Evaluating the Safety and Effectiveness of the Omnipod Horizon™ CGM-informed Bolus Calculator in Patients with Type 1 Diabetes

IDE G200018

Version 3.0

July 20, 2020

Insulet Corporation

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Acton, MA 01720

PROTOCOL APPROVAL

Evaluating the Safety and Effectiveness of the Omnipod Horizon™ CGM-informed Bolus Calculator in Patients with Type 1 Diabetes

IDE G200018

Version 2.0

April 24, 2020

Trang Ly MBBS FRACP PhD - SVP, Clinical and Medical Director, Insulet Corporation — 08June2020 — Date

Bonnie Dumais, Senior Director of Clinical Affairs, Insulet Corporation — 06 Jun 2020 — Date

Julie Perkins - Senior Director, Quality and Regulatory, Insulet Corporation — 08 June 2020 — Date

INVESTIGATOR STATEMENT

Evaluating the Safety and Effectiveness of the Omnipod Horizon™ CGM-informed Bolus Calculator in Patients with Type 1 Diabetes

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

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

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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™ CGM-informed Bolus Calculator in Patients with Type 1 Diabetes
Protocol ID	G200018
Purpose	To evaluate the safety and effectiveness of the Omnipod Horizon™ CGM-informed Bolus Calculator in patients with type 1 diabetes during Manual Mode operation.
Design	This study is a single-arm, multi-center, prospective clinical study
Enrollment	A total of up to 42 subjects will be enrolled in the study in order to obtain a minimum of 30 evaluable subjects. Subjects may be recruited from the Omnipod Horizon™ Pivotal Study (G190270) prior to their commencement or recommencement of the preschool pivotal study. The study will use the Omnipod Horizon™ System in Manual Mode and will consist of two outpatient phases: 1) 7 days of Omnipod Horizon™ use in Manual Mode *without* a connected CGM using manual entry of BG values to deliver boluses (Phase 1) followed by; 2) 7 days of Omnipod Horizon™ use in Manual Mode *with* a connected CGM using the CGM-informed bolus calculator to deliver boluses (Phase 2) Subjects will be enrolled across 4-7 clinical study sites. The 30 evaluable subjects will be comprised of three age cohorts as follows: • 15 subjects aged 18-70 years • 10 subjects aged 6-17.9 years • 5 subjects aged 2-5.9 years
Indication	The Omnipod Horizon™ CGM-informed bolus calculator is intended to calculate a meal and correction bolus based upon carbohydrate entry, current CGM value and trend to reach a pre-specified target glucose level.
Study duration	The study is expected to be completed within 6 months which includes clinical site initiation to completion of all data entry and monitoring procedures. As subjects aged 6-70 years are expected to complete the study prior to the start of enrollment of subjects aged 2-5.9 years, two separate clinical reports will be generated.
Investigational devices	The Omnipod Horizon™ Automated Insulin Delivery System is comprised of the following components: • Omnipod Horizon™ tubeless, insulin delivery alternate controller enabled (ACE) pump (Pod) • Omnipod Horizon™ Personal Diabetes Manager (PDM) which is a Samsung J3 locked down android device that operates the Omnipod Horizon™ Automated Insulin Delivery App • Dexcom G6 - Continuous Glucose Monitoring (CGM) system
Non-investigational,	• Contour® Next One blood glucose meter (Ascensia Diabetes Care, 5 Wood Hollow Road, Parsippany, NJ 07054 USA)

commercially available devices	• Precision Xtra ketone meter (Abbott Diabetes Care Inc., 1360 South Loop Road, Alameda, CA 94502 USA)
Primary objective	To evaluate the safety of the Omnipod Horizon™ CGM-informed bolus calculator in patients with type 1 diabetes during Manual Mode operation.
Primary endpoints	The primary objective will be to evaluate the safety of the CGM-informed bolus calculator (Phase 2) using the following endpoints as measured by the system CGM: Glucose metrics during the 4-hour post bolus period from Phase 2 will be compared to Phase 1: • % of time < 70 mg/dL • % of time > 180 mg/dL
Secondary objective	To evaluate additional glycemic measures of effectiveness of the Omnipod Horizon™ CGM-informed bolus calculator during Manual Mode operation.
Secondary endpoints	The secondary objective will be evaluated using the following per subject effectiveness endpoints: Glucose metrics during the 4-hour post bolus period from Phase 2 will be compared to Phase 1: • Mean glucose • % of time < 54 mg/dL • % of time ≥ 250 mg/dL • % of time ≥ 300 mg/dL • % of time in range 70-180 mg/dL Glucose metrics from Phase 2 will be compared to Phase 1 during the day (6AM up to 12AM), overnight (12AM up to 6AM), and overall: • Mean glucose • % of time < 54 mg/dL • % of time < 70 mg/dL • % of time > 180 mg/dL • % of time ≥ 250 mg/dL • % of time ≥ 300 mg/dL • % of time in range 70-180 mg/dL • % of time in range 70-140 mg/dL • Standard deviation • Coefficient of variation
Eligibility criteria	***Inclusion Criteria*** Subjects must meet all the following criteria to be included in the study: 1. Age at time of consent/assent 2-70 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. Must be a current Omnipod user, or have used an Omnipod in the past 5. Investigator has confidence that the subject, parent, or legal guardian, can successfully operate all study devices and can adhere to the protocol 6. Willing to use only the following types of Insulin during the study: Humalog,

