Insulet

Safety and Efficacy of the Omnipod® 5 Automated Insulin Delivery System in Adults with Type 2 Diabetes

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KEY ROLES

*Provide a list of individuals, companies, and/or groups serving in **key roles** in the conduct or oversight of the trial. This should include the medical monitor, investigator appointed by the sponsor to assist in coordinating the work of this investigation (Protocol Chair/Coordinating Investigator), JCHR Protocol Director/Principal Investigator (PD/PI), and any clinical laboratory(ies), reading centers, or other key central units.*

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LIST OF ABBREVIATIONS

Add any abbreviations used in the protocol document. The use of abbreviations should be minimized to only those that are commonly known.

ABBREVIATION	DEFINITION
ADA	American Diabetes Association
ACE	Alternate Controller Enabled
ADE	Adverse Device Effect
AE	Adverse Event
AID	Automated Insulin Delivery
APRMS	Artificial Pancreas Remote Monitoring System
BG	Blood Glucose
BLE	Bluetooth Low Energy
BMI	Body Mass Index
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CRO	Contract Research Organization
CSII	Continuous Subcutaneous Insulin Infusion
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic Ketoacidosis
dL	Deciliter
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
FDA	Food and Drug Administration
HCS	Hypoglycemia Confidence Scale
HHS	Hyperosmolar Hyperglycemic Syndrome
HRPP	Human Research Protection Program
ICF	Informed Consent Form
iCGM	Integrated Continuous Glucose Monitoring
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDE	Investigational Device Exemption
IOB	Insulin on Board
IRB	Institutional Review Board
JCHR	Jaeb Center for Health Research

ABBREVIATION	DEFINITION
MDI	Multiple Daily Injections
mg	Milligram
mmol	Millimole
PD	Protocol Director
PDM	Personal Diabetes Manager
PI	Principal Investigator
POC	Point of Care
PSQI	Pittsburgh Sleep Quality Index
SAE	Serious Adverse Event
T2D	Type 2 Diabetes
T2-DDAS	Type 2 Diabetes Distress Assessment System
TDI	Total Daily Insulin
UADE	Unanticipated Adverse Device Effect

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: Safety and Efficacy of the Omnipod® 5 Automated Insulin Delivery System in Adults with Type 2 Diabetes

Protocol Version/Date: V3.2 February 27, 2024

I have read the protocol specified above. In my formal capacity as a Site Principal Investigator, my duties include ensuring the safety of the study participants enrolled under my supervision and providing the Jaeb Center for Health Research, which serves as the Coordinating Center for the protocol, with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site.

This trial will be carried out in accordance with ICH E6 Good Clinical Practice (GCP) and as required by the following (use applicable regulations depending on study location and sponsor requirements; examples follow): United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

As the Principal Investigator, I will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), or other approved Ethics Committee, except where necessary to eliminate an immediate hazard(s) to the trial participants.

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Participants Protection Training and Good Clinical Practice Training. Further, I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Investigator's Signature _____ Date: _____ / _____ / _____
dd mmm yyyy

Investigator's Name: _____

Site Name/Number: _____

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PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	Safety and Efficacy of the Omnipod® 5 Automated Insulin Delivery System in Adults with Type 2 Diabetes
Précis	This single-arm, multi-center, prospective study will evaluate the safety (primary) and efficacy (secondary) of the Omnipod® 5 Automated Insulin Delivery System in adults with type 2 diabetes requiring insulin therapy.
Investigational Device	Omnipod® 5 Automated Insulin Delivery System, comprised of the following components: • Omnipod 5 Pod • Omnipod 5 App (installed on the Insulet-provided Controller or smart phone)
Objectives	Primary Objective: • To evaluate the safety of the Omnipod 5 System in adults with type 2 diabetes. Secondary Objectives: • To evaluate the efficacy of the Omnipod 5 System in adults with type 2 diabetes. • To evaluate glycemia measures of efficacy of the Omnipod 5 System and quality of life of Omnipod 5 System users.
Study Design	Single-arm, multi-center, prospective study
Number of Sites	~20-25 sites in the United States
Endpoints	Safety Primary Endpoint: Change in HbA1c at 13 weeks from baseline • Tested first for non-inferiority (non-inferiority limit 0.3%) and then if non-inferiority is demonstrated, tested sequentially for superiority Additional Safety Endpoints: 1. Severe hypoglycemia 2. Hospitalization/ER for severe hypoglycemia 3. Hyperosmolar hyperglycemic syndrome (HHS)/ diabetic ketoacidosis (DKA) 4. Hospitalizations or ER related to hyperglycemia or hypoglycemia in the previous 3 months vs. study 3 months 5. Other related serious adverse events 6. Reportable device-related adverse events Additional Efficacy Endpoints Secondary Efficacy Endpoints (change from baseline): The following secondary endpoints will be tested hierarchically if the primary HbA1c analyses for non-inferiority followed by testing for superiority are statistically significant

PARTICIPANT AREA	DESCRIPTION
	1. Mean glucose 2. Change in % time 70-180 mg/dL (superiority) 3. Change in % time 70-140 mg/dL (superiority) 4. Change in % time ≥ 300 mg/dL (superiority) 5. Change in % time > 250 mg/dL (superiority) 6. Change in % time > 180 mg/dL (superiority) 7. % time < 70 mg/dL (noninferiority; non-inferiority limit 2.0%) 8. % time < 54 mg/dL (noninferiority; non-inferiority limit 0.5%) 9. Change from baseline in T2-DDAS total score (superiority) 10. % Meeting MCID for T2-DDAS 11. Change from baseline in PSQI total score (superiority) 12. % Meeting MCID for PSQI 13. Change from baseline in HCS total score (superiority) 14. % Meeting MCID for HCS 15. % time <70 mg/dL (superiority) 16. % time <54 mg/dL (superiority) 17. Coefficient of variation (superiority) Exploratory Endpoints: 1. Change in total daily insulin dose 2. Change in body mass index (BMI) 3. Average reduction in the number of non-insulin glucose lowering agents 4. Change in percent of participants using insulin as a monotherapy or insulin + metformin. 5. % of participants achieving HbA1c under 7% 6. % of participants achieving HbA1c under 8% 7. % of participants achieving time in range 70-180 mg/dL >70% 8. % of participants achieving time <70 mg/dL <4% 9. % of participants achieving time <54 mg/dL <1% 10. % of participants achieving time in range 70-180 mg/dL >70% and time <70 mg/dL <4% 11. Prolonged hyperglycemia events >250 mg/dL lasting at least 120 minutes 12. Change in lipids (Total Cholesterol: HDL, LDL and triglycerides)
Population	***Inclusion Criteria:*** Participants must meet all of the following criteria to be included in the study: 1. Age at time of consent 18-75 years 2. Diagnosed with type 2 diabetes, on current insulin regimen for at least 3 months prior to screening (i.e. Basal-bolus, basal only or pre-mix) 3. Basal bolus (long-acting insulin and rapid acting analog) or pre-mix users with A1C <12.0% OR basal users on long or intermediate acting insulin only with A1C ≥ 7.0% and < 12.0% ~~4.~~ Willing to use only the following types of U-100 insulin during the study: Humalog U-100, Novolog, or Admelog 5. Participant agrees to provide their own insulin for the duration of

PARTICIPANT AREA	DESCRIPTION
	the study 6. Stable doses over the preceding 4 weeks of other glucose-lowering medications as determined by Investigator 7. Stable doses of weight loss medications over the preceding 4 weeks and throughout the study that may affect glycemic control directly and/or indirectly, except for a dose reduction or discontinuation, as determined by Investigator 8. Willing to wear the system continuously throughout the study 9. Deemed appropriate for pump therapy per investigator's assessment considering previous history of severe hypoglycemic and hyperglycemic events, and other comorbidities 10. Investigator has confidence that the participant has the cognitive ability and can successfully operate all study devices and can adhere to the protocol 11. Able to read and understand English or Spanish 12. Willing and able to sign the Informed Consent Form (ICF) 13. If female of childbearing potential, willing and able to have pregnancy testing ***Exclusion Criteria:*** Participants who meet any of the following criteria will be excluded from the study: 1. Use of an AID pump in automated mode within 3 months prior to screening 2. Any medical condition which in the opinion of the investigator, would put the participant at an unacceptable safety risk, such as untreated malignancy, unstable cardiac disease, unstable or end-stage renal disease, and/or eating disorders (i.e. anorexia/bulimia) 3. 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 12 months prior to screening 4. Any planned surgery during the study which could be considered major in the opinion of the investigator 5. History of more than 1 severe hypoglycemic event in the 6 months prior to screening 6. History of more than 1 episode of diabetic ketoacidosis (DKA) or Hyperosmolar hyperglycemic syndrome (HHS) in the 6 months prior to screening; unrelated to an intercurrent illness; kinked, dislodged, or occluded cannula; or initial diabetes diagnosis 7. Blood disorder or dyscrasia within 3 months prior to screening, including use of hydroxyurea, which in the investigator's opinion could interfere with determination of HbA1c 8. Plans to receive blood transfusion over the course of the study 9. Has taken oral or injectable steroids within 8 weeks prior to screening or plans to take oral or injectable steroids during the study 10. Unable to tolerate adhesive tape or has any unresolved skin condition

PARTICIPANT AREA	DESCRIPTION
	that could impact sensor or pump placement 11. Pregnant or lactating, planning to become pregnant during the study, 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); childbearing potential means that menstruation has started, and the participant is not surgically sterile or greater than 12 months post-menopausal) 12. Participation in another clinical study using an investigational drug or device other than the Omnipod 5 in the 30 days prior to screening or intends to participate during the study period 13. 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 14. Participant is an employee of Insulet, an Investigator or Investigator's study team, or immediate family member (spouse, biological or legal guardian, child, sibling, parent) of any of the aforementioned
Sample Size	Up to 400 screened participants to provide a cohort of 300 initiating use of the Omnipod 5 system and at least 275 completing the trial. A minimum of 60 and maximum of 125 participants using basal only.
Treatment Groups	Single-arm intervention that consists of 13 weeks of treatment using the Omnipod 5 System
Participant Duration	~15-17 weeks (allowing for screening and scheduling)
Study Duration (planned)	~8-10 months
Protocol Overview/Synopsis	The study will consist of a 14-day standard therapy phase to capture baseline glycemic management followed by 13 weeks of treatment using the Omnipod 5 System. This is an outpatient study with unrestricted meals and activity, designed to emulate real world use. After the initial screening and enrollment visits, participants will have an in-clinic or virtual visit at least monthly. Devices will be returned at the end of the 13-week treatment period. During the treatment period participants will undergo supervised exercise and meal challenges. Meal challenges will take place over 4 days. Meal challenges will consist of matched meals where participants will bolus on Days 1 and 3 for their selected meal. On Days 2 and 4 participants will consume a matched meal to Days 1 and 3 and not bolus. The exercise challenges will take place on 3 days and will consist of 1 hour of mild intensity and 30 minutes of moderate intensity exercise.

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SCHEDULE OF STUDY VISITS AND PROCEDURES

Table 1: Schedule of Study Visits and Procedures

	Screening	Standard Therapy		Treatment Phase							
Visit Number	1[a]	2[a]	3[a]	4[a]	5	6	7	8	9	24-HR FU	EW[d]
Study Day	-	-	-	0	1	14	30	60	90	91	
Visit Window	-	0 to 7d	0 to 28d	0 to 30d	+1d	±3d	±3d	±3d	±3d	-	
Virtual (V) or Office (O) Visit	O	O	O	O	V/O[c]	V/O[c]	V/O[c]	V/O[c]	O	V	O
Screening											
Informed Consent	X										
Confirm eligibility (Inclusion/Exclusion criteria assessed)	X										
Laboratory Assessments											
HbA1c (Central Lab) and Lipid Panel				X					X		X
HbA1c (Point of Care (POC) for eligibility)	X										
Serum Creatinine, C-peptide and GAD antibody (Central Lab)				X							
Pregnancy Test (urine dipstick) for women of childbearing potential	X			X							
Clinical Assessments											
Medical History	X										
Demographics (age, sex, race and ethnicity)	X										
Concomitant medications	X	X	X	X	X	X	X	X	X		X
Height	X										

	Screening	Standard Therapy		Treatment Phase							
Visit Number	1[a]	2[a]	3[a]	4[a]	5	6	7	8	9	24-HR FU	EW[d]
Study Day	-	-	-	0	1	14	30	60	90	91	
Visit Window	-	0 to 7d	0 to 28d	0 to 30d	+1d	±3d	±3d	±3d	±3d	-	
Virtual (V) or Office (O) Visit	O	O	O	O	V/O[c]	V/O[c]	V/O[c]	V/O[c]	O	V	O
Weight	X			X					X		X
Vital signs[b]	X			X	X	X	X	X	X		X
Electrocardiogram (ECG)	X										
Average total daily insulin (self-reported over ~ 7 days)	X										
Average total basal insulin (self-reported over ~ 7 days)	X										
Average total bolus insulin (self-reported over ~ 7 days)[g]	X										
Training on Glucagon administration and treatment of hypo/hyperglycemia				X							
Adverse events		X	X	X	X	X	X	X	X		X
Review insulin dosing		X	X	X							
Training on carbohydrate counting			X[h]								
Questionnaires											
T2-DDS		X							X		X
HCS		X							X		X
PSQI		X							X		X
System Opinion									X		X

	Screening	Standard Therapy		Treatment Phase							
Visit Number	1[a]	2[a]	3[a]	4[a]	5	6	7	8	9	24-HR FU	EW[d]
Study Day	-	-	-	0	1	14	30	60	90	91	
Visit Window	-	0 to 7d	0 to 28d	0 to 30d	+1d	±3d	±3d	±3d	±3d	-	
Virtual (V) or Office (O) Visit	O	O	O	O	V/O[c]	V/O[c]	V/O[c]	V/O[c]	O	V	O
Study Devices											
Study device training (BG meter and CGM)		X[f]									
Dispense BG meter		X[e]									
QC testing of BG meter by site		X									
Placement of Dexcom G6 CGM		X									
CGM Assessment			X								
Omnipod 5 training				X							
Dispense/Return Omnipod 5 System				X					X		X
APRMS Data Portal initiation/discontinuation				X					X		X
Complaints/device deficiencies			X	X	X	X	X	X	X		X
BG meter data review (if available)				X	X	X	X	X	X		X
Omnipod 5/Sensor data review					X	X	X	X	X		X
Advise on insulin adjustment for transition to pump therapy			X								
Follow-up for transition to pre-study therapy										X	

	Screening	Standard Therapy		Treatment Phase							
Visit Number	1[a]	2[a]	3[a]	4[a]	5	6	7	8	9	24-HR FU	EW[d]
Study Day	-	-	-	0	1	14	30	60	90	91	
Visit Window	-	0 to 7d	0 to 28d	0 to 30d	+1d	±3d	±3d	±3d	±3d	-	
Virtual (V) or Office (O) Visit	O	O	O	O	V/O[c]	V/O[c]	V/O[c]	V/O[c]	O	V	O

[a] Visits 1-4 may be completed on the same day if participant qualifies

[b]Vital signs include body temperature, respirations, pulse, and blood pressure should be performed at visits 4-9 if in person

[c]Visits identified as "V/O" can either be conducted in person at the clinical site or virtually. Visits identified as "O" can only be conducted in person at the clinical site. Vital signs are not required at any virtual visit, however, BG meter and CGM data review should still occur

[d]Early withdrawal visit will only be conducted for participants who complete visit 4 and discontinue prior to visit 9

[e]BG meter must pass at least one level of quality control testing prior to dispensing

[f] Dispensed BG meters do not need to be returned to sponsor

[g] For Basal-bolus subjects only

[h]Participants will not be required to transition to carbohydrate counting and may continue to use a fixed-bolus regimen in collaboration with the study investigator

Abbreviations: S=Screening; EW=Early Withdrawal; QC=Quality Control Testing; FU=Follow-up Visit

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Chapter 1: Background Information

1.1 Introduction

Diabetes is a significant health issue in the United States with over 37 million people living with either type 1 (T1D) or type 2 (T2D) diabetes. T2D is the most prevalent and accounts for approximately 90% of these cases [1]. Like T1D, T2D is a disorder affecting the normal homeostatic regulation of blood glucose. Unlike T1D which is the result of the total loss of beta cells resulting in insulinopenia, T2D develops due to impaired insulin action along with a partial but progressive loss of beta cell mass that manifests clinically as hyperglycemia. Without proper management, people who have T2D are at an increased risk of microvascular complications such as retinopathy, nephropathy, and neuropathy and macrovascular complications including cardiovascular and peripheral vascular disease. Additionally, the long-term consequences of inadequately controlled hyperglycemia results in diabetes being the leading cause of blindness, kidney disease, and amputation in the United States [2]. The burden of care is significant for all patients with T2D and the current treatment options remain in need of improvement.

