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Study Title	Evaluation of Extended Wear Infusion Set (EWIS) in Patients with Type 1 Diabetes
NCT Number	NCT04113694
Document Description	Statistical Analysis Plan (Version 2.0)
Document Date	19-NOV-2020

Medtronic	**CONFIDENTIAL**	**DOCUMENT/RECORD**

Document Name		**RAD Version**
Statistical Analysis Plan		2.0

Title	CEP298

APPROVALS

Signed By	**Meaning of Signature**	**Date/Time (UTC)**
███████████	Document Approver	11/19/2020 04:44:13
███████████	Document Approver	11/19/2020 17:33:40
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Statistical Analysis Plan

Clinical Investigation Plan Title	Evaluation of Extended Wear Infusion Set (EWIS) in Patients with Type 1 Diabetes
Clinical Investigation Plan Identifier	CEP298
Sponsor/Local Sponsor	Medtronic MiniMed, Inc. ("Medtronic") 18000 Devonshire St Northridge, CA 91325 866.948.6633

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1.　Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	██████ Biostatistician
2.0	• Updated to 056-F286, Statistical Analysis Plan Template Version B • Updated version number and version date • Updated the following sections 　○ Section 7.1.3 updated definition of ITT and PP; specified analysis including primary, secondary, and descriptive endpoints. 　○ Section 7.4 specified the case of partially missing dates, times. 　○ Updated Section 7.11 due to the definition of ITT and PP.	██████ Biostatistician

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2.   List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
ADE	Adverse Device Effect
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CSII	Continuous Subcutaneous Insulin Infusion
DKA	Diabetic Ketoacidosis
EWIS	Extended Wear Infusion Set
FDA	United States Food and Drug Administration
GENMOD	Generalized Linear Model
HbA1c	Glycosylated hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IEC	Independent Ethic Committee
IFU	Instructions for Use
IRB	Institutional Review Board
ITT	Intention to Treat
MC2	Medtronic Core Clinical Solutions
OC-RDC	Oracle Clinical Remote Data Capture
PP	Per Protocol
RF	Radio Frequency
SAE	Serious Adverse Event
SADE	Serious Adverse Device Events
SMBG	Self-Monitoring of Blood Glucose
TLS	Transport Layer Security
UADE	Unanticipated Adverse Device Effect

3.   Introduction

Continuous subcutaneous insulin infusion (CSII) is an effective method for diabetic treatment. However, using current infusion sets, the insulin absorption decreases requiring patients to change infusion set every 2-3 days. Currently, the MiniMed Quick-set™ infusion sets are limited to 48-72 hours use (or per instruction by healthcare professionals). Medtronic Extended Wear Infusion Set (EWIS, MMT-405) should enhance patient wear time up to 7 days. This is done while maintaining insulin formulation stability (including physical, chemical, and microbiological stability) during infusion through the pump/infusion set system over extended time (up to 7 days).

This EWIS investigational device, as well as the early EWIS versions, has been used in previous animal/human feasibility trials, where the investigational device successfully extended the effective subcutaneous insulin infusion duration up to 7 days.

The purpose of this study is to collect confirmatory clinical data to support 6 or 7 days wear of EWIS.

4.   Study Objectives

The objective of this study is to evaluate the EWIS in patients with type 1 diabetes on insulin pump therapy.

5.   Investigation Plan

This study is a multi-center, non-randomized, prospective single arm study with type 1 patients with diabetes on insulin pump therapy with Continuous Glucose Monitoring (CGM).

The study is anticipated to last approximately 12 months from first subject enrollment to completion of all data entry. Subjects can expect to participate for approximately 12-16 weeks.

A total of up to 300 subjects will be enrolled at up to 20 investigational centers in the US in order to have 240 subjects meeting eligibility criteria. Each subject will wear their own MiniMed™ 670G insulin system. Each subject will be given 12 infusion sets to wear (each infusion set for at least 174 hours, or until infusion set failure if this occurs before 174 hours). The infusion set with the longest length (43 in) will be used for this study. Subjects will change insulin reservoirs at least every 174 hours. The infusion set(s) or reservoir(s) can be replaced independent of each other as referenced in the subject instructions. The time of infusion set insertion will be taken from Daily Log.