	Novolog, Admelog, or Apidra 7. Must be willing to use the Omnipod Horizon™ in Manual Mode only and agree not to use Automated Mode functionality 8. Must be willing to use the Omnipod Horizon™ bolus calculator without a connected CGM for the first 7-days of Manual Mode (Phase 1) while manually entering BG values to deliver boluses 9. Must be willing to use the Omnipod Horizon™ bolus calculator with a connected CGM for the last 7-days of Manual Mode (Phase 2) using the CGM-informed bolus calculator to deliver boluses 10. Willing to wear the system continuously throughout the study 11. For subjects not currently enrolled in the Omnipod Horizon™ Pivotal Study (G190270), A1C <10% 12. Must be willing to use the Dexcom App on the Omnipod Horizon™ PDM as the sole source of Dexcom data (except for the Dexcom Follow App) 13. Able to read and speak English fluently (if subject is a young child then Caregiver must meet the criteria) 14. Willing and able to sign the Informed Consent Form (ICF) and/or has a parent/guardian willing and able to sign the ICF. Assent will be obtained from subjects aged < 18 years per State requirements. 15. For subjects aged 2-5.9 years of age, parents or trained caregivers agree to be physically present during the decision and delivery of insulin boluses for this age group, as well as agree to be available for glucose monitoring and treatment during the 4-hour post bolus period. ***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 or infusion set failure 4. Plans to receive blood transfusion over the course of the study 5. Currently diagnosed with anorexia nervosa or bulimia 6. Acute or chronic kidney disease or currently on hemodialysis 7. History of adrenal insufficiency 8. Has taken oral or injectable steroids within the past 8 weeks or plans to take oral or injectable steroids during the study 9. Unable to tolerate adhesive tape or has any unresolved skin condition in the area of sensor or pump placement 10. Plans to use insulin other than U-100 insulin intended for use in the study device during the study 11. Use of non-insulin anti-diabetic medication other than metformin (e.g. GLP1 agonist, SGLT2 inhibitor, DPP-4 inhibitor, pramlintide) 12. 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 13. Clinical signs of hypothyroidism and hyperthyroidism 14. 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) 15. Currently participating or plans to participate in another clinical study using an investigational drug or device other than Omnipod Horizon™. Subjects may be recruited from the Omnipod Horizon Pivotal Study (G190270).

	16. Unable to follow clinical protocol for the duration of the study or is otherwise deemed unacceptable to participate in the study per the investigator's clinical judgment
Study schedule overview	The study schedule consists of the following two outpatient phases: 1) 7 days of Omnipod Horizon™ use in Manual Mode *without* a connected CGM using manual entry of BG values to deliver boluses (Phase 1) followed by; 2) 7 days of Omnipod Horizon™ use in Manual Mode *with* a connected CGM using the CGM-informed bolus calculator to deliver boluses (Phase 2) Following subject screening, system training and enrollment, subjects will commence Phase 1 of the study. Subjects will be trained to use the Manual Mode feature of the system including how to use the bolus calculator using manual entry of BG values and by using the CGM-informed bolus calculator. After completion of the first 7 days of the Manual Mode phase using the Omnipod Horizon™ without a connected CGM (Phase 1), subjects will transition to the next 7 days of the Manual Mode phase using the system with a connected CGM using the CGM-informed bolus calculator to deliver boluses (Phase 2). Upon completion of this study, subjects aged 6-70 previously enrolled in the Omnipod Horizon™ Pivotal Study (G190270) will recommence the pivotal study. Upon completion, or withdraw from this study, subjects aged 2-5.9 may commence the Standard Therapy phase of the preschool pivotal study.

GLOSSARY OF ACRONYMS

ACE	Alternate Controller Enabled
ADE	Adverse Device Effect
AE	Adverse Event
AGC	Automated Glucose Control
BG	Blood Glucose
BLE	Bluetooth Low Energy
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CRA	Clinical Research Associate
CRO	Contract Research Organization
CV	Curricula Vitae
DD	Device Deficiency
DKA	Diabetic Ketoacidosis
dL	Deciliter
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ITT	Intention to Treat
MD	Doctor of Medicine
mg	Milligram
mITT	Modified Intention to Treat
mmol	Millimole
MM	Medical Monitor
MPC	Model Predictive Control
PDM	Personal Diabetes Manager
POC	Point of Care
PI	Principal Investigator
pMPC	Personalized Model Predictive Control
PP	Per Protocol
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SMP	Safety Management Plan
TSH	Thyroid Stimulating Hormone
TDI	Total Daily Insulin
UADE	Unanticipated Adverse Device Effect

1 INTRODUCTION

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

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

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

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

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

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

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

Insulet has developed the Omnipod Horizon™ Automated Insulin Delivery 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.

A novel feature of Omnipod Horizon™ is the design of the bolus calculator which allows the user to import the CGM value and trend by pressing a simple button – *Enter CGM* – within the bolus calculator to calculate a correction dose. Both the CGM value and trend are important inputs for correction dose recommendation. Existing insulin delivery systems require the user to manually enter a blood glucose or sensor glucose value into the bolus calculator and this is subject to human error and places additional burden on the user to calculate the dose based on trend: *"If I'm 200mg/dL and rising quickly, how much extra should I give? A little extra or a lot extra?".* The Omnipod Horizon™ bolus calculator has been designed to seamlessly and safely suggest a bolus amount to the user by incorporating available inputs that are available with CGM integration with insulin delivery, including insulin on board.

Through extensive in-silico testing, a proprietary bolus calculator has been developed by Insulet and is embedded in the Omnipod Horizon™ system. The bolus calculator can import CGM and trend as long as the pod has an available CGM value. A 3-month outpatient pivotal trial of Omnipod Horizon™ is currently underway however, it is expected that users will primarily use the system in Automated Mode. This study is designed to evaluate the safety and effectiveness of Omnipod Horizon™ System CGM-informed bolus calculator during Manual Mode operation. These data will supplement the extensive in-silico analysis to support safety and effectiveness of the Omnipod Horizon bolus calculator in clinical use.

