SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Artificial Pancreas Device System, Threshold Suspend
Device Trade Name:	MiniMed 530G System with Threshold Suspend featuring SmartGuard™ technology
Device Procode:	OZO
Applicant's Name and Address:	Medtronic MiniMed 18000 Devonshire Street Northridge, CA 91325
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P120010/S046
Date of FDA Notice of Approval:	October 2, 2015
Expedited:	Expedited by policy[1]

II. INDICATIONS FOR USE

MiniMed 530G System with Threshold Suspend featuring SmartGuard™ technology
The MiniMed 530G System is intended for continuous delivery of basal insulin (at user selectable rates) and administration of insulin boluses (in user selectable amounts) for the management of diabetes mellitus in persons, sixteen years of age and older, requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin. The MiniMed 530G System can be programmed to automatically suspend delivery of insulin when the sensor glucose value falls below a predefined threshold value.

The MiniMed 530G System consists of the following devices that can be used in combination or individually: MiniMed 530G Insulin Pump, Enlite™ Sensor, Enlite™ Serter, the MiniLink Real-Time System, the Bayer Contour NextLink glucose meter, CareLink® Professional Therapy Management Software for Diabetes, and CareLink® Personal Therapy Management Software for Diabetes. The system requires a prescription.

[1] The Office of In Vitro Diagnostics and Radiological Health has determined that all devices intended to non-invasively monitor blood glucose, and similar devices, will be treated as expedited submissions per the Food and Drug Administration Modernization Act (FDAMA) of 1997 Section 215(b).

The MiniMed 530G System is not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a finger stick may be required. All therapy adjustments should be based on measurements obtained using a home glucose monitor and not on values provided by the MiniMed 530G System.

The MiniMed 530G System is not intended to be used directly for preventing or treating hypoglycemia but to suspend insulin delivery when the user is unable to respond to the Threshold Suspend alarm to take measures to prevent or treat hypoglycemia himself. Therapy to prevent or treat hypoglycemia should be administered according to the recommendations of the user's Health Care Provider.

Enlite® Sensor
The Enlite Sensor is intended for use with Medtronic MiniMed 530G Insulin pump (models MMT-551, MMT-751) to continuously monitor glucose levels in persons with diabetes.

Enlite® Serter
The Enlite Serter is used as an aid for inserting the Enlite sensor. It is indicated as a single-patient use device and it is not intended for multiple-patient use.

MiniLink Real-Time System
The MiniLink Real Time System consists of the MiniLink Transmitter, a tester and a charger. When connected to a sensor that is inserted in the body, the transmitter automatically initializes the sensor and begins to periodically send glucose data to the pump using a radio signal.

III. CONTRAINDICATIONS

- Pump therapy is not recommended for people who are unwilling or unable to perform a minimum of four blood glucose tests per day.

- Pump therapy is not recommended for people who are unwilling or unable to maintain contact with their healthcare professional.

- Pump therapy is not recommended for people whose vision or hearing does not allow recognition of pump signals and alarms.

- Do not use the Enlite Serter on products other than the Enlite sensor. Medtronic cannot guarantee this product's safety or efficacy if used on other products.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the MiniMed 530G labeling.

V. DEVICE DESCRIPTION

The MiniMed 530G System is comprised of the following devices:

MiniMed 530G Insulin Pump

The MiniMed 530G Insulin Pump is an ambulatory, battery operated, rate-programmable infusion pump designed to deliver insulin from a reservoir. The reservoir is driven by a motor to deliver patient determined basal rate profiles and patient selected bolus amounts of insulin into the subcutaneous tissue through an infusion set.

The MiniMed 530G Insulin Pump is offered in two models (MMT-551 and MMT-751). The difference between models MMT-551 and MMT-751 is the size of the device housing to accommodate different reservoir sizes. Model MMT-551 is compatible with a 1.8 ml reservoir and model MMT-751 can be used with either the 1.8mL or the 3.0 ml reservoir. Other than the size difference in the pump case housing all other aspects of the device (PCBA, drive motor, LCD, etc.) are the same between the two models.

The MiniMed 530G Insulin Pump is similar to the Paradigm REAL-Time REVEL pump (P980022/S031, S089) hardware and software platform. The only hardware difference between the two devices is an update to the keypad overlay to include the color green to the circle around the ACT button. This is a cosmetic change and it does not affect the pump performance, function or intended use.

The major difference between MiniMed 530G Insulin Pump and the Paradigm REAL-Time REVEL insulin pump is the application software. In addition to the features carried over from the Paradigm REVEL pump, the software was updated to incorporate feature enhancements to the glucose monitoring and insulin delivery features. The feature enhancements that were included in the MiniMed 530G Insulin Pump are as follows:

- 'Threshold Suspend' tool with 60-90 mg/dL threshold range
- The sensor life has changed from three days to six days (resulting in changes to the software)
- Modified sensor calibration algorithm for the Enlite Sensor
- Blood Glucose units set to mg/dL (no longer user selectable)
- Enhanced Radio Frequency (RF) communication security features

The MiniMed 530G Insulin Pump is designed to receive and display real-time glucose values received from the provided transmitter. Enlite sensor signals are transmitted from the transmitter to the MiniMed 530G Insulin Pump via RF telemetry and converted into glucose concentrations based on calibration values from commercially available blood glucose meters. Signals are updated and transmitted to the pump every five minutes.

The real time sensor glucose values, displayed by the MiniMed 530G Insulin Pump, are not intended to be used directly for making therapy adjustments. The patient can use the tracking and trending of sensor glucose values to help determine if an unplanned finger stick measurement may be needed. In addition, sensor glucose values should not be used to modify insulin therapy. All insulin therapy adjustments should be based on

measurements obtained using a blood glucose meter and not based on the sensor glucose value displayed by the MiniMed 530G Insulin Pump.

The most significant difference between MiniMed 530G Insulin Pump and previously approved insulin pumps is the inclusion of the 'Threshold Suspend' tool. This new tool provides the patient the means to set the pump to temporarily suspend insulin delivery automatically when the sensor glucose level is equal to or less than a selected threshold. The patient has the capability to select a 'Threshold Suspend' threshold within the 60 mg/dL to 90 mg/dL range. When the 'Threshold Suspend' tool is set to 'ON', the system compares the sensor glucose value and the programmed Suspend threshold whenever the sensor glucose value is updated (every five minutes). The use of the Threshold Suspend tool is optional and the patient can turn the tool 'ON' and 'OFF'.

When the sensor glucose value is below the set threshold, an alarm and siren occurs and the patient may elect to continue or cancel the temporary pump suspension of insulin delivery.

If the user does not respond to the alarm or siren, the pump will automatically suspend for two hours. At the end of the two hours, insulin delivery will resume and the system will be unable to suspend the pump automatically for four hours post-insulin resumption even if the sensor glucose value is below the threshold.

If the user cancels the suspension of insulin delivery, the system will continue to deliver insulin at the programmed basal rate until the next time the sensor glucose value is below the set threshold value. The alarm and siren will then re-sound, and the pump will suspend (unless canceled by the user). The interval between the cancellation of the Threshold Suspend and the next possible threshold alarm will be the duration of the patient's specified Low Alert Repeat (5-60 minutes).

If the patient responds to the alarm or siren by electing to accept the insulin suspension, the pump will suspend. At the end of the two hours, the pump will resume insulin delivery until the next sensor glucose value is below the set threshold suspend value. The interval between the accepted Threshold Suspend and the next possible threshold alarm will be the duration of the patient's specified Low Alert Repeat (5-60 minutes). This means that it is possible for the system to suspend insulin delivery for two hours, followed by a minimal amount of insulin delivery (5 minutes), and re-suspend insulin delivery for two more hours. This loop can be continued for as long as the patient acknowledges the pump suspension (by electing to continue) and the sensor value remains below the set threshold value.

The patient can cancel the temporary pump suspension at any time during the two-hour period regardless if the suspension occurred because he/she was not able to respond to the initial alarm or he/she accepted the suspension.

The MiniMed 530G Insulin Pump is capable of storing 90 days of pump history and glucose sensor data. The pump has a graphical display that the patient can use to view the glucose history for the past 3, 6, 12 and 24 hours, high/low glucose alarms and

display of retrospective glucose trend information.

Stored pump history and glucose data can be downloaded to a personal computer for review and analysis, to track patterns and improve diabetes management. Data is downloaded from the pump to CareLink therapy management software.

Enlite Glucose Sensor (MMT-7008)
The Enlite sensor is a single-use, disposable component, which is intended for use with MiniMed 530G Insulin Pump to continuously monitor glucose levels. It is inserted into the subcutaneous tissue of the patient and connected to a transmitter device, the MiniLink Real-Time System (model MMT-7707). The sensor/tube assembly is flexible and has a small cross-section designed to minimize pain and discomfort during use. A rigid introducer needle aids in the insertion of the sensor into the subcutaneous tissue, and retracts into the polycarbonate hub after use. This is intended to prevent accidental needle sticks and allows for safe disposal once the sensor is in place. The sensor/base assembly connects to the transmitter, which in turn communicates with the 530G insulin pump. The Enlite Sensor is intended to be worn for up to six days.