The progressive nature of T2D often requires the eventual introduction of insulin injection therapy to improve glycemic control. Unfortunately, even after initiation of insulin therapy the number of patients with T2D who reach glycemic control to improve quality of life remains low [3, 4]. Over the past 10 years, a growing number of publications have reported the advantages of Continuous Subcutaneous Insulin Infusion (CSII) systems compared with multiple daily injections (MDI) for patients with T2D [5-8]. The use of CSII generally led to improved glycemic control and reduction in daily insulin dose [9-12]. Additionally, CSII was shown to be an effective alternative for patients with T2D failing to achieve glycemic control with the use of non-insulin agents [8, 13-15] .

Furthermore, advances in diabetes technology including the miniaturization of pumps and the introduction of continuous glucose monitors (CGM) offer promising therapeutic options for diabetes care. The use of automated insulin delivery (AID) that combines CGM with algorithm-driven insulin delivery can potentially improve glycemic control and reduce the duration of both hyperglycemia and hypoglycemia [16]. While many studies of AID in patients with T1D have shown the safety and feasibility of the approach in improving glycemic control and reducing the risk of hypoglycemia [17-20] , there have been only a few studies in patients with T2D [16, 21]. In a feasibility study of insulin-naive patients with T2D, 24 h of fully closed-loop insulin delivery resulted in improvement of time in range, with a greater benefit observed overnight, and no risk of hypoglycemia [21]. Data in the outpatient setting for T2D is further limited. In a poster presentation of real-world use of the Minimed 670G system by 456 patients with T2D, users were found to have improved time in range (70-180 mg/dL) of 74.5% during Automated Mode vs. 67.8% in Manual Mode, facilitated by a reduction in time spent in the hyperglycemic range [22]. This data is promising and supports the potential use of AID systems in patients with T2D, in particular for those with suboptimal glycemic outcomes.

The Omnipod® 5 Automated Insulin Delivery System (Omnipod 5 System) has a novel algorithm with customizable glucose targets and unique configuration utilizing a tubeless insulin pump (Pod), which is a small (3.9 x 5.2 x 1.45 cm) adhesive patch pump worn on the body. The cannula is automatically deployed directly under the Pod, creating an infusion site without external tubing. The Pod is waterproof (IP28) and is worn continuously for up to 72 hours. All user interactions are conducted wirelessly through a mobile app on a smartphone. The insulin

delivery algorithm is located on the Pod, and the glucose sensor communicates directly with the Pod through Bluetooth® wireless technology. Therefore, the system can continuously provide automated insulin delivery (AID) via the wearable on-body components alone (Pod and sensor), without the smartphone controller needing to be nearby.

Omnipod 5 was developed through several feasibility studies [23-26]. Subsequently, it was evaluated in a prospective, multi-center, single-arm safety study and shown to be safe and effective in the glycemic management of children, adolescents, and adults ages 2 to 70 years with type 1 diabetes, with minimal episodes of severe hypoglycemia and diabetic ketoacidosis, in addition to significant improvements in glycemic outcomes, including decreased HbA1c and increased time in range, 70-180 mg/dL [17, 24, 27, 28]. Among 111 children and 124 adults, HbA1c was reduced by 0.71% from 7.67 ± 0.95% to 6.99 ± 0.63% and by 0.38% from 7.16 ± 0.86% to 6.78 ± 0.68%, respectively. Additionally, the percentage of time in range increased by 15.6 ± 11.5% in children and 9.3 ± 11.8% adults with the use of Omnipod 5 [17].

1.2 Rationale and Objective

There is reasonable evidence available demonstrating the safety and efficacy of the Omnipod 5 System in patients with T2D in the outpatient setting. In the Omnipod 5 T2D feasibility study, 24 participants completed 8 weeks of system use and experienced improved glycemic outcomes including significant improvements in TIR and less time with glucose values ≥250 mg/dL, with an overall reduction in HbA1c by 1.3%. Additionally, the incidence of hypoglycemia <54mg/dL while using the Omnipod 5 did not increase [29] supporting safe use in this population. Following the 8-week study, 22 participants continued using the system for an additional 6 months in an optional extension phase. This group experienced a total decrease in HbA1c of 1.6% between baseline (9.4%) and the end of the ~8-month period of use (7.8%). The incidence of hypoglycemia <54 mg/dL remained low throughout this period (median 0.02% of time). The main study plus the extension study provided 4,325 total person-days of data of system use in a prospective study setting [30].

Additionally, based on cloud-connected device data (data on file), Insulet is aware that approximately 4,800 users of Omnipod 5 in the real world aged ≥18 years have self-reported type 2 diabetes as of December 6 2022. For those who have used the system for at least 3 months (n=1,368), the average time in range was 63.9% with minimal time below 70mg/dL (median 0.2%, IQR 0.07% to 0.66%). Within this group, the 110mg/dL, 120mg/dL, 130mg/dL, 140mg/dL, and 150mg/dL target settings were used for 57.8%, 31.0%, 5.8%, 2.6%, and 2.8% of time overall, resulting in 92,363, 49,626, 9,261, 4,161, and 4,452 person-days of data collected at each respective target. In total, there has been approximately 780 patient-years of device use accumulated to date for the type 2 population alone.

Although these results are encouraging, further evaluation of the Omnipod 5 System in a prospective cohort in a heterogenous group of participants is needed. Therefore, we propose a pivotal study with the primary objective to evaluate the safety and efficacy of the Omnipod 5 System in 300 participants with T2D over approximately 3 months of system use.

Poor glycemic control is well-known to influence the development of complications in T2D. Therefore, in assessing the safety of an insulin delivery system it is essential to know that people with T2D using the system do not suffer from worsening glycemic control. Since A1c is the gold standard for long term glycemic control we will use this measurement as our primary

safety endpoint in this pivotal study. We expect that study participants will see no deterioration in glycemic control after initiating therapy with Omnipod 5.

While short term measurements of glycemic control are of interest and will be analyzed, additional safety endpoints will be assessed in order to provide a comprehensive view of safety, including hyperglycemia requiring hospitalization and severe hypoglycemia. While mild hyperglycemia is common in the T2D patient population we will be recruiting for this study, it is uncommon to be severe enough to result in hospitalization or other severe adverse events. Hypoglycemia is also an important safety endpoint and will be reported. However, in routine care, mild hypoglycemic events can be missed by patients and hence underdiagnosed. In addition, patients must check their blood glucose level when potential symptoms occur to confirm the presence of hypoglycemia, otherwise hypoglycemia may be over diagnosed by the patient based on symptoms alone. Yet, it is recognized that this confirmation does not necessarily happen. Clearly, severe hypoglycemia resulting in hospitalization or need for assistance will not be over or underdiagnosed, but such events tend to be very uncommon in T2D and as such may not prove to be a robust measure of safety alone.

1.3 Study Objectives

Primary Objective:

- To evaluate the safety of the Omnipod 5 System in adults with type 2 diabetes.

Secondary Objectives:

- To evaluate the efficacy of the Omnipod 5 System in adults with type 2 diabetes.
- To evaluate glycemia measures of efficacy of the Omnipod 5 System and quality of life of Omnipod 5 users.

Chapter 2: Study Devices

2.1 Investigational Device: Omnipod 5 System

The Omnipod 5 System is comprised of two components:

- Omnipod 5 Pod (insulin infusion pump with SmartAdjust technology)
- Omnipod 5 App (installed on the Insulet provided Controller or smart phone).

The Dexcom G6 CGM (sold separate and manufactured by Dexcom) is required for use with Omnipod 5 for automated insulin delivery.

The Omnipod 5 Pod interacts with the Omnipod 5 App and a CGM (sensor) via secure Bluetooth technology. With SmartAdjust technology, the system receives glucose values and trend data from the CGM (sensor), automatically calculates insulin dose, and sends delivery commands to the Pod for delivery of insulin. Insulin is delivered through a soft cannula that is automatically inserted by the Pod into the subcutaneous tissue.

The system can work in Automated Mode and Manual Mode. In Automated Mode (SmartAdjust technology activated), the system calculates insulin micro-boluses every five minutes based upon the current and predicted glucose over a 60-minute prediction horizon. The Omnipod 5 Algorithm adjusts its insulin delivery based on several factors including a user-set glycemic

target (110-150 mg/dL) and the user's Total Daily Insulin (TDI). In Manual Mode, the system operates by delivering insulin at programmed basal rates like a standard insulin pump.

The Omnipod 5 App contains a SmartBolus Calculator that is used to deliver meal bolus doses of insulin based on entered carbohydrates as well as sensor and trend data. The SmartBolus Calculator works in both Automated and Manual Modes.

The Omnipod 5 System (with SmartAdjust technology activated) can automatically adjust delivery of insulin based on CGM sensor values and can pause delivery of insulin when the glucose sensor value falls below or is predicted to fall below predefined threshold values. The Omnipod 5 System is currently interoperable with the Dexcom G6 CGM. Participants will be provided a User Guide.

Figure 1: System components of the Omnipod 5 System

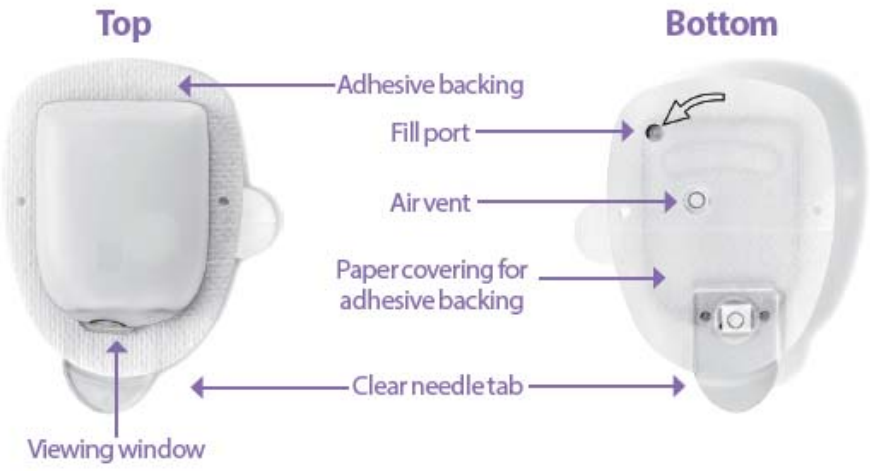

Figure 2: Omnipod 5 Pod

2.1.1 Indications for Use

The Omnipod 5 ACE Pump (Pod) is intended for the subcutaneous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. The Omnipod 5 ACE Pump is able to reliably and securely communicate with compatible, digitally connected devices, including automated insulin dosing software, to receive, execute, and confirm commands from these devices. The Omnipod 5 ACE Pump is intended for single patient, home use and requires a prescription.

SmartAdjust™ technology is intended for use with compatible integrated continuous glucose monitors (iCGM) and alternate controller enabled (ACE) pumps to automatically increase, decrease, and pause delivery of insulin based on current and predicted glucose values. SmartAdjust™ technology is intended for the management of type 1 diabetes mellitus in persons 2 years of age and older and type 2 diabetes mellitus in persons 18 years of age and older. SmartAdjust™ technology is intended for single patient use and requires a prescription. The SmartBolus Calculator is software intended for the management of diabetes in persons aged 2 and older requiring rapid-acting U-100 insulin. The SmartBolus Calculator calculates a suggested bolus dose based on user-entered carbohydrates, most recent sensor glucose value (or blood glucose reading if using fingerstick), rate of change of the sensor glucose (if applicable), insulin on board (IOB), and programmable correction factor, insulin to carbohydrate ratio, and target glucose value. The SmartBolus Calculator is intended for single patient, home use and requires a prescription.

2.2 Continuous Glucose Monitoring

The study continuous glucose monitor (CGM) will include an unmodified Dexcom G6 Mobile transmitter and sensors. This is an FDA-cleared device system with no changes to its hardware or firmware components. The CGM sensor will be placed per the manufacturer instructions and will be replaced at least every ten days. When the Dexcom G6 CGM is paired with the Omnipod 5 System, it will communicate via Bluetooth Low Energy (BLE). Glucose values from the sensor will be sent to the algorithm residing on the Pod and used in insulin dosing adjustments.

2.3 Blood Glucose Meter and Strips

- All study blood glucose meters will be QC tested prior to being dispensed to a participant. A tested meter will not be used in a study if it does not read within the target range per manufacturer labeling.
- Participants will be reminded to use the study BG meter for all fingerstick BG measurements. Participants will be asked to perform fingerstick blood glucose measurements in accordance with the labelling of the study CGM device.

2.4 Investigational Device Returns

Any damaged investigational devices or investigational devices related to a suspected deficiency or adverse event must be returned to the study Sponsor. Additionally, all Omnipod 5 controllers and CGM receivers should be returned to the Sponsor at the end of study.

Undispensed or unused investigational devices should be returned or disposed of per Sponsor instruction.

2.4.1 Study Device Accountability Procedures

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

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. Additional device accountability procedures will be detailed in the site procedures manual.

Chapter 3: Study Enrollment and Screening

3.1 Participant Recruitment and Enrollment

Enrollment will proceed with the goal of at least 300 participants initiating use of the Omnipod 5 System and at least 275 participants completing the trial. A maximum of 400 individuals may be screened in order to achieve this goal. A minimum of 60 and maximum of 125 participants using basal only will be enrolled. The number of participants with POC HbA1c less than 7.0% should not exceed 20% of participants initiating use of the Omnipod 5 System.

Study participants will be recruited from ~20-25 clinical centers in the United States representative of community endocrinology practice and primary care. It is anticipated that each site will enroll approximately 8-15 participants who initiate use of the Omnipod 5 system; however, sites may enroll additional participants with Sponsor pre-approval, as necessary, to reach the enrollment goal. Each site will not exceed 20% of the overall enrollment goal for the study.

Individuals generally will be recruited from each site's existing patient population or from a pool of individuals who contact the site. The JCHR IRB is the "Central IRB" for this study. Sites may rely on the Central IRB or their local IRB. Central and local IRB requirements regarding

recruitment materials and policies will be adhered to. Study recruitment methods may consist of the following:

- Reviewing pre-existing databases at the clinical sites to identify patients who may be eligible. Those identified will be contacted via IRB-approved mailing sent through post, email, or via phone and will be provided information about the study and how to proceed if potentially interested;
- IRB-approved press release announcing study and study fact sheet;
- Support groups, patient education classes, and not-for-profit community support groups
- IRB-approved paper and digital advertisements, brochures, postcards, flyers, and/or newsprint advertisements;
- IRB-approved digital advertisements posted on social media sites like LinkedIn, Twitter, YouTube, Instagram, Facebook, and other public forums managed by a clinical trial site or Sponsor.
- In-person recruitment of patients seen in the clinic; and
- An IRB-approved website dedicated to clinical trial recruitment.

All recruitment methods and specific advertising materials will be approved by the Central IRB (and local IRB as required) prior to their implementation.

3.1.1 Enrollment of Underrepresented Racial and Ethnic Populations

This study plans to recruit underrepresented racial and ethnic populations. According to Diabetes in America, 3rd edition, the distribution of Race/Ethnicity among persons with diagnosed diabetes in non-Hispanic Asian/Pacific Islander, Black (non-Hispanic) and Hispanic populations was found to be 4.1%, 15.8% and 14.8%, respectively [31] . Therefore, out of our total study cohort of 300 participants we will aim to reach study-wide enrollment goals based on Table 2.

Table 2: Approximate Goals for Enrollment of Underrepresented Racial and Ethnic Populations

RACIAL/ETHNIC CATEGORY	DISTRIBUTION OF RACE/ETHNICIY AMONG PERSONS WITH DIAGNOSED DIABETES	ANTICIPATED NUMBER OF PARTICIPANTS BY RACE/ETHNICITY BASED ON STUDY SAMPLE SIZE	ENROLLMENT GOAL
Asian/Pacific Islander (non-Hispanic)	4.1%	~12	~10-15
Black (non-Hispanic)	15.8%	~47	~40-45
Hispanic	14.8%	~44	~40-45

3.1.2 Additional Enrollment Goals

In addition, this study plans to enroll participants representative of our intended use population of adults with T2D. Therefore, out of our total study cohort of 300 participants we will aim to reach study-wide enrollment goals based on Table 3.

