness objective	To evaluate the effectiveness of the Omnipod Horizon™ Automated Glucose Control System.
Primary effectiveness endpoints	• A1C after at least 6 weeks of continuous Phase 2 participation compared to baseline • A1C at Visit 16, 19, 21, and 23 compared to baseline • Percentage of time in range (70-180 mg/dL) during Phase 2 and separately during Phase 3 of the hybrid closed-loop phase compared to Phase 1 (standard therapy)
Secondary objective	To evaluate additional glycemic measures of effectiveness of the Omnipod Horizon™ Automated Glucose Control System

Secondary endpoints	The secondary objective will be evaluated using the following per subject endpoints *with* prespecified hypotheses:
	
	• Glucose metrics from system CGM during the hybrid closed-loop phase for Phase 2 will be compared to Phase 1 overall:
	  • % of time > 180 mg/dL
	  • % of time < 70 mg/dL
	
	Additional per subject secondary endpoints *without* prespecified hypotheses used to evaluate the secondary objective include:
	
	• A1C:
	  • A1C after at least 8 weeks of continuous Phase 2 participation at the end of Phase 2 (Visit 13), at 6 months (Visit 16), and at the end of Phase 3 (Visit 23; approximately 15 months)
	  • Change from baseline in A1C after at least 6 weeks of continuous Phase 2 participation, after at least 8 weeks of continuous Phase 2 participation at the end of Phase 2 (Visit 13), at 6 months (Visit 16), and at the end of Phase 3 (Visit 23; approximately 15 months)
	  • Proportion of subjects demonstrating an improvement from baseline in A1C after at least 6 weeks of continuous Phase 2 participation, after at least 8 weeks of continuous Phase 2

	participation at the end of Phase 2 (Visit 13), at 6 months (Visit 16), and at the end of Phase 3 (Visit 23; approximately 15 months)
	
	• Glucose metrics from system CGM during the hybrid closed-loop phase during Phase 2, and separately during Phase 3, will be compared to Phase 1 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
	
	• Percentage of time in hybrid closed-loop as proportion of overall device usage time during Phase 2, and separately during Phase 3
	• Glucose management indicator (GMI) based on overall mean glucose during Phase 2, and separately during Phase 3 will be compared to Phase 1
	• Insulin requirements during Phase 2, and separately during Phase 3 will be compared to Phase 1:
	
	  • Total daily insulin (TDI) (units, units/kg)
	  • Total daily basal insulin (units, units/kg)
	  • Total daily bolus insulin (units, units/kg)
	
	• Change from baseline in BMI (kg/m^2) at end of Phase 2, and at end of Phase 3,

Patient Reported Outcomes	Various subject- and caregiver-completed questionnaires will be used to evaluate general and disease-specific quality of life, and device usability.
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 travel to and participate in meal and exercise challenges during 5-days of the hybrid closed-loop phase 8. Willing to wear the system continuously throughout the study 9. A1C <10% at screening visit 10. 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 11. 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 12. Able to read and speak English fluently 13. 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 in the past 6 months 3. History of DKA 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 other than the Omnipod Horizon™ Automated Glucose Control System 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 three phases: 1) 14-day outpatient standard therapy phase (Phase 1) 2) 13-week outpatient hybrid closed-loop phase (Phase 2) o A subset of subjects will participate in 5-days of supervised challenges o Phase 2 excludes periods due to a study pause 3) 12-month hybrid closed-loop extension phase (Phase 3) 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. Subjects in each cohort will participate in prescribed challenges during any consecutive 5-day period during Phase 2 of the hybrid closed-loop phase. Subjects who complete Phase 2 can commence their participation in the extension phase (Phase 3). Note: Subjects having completed the prepivotal study may participate in this pivotal study and begin at Visit 5 of Phase 2 (hybrid closed-loop) since Phase 1 (standard therapy) was completed as part of the prepivotal study and is not required to be repeated.

GLOSSARY OF ACRONYMS

ACE	Alternate Controller Enabled
ADA	American Diabetes Association
ADE	Adverse Device Effect
AE	Adverse Event
AID	Automated Insulin Delivery
AWS	Amazon Web Services
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
DSMB	Data Safety Monitoring Board
DTSQ	Diabetes Treatment Satisfaction Questionnaire
dL	Deciliter
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGV	Estimated Glucose Value
FDA	Food and Drug Administration
GMI	Glucose Management Indicator
HABS	Hypoglycemic Attitudes and Behavior Scale
HCL	Hybrid Closed Loop
HDP	Horizon Data Portal
HF	Human Factors
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
iCGM	Interoperable Continuous Glucose Monitoring
IDSS	Insulin Delivery Satisfaction Survey
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
PAID	Problem Areas In Diabetes
PDM	Personal Diabetes Manager
PHI	Protected Health Information
POC	Point of Care
pMPC	Personalized Model Predictive Control
PP	Per Protocol
PSQI	Pittsburgh Sleep Quality Index
PTOF	Pump Therapy Order Form
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SMP	Safety Management Plan
SUS	System Usability Scale
T1DDS	Type 1 Diabetes Distress Scale
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 pivotal study is designed to evaluate the safety and effectiveness of Omnipod Horizon™ System. Maximum stressors to the system, by way of prescribed exercise and meal challenges, will be assessed during 5 days of the hybrid closed-loop phase with a subset of the enrolled subjects. The challenges will consist of prolonged periods of moderate to high intensity exercise as well as meal challenges. Challenges will be conducted in an environment closely monitored by clinical staff.

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. As with the cleared Omnipod® DASH System, the Pod of the Omnipod Horizon™ System will come pre-packaged in a sterile container with a fill needle and a fill syringe. **Figure 2** below is a representation of the Pod.

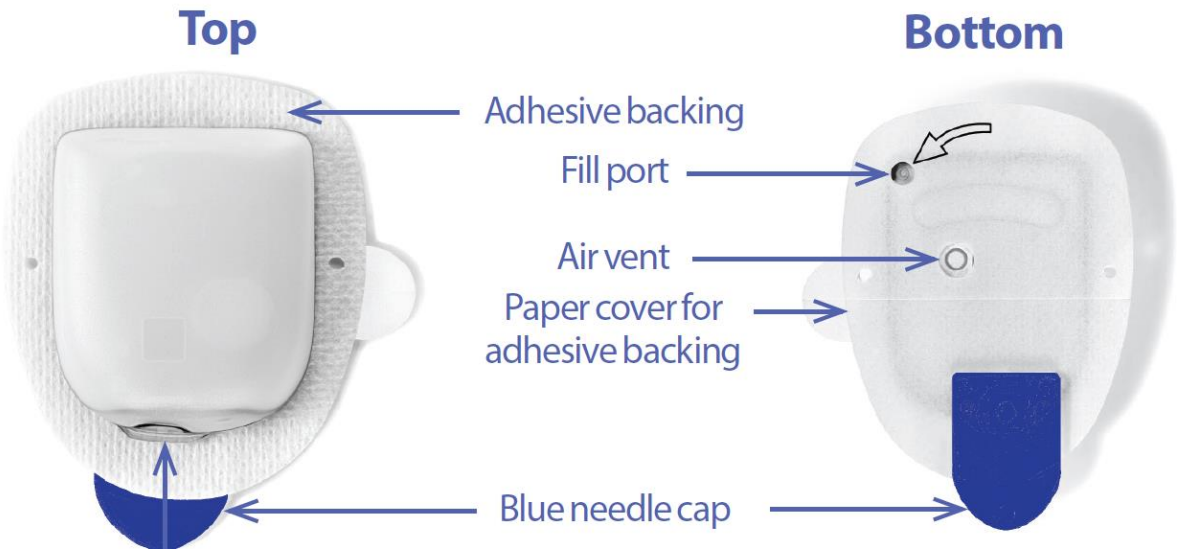


Figure 2: The Pod of the Omnipod Horizon™ ACE pump

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.