Enlite Serter (MMT-7510)
The Enlite Serter was designed for aiding in the insertion of the Enlite Sensor. It is intended to be used by a patient or a clinician to introduce the sensor into the subcutaneous tissue at a fixed depth, with minimal discomfort and technique dependency, and with minimal exposure of the sensor needle.

MiniLink Real-Time System:
The MiniLink Real-Time System consists of the MiniLink Transmitter (model MMT-7703), Charger (model MMT-7705), and Tester (model MMT-7726).

The MiniLink Transmitter provides power to the sensor and measures the sensor signal current (I_{SIG}). The I_{SIG} is an electrical current level that is proportional to the glucose level in the subcutaneous interstitial fluid of the patient. The I_{SIG} is converted to a digital signal, and is filtered to reduce noise artifact. The digital signal is then transmitted to a receiving device through RF link once every 5 minutes. The MiniLink Transmitter is intended to provide the patient with the convenience of viewing real-time glucose values that can be analyzed to track patterns and improve overall diabetes management. Real-time glucose values are not intended to be used directly for making therapy adjustment, but rather to provide an indication that unplanned finger stick with a home blood glucose monitor may be needed.

Accessories:
The following accessories are compatible with the MiniMed 530G System:

Reservoirs and Infusion Sets	
Paradigm Reservoir	MMT-326A, MMT-332A
MiniMed Mio Infusion Set	MMT-921, MMT-923, MMT-925, MMT-941, MMT-943, MMT-945, MMT-965, MMT-975

MiniMed Silhouette Infusion Set	MMT-368, MMT-369, MMT-370, MMT-377, MMT-378, MMT-381, MMT-382, MMT-383, MMT-384
MiniMed Sure-T Infusion Set	MMT-862, MMT-864, MMT-866, MMT-874, MMT-876, MMT-886
MiniMed Quick Set Infusion Set	MMT-386, MMT-387, MMT-394, MMT-396, MMT-397
Paradigm Polyfin Infusion Set	MMT-312S, MMT-312L
Paradigm Sof-Set Infusion Set	MMT-317, MMT-318, MMT-324, MMT-325
RF Communication Devices	
CareLink USB	MMT-7305
ComLink Communication Device	MMT-7304
Paradigm Remote Control/ Programmer	MMT-503

Bayer Contour NextLink glucose meter (k122370)[2]:
The Bayer CONTOUR NEXT LINK Wireless Blood Glucose Monitoring System can directly communicate with the MiniMed 530G System. It consists of a small handheld electronic device, dry reagent strips and liquid controls to be used for the measurement of glucose in capillary whole blood by persons with diabetes. Blood glucose results are displayed in the meter window and stored in the meter's memory. The COUNTOUR NEXT LINK meter also contains RF functions to send Blood Glucose Meter results to the MiniMed 530G System.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Control of diabetes can be achieved through a combination of methods and behaviors. Self behaviors include healthy eating, taking the clinically indicated medications, and being active. Persons with diabetes may also administer insulin by injection or by using other insulin infusion pumps as prescribed by his/her physician. Methods of controlling glucose levels (glycemic control) have been shown to reduce severe diabetes-related complications. Methods of monitoring glycemic control include periodic measurement of Hemoglobin A_{1c} (HbA_{1c}), which reflects blood glucose control over a three month period. Self-monitoring of blood glucose using glucose meters and test strips provides quantitative measurements of blood glucose at a single point in time for patients and their healthcare providers to monitor the effectiveness of glycemic control and make more immediate treatment modifications.

2 As stated in FDA's final guidance, *The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Artificial Pancreas Device Systems*, because the intended use of an APDS is different than the intended use of a continuous glucose monitor (CGM), FDA believes additional information will be needed for blood glucose devices (BGD) that are part of an APDS compared to the information required for a BGD that is part of a CGM. The Agency does not intend to request this information for one year following the publication of this notice for the BGD component of APDS submissions. The original PMA submission, P120010, was received for review by the Agency within one year of guidance publication. For future APDS submissions, PMAs for APDS should include complete information (e.g., manufacturing, specifications, etc.) for the BGD component of the APDS.

Each alternative method for monitoring glycemic control has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle. The Medtronic MiniMed 530G System is the first device of its kind to suspend insulin when a sensor detects a pre-defined glucose threshold.

VII. MARKETING HISTORY

The MiniMed 530G System has been marketed in the United States since September 2013. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g. complications) associated with the use of the device.

The following events are possible adverse device effects of inserting a sensor into your skin: local infection, inflammation, pain or discomfort, bleeding at the glucose sensor insertion site, bruising, itching, scarring or skin discoloration, hematoma, tape irritation, sensor or needle fracture during insertion, wear or removal. There were no reports of subject death, unanticipated adverse device effect (UADE), diabetic ketoacidosis, or serious adverse events related to the device or study procedure during any of the clinical studies (G110044, G110131/A001 and G100028). No sensor breakage was documented in the clinical studies supporting approval of this device. Reported sensor breakage rate with similar devices has been very low, however, and this study was not powered or designed to assess the rate of breakage.

A minor risk of the CGM is that patients may need to perform unnecessary fingersticks to evaluate their blood glucose when the CGM gives false positive hypoglycemic and hyperglycemic readings or alerts. There is also a minor risk of skin irritation, inflammation, or infection due to either the sensor needle or the adhesive. However, CGM devices allow patients to measure the interstitial glucose at near continuous intervals to obtain a 24 hour picture of their glucose profile, especially during the night. Tracking and trending information is of value to patients and outweighs minor risks associated with fingersticks and the sensor.

There are additional risks due to missed alerts and false negative hypoglycemic and hyperglycemic readings related to patients not being alerted to the need to perform a fingerstick to detect hypoglycemia or hyperglycemia. Additionally, there is a risk associated with false alerts and false positive hypoglycemia and hyperglycemia readings related to the need to perform unnecessary fingersticks to confirm an erroneous low or high reading. Patients who only use blood glucose meters to manage their diabetes without the aid of a CGM would also be unaware of the need to perform additional testing to detect an abnormal blood sugar (unless they were exhibiting symptoms of an abnormal blood glucose).

The risks of inaccurate Enlite sensor glucose results is not unreasonably higher than the risk of managing diabetes with a blood glucose meter alone and these include incorrect tracking and trending or threshold detection; increased false negative and false positive low threshold alerts and alarms or high threshold alerts, and incorrect rate of change calculations that could adversely affect treatment decisions.. However, if the patient relies on sensor glucose values and does not perform fingerstick blood glucose tests as recommended (4-7 times daily) the risks of CGM use increases; especially if the sensor error results in failure to detect glucose out of the target glucose range (failure of Low and High alerts) or incorrect insulin dosing.

Inaccurate calculation of the rate of change of interstitial glucose by the CGM could result in failure to identify trends of increasing or decreasing glucose and alerts to the patient that an unplanned blood glucose check should be performed. Rate of change detection errors result in the patient losing the opportunity to perform additional blood glucose tests and take appropriate measures to stop a trend of increasing or decreasing glucose levels that could lead to serious hypoglycemia or hyperglycemia. Inaccurate calculation of the rate of change of glucose could also lead to unnecessary additional blood glucose tests. As discussed above the risk of using sensor rate of change information for making treatment decisions, rather than as a prompt for unplanned blood glucose checks, increases the risk of CGM use.

There are risks associated with using the Threshold Suspend tool. As with the sensor based alerts, the threshold alarm is subject to sensor errors that can result in missed hypoglycemia and no pump suspension, or inappropriate pump suspension when blood glucose is above the sensor suspend threshold (suspension in the absence of hypoglycemia) potentially resulting in hyperglycemia and ketosis. Under certain conditions of use after the initial 2-hour suspension the pump will resume insulin delivery but can re-suspend after a short period of time (as little as 5-minutes) rather than after 4 hours. Repeated pump suspensions, especially if the initial suspension was in error, increases the risk of more severe hyperglycemia, ketosis, and possibly DKA. Patients using insulin pumps can manually suspend insulin or set a temporary basal rate of zero at any time, which can also result in hyperglycemia, ketosis, and possibly DKA if the interruption of insulin delivery is prolonged. Data from the ASPIRE study (G110044/S002) suggested that the use of the Threshold Suspend feature may potentially worsen glycemic control. Increased incidences of blood and urine ketones were observed in the Threshold Suspend group as compared to the Control group. When ketone levels were reported, the mean blood ketone concentration was higher in the Threshold Suspend group than in the Control group. In addition, more patients in the Threshold Suspend group reported positive ketone values when they exhibited symptoms (nausea, vomiting or abdominal pain). These hyperglycemia risks might be further amplified in patients with worse baseline control compared to those enrolled in the ASPIRE study. The risks of the Threshold Suspend tool can be mitigated if patients do not rely on the tool for treating or mitigating hypoglycemia if they are aware of Low Alerts or Threshold Suspend alarms, perform blood glucose checks, and treat hypoglycemia as instructed by their healthcare providers. Patients should also not rely on the sensor to detect hypoglycemia and perform blood glucose checks in response to symptoms of hypoglycemia.

