Insulet

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

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PROTOCOL SUMMARY

Title	Safety and Efficacy of the Omnipod® 5 Automated Insulin Delivery System in Adults with Type 2 Diabetes
Purpose	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 Key Secondary Endpoints The following secondary endpoints will be tested hierarchically if the primary HbA1c analyses for non-inferiority followed by testing for superiority are statistically significant 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; margin = 2.0%) 8. % time < 54 mg/dL (noninferiority; margin = 0.5%) 9. T2-DDAS total score (superiority) 10. Change in % T2-DDAS total score >5.0 (high distress) 11. PSQI total score (superiority) 12. Change in % PSQI total score ≥2.0 (poor sleep) 13. 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)
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 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 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
Study Methods	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.
Statistical Methods	A hierarchical testing scheme will be used to test for statistical significance of the change in the primary and key secondary outcomes listed above over 13 weeks of treatment. 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: • Non-inferiority test for mean change in HbA1c from the Standard Therapy period to the Treatment period (e.g., HbA1cTreatment - HbA1cStandard = μ_δ) at alpha=0.025 with non-inferiority margin on 0.3%. • Superiority test (two-sided) for μ_δ = 0 at alpha=0.05. Summary statistics appropriate to the distribution will be generated for the Standard Therapy and Treatment periods, as well as for the difference (HbA1cTreatment – HbA1cStandard). 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. If statically significant results (i.e., p ≥ 0.05) are obtained for the primary endpoints, the key secondary outcomes will be tested hierarchical in the order listed above. If any of the key secondary outcomes fail to give a statistically significant result, 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. All adverse events and additional safety outcomes listed above 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.

	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. 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.

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