Investigators will have access to all uploaded data and be able to view historical trends. The HDP will function as the data management review platform for this study.

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. A total of up to 240 subjects aged 6-70 years with type 1 diabetes will be enrolled in the study in order to obtain a minimum of 200 evaluable subjects, 100 evaluable subjects in each age cohort (Table 1: Cohorts). Subjects will be considered evaluable if they have at least 8 weeks of data during Phase 2.

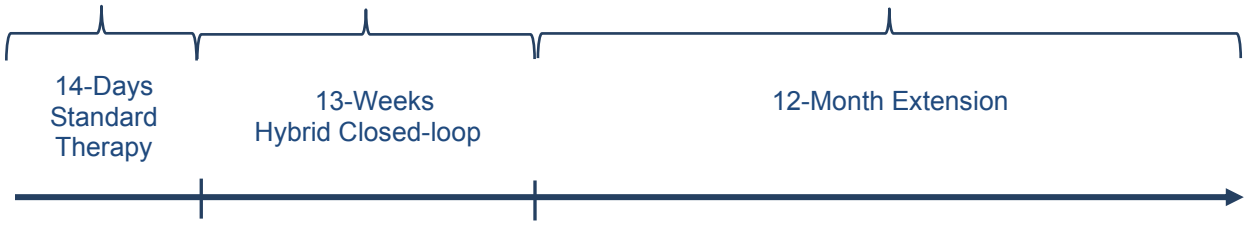
Subjects will be enrolled across 12-20 clinical study sites. Subjects who have previously participated during the feasibility studies may be enrolled in the pivotal study and will be assigned a new subject identification number. Subjects who have participated in the prepivotal study may participate in the pivotal study if it has been deemed safe for their continuation in the study and will retain their prepivotal subject identification number.

The study schedule consists of the following three phases:

1) 14-day outpatient standard therapy phase (Phase 1)
2) 13-week outpatient hybrid closed-loop phase (Phase 2)
   - A subset of subjects will participate in 5-days of supervised challenges
   - Phase 2 excludes periods due to a study pause
3) 12-month hybrid closed-loop extension phase (Phase 3)

Note: Subjects having completed the prepivotal study may participate in this pivotal study and begin at Phase 2 since Phase 1 was completed as part of the prepivotal study and is not required to be repeated.

Figure 2: Study Schedule Timeline



Cohorts are defined as shown in **Table 1**:

Table 1: Cohorts

Cohort (Name)	Age Range	N (minimum evaluable for primary endpoint)
Adults	14-70 years	100
Children	6-13.9 years	100

Following subject screening, enrollment, and device training, subjects will commence the 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 Phase 1 (the standard therapy phase), subjects will be trained on the system and transition to Phase 2 (13-week hybrid closed-loop phase) initiating

treatment with the Omnipod Horizon™ System. Subjects in each cohort will participate in prescribed challenges during any consecutive 5-days of the 13-week hybrid closed-loop phase. Phase 2 will be followed by a 12-month hybrid closed-loop phase (Phase 3).

Tables 2 and 4 outline the schedule of assessments for each phase of the study.

Table 2: Schedule of Assessments for Phase 1 and Phase 2

Assessment Schedule	Screening	ST1	ST2	Hybrid Closed-Loop (HCL)											EW[a]
	Phase 1[e]			Phase 2[c]											
Visit Number	1	2	3	4	5[e]	6	7	8	9	10	11	12	13	UV[b]	
Study Day/Visit Window[l]	-30 to -14d HCL start	-14d to HCL start	-1d to HCL start	1	2 ±1d	3 ±1d	10 ±3d	24 ±3d	38 ±3d	52 ±3d	66 ±3d	80 ±3d	94 ±3d	N/A	
Telephone (T) or Office (O) Visit	O	O	O	O	T/O	T/O[f]	T/O[f]	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												X		X
TSH	X														
Creatinine Level	X														
Pregnancy Test	X			X			X		X				X		
Clinical Assessments															
Informed Consent	X				X[g]										
Medical History (including demographics)	X														
Confirm Eligibility	X				X[g]										
Concomitant medications	X	X[h]		X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
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											
Height	X												X		X
Weight	X												X		X
Vital signs	X						X		X				X		X
Electrocardiogram[d] (if applicable)	X														
Adverse events		X	X	X	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]

Assessment Schedule	Screening	ST1	ST2	Hybrid Closed-Loop (HCL)											EW[a]
	Phase 1[e]			Phase 2[c]											
Visit Number	1	2	3	4	5[e]	6	7	8	9	10	11	12	13	UV[b]	
Study Day/Visit Window[l]	-30 to -14d HCL start	-14d to HCL start	-1d to HCL start	1	2 ±1d	3 ±1d	10 ±3d	24 ±3d	38 ±3d	52 ±3d	66 ±3d	80 ±3d	94 ±3d	N/A	
Telephone (T) or Office (O) Visit	O	O	O	O	T/O	T/O[f]	T/O[f]	T/O[f]	T/O[f]	T/O[f]	T/O[f]	T/O[f]	T/O[f]	T/O[f]	O
Questionnaires															
See Table 4 for specific questionnaires	X	X											X		X
Study Devices															
Training on Glucagon administration and information on treatment of hypo/hyperglycemia		X													
Horizon Data Portal initiation/discontinuation				X									X		X
Study device training		X[i]		X[j]											
Dispense/Return BG/Ketone meter, and CGM		X											X		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[k]	X												
Dispense/Return Horizon System				X									X		X
Complaints/device deficiencies				X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
Device uploads				X	X	X	X	X	X	X	X	X	X		X
Data review				X	X	X	X	X	X	X	X	X	X	X	X

Table 3: Schedule of Assessments for Phase 3

Assessment Schedule	Hybrid Closed-Loop (HCL)											
	Phase 3											
Visit Number	14	15	16	17	18	19	20	21	22	23	UV	EW
Study Day/Visit Window	120 ± 5d	150 ± 5d	180 ± 5d	210 ± 5d	240 ± 5d	270 ± 5d	315 ± 5d	360 ± 5d	405 ± 5d	450 ± 5d		
Telephone (T) or Office (O) Visit	T/O[f]	T/O[f]	T/O[f]	T/O[f]	T/O[f]	T/O[f]	T/O[f]	T/O[f]	T/O[f]	O	T/O[f]	O
Laboratory Assessments												
A1C			X			X		X		X		X
Pregnancy Test			X[f]			X[f]						
Clinical Assessments												
Informed Consent						X[m]						
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Height										X		X
Weight										X		X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Study Devices												
Return Horizon System										X		X
Complaints/Device Deficiencies	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
Device Uploads (BG/Ketone Meter)	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X		X
Data Review	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]

Abbreviations: S=Screening; ST1=Standard Therapy Day One; HCL=Hybrid Closed-loop; EW=Early Withdrawal; QC=Quality Control Testing; 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. For unscheduled visits pertaining to a study pause and recommencement, sites should follow the assessments as defined in section 9.10.