Risks of the pump hardware problems include the following possible hypoglycemia from over-delivery of insulin due to a hardware defect; as well as hyperglycemia and ketosis possibly leading to ketoacidosis due to inappropriate insulin suspension or pump failure resulting in cessation of all insulin delivery due to either a hardware defect or software anomaly

For information on adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

The MiniMed 530G System remains unchanged as the result of this Panel-Track Supplement. Please refer to the Summary of Safety and Effectiveness Data (SSED) of the original PMA (P120010) for laboratory studies that supported the approval of the MiniMed 530G System.

B. Animal Studies

None

C. Additional Studies

None

X. SUMMARY OF PRIMARY CLINICAL STUDIES

Note: The original PMA approval was based on two pivotal in-clinic studies to establish a reasonable assurance of safety and effectiveness of the MiniMed 530G System for its intended use, including the accuracy performance of the Enlite sensor. The in-clinic studies were performed in the United States under IDE # G110131/A001 (Enlite Sensor Accuracy) and G100028 (Threshold Suspend). Please refer to the Summary of Safety and Effectiveness Data (SSED) of the original PMA (P120010) for details on those studies.

In this Panel-Track Supplement, the applicant performed the ASPIRE (Automation to Simulate Pancreatic Insulin REsponse) in-home study (G110044/S002) to evaluate the safety and effectiveness of the Threshold Suspend (TS, or Low Glucose Suspend (LGS)) feature in the home setting for 3 months. A summary of this clinical study is presented below.

CLINICAL STUDY	IDE Number	PATIENT POPULATION	STUDY DESIGN
ASPIRE (Automation to Simulate Pancreatic Insulin Response): Pivotal In Home study to determine effect of the low glucose suspend (LGS) feature in sensor-augmented pumps	G110044/S002	Adult and pediatric (Age 16-70)	A multi-center, in-home, randomized parallel adaptive study with type 1 diabetes to compare Hemoglobin A1c (HbA1c) and CGM-based nighttime low sensor glucose events in a treatment arm to a control arm.

A. Study Design

This is a multi-center, in home, randomized parallel adaptive study with type 1 diabetes (ages 16-70) designed to compare HbA1c and CGM-based nighttime low sensor glucose events in a treatment arm to a control arm. Arms are defined as:

- Treatment Arm (Threshold Suspend) using Paradigm® VEO™ Pump (equivalent to the MiniMed 530G insulin pump[3])
- Control Arm using Paradigm® Revel™2.0 Pump

The study was conducted at a total of nineteen sites and was completed on February 13, 2013. In total, 414 subjects were enrolled (including screen failures), of which 247 were randomized successfully. The study included a 2-4 weeks run-in period, followed by a 3-month study phase. Each subject's participation in the study is comprised of 5 scheduled office visits and 2 scheduled telephone visits over the course of approximately 4-5 months (inclusive of the screening visit). The visit schedule was as follows:

- Screening Visit 1 – Day 0 – Consent and Screening
- Run-in Visit 2 – Day 8 (± 6 days) - Study and device training; Pump Start
- Run-in Visit 3 - Day 21 (± 7 days) – All Subjects: Pump Follow-Up; Start Pump CGM Enlite sensor; Start of CGM Run-in and 14 day sensor wear compliance window
- Run-in Visit 4 - Day 35 (+ 7 days) - All subjects: End of 2 week run-in; Randomization (if qualified)

3. The MiniMed 530G Insulin Pump is a derivative product of the Paradigm pump platform (including the Paradigm VEO pump). Both devices utilize the same hardware, as well as share the same base application code and a majority of the same software features. These features include the sensor glucose calibration algorithm and "Threshold Suspend" algorithm. The differences between the Paradigm VEO pump and the MiniMed 530G pump are that the Paradigm VEO pump has: i) a wider programmable range for the "Threshold Suspend" feature (40-110 mg/dL vs. 60-90 on the 530G pump); ii) an "auto-calibration" feature which allows blood glucose meter readings to be used automatically for sensor calibration; and iii) a larger maximum bolus (75 units vs. 25 units on the MiniMed 530G pump). For the purpose of this study, the Threshold Suspend setting on the VEO pump was limited to 60 mg/dL to 90 mg/dL (same as the MiniMed 530G pump), the "auto-calibration feature on the VEO pump was disabled, and the maximum bolus was set to allow no more than 25 units for a single bolus at all times.

- Repeat Run-in Visit - Day 49 (+ 7 days) - End of repeat CGM Run-in; Visit applies only to subjects who have repeated sensor wear during the run-in; Randomization
- Telephone Visit 5 – Day 42 or Day 56 (± 6 days) Treatment phase check-in Visit (first of 2)
- Telephone Visit 6 – Day 63 or Day 77 (± 7 days) Treatment phase check-in Visit (second of 2)
- End of Study Visit 7 – End of treatment period; end of study

All subjects used the Paradigm® Revel 2.0 insulin pump during the run-in period. During the run-in period Subjects must demonstrate 2 or more incidents of nighttime (10pm – 8am) low sensor glucose (CGM < 65mg/dL) events over a 2 week period. The run-in period could be completed in either 2 weeks or 4 weeks.

- Subjects who met the nighttime low sensor glucose events requirement within the first 2 weeks of run-in and satisfy all other randomization criteria were randomized at 1:1 ratio to either the THRESHOLD SUSPEND or CONTROL Group at visit 4. Subjects randomized at Visit 4 do not return for the Run-in Repeat Visit.
- Subjects who did not meet the nighttime low sensor glucose events requirement after the first 2 weeks of the run-in period were asked to repeat and complete an additional 2 weeks of run-in when they came in at visit 4. Subjects who completed the requirement during the following 2 weeks and met all other randomization criteria were randomized at the Run-in Repeat Visit.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the ASPIRE in-home study (G110044/S002) was limited to patients who met the following *inclusion criteria*:

   General Enrollment:

   Subjects were considered for enrollment in the In Home study if they met all of the following criteria:

   (1) Subject is age 16 - 70 years at time of screening
   (2) Subjects who are 16-21 years are determined by the investigator to have the appropriate, requisite support (family, caregiver or social network) to successfully participate in this study
   (3) Subjects who are determined by the investigator to be psychologically sound in order to successfully participate in this study
   (4) Subject was <40 years at disease onset
   (5) Subject has been diagnosed with type 1 diabetes ≥ 2 years
   Note: Determination of classification for diabetes will be based on American Diabetes Association Clinical Practice Guidelines accounting for several patient characteristics such as age of onset, patient's weight or BMI, history of diabetic ketoacidosis, history of therapy management, and medical records if available.
   (6) Subject tests negative for stimulated (mixed meal) C-peptide [6 ml/kg of BOOST® Nutritional Drink up to maximum of 360 ml should be ingested at baseline within 5 minutes. C-peptide levels should be drawn at baseline and

at 2 hours (+/- 10 minutes). C-peptide value must be < 0.45 nmol/L] approximately 2 hours after ingestion of BOOST®]

(7) Subject is willing to perform 4 finger stick blood glucose measurements daily
(8) Subject is willing to perform required sensor calibrations
(9) Subject is willing to wear the system continuously throughout the study
(10) Subject is willing to keep a log to record at minimum:
    a) Sick days
    b) Days with exercise and days with symptoms of low glucose
(11) Subject has an HbA1c value 5.8% to 10.0% (as processed by Central Lab) at time of screening visit
    Note: All collected blood specimens were sent to and tested by a Central Laboratory certified by the National Glycohemoglobin Standardization Program (NGSP). HbA1c testing must follow NGSP standards.
(12) Subjet must have one of the following device therapy inclusion criteria:
    a) Pump therapy for >6 months with real time CGM for >3 months prior to Screening
    b) Pump therapy for >6 months prior to Screening
(13) Subject has been followed by a well trained diabetes health care provider(s) for 6 months prior to screening
(14) Subject is willing to upload data weekly from the study pump, must have Internet access and a computer system that meets the requirements for uploading the study pump
(15) If subject has celiac disease, it has been adequately treated as determined by the investigator
(16) Subject is willing to take one of the following insulins and can financially afford to use either of the 2 insulin preparations throughout the course of the study (i.e., co-payments for insulin with insurance or able to pay full amount)
    a) Humalog® (insulin lispro injection)
    b) NovoLog® (insulin aspart)

Treatment Period Inclusion Criteria:

Subjects could be randomized to participate in the treatment period of the study if they met the above inclusion criteria as well as all of the following criteria:

(1) Subjects must demonstrate at least 2 incidents of nighttime (10pm – 8am) low sensor glucose event (sensor glucose value <65mg/dL) over a 2 week run-in period.
    a) Each episode must last 20 minutes and the CareLink reports must demonstrate that subjects did not have any pump interactions during this time
    b) Subjects who do not demonstrate 2 separate nighttime low sensor glucose events during the first 2 weeks of the run-in period may repeat the run-in period for 2 more weeks
    c) During the second 2 week period, subjects must demonstrate 2 incidents of nighttime low sensor glucose events

(2) Subject has worn CGM for the prescribed amount of time (≥80%) during the run-in phase
   a) Successful sensor wear is defined as recording cumulative sensor data:
      i. With 2 weeks of run in: 3,225 glucose sensor data point (equivalent to 11.2 days of sensor wear)
      ii. If a subject repeats the run-in period, sensor compliance must also be demonstrated during the repeat

(3) Subject has demonstrated ability to comprehend study procedures during the run-in phase, as evaluated by appropriate research staff

Patients were <u>not</u> permitted to enroll in the ASPIRE in-home study if they met any of the following *exclusion criteria*:

(1) Subject has a history of 2 or more episodes of severe hypoglycemia, which resulted in any the following during the 6 months prior to screening:
   a) Medical assistance (i.e. Paramedics, Emergency room or Hospitalization)
   b) Coma
   c) Seizures
(2) Subject is unable to tolerate tape adhesive in the area of sensor placement
(3) Subject has any unresolved adverse skin condition in the area of sensor placement (e.g., psoriasis, rash, Staphylococcus infection)
(4) Women of child-bearing potential who have a positive pregnancy test at screening or plan to become pregnant during the course of the study
(5) Subject has had any of the following new diagnoses within 1 year of screening: myocardial infarction, unstable angina, coronary artery bypass surgery, coronary artery stenting, transient ischemic attack, cerebrovascular accident, angina, congestive heart failure, ventricular rhythm disturbances or thromboembolic disease
(6) Subject is being treated for hyperthyroidism at time of screening
(7) Subject has an abnormality (out of upper reference range, as processed by Central Lab) in creatinine at time of screening visit
(8) Subject has an abnormality (out of reference range, as processed by Central Lab) in thyroid- stimulating hormone (TSH) at time of screening visit
(9) Subject has taken any oral, injectable, or IV steroids within 8 weeks from time of screening visit, or plans to take any oral, injectable, or IV steroids during the course of the study
(10) Subject is actively participating in an investigational study (drug or device) wherein he/she has received treatment from an investigational study drug or investigational study device in the last 2 weeks
(11) Subject has been hospitalized or has visited the emergency room in the 6 months prior to screening resulting in a **primary diagnosis** of uncontrolled diabetes
(12) Subject is currently abusing illicit drugs
(13) Subject is currently abusing prescription drugs
(14) Subject is currently abusing alcohol
(15) Subject is using pramlintide (Symlin) at time of screening

(16) Subject has a history of visual impairment which would not allow subject to participate in the study and perform all study procedures safely, as determined by the investigator
(17) Subject has elective surgery planned that requires general anesthesia during the course of the study
(18) Subject is a shift worker with working hours between 10pm and 8am.
(19) Subject has a sickle cell disease, hemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening
(20) Subject plans to receive red blood cell transfusion or erythropoietin over the course of study participation
(21) Subject diagnosed with current eating disorder such as anorexia or bulimia
(22) Subject plans to use significant quantity of herbal preparations (use of over the counter herbal preparation for 30 consecutive days or longer period during the study) or significant quantity of vitamin supplements (four times the recommended daily allowance used for 30 consecutive days or longer period during the study) during the course of their participation in the study
(23) Subject has been diagnosed with chronic kidney disease that results in chronic anemia
(24) Subject is on dialysis

2. Follow-up Schedule

At the end of study, subjects removed all study devices. Investigational center staff reviewed the surveillance reports, documented any Adverse Device Effects (including irritations) in the electronic case report forms (eCRF) and evaluated safety issues related to system use during the study. No long-term follow up was included in this study protocol.

3. Clinical Endpoints

The sponsor pre-specified a primary safety endpoint regarding the change of HbA1c level from randomization to the end of the study, and a primary effectiveness endpoint regarding the reduction of the Area Under the Curve (AUC) for nighttime low sensor glucose events (≤ 65 mg/dL) during the 3-month study phase between the Threshold Suspend and the Control group. While the study met both primary endpoints, it is important to note that the study results did not demonstrate that use of the Threshold Suspend feature would not worsen glycemic control, or that use of the Threshold Suspend feature could reduce nocturnal hypoglycemia for the following reasons:

a. The HbA1c results (see Section D.1, *Safety Results*) alone are inadequate to demonstrate use of the Threshold Suspend feature is not associated with deterioration of glycemic control, since other data from the ASPIRE study suggest a trend towards higher glucose levels in patients using the Threshold Suspend feature, and that ketones were more common in patients using Threshold Suspend. Ketones are an important measure of risk associated with high blood sugar and are an early sign of risk for diabetic ketoacidosis (DKA).

b. Reduction of the Area Under the Curve for nighttime low sensor glucose events (≤ 65 mg/dL) in the Threshold Suspend group (see Section D.2, *Effective Results*) should not be interpreted as being equivalent to the reduction of nocturnal hypoglycemia because hypoglycemia (severe hypoglycemia) is a clinical diagnosis based on the American Diabetes Association consensus report[4].
c. The study only included patients who had a history of nighttime low sensor glucose values. To be included in the study, patients had to have at least two low sensor glucose events (≤ 65 mg/dL) that lasted 20 minutes or longer during the run-in phase. Fifty-seven (57) out of 320 patients (i.e., 18% of the study population) did not meet the criteria of the run-in phase to enter the study. As such, results of the ASPIRE study may not be generalizable to all users of the MiniMed 530G System.

B. Accountability of PMA Cohort

A total of 414 patients were enrolled and assessed for eligibility. 78 subjects failed the screening at Visit 1 and 16 subjects withdrew prior to the run-in phase.

Of the 320 subjects entering the run-in phase, 73 were not randomized; 57 did not meet the required number of nocturnal hypoglycemic events or the minimum sensor wear requirement, and 16 patients were withdrawn in the run-in phase (one subject withdrew after an adverse event due to skin irritation from sensor wear).

A total of 247 subjects were randomized, 121 to the Threshold Suspend arm and 126 to the Control arm, with 240 subjects completing the study. Of the 7 subjects who withdrew early, 5 withdrew from the Threshold Suspend arm and 2 withdrew from the Control arm. At randomization, the two arms groups were similar with respect to mean (±SD) HbA1c concentration.

C. Study Population Demographics and Baseline Parameters

Subject demographic and other baseline characteristics for all subjects randomized are displayed in Tables 1 and 2 below.

Table 1. Baseline Demographic Characteristics of Subjects Who Underwent Randomization

Characteristic	All Subjects	Threshold Suspend Group	Control Group
Number of Subjects Randomized (N)	**247**	**121**	**126**
Age (Years)			
N	247	121	126

4. Seaquist ER, et al. "Hypoglycemia and diabetes: A report of a workgroup of the American Diabetes Association and the Endocrine Society." Diabetes Care. 2013 May; 35(5): 1384-1395.

Characteristic	All Subjects	Threshold Suspend Group	Control Group
Mean (SD)	43.3 (13.41)	41.6 (12.83)	44.8 (13.82)
Median	44.0	43.0	46.5
Min, Max	16.0, 70.0	16.0, 69.0	16.0, 70.0
Gender N(%)			
Female	151 (61.1%)	75 (62.0%)	76 (60.3%)
Male	96 (38.9%)	46 (38.0%)	50 (39.7%)
Race N(%)			
White	241 (97.6%)	119 (98.3%)	122 (96.8%)
Asian	2 (0.8%)	2 (1.7%)	0 (0.0%)
Black/African American	4 (1.6%)	0 (0.0%)	4 (3.2%)
Ethnicity N(%)			
Hispanic/Latino	6 (2.4%)	2 (1.7%)	4 (3.2%)
Non-Hispanic/Latino	241 (97.6%)	119 (98.3%)	122 (96.8%)
Diabetes History (Years)			
N	243	120	123
Mean (SD)	26.9 (12.58)	27.1 (12.49)	26.7 (12.72)
Median	25.9	25.8	25.9
Min, Max	2.4, 61.8	2.4, 61.8	3.1, 58.0
More than 3 Months of CGM			
Yes	142 (57.5%)	74 (61.2%)	68 (54.0%)
No	105 (42.5%)	47 (38.8%)	58 (46.0%)
Insulin Type N(%)			
insulin lispro	113 (45.7%)	64 (52.9%)	49 (38.9%)
insulin aspart	134 (54.3%)	57 (47.1%)	77 (61.1%)
Height (cm)			
N	247	121	126
Mean (SD)	170.0 (9.57)	169.5 (9.90)	170.4 (9.26)
Median	168.2	167.6	169.7
Min, Max	150.2, 195.6	150.2, 192.0	151.4, 195.6
Weight (kg)			
N	247	121	126
Mean (SD)	79.3 (15.49)	79.6 (15.91)	79.1 (15.13)
Median	78.3	76.3	78.7
Min, Max	48.7, 126.5	49.1, 126.5	48.7, 120.4