Table 3: Approximate Goals for Enrollment of the US T2D Population

	ENROLLMENT GOAL (N=300)	ANTICIPATED MINIMUM NUMBER OF PARTICIPANTS
Insulin usage	25% <100 units 20% 100-150 units 5% > 150 units	~75 ~60 ~15
Baseline medication regimen	20% SGLT-2 or GLP-1 5% both SGLT-2 and GLP-1	~60 ~15
Baseline glycemia	40% HbA1c 8-12% 15% HbA1c >9%-<12%	~120 ~45 (subset of 120 above)
Non-carbohydrate counting insulin dosing	20% upon entry to study	~60

3.1.3 Informed Consent and Authorization Procedures

Potential eligibility will be assessed during screening at Visit 1. Before completing any procedures or collecting any data, informed consent will be obtained by electronic means via the 21 CFR 11 compliant JCHR eConsent application (or on paper if necessary).

The study protocol will be discussed with the potential study participant by study staff. The potential study participant will be given the Informed Consent Form to read. Potential study participants will be encouraged to discuss the study with family members and their personal physicians(s) before deciding whether to participate in the study.

As part of the informed consent process, each participant will be asked to sign an authorization for release of personal information, electronically (or on paper if required by the institution). The investigator will review the study-specific information that will be collected and to whom that information will be disclosed. After speaking with the participant, questions will be answered about the details regarding consent and authorization. The informed consent process is discussed further in section 11.3.

A participant is considered enrolled when the informed consent form has been fully signed.

3.2 Participant Inclusion Criteria

Individuals must meet all of the following inclusion criteria in order to be eligible to participate in the study.

1. Age at time of consent 18-75 years
2. Diagnosed with type 2 diabetes, on current insulin regimen for at least 3 months prior to screening (i.e. Basal-bolus, basal only or pre-mix)
3. Basal bolus (long-acting insulin and rapid acting analog) or pre-mix users with A1C <12.0% OR basal users on long or intermediate acting insulin only with A1C $\geq$ 7.0% and < 12.0%
4. ~~4.~~ Willing to use only the following types of U-100 insulin during the study: Humalog U-100, Novolog, or Admelog
5. Participant agrees to provide their own insulin for the duration of the study
6. Stable doses over the preceding 4 weeks of other glucose-lowering medications as

determined by Investigator
7. Stable doses of weight loss medications over the preceding 4 weeks and throughout the study that may affect glycemic control directly and/or indirectly, except for a dose reduction or discontinuation, as determined by Investigator.
8. Willing to wear the system continuously throughout the study
9. Deemed appropriate for pump therapy per investigator's assessment considering previous history of severe hypoglycemic and hyperglycemic events, and other comorbidities
10. Investigator has confidence that the participant has the cognitive ability and can successfully operate all study devices and can adhere to the protocol
11. Able to read and understand English or Spanish
12. Willing and able to sign the Informed Consent Form (ICF)
13. If female of childbearing potential, willing and able to have pregnancy testing

3.3 Participant Exclusion Criteria

Individuals meeting any of the following exclusion criteria at baseline will be excluded from study participation.

1. Use of an AID pump in automated mode within 3 months prior to screening
2. Any medical condition which in the opinion of the investigator, would put the participant at an unacceptable safety risk, such as untreated malignancy, unstable cardiac disease, unstable or end-stage renal disease, and/or eating disorders (i.e. anorexia/bulimia)
3. 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 12 months prior to screening
4. Any planned surgery during the study which could be considered major in the opinion of the investigator
5. History of more than 1 severe hypoglycemic event in the 6 months prior to screening
6. History of more than 1 episode of diabetic ketoacidosis (DKA) or Hyperosmolar hyperglycemic syndrome (HHS) in the 6 months prior to screening; unrelated to an intercurrent illness; kinked, dislodged, or occluded cannula; or initial diabetes diagnosis
7. Blood disorder or dyscrasia within 3 months prior to screening, including use of hydroxyurea, which in the investigator's opinion could interfere with determination of HbA1c
8. Plans to receive blood transfusion over the course of the study
9. Has taken oral or injectable steroids within 8 weeks prior to screening or plans to take oral or injectable steroids during the study
10. Unable to tolerate adhesive tape or has any unresolved skin condition that could impact sensor or pump placement
11. Pregnant or lactating, planning to become pregnant during the study, 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; childbearing potential means that menstruation has started, and the participant is not surgically sterile or greater than 12 months post-menopausal)
12. Participation in another clinical study using an investigational drug or device other than the Omnipod 5 in the 30 days prior to screening or intends to participate during the study period

13. 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
14. Participant is an employee of Insulet, an Investigator or Investigator's study team, or immediate family member (spouse, biological or legal guardian, child, sibling, parent) of any of the aforementioned

3.4 Visit 1 - Screening and Eligibility

Visit 1 will be conducted at the clinical study site. This visit will assess eligibility. Participants who have signed the informed consent and appear to meet the eligibility criteria will continue to the screening assessments which will be performed at the clinical study site.

3.4.1 Data Collection and Testing

The following procedures will be performed according to Table 1: Schedule of Study Visits and Procedures and data collected/eligibility criteria will be checked and documented:

- Signing of informed consent
- Review of inclusion/exclusion criteria and confirmation of eligibility
- Assessment of HbA1c via local point of care (for eligibility)
- Urine pregnancy test for all women who have reached menarche and are premenopausal (≤ 12 months post-menopausal) and are not surgically sterile
- Medical history
- Average total daily insulin (self-reported over ~7 days)
- Average total basal insulin (self-reported over ~7 days)
- Average total bolus Insulin (self-reported over ~7 days)
- Demographics (date of birth, sex, race and ethnicity)
- Concomitant medications
- Height
- Weight
- Vital Signs
- Electrocardiogram (ECG)

Screening procedures will last approximately 2 hours.

3.4.2 Screen Failures

Individuals who do not initially meet study eligibility requirements may be rescreened at a later date per investigator discretion.

3.5 Visit 2 - Start of Standard Therapy

Visit 2 will mark the commencement of the standard therapy period. This visit will be conducted at the clinical study site and may be combined with Visit 1, pending participant eligibility. Standard Therapy can commence once the screening visit is complete but must begin no later than 7 days after the screening visit. The following must be completed on Visit 2 according to Table 1: Schedule of Study Visits and Procedures:

- Questionnaires (must be completed prior to placing the study Dexcom G6 CGM)
- Study device training (BG meter and Dexcom G6 CGM)
- Dispense BG meter
- QC testing of BG meter (must pass at least 1 level of QC testing prior to dispensing)
- Placement of Dexcom G6 CGM

If the visit is not combined with Visit 1, the following also must be completed:

- Concomitant medications
- Adverse Events
- Review insulin dosing

All participants will satisfy a minimum requirement of CGM data collection using the Dexcom G6 CGM. Following standard therapy, all participants must wear only the Dexcom G6 CGM for the remainder of the study.

Participants will be instructed to use only fingersticks when measuring blood glucose levels with the blood glucose meter.

3.5.1 Non-Dexcom CGM Users

At the commencement of standard therapy, participants who do not use a Dexcom G6 CGM will be dispensed a blinded Dexcom G6 CGM. Participants will be trained on sensor insertion and optional calibration procedures in accordance with manufacturer labeling. The CGM will be placed by the participant under the supervision of study staff and it will be confirmed that it was done properly. Participants will be instructed on use and care of the sensor and on placing a new sensor after 10 days (or sooner if necessary). Participants will commence the 14-day data collection period.

Non-Dexcom CGM users will also be required to participate in the entire standard therapy 14-day period. They may opt to keep using their current unblinded CGM during the standard therapy period, however, no data from their current CGM will be used for the study.

3.5.2 Current Dexcom G6 CGM Users

Current Dexcom G6 users may be exempt from the standard therapy 14-day period if they are willing and able to:

- Provide 14 days of CGM data from the past 30 days
- Meet the criteria of at least 3400 readings of CGM data during any consecutive 14 days

The site staff will review the Dexcom G6 use and data criteria to see if they have met the exemption criteria. If the exemption criteria are not met, participants may choose to continue to collect data until they meet the criteria or will be required to participate in the entire 14-day standard therapy period consistent with the requirements for non-Dexcom G6 users. If participants meet the criteria, they will be immediately eligible to proceed with Visit 3, in which case Visit 1, Visit 2, and Visit 3 may occur on the same day.

3.5.3 Questionnaires

Participants will complete the following questionnaires:

1. ***Type 2 Diabetes Distress Assessment System (T2-DDAS)***

   The T2-DDAS is a 29-item survey that assesses overall core level of distress and seven sources of diabetes distress for type 2 adults. The seven common and specific sources of distress are: (1) Management Demands, (2) Hypoglycemia, (3) Interpersonal Issues, (4) Healthcare Provider, (5) Shame/Stigma, (6) Long-Term Health and (7) Healthcare Access. Items are scored on a 5-point scale from not a problem to a very serious problem. It is administered before and at the end of the intervention. Administration time is 5 minutes.

2. ***Hypoglycemia Confidence Scale (HCS)***

The HCS is a 9-item self-report scale that examines the degree to which people with diabetes feel able, secure, and comfortable regarding their ability to stay safe from hypoglycemic-related problems. It has been validated for use in adults with type 1 diabetes and insulin-using type 2 diabetes. Administration time is approximately 5 minutes.

3. Pittsburgh Sleep Quality Index (PSQI)

The PSQI assesses sleep quality over a 1-month interval. The survey includes 10 self-rated items. Administration time is approximately 5 minutes.

3.6 Visit 3 – End of Standard Therapy

Visit 3 will occur at the end of the Standard Therapy period. Insulin dosing and adjustments should be reviewed at this visit, based on Section 3.6.3. Previous CGM users will be instructed to remove their personal CGM. All participants should only use the study-provided Dexcom G6 CGM device from this visit onwards.

The following must be completed during Visit 3 according to Table 1: Schedule of Study Visits and Procedures:

- CGM Assessment (conducted first in the event the visit needs to be rescheduled so the participant can capture additional CGM data if necessary)

The following procedures will be done once sufficient CGM data have been confirmed:

- Training on carbohydrate counting as needed. Participants will not be required to transition to carbohydrate counting and may continue to use a fixed-bolus regimen in collaboration with the study investigator
- Advise on insulin adjustment for transition to pump therapy, if needed

If the visit is not combined with Visit 1, the following also must be completed:

- Concomitant medications
- Adverse Events
- Review insulin dosing
- Complaints and Device Deficiencies

3.6.1 CGM Assessment

Sites will upload the data from the Dexcom G6 to review the CGM data. If the minimum CGM criteria has not been met, the CGM wear can be extended. All CGM data collection must be completed by Visit 3. Those who successfully use the Dexcom G6 and capture at least 3400 readings of CGM data over the 14-day period will continue.

3.6.2 Review of Medications, Medical Conditions and Adverse Events

Participants will be asked about any changes to medications and medical conditions as well as possible adverse events that may have occurred since the last visit to verify that the participant remains eligible for the trial.

3.6.3 Review of Insulin Dosing and Insulin Adjustments

The insulin dosing the participant has been using will be reviewed. Participants will be advised on insulin adjustments to make to transition to pump therapy. These recommendations will be based on investigator judgment from review of insulin dosing and the CGM data collected in the

prior 14 days. Depending on insulin adjustment, the participant may proceed with V4 immediately or up to 5 days following V3, per investigator judgement. If the participant requires a 1-2 day insulin adjustment period before preceding to V4, this should not occur more than 1 day before V3. For current pump with Dexcom G6 users, who have fulfilled the CGM exemption criteria and do not require adjustments to their insulin dosing, Visits 1-4 can occur on the same day.

Chapter 4: Treatment Phase

During the 13-week treatment phase, all participants will be asked to do the following:

- Change the Pod at least once every 72 hours. Participants who have a high TDI may need to change their Pod earlier than the expected 3 days of Pod wear.
- Change their sensor per manufacturer's instructions or sooner if necessary
- Participants will be encouraged to estimate the grams of carbohydrates for each meal or snack per their usual routine.
- Treat themselves per their usual routine if they become hypoglycemic or hyperglycemic or have symptoms of either at any time during the study
- Follow their pre-exercise management such as insulin reduction for meal boluses, consumption of snacks, or adjusting their insulin delivery settings.
- Not initiate weight loss medications or glucose-lowering medications or change dose of such medications in use at enrollment except for safety during the study period.

4.1 Visit 4 – Omnipod 5 Initiation Visit

Visit 4 will be conducted at the clinical study site on study day 0. All scheduled assessments will be performed according to Table 1: Schedule of Study Visits and Procedures. The following must be completed during Visit 4:

- Blood draw to send specimens to central lab. Specimens will be collected for
  - HbA1c
  - Serum Creatinine, C-Peptide, GAD Antibody and Lipids (fasting not required) - total cholesterol, low density lipoprotein [LDL] cholesterol, high density lipoprotein [HDL] cholesterol, triglycerides
- Urine pregnancy test for all women who have reached menarche and are premenopausal (≤ 12 months post-menopausal) and are not surgically sterile
- Weight
- Vital signs
- Training on glucagon administration and treatment of hypo/hyperglycemia
- Omnipod 5 training
- Dispense Omnipod 5
- APRMS data portal initiation

If the visit is not combined with Visit 1, the following also must be completed:

- Concomitant medications
- Adverse Events
- Review insulin dosing
- BG meter review (if available)
- Complaints and Device Deficiencies

If Visit 4 is not completed within 30 days of screening (Visit 1), participants must be rescreened and complete standard therapy if they do not meet the CGM exemption criteria in section 3.5.2. If a participant needs to be rescreened, the ECG and completion of questionnaires do not need to be repeated.

4.1.1 Training on Glucagon Administration and Hypo/Hyperglycemia

In the event of hypoglycemia, defined as a glucose level < 70 mg/dL, or symptoms of hypoglycemia, participants will be advised to treat with fast acting carbohydrates. Participants should recheck their glucose after 10-15 minutes. If their glucose is still < 70 mg/dL or they are symptomatic, they should take additional fast acting carbohydrates and retest in 10-15 minutes. The process should continue until their glucose is > 70 mg/dL.

Participants should be advised that in case of severe hypoglycemia they may need to have glucagon administered. Severe hypoglycemia is defined as an event requiring assistance of another person due to altered consciousness.

In the event of unexplained hyperglycemia, where the sensor is ≥300mg/dL for 1 hour or, ≥400 mg/dL at any point, blood glucose (measured with BG meter) should be checked. When using the Omnipod 5 system, if BG is ≥300 mg/dL, an occlusion or dislodged cannula should be suspected. The Pod should be removed, and the participant will be instructed to replace the Pod at a different location on the body. Participants should contact the clinical site for further instructions to determine whether an additional injection of insulin is required.

4.1.2 Training on Omnipod 5 System

Clinical study staff will go through step-by-step instruction during the initial device set up and confirm that study participants understand how to set up and use the Omnipod 5 device with the Pod Start Checklist as a guide. Prior to completing Visit 4 and discharging the participant, clinical study staff will confirm that the participant understands the Omnipod 5 System, including how to administer a bolus, and that all questions are answered. The recommended starting target glucose is 120 mg/dL, however, the appropriate target glucose should be selected in consultation with the investigator. Participants must exhibit safe and competent use of the Omnipod 5 System before using the system at home. Participants will also be advised to follow up with the clinical study staff any time they have questions or concerns throughout the duration of the study.

4.2 Target Glucose Challenges

The first 60 participants to complete Visit 4 will immediately take part in the target glucose challenges over 9 days, following device onboarding. Participants will start at the target glucose of 150 mg/dL and subsequently decrease to 140 mg/dL and 130 mg/dL after spending approximately 72 hours at each target according to Table 4. Participants should be contacted after approximately 72 hours to update the target setting. If a participant is unable to be contacted, the glucose target setting may be extended by up to 24 hours and this would not constitute a protocol deviation. If one of the target glucose settings is extended, any subsequent target should still take place for approximately 72 hours.

These target glucose settings will be reviewed by clinical staff at scheduled visits and through the remote monitoring system, APRMS, to ensure safety is maintained and requirements are met. If there are safety concerns observed by the investigator during the challenge, the participant will be advised to change their target glucose setting while the investigator verifies the change using APRMS. The target glucose challenges will be performed separately from the

meal and exercise challenges. At the conclusion of the challenges, participants may choose their desired target glucose in consultation with the investigator.