Infusion set failure used to determine primary endpoint is defined as any one of the following:

- Unexplained Hyperglycemia is defined as the following (See CEP298 Primary Effectiveness Endpoint Sections 4.2.2 and 13.5.2):
    - The study meter glucose >250 mg/dL (>3 hours post-meal) which may include time during subject's sleeping hours
    - Failure of a correction dose(s) to lower the study meter glucose by at least 50 mg/dL.
    - One additional correction dose may be given after first correction dose and recommended to use the bolus calculator. The infusion set may remain in the body if the glucose improves after second correction dose within 90 minutes. Please note: if the glucose improves after the correction doses, and the infusion set does not need to be changed then this would NOT be considered an adverse event (e.g. unexplained hyperglycemia) and NOT considered an infusion set failure.
    - SMBG should be checked every 60 minutes during this time
- The presence of serum ketones ≥ 0.6 mmol/L with a study meter glucose >250 mg/dL in the absence of illness and blood glucose that does not respond to insulin correction dose(s) as described above. (See CEP298 Primary Safety Endpoint Sections 4.2.1 and 13.5.1)
- There are signs of infection at the infusion site (i.e. erythema (> 1 cm in diameter) with warmth, pain, and/ or induration). (See CEP298 Primary Safety Endpoint Section 4.2.1 and 13.5.1)

Other known causes of infusion set failures which may or may not associated with hyperglycemia will be collected and analyzed as part of the overall safety assessment:

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- Accidental removals
- Leakage
- Loss of insertion (e.g. patient does not appear to be receiving insulin within 12 hours after infusion set is inserted)
- Kinked or bent cannula
- Removal due to discomfort at site
- Mechanical failure
- Adhesive issue

All severe hyperglycemic events as defined in CEP298 Section 10.2 will be summarized: whether they are device related or not or whether they are associated with infusion set failure or not.

At home, the subject will be expected to inspect their infusion site on a daily basis and if they observe signs of infection (i.e. erythema > 1 cm in diameter with warmth, pain, and/ or induration) at the infusion site, they should call the investigational center. Also, subjects are requested to upload data from their insulin pump and CONTOUR® NEXT LINK 2.4 study meter into CareLink™ Personal For Clinical Research weekly. In addition to the study procedures, the subjects are to continue their standard routine care.

At each study visit, insulin pump and CONTOUR® NEXT LINK 2.4 study meter will be uploaded into CareLink™ Personal For Clinical Research.

Subjects will be instructed to test their blood glucose using the CONTOUR® NEXT LINK 2.4 study meter at least 4-6 times each day (before meals and bedtime). Subjects will be instructed to check blood ketones using a Precision Xtra™* ketone meter if the CONTOUR® NEXT LINK 2.4 study meter reading is greater than 250 mg/dL (ketones do not need to be checked if it is less than 3 hours post-prandial).

Subjects will be required to upload their pump and glucose meter at Visit 2 in order to obtain the previous month of CareLink™ data.

Subjects will be considered for enrollment in the study if they meet all of the following criteria:
1. Subject is age 18 – 80 years at the time of screening
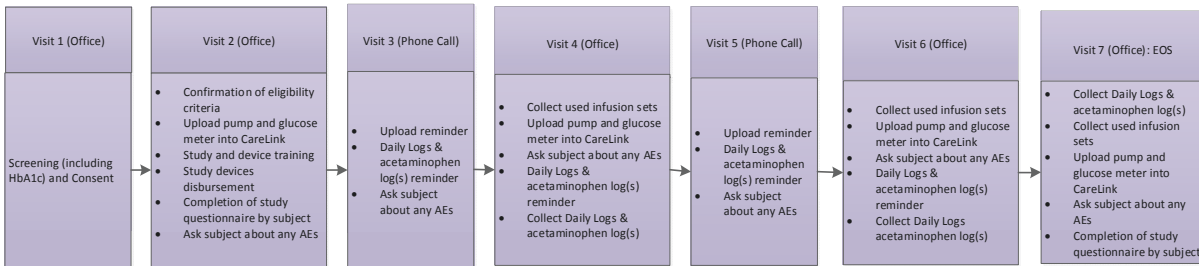2. Subject has type 1 diabetes for more than one year