Training and operation of the Omnipod Horizon™ System is identical in order to use the product with CGM informed Manual Mode or Automated Mode i.e. it is not possible to disable the Automated Mode functionality and still enable CGM integration. Therefore, this clinical protocol is similar to protocols under IDE G190267 and G190270.

2 OMNIPOD HORIZON™ SYSTEM STUDY DEVICE OVERVIEW

This study is designed to evaluate the safety and effectiveness of Omnipod Horizon™ System CGM-informed bolus calculator during Manual Mode operation. Manual Mode operation has similar functionality comparable to commercially available standalone pumps such as Omnipod Insulin Management System and Omnipod® DASH and may be chosen by the user when they desire full control of their insulin delivery as opposed to automated insulin delivery offered with Automated Mode. The Omnipod Horizon™ System is described below, however, this study will be restricted to Manual Mode operation ONLY.

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. The system also operates in Manual Mode and uses the user-entered programmed basal and bolus calculator settings.

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.

In this study, participants will be instructed to NOT use Automated Mode. This study will be restricted to Manual Mode operation ONLY.

The Omnipod Horizon™ System will include two apps on a locked-down smartphone (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™ 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 sensor glucose, 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.

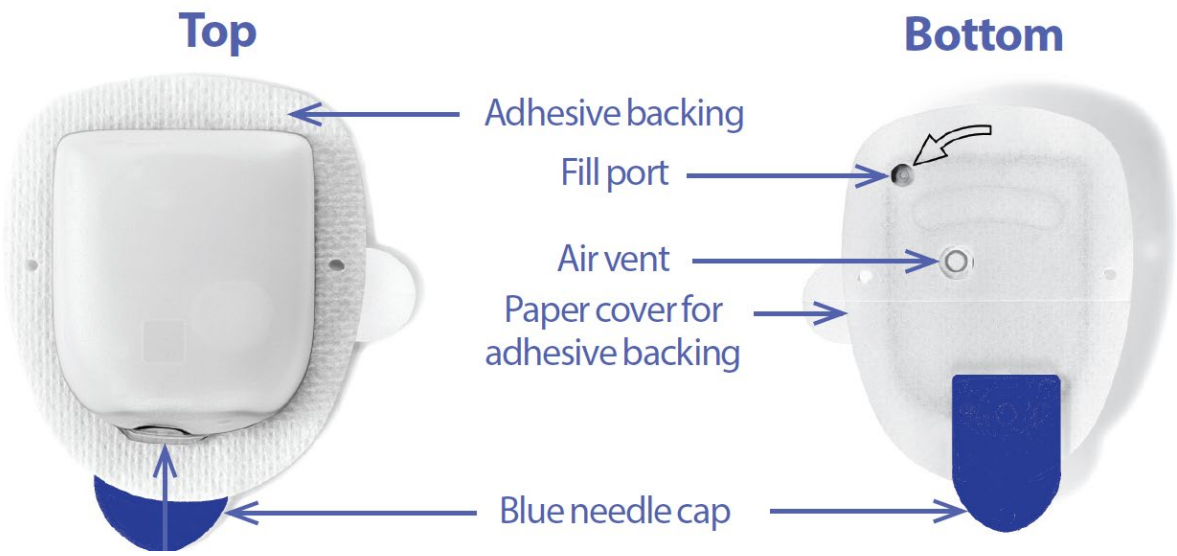

Figure 2: The Pod of the Omnipod Horizon™ ACE pump

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.

2.1.4 CGM-informed Bolus Calculator

Omnipod Horizon™ will allow for ease of population of CGM values within the bolus calculator, to allow for safe and improved usability for the calculation of meal and correction boluses.

The system uses estimated glucose values from Dexcom's G6 iCGM to guide both the automatic insulin delivery algorithm in Automated Mode and in calculating correction boluses when initiated by the user in both Manual and Automated Mode.

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 (with connected CGM), 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's CGM-informed bolus calculator in patients with type 1 diabetes during Manual Mode operation.

5.2 Study Design

This is a single-arm, multi-center, prospective clinical study. A total of up to 42 subjects aged 2-70 years with type 1 diabetes will be enrolled in the study in order to obtain a minimum of 30 evaluable. Subjects aged 6-70 may be recruited from the Omnipod Horizon™ Pivotal Study (G190270) prior to their recommencement of the pivotal study after study pause. Subjects aged 2-5.9 may be recruited from

the pivotal study but must complete, or withdraw from this study before commencement of the Standard Therapy phase of the preschool pivotal study.

The study schedule consists of two outpatient phases:

1) 7 days of Omnipod Horizon™ use in Manual Mode ***without*** a connected CGM using manual entry of BG values to deliver boluses (Phase 1) followed by;
2) 7 days of Omnipod Horizon™ use in Manual Mode ***with*** a connected CGM using the CGM-informed bolus calculator to deliver boluses (Phase 2)

Subjects will be enrolled across 4-7 clinical study sites. The 30 evaluable subjects will be comprised of three age cohorts as follows:

- 15 subjects aged 18-70 years
- 10 subjects aged 6-17.9 years
- 5 subjects aged 2-5.9 years

Following subject screening, and enrollment, subjects will commence the first 7-day Manual Mode phase of the study.

Subjects not currently enrolled in the Omnipod Horizon™ Pivotal Study (G190270) will train to use the Manual Mode feature of the system including how to use the bolus calculator using manual entry of BG values or by using the CGM-informed bolus calculator.