Table 4: Target Glucose Challenges

	Number of Target Glucose Challenge Days								
	1	2	3	4	5	6	7	8	9
Target Glucose	150 mg/dL			140 mg/dL			130 mg/dL		

4.3 Visits 5-8

Visits 5-8 will be conducted either at the clinical study site or virtually and the following procedures will be performed at each visit according to Table 1: Schedule of Study Visits and Procedures:

- Concomitant medications
- Vital signs (for in person visits)
- Adverse events
- Complaints/device deficiencies
- BG meter data review (if available)
- Omnipod 5 data review

Review of Omnipod 5 and BG meter data may result in device adjustments for safety concerns but not solely for optimization purposes. Any changes should be documented and a justification for the adjustment should be provided.

4.4 Meal and Exercise Challenge Visits

All study participants will complete supervised meal and exercise challenges. Participants who do not undergo the target glucose challenges may commence the meal and exercise challenges after Visit 5 and must complete the challenges prior to Visit 9. If a participant is completing the target glucose challenge, they should not begin the meal and exercise challenges until finished. All challenges will be conducted while in Automated Mode. Every effort will be made to conduct the meal and exercise challenges according to Table 5, however, challenges that do not occur on consecutive days will not constitute a protocol deviation. Meal and exercise challenges should not occur on the same day. Participants will undergo these challenges at home following scheduling with study site staff and when a companion is present. A companion is defined as a friend, partner, or family member who can stay with the study participant during the challenges. Prior to beginning the challenges, study staff will confirm that the participants and their companion understand and are capable of glucagon administration as well as calling 911 in the case of an emergency. Additionally, participants will be instructed that they should have glucagon, glucose tablets, and other supplies used for the treatment of diabetic emergencies available.

Table 5: Meal and Exercise Challenges

Challenges	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
High Carbohydrate Meal (≥ 60 grams)	With Bolus Day 1 and 2 Matched Meal	No Bolus Day 1 and 2 Matched Meal	With Bolus Day 3 and 4 Matched Meal	No Bolus Day 3 and 4 Matched Meal	N/A	N/A	N/A
Exercise includes: • **30 minutes of moderate intensity exercise** • **1-hour of mild intensity exercise**	N/A	N/A	N/A	N/A	X	X	X

768

769 ### 4.4.1 Meal Challenges

770 Meal challenges should take place over 4 days. On Days 1 and 3 participants will bolus for their
771 selected meal. On Days 2 and 4, participants will consume a matched meal to Days 1 and 3,
772 respectively, and not bolus. Every effort should be made for the matched meal challenges to
773 occur within a few days of each other. Meals will consist of ≥60g of carbohydrate. Throughout
774 the meal, the clinical site staff will be available to confirm glucose levels by APRMS.
775 Completion of the meal challenges will be assessed at the 1-hour postprandial mark by
776 confirming participants CGM value in APRMS. All participants are expected to complete the
777 meal challenges regardless of whether they are able to complete the exercise challenges. A
778 companion should be available during the challenge and for at least 1 hour after the meal is
779 complete.

780 ### 4.4.2 Exercise Challenges

781 Prior to any participant starting the exercise challenges, their baseline ECG should be reviewed.
782 Participants with an abnormal electrocardiogram consistent with increased risk of arrhythmia,
783 ischemia, or prolonged QTc interval (> 450 ms) will not be permitted to undergo the exercise
784 challenges. All participants will complete the exercise challenges unless there are safety
785 concerns per investigator's assessment or other limitations that preclude their participation. A
786 companion needs to be available during the period of moderate intensity exercise and needs to
787 stay for the overnight period following exercise.

788 Exercise challenges will take place on 3 days and consist of 1 hour of low intensity and 30
789 minutes of moderate intensity exercise. The low and moderate intensity exercise may be
790 completed all at once or may be separated as long as they are both completed on the same
791 day. Low intensity exercise is defined as non-sedentary behaviors such as walking at 2.0 miles

per hour, cooking activities, or light housekeeping [32] . Moderate intensity exercise includes activities defined using the CDC guidelines,

Table 6: Moderate Intensity Exercise[33] .

Participants may engage in moderate intensity exercise if their CGM value is ≥70 mg/dL with the corresponding CGM trend either steady or increasing. Participants whose CGM value is <100 mg/dL will be instructed to consume carbohydrates before starting the moderate intensity exercise. Throughout the moderate intensity exercise duration, clinical site staff trained in the assessment and treatment of diabetic emergencies will monitor glucose levels by APRMS. At the end of the 30-minutes of moderate intensity exercise, study staff will confirm that the CGM reading is between 70-300 mg/dL and the CGM trend is not rapidly increasing or decreasing. Once this has been confirmed the participant will be discharged from active monitoring. After completion of each day of exercise challenges, participants will be advised on post-exercise meals and insulin boluses by the study investigator and will follow-up with site staff by phone or videoconference.

Table 6: Moderate Intensity Exercise

	Adults (18-64)	Older Adults (65+)
Moderate Intensity Activities	• Walking/jogging 2.5 miles per hour • Bicycling • Aerobics	• Walking/hiking • Jogging • Bicycling • Aerobics

During the exercise challenges, participants will be encouraged to:

- Treat themselves per their usual routine if they become hypoglycemic or hyperglycemic or have symptoms of either at any time during the exercise challenge.
- Follow their pre-exercise management such as insulin reduction for meal boluses, consumption of snacks, or adjusting their insulin delivery settings, if applicable. All pre-exercise management strategies will be recorded for each exercise session.

Exercise should be stopped if the participant develops chest pain or pressure, undue shortness of breath, participant feels unwell, signs of poor perfusion (e.g., light-headedness, confusion, ataxia, pallor, cyanosis, nausea, or cold and clammy skin, etc.), or if the participant chooses to stop. Participants or companions should call 911 in the event of an emergency. If exercise is stopped prematurely for any reason, site staff should be notified immediately. The study investigator should follow up to assess the participant. Inability to complete the 3 days of exercise due to an injury where participation may exacerbate the condition will not be considered a protocol deviation. Ability to participate will be up to the discretion of the investigator. Participants will be withdrawn from continuing the exercise challenges if glucagon was administered, 911 was called, if the participant needed to visit the ER, or had other symptoms that could indicate a safety concern per investigator discretion.

Challenges do not need to take place on consecutive days, however, if challenges are not, the site will be required to conduct follow-up telephone calls 12-36 hours after the challenge is complete.

4.5 Visit 9

Visit 9 will be conducted at the clinical study site on study day 90. The following procedures will be performed according to Table 1: Schedule of Study Visits and Procedures:

- Blood draw to send specimens to central lab. Specimens will be collected for
  - HbA1c
  - Lipids (fasting not required) - total cholesterol, low density lipoprotein [LDL] cholesterol, high density lipoprotein [HDL] cholesterol, triglycerides
- Review of concomitant medications
- Weight
- Vital signs
- Assessment of Adverse Events
- Questionnaires
  - HCS, T2-DDAS, PSQI and System Opinion
- Return Omnipod 5 System
- APRMS data portal discontinuation
- Complaints/device deficiencies since last visit
- BG meter data review (if available)
- Omnipod 5 data review

In addition to the Questionnaires administered at baseline, the System Opinion questionnaire will be administered to evaluate the patient experience with the Omnipod 5. It will take approximately 5 minutes to complete. Prior to discharge from the study, the participant's CGM value must be >80 mg/dL with a steady or increasing trend. Clinical staff will instruct the participant on how to transition to their recommended therapy per their healthcare professional. Participants will receive a follow-up phone call 24 hours after transitioning to their post-study therapy to ensure a safe transition.

Chapter 5: Other Visits

5.1 Early Withdrawal Visit (If Applicable)

Participants who initiate use of the Omnipod 5 System but discontinue prior to Visit 9 will be asked to complete a final study visit.

The procedures that would be completed at Visit 9 will be completed at the Early Withdrawal Visit. Early withdrawal visit will only be conducted for participants who complete visit 4 and discontinue prior to visit 9.

5.2 Unscheduled Contacts

Aside from scheduled visits, participants may require an unscheduled visit either virtually or in person at the clinical study site. This visit will include, at a minimum:

- Assessment of AEs

- Complaints/device deficiencies since last visit
- BG meter data review (if available)
- Omnipod 5/sensor data review

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

Additional contacts may also occur via telephone or email. Unscheduled contacts should be documented when there is meaningful contact with the participant, such as when updating device settings, participant retraining, device questions, or any in-person contact. Basic or minor contacts to discuss participant visit scheduling, participant reminders, and/or requests for or providing additional supplies should not be documented as an unscheduled contact.

Contact for changes to the target glucose settings during the target challenges should be recorded as an unscheduled contact, however, the visit does not require that the following items be included:

- BG meter data review (if available)
- Omnipod 5/sensor data review

AE's and complaints/device deficiencies should still be reviewed.

5.3 Lost to Follow-up

Every effort will be made to contact a participant in the event of a missed scheduled visit. A participant 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 participant and specify the reason for early withdrawal as lost to follow-up.

Chapter 6: Potential Risks and Benefits

6.1 Known Potential Risks

6.1.1 Potential Risks of the Omnipod 5 System

There are known risks and benefits with using the Omnipod 5 System. Most of the risks are not unique to the study and are typical for patients using insulin pumps, sensors, and BG meters. The following are possible reasons the system may deliver too much insulin or incorrectly stop insulin delivery:

- CGM sensor reads higher or lower than the actual glucose level which increases risk for hypoglycemia and hyperglycemia with automated insulin delivery systems;
- Device malfunctions that could produce a suspension of insulin delivery or over delivery of insulin and/or Omnipod 5 System use or misuse.

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)

Other potential risk associated with using the Controller:

- Risk of overheating of the Omnipod 5 Controller charging port and cable, including the cable melting, deforming or discoloring. The excess heat may cause minor burns if those areas of the controller are touched or in rare instances may lead to fire.

6.1.2 Risk of Hypoglycemia

As with any person having diabetes and using insulin, there is always a risk of having hypoglycemia. The frequency of hypoglycemia should be no more and possibly less than it would be as part of daily living. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. There is the possibility of fainting or seizures (convulsions) and that for a few days the participant may not be as aware of symptoms of hypoglycemia. In very rare cases, coma or death may occur related to insulin administration, pump use or misuse, or Omnipod 5 System use or misuse.

6.1.3 Risk of Hyperglycemia

Users are at increased risk for developing hyperglycemia if insulin delivery is interrupted during use of the Pod. If it is untreated, prolonged hyperglycemia in T2 diabetes can lead to diabetic hyperosmolar hyperglycemic syndrome (HHS) or in rare instances Diabetic Ketoacidosis (DKA). HHS or DKA can cause symptoms such as breathing difficulties, shock, coma, or death. Further, occlusions can interrupt insulin delivery and lead to hyperglycemia or HHS. This could occur if insulin delivery is attenuated or suspended for an extended period or if the pump is not working properly. A CGM functioning poorly and significantly under-reading glucose values could lead to inappropriate suspension of insulin delivery.

6.1.4 Venipuncture Risks

Venipuncture blood draws can cause some common reactions like pain, bruising, or redness at the sampling site. Less common reactions include bleeding from the sampling site, formation of a small blood clot or swelling of the vein and surrounding tissues, fainting, and rarely infection.

6.1.5 Fingerstick Risks

About 1 drop of blood will be removed by fingerstick for measuring blood glucose and sometimes HbA1c or other tests. This is a standard method used to obtain blood for routine hospital laboratory tests. Discomfort or minor pain is common at the time of lancing. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. A small scar may persist for several weeks. The risk of local infection is less than 1 in 1000. This should not be a significant contributor to risks in this study as fingersticks are part of the usual care for people with diabetes.

6.1.6 CGM Sensor Insertion Risks

There is a low risk for developing a local skin infection at the site of the sensor needle placement. These occur very infrequently, but, if an infection was to occur, oral and/or topical antibiotics can be used. There may be bleeding at the insertion site and bleeding under the skin causes a bruise (1 in 10 risk).

Skin irritation or allergic reactions may occur from the adhesives used to secure the CGM sensor.

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

6.1.7 Questionnaires

As part of the study, participants will complete questionnaires, which include questions about their private attitudes, feelings and behavior related to the investigational equipment as well as managing diabetes. It is possible that some people may find these questionnaires to be mildly upsetting. Similar questionnaires have been used in previous research and these types of reactions have been uncommon.

6.1.8 Other Risks

Data downloaded from the CGM, pump, and the blood glucose meter will be collected for the study as measures of diabetes self-management behaviors. Some people may be uncomfortable with the researchers' having such detailed information about their daily diabetes habits.

6.2 Known Potential Benefits

One purpose of this research is to improve glycemic control (e.g., reduce hyperglycemia and variability). It is expected that this protocol will yield increased knowledge about using the Omnipod 5 System to control the glucose level and will collect data for submission to the FDA. The individual participant may not benefit from study participation.

6.3 Risk Assessment

The protocol is considered a significant risk device study. Although the Omnipod 5 System is approved for use in individuals with type 1 diabetes, it is not approved for use in type 2 diabetes and will be considered an investigational use of the Omnipod 5 System. Therefore, an investigational device exemption (IDE) from the U.S. Food and Drug Administration (FDA) is required to conduct the study.

Chapter 7: Unanticipated Problem, Adverse Event, and Device Issue Reporting

7.1 Unanticipated Problems

Site investigators will promptly report all unanticipated problems meeting the criteria below on an eCRF. Sites relying on the Central IRB must report potential Unanticipated Problems to the IRB within seven (7) calendar days of recognition. For this protocol, an unanticipated problem is an incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places participants or others at a greater risk of harm than was previously known or recognized (including physical, psychological, economic, or social harm)

The Sponsor (or CRO on behalf of the Sponsor) also will report to the Central IRB all potential unanticipated problems not directly involving a specific site such as unanticipated problems that occur study-wide or at another participating entity such as a vendor. These instances must be reported to the Central IRB within seven (7) calendar days of recognition. The Director of the JCHR Human Research Protection Program (HRPP) will report to the appropriate regulatory authorities if the IRB determines that the event indeed meets the criteria of an Unanticipated Problem requiring additional reporting to fulfill the reporting obligations of the HRPP.

7.2 Adverse Events

7.2.1 Definitions

Adverse Event (AE): Any untoward medical occurrence (including laboratory findings) associated with study procedures, the use of a device, biologic, or drug in humans, including any comparator used, whether or not the event is considered related (i.e., irrespective of the relationship between the adverse event and the device(s) under investigation).

To further clarify, an adverse event is any unintended disease or injury, or untoward clinically significant clinical sign (including abnormal laboratory findings) in a research participant that manifests while in the study if it was not present before enrolling in the study, or if it was present before enrolling, it has increased in severity, frequency or type since enrolling in the study. For this purpose, a participant is considered enrolled once the participant has signed the consent form.

Serious Adverse Event (SAE): Any untoward medical occurrence that results in any of the following outcomes:

- Death.
- A life-threatening adverse event; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).

- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical and surgical intervention to prevent one of the outcomes listed in this definition. Note: If either the Sponsor or investigator believes that the event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting. See 21 CFR 312 for more information.

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 (21 CFR 812.3(s)).

Adverse Device Effect (ADE): An adverse event related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. This includes comparator if the comparator is a medical device. (Note that an Adverse Event CRF is to be completed in addition to a Device Deficiency or Issue CRF, unless excluded from reporting as defined in section 7.3).

Comparator: Medical device, therapy (e.g., active treatment, normal clinical practice), placebo or no treatment, used in the control group in a clinical investigation. (ISO 14155:2020)

Device Complaints and Malfunctions: A device complication or complaint is something that happens to a device or related to device performance, whereas an adverse event happens to a participant. A device complaint may occur independently from an AE, or along with an AE. An AE may occur without a device complaint or there may be an AE related to a device complaint. A device malfunction is any failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed. (21 CFR 803.3). Note: for reporting purposes, sites will not be asked to distinguish between device complaints and malfunctions.

Use Error: User action or lack of user action while using the medical device (3.34) that leads to a different result than that intended by the manufacturer or expected by the user. Includes the inability of the user to complete a task. Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment. Users might be aware or unaware that a use error has occurred. An unexpected physiological response of the patient is not by itself considered a use error. A malfunction of a medical device that causes an unexpected result is not considered a use error. (ISO 14155:2020)

7.2.2 Reportable Adverse Events

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

1. An SAE as defined in section 7.2.1
2. An ADE as defined in section 7.2.1, unless excluded from reporting in section 7.3
3. An AE as defined in 7.2.1 occurring in association with a study procedure
4. An AE as defined in 7.2.1 not related to a device issue which leads to temporary or permanent discontinuation of a study device
5. An AE as defined in 7.2.1 that affects the participant's ability to complete any study procedures
6. An AE as defined in 7.2.1 for which a visit is made to a hospital emergency department
7. Hypoglycemia meeting the reporting criteria in section 7.2.3
8. Hyperglycemia event meeting the reporting criteria in section 7.2.4.
9. An AE as defined in section 7.2.1 considered to be related to either ineffective insulin (e.g., insulin exposed to high temperature that loses potency), signs or symptoms related to insulin infusion, or changing of type of insulin related to an AE.