Characteristic	All Subjects	Threshold Suspend Group	Control Group
BMI (kg/m^2)			
N	247	121	126
Mean (SD)	27.4 (4.50)	27.6 (4.72)	27.1 (4.27)
Median	26.7	26.2	26.8
Min, Max	19.2, 44.0	19.6, 44.0	19.2, 42.0
A1C at Screening (%)			
N	247	121	126
Mean (SD)	7.5 (0.89)	7.5 (0.86)	7.6 (0.91)
Median	7.4	7.4	7.5
Min, Max	5.8, 10.0	5.8, 10.0	5.9, 9.9
A1C at Randomization (%)			
N	246	120	126
Mean (SD)	7.2 (0.74)	7.3 (0.71)	7.2 (0.77)
Median	7.1	7.2	7.1
Min, Max	5.7, 9.7	5.9, 9.7	5.7, 9.6

Table 2. Baseline Demographic Characteristics of Subjects Who Underwent Randomization, Stratified by Age and BMI.

Demographic Characteristic	All Subjects	Threshold-Suspend Group	Control Group
Number of Subjects Randomized	**(N=247)**	**(N=121)**	**(N=126)**
Age			
16-21 years	14 (5.7%)	6 (5.0%)	8 (6.3%)
>=22 years	233 (94.3%)	115 (95.0%)	118
BMI			
Morbidly Obese Subjects (BMI >= 40 kg/m^2)	3 (1.2%)	2 (1.7%)	1 (0.8%)
Normal Weight Subjects (BMI 18.5 to 24.99 kg/m^2)	74 (30.0%)	34 (28.1%)	40 (31.7%)
Overweight and Obese Subjects (BMI 25 to 40 kg/m^2)	170 (68.8%)	85 (70.2%)	85 (67.5%)

D. Safety and Effectiveness Results

1. Safety Results

At the randomization visit, the mean HbA1c measurement was 7.26% in the 120 Threshold Suspend group participants and 7.21% in the 126 Control group participants who had available HbA1c data (Table 3). At the end of study, the mean HbA1c measurement was 7.24% in the 116 Threshold Suspend group participants and 7.14% in the 124 Control group participants who had available HbA1c data. For participants with both randomization and end-of-study HbA1c (N = 116 in TS group, N = 124 in Control group), the mean of HbA1c change from randomization to end of study was 0.00% in the TS group and -0.04% in the Control group (Table 4).

Table 3. Summary of Change in HbA1c (%) from Randomization to End of 3-Month Study

	Threshold Suspend Group		**Control Group**	
	Randomization HbA1c	End of Study HbA1c	Randomization HbA1c	End of Study HbA1c
Mean (SD)	7.26 (0.71)	7.24 (0.67)	7.21 (0.77)	7.14 (0.77)
Number of Subjects	120	116	126	124

Table 4. Additional Descriptive Statistics for A1C Analysis of Study Groups

	Threshold Suspend Group	**Control Group**
Number of Subjects with both randomization and end-of-study HbA1c	116	124
Mean(SD)	0.00(0.44)	-0.04(0.42)
Difference in the mean change in HbA1c (Threshold Suspend – Control)	0.04	

IMPORTANT: While the study results did not indicate a significant impact of the Threshold Suspend feature on the HbA1c level among the study participants, the data is insufficient to conclude that use of the Threshold Suspend feature does not affect glycemic control due to several important limitations of the study design:

- The study lasted 3 months and subjects were only required to turn on the Threshold Suspend feature between 10 pm and 8 am. Therefore, the subject's exposure to Threshold Suspend is not long enough to measure its full impact on HbA1c.
- The study did not collect enough blood glucose or ketone test results from patients who may have been experiencing symptoms associated with hyperglycemia to determine if Threshold Suspend increased the risk of high blood sugars (hyperglycemia).

- The study results did suggest that ketones were more common in patients using Threshold Suspend (see Tables 7-9 below). Ketones are an important measure of risk associated with high blood sugar and are an early sign of risk for diabetic ketoacidosis (DKA), a rare but serious condition associated with prolonged periods of high blood sugars.
- The study results found a trend towards higher glucose level in patients using Threshold Suspend (as measured by the Hyperglycemia AUC with sensor glucose value > 180 mg/dL, see below). This measure is important because patients using insulin pump therapy, whether using Threshold Suspend or not, are typically using rapid acting insulin. Since stopping the delivery of rapid-acting insulin can quickly lead to increased blood sugars the automatic suspension of insulin delivery associated with Threshold Suspend can increase this risk.

  Hyperglycemia AUC
  Combined (day and night), the subject mean percent of time when the sensor glucose values were in the >180 mg/dL range was higher in the Threshold Suspend group compared to the Control group (31.1% vs. 30.0%); in the >240 mg/dL range the percentages are same between two groups (11.1% vs. 11.1%); in the > 300mg/dL range, the percentage is lower in the Threshold Suspend group compared to the Control group (3.2% vs. 3.5%).

  Overall, in terms of sensor glucose AUC and duration in the hyperglycemic range, the Threshold Suspend users experienced a greater AUC of 2.3% at night and a longer duration of 3.7% combined day and night as compared to the Control group in the >180 mg/dL range.

Adverse effects that occurred in G110044/S002:

- There were no reports of subject death during the study.
- There were no reports of unanticipated adverse device effects (UADEs) during the study.
- There were no reports of diabetic ketoacidosis (DKA) during the study
  - A limitation of the study was that blood tests of serum bicarbonate and pH levels were not always obtained when symptoms of potential DKA were present. As a result, the actual number of episodes of mild or severe DKA may have exceed the number of reported events and therefore it cannot be conclusively determined that the use of the Threshold Suspend feature is not associated with an increased risk of hyperglycemia and mild or severe DKA.
- There were 8 severe hypoglycemic events during the course of the study.
  - 4 severe hypoglycemic events occurred prior to the Study Phase
  - 4 severe hypoglycemic events occurred in the Control Group during the Study Phase.
  - No severe hypoglycemic events occurred in the Threshold Suspend Group.
- There were 19 device- or procedure-related adverse events during the 3-month Study Phase.

- 1 patient had prolonged pump suspensions (a device performance issue) that did not result in an adverse event.

A summary of adverse events can be found in Table 5 below.

Table 5. Summary of Adverse Event Information

	Run in Phase	Study Phase	
		Threshold Suspend	Control
Serious adverse events related to study device or study procedure.	0	0	0
Serious adverse events NOT related to study device or study procedure: • 4 reported serious adverse events in the run-in phase were: o Radiculopathy resulting in laminectomy in 1 patient o Ischemia and stent placement in 1 patient o Coronary artery disease in 1 patient o Atypical chest pain in 1 patient. • 2 reported serious adverse events in the study phase were: o Severe hypoglycemia in 1 patient* o Pneumonia in 1 patient.	4	0	2
Adverse events not related to study device or study procedure	114	46	53
Adverse events related to study device or study procedure			
Skin-related**	20	4	12
Infusion set-related, resulting in severe hyperglycemia (blood glucose>300 mg/dL with ketones >0.6 mmol/L, and did not meet the criteria for DKA)	2	3	0
Infusion set-related, resulting in hyperglycemia	1	0	0
Syncope	1	0	0
Emesis from mixed meal tolerance test used to assess C-peptide	1	0	0
Pump priming issue and hypoglycemia	1	0	0
Total	144	53	67

* One subject experienced a seizure that was determined by the investigator to be related to severe hypoglycemia. This incidence was reported as a serious adverse event.

**Skin related events included skin irritation, skin infection, rash, bleeding, bruising (ecchymosis), redness, rash, abrasion, dermatitis and pruritus.

Severe Hypoglycemia:
Severe hypoglycemia was defined as a low blood glucose (BG) resulting in coma, seizure or requiring medical assistance.

Run-In Phase
- 4 severe hypoglycemic events occurred during the Run-In Phase.
  - In 3 of these events, the subject was not wearing a sensor at time of incident.
  - In the 4th event, the subject received multiple low glucose alerts with no treatment noted.

Study Phase
- No severe hypoglycemic events occurred in the Threshold Suspend Group during the Study Phase.
- 4 severe hypoglycemic events occurred in Control Group (rate of 0.13 severe hypoglycemic events per patient year.
  - In 1 of these events, the subject had a seizure that was determined to be related to hypoglycemia. Several hours before this event an over-correction occurred while treating hyperglycemia.
- No severe hypoglycemic events or seizures were related to study device or study procedure.