[c]Challenges can occur during any consecutive 5-days during Phase 2 of the hybrid closed-loop phase. A follow up telephone visit will occur the following day after the conclusion of the challenge period.
[d]Electrocardiogram required for subjects >50 years old or with diabetes duration >20 years
[e]Subjects extending into the pivotal study from the prepivotal study will initiate their participation at Visit 5 of pivotal Phase 2.
[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. Vital signs, device uploads/data review from the BG and Ketone meter, and pregnancy tests are not required at any visit conducted via telephone.
[g]Prepivotal subjects extending into pivotal will be required to reconsent. If original prepivotal screening is within 45 days prior to the start of Phase 2 in the pivotal study, subjects will not require rescreening. All subjects must reconsent prior to commencing the extension phase (Phase 3) on or before Visit 13.
[h]Documentation only applicable if there are changes from previous assessment
[i]Study device training for the CGM, blood glucose and ketone meters
[j]Study device training for the Omnipod Horizon™ System
[k]Subjects deemed exempt from wearing the study CGM for 14-days will be eligible to immediately commence the hybrid closed-loop phase at Visit 4 and may skip Visit 3/ST2 (in which case, Visit 1, Visit 2/ST1 and Visit 4 may all occur on the same day)
[l]In the event of overlapping visit windows, no visits occurring during Phase 2 are to occur on the same date, except for challenge visit days. It is acceptable for a challenge visit to occur on the same date as a Phase 2 visit
[m]Subjects continuing in the study are to be consented for both the first 6-month and the second 6-month interval of Phase 3. Consent for each interval must occur on or any time before commencing that study interval (e.g. consent for first 6-months of Phase 3 must occur on or before Visit 13, consent for second 6-months of Phase 3 must occur on or before Visit 19).
[n]Data review for Horizon Automated Mode to occur at all visits

Table 4: Questionnaires

Visit	Age Groups*				
	Adult (ages 18-70)	**Teen (ages 12-17.9)**	**Caregiver of Teen (ages 12-17.9)**	**Pediatric (ages 6-11.9)**	**Caregiver of Pediatric (ages 6-11.9)**
Screening	Clarke	Clarke	n/a	n/a	Clarke
Visit 2 (Phase 1)	WHO-5 EQ-5D-5L T1DDS DTSQs Hypoglycemia Confidence Scale HABS PSQI IDSS (T1) SUS	WHO-5 EQ-5D-5L PAID-Teen Hypoglycemia Confidence Scale PSQI SUS	WHO-5 DTSQs P-PAID-Teen Hypoglycemia Confidence Scale PSQI IDSS (T1)	EQ-5D-Y PAID-Child	WHO-5 DTSQs P-PAID-Child Hypoglycemia Confidence Scale PSQI IDSS (T1) SUS
End of Phase 2 (~13 weeks) or Early Withdrawal	WHO-5 EQ-5D-5L T1DDS DTSQc Hypoglycemia Confidence Scale HABS PSQI IDSS (T1) SUS INSPIRE-Adult Clarke Human Factors	WHO-5 EQ-5D-5L PAID-Teen Hypoglycemia Confidence Scale PSQI SUS INSPIRE-Youth Clarke Human Factors	WHO-5 DTSQc P-PAID-Teen Hypoglycemia Confidence Scale PSQI IDSS (T1) INSPIRE-Parent	EQ-5D-Y PAID-Child INSPIRE-Youth	WHO-5 DTSQc P-PAID-Child Hypoglycemia Confidence Scale PSQI IDSS (T1) SUS INSPIRE-Parent Clarke Human Factors

*Some questionnaires require completion by both the subject and the caregiver. Caregivers completing questionnaires must be the caregiver that provided consent for study participation, or subsequently signed a consent form. It is preferable that the caregiver completing a questionnaire at screening or Visit 2 is the same caregiver completing questionnaires at the End of Phase 2 (~13 weeks of hybrid closed-loop participation) or at the time of withdrawal from the study. No questionnaires will be completed during or at the conclusion of Phase 3.

6 OBJECTIVES AND ENDPOINTS

6.1 Primary Safety Objective

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

6.1.1 Primary Safety Endpoints

The primary safety objective will be evaluated by summarizing the following events during Phase 2, and separately during Phase 3:

- Incidence rate of severe hypoglycemia (events per person months)
- Incidence rate of diabetic ketoacidosis (DKA) (events per person months)

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 Endpoints

There are two primary effectiveness endpoints.

- A1C after at least 6 weeks of continuous Phase 2 participation compared to baseline
- A1C at Visit 16, 19, 21, and 23 compared to baseline
- Percentage of time in range (70-180 mg/dL) during Phase 2 and separately during Phase 3 of the hybrid closed-loop phase as compared to Phase 1 (standard therapy)

6.3 Secondary Objective

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

6.3.1 Secondary Endpoints

The secondary objective will be evaluated using the following per subject endpoints *with* prespecified hypotheses:

- Glucose metrics from system CGM during the hybrid closed-loop phase for Phase 2 will be compared to Phase 1 overall:
    - % of time > 180 mg/dL
    - % of time < 70 mg/dL

Additional per subject secondary endpoints *without* prespecified hypotheses used to evaluate the secondary objective include:

- A1C:
    - A1C after at least 8 weeks of continuous Phase 2 participation at the end of Phase 2 (Visit 13), at 6 months (Visit 16), and at the end of Phase 3 (Visit 23; approximately 15 months)
    - Change from baseline in A1C after at least 6 weeks of continuous Phase 2 participation, after at least 8 weeks of continuous Phase 2 participation at the end of Phase 2 (Visit 13), at 6 months (Visit 16), and at the end of Phase 3 (Visit 23; approximately 15 months)
    - Proportion of subjects demonstrating an improvement from baseline in A1C after at least 6 weeks of continuous Phase 2 participation, after at least 8 weeks of continuous Phase 2 participation at the end of Phase 2 (Visit 13), at 6 months (Visit 16), and at the end of Phase 3 (Visit 23; approximately 15 months)

- Glucose metrics from system CGM during the hybrid closed-loop phase during Phase 2, and separately during Phase 3, will be compared to Phase 1 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

- Percentage of time in hybrid closed-loop as proportion of overall device usage time during Phase 2, and separately during Phase 3
- Glucose management indicator (GMI) based on overall mean glucose during Phase 2, and separately during Phase 3 will be compared to Phase 1
- Insulin requirements during Phase 2, and separately during Phase 3 will be compared to Phase 1:

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

- Change from baseline in BMI (kg/m2) at end of Phase 2, and at end of Phase 3.

6.4 Exploratory Endpoints

Analysis of the following exploratory endpoints will be considered. The analyses may be used for internal research purposes and/or scientific presentations and/or manuscripts and may not all be provided in a regulatory submission:

- Number of hypoglycemic and hyperglycemic events as measured by the system CGM during the hybrid closed-loop phase will be compared to the standard therapy phase
- Glucose metrics from the system CGM during the hybrid closed-loop phase stratified by device mode
- Change from baseline in A1C and BMI at the last follow-up visit given at least 6-weeks of participation during Phase 2
- Change from baseline in A1C after at least 6 weeks of continuous Phase 2 participation, stratified by baseline A1C (e.g. A1C ≥7.5%, ≥9.0%)
- Proportion of subjects with A1C <7.0% at baseline and after at least 6 weeks of continuous Phase 2 participation; similar analyses using A1C cutoffs of <7.5%, <8.0% and <9.0%
- Proportion of subjects with change from baseline in A1C after at least 6 weeks of continuous Phase 2 participation of >0.5% and >1.0%
- Proportion of subjects who either had an improvement from baseline of >1.0% in A1C or A1C <7.0% after at least 6 weeks of continuous Phase 2 participation
- Percentage of time the CGM was used during the hybrid closed-loop phase
- Number of meal and correction boluses
- Compare glycemic outcomes (e.g., time in range <70 mg/dL, time in range >180 mg/dL) by bolus frequency per day
- Compare glycemic outcomes (e.g., time in range <70 mg/dL, time in range >180 mg/dL) by use of CGM informed bolus calculator (i.e., days with CGM informed bolus calculator used at least once and days without CGM informed bolus calculator use)
- Post-prandial glucose response including time to peak glucose, peak glucose concentration, peak glucose excursion, to meals with bolus (challenge days 1 and 3) vs no bolus (challenge days 2 and 4)
- Glycemic outcomes and other measures based on evaluable subjects (i.e., those subjects with at least 8-weeks of data during the hybrid closed-loop phase)