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

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 CRF online. Each AE CRF is reviewed by the Medical Monitor to assess safety and to verify the coding and the reporting that is required.

7.2.3 Hypoglycemic Events

Hypoglycemia not associated with an Adverse Device Effect or discontinuation of the study device is only reportable as an adverse event when one of the following criteria is met:

- A hypoglycemic event occurred meeting the following definition of 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. 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 glucose measurements are not available during such an event, neurological recovery attributable to the restoration of glucose to normal is considered sufficient evidence that the event was induced by a low glucose concentration.
- Evaluation or treatment was obtained at a health care provider facility for an acute event involving hypoglycemia, or the participant contacted the site and received guidance following the occurrence of an acute event involving hypoglycemia
- Hypoglycemia occurred that was associated with an ADE as defined in section 7.2.1
- Study device discontinued due to hypoglycemia

When a severe hypoglycemic event occurs (as defined above), a Hypoglycemia CRF should be completed in addition to the Adverse Event CRF. Severe hypoglycemic events should be considered serious adverse events with respect to reporting requirements. When a severe hypoglycemic event occurs during use of a study device, it generally will be considered

unrelated to the device (per section 7.2.8) if the device functioned as intended and there does not appear to be a flaw in how the device is intended to function.

7.2.4 Hyperglycemic Events

Hyperglycemia not associated with an Adverse Device Effect or discontinuation of the study device is only reportable as an adverse event when one of the following criteria is met:

- evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia, or the participant contacted the site and received guidance on how to manage the hyperglycemia
- the event involved hyperosmolar hyperglycemic syndrome (HHS), as defined by the American Diabetes Association (ADA) and described below
  - Symptoms such as polyuria, polydipsia, nausea, or vomiting;
  - Plasma glucose levels are very elevated (typically > 600 mg/dL);
  - Plasma effective osmolarity is >320 mOsm/L;
  - Absence of significant ketones; and
  - Treatment provided in a health care facility
- Hyperglycemia occurred that was associated with an ADE as defined in section 7.2.1
- Study device discontinued due to hyperglycemia
- the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below
  - 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 (or CO2) <15; and
  - Treatment provided in a health care facility

When a hyperglycemic event qualifies as an SAE as defined in section 7.2.1, a Hyperglycemia/DKA CRF should be completed in addition to the Adverse Event CRF. Events meeting HHS or DKA criteria should be considered serious adverse events with respect to reporting requirements. Hyperglycemia events not meeting criteria for HHS or DKA generally will not be considered serious adverse events unless one of the SAE criteria in section 7.2.1 is met.

When a hyperglycemia/HHS or DKA event occurs during use of a study device, it generally will be considered unrelated to the device (per section 7.2.5) if the device functioned as intended and there does not appear to be a flaw in how the device is intended to function.

7.2.5 Relationship of Adverse Event to Study Investigational Device

The study investigator will assess the relationship of any adverse event to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the study device. The Medical Monitor also will make this assessment, which may or may not agree with that of the study investigator. Reporting requirements will be based on the Medical Monitor's assessment as the Sponsor's representative.

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

- **Unrelated:** The AE is clearly not related to a study drug/device and a likely alternative etiology exists such as an underlying disease, environmental or toxic factors or other therapy.
- **Unlikely Related:** The AE does not follow a reasonable temporal sequence during or after use of study drug/device and a more likely alternative etiology exists such as an underlying disease, environmental or toxic factors, or other therapy.
- **Possibly Related:** The AE occurred in a reasonable time during or after use of study drug/device; but could be related to another factor such as an underlying disease, environmental or toxic factors, or other therapy; and there is a possible, though weak, scientific basis for establishing a causal association between the AE and the study drug/device.
- **Probably Related:** The AE occurred in a reasonable time during or after use of study drug/device; is unlikely to be related to another factor such as an underlying disease, environmental or toxic factors, or other therapy; and there is a plausible, though not strong, scientific basis for establishing a causal association between the AE and the study drug/device.
- **Definitely Related:** The AE occurred in a reasonable time during or after use of study drug/device; cannot be explained by another factor such as an underlying disease, environmental or toxic factors, or therapy; and there is a strong scientific basis for establishing a causal association between the AE and the study drug/device.

Where these relatedness categories are used, events determined to be Possibly Related, Probably Related, or Definitely Related will be considered to meet the *reasonable possibility* causality standard for relatedness and necessitate reporting as required (see 21 CFR 312.32 for more information).

7.2.6 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.

7.2.7 Expectedness

For a serious adverse event that is considered possibly related to study device, the Medical Monitor will classify the event as unexpected if the nature, severity, or frequency of the event is not consistent with the risk profile of the device.

7.2.8 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary. To facilitate coding, the site will enter a preliminary MedDRA code which the Medical Monitor may accept or change (the Medical Monitor's MedDRA coding will be used for all reporting). The Medical Monitor will review the investigator's assessment of causality and may agree or disagree. Both the investigator's and Medical Monitor's assessments will be recorded. The Medical Monitor will have the final say in determining the causality as well as whether an event is classified as a serious adverse event and/or an unanticipated adverse device effect.

7.2.9 Outcome of Adverse Events

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

- RECOVERED/RESOLVED (COMPLETE RECOVERY) – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RECOVERED/RESOLVED WITH SEQUELAE – AE/SAE where the participant recuperated but retained pathological conditions resulting from the prior disease or injury. 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.
- ONGOING (NOT RECOVERED/NOT RESOLVED) – An ongoing AE/SAE is defined as an ongoing event 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.
    - 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.
- ONGOING (MEDICALLY STABLE) – AE/SAE is ongoing, but medically stable. For example, a chronic condition where no further change is expected.

If any reported adverse events are ongoing when a participant completes the study (or withdraws), adverse events classified as UADEs or related SAEs will be followed until they are either resolved, or have no prospect of improvement or change, even after the participant has completed all applicable study visits/contacts. For all other 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.

If a participant is lost to follow up and participant outcome cannot be determined, outcome classification will be the last known outcome.

7.3 Reportable Device Issues

All UADEs and ADEs as defined in section 7.2.1 will be reported on both a Device Issue CRF and AE CRF, except for skin reactions from CGM sensor placement or Pod placement that do not require pharmacologic treatment.

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 Issue CRF assuming criteria for a UADE or ADE have not been met:

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

7.4 Timing of Event Reporting

SAEs possibly related to a study device or study participation and UADEs must be reported by the investigator to the Sponsor within twenty-four (24) hours of the site becoming aware of the event. This can occur via phone or email, or by completion of the AE CRF and Device Issue CRF if applicable. If the AE CRF is not initially completed, it should be completed as soon as possible after there is sufficient information to evaluate the event. All other reportable ADEs and other reportable AEs should be submitted by completion on the respective CRF within seven (7) days of the site becoming aware of the event.

The Sponsor will notify all participating investigators of any adverse event that is serious, related, and unexpected. Notification will be made within ten (10) working days after the Sponsor becomes aware of the event.

Each principal investigator is responsible for reporting serious study-related adverse events to, and abiding by any other reporting requirements of, his/her Institutional Review Board or Ethics Committee and the Central IRB (as applicable). Where the site is relying on the Central IRB, sites must report all serious, related adverse events within seven (7) calendar days.

Upon receipt of a qualifying event, the Sponsor will investigate the event to determine if a UADE has occurred, and if indicated, report the results of the investigation to all overseeing IRBs, and the FDA within ten (10) working days of the Sponsor becoming aware of the UADE per 21CFR 812.46(b) (2). The Sponsor in conjunction with 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 five (5) working days after the Sponsor makes this determination and no later than fifteen (15) working days after first receipt notice of the UADE. The investigator(s) may then be required to provide approval or acknowledgment of receipt of that notification and must submit to their overseeing IRB as required.

The investigators are also required to report, without unjustified delay, all device deficiencies that could have led to a UADE, including device deficiencies, irrespective of whether an adverse event occurred.

7.5 Safety Oversight

The study Medical Monitor will review all adverse events and adverse device events that are reported during the study. SAEs typically will be reviewed within twenty-four (24) hours of reporting. Other AEs typically will be reviewed on a weekly basis.

The Sponsor and Clinical Study Director will be informed of all cases of severe hypoglycemia and HHS/DKA and the Medical Monitor's assessment of relationship to the study device; and informed of all reported device issues.

7.6 Stopping Criteria

7.6.1 Participant Discontinuation of Study Device

In the case of an unanticipated system malfunction resulting in a severe hypoglycemia or HHS/DKA event (or a malfunction that could have led to severe hypoglycemia or HHS/DKA), use of the study device will be suspended while the problem is diagnosed. The UADE will be reported to the IRB and FDA. After assessment of the problem and any correction, use of the Omnipod 5 System will not be restarted until approval is received from the IRB and FDA.

In the absence of a device malfunction, 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 HHS/DKA as defined in section 7.2.4
- Two distinct severe hypoglycemia events as defined in section 7.2.3
- One episode of HHS/DKA as defined in section 7.2.4 and one severe hypoglycemia event as defined in section 7.2.3

Each HHS/DKA or severe hypoglycemia event will be reviewed by the Medical Monitor with respect to determination of cause and whether the occurrence of the event can be attributed to use of the study device.

An additional requirement for continued study device use following a single HHS/DKA or severe hypoglycemic event will be that the site investigator believes that the event is unlikely to recur and that it is safe for the participant to continue to use the system. Additionally, 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 study device, use will be discontinued.

Even if the study device system is discontinued, the participant will be asked to remain in the study through the final study visit for safety and data collection.

7.6.2 Criteria for Suspending or Stopping Overall Study

In addition to the suspension of device use due to a UADE as described in section 7.2.1, study activities could be similarly suspended if the manufacturer of any constituent 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.

Additionally, the Medical Monitor may request suspension of study activities or stoppage of the study if deemed necessary based on the totality of safety data available.

Chapter 8: Miscellaneous Considerations

8.1 Drugs Used as Part of the Protocol

Participants will use their personal insulin during the study- Humalog U-100, Novolog, or Admelog.

8.2 Collection of Medical Conditions and Medications

Pre-Existing Condition: Any medical condition that is either present at screening, a chronic disease, or a prior condition that could impact the participant's health during the course of the study (e.g., prior myocardial infarction or stroke).

Medical Conditions During the Study: In addition to conditions meeting the reporting requirements for an adverse event or device issue as described above, the following medical conditions should also be reported (reported as medical conditions and not adverse events: (1) new diagnosis or identification of a chronic disease that was present before enrollment, (2) a change of diagnosis of a previously existing medical condition that is not associated with an exacerbation after enrollment, and (3) any medical condition that could affect the participant's ability to carry out any aspect of the protocol or could affect an outcome assessment that was not previously reported but was already in existence prior to enrollment.

Medications: All medication for the treatment of chronic pre-existing conditions, medical conditions, and/or adverse events that the participant is currently taking at screening or during the course of the study should be recorded. Nutraceuticals and preventative treatment also should be recorded. Medications only taken as needed can be recorded with an ongoing frequency of "PRN" or can be recorded when used during the study. Glucagon for treatment of severe hypoglycemia will only be recorded if used during the study.

8.3 Prohibited Medications, Devices, Treatments, and Procedures

Only insulins approved for the study pump can be used with the Omnipod 5 System.

Hydroxyurea cannot be used due to potential interference with the CGM sensor.

8.4 Rescue Medications

All participants will be advised to have a commercially available glucagon preparation for treatment as needed of severe hypoglycemia and will be given a prescription to fill if necessary.

8.5 Pregnancy Reporting

If pregnancy occurs, the study intervention will be discontinued while continuing safety follow up and data collection. The occurrence of pregnancy will be reported to the Sponsor, Coordinating Center and to the JCHR IRB on the Unanticipated Problem form within seven (7) calendar days of becoming aware of the pregnancy.

8.6 Participant Compensation

Participant compensation will be specified in the informed consent form.

8.7 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. For participants who withdraw, their data will be used up until the time of withdrawal.

For participants who withdraw, site staff will help them transition to their own insulin therapy safely.

8.8 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the Coordinating Center, the Jaeb Center for Health Research in Tampa, FL. Other entities or individuals who may receive or view study data will be described in the informed consent form.

8.9 General Considerations

The study is being conducted in compliance with the policies described in the study policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice (GCP).

Site staff shall refer participants to the appropriate user guide (Omnipod 5, Dexcom G6, and blood glucose meter) regarding contraindications, warnings, and precautions.

When feasible, data will be directly collected in electronic case report forms, which will be considered the source data.

Any medical advice needed by the participants during their participation that is not directly related to the study protocol should be obtained in the usual manner with their own physician.

If there is a temporary extended study stoppage, the duration of the study may be extended so that participants will have 13 weeks of Omnipod 5 System use.

8.10 Resources for Participants

Questions relating to study procedures will be dealt with by a site staff member on call. Participants will be referred to their own medical providers for issues not directly related to the study and to local Emergency Medical Services for medical emergencies.
Participants will be instructed to contact the study staff for any technical issues that arise with the study devices. The site staff will escalate the issue to Insulet for technical support as needed.

Chapter 9: Statistical Considerations

9.1 Statistical and Analytical Plans

The approach to sample size and statistical analyses are summarized below.

This study will occur over two periods: a Standard Therapy Period where participants use their standard insulin therapy with a Dexcom CGM sensor and a 13-week Treatment Period where participants use the Omnipod AID System.

9.2 Sample Size and Power Calculations

The sample size of 275 participants initiating use of the AID system and completing the 3-month study was selected to ensure sufficient exposure of system use by participants using MDI insulin therapy, basal only insulin therapy, and non-insulin glucose lowering medications.

For power calculations, the standard deviation for the change in HbA1c from baseline to outcome has been estimated using the data from a pilot study using the Omnipod 5 AID system in type 2 diabetes, from the pivotal trial using the Omnipod 5 AID system in type 1 diabetes, and from the pivotal trial using the Control-IQ system in type 1 diabetes. In the Omnipod 5 pilot study in type 2 diabetes, the standard deviation for change in HbA1c from baseline to outcome at 2 months was 0.7% (baseline HbA1c was 9.4%). In the Omnipod 5 pivotal trial for participants with type 1 diabetes age 14-70 years, the standard deviation was 0.5%; however, mean baseline HbA1c was 7.2% which is much lower than what is anticipated in this trial. In the Control-IQ pivotal trial for adolescents and adults with type 1 diabetes, the standard deviation was 0.7% for the cohort with baseline HbA1c ≥7.5%. Based on these data, a standard deviation of 0.7% is a reasonable estimate. To be more conservative, a standard deviation of 0.8% has been used in the power calculations.

With 275 participants completing the trial, statistical power will be >99% for the primary endpoint analysis assessing non-inferiority of the 13-week HbA1c levels compared with the baseline levels for a non-inferiority limit of 0.3% and type 1 error rate of 2.5% (one-sided). Statistical power also is >99% for a test of superiority comparing the 13-week HbA1c levels to baseline levels assuming a true mean difference of -0.4% or higher and type 1 error rate of 5% (2-sided).

9.2.1 Statistical Power in Subgroups

Power for evaluating non-inferiority (assuming the true population value for HbA1c change from baseline is zero and non-inferiority limit = 0.3%) and superiority (assuming true change of -0.4%) for change in HbA1c in subgroups (such as pre-study MDI users, basal insulin only users, users of non-insulin glucose lowering medications) is provided below, assuming a type 1 error = 5% (2-sided). Note that if the true change in HbA1c is as little as 0.1%, then the power calculations for non-inferiority will be identical to those shown below for superiority.

	Statistical Power	
# Participants in Subgroup Completing the Trial	**Non-inferiority**	**Superiority**
20	36%	57%
30	51%	75%
40	64%	87%
50	74%	93%
75	89%	99%
100	96%	>99%
125	99%	>99%

For testing for non-inferiority (assuming the true population value for HbA1c change from baseline is zero and non-inferiority limit = 0.3%), sample size for participants completing the trial is calculated to be 58 for 80% power and 77 for 90% power. Assuming a true population HbA1c change of as little as 0.1%, sample size would be 34 for 80% power and 44 for 90% power.