Study specific inclusion criteria
3. Subject is on the MiniMed™ 670G insulin pump therapy within 1 year prior to screening and willing to utilize Auto Mode and CGM with Guardian™ Sensor (3) during the study.
4. Subject is willing and able to perform study procedures as per investigator discretion
5. Subject is willing to take one of the following insulins and can financially support the use of 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)

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Subjects who meet any of the following criteria are not eligible for study participation and **these exclusion criteria are study specific**:

1. 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.
2. Subject is female and has a positive pregnancy screening test
3. Subject is female of child bearing age and who is sexually active should be excluded if she is not using a form of contraception deemed reliable by investigator
4. Subject is female and plans to become pregnant during the course of the study
5. Subject has Glycosylated hemoglobin (HbA1c) > 8.5 % at time of screening.
   Note: All HbA1c blood specimens will be sent to and tested by a NGSP certified Central Laboratory. HbA1c testing must follow National Glycohemoglobin Standardization Program (NGSP) standards.
6. Subject has had a history of 1 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 [ER] or Hospitalization)
   b. Coma
   c. Seizures
7. Subject has taken any oral, injectable, or IV glucocorticoids within 8 weeks from time of screening visit, or plans to take any oral, injectable, or IV glucocorticoids during the course of the study.
8. Subject is unable to tolerate tape adhesive in the area of infusion set
9. Subject has any unresolved adverse skin condition in the area of infusion set placement (e.g., psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection)
10. Subject has infection in the area of infusion set placement at time of screening
11. Subject has had Diabetic Ketoacidosis (DKA) in the 12 months prior to screening visit.
12. Subject is currently abusing illicit drugs
13. Subject is currently abusing alcohol
14. Subject is on dialysis (for renal failure)
15. Subject has history of adrenal disorder
16. Subject has a history of inpatient psychiatric treatment in the past 6 months prior to screening
17. Subject has any condition that the Investigator believes would interfere with study participation
18. 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
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 is using pramlintide (Symlin), SGLT2 inhibitors, GLP agonists, biguanides, DPP-4 inhibitors or sulfonylureas more than 2 weeks from time of screening
22. Subject has been diagnosed with chronic kidney disease requiring dialysis or resulting in chronic anemia

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23. Subject has history of cardiovascular disease defined as any ischemic related event or clinically significant arrythmia.
24. Subject has hypothyroidism and has out of reference range thyroid-stimulating hormone (TSH) on screening visit (prior labs in the last 3 months are sufficient). Subject may repeat TSH draw to verify eligibility if not in range

Visit 1 (Office)	Visit 2 (Office)	Visit 3 (Phone Call)	Visit 4 (Office)	Visit 5 (Phone Call)	Visit 6 (Office)	Visit 7 (Office) : EOS
Screening (including HbA1c) and Consent	• Confirmation of eligibility criteria • Upload pump and glucose meter into CareLink • Study and device training • Study devices disbursement • Completion of study questionnaire by subject • Ask subject about any AEs	• Upload reminder • Daily Logs & acetaminophen log(s) reminder • Ask subject about any AEs	• Collect used infusion sets • Upload pump and glucose meter into CareLink • Ask subject about any AEs • Daily Logs & acetaminophen log(s) reminder • Collect Daily Logs & acetaminophen log(s)	• Upload reminder • Daily Logs & acetaminophen log(s) reminder • Ask subject about any AEs	• Collect used infusion sets • Upload pump and glucose meter into CareLink • Ask subject about any AEs • Daily Logs & acetaminophen log(s) reminder • Collect Daily Logs acetaminophen log(s)	• Collect Daily Logs & acetaminophen log(s) • Collect used infusion sets • Upload pump and glucose meter into CareLink • Ask subject about any AEs • Completion of study questionnaire by subject