6.5 Patient Reported Outcomes

Various subject- and caregiver-completed questionnaires will be used to evaluate general and disease-specific quality of life, and device usability. These include, but are not limited to:

- WHO-5
- EQ-5D
- PAID
- T1DDS
- DSTQ
- Hypoglycemia Confidence
- HABS
- PSQI
- IDSS (T1)
- SUS
- INSPIRE

- Human Factors Questionnaire
- Clarke Questionnaire

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. The prepivotal study will be conducted in parallel to the pivotal study and will include a minimum of 36-subjects between the ages of 6-70 years participating in a standard therapy phase followed by the hybrid closed-loop phase. The prepivotal study will be conducted at up to 8 clinical study sites. The prepivotal study outpatient hybrid closed-loop phase includes 14-days of hybrid closed-loop. Prepivotal study subjects that are eligible to extend their participation into the pivotal study do not require rescreening if their original screening is within 45-days prior to Visit 5, which is their start of Phase 2 in the pivotal study. Prepivotal subjects do not need to participate in the standard therapy phase of the pivotal study since this phase was completed as part of the prepivotal study and is not required to be repeated.

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 for Phase 1 and Phase 2

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).

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 the following types of insulin during the study: Humalog, Novolog, Admelog or Apidra during the study
7. Must be willing to travel to and participate in meal and exercise challenges during 5-days of the hybrid closed-loop phase
8. Willing to wear the system continuously throughout the study
9. A1C <10% at screening visit
10. 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
11. 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
12. Able to read and speak English fluently
13. 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 12.3.3) in the past 6 months

3. History of DKA (as defined in Section 12.3.4) 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 other than the Omnipod Horizon™ Automated Glucose Control System 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 4: 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 for Phase 1 and Phase 2
  - 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 pivotal 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 for Phase 1 and Phase 2.

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.

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 (ST1/Visit 2) 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 immediately eligible to commence the hybrid closed-loop phase starting at Visit 4.

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. If a pump naïve subject is also a current G6 user that meets the criteria as stated above, the subject will complete the saline trial prior to enrollment in the study.

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 for Phase 1 and Phase 2. 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 of pump settings/MDI dosing
- Assessment of AEs
- Completion of questionnaires (see Table 4: 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 (Enrollment)
    - 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 up to 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 for Phase 1 and Phase 2. This visit will include:

- Assessment of AEs
- 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 up to 30-days, 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 the Table 2: Schedule of Assessments for Phase 1 and Phase 2.

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 challenge visits 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 4: Questionnaires)

Subjects will have scheduled follow-up visits according to Table 2: Schedule of Assessments for Phase 1 and Phase 2 and complete questionnaires according to Table 4: Questionnaires. Visits will be conducted either in person at the clinical study site or over the telephone or videoconference. Subjects may also choose to use email or text as a substitute for their scheduled telephone visit. In the event of overlapping visit windows, no visits occurring during Phase 2 are to occur on the same date, with the exception of challenge visit days.

The duration of the hybrid closed-loop phase for Phase 2 will last ~13-weeks (the 13 weeks may not be continuous).

9.1 Challenge Visits

A subset of subjects will take part in the prescribed supervised challenges per the defined sample sizes in Table 5: Sample Size of Subjects Enrolled in Challenges until the minimum number of subjects for each cohort subset has been satisfied. Subjects will participate in prescribed challenges during any consecutive 5-days of the hybrid closed-loop phase. Subjects should be in Automated Mode during the challenges. Every effort will be made to conduct challenges over 5 consecutive days however challenges that occur on non-consecutive days will not constitute a protocol deviation, nor will performing the challenges out of order as long as all prescribed challenges are completed. If challenge visits are not conducted on consecutive days, the site will be required to conduct follow-up telephone visits 12-36 hours after each non-consecutive visit. Challenge visits may occur on the same date as any other Phase 2 visit.

Table 5: Sample Size of Subjects Enrolled in Challenges

Cohort (Ages)	Minimum Number of Subjects (N)
14-70 years	N=60
6-13.9 years	N=100

Subjects will travel to a central location each day where they will be closely monitored by clinical staff throughout the challenges. Alternatively, if subjects are self-isolating during the COVID-19 pandemic, they may complete these challenges at home if a companion or caregiver is present and communicates completion of activities to the site staff by phone or videoconference. Sites can supervise glucose levels by monitoring the Horizon Data Portal.

During the 5-day exercise and meal challenges, subjects will be supervised by clinical site staff trained in the assessment and treatment of diabetic emergencies. Clinical site staff or companions/caregivers will be equipped with emergency supplies including glucose tablets, glucagon, and other supplies used for the treatment of diabetic emergencies. Subjects may participate in exercise if their CGM value is ≥70 mg/dL with the corresponding CGM trend either steady or increasing. Subjects will be discharged from each day of challenges when they meet the CGM criteria between 70-300 mg/dL on two consecutive checks for the last 30-minutes of their participation given that the CGM trend is not rapidly increasing or decreasing at these timepoints.

Challenges can occur in a group setting with multiple subjects.

The challenges will include:

Table 6: Challenges

Challenges	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
High Carbohydrate Meal (≥ 60 grams)	X With Bolus Day 1 and 2 Matched Meal	X No Bolus Day 1 and 2 Matched Meal	X With Bolus Day 3 and 4 Matched Meal	X No Bolus Day 3 and 4 Matched Meal	X With Bolus	
Exercise to include both: • **One-hour minimum of moderate or greater intensity exercise[12]** • **Two-hour minimum of mild or greater intensity exercise[27]**	X	X	X	X	X	
Follow-up Telephone Visit (12-36h post challenges)						X

Moderate intensity exercise is defined using the CDC guidelines[12] (Table 7):

Table 7: 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

Low intensity exercise is defined using the US Department of Health and Human Services Physical Activity Guidelines for Americans and includes waking non-sedentary behaviors such as walking at 2.0 miles per hour, cooking activities, or light housekeeping. [27]

During the challenge visits, subjects will be encouraged to:

- 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 exercise challenge.

Subjects will be offered a snack prior to their release from the site upon discharge.

Inability to complete the 5-days of exercise due to an injury where participation may exacerbate the condition will not be considered a protocol deviation. Ability to participate will be up to the discretion of the investigator.

9.2 Visit 4

Visit 4 represents the commencement of Phase 2 (hybrid closed-loop phase) for subjects that did not participate in the prepivotal study and will be conducted in person at the clinical site on Study Day 1. All scheduled assessments will be performed according to Table 2: Schedule of Assessments for Phase 1 and Phase 2. 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
- Initiation of Horizon Data Portal monitoring

- 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.

- Subjects may choose their desired target BG ranging between 110-150 mg/dL in increments of 10mg/dL, although the default and recommended setpoint is 120 mg/dL.
- 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)
  - Investigators may use the Insulet-provided Patient Therapy Order Form (PTOF) as a guide to transition subjects from MDI to pump therapy (Appendix A)

If a subject is a current Dexcom G6 User and Visit 2 and Visit 4 occur on the same day, average total daily insulin and pump settings/MDI dosing only needs to be collected once. Further, if Visit 1 and Visit 4 occur on the same day, only one pregnancy test is required.

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.