For testing for superiority (true change 0.4%), sample size for trial completers is 34 for 80% and 44 for 90%.

9.3 Statistical Hypotheses

HbA1c

Two sets of hypotheses will be tested for the primary outcome HbA1c. One test for non-inferiority with a limit of 0.3% and another test for superiority. As noted below, these will be tested in a hierarchy (sequential testing) to control the type 1 error rate. More specifically:

Let μ_δ denote the mean change in HbA1c from baseline to 13 weeks.

Non-inferiority:

- Null hypothesis (H_0): $\mu_\delta \geq 0.3\%$ (the change in HbA1c from baseline to 13 weeks is greater than or equal to 0.3%).
- Alternate hypothesis (H_a): $\mu_\delta < 0.3\%$ (the change in HbA1c from baseline to 13 weeks is less than 0.3%.

Superiority:

- Null hypothesis (H_0): $\mu_\delta = 0$ (there is no difference in change in HbA1c from baseline to 13 weeks).
- Alternate hypothesis (H_a): $\mu_\delta \neq 0$ (there is a change in HbA1c from baseline to 13 weeks).

Additional Key Endpoints

The additional key endpoints to be tested in a hierarchical fashion are listed in section 9.4.3.

For % time < 70 mg/dL and % time <54 mg/dL, two sets of hypotheses will be tested. One test for non-inferiority and another test for superiority. More specifically:

Let μ_δ denote the mean change in the endpoint from baseline to 13 weeks.

% Time <70 mg/dL

Non-inferiority:

- Null hypothesis (H_0): $\mu_\delta \geq 2\%$ (the change in % time <70 mg/dL from baseline to 13 weeks is greater than or equal to 2%).
- Alternate hypothesis (H_a): $\mu_\delta < 2\%$ (the change in % time <70 mg/dL from baseline to 13 weeks is less than 2%.

Superiority:

- Null hypothesis (H_0): $\mu_\delta = 0$ (there is no difference in change in % time <70 mg/dL from baseline to 13 weeks).
- Alternate hypothesis (H_a): $\mu_\delta \neq 0$ (there is a change in % time < 70 mg/dL from baseline to 13 weeks).

% Time <54 mg/dL

Non-inferiority:

- Null hypothesis (H_0): $\mu_\delta \geq 0.5\%$ (the change in % time <54 mg/dL from baseline to 13 weeks is greater than or equal to 0.5%).
- Alternate hypothesis (H_a): $\mu_\delta < 0.5\%$ (the change in % time <54 mg/dL from baseline to 13 weeks is less than 0.5%.

Superiority:

- Null hypothesis (H_0): $\mu_\delta = 0$ (there is no difference in change in % time <54 mg/dL from baseline to 13 weeks).
- Alternate hypothesis (H_a): $\mu_\delta \neq 0$ (there is a change in % time < 54 mg/dL from baseline to 13 weeks).

Other Key Secondary Endpoints

Similar hypotheses will be tested for superiority for the other metrics listed below in Section 9.4.3.

9.4 Outcome Measures

9.4.1 Primary Endpoint

- Change in HbA1c from baseline to 13 weeks
  - Safety Endpoint: Change in HbA1c tested for non-inferiority (non-inferiority margin 0.3%)
  - Efficacy Endpoint: Change in HbA1c tested for superiority (tested only if non-inferiority has been met for the safety endpoint)

9.4.2 Additional Safety Endpoints:

1. Severe hypoglycemia
2. Hospitalization/ER for severe hypoglycemia
3. Hyperosmolar hyperglycemic syndrome (HHS)/ diabetic ketoacidosis (DKA)
4. Hospitalizations or ER related to hyperglycemia or hypoglycemia in the previous 3 months vs. study 3 months
5. Other serious adverse events
6. Reportable device-related adverse events

9.4.3 Additional Key Secondary Endpoints

The following key secondary endpoints listed below will be tested in a hierarchical fashion to preserve the type 1 error rate as described in section 9.7.

1. Mean glucose
2. Change in % time 70-180 mg/dL (superiority)
3. Change in % time 70-140 mg/dL (superiority)
4. Change in % time ≥ 300 mg/dL (superiority)
5. Change in % time > 250 mg/dL (superiority)
6. Change in % time > 180 mg/dL (superiority)
7. % time < 70 mg/dL (noninferiority; non-inferiority limit 2.0%)
8. % time < 54 mg/dL (noninferiority; non-inferiority limit 0.5%)
9. Change from baseline in T2-DDAS total score (superiority)
10. % Meeting MCID for T2-DDAS
11. Change from baseline in PSQI total score (superiority)
12. % Meeting MCID for PSQI
13. Change from baseline in HCS total score (superiority)

14. % Meeting MCID for HCS
15. % time <70 mg/dL (superiority)
16. % time <54 mg/dL (superiority)
17. Coefficient of variation (superiority)

9.4.4 Exploratory Endpoints:

1. Change in total daily insulin dose
2. Change in body mass index (BMI)
3. Average reduction in the number of non-insulin glucose lowering agents
4. Change in percent of participants using insulin as a monotherapy or insulin + metformin.
5. % of participants achieving HbA1c <7%
6. % of participants achieving HbA1c <8%
7. % of participants achieving time in range 70-180 mg/dL >70%
8. % of participants achieving time <70 mg/dL <4%
9. % of participants achieving time <54 mg/dL <1%
10. % of participants achieving time in range 70-180 mg/dL >70% and time <70 mg/dL <4%
11. Prolonged hyperglycemia events >250 mg/dL lasting at least 120 minutes. An event is considered terminated when sensor glucose is $\leq$ 180 mg/dL for at least 15 minutes.
12. Change in lipids (Total Cholesterol: HDL, LDL and triglycerides)

9.4.5 Calculation of CGM metrics

- Baseline values will be calculated from the CGM data collected over all 24 hours of the day during the Standard Therapy Period.
- Follow-up (outcome) values will be calculated from CGM data collected over all 24 hours of the day during the 13-week Treatment Period beginning at Visit 4.
    - CGM endpoint calculations will exclude CGM readings during (1) the supervised exercise challenges from the start of the challenge until 6am the next morning, (2) the meal challenges from the start of the challenge for 4 hours, and (3) the 9 days of target challenges performed by a subset of participants.
- Separate values for each CGM metric will be calculated for:
    - Overall: 24 hours of the day
    - Daytime: CGM readings from 6:00 am – 11:59 pm
    - Nighttime: CGM readings from midnight – 5:59 am
- CGM values will be calculated for each type of challenge as described in Sections 9.9 and 9.10
- CGM values will be calculated separately during the target challenges as described in Section 9.11
- An additional overall analysis will include all CGM data collected during follow up including the data collected during the exercise, meal, and target challenges as described in Section 9.20

9.5 Analysis Datasets and Sensitivity Analyses

Safety analyses will include all participants who initiate the 13-week Treatment Period at visit 4. Adverse events occurring during the preceding Standard Therapy Period will be reported separately.

Testing of change in HbA1c from baseline to 13 weeks for both non-inferiority and for superiority will include all participants who have HbA1c values at both baseline and 13 weeks. The following sensitivity analyses will be conducted to handle any missing HbA1c values for both the superiority and non-inferiority analyses:

- Multiple imputation using Rubin's method (assumes MAR)
- Tipping point analysis will assess what magnitude of bias from selective dropout would be necessary to alter the conclusion

CGM analyses for the secondary endpoints listed in section 9.4.3 and section 9.4.4 will not include participants with <168 hours of CGM data during the 13-week Treatment Period.

A per-protocol analysis will be limited to participants who meet all of the following criteria: (1) used the Omnipod 5 system in automated mode for at least 80% of the time during the 13-week Treatment Period, (2)have both baseline and 13-week HbA1c values, and (3) have no major protocol deviations. If fewer than 10% of the study participants would be excluded based on these criteria, then the per-protocol analysis will not be performed.

9.6 Safety Analyses

For the primary outcome of non-inferiority of HbA1c, a paired t-test will be performed with non-inferiority limit of 0.3.

All reportable adverse events will be tabulated separately for the Standard Therapy Period and the Treatment Period. The number of events and the event rate per 100 person-years during the Treatment Period will be calculated for each of the safety outcomes listed in section 9.4.1.

McNemar's test will be used to compare the percentage of participants with a hospitalization or ER visit related to hyperglycemia or hypoglycemia during the 13-week Treatment Period compared with the 13-week period prior to enrollment.

9.7 Analysis of Efficacy Endpoints

Summary statistics appropriate to the distribution (e.g., mean and standard deviation, or median and quartiles) will be tabulated for HbA1c at 13 weeks and change in HbA1c from baseline. A pre- and post- comparison of HbA1c will be performed using a paired t-test for superiority. If the paired differences (i.e., change values) do not follow an approximate normal distribution, then robust regression using an M-estimator will be used.

To preserve the overall type 1 error rate, formal testing of HbA1c for superiority and the key secondary endpoints listed in section 9.4.3 will only be performed if the primary analysis for non-inferiority of HbA1c described above results in a statistically significant finding ($p < 0.05$). In that case, HbA1c will then be tested for superiority and if that is also statistically significant at 0.05 then the key secondary endpoints will be evaluated using methods similar to those described above for the primary analysis for non-inferiority (change in % time <70 and <54 mg/dl) and superiority (the other outcomes listed in Section 9.4.3). Formal testing will be done in a hierarchical manner in the order 1 through 14 listed above in section 9.4.3. If any of the outcomes on this list fail to give a statistically significant result (i.e., $p \geq 0.05$), then formal testing will stop and p-values will not be given for any outcomes further down on the list. Summary

statistics and confidence intervals will be given for each outcome regardless of statistical significance. Note that each of the CGM metrics in the hierarchical listing refers to the overall 24-hour version.

9.8 Exploratory Endpoints

Analysis of the exploratory endpoints listed above will be done without any adjustment for multiple comparisons. This will include the daytime and nighttime values for each of the CGM metrics listed above. Continuous outcomes will be analyzed using the methods described above for the primary outcome. Pre- and post- comparisons for binary outcomes will be done using McNemar's test.

9.9 Exercise Sessions

Adverse events occurring during the exercise sessions will be tabulated.

Information collected about the type and duration of exercise and the pre-moderate exercise preparatory steps will be tabulated.

Descriptive statistics will be calculated for the following CGM metrics during/following exercise:

- Mean glucose
- %time in range 70-180 mg/dL
- % time >180 mg/dL
- % time <70 mg/dl
- % time <54 mg/dL
- Nadir glucose
- % of exercise sessions with nadir < 70 mg/dl
- Excursion (baseline minus nadir)

Each of these metrics will be calculated:

- During exercise
- During exercise and including the 2 hours following moderate exercise
- Subsequent overnight midnight to 5:59am

9.10 Meal Challenges

Adverse events during each meal challenge will be tabulated.

Descriptive statistics will be calculated for the following CGM metrics during and for 4 hours following each type of meal challenge (usual bolus and missed-meal bolus)

- Mean glucose
- % time in range 70-180 mg/dL
- % time >180 mg/dL
- % time >250 mg/dL
- % time >300 mg/dL
- % time <70 mg/dL
- % time <54 mg/dL
- Peak glucose
- Excursion (peak minus baseline)

9.11 Target Challenges

A sample of 60 participants will participate in the 9 days of target challenges, which will include approximately 72 hours of AID system use at each of the following 3 target blood glucoses: 130 mg/dL, 140 mg/dL, and 150 mg/dL.

Adverse events occurring with each of the target glucose levels will be tabulated.

Descriptive statistics will be calculated for the following CGM metrics for each glucose target:

- Mean glucose
- % time in range 70-180 mg/dL
- % time >180 mg/dL
- % time >250 mg/dL
- % time <70 mg/dL
- % time <54 mg/dL

9.12 Intervention Adherence

Descriptive summary statistics will be given for the percentage of time that the Omnipod 5 system is in automated mode and the amount of CGM use over the 13-week Treatment Period.

9.13 Protocol Adherence and Retention

The following measures of adherence will be tabulated during the 13-week Treatment Period:

- Number of protocol deviations
- Flow chart accounting for all enrolled participants up to the end of study
- Number and reasons for participant withdrawals prior to the end of the study
- Number of participants who stopped using the Omnipod 5 system in automated mode and reasons.
- Number of and reasons for unscheduled visits and phone contacts

9.14 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the cohort of all enrolled participants will be summarized in a table using summary statistics appropriate to the distribution of each variable.

9.15 Device Issues

Device malfunctions requiring study team contact and other reported device issues will be tabulated.

9.16 Planned Interim Analyses

No formal interim efficacy analyses are planned.

9.17 Sub-Group Analyses

Efficacy and safety analyses described above will be replicated separately for participants using MDI pre-study and for participants using basal only pre-study.

Pre- and post- comparisons for HbA1c and selected CGM metrics, will be replicated within the subgroups defined by the following factors:

- Use of SGLT2i, GLP1a, and/or DPP4i
- Baseline HbA1c

- <7%
- 7.0-7.9%
- 8.0-8.9%
- ≥9.0%

- Race/ethnicity (non-Hispanic White versus Other)
- Prestudy carbohydrate counting (yes vs. no)
- Baseline C-peptide (continuous variable: cutpoints for display to be determined)
- Additional subgroup analyses will be defined in the statistical analysis plan.

9.18 Multiple Comparison/Multiplicity

There will be no adjustment for safety endpoints. The overall type 1 error for the primary efficacy outcome and key secondary efficacy endpoints will be controlled using a hierarchical testing procedure as described in section 9.7. There will be no adjustment for exploratory endpoints.

9.19 Additional Tabulations

The following will be tabulated with no formal statistical testing:

- Non-insulin glucose lowering agents used during the Standard Therapy Period and Treatment Period

9.20 Additional Exploratory Analyses

The following additional analyses will be performed:

- Separate safety and efficacy analyses in (1) participants using basal-bolus insulin therapy or pre-mix insulin prior to the study and (2) participants using basal insulin only prior to the study
- Separate CGM analyses using CGM metrics calculated for the entire 13-week follow-up period (including the challenge periods) and compared with the baseline CGM metrics using paired t tests or nonparametric approaches depending on the distribution of the data for continuous variables and McNemar's test for binary variables.
- Separate safety and efficacy analyses excluding participants who are positive for GAD antibodies (if GAD antibodies are present in ≥5% of participants)
- Separate safety and efficacy analyses in participants using an SGLT2 inhibitor, GLP-1 receptor agonist or both
- Separate efficacy and safety analyses in participants with total daily insulin >100 units
  - Safety and efficacy endpoints also will be explored in participants with total daily insulin dose >150 units

Chapter 10: Data Collection and Monitoring

10.1 Case Report Forms and Other Data Collection

The main study data are collected on electronic case report forms (CRFs). When data are directly collected in electronic case report forms, this will be considered the source data. For any data points for which the eCRF is not considered source (e.g., lab results that are transcribed from a printed report into the eCRF), the original source documentation must be maintained in

the participant's study chart or medical record. This source must be readily verifiable against the values entered into eCRF.

The investigator is responsible for the accuracy and completeness of data reported on the eCRFs. Each set of participant eCRFs must be reviewed and signed by the investigator in the Electronic Data Capture (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.

Electronic device data files are obtained from the study software and individual hardware components. These electronic device files are considered the primary source documentation.

Laboratory measurements will be made by the central laboratory and the data will be transmitted directly to the Coordinating Center.

10.2 Electronic Device Outputs

10.2.1 Omnipod 5 System Data

The study will collect insulin delivery and sensor data from the Omnipod 5 System. All insulin delivery and sensor data from the Omnipod 5 System will be stored on the device and exported to the Insulet Cloud. Data will be saved in a compatible format that will be extractable for statistical analysis purposes.

The Insulet Cloud is an information system, facilitating communication of comprehensive data originating from the Omnipod 5 application to third party data management systems. Through secure network protocols, the system receives and transfers robust data through validation processes consistent with Insulet Quality Management System (QMS). Data in transit incorporates AES128 encryption from the Omnipod application to cloud. Cloud internal communications leverage EAS256 encryption for data in transit and at rest.

10.2.2 Sensor Data

The study will collect sensor data from the sensor device for all participants. Sensor data for participants actively using Omnipod 5 will be stored and exported to the Cloud. During Standard Therapy, sensor data will be retrieved from the sensor device and uploaded to the clinical database during the participant's site visits. Sensor data will be saved in a compatible format that will be extractable for statistical analysis purposes.

10.2.3 BG Meter Data

This study will also utilize measurements from a BG meter. BG meter data, in any format, may be uploaded to the database if requested.