Severe Hyperglycemia
Severe hyperglycemia was defined as BG >300 mg/dL with blood ketones >0.6mmol/L or accompanied by symptoms of nausea, vomiting or abdominal pain.

There were a total of 12 severe hyperglycemic events reported by investigators during the course of the study. Of the 12 reported events. 6 occurred prior to the start of the Study Phase and 6 occurred during the Study Phase including 4 in the Threshold Suspend Group and 2 in the Control Group.

Table 6. Summary of Severe Hypoglycemia, Severe Hyperglycemia and Seizures Reported During Run-In and Study Phases.

	Run-In Phase	Study Phase	
		Threshold Suspend Group	Control Group
Severe Hypoglycemic Events*	*4*	0	4
Seizures**	*0*	0	1
Severe Hyperglycemic Events***	*6*	4	2

** Severe hypoglycemia defined as low blood glucose resulting in coma or seizure or requiring medical assistance.*

*** This incidence of seizure was related to severe hypoglycemia.*
**** Severe hyperglycemia defined as blood glucose >300 mg/dL with blood ketones >0.6mmol/L or accompanied by symptoms of nausea, vomiting or abdominal pain.*

In addition to documented severe hyperglycemic events, there were increased measurements of ketones and higher overall Hyperglycemia AUC in the Threshold Suspend Group. These data suggested an increased incidence of ketonuria and higher mean blood ketone values in the Threshold Suspend group. An increased incidence of ketonuria or high mean blood ketone values could suggest an increased risk of hyperglycemia and DKA.

Patients during the study were instructed to check their urine ketones daily. Data provided in Table 7 provides average daily urine ketone values. Table 8 provides a summary of mean blood ketone measurements taken from patients when they were hyperglycemic. Table 9 provides a summary of mean blood ketone measurements taken from patients who had symptoms attributed to DKA such as nausea, vomiting and abdominal pain. The results in these three tables suggest a trend toward higher urine and blood ketone levels in the Threshold Suspend Group.

Table 7. Summary of Daily Urine Ketone Values in Each Arm

Category (Number of values)	Threshold Suspend Group	Control Group
Negative	94.84% (8479)	96.23% (8889)
Trace	3.31% (296)	2.68% (296)
Small	1.12% (100)	0.62% (57)
Moderate	0.53% (47)	0.27% (25)
Large	0.20% (18)	0.19% (18)

Table 8. Summary of blood ketone values (mmol/L) in Each Arm

Category (Number of values)	Threshold Suspend Group	Control Group
Number of times ketones were reported	340	242
Mean (SD)	0.31 (0.48)	0.28 (0.55)

Table 9. Summary of blood ketone values (mmol/L) only when subjects had symptoms of nausea, vomiting and abdominal pain each arm

Category (Number of values)	Threshold Suspend Group	Control Group
Number of times ketones were reported	24*	3
Mean (SD)	0.65 (0.98)	0.13 (0.06)

*In the Threshold Suspend group, there were 15 blood ketone measurements collected from 1 subject with symptom of abdominal pain attributed to Gallstones.

2. Effectiveness Results

Key effectiveness outcomes are presented in Tables 10 to 19.

Table 10. Descriptive Summary of the Area-Under-Curve (AUC, mg/dL x min), Duration and Minimum Sensor Glucose for Nighttime Low Sensor Glucose Event (≤ 65 mg/dL), Lasting 20 Minutes or Longer in the Study Phase

	Threshold Suspend Group	**Control Group**
Number of Events	2025	3002
Mean AUC (SD)	980 (1200.1)	1568 (1994.9)
Median AUC	575	798
Min AUC, Max AUC for all nighttime low sensor glucose events	0, 9685	0, 16970
Difference between arms in the mean AUC	-588	
Mean Duration (min)	85.1	119.3
Mean Minimum Sensor Glucose (mg/dL)	50.4	48.8

Table 11. Comparison of All Nighttime Low Sensor Glucose Events for Any Duration in the Study Phase, Categorized by Minimum Sensor Glucose

	Number of Events		**Duration (minutes)**		**Mean Minimum Sensor Glucose (mg/dL)**	
Sensor Glucose	Threshold Suspend	Control	Threshold Suspend	Control	Threshold Suspend	Control
≤ 50 mg/dL	879	1,623	41.1	50.0	44.6	44.2
≤ 60 mg/dL	1,897	2,677	45.9	55.3	51.7	51.1
≤ 70 mg/dL	3,225	3,665	50.6	61.8	59.4	58.3

Table 12. Comparison of Day-and-Night Low Sensor Glucose Events for Any Duration in the Study Phase, Categorized by Minimum Sensor Glucose

	Number of Events		**Duration (minutes)**		**Mean Minimum Sensor Glucose (mg/dL)**	
Sensor Glucose	Threshold Suspend	Control	Threshold Suspend	Control	Threshold Suspend	Control
≤ 50 mg/dL	1,984	3,433	28.2	35.1	44.9	44.5
≤ 60 mg/dL	4,751	6,537	31.2	37.7	52.3	51.7
≤ 70 mg/dL	7,971	9,468	36.6	43.6	59.8	58.7

Table 13. Summary of the Rate of Nighttime Low Sensor Glucose Event (≤ 65 mg/dL) in Each Arm

	Threshold Suspend Group	Control Group
Number of subjects	121	126
Total number of event nights (defined as the number of nights with 1 or more hypoglycemic events)	1839	2489
Total number of sensor-wearing nights (defined as any night where a subject wore a sensor for any period of time)	9052	9247
Event rate (defined as the total number of event nights/total number of sensor wearing nights)	20.3%	26.9%

Table 14. Sensor Glucose Distribution (<70mg/dL), Night-Time Only

Sensor Glucose Range	Threshold Suspend Group	Control Group	Change
< 50 mg/dL	1.2%	2.8%	-1.6%
50 to 60 mg/dL	1.8%	3.1%	-1.3%
60 to 70 mg/dL	3.0%	4.1%	-1.1%
Total (< 70 mg/dL)	6.0%	10.0%	-4.0%

Table 15. Sensor Glucose Distribution, Combined Day- and Night-Time (<70mg/dL)

Sensor Glucose Range	Threshold Suspend Group	Control Group	Change
< 50 mg/dL	0.9%	1.9%	-1.0%
50 to 60 mg/dL	1.6%	2.5%	-0.9%
60 to 70 mg/dL	2.8%	3.7%	-0.9%
Total (< 70 mg/dL)	5.3%	8.1%	-2.8%

Insulin Delivery Suspension

Table 16. Automatic Insulin-Suspension Events (Nighttime Only vs Combined Day and Night)

	Night Only	**Combined Day and Night**
Number of Threshold Suspend events per patient night (Mean)	0.77	2.08
Median duration of Threshold Suspend events (Minutes)	11.9	1.42
Mean duration of Threshold Suspend events (Minutes)	39.4	25.5
Percent of Threshold Suspend events that lasted less than 5 minutes	43.1%	56.3%
Percent of Threshold Suspend events that lasted for 2 hours	19.6%	9.4%
Number of 2-hour Threshold Suspend events	1,444	1,873

Table 17. Duration of Night-time Insulin Suspension (Study Phase, Threshold Suspend Group)

Duration of Threshold Suspend Events	**Number of Events (%)**
≤ 10 minutes	3,630 (49.2%)
10 - ≤ 20 minutes	572 (7.7%)
20 - ≤ 30 minutes	317 (4.3%)
30 - ≤ 40 minutes	281 (3.8%)
40 - ≤ 50 minutes	218 (3.0%)
50 - ≤ 60 minutes	186 (2.5%)
60 - ≤ 70 minutes	171 (2.3%)
70 - ≤ 80 minutes	149 (2.0%)
80 - ≤ 90 minutes	131 (1.8%)
90 - ≤ 100 minutes	131 (1.8%)
100 - ≤ 110 minutes	89 (1.2%)
110 - ≤ 120 minutes*	1,511 (20.5%)

* During the study, there were 15 Threshold Suspend events that lasted longer than 122 minutes. A Threshold Suspend event lasting > 122 minutes is out of product specification. Of those 15 events, 11 lasted between 122 – 130 min. There were four events lasting more than 130 minutes, each lasting approximately 4.7 hours to 6.8 hours. All four of these incidences occurred in one subject. None of the prolonged insulin suspends resulted in an adverse event. The root cause of these out-of-specification insulin suspends was subsequently fixed.

During night-time, insulin was most likely (49.2%) to be suspended for 10 minutes or less. But one out of five (20.5%) Threshold Suspend events lasted for 110 minutes or longer. For Threshold Suspend events that lasted two hours (120 minutes), the trend of sensor glucose values before, during and after the two-hour Threshold Suspend event are summarized in Table 18 below. Time 0 in the table represents the onset of Threshold Suspend event.