9.3 Visit 5

Visit 5 will be conducted either over the telephone or in person at the clinical study site on Study Day 2 ± 1-day for subjects commencing the hybrid closed-loop phase during Visit 4. For subjects extending their participation from the prepivotal study, the visit may be conducted in person at the clinical study site or over the telephone. This visit will include:

- Informed consent for subjects extending their participation from prepivotal (Informed Consent may occur at any time during the prepivotal study but must occur prior to commencing the pivotal study)
- Establishing eligibility for subjects extending their participation from prepivotal
- 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 for subjects extending their participation from prepivotal and the visit was conducted in the office
- Data review of Automated Mode use by clinician

9.4 Visit 6

Visit 6 will be conducted either over the telephone or in person at the clinical study site on Study Day 3 ± 1 day. 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
- Data review of Automated Mode use by clinician

9.5 Visit 7

Visit 7 will be conducted either over the telephone or in person at the clinical study site on Study Day 10 ± 3-days. This visit will include:

- A pregnancy test for women of childbearing potential (if visit is conducted in person at the clinical study site)
- Review of concomitant medications
- Assessment of vital signs (if visit is conducted in person 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 in person at the clinical study site)
- Data review of Automated Mode use by clinician

9.6 Visit 8

Visit 8 will be conducted either over the telephone or in person at the clinical study site on Study Day 24 ± 3-days. 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
- Data review of Automated Mode use by clinician

9.7 Visit 9

Visit 9 will be conducted either over the telephone or in person at the clinical study site on study day 38 ± 3-days. This visit will include:

- A pregnancy test for women of childbearing potential (if visit is conducted in person at the clinical site).
- Review of concomitant medications
- Assessment of vital signs (if visit is conducted in person at the clinical 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 in person at the clinical site)
- Data review of Automated Mode use by clinician

9.8 Visits 10, 11 and 12

Visits 10, 11 and 12 will be conducted either over the telephone or in person at the clinical study site on Study Day 52, 66, and 80 ± 3-days. 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
- Data review of Automated Mode use by clinician

9.9 Visit 13 (End of Phase 2)

Visit 13 will be conducted either over the telephone or in person at the clinical study site on Study Day 94 ± 3 days. This visit will include:

- A1C (blood draw sent to NGSP laboratory)
- Pregnancy test for women of childbearing potential (if visit is conducted in person at the clinical site)
- Review of concomitant medications
- Height (if visit is conducted in person at the clinical site)
- Weight (if visit is conducted in person at the clinical site)
- Assessment of vital signs (if visit is conducted in person at the clinical site)
- Assessment of AEs since last visit
- Completion of questionnaires (See Table 4: 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
  - Human Factors (HF) Questionnaire
    - Measures trust in the Horizon System

  - Clarke Questionnaire
- Discontinuation of Horizon Data Portal monitoring if not continuing into Phase 3
- Return study devices if not continuing into Phase 3 (Omnipod Horizon™ System, CGM, BG and ketone meters)
- Complaints/device deficiencies such as occlusion alarms and system hazard alarms since last visit
- Device uploads for BG and ketone meter
- Data review of Automated Mode use by clinician

This visit will mark the discontinuation of Phase 2 and mark the end of the study for subjects not continuing to Phase 3.

9.10 Unscheduled Visits (Phase 2)

Aside from scheduled visits, subjects may require an unscheduled visit either by telephone (inclusive of email or text options) or in person at the clinical study site. All scheduled assessments will be performed according to Table 2: Schedule of Assessments for Phase 1 and Phase 2. This visit will include, at a minimum:

- 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 (recommendation only if visit is conducted at the clinical site)
- Data review of Automated Mode use by clinician

During the Phase 2 study pause, subjects that wish to continue to use the Omnipod Horizon™ System in Manual Mode or subjects that wish to go back to using their own system during the pause will have either telephone or in person visits every 4 weeks ± 5 days from their last scheduled or unscheduled visit until the study resumes.

Subjects will continue to be provided study supplies during the study pause if they wish to continue in the study.

If subjects have been in the pivotal hybrid closed-loop phase for ≥ 35 days prior to pausing Automated Mode, subjects may be requested to submit to an A1C lab draw as soon as possible after pausing Automated Mode. The A1C lab draw does not have to coincide with a scheduled or an unscheduled visit.

Sites will ensure subjects that are continuing to use the system in Manual Mode do not enter Automated Mode during the study pause.

- Sites will be asked to check the Horizon Data portal once per week to make sure subjects have not entered Automated Mode
- If a subject is found to be in Automated Mode, the subject will be given a warning. If the same subject is found to be in Automated Mode a second

time, the subject will be instructed to return the investigational device to the site until a software fix is available

Subjects that do not wish to continue their study participation will be withdrawn from the study.

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.

9.11 Recommencing After a Pause

The recommencement visit or visits may be conducted either over the telephone or in person at the clinical study site preferably within 5 business days of recommencing Phase 2 of the study. The assessments required prior to the recommencement of Phase 2 will include:

- Informed consent (may be conducted over telephone or email and will contain language for the study recommencement and the extension phase)
- Optional A1C (blood draw sent to NGSP laboratory)
- Pregnancy test for women of childbearing potential. If subject is not able to attend in person, they may conduct the test at home and report result to the site.
- 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)
- Assessment of AEs
- Return Horizon System to subject (if applicable)
- Update of PDM software by the study site or provide subject with a new, updated PDM
- Resume Phase 2 of hybrid closed-loop including the following (as applicable):
    - Entry of Dexcom Transmitter ID into Horizon™ PDM
    - Initiation of Horizon™ Data Portal monitoring
    - Removal of the subject's personal insulin pump
- Complaints/device deficiencies for study devices
- Device uploads for BG and ketone meter (if visit is conducted in person at the clinical site)
- Data review by clinician will include therapy during the pause

All subjects will resume the study where they left off with respect to the visit schedule. For example, a subject that started Phase 2 (of hybrid closed-loop) on 01 February

2020, completed Visit 8 on 24 February 2020 and paused participation on 28 February 2020 has completed 28 days of Phase 2 participation. If the subject resumes Phase 2 on 01 May 2020, this date is equivalent to Day 29 of Phase 2 participation. The next scheduled study visit would be Visit 9 that should occur on Study Day 38 ± 3 days. In this example, Visit 9 should occur between the 7 May and 13 May 2020, inclusive, with the optimal date being 10 May 2020. All subsequent visits will occur as scheduled.

A total of up to 42 subjects will defer recommencement of Phase 2 to participate in a parallel study (G200018) to evaluate the safety and effectiveness of the Omnipod Horizon™ CGM-informed bolus calculator. Once the subset of subjects complete the study, they will recommence Phase 2 of the Omnipod Horizon pivotal study (G190270).

9.12 Early Withdrawal (Phase 2)

Any subject may withdraw early from the study at any time for any reason. Upon withdrawal, assessments will be performed following Table 2: Schedule of Assessments for Phase 1 and Phase 2. 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:

- A1C (blood draw sent to NGSP laboratory)
- Review of concomitant medications
- Height
- Weight
- Assessment of vital signs
- Assessment of AEs since last visit
- Completion of questionnaires (see Table 4: 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
  - Human Factors (HF) Questionnaire
    - Measures trust in the Horizon System
  - Clarke Questionnaire
- Discontinuation of Horizon Data Portal 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 reason for withdrawal will be recorded, and their 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.

10 HYBRID CLOSED-LOOP – PHASE 3

The hybrid closed-loop Phase 3 extension will commence at **Visit 13** upon conclusion of hybrid closed-loop Phase 2 and after all assessments are performed according to Table 2: Schedule of Assessments for Phase 1 and Phase 2. Phase 3 assessments are to be performed according to Table 3: Schedule of Assessments for Phase 3.

For subjects that do not extend their participation into the extension phase, the reason for study exit at Visit 13 will be documented. This will not be considered an early withdrawal from the study.

Subjects extending their participation into the extension phase are to be consented for both the first 6-month and the second 6-month interval of Phase 3. Consent for each interval must occur on or any time before commencing that study interval (e.g. consent for first 6-months of Phase 3 must occur on or before Visit 13, consent for second 6-months of Phase 3 must occur on or before Visit 19).