10.2.4 Participant Identifiers

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

10.3 Study Records Retention

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor. 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.

10.4 Quality Assurance and Monitoring

Designated JCHR personnel and personnel designated by the Sponsor will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements, as well as to ensure that the rights and wellbeing of trial participants are protected and that the reported trial data are accurate, complete, and verifiable. Adverse events will be prioritized for monitoring.

A risk-based monitoring plan will be developed and revised as needed during the study, consistent with FDA's risk-based monitoring guidance, "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013). Study conduct and monitoring will conform with 21 Code of Federal Regulations (CFR) 812. The monitoring plan details who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

The data of most importance for monitoring at the site are participant eligibility and adverse events. Therefore, the monitoring plan will focus on these areas. As much as possible, remote monitoring will be performed in real-time with on-site monitoring performed to evaluate the verity and completeness of critical data and processes. Elements of the monitoring plan may include:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of Institutional Review Board (IRB) coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- On-site monitoring (site visits): source data verification, site visit report
- Investigational Product accountability
- Communications with site staff
- Patient retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities

- Adverse event reporting and monitoring

JCHR representatives, Sponsor representatives or their designees may visit the study facilities at any time to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. Clinical sites will provide direct access to all trial-related facilities/equipment, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.5 Protocol Deviations

A protocol deviation is any noncompliance with federal regulation, the clinical trial protocol, GCP, IRB requirements, or procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. A significant (or major) deviation is any deviation that departs from the established materials in such a way that it poses an increase in the risk to participants, adversely affects the welfare, rights, or safety of the research participants, or negatively influences the scientific study integrity. As a result of a significant deviation, a corrective and preventive action plan shall be developed by the site and implemented promptly.

The site PI/study staff is responsible for knowing and adhering to IRB requirements (both Central and local as applicable). Further details about the handling of protocol deviations will be included in the monitoring plan.

Chapter 11: Ethics/Protection of Human Participants

11.1 Ethical Standards

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

11.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

11.3 Informed Consent Process

11.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights

as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant's electronic (or handwritten if required) signature will be obtained prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.3.2 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

The study monitor, other authorized representatives of the Sponsor/Coordinating Center, representatives of the IRB, regulatory agencies or company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Coordinating Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the Coordinating Center research staff and Sponsor will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Coordinating Center.

11.3.1 Future Use of Data

Data collected for this study will be analyzed and stored at the Coordinating Center. After the study is completed, the de-identified data will be archived at the Jaeb Center. Companies that have provided devices, drugs, or supplies may be provided access to the study data as indicated in the participant informed consent form. The Sponsor will be provided a full dataset at the end of the study.

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Safety and Efficacy of the Omnipod® 5 Automated Insulin Delivery System in Adults with Type 2 Diabetes

Statistical Analysis Plan

Version 3.1

16 April 2024

Based on Protocol Version V3.2 27Feb2024

Note: Table shells are included in a separate document

Table of Contents

1. Study Overview

This document outlines the statistical analyses to be performed for the SECURE T2D single arm study.

The protocol is a 13-week single arm intervention multi-center prospective study split over a Standard Therapy period (14 days) followed by a Treatment period (13 weeks) designed to evaluate the safety and efficacy of the Omnipod 5 automated insulin delivery (AID) system in adults with type 2 diabetes (T2D). This will be done by evaluating the change in HbA1c % from the Standard Therapy to Treatment periods.

A maximum of 400 subjects will be screened for participation, with the at least 275 completing the study, across ~20-25 sites in the United States.

Major eligibility criteria include:

- 18-75 years old
- Diagnosed with T2D
- On current insulin regimen for at least 3 months
- Willing to exclusively use one of the following types of U-100 insulin:
  - Humalog U-100
  - Novolog
  - Admelog

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	Screening	Standard Therapy		Treatment Phase							
Visit Number	1[a]	2[a]	3[a]	4[a]	5	6	7	8	9	24-HR FU	EW[d]
Study Day	-	-	-	0	1	14	30	60	90	91	
Visit Window	-	0 to 7d	0 to 28d	0 to 30d	+1d	±3d	±3d	±3d	±3d	-	
Virtual (V) or Office (O) Visit	O	O	O	O	V/O[c]	V/O[c]	V/O[c]	V/O[c]	O	V	O
Screening											
Informed Consent	X										
Confirm eligibility (Inclusion/Exclusion criteria assessed)	X										
Laboratory Assessments											
HbA1c (Central Lab) and Lipid Panel				X					X		X
HbA1c (Point of Care (POC) for eligibility)	X										
Serum Creatinine, C-peptide and GAD antibody (Central Lab)				X							
Pregnancy Test (urine dipstick) for women of childbearing potential	X			X							
Clinical Assessments											
Medical History	X										
Demographics (age, sex, race and ethnicity)	X										
Concomitant medications	X	X	X	X	X	X	X	X	X		X
Height	X										
Weight	X			X					X		X
Vital signs[b]	X			X	X	X	X	X	X		X

	Screening	Standard Therapy		Treatment Phase							
Visit Number	1[a]	2[a]	3[a]	4[a]	5	6	7	8	9	24-HR FU	EW[d]
Study Day	-	-	-	0	1	14	30	60	90	91	
Visit Window	-	0 to 7d	0 to 28d	0 to 30d	+1d	±3d	±3d	±3d	±3d	-	
Virtual (V) or Office (O) Visit	O	O	O	O	V/O[c]	V/O[c]	V/O[c]	V/O[c]	O	V	O
Electrocardiogram (ECG)	X										
Average total daily insulin (self-reported over ~ 7 days)	X										
Average total basal insulin (self-reported over ~ 7 days)	X										
Average total bolus insulin (self-reported over ~ 7 days)[g]	X										
Training on Glucagon administration and treatment of hypo/hyperglycemia				X							
Adverse events		X	X	X	X	X	X	X	X		X
Review insulin dosing		X	X	X							
Training on carbohydrate counting			X[h]								
Questionnaires											
T2-DDS		X							X		X
HCS		X							X		X
PSQI		X							X		X
System Opinion									X		X
Study Devices											

	Screening	Standard Therapy		Treatment Phase							
Visit Number	1[a]	2[a]	3[a]	4[a]	5	6	7	8	9	24-HR FU	EW[d]
Study Day	-	-	-	0	1	14	30	60	90	91	
Visit Window	-	0 to 7d	0 to 28d	0 to 30d	+1d	±3d	±3d	±3d	±3d	-	
Virtual (V) or Office (O) Visit	O	O	O	O	V/O[c]	V/O[c]	V/O[c]	V/O[c]	O	V	O
Study device training (BG meter and CGM)		X[f]									
Dispense BG meter		X[e]									
QC testing of BG meter by site		X									
Placement of Dexcom G6 CGM		X									
CGM Assessment			X								
Omnipod 5 training				X							
Dispense/Return Omnipod 5 System				X					X		X
APRMS Data Portal initiation/discontinuation				X					X		X
Complaints/device deficiencies			X	X	X	X	X	X	X		X
BG meter data review (if available)				X	X	X	X	X	X		X
Omnipod 5/Sensor data review					X	X	X	X	X		X
Advise on insulin adjustment for transition to pump therapy			X								
Follow-up for transition to pre-study therapy										X	

	Screening	Standard Therapy		Treatment Phase							
Visit Number	1[a]	2[a]	3[a]	4[a]	5	6	7	8	9	24-HR FU	EW[d]
Study Day	-	-	-	0	1	14	30	60	90	91	
Visit Window	-	0 to 7d	0 to 28d	0 to 30d	+1d	±3d	±3d	±3d	±3d	-	
Virtual (V) or Office (O) Visit	O	O	O	O	V/O[c]	V/O[c]	V/O[c]	V/O[c]	O	V	O

[a] Visits 1-4 may be completed on the same day if participant qualifies

[b]Vital signs include body temperature, respirations, pulse, and blood pressure should be performed at visits 4-9 if in person

[c]Visits identified as "V/O" can either be conducted in person at the clinical site or virtually. Visits identified as "O" can only be conducted in person at the clinical site. Vital signs are not required at any virtual visit, however, BG meter and CGM data review should still occur

[d]Early withdrawal visit will only be conducted for participants who complete visit 4 and discontinue prior to visit 9

[e]BG meter must pass at least one level of quality control testing prior to dispensing

[f] Dispensed BG meters do not need to be returned to sponsor

[g] For Basal-bolus subjects only

[h]Participants will not be required to transition to carbohydrate counting and may continue to use a fixed-bolus regimen in collaboration with the study investigator

Abbreviations: S=Screening; EW=Early Withdrawal; QC=Quality Control Testing; FU=Follow-up Visit

2. Comparison to Protocol

The author of this document has confirmed the analyses described here are consistent with Version 3.2 of the protocol. Should there be any discrepancy between the associated protocol and this SAP, the content of the SAP shall prevail.

3. Statistical Hypotheses

The primary outcome of interest is HbA1c. Change in HbA1c will be tested for non-inferiority, comparing the HbA1c results from the Standard Therapy period to the Treatment period; if non-inferiority is established, superiority will be tested. The details are as follows:

a. Non-inferiority test for mean change in HbA1c from the Standard Therapy period to the Treatment period (e.g., $HbA1c_{Treatment}$ - $HbA1c_{Standard} = \mu_\delta$) at alpha=0.025 with non-inferiority margin on 0.3%.
b. Superiority test (two-sided) for $\mu_\delta = 0$ at alpha=0.05.

The hypotheses are defined below:

Non-inferiority

- *Null Hypothesis*: $\mu_\delta \geq 0.3\%$ (change in HbA1c greater than or equal to 0.3% from baseline to 13 weeks).
- *Alternative Hypothesis*: $\mu_\delta < 0.3\%$ (change in HbA1c less than 0.3% from baseline to 13 weeks).

Superiority

- *Null Hypothesis*: $\mu_\delta = 0$ (no change in HbA1c from baseline to 13 weeks).
- *Alternative Hypothesis*: $\mu_\delta \neq 0$ (there is a change in HbA1c from baseline to 13 weeks)

4. Sample Size

The sample size is a convenience size of up to 400 screened participants to provide a cohort of 300 initiating use of the Omnipod 5 system and with the goal of 275 participants completing the trial. Furthermore, a minimum of 60 and maximum of 125 basal-only participants will be enrolled.

To better understand the potential variance in the change in HbA1c that may be encountered, standard deviations were calculated for the change in HbA1c from the pilot trial of the Omnipod 5®AID system in T2D, pivotal trial of the Omnipod 5® AID system in T1D, and the pivotal trial using the Control-IQ system in T1D. Standard deviations in these studies ranged from 0.5-0.7%; thus, a conservative estimate of 0.8% was used in the power calculations.

With 275 participants completing the trial, statistical power will be >99% for the primary endpoint analysis assessing non-inferiority of the 13-week HbA1c levels compared with the baseline levels with a non-inferiority limit of 0.3% and a type 1 error rate of 2.5% (one-sided). Statistical power is also >99% for a test of superiority comparing the 13-week HbA1c levels to baseline levels assuming a true mean difference of -0.4% or higher and type 1 error rate of 5% (two-sided).

Power for evaluating non-inferiority (assuming the true population value for HbA1c change from baseline is zero and non-inferiority limit = 0.3%) and superiority (assuming true change of -0.4%) for change in HbA1c in subgroups (such as pre-study MDI users, basal insulin only users, users of non-insulin glucose lowering medications) is provided below, assuming a type 1 error = 5% (2-sided). Note that if the true change in HbA1c is as little as 0.1%, then the power calculations for non-inferiority will be identical to those shown below for superiority.

	Statistical Power	
# Participants in Subgroup Completing the Trial	**Non-inferiority**	**Superiority**
20	36%	57%
30	51%	75%
40	64%	87%
50	74%	93%
75	89%	99%
100	96%	>99%
125	99%	>99%

For testing for non-inferiority (assuming the true population value for HbA1c change from baseline is zero and non-inferiority limit = 0.3%), sample size for participants completing the trial is calculated to be 58 for 80% power and 77 for 90% power. Assuming a true population HbA1c change of as little as 0.1%, sample size would be 34 for 80% power and 44 for 90% power.

For testing for superiority (true change 0.4%), sample size for trial completers is 34 for 80% and 44 for 90%.

5. Outcome Measures

5.1 Primary Endpoints

- Safety: Non-inferiority for change in HbA1c from baseline to 3 months (non-inferiority margin 0.3%).
- Efficacy: If non-inferiority is established, change in HbA1c will be tested for superiority.

5.2 Additional Safety Endpoints

1. Severe hypoglycemia
2. Hospitalization/ER for severe hypoglycemia
3. Hyperosmolar hyperglycemic syndrome (HHS)/diabetic ketoacidosis (DKA)
4. Hospitalizations or ER related to hyperglycemia or hypoglycemia in previous 3 months vs. study 3 months
5. Other related serious adverse events
6. Reportable device-related adverse events

5.3 Additional Key Secondary Endpoints

The statistical testing scheme for the key secondary endpoints is described in **Section 8.**

1. Mean glucose (superiority)
2. Change in % time 70-180 mg/dL (superiority)
3. Change in % time 70-140 mg/dL (superiority)
4. Change in % time ≥300 mg/dL (superiority)
5. Change in % time >250 mg/dL (superiority)
6. Change in % time >180 mg/dL (superiority)
7. % time <70 mg/dL (noninferiority; non-inferiority limit 2.0%)
8. % time <54 mg/dL (noninferiority; non-inferiority limit 0.5%)
9. Change from baseline in T2-DDAS total score (superiority)
10. Change in % T2-DDAS total score ≥2.0 (high distress)
11. Change from baseline in PSQI total score (superiority)
12. Change in % PSQI total score >5.0 (poor sleep)
13. Change from baseline in HCS total score (superiority)
14. Change in % HCS total score <3.0 (low confidence)
15. % time <70 mg/dL (superiority)
16. % time <54 mg/dL (superiority)
17. Coefficient of variation (superiority)

5.4 Exploratory Endpoints

1. Change in total daily insulin dose
2. Change in body mass index (BMI)
3. Average reduction in the number of non-insulin glucose lowering agents
4. Change in percent of participants using insulin as a monotherapy or insulin + metformin
5. % of participants achieving HbA1c <7%
6. % of participants achieving HbA1c <8%
7. % of participants achieving time in range 70-180 mg/dL >70%
8. % of participants achieving time <70 mg/dL <4%
9. % of participants achieving <54 mg/dL <1%
10. % of participants achieving time in range 70-180 mg/dL >70% and time <70 mg/dL <4%
11. Prolonged hyperglycemia events >250 mg/dL lasting a minimum of 120 minutes. An event is considered terminated when sensor glucose ≤180 mg/dL for at least 15 minutes.
12. Change in lipids (total cholesterol, HDL, LDL, and triglycerides)

5.5 HbA1c Window

Any HbA1c measurements outside the analysis window of 42-119 days (6-17 weeks) from AID initiation will be treated as missing data.

5.6 Calculation of CGM Metrics

- Baseline values will be taken from the 14-day Standard Therapy period, using all 24 hours of CGM data each day. For participants who are exempt from the Standard Therapy period, 14 days of CGM data will be used from the past 30 days prior to screening.
- Follow-up values will be calculated using CGM data from the 13-week Treatment Period starting on Visit 4. Values will exclude:
  - CGM readings during supervised exercise challenges from the start of the challenge until 6 AM the next morning.
  - CGM readings during the meal challenges (start of meal challenge to 4 hours after the challenge)
  - CGM readings during the 9 days of the target challenge performed by a subset of participants.
- Separate values for each CGM metric will be calculated for each participant for:
  - Overall: 24 hours of the day
  - Daytime: CGM readings from 6:00 am – 11:59 pm
  - Nighttime: CGM readings from 12:00 am – 5:59 am
- For the Glucose Target Challenge, CGM metrics will be calculated for each target glucose level (150 mg/dL, 140 mg/dL, and 130 mg/dL) for which at least 12 hours of CGM data are available.
- For the Meal Challenge, CGM metrics will be tabulated for each meal plus the 4 hours after the meal is consumed (total of four meals) meals with bolus and meals without bolus. Paired differences between meals with and without bolus will also be calculated for each participant who has at least 4 hours of CGM data available for both meal types (with and without bolus).
- Exercise Challenge CGM metrics will be calculated during the exercise session, during the exercise session plus the 2 hours following the session, and the overnight (midnight to 5:59 am) following the session.