Table 18. Glucose Trends Before, During and After Two-Hour Insulin Suspension Events (Study Phase, Threshold Suspend Group)

Time Point (minutes)	Sensor Glucose (mg/dL)		Number of Sensor Glucose Values
	Mean	SD	
-180	158.7	62.8	895
-175	158.0	62.5	904
-150	150.9	59.1	933
-120	139.2	53.3	977
-90	126.2	44.1	1012
-60	109.3	32.5	1057
-30	88.8	19.7	1156
-5	69.2	8.4	1423
0*	65.6	6.7	1438
5*	64.1	7.1	1435
30*	65.2	16.9	1426
60*	69.8	24.7	1408
90*	78.2	32.1	1393
120*	92.6	40.7	1385
180	144.7	57.5	1185
240	168.8	64.6	1136
300	174.3	65.0	1074
360	171.6	64.9	1042

* During the Threshold Suspend event.

On average, the sensor glucose value was 109.3 mg/dL one hour before the Threshold Suspend alarm was triggered, and remained below 70 mg/dL for the first hour after the Threshold Suspend alarm was triggered. At the end of the two-hour Threshold Suspend event, sensor glucose was 92.6 mg/dL and continued to rise for the next 2 hours, reaching 168.8 mg/dL at T=240 minutes (2 hours after the Threshold Suspend event was over).

In the two hours after a two-hour Threshold Suspend event, the percentage of sensor glucose values < 70 mg/dL dropped from 33.1% to 3.9% and the percentage of sensor glucose values >200 mg/dL increased from 2.2% to 26.0% (please see Table 19).

Table 19. Sensor Glucose (SG) Distribution after a Two-Hour Threshold Suspend Event

	Immediately After a Two-Hour Threshold Suspend Event	**Two-Hours After a Two-Hour Threshold Suspend Event**
SG values <70 mg/dL	33.1%	3.9%
SG values 70-200 mg/dL	64.8%	70.2%
SG values >200 mg/dL	2.2%	26.0%
Average SG (mg/dL, mean±SD)	92.6 ± 40.7	168.8 ± 64.6

3. Subgroup Analyses

Performance of the Threshold Suspend feature was evaluated within study population subgroups, such as age (16-21 years old, 22 years old and above), prior CGM experience (> or < 3 months), types of insulin (Humalog or Novolog).

Although the study was not powered for analysis of subpopulations, no significant differences in performance were noted based on these subgroup analyses.

Note: Of the 247 subjects who completed study, only 14 were between the ages of 16-21 years of old. The ASPIRE labeling addendum included the following statement to explain the limitation of the small pediatric cohort: "*Due to the relatively small number of pediatric subjects, no conclusions can be made regarding whether or not the safety and efficacy of the threshold suspend feature is the same for patient 16 through 21 years old as for patients 22 years and older*".

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 19 investigators. Except one clinical investigator, all had no disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The site of the clinical investigator with disclosable financial interest, among several others, was inspected by the FDA's Bioresearch Monitoring (BIMO) program and found to be in compliance. The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Clinical Chemistry and Clinical Toxicology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates

information previously reviewed by this panel. The potential benefits and risks of the threshold suspend tool has also been publicly discussed in several meetings, including a meeting on Artificial Pancreas Device Systems held in 2010 and co-sponsored by the FDA and the National Institutes of Health.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The MiniMed 530G System is not intended to be used directly for preventing or treating hypoglycemia but to suspend insulin delivery when the user is unable to respond to the Threshold Suspend alarm.

The ASPIRE in-home pivotal clinical study was designed to demonstrate that use of the Threshold Suspend feature in patients with a history of nighttime low sensor glucose events (CGM glucose ≤ 65 mg/dL for ≥ 20 minutes) is effective in reducing the duration and magnitude of nighttime low sensor glucose events. Results from the ASPIRE study indicate that use of the Threshold Suspend feature can reduce the frequency (event rate, 20.3% in the Threshold Suspend group vs. 26.9% in the Control group) and the magnitude and duration (measured by Area-Under-the-Curve, event duration and minimum sensor glucose value). However, it is important to note that hypoglycemia is a clinical diagnosis based on the ADA consensus report. Endpoints in this study, including the Area-Under-the-Curve (AUC), duration and magnitude (or minimum sensor glucose value) of nighttime low sensor glucose events are based on CGM measurements of interstitial glucose concentrations and should not be interpreted as surrogate endpoints for clinical hypoglycemia. In addition, the ASPIRE study only included patients who had a history of nighttime low sensor glucose values. To be included in the study, patients had to have at least two low sensor glucose events (≤ 65 mg/dL) that lasted 20 minutes or longer during the run- in phase. As such, the magnitude of reduction in low sensor glucose event may be less significant in patients with fewer nighttime low sensor glucose events at baseline.

Data from the ASPIRE study supports the effectiveness of this device for its intended use. No conclusions can be made regarding the effectiveness of this device in reducing the rate, duration or severity of hypoglycemia. The extent of reduction in low sensor glucose event may vary in users with different historic rates of nighttime low glucose events.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory data, previous clinical data to support the original PMA approval as well as on data collected in the ASPIRE study as described above.

The following events are possible adverse device effects of inserting a sensor into the skin: local infection, inflammation, pain or discomfort, bleeding at the glucose sensor insertion site, bruising, itching, scarring or skin discoloration, hematoma, tape

irritation, sensor or needle fracture during insertion, wear or removal. There were no reports of subject death, unanticipated adverse device effect (UADE), diabetic ketoacidosis, or serious adverse events related to the device or study procedure during any of the clinical studies (G110044, G110131/A001 and G100028). No sensor breakage was documented in the clinical studies supporting approval of this device. Reported sensor breakage rate with similar devices has been very low, however, and this study was not powered or designed to assess the rate of breakage.

A minor risk of the CGM is that patients may need to perform unnecessary fingersticks to evaluate their blood glucose when the CGM gives false positive hypoglycemic and hyperglycemic readings or alerts. There is also a minor risk of skin irritation, inflammation, or infection due to either the sensor needle or the adhesive. However, CGM devices allow patients to measure the interstitial glucose at near continuous intervals to obtain a 24 hour picture of their glucose profile, especially during the night. Tracking and trending information is of value to patients and outweighs minor risks associated with fingersticks and the sensor.

There are additional risks due to missed alerts and false negative hypoglycemic and hyperglycemic readings related to patients not being alerted to the need to perform a fingerstick to detect hypoglycemia or hyperglycemia. Additionally, there is a risk associated with false alerts and false positive hypoglycemia and hyperglycemia readings related to the need to perform unnecessary fingersticks to confirm an erroneous low or high reading. Patients who only use blood glucose meters to manage their diabetes without the aid of a CGM would also be unaware of the need to perform additional testing to detect an abnormal blood sugar (unless they were exhibiting symptoms of an abnormal blood glucose).

The risks of inaccurate Enlite sensor glucose results is not unreasonably higher than the risk of managing diabetes with a blood glucose meter alone and these include incorrect tracking and trending or threshold detection; increased false negative and false positive low threshold alerts and alarms or high threshold alerts, and incorrect rate of change calculations that could adversely affect treatment decisions.. However, if the patient relies on sensor glucose values and does not perform fingerstick blood glucose tests as recommended (4-7 times daily) the risks of CGM use increases; especially if the sensor error results in failure to detect glucose out of the target glucose range (failure of Low and High alerts) or incorrect insulin dosing.

Inaccurate calculation of the rate of change of interstitial glucose by the CGM could result in failure to identify trends of increasing or decreasing glucose and alerts to the patient that an unplanned blood glucose check should be performed. Rate of change detection errors result in the patient losing the opportunity to perform additional blood glucose tests and take appropriate measures to stop a trend of increasing or decreasing glucose levels that could lead to serious hypoglycemia or hyperglycemia. Inaccurate calculation of the rate of change of glucose could also lead to unnecessary additional blood glucose tests. As discussed above the risk of using sensor rate of change information for making treatment decisions, rather than as a prompt for unplanned blood glucose checks, increases the risk of CGM use.

There are risks associated with using the Threshold Suspend tool. As with the sensor based alerts, the threshold alarm is subject to sensor errors that can result in missed hypoglycemia and no pump suspension, or inappropriate pump suspension when blood glucose is above the sensor suspend threshold (suspension in the absence of hypoglycemia) potentially resulting in hyperglycemia and ketosis. Under certain conditions of use after the initial 2-hour suspension the pump will resume insulin delivery but can re-suspend after a short period of time (as little as 5-minutes) rather than after 4 hours. Repeated pump suspensions, especially if the initial suspension was in error, increases the risk of more severe hyperglycemia, ketosis, and possibly DKA. Patients using insulin pumps can manually suspend insulin or set a temporary basal rate of zero at any time, which can also result in hyperglycemia, ketosis, and possibly DKA if the interruption of insulin delivery is prolonged.