During the hybrid-closed loop extension phase, subjects will continue to perform 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 challenge visits as specified
- Change their CGM per manufacturer's instructions or sooner if necessary
- Change the Pod at least once every 72 hours

Subjects will have scheduled follow-up visits. Visits will be conducted either 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 extension phase will last approximately 12-months.

Subjects will be encouraged to call the clinical study site at any time with any concerns.

10.1 Visit 14

Visit 14 will be conducted either over the telephone or in person at the clinical study site on Study Day 120 ± 5 days. This visit will include:

- Review of concomitant medications
- Assessment of adverse events since previous 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 site)
- Data review of Automated Mode use by clinician

10.2 Visit 15

Visit 15 will be conducted either over the telephone or in person at the clinical study site on Study Day 150 ±5 days. 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 (if visit is conducted at the clinical site)
- Data review of Automated Mode use by clinician

10.3 Visit 16

Visit 16 will be conducted either over the telephone or in person at the clinical study site on Study Day 180 ± 5 days. This visit will include:

- A1C (blood sample sent to NGSP laboratory)
- A pregnancy test for women of childbearing potential (if visit is conducted in person at the clinical site)
- 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 site)
- Data review of Automated Mode use by clinician

10.4 Visits 17 and 18

Visits 17 and 18 will be conducted either over the telephone or in person at the clinical study site on Study Day 210 ± 5 days and Study Day 240 ± 5 days, respectively. 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 site)
- Data review of Automated Mode use by clinician

10.5 Visit 19

Visit 19 will be conducted either over the telephone or in person at the clinical study site on Study Day 270 ± 5 days. This visit will include:

- A1C (blood sample sent to NGSP laboratory)
- Pregnancy test for women of childbearing potential (if visit is conducted in person at the clinical site)
- Informed Consent (consent for second 6-month interval of Phase 3 may occur on or any time before this visit)
- 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 of Automated Mode use by clinician

10.6 Visit 20

Visit 20 will be conducted either over the telephone or in person at the clinical study site on Study Day 315 ± 5 days. This visit will include:

- Review of concomitant medications
- Assessment of AEs since previous 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 site)
- Data review of Automated Mode use by clinician

10.7 Visit 21

Visit 21 will be conducted either over the telephone or in person at the clinical study site on Study Day 360 ±5 days. This visit will include:

- A1c (blood sample sent to NGSP laboratory)
- Review of concomitant medications
- Assessment of AEs since previous 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 site)
- Data review of Automated Mode use by clinician

10.8 Visit 22

Visit 22 will be conducted either over the telephone or in person at the clinical study site on Study Day 405 ± 5 days. This visit will include:

- Review of concomitant medications
- Assessment of AEs since previous 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 site)
- Data review of Automated Mode use by clinician

10.9 Visits 23 (end of study)

Visits 23 will be conducted in person at the clinical study site on Study Day 450 ± 5 days. This visit will include:

- A1c (blood sample sent to NGSP laboratory)
- Review of concomitant medications
- Height
- Weight
- Assessment of AEs since previous visit
- Return study devices (Omnipod Horizon™ System, CGM, BG and ketone meters)
- Complaints/device deficiencies such as occlusion alarms and system hazard alarms since last visit
- Device uploads for BG and ketone meter
- Data review of Automated Mode use by clinician

10.10 Unscheduled Visits (Phase 3)

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 3: Schedule of Assessments for Phase 3. This visit will include, at a minimum:

- Review of concomitant medications

- Assessment of AEs since last visit
- Complaints/device deficiencies such as occlusion alarms and system hazard alarms since last visit
- Data review of Automated Mode use by clinician

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

10.11 Early Withdrawal (Phase 3)

Any subject may withdraw early from the study at any time for any reason. Upon withdrawal, assessments will be performed following Table 3: Schedule of Assessments for Phase 3. 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:

- A1C (blood sample sent to NGSP laboratory)
- Review of concomitant medications
- Height
- Weight
- Assessment of AEs since last visit
- Return study devices (Omnipod Horizon™ System, CGM, BG and ketone meters)
- 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 reason for withdrawal will be recorded, and their 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.

10.12 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.

11 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.

12 SAFETY

12.1 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 and/or hyperglycemia as a result of over or under delivery of insulin due to a device defect, failure or malfunction of any of the system components.
- 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.

12.2 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.

12.3 Adverse Events

12.3.1 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 (ADE) 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]

An event that occurs solely due to participant (i.e., user) error in which the device functions properly generally will not be considered an ADE unless it is determined that the instructions on the screen of the device or user manual (or similar training materials) may have contributed to the event (note: the event may still meet criteria for reporting as an adverse event).

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.

12.3.2 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 2 and 3 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. Hyperglycemia/Ketotic Events as defined

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.

12.3.3 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.

12.3.4 Hyperglycemic/Ketotic Events

Hyperglycemia is only reportable as an adverse event when any 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.

12.3.5 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.

12.3.6 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.

12.3.7 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.

12.4 Reportable Device Issues

Device complaints and device 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

12.5 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 competed 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 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 will 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.

12.6 Safety Oversight

The study Medical Monitor will review all adverse events and adverse device 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, 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.

12.7 Stopping Criteria

12.7.1 Participant Discontinuation of Study Participation

In the case of a UADE, the Medical Monitor will determine if the use of the study device will be suspended while the problem is diagnosed. The use of the study device may continue if the Medical Monitor believes the event is explainable, unlikely to reoccur and that it is safe for the subject to continue using the device. Alternately, the Medical Monitor may request the study subject, or all study subjects, to stop using the study device or to only use in Manual Mode. Should all study subjects be required to stop using the study device or to only use in Manual Mode due an UADE, use of the study device or Automated Mode 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.

12.7.2 Criteria for Suspending or Stopping Overall Study

Stopping criteria for Phase 2 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. Stopping rules may be modified for the Phase 3 extension.

In consideration of adverse events rates occurring in this proposed study, 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 8: T1D Exchange Rates of Severe Hypoglycemia and Diabetic Ketoacidosis10,26provides a summary of these published rates.

Table 8: 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.

12.8 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 study and review Severe Hypoglycemia and DKA as well compiled safety data at periodic intervals to determine if the stopping rules apply. Stopping rules may be modified for the Phase 3 extension.

Compiled safety data may include listings of protocol deviations, device deficiencies, subject terminations, and/or subject withdrawals related to device or procedure safety. 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 the hybrid closed-loop phase (and prior to commencement of Pivotal Phase 2 for any subjects that did not participate in Prepivotal Phase 2), at the conclusion of the prepivotal study, after at least 80 pivotal subjects have completed study visit 7 (24 ± 3 days of HCL therapy), and after the end of Phase 3. Additional reviews 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.

12.9 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.
- 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).

13 STATISTICAL CONSIDERATIONS

13.1 Definition of Phase 2 and Phase 2 Participation

For the majority of subjects, Phase 2 of hybrid closed-loop data will include both data collected prior to a study pause and data collected after the recommencement. Unless otherwise specified, any data that may have been collected during a study pause (including but not limited to CGM readings from the Horizon system while in Manual Mode), will be excluded from analyses.

Continuous Phase 2 participation refers to the length of time on the Horizon system (either in Automated on Manual Modes) and is calculated as:

- Commencement of Phase 2 until a study pause (for subjects who started Phase 2 prior to a study pause)
- Recommencement until discontinuation from the Horizon system or end of Phase 2 (for subjects who started Phase 2 prior to a study pause)
- Commencement of Phase 2 until discontinuation from the Horizon system or end of Phase 2 (for subjects who started Phase 2 after a study pause)

If a subject has ≥6 weeks on the Horizon system during Phase 2 prior to a study pause and ≥6 weeks on the Horizon system during Phase 2 after the recommencement, the longer interval will be used for analysis of A1C. Specifically, the A1C associated with the longer interval, if available, will be used for the analysis of the A1C endpoints.