After completion of the first 7 days of the Manual Mode phase using the Omnipod Horizon™ without a connected CGM, subjects will transition to the next 7 days of the Manual Mode phase using the system with a connected CGM using the CGM-informed bolus calculator to deliver boluses.

Table 1 outlines the schedule of assessments for each phase of the study.

Table 1: Schedule of Assessments

Assessment Schedule	Screening	Horizon™ Manual Mode (MM)						EW[a]
		PHASE 1 7-days of MM (without CGM connected)		PHASE 2 7-days of MM (with CGM connected)				
Visit Number	1[e]	2[e]	3	4	5	6	UV[b]	
Study Day/Visit Window	Within 30 days prior to or same day as Phase 1 start[g]	1d	3d ±1d	8d ±1d	10 ±1d	14 ±1d	N/A	
Telephone (T) or Office (O) Visit	T/O[h]	T/O[h]	T/O[d]	T/O[d]	T/O[d]	T/O[d]	T/O[d]	T/O
Laboratory Assessments								
A1C (POC)[g]	X							
Pregnancy Test[i]	X							
Clinical Assessments								
Informed Consent	X							
Medical History (including demographics)[g]	X							
Confirm Eligibility	X							
Concomitant medications	X	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]
Height[g]	X							
Weight[g]	X							
Vital signs[g]	X					X		X
Adverse events		X	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]

Assessment Schedule	Screening	Horizon™ Manual Mode (MM)						EW[a]
		PHASE 1 7-days of MM (without connected CGM)		PHASE 2 7-days of MM (with connected CGM)				
Visit Number	1[e]	2	3	4	5	6	UV[b]	
Study Day/Visit Window	Within 30 days prior to or same day as Phase 1 start[g]	1d	3d ±1d	8d ±1d	10 ±1d	14 ±1d	N/A	
Telephone (T) or Office (O) Visit	T/O[h]	T/O[h]	T/O[d]	T/O[d]	T/O[d]	T/O[d]	T/O[d]	T/O[d]
Study Devices								
Training on Glucagon administration and information on treatment of hypo/hyperglycemia[f]		X						
Study device training Omnipod Horizon™ (including CGM), BG/Ketone meter[f]		X						
Dispense/Return Omnipod Horizon™ (including CGM), QC tested BG/Ketone meter[f]		X				X		X
Removal of subject's personal insulin pump[f]		X						
Placement of the Omnipod Horizon™ on body[f]		X						
Enrollment		X						
Pairing the CGM transmitter to the Dexcom App on the PDM				X				

Assessment Schedule	Screening	Horizon™ Manual Mode (MM)						EW[a]
		PHASE 1 7-days of MM (without connected CGM)		PHASE 2 7-days of MM (with connected CGM)				
Visit Number	1[e]	2	3	4	5	6	UV[b]	
Study Day/Visit Window	Within 30 days prior to or same day as Phase 1 start[g]	1d	3d ±1d	8d ±1d	10 ±1d	14 ±1d	N/A	
Telephone (T) or Office (O) Visit	T/O[h]	T/O[h]	T/O[d]	T/O[d]	T/O[d]	T/O[d]	T/O[d]	T/O[d]
Complaints/device deficiencies		X	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]
Data review			X	X	X	X	X	X
BG/Ketone Device uploads				X[d]		X[d]	X[d]	X

Abbreviations: S=Screening; MM=Manual Mode; EW=Early Withdrawal; QC=Quality Control; UV=Unscheduled Visit

[a]Early withdrawal visit will be conducted for enrolled subjects that did not complete both Manual Mode phases.

[b]Unscheduled visits will serve as extra study visits, if needed. All unscheduled visits must obtain the defined schedule of assessments. These visits should not be documented for appointment confirmation, device shipments, general inquiries, or for activities covered by other assessments.

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

[d]Visits identified as "T/O" can either be conducted in person at the clinical site or over the telephone. If conducted over the telephone, vital signs and device uploads are not required. Visits identified as "O" can only be conducted in person at the clinical site.

[e]Visit 1 and Visit 2 may occur on the same day - Any assessment required by both visits will only need to be completed once. All Visit 1 assessments do not need to occur on the same day as long as the assessments occur within 30 days prior to Visit 2, or for subjects currently enrolled in Omnipod Horizon™ Pivotal Study (G190270).

[f]Only applicable if subject is not currently enrolled in the Omnipod Horizon™ Pivotal Study (G190270).

[g]For subjects aged 6-70 currently enrolled in the Omnipod Horizon™ Pivotal Study (G190270), specified screening assessments are not required if they were done for the Pivotal study, and there are no significant changes from the Pivotal study screening assessments. For subjects aged 2-5.9 that plan to

participate in the Pivotal study, the specified screening assessments only need to be collected once as long as they are completed within the timeframe required by both studies.

[h]For subjects not currently enrolled in the Omnipod Horizon™ Pivotal Study (G190270) this visit must be conducted in person at the clinical study site.

[i]If subject is currently enrolled in the Omnipod Horizon™ Pivotal Study (G190270) and not able to attend in person, they may conduct the pregnancy test at home and report result to the site.

6 OBJECTIVES AND ENDPOINTS

6.1 Primary Objective

The primary objective of this study is to evaluate the safety of the Omnipod Horizon™ CGM-informed bolus calculator in patients with type 1 diabetes during Manual Mode operation.

6.1.1 Primary Endpoints

The primary objective will be to evaluate the safety of the CGM-informed bolus calculator using the following endpoints as measured by the system:

Glucose metrics during the 4-hour post bolus period from Phase 2 will be compared to Phase 1:

- % of time < 70 mg/dL
- % of time > 180 mg/dL

6.2 Secondary Objective

The secondary objective of this study is to evaluate additional glycemic measures of effectiveness of the Omnipod Horizon™ CGM-informed bolus calculator during Manual Mode operation.