Data from the ASPIRE study (G110044/S002) suggested that the use of the Threshold Suspend feature may potentially worsen glycemic control. Increased incidences of blood and urine ketones were observed in the Threshold Suspend group as compared to the Control group. When ketone levels were reported, the mean blood ketone concentration was higher in the Threshold Suspend group than in the Control group. In addition, more patients in the Threshold Suspend group reported positive ketone values when they exhibited symptoms (nausea, vomiting or abdominal pain). These hyperglycemia risks might be further amplified in patients with worse baseline control compared to those enrolled in the ASPIRE study. The risks of the Threshold Suspend tool can be mitigated if patients do not rely on the tool for treating or mitigating hypoglycemia if they are aware of Low Alerts or Threshold Suspend alarms, perform blood glucose checks, and treat hypoglycemia as instructed by their healthcare providers. Patients should also not rely on the sensor to detect hypoglycemia and perform blood glucose checks in response to symptoms of hypoglycemia.

Risks of the pump hardware problems include the following possible hypoglycemia from over-delivery of insulin due to a hardware defect; as well as hyperglycemia and ketosis possibly leading to ketoacidosis due to inappropriate insulin suspension or pump failure resulting in cessation of all insulin delivery due to either a hardware defect or software anomaly

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in previous clinical data to support the original PMA approval as well as on data collected in the ASPIRE study as described above.

The MiniMed 530G System is intended to assist patients in the management of their diabetes. The insulin infusion pump allows for continuous subcutaneous infusion of insulin at patient determined variable basal rates and intermittent patient directed bolus administration. The continuous glucose monitor provides near-continuous

interstitial glucose measurement by subcutaneous sensor and tracking and trending information to supplement blood glucose measurements.

The CGM component is intended to supplement self-monitoring of blood glucose to track and trend interstitial glucose levels as estimates of glucose excursions in the blood. The adjustable hypoglycemia and hyperglycemia alerts are intended to warn patients that they need to test their blood sugar to see if they need to take action to treat or prevent a hypoglycemic or hyperglycemic event. CGM measurements, which are performed every 5 minutes for 6 days via an indwelling sensor provide tracking and trending information to supplement the glucose meter measurements made four to seven times a day.

The use of the continuous glucose monitor gives patients and healthcare providers glucose tracking and trending information not feasible using traditional blood glucose monitoring as blood glucose meters only provide information about discrete, intermittent blood glucose levels. Patients and healthcare providers can review the tracking and trending data by day and time of day such as daytime or night time when fewer fingersticks are performed. The CGM includes a software package to aid in the evaluation of glucose trends over several days to detect patterns which may indicate a need to adjust therapy such as changes to basal rates and bolus dose instructions.

Furthermore, the continuous glucose monitors provide real time knowledge of interstitial glucose levels that can be displayed on the system screen. The system can be set to provide notifications based on sensor trends or thresholds adding information unavailable by traditional discrete monitoring. Trending information can be used to provide rate of change alerts that notify the patient that interstitial glucose is increasing or decreasing at a rate that raises concern for hyperglycemia or hypoglycemia. Threshold settings allow for high alerts, low alerts, and Threshold Suspend alarms. With the guidance of their healthcare provider the patient can set predictive or reactive high or low threshold to notify him or her that the sensor glucose is approaching (the case of the predictive) or has reached (in the case of the reactive) threshold of concern; the threshold for the Threshold Suspend tool can be similarly set to alarm and temporarily suspend insulin. These alerts and alarms are especially helpful for individuals with hypoglycemia unawareness (these individuals may develop severe hypoglycemia with loss of consciousness, seizures, or rarely death without the normal warning symptoms), or during the night when patients may have prolonged hypoglycemia that does not waken them and could proceed to severe hypoglycemia if not treated in time. Traditional blood glucose monitoring is not able to capture these potentially dangerous episodes of asymptomatic hypoglycemia. Therefore, if used as intended, this device provides significant benefit to patients not possible with traditional glucose monitoring.

The Threshold Suspend tool is an optional tool to temporarily suspend insulin delivery when the sensor glucose value reaches or goes below a preset threshold between 60 and 90 mg/dL. Hypoglycemia results because of a mismatch between the available insulin and glucose. When patients are aware of hypoglycemia by symptoms and or blood glucose check they have been instructed to treat with

carbohydrates (glucose), potentially suspend the insulin pump, and repeat a blood glucose check to ensure that their blood glucose is increasing to a safer range. However, patients can have hypoglycemia unawareness and or sleep through sensor based alerts so they are unable to treat low blood glucose as instructed. Therefore, temporarily suspending insulin delivery is a limited approach to decreasing the insulin-to-carbohydrate mismatch. The currently available technology allows for the sensor to measure interstitial glucose and suspend insulin delivery when a patient set threshold has been reached. The pump will resume insulin delivery after 2-hours have elapsed unless the patient ends the suspension earlier. Because patients with type 1 diabetes are absolutely dependent on insulin, longer suspensions increase the risk of serious hyperglycemia and ketosis.

Severe hypoglycemia can lead to seizures, unconsciousness and even death. Fear of hypoglycemia can limit the ability to adequately control hyperglycemia (which is associated with long term complications). The Threshold Suspend tool is the first step toward a fully autonomous system. Results from the ASPIRE study indicated that use of the Threshold Suspend feature can help to reduce the magnitude and duration of low sensor glucose events at night. Reduction in the magnitude and duration of nighttime low sensor glucose event in turn is likely to decrease the risk of nocturnal hypoglycemia. The greatest potential benefit of the Threshold Suspend may be for patients who have a history of hypoglycemia and who are unlikely to respond to CGM alarms and alerts at night. Potential risks of the Threshold Suspend tool include hyperglycemia, ketosis and ketoacidosis. Although not statistically powered, data from the ASPIRE in-home study suggested that using the Threshold Suspend feature may increase the risk of hyperglycemia and/or ketosis. Never-the-less, if used as intended and not as the primary method for the preventing hypoglycemia, the Threshold Suspend tool is likely to provide more benefit than risk.

The MiniMed 530G insulin pump remains unchanged as a result of this supplement. Benefits of insulin therapy with continuous insulin infusion include the ability to administer insulin frequently without repeated injection; the ability to set different basal rates through the day to better match basal insulin requirements which may fluctuate during the course of the day; the ability to calculate active insulin remaining from previous boluses to avoid “insulin stacking”, which can lead to hypoglycemia; the ability to administer bolus doses over an extended time; and the ability of patient to calculate appropriate bolus insulin doses based on and their individual needs.

Risks of the CGM and Sensor include the following:

- Sensor error resulting in incorrect tracking and trending or threshold detection; increased false negative and false positive low threshold alerts and alarms or high threshold alerts, and incorrect rate of change calculations that could adversely affect treatment decisions.
- Skin irritation, inflammation, or infection due to either the sensor needle or the adhesive
- Sensor may break leaving a sensor fragment under the skin

Risks of the Threshold Suspend tool include the following:

- The Threshold Suspend may inappropriately suspend insulin when blood glucose is above the sensor suspend threshold
- The Threshold Suspend may not appropriately suspend insulin when the blood glucose is at or below the sensor threshold suspend level
- Hyperglycemia and ketosis from automatic insulin suspension.

Risks of the pump hardware problems include the following:

- Hypoglycemia from over-delivery of insulin due to a hardware defect
- Hyperglycemia and ketosis possibly leading to ketoacidosis due to inappropriate insulin suspension or pump failure resulting in cessation of all insulin delivery due to either a hardware defect or software anomaly

Results from the ASPIRE study suggested that there were increased risks of hyperglycemia and potential DKA in subjects using the Threshold Suspend feature.

- Both blood ketones and urine ketones were more common in patients using Threshold Suspend. In addition,
- There was a trend towards higher glucose level in patients using Threshold Suspend (Hyperglycemia AUC with sensor glucose value > 180 mg/dL).

Though not definitive, these findings raise concern that there could be an increased risk for complications of hyperglycemia with use of the Threshold Suspend feature. This might be further amplified in patients with worse baseline control than the mean for the study population.

This supplement sought the addition of information in the labeling of this device which is already on the market. The potential risks for hyperglycemia and DKA identified above will be more transparent to the patient and their physician now that they are adequately described in the labeling.

In conclusion, given the available information above, the data support that the probable benefits continue to outweigh the probable risks of this device for the proposed intended use.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

The results of the pre-clinical testing and clinical trials to assess the performance of the MiniMed 530G System establish reasonable assurance that this system is safe and effective for its intended use when utilized in accordance with product labeling as an adjunct to information obtained from standard home glucose monitoring devices.

The benefits of using the System, as discussed above, outweigh the risks. In addition, the risks of using the System to determine diabetes therapy are mitigated by labelling.

The data presented in this submission continue to support the use of this device in the intended use population. The addition of information to the labelling about the potential for mild DKA and other limitations based on ASPIRE study results will aid patients and their healthcare providers in the safe use of this device.

XIII. CDRH DECISION

CDRH issued an approval order on October 2, 2015. The final conditions of approval are cited in the approval order.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.