5.7 Calculation of Questionnaire total scores

There are three questionnaires being completed by participants:

- Type 2 Diabetes Distress Assessment System (T2-DDAS)
- Hypoglycemia Confidence Scale (HCS)
- Pittsburgh Sleep Quality Index (PSQI)

These will be completed at the start of the Standard Therapy period (Visit 2) and then again at the final visit of the Treatment period (Visit 9). For each questionnaire, and the total scores will be summed for each questionnaire to get a total score for each questionnaire.

For PSQI, there are 7 subscores:

- Duration of sleep (PSQIDURAT)
- Sleep disturbance (PSQIDISTURB)
- Sleep latency (PSQILATEN)
- Dysfunctional days due to sleepiness (PSQIDAYSDYS)
- Sleep efficiency (PSQIHSE)
- Overall sleep quality (PSQISLPQUAL)
- Medications needed for sleep (PSQIMEDS)

Question 1-9, according to the PSQI scoring manual, must be completed; if not answered, any scores requiring an answer for those questions cannot be calculated. Lower scores indicate better sleep quality. Additional details for scoring can be found in the scoring manual.

There is no subscore for the HCS questionnaire. A scaled total score will be generated for the HCS total score. This will be done by summing the questions as usual by individual and then dividing by the number of questions answered. Higher scores equate to more confidence in treating and avoiding hypoglycemia.

For T2-DDAS, there are eight subscores:

- Degree of, intensity, or amount of core diabetes stress
- Hypoglycemia
- Long-term health
- Healthcare provider
- Interpersonal issues
- Shame/stigma
- Healthcare access
- Management demands

The T2-DDAS scoring manual describes score calculations. Higher scores equate to more stress/distress.

At least 75% of the items must be non-missing for the score/subscore to be calculated. Otherwise, it will be considered missing data.

6. Description of Statistical Methods

6.1 General Approach

All variables will be examined for normality of their distributions and, if applicable, standard residual diagnostics will be performed. If values are highly skewed, then a nonparametric or robust regression M-estimation method will be used instead.

6.2 Analysis Cohorts

Primary and Secondary Analyses:

- HbA1c analyses will include all participants who have values at both baseline and 13 weeks or early withdrawal if done 42-119 days from the initiation of AID.
- CGM analyses will include all participants with ≥168 hours of CGM data during each of the Standard Therapy Period and the 13-week Treatment Period.

Per Protocol (PP) Analyses:

- PP analysis will be limited to participants who used the Omnipod 5 system in automated mode for at least 1,747 hours during the 13-week Treatment Period (80% of study time) and who have both baseline and 13-week HbA1c values. If fewer than 10% of the study participants would be excluded based on this criterion, then the PP analysis will not be performed.

Safety Analyses:

- Safety analyses will include all enrolled participants.

Sensitivity Analyses:

- Primary analysis will be done with complete cases only. Sensitivity analyses will be conducted to handle missing HbA1c values for both the superiority and non-inferiority analyses:
  - Multiple imputation using Rubin's method (assumes MAR)
  - Tipping point analysis will assess what magnitude of bias from selective dropout would be necessary to alter the conclusion.

7. Primary Analysis of HbA1c (non-inferiority and superiority)

The primary outcome in this study is change in HbA1c from Standard Therapy period to the end of the Treatment period. Primary analysis will be done for the complete cases. Statistical testing of the primary outcome will be done using a hierarchical method in the manner as follows:

1. Non-inferiority
2. Superiority

Summary statistics appropriate to the distribution will be generated for the Standard Therapy and Treatment periods, as well as for the difference ($HbA1c_{Treatment} - HbA1c_{Standard}$).

A paired t-test will be used to compare the change in HbA1c from Standard Therapy to the end of the Treatment periods. It is expected the change in HbA1c will follow a relatively normal distribution. If not normally distributed, robust regression using M-estimation with the Huber weight function will be used instead of a pair t-test. A point estimate and 95% confidence interval will be given for the mean change in HbA1c from baseline to 13 weeks.

8. Hierarchical Testing of Primary and Key Secondary Endpoints

A hierarchical testing scheme will be used to test for statistical significance of the change in the primary and key secondary outcomes over 13 weeks of treatment in the order as follows:

1. HbA1c (non-inferiority, primary see above)
2. HbA1c (superiority; primary see above)
3. Mean glucose (superiority)
4. % time 70-180 mg/dL (superiority)
5. % time 70-140 mg/dL (superiority)
6. % time ≥300 mg/dL (superiority)
7. % time >250 mg/dL (superiority)
8. % time >180 mg/dL (superiority)
9. % time <70 mg/dL (non-inferiority, margin=2.0%)
10. % time <54 mg/dL (non-inferiority, margin=0.5%)
11. T2-DDAS total score (superiority)
12. Change in % T2-DDAS total score ≥2.0 (high distress) (meeting MCID)
13. PSQI total score (superiority)
14. Change in % PSQI total score >5.0 (poor sleep) (meeting MCID)
15. HCS total score (superiority)
16. Change in HCS total score <3.0 (low confidence) (meeting MCID)
17. % time <70 mg/dL (superiority)
18. % time <54 mg/dL (superiority)
19. Coefficient of variation (superiority)

If any of the outcomes on this list fail to give a statistically significant result (i.e., $p \geq 0.05$), then formal testing will stop and p-values will not be given for any outcomes further down on the list. Summary statistics and confidence intervals will be given for each outcome regardless of statistical significance. Note that each of the CGM metrics in the hierarchical listing refers to the overall 24-hour version.

8.1 CGM Metrics

Descriptive statistics will be supplied for each secondary CGM metric from the Standard Therapy and Treatment periods, as well as for the change in CGM metrics between the two periods (Treatment – Standard Therapy).

A paired t-test will be used to compare the change in CGM metrics from Standard Therapy to the end of the Treatment periods. It is expected the change in the CGM metrics will follow a relatively normal distribution, while measures for hypoglycemia are expected to be skewed at baseline and 13 weeks. If not normally distributed, robust regression using M-estimation with the Huber weight function will be used instead of a pair t-test. A point estimate and 95% confidence interval will be given for the mean change in CGM metrics from baseline to 13 weeks.

Statistical testing will be done in a hierarchical manner as laid out above (**Section 8**). All CGM metrics will be tested for two-sided superiority (α=0.05); however, the hypoglycemia metrics will be tested for non-inferiority first, as described below:

% time <70 mg/dL

Non-inferiority

- *Null Hypothesis*: $\mu_\delta \geq 2\%$ (change in % time <70 mg/dL greater than or equal to 2% from baseline to 13 weeks).
- *Alternative Hypothesis*: $\mu_\delta < 2\%$ (change in % time <70 mg/dL less than 2% from baseline to 13 weeks).

Superiority

- *Null Hypothesis*: $\mu_\delta = 0$ (no change in % time <70 mg/dL from baseline to 13 weeks).
- *Alternative Hypothesis*: $\mu_\delta \neq 0$ (there is a change in % time <70 mg/dL from baseline to 13 weeks)

% time <54 mg/dL

Non-inferiority

- *Null Hypothesis*: $\mu_\delta \geq 0.5\%$ (change in % time <54 mg/dL greater than or equal to 0.5% from baseline to 13 weeks).
- *Alternative Hypothesis*: $\mu_\delta < 0.5\%$ (change in % time <54 mg/dL less than 0.5% from baseline to 13 weeks).

Superiority

- *Null Hypothesis*: $\mu_\delta = 0$ (no change in % time <54 mg/dL from baseline to 13 weeks).
- *Alternative Hypothesis*: $\mu_\delta \neq 0$ (there is a change in % time <54 mg/dL from baseline to 13 weeks)

CGM metrics will also be tabulated by daytime, nighttime, and overall, as described in **Section 5.5**.

8.2 Questionnaires

Descriptive statistics will be tabulated for each survey for the Standard Therapy period, Treatment period, and the change from Standard Therapy to Treatment in total score (total $\text{score}_{\text{Treatment}}$ – total $\text{score}_{\text{Standard}}$); this will also be done for subscores, when present. The distribution of the total scores for each survey will be assessed for normality and, if skewed, non-parametric methods will be used to determine the median and variance for comparison.

If the difference in total score is found to be normally distributed, a paired t-test will be used to assess statistical difference from the Standard Therapy to Treatment periods. Non-parametric tests (e.g., Wilcoxon) will be used if the distributions are skewed. No statistical testing will be done for change subscores but 95% confidence intervals will be presented.

To assess for clinically meaningful improvements from baseline, binary outcomes will be defined for:

- T2-DDAS total score ≥2.0 (high distress)
- PSQI total score >5.0 (poor sleep)
- HCS total score <3.0 (low confidence)

Percentages for each of these will be compared for 13 weeks versus baseline using the CSM exact test for paired binary outcomes.

9. Safety Analyses

For the primary outcome of non-inferiority of change in HbA1c, a paired t-test will be performed with a non-inferiority margin of 0.3%, as described in **Section 7**.

All adverse events and safety outcomes described in **Section 5.1** will be tabulated for each period (Standard Therapy and Treatment). The number of events and event rate per 100 person-years during the Treatment period will also be calculated. Adverse events reported by sites using MedDRA coding per protocol will be converted by medical monitor to Sponsor classification for this study. Sponsor reporting of adverse events will not use MedDRA coding.

The Medical Monitor's assessment of an adverse event will be used as the final classification of the event for reports, labeling and publications or presentations. Any discrepancies between an Investigator and the Medical Monitor will be disclosed in the final clinical study report.

McNemar's test will be used to compare the percentage of participants with hospitalization or ER visits related to hyper- or hypoglycemia during the 13-week Treatment period compared with the 13-week period prior to enrollment.

10 Target Glucose Challenge

The first 60 participants to complete Visit 4 in the study will be entered in a target glucose challenge. This challenge will be conducted over 9 days, as shown in the figure below:

	Number of Target Glucose Challenge Days								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Target Glucose	150 mg/dL			140 mg/dL			130 mg/dL		

The first approximately 72 hours of the challenge, the target glucose setting will be adjusted to 150 mg/dL. After three days, the glucose target will be adjusted to 140 mg/dL. After an additional three days, the glucose target will be set to 130 mg/dL. Completion of the entire target challenge is not required to be included as one of the 60 participants assigned to the target challenge.

Adverse events for each target glucose level will be tabulated, as well as descriptive statistics for the following CGM metrics:

- Mean glucose
- % time 70-180 mg/dL

- % time >180 mg/dL
- % time >250 mg/dL
- % time <70 mg/dL
- % time <54 mg/dL

11 Supervised Exercise/Meal Sessions

11.1 Meal Challenge

All participants will complete the meal challenge. The meal challenge consists of 4 days. On Days 1 and 3, a bolus will be given with a select meal (meal must be ≥60 g of carbohydrates). On Days 2 and 4, a matched meal will be consumed without the bolus.

Adverse events for each meal challenge will be tabulated, as well as descriptive statistics for the following CGM metrics:

- Mean glucose
- % time 70-180 mg/dL
- % time >180 mg/dL
- % time >250 mg/dL
- % time ≥300 mg/dL
- % time <70 mg/dL
- % time <54 mg/dL
- Excursion (peak glucose minus baseline)

These metrics will be calculated during the meal session as well as the 4 hours following each meal session. The paired difference between meals with and without bolus will be calculated for the above CGM metrics for each participant.

11.2 Exercise Challenge

All participants with an approved ECG and without any safety concerns from investigators will complete the exercise challenge. The exercise challenge will consist of 3 sessions, each lasting 1 hour of mild intensity and 30 minutes of moderate intensity exercise.

The number of adverse events occurring during the exercise sessions will be tabulated, as well as descriptive statistics for the following CGM metrics:

- Mean glucose
- % time 70-180 mg/dL
- % time >180 mg/dL
- % time <70 mg/dL
- % time <54 mg/dL
- Nadir glucose
- % of exercise sessions with nadir <70 mg/dL
- Excursion (baseline glucose minus nadir glucose)

These metrics will be tabulated as follows:

- During exercise sessions
- During exercise and including the 2 hours following moderate exercise
- Subsequent overnight (midnight to 5:59 am)

Additionally, the proportion of participants with CGM readings <70 mg/dL and >300 mg/dL for each of the exercise periods described above will be tabulated.

CGM metrics will be calculated by individual per exercise session, averaged across all exercise sessions by individual, and then summarized overall for each CGM metric. This will be done for each exercise period listed above (e.g., during, during + 2 hours, subsequent overnight).

12 Intervention Adherence

Summary statistics for the percentage of time the Omnipod 5 system is in automated mode and the amount of CGM use over the 13-week Treatment period will be tabulated.

13 Adherence and Retention Analysis

To assess adherence, the follow metrics will be tabulated for the Treatment period:

- Number of protocol deviations
- Flow chart accounting for all enrolled participants up to the end of the study
- Number and reasons for participant withdrawals prior to the end of the study
- Number of participants who stopped using the Omnipod 5 system in automated mode and reasons
- Number of and reasons for unscheduled visits and phone contacts

14 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the cohort of all enrolled participants will be summarized in a table using summary statistics appropriate to the distribution of each variable. Baseline characteristics include, but are not limited to, the following:

- Age
- Race/ethnicity
- Gender
- Income, education, and/or insurance status
- Diabetes duration
- BMI

15 Device Issues

Reported device issues will be tabulated. All device issues will be reported except the following issues (unless related to an adverse event):

- CGM sensor lasting fewer days than stated by manufacturer
- CGM adherence issues
- Insulin pod lasting fewer days than stated by manufacturer
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- Intermittent device component disconnections/communication failures not requiring system replacement or workarounds/resolutions not specified in the user guide/manual
- Device issues addressed in the user manual/guide not requiring additional troubleshooting

16 Planned Interim Analyses

No formal interim analyses are planned.

17 Subgroup Analyses

For the safety and efficacy outcomes described in **Sections 5.1** and **5.2**, the analyses will be replicated for those on multiple daily injections (MDI) pre-study enrollment and for participants who are only using basal insulin pre-study enrollment.

Change in HbA1c, TIR, mean glucose (mg/dL), % time <70 mg/dL, and % time >250 mg/dL from Standard Therapy to Treatment period will be evaluated for the following subgroups:

- Use of sodium-glucose cotransporter-2 inhibitors (SGLT2i), glucagon-like peptide 1 agonists (GLP1a), and/or dipeptidyl peptidase 4 inhibitors (DDP4i).
- Baseline HbA1c:
  - <7%
  - 7.0-7.9%
  - 8.0-8.9%
  - ≥9.0%
- Pre-study carbohydrate counting:
  - Yes
  - No
- Baseline C-peptide (continuous variable: cutpoints for display to be determined)
- Race/ethnicity
  - White, non-Hispanic
  - Black, non-Hispanic
  - Latino(x)/Hispanic

  Additional racial/ethnic groups may be analyzed depending on sample size.
- Gender
  - Female
  - Male
- Age
  - 18-<30 years old
  - 30-<45 years old
  - 45-<60 years old
  - ≥60 years old

- Income
  - <$50,000/year
  - $50,000-<$100,000/year
  - $100,000-<$200,000/year
  - ≥$200,000/year
- Education
  - No high school diploma
  - High school diploma/GED
  - Some college, no degree
  - Associate's degree
  - Bachelor's degree
  - Master's degree
  - Doctorate (e.g., PhD, EdD)
  - Professional (e.g., MD, JD)
- Insurance
  - Private
  - Medicare
  - Medicaid
  - Military
  - Other government-sponsored
  - Do not wish to answer/not reported
  - None

The subgroups listed above will be evaluated using a linear regression model (or robust regression if difference metrics are skewed) with change in HbA1c or chosen CGM metric as the dependent variable and the chosen subgroup as the independent variable. Interactions, in the case of >2 categories for an independent variable, will only be considered when investigating non-insulin reducing agents (e.g., SGLT2i, GLP1a, and DDP4i); in all other subgroup models, only main effects will be considered.

18 Multiple Comparisons/Multiplicity

The overall type I error rate will be controlled for the primary safety/efficacy outcomes and secondary efficacy endpoints using a hierarchical testing procedure as described in **Section 7** and **8.**

For additional secondary analyses outside the statistical hierarchy, the false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure in the following groups:

- CGM metrics and HbA1c for MDI and basal only
- Questionnaires
- Subgroup analysis (e.g., gender, race, ethnicity, non-insulin glucose lowering agents, baseline HbA1c)

19 Exploratory Analyses

No p-values will be calculated for the following analyses.

- The metrics listed in **Section 5.4** will be reported with the appropriate summary statistics.

20 Additional Tabulations/Analyses

The number of non-insulin glucose lowering agents used during the Standard Therapy and Treatment periods will be tabulated (no formal statistics).