6.2.1 Secondary Endpoints

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

Glucose metrics during the 4-hour post bolus from Phase 2 will be compared to Phase 1:

- Mean glucose
- % of time < 54 mg/dL
- % of time ≥ 250 mg/dL
- % of time ≥ 300 mg/dL
- % of time in range 70-180 mg/dL

Glucose metrics from Phase 2 will be compared to Phase 1, during the day (6AM up to 12AM), overnight (12AM up to 6AM), and overall:

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

- Coefficient of variation

7 SUBJECT SELECTION 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 current or prior Omnipod users. Subjects aged 6-70 from the Omnipod Horizon™ Pivotal Study (G190270) may participate in this study during the study pause and must complete this study prior to their recommencement of the pivotal study. Subjects aged 2-5.9 may be recruited from the pivotal study but must complete or withdraw from this study before commencement of the Standard Therapy phase of the preschool pivotal study. Potential subjects will be selected at each clinical study site and screened accordingly. 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. A point of care (POC) A1C will be used at screening to determine eligibility.

7.1 Visit 1

Visit 1 will be conducted either over the telephone or in person at the clinical study site. This visit will assess subject's eligibility and will include:

- Signing of informed consent/assent
- Review of inclusion/exclusion criteria
- Screening assessments performed following Table 1: Schedule of Assessments

Informed Consent

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 prior to completing any screening assessments. A parent/guardian must sign the ICF for subjects <18 years of age. Assent will be obtained from subjects aged <18 years per State requirements. Failure to provide informed consent/assent will render the subject ineligible for the study. Due to utilizing screening assessments for subjects aged 6-70 years that are participating in the Omnipod Horizon™ Pivotal Study, the date of consent for this study will occur much later than the date of the screening assessments.

Due to restrictions in place for the COVID-19 pandemic, sites may perform the informed consent process over the telephone per their site's procedures.

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). If the subject is also participating in

the Omnipod Horizon™ Pivotal Study, they may retain their same subject identification number for both studies.

Inclusion Criteria

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

1. Age at time of consent/assent 2-70 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. Must be a current Omnipod user, or have used an Omnipod in the past
5. Investigator has confidence that the subject, parent, or legal guardian, can successfully operate all study devices and can adhere to the protocol
6. Willing to use only the following types of Insulin during the study: Humalog, Novolog, Admelog, or Apidra
7. Must be willing to use the Omnipod Horizon™ in Manual Mode only and agree not to use Automated Mode functionality
8. Must be willing to use the Omnipod Horizon™ bolus calculator without a connected CGM for the first 7-days of Manual Mode (Phase 1) while manually entering BG values to deliver boluses
9. Must be willing to use the Omnipod Horizon™ bolus calculator with a connected CGM for the last 7-days of Manual Mode (Phase 2) using the CGM-informed bolus calculator to deliver boluses
10. Willing to wear the system continuously throughout the study
11. For subjects not currently enrolled in the Omnipod Horizon™ Pivotal Study (G190270), A1C <10%
12. Must be willing to use the Dexcom App on the Omnipod Horizon™ PDM as the sole source of Dexcom data (except for the Dexcom Follow App)
13. Able to read and speak English fluently (if subject is a young child then Caregiver must meet the criteria)
14. Willing and able to sign the Informed Consent Form (ICF) and/or has a parent/guardian willing and able to sign the ICF. Assent will be obtained from subjects aged <18 years per State requirements.
15. For subjects aged 2-5.9 years of age, parents or trained caregivers agree to be physically present during the decision and delivery of insulin boluses for this age group, as well as agree to be available for glucose monitoring and treatment during the 4-hour post bolus period.

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 or infusion set failure
4. Plans to receive blood transfusion over the course of the study
5. Currently diagnosed with anorexia nervosa or bulimia

6. Acute or chronic kidney disease or currently on hemodialysis
7. History of adrenal insufficiency
8. Has taken oral or injectable steroids within the past 8 weeks or plans to take oral or injectable steroids during the study
9. Unable to tolerate adhesive tape or has any unresolved skin condition in the area of sensor or pump placement
10. Plans to use insulin other than U-100 insulin intended for use in the study device during the study
11. Use of non-insulin anti-diabetic medication other than metformin (e.g. GLP1 agonist, SGLT2 inhibitor, DPP-4 inhibitor, pramlintide)
12. 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
13. Clinical signs of hypothyroidism and hyperthyroidism
14. 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)
15. Currently participating or plans to participate in another clinical study using an investigational drug or device other than Omnipod Horizon™. Subjects may be recruited from the Omnipod Horizon™ Pivotal Study (G190270).
16. 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 appear to meet the eligibility criteria and have signed the informed consent will continue to the screening visit which will be performed either over the phone (for subjects currently enrolled in the Omnipod Horizon™ Pivotal Study (G190270) or at the clinical study site.

Screening assessments must be completed within 30 days prior to the Phase 1 start date (assessments do not need to but may be completed on the same day). The assessments will include:

- Medical history (including prior and current medical conditions and surgical history)*
- Demographics (age, gender, race)
- Point of care A1C*
- Pregnancy test for women of childbearing potential
- Review of concomitant medications
- Height (if visit is conducted in person at the clinical study site)*
- Weight (if visit is conducted in person at the clinical study site)*
- Vital signs (if visit is conducted in person at the clinical study site)*

*For subjects currently enrolled in the Omnipod Horizon™ Pivotal Study (G190270), specified screening assessments are not required if they were done for the Pivotal study, and there are no significant changes from the Pivotal study screen

assessments. For subjects aged 2-5.9 that plan to participate in the Pivotal study, the specified screening assessments only need to be collected once, as long as they are completed within the timeframe required by both studies.