13.2 Objectives and Endpoints

13.2.1 Primary Safety Objective

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

13.2.1.1 Primary Safety Endpoints

The primary safety objective will be evaluated by summarizing the following events during Phase 2, and separately during Phase 3:

- Incidence rate of severe hypoglycemia (events per person months)
- Incidence rate of diabetic ketoacidosis (DKA) (events per person months)

13.2.2 Primary Effectiveness Objective

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

13.2.2.1 Primary Effectiveness Endpoints

There are two primary effectiveness endpoints.

- A1C after at least 6 weeks of continuous Phase 2 participation compared to baseline
- A1C at Visit 16, 19, 21, and 23 compared to baseline
- Percentage of time in range (70-180 mg/dL) during Phase 2 and separately during Phase 3 of the hybrid closed-loop phase as compared to Phase 1 (standard therapy)

A1C – Phase 2

A1C after at least 6 weeks of continuous Phase 2 participation will be compared to baseline A1C as measured by the core laboratory by calculating the change from baseline in A1C at the appropriate follow-up visit for each subject. Given the nature of this measure, continuous device use is essential for unbiased measurement of A1C. Therefore, the follow-up A1C used in the analysis of this endpoint will include only data from the subjects with at least 6 weeks of continuous Phase 2 participation, either prior to study pause or after recommencement, depending on the length of continuous participation and availability of the A1C measurements. The A1C collected at the latest follow-up visit during Phase 2 will be used, assuming it was collected after at least 6 weeks of subject's participation in Phase 2.

The change in A1C is calculated as A1C at follow-up minus baseline A1C (where negative change indicates decrease or improvement in A1C). The null hypothesis associated with this endpoint states that the mean change in A1C is greater than or equal to zero. Rejection of the null hypothesis indicates that the observed data support the alternative hypothesis that the mean change in A1C is less than zero.

The hypotheses associated with the first primary endpoint are defined as:
H_0: $\mu \geq 0$
H_1: $\mu < 0$
where μ is the mean of the per subject differences in A1C from baseline to follow-up.

A1C – Phase 3

A1C at Visit 16 (~6 months total HCL participation) will be compared to baseline A1C as measured by the core laboratory by calculating the change from baseline in A1C at follow-up visit for each subject.

The change in A1C is calculated as A1C at follow-up minus baseline A1C. There are no hypotheses associated with this endpoint.

Percentage of Time in Range 70-180 mg/dL – Phase 2

The percentage of time in range 70-180 mg/dL during Phase 2of the hybrid closed-loop phase will be compared to standard therapy by calculating the change between the time in range percentages between Phase 2of hybrid closed-loop and Phase 1 (standard therapy) for each subject. The change in percentage of time in range 70-180 mg/dL is calculated as the percentage of time in range during Phase 2 minus the percentage of time in range during Phase 1 (where positive change indicates increased time in range). The null hypothesis associated with this endpoint states that the mean change in percentage of time in range 70-180 mg/dL is less than or equal to zero. Rejection of the null hypothesis indicates that the observed data support the alternative hypothesis that the mean change in percentage of time in range 70-180 mg/dL is greater than zero.

The hypotheses associated with the this primary endpoint are defined as:
H_0: $\mu \leq 0$
H_1: $\mu > 0$
where μ is the mean of the per subject differences in percentage of time in range 70-180 mg/dL during Phase 2 of hybrid closed-loop phase compared to Phase 1.

Percentage of Time in Range 70-180 mg/dL – Phase 3

The percentage of time in range 70-180 mg/dL during Phase 3 of the hybrid closed-loop phase will be compared to standard therapy by calculating the change between the time in range percentages between Phase 3 of hybrid closed-loop and Phase 1 (standard therapy) for each subject. The change in percentage of time in range 70-180 mg/dL is calculated as the percentage of time in range during Phase 3 minus the percentage of time in range during Phase 1. There are no hypotheses associated with this endpoint.

13.2.3 Secondary Objective

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

13.2.4 Secondary Endpoints

The secondary objective will be evaluated using the following per subject endpoints *with* prespecified hypotheses:

- Glucose metrics from system CGM during the hybrid closed-loop phase for Phase 2 will be compared to Phase 1 overall:
    - % of time > 180 mg/dL
    - % of time < 70 mg/dL

Additional per subject secondary endpoints *without* prespecified hypotheses used to evaluate the secondary objective include:

- A1C:

  - A1C after at least 8 weeks of continuous Phase 2 participation at the end of Phase 2 (Visit 13), at 6 months (Visit 16), and at the end of Phase 3 (Visit 23; approximately 15 months)
  - Change from baseline in A1C after at least 6 weeks of continuous Phase 2 participation, after at least 8 weeks of continuous Phase 2 participation at the end of Phase 2 (Visit 13), at 6 months (Visit 16), and at the end of Phase 3 (Visit 23; approximately 15 months)
  - Proportion of subjects demonstrating an improvement from baseline in A1C after at least 6 weeks of continuous Phase 2 participation, after at least 8 weeks of continuous Phase 2 participation at the end of Phase 2 (Visit 13), at 6 months (Visit 16), and at the end of Phase 3 (Visit 23; approximately 15 months)

- Glucose metrics from system CGM during the hybrid closed-loop phase during Phase 2, and separately during Phase 3 will be compared to Phase 1 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

- Percentage of time in hybrid closed-loop as proportion of overall device usage time during Phase 2, and separately during Phase 3
- Glucose management indicator (GMI) based on overall mean glucose during Phase 2, and separately during Phase 3 will be compared to Phase 1
- Insulin requirements during Phase 2, and separately during Phase 3 will be compared to Phase 1:

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

- Change from baseline in BMI (kg/m^2) at end of Phase 2, and at end of Phase 3

Percentage of Time in Range >180 mg/dL

The percentage of time in range >180 mg/dL during Phase 2 of hybrid closed-loop phase will be compared to standard therapy (Phase 1) by calculating the change between the time in range percentages between Phase 2 and Phase 1 for each subject. The change in percentage of time in range >180 mg/dL is calculated as

the percentage of time in range during Phase 2 minus the percentage of time in range during Phase 1. The null hypothesis associated with this endpoint states that the mean change in percentage of time in range >180 mg/dL is greater than or equal to zero. Rejection of the null hypothesis indicates that the observed data support the alternative hypothesis that the mean change in percentage of time in range >180 mg/dL is less than zero.

The hypotheses associated with this secondary effectiveness endpoint are defined as:
H_0: $\mu \geq 0$
H_1: $\mu < 0$
where μ is the mean of the per subject differences in percentage of time in range >180 mg/dL during Phase 2 of hybrid closed-loop compared to the standard therapy phase (Phase 1).

Percentage of Time in Range <70 mg/dL

The percentage of time in range <70 mg/dL during Phase 2 of hybrid closed-loop phase will be compared to standard therapy (Phase 1) by calculating the change between the time in range percentages between Phase 2 and Phase 1 for each subject. The change in percentage of time in range <70 mg/dL is calculated as the percentage of time in range during Phase 2 minus the percentage of time in range during Phase 1. The null hypothesis associated with this endpoint states that the mean change in percentage of time in range <70 mg/dL is greater than or equal to zero. Rejection of the null hypothesis indicates that the observed data support the alternative hypothesis that the mean change in percentage of time in range <70 mg/dL is less than zero.

The hypotheses associated with this secondary effectiveness endpoint are defined as:
H_0: $\mu \geq 0$
H_1: $\mu < 0$
where μ is the mean of the per subject differences in percentage of time in range <70 mg/dL during Phase 2 of hybrid closed-loop compared to the standard therapy phase (Phase 1).