8 OMNIPOD HORIZON™ MANUAL MODE

The Omnipod Horizon™ Manual Mode will consist of two outpatient phases:

1. 7 days of Omnipod Horizon™ use in Manual Mode ***without*** a connected CGM using manual entry of BG values to deliver boluses (Phase 1) followed by;
2. 7 days of Omnipod Horizon™ use in Manual Mode ***with*** a connected CGM using the CGM-informed bolus calculator to deliver boluses (Phase 2)

Enrollment

Subjects who meet all eligibility criteria and have completed all screening assessments will continue to enrollment. A subject is enrolled in the study at the commencement of Visit 2. 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 before enrollment, the subject will not continue in the study. No additional study assessments will be required. The reason for study exit will be clearly documented.

8.1 Phase 1

8.1.1 Visit 2

Visit 2 represents the commencement of the first 7 days of Manual Mode (Phase 1) and will be conducted either over the telephone or in person at the clinical study site on Day 1. This visit will include:

- Review of concomitant medications
- Assessment of adverse events
- Training on Glucagon administration and information on treatment of hypo/hyperglycemia (if training was not previously performed while participating in the Omnipod Horizon™ Pivotal Study (G190270)
- Study device training per manufacturer's instructions (BG and ketone meters), (if training was not previously performed while participating in the Omnipod Horizon™ Pivotal Study (G190270)
- Omnipod Horizon™ System device training conducted by trained clinical site staff (if training was not previously performed while participating in the Omnipod Horizon™ Pivotal Study (G190270)
    - Subjects will be trained on operating Omnipod Horizon™ in Manual Mode.
    - 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. Subjects should enter settings similar to their usual settings as appropriate.
    - 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, setting up low (recommended to be 70 mg/dL or higher) and high glucose alerts (recommended to be 300 mg/dL or lower), setting up Dexcom Follow as desired, and calibrating their CGM as required, per the manufacturer's instructions
    - Subjects will be trained to use the Bolus Calculator, entering in estimated carbs for meals and manually entering a BG value
    - Subjects may choose their desired target BG ranging between 110-150 mg/dL in increments of 10 mg/dL for the bolus calculator

- Dispense Omnipod Horizon™ System, including CGM (if System was not previously dispensed while participating in the Omnipod Horizon™ Pivotal Study (G190270)
- QC testing of BG and ketone meter (if devices were not previously dispensed while participating in the Omnipod Horizon™ Pivotal Study (G190270)
    - Must pass as least one level of quality control testing prior to dispensing. QC testing may occur at any time prior to dispensing to subject.
- Removal of the subject's personal insulin pump (if not currently using the Omnipod Horizon™ System in Manual Mode)
    - Investigators should use the Insulet-provided Patient Therapy Order Form (PTOF) to document pump settings (Appendix A)
- Placement of the Omnipod Horizon™ on body (if not currently using the Omnipod Horizon™ System in Manual Mode)
- CGM sensor placement (if not currently wearing Omnipod Horizon™ study CGM)
    - Approved anatomical locations for CGM sensor placement will be reinforced as well as the importance of using approved locations
- Assessment of complaints and/or device deficiencies
- Each subject will initiate their treatment marking their commencement of the first 7 days of Manual Mode (Enrollment and Phase 1).

Subjects will be dispensed the following devices and supplies (if not currently enrolled in the Omnipod Horizon™ Pivotal Study (G190270)):

- Omnipod Horizon™ PDM and Pods
- Dexcom transmitter
- Dexcom sensors
- Contour® Next One blood glucose meter
- Contour® Next One blood glucose meter test strips
- Lancets
- Precision Xtra blood ketone meter
- Precision Xtra blood ketone meter test strips

During the first 7 days of Manual Mode, subjects will be instructed to:

- Use the bolus calculator to administer meal boluses for all meals when carbohydrates are consumed as well as to administer correction boluses, when desired. For meal boluses, subjects will estimate the grams of carbohydrates for each meal, enter the carbohydrate estimate into the bolus calculator, check and manually enter their BG value into the bolus calculator and administer their meal bolus. For correction boluses, subjects will check and enter their BG value into the bolus calculator and administer their correction bolus. The timing of the bolus delivery will be per each subject's typical dosing routine.
- Consume meals and snacks of their own choosing.
- Subjects may adjust their basal rates or use advanced features such as Temp Basal and Extended Bolus per usual
- 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
- Change their CGM per manufacturer's instructions or sooner if necessary
- Change the Pod at least once every 72 hours
- For subjects aged 2-5.9 years of age, parents or trained caregivers will be instructed that they need to be physically present during the decision and delivery of insulin boluses for this age group, as well as be available for glucose monitoring and treatment during the 4-hour post bolus period.

Subjects and caregivers will be reminded to NOT use the system in Automated Mode for the duration of the 14-day study. Any use of automated mode will be considered a protocol deviation.

Subjects not currently enrolled in the Omnipod Horizon™ Pivotal Study (G190270) 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. 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.

8.1.2 **Visit 3**

Visit 3 will be conducted either over the telephone or in person at the clinical study site on Day 3 ±1d. This visit will include:

- Review of concomitant medications
- Assessment of adverse events
- Assessment of complaints and/or device deficiencies
- Data review by clinician to ensure that subject is delivering boluses as instructed during Visit 2

8.2 Phase 2

8.2.1 Visit 4

Visit 4 will be conducted either over the telephone or in person at the clinical site on Day 8 ±1d. This visit will mark the start of Phase 2, which is 7-days of Manual Mode with a connected CGM using the CGM-informed bolus calculator to deliver boluses. This visit will include:

- Review of concomitant medications
- Assessment of adverse events
- Pairing the CGM transmitter to the Horizon App on the PDM
- Assessment of complaints and/or device deficiencies
- Data review by clinician to ensure that subject was delivering boluses as instructed during Visit 2.
- Upload BG and ketone meter data (if visit is conducted in person at the clinical study site)

During this visit subjects will be instructed to:

- Use the CGM-informed bolus calculator to administer meal boluses for all meals when carbohydrates are consumed as well as to administer correction boluses, when desired. For meal boluses, subjects will estimate the grams of carbohydrates for each meal, enter the carbohydrate estimate into the bolus calculator, choose 'Enter CGM' to populate the bolus calculator and administer their meal bolus. For correction boluses, subjects will choose 'Enter CGM' to populate the bolus calculator and administer their correction bolus. The timing of the bolus delivery will be per each subject's typical dosing routine.
- Consume meals and snacks of their own choosing.
- Subjects may adjust their basal rates or use advanced features such as Temp Basal and Extended Bolus per usual
- 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
- Change their CGM per manufacturer's instructions or sooner if necessary
- Change the Pod at least once every 72 hours
- For subjects aged 2-5.9 years of age, parents or trained caregivers will be instructed that they need to be physically present during the decision and delivery of insulin boluses for this age group, as well as be available for glucose monitoring and treatment during the 4-hour post bolus period.

8.2.2 Visit 5

Visit 5 will be conducted either over the telephone or in person at the clinical study site on Day 10 ±1d. This visit will include:

- Review of concomitant medications

- Assessment of adverse events
- Assessment of complaints and/or device deficiencies
- Data review by clinician to ensure that subject is delivering boluses as instructed during Visit 4

8.2.3 Visit 6 (End of Study)

Visit 6 will be conducted either over the telephone or in person at the clinical study site on Day 14 ±1d. This visit will include:

- Review of concomitant medications
- Assessment of vital signs (if visit is conducted in person at the clinical study site)
- Assessment of adverse events
- Return of devices (if not commencing or recommencing their participation in the Omnipod Horizon™ Pivotal Study (G190270). Subjects aged 2-5.9 may hold onto their devices if continuing onto the Pivotal study, but must return to using their standard therapy for the Pivotal study Standard Therapy Phase.)
- Assessment of complaints and/or device deficiencies
- Data review by clinician to ensure that subject was delivering boluses as instructed during Visit 4
- Upload BG and ketone meter data (if visit is conducted in person at the clinical study site)

This visit will mark the end of this study for each subject.

8.3 Unscheduled Visits

Aside from scheduled visits, subjects may require **Unscheduled Visits (UV)** either by telephone or in person at the clinical study site. This visit will include:

- Review of concomitant medications
- Assessment of adverse events
- Assessment of complaints and/or device deficiencies
- Data review by clinician to ensure that subject was delivering boluses according to the correct study phase
- Upload BG and ketone meter data (if visit is conducted in person at the clinical study site)

All UVs must obtain the defined schedule of assessments. Additional assessments may be warranted at the discretion of the investigator. UVs should not be documented for appointment confirmation, device shipments, general inquiries, or for activities covered by other assessments.

8.4 Early Withdrawal

Any subject may withdraw early from the study at any time for any reason. 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. Upon withdrawal, assessments will be performed according to the Table 1: Schedule of Assessments. This visit will include:

- Review of concomitant medications
- Assessment of vital signs (if visit is conducted in person at the clinical study site)
- Assessment of adverse events
- Return of devices (if not commencing or recommencing their participation in the Omnipod Horizon™ Pivotal Study (G190270). Subjects aged 2-5.9 may hold onto their devices if continuing onto the Pivotal study, but must agree to return to using their standard therapy for the Pivotal study Standard Therapy Phase)
- Assessment of complaints and/or device deficiencies
- Data review by clinician ensure that subject was delivering boluses according to the correct study phase
- Upload BG and ketone meter data (if visit is conducted in person at the clinical study site)

An early withdrawal visit should be conducted at the clinical study site when possible. The subject will be requested to return their study devices to the site, 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.

8.5 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.

9 SPONSOR REPRESENTATIVES

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

10 SAFETY

10.1 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 or malfunction.

- 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 potential benefits from this study. The Omnipod Horizon™ CGM-informed bolus calculator is intended to utilize both CGM value and trend to deliver a safe correction bolus and improve ease of use.

10.2 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 >300 mg/dL for ≥1 hour or >250 mg/dL for ≥2 hours, 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.

10.3 Adverse Events

10.3.1 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.

10.3.2 **Reportable Adverse Events**

Adverse events will be assessed on an ongoing basis throughout the study. Adverse event reporting will begin at the time of enrollment (i.e., insertion of the CGM sensor) and continue 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 enrollment 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.

10.3.3 **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.

10.3.4 **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.

10.3.5 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.

10.3.6 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.

10.3.7 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.

10.4 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, transmitter 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

10.5 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 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.

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.

10.6 Stopping Criteria

10.6.1 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.

10.6.2 Criteria for Suspending or Stopping Overall Study

Study activities will be 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. The Medical Monitor 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.

10.7 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 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.

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

11 STATISTICAL CONSIDERATIONS

11.1 General Statistical Methods

Standard statistical methods will be employed to analyze all data. All data collected in this study will be documented using summary tables and subject data listings. Continuous variables will be summarized using descriptive statistics, including counts, 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.

Data from different centers will be pooled for all analyses. Data will be summarized by age cohort.

As subjects aged 6-70 years are expected to complete the study prior to the start of enrollment of subjects aged 2-5.9 years, two separate clinical reports will be generated.