13.3 Sample Size

This is a single-arm, multi-center, prospective study. The sample size and study duration were determined to allow for adequate safety profile of the investigational device. The study will be claimed successful if rates of Severe Hypoglycemia and DKA during Phase 2 are considered acceptable compared to published rates.

In addition, a statistically powered sample size was determined for the two Phase 2 primary effectiveness endpoints. Since each of the Phase 2 primary effectiveness endpoints will be evaluated separately, the significance level will be adjusted so that the overall type I error can be maintained at one-sided 2.5% and each endpoint will be tested at one-sided 1.25%.

13.3.1 Primary Endpoint of A1C After at Least 6 Weeks of Continuous Phase 2 Participation Compared to Baseline

The sample size estimation is based on the following assumptions:

- Mean difference between paired observations of A1C after at least 6 weeks of continuous Phase 2 participation compared to baseline is -0.5%
- Standard deviation of the difference between paired observations of A1C after at least 6 weeks of continuous Phase 2 participation compared to baseline is 0.8%
- Power of 90% and one-sided significance level of 1.25%

The estimates for the mean difference and standard deviation of the difference between the paired observations were obtained from previous Omnipod studies, where subjects experienced a mean change in A1C of 0.38% over 3 months (standard pump therapy only), from 8.1 to 7.7%, n=85 *(data on file)*. Based on the above assumptions, 35 subjects are required to provide evaluable data.

13.3.2 Primary Endpoint of Percentage of Time in Range 70-180 mg/dL During Phase 2 of Hybrid Closed-Loop Compared to Phase 1

The sample size estimation is based on the following assumptions:

- Mean difference between paired observations of percentage of time in range 70-180 mg/dL during Phase 2 of hybrid closed-loop compared to the Phase 1 is 10%
- Standard deviation of the difference between paired observations of percentage of time in range 70-180 mg/dL during Phase 2 of hybrid closed-loop compared to Phase 1 is 15%
- Power of 90% and one-sided significance level of 1.25%

The estimates for the mean difference and standard deviation of the difference between the paired observations were obtained from recent Omnipod studies, G170012 and G170143, where subjects experienced a mean change in percentage of time in range 70-180 mg/dL of 10.0 ± 15.1% and 13.8 ± 14.6%, respectively. Based on the above assumptions, 31 subjects are required to provide evaluable data.

To gather adequate safety and effectiveness data on the performance of the Omnipod Horizon™ System, a total of up to 240 subjects will be enrolled in the study in order to obtain a minimum of 200 evaluable subjects.

Subjects will be enrolled at up to 20 clinical study sites. No single site should enroll more than 24 subjects for each age cohort.

A subset of subjects will take part in the prescribed exercise challenges per the defined sample sizes until the minimum number of subjects for each cohort subset has been satisfied. The enrollment cap for the exercise challenges will follow a similar logic as above for total enrollment and will be detailed in the Statistical Analysis Plan.

13.4 Analysis Sets

The following analysis sets are planned for the study and will apply to the endpoints through the end of Phase 2. There are no prespecified analysis sets for Phase 3; all available data will be used to summarize Phase 3 endpoints:

13.4.1 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.

13.4.2 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.

13.4.3 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 hybrid closed-loop (Automated) modes over a minimum duration of 10 weeks and have completed the study without major protocol deviations. The Manual Mode use during study pause does not contribute to the minimum system use requirement. The PP analysis set will be used as supportive analysis for the 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.

13.5 Analysis of Primary and Secondary Endpoints

Both Phase 2 primary effectiveness endpoints will be tested independently of each other for statistical significance using a paired t-test at a one-sided significance level of 1.25%.

If at least one of the Phase 2 primary effectiveness endpoints are found to be significant, the testing for Phase 2 secondary endpoints can commence. The details on how the family-wise error rate will be maintained at the 2.5% significance level (one-sided) will be provided in the Statistical Analysis Plan (SAP). In addition, the Phase 2 primary effectiveness endpoints may also be tested for significance within a smaller cohort of subjects (such as based on age). The details of subgroup analyses and testing will also be detailed in the SAP. At a minimum, the Phase 2 primary effectiveness endpoints will be presented by existing Dexcom G6 use at the time of screening (users and non-users) and by participation in the prepivotal study (those who participated in the prepivotal study and those who did not).

There are no hypotheses associated with the other Phase 2 secondary endpoints or any of the Phase 3 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 Phase 2 primary and secondary 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 will be compared to the data collected in the hybrid closed-loop phase of the study.

13.5.1 Time in Range Endpoints

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

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

13.6 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.

13.7 Safety Analyses

13.7.1 Evaluation of Adverse Events

All adverse events reported over the course of the study will be summarized and tabulated by study phase, event category, seriousness, severity, and relationship to the study procedure 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 endpoints will be presented by existing Dexcom G6 use at the time of screening (users and non-users) and by participation in the prepivotal study (those who participated in the prepivotal study and those who did not).

Adverse events that were reported during study pause will be listed separately.

13.7.2 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.

Device deficiencies that were reported during study pause will be listed separately.

13.8 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.

13.9 General Statistical Methods

Standard statistical methods will be employed to analyze all data. Data collected in this study will be presented 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.

13.10 Missing Data

All practical monitoring and follow-up steps will be taken to ensure complete and accurate data collection. All analyses will be based on available data only; no imputation for missing data is planned.

13.11 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.

Additional details regarding statistical analyses will be provided in the Statistical Analysis Plan (SAP) which will be prepared prior to data analysis. If discrepancies exist between the protocol and the SAP, the SAP will prevail. Any deviations from the finalized SAP will be described in the final study report.

14 DATA HANDLING AND QUALITY ASSURANCE

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

14.1 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.

14.2 Electronic Device Outputs

14.2.1 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.

14.2.2 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.

14.2.3 BG and Ketone Meter Data

This study will also utilize measurements from a BG and ketone meter. BG and Ketone meter data, in any format, will be uploaded to the database.

14.3 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.

14.4 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.

14.5 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.

14.6 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.

14.7 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.

15 STUDY ETHICS AND CONDUCT

15.1 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).

15.2 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.

15.3 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.

15.4 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.

15.5 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.

15.6 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.

15.7 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.

15.8 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.

15.9 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.

15.9.1 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.

15.9.2 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.

15.10 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.

15.11 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 PDMs will be returned to the Sponsor after completion of the study.

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

15.12 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

15.13 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.

15.14 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 A

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 _____ units/day x 0.75 = _____ units *Pre-Pump TDD* *Pump TDD*		**Weight kg x 0.5** or **lbs x 0.23** _____ kg x 0.5 = _____ units OR _____ lbs. x 0.23 = _____ units *Pump TDD* *Pump TDD*
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)*		_____ units/day x 0.5 = _____ units *Pump TDD* *Total Daily Basal*
Initial Basal Rate *(Total Daily Basal / 24 hours = Initial Basal Rate)*		_____ units/24 hours = _____ U/hr *Total Daily Basal* *Initial Basal Rate*
Bolus Settings		
Insulin to Carb Ratio *(450/TDD = Insulin to Carb Ratio)*		450/_____ units/day = _____ grams/unit *TDD* *Insulin to Carb Ratio*
Correction Factor *(1700/Pump TDD = Correction Factor)*		1700/_____ units/day = _____ mg/dL/unit *Pump TDD* *Correction Factor*
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 _____

Reference: Grunberger, G, Abelseth, J, Bode, B., et al. Consensus Statement by the American Association of Clinical Endocrinologist/American College of Endocrinology Insulin Pump Management Task Force. *Endocrine Practice*. 2014; 20 (5), 463-489.