11.2 Sample Size

This is a non-powered, single-arm, multi-center, observational study. The sample size for the study is not hypothesis-driven and has been chosen to gather adequate clinical data on the performance of the Omnipod Horizon™ System's CGM-informed bolus calculator and summarize its safety profile.

Up to 42 subjects may be enrolled in the study cross 4-7 clinical study sites in order to obtain approximately 30 evaluable subjects. The evaluable subjects will be comprised of three age cohorts as follows:

- 15 subjects aged 18-70 years
- 10 subjects aged 6-17.9 years
- 5 subjects aged 2-5.9 years

11.3 Objectives and Endpoints

11.3.1 Primary Objective

The primary objective of this study is to evaluate the safety of the Omnipod Horizon™ System's CGM-informed bolus calculator in patients with type 1 diabetes during Manual Mode operation.

11.3.2 Primary Endpoints

The primary objective will be to evaluate the safety of the CGM-informed bolus calculator (Phase 2) using the following endpoints as measured by the system CGM:

Glucose metrics during the 4-hour post bolus period from Phase 2 will be compared to Phase 1:

- % of time < 70 mg/dL
- % of time > 180 mg/dL

11.3.3 Secondary Objective

The secondary objective of this study is to evaluate additional glycemic measures of effectiveness of the Omnipod Horizon™ CGM-informed bolus calculator during Manual Mode operation.

11.3.4 Secondary Endpoints

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

Glucose metrics during the 4-hour post bolus period from Phase 2 will be compared to Phase 1:

- Mean glucose
- % of time < 54 mg/dL
- % of time ≥ 250 mg/dL
- % of time ≥ 300 mg/dL
- % of time in range 70-180 mg/dL

Glucose metrics from Phase 2 will be compared to Phase 1 during the day (6AM up to 12AM), overnight (12AM up to 6AM), and overall:

- Mean glucose

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

11.4 Analysis Sets

The following analysis sets are planned for the study:

11.4.1 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 endpoints) will be based on the ITT analysis set.

11.4.2 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 Manual Mode with a connected CGM phase of the study (Phase 2) successfully. The mITT analysis set will be used as the primary analysis for the primary and secondary endpoints and other clinical outcome data.

11.4.3 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 (approximately 5.6 days) during Phase 2 of the study without major protocol deviations. 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.

11.5 Analysis of Primary and Secondary Endpoints

There are no hypotheses associated with any of the primary or secondary 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 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 during Phase 2 of the study will be compared to the data collected during Phase 1 of the study.

All statistical comparisons will be conducted at a two-sided significance level of 5% using a paired t-test or two sample t-test, as appropriate. If the assumptions for parametric test are grossly violated, a non-parametric method such as Wilcoxon signed rank test may be used. Since the results of endpoint analyses will not be used to support clinical claims, no adjustment for multiplicity will be performed.

11.5.1 Calculation of Percentage of Time in Range

Several effectiveness endpoints involve calculation of percentage of time in a specific glycemic range, including primary endpoints. These endpoints will be based on the direct output from a device (either a CGM or The Omnipod Horizon™ Automated Glucose Control System). The percentage of time in range (TIR) will be calculated as:

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

The following CGM records will be excluded from analysis, and therefore, from calculation of TIR endpoints:

- No glucose value is provided in the device output, such as due to an error or device deficiency during which the device does not record glucose readings

11.6 Safety Analyses

11.6.1 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 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.

11.6.2 Evaluation of Device Deficiencies

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

11.7 Baseline Characteristics

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

11.8 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.

11.9 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.

12 DATA HANDLING AND QUALITY ASSURANCE

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

12.1 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.

12.2 Electronic Device Outputs

12.2.1 PDM Data

This study will utilize insulin delivery data from the PDM device. All insulin delivery data and all CGM readings (when there is a connected transmitter) from the Manual Mode 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.

12.2.2 CGM Data

This study will utilize CGM measurements from the CGM device. CGM data will be saved in a compatible format that will be extractable for statistical analysis purposes.

12.2.3 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.

12.3 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.

12.4 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 document 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.

12.5 Inspection of Records

The Sponsor or its designee may perform quality assurance site and study file audits at the site. 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.

12.6 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.

12.7 Device Accountability

Investigators will be responsible for investigational device accountability, reconciliation, and records maintenance throughout the course of the investigation. As it is expected most subjects will participate in both studies, all device accountability will be tracked as part of the Omnipod Horizon Pivotal Study and the inventory can be used for either study. 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.

13 STUDY ETHICS AND CONDUCT

13.1 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).

13.2 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.

13.3 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.

13.4 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.

13.5 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), 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.

13.6 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.

13.7 Protocol Deviations

The investigator will not deviate from the protocol without prior written approval from the Sponsor except in medical emergencies or inadvertently. 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 eCRF. Protocol deviations should be reported to the IRB 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.

13.8 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.

13.9 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.

13.9.1 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.

13.9.2 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

13.10 Clinical Site Training

The training of appropriate clinical site personnel will be the responsibility of the Sponsor or its designee. Sites will not be required to be retrained on the study devices since the sites have previously been trained during the execution of the Omnipod Horizon™ Pivotal Study (G190270). To ensure proper device usage, uniform data collection, and protocol compliance, the Sponsor or designee will present a training overview 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.

13.11 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 if the subject is not continuing in the Omnipod Horizon™ Pivotal Study (G190270).

The Dexcom G6 CGM sensor (the component of the system that enters the skin), and the Dexcom G6 CGM transmitter (the component of the system that attaches to the sensor to transmit the signal).

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

13.12 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

13.13 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.

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

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

Physician Name _____ Signature _____ Date _____

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