6.   Determination of Sample Size

The infusion set failure rate due to unexplained hyperglycemia (i.e. suspected occlusion) of 16% (FDA response Q180616/S001), around 20% upper limit, was used when generating simulation dataset for Day 6 and Day 7 evaluations, as supported by discussions with the Agency. Sample size estimation was performed based on data from Dr. Buckingham EWIS data in 2018 (20 subjects each wore 2 EWIS infusion sets with no missing data). The suspected occlusion occurrence rate was 12.5%. Subjects were sampled to enter the simulation dataset with a vector of 12 measurements (12 EWIS wears). The resulting simulation datasets have correlated occurrence rates. Therefore, a repeated-measure Generalized Linear Model (GENMOD) was used to determine the upper boundary of the occurrence rate. Using all available data for each subject, the intercept of a null GLM model, with a repeated factor for infusion set wear day, was used to estimate the overall occurrence rates. A simulation was performed 1000 times and the upper boundary of the intercept of the GENMOD was tested against the critical value of 20%. The results of the simulation indicated that a sample size of 100 per insulin group will yield power of over 80% to demonstrate that the infusion set failure rate due to unexplained hyperglycemia is not inferior to 20%, with two sided 0.05 significance level, which will ensure that ≤16% rate is achieved.

So, a total of up to 300 subjects will be enrolled at up to 20 investigational centers in the US in order to have 240 subjects meeting eligibility criteria. Subjects will be replaced who have early withdrawal.

- Insulin Utilization
    - N = 100 Humalog™*
    - N = 100 Novolog™*

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7.   Statistical Methods

7.1   Study Subjects

7.1.1   Disposition of Subjects
The number of subjects enrolled in the study will be presented. The reasons for discontinuing prior to study completion will be summarized.

7.1.2   Clinical Investigation Plan (CIP) Deviations
All protocol deviations will be presented in the listings.

7.1.3   Analysis Sets
- Intention to Treat (ITT) Population

    The primary study population is the Intention to Treat (ITT) population with at least one EWIS Infusion set inserted. Primary, secondary effectiveness endpoints, and descriptive endpoints will be evaluated for ITT population.

- Per Protocol (PP) Population

    The Per Protocol (PP) population will include all subjects with no major deviations (i.e., meet the inclusion/exclusion criteria) and complete 12 sets of infusion set wears. Primary and secondary effectiveness endpoints will be evaluated for PP population.

- Safety Population

    The Safety Population will include all enrolled subjects.

7.2   General Methodology

7.2.1   Primary Safety Endpoint

- Incidence of Serious Adverse Events (SAE)
- Incidence of Serious Adverse Device Effects (SADE)
- Incidence of Unanticipated Adverse Device Effects (UADE)
- Incidence of Severe Hypoglycemia
- Incidence of Severe Hyperglycemia
- Incidence of DKA
- Incidence of skin infections at infusion set insertion site

7.2.2   Primary Effectiveness Endpoint

The primary effectiveness endpoints will be independently evaluated in blocks of 2 in the study. Analysis will be done in the blocks of 2 insulin types as:
- Novolog™*

• Humalog™*

Rate of infusion set failure due to unexplained hyperglycemia (i.e. suspected occlusion) at the end of Day 6. The rate of infusion set failure is defined as the number of infusion set removals associated with unexplained hyperglycemia divided by total number of infusion sets inserted.

7.2.3   Secondary Effectiveness Endpoint

The secondary effectiveness endpoints will be evaluated only when the primary endpoint is met. This analysis will be independently done in blocks of 2 insulin types in the study:

• Novolog™*
• Humalog™*

Rate of infusion set failure due to unexplained hyperglycemia (i.e. suspected occlusion) at the end of Day 7. The rate of infusion set failure is defined as the number of infusion set removals associated with unexplained hyperglycemia divided by total number of infusion sets inserted.

7.2.4   Descriptive Endpoints

• Descriptive summary of all infusion set failures and the day they failed. All causes of infusion set failures, such as removal due to discomfort of site, accidental removals, kinked or bent cannula, leakage, loss of insertion (e.g. patient does not appear to be receiving insulin within 12 hours after infusion set is inserted), mechanical failure, and adhesive issue will be collected and analyzed.

• HbA1c changes from baseline to the end of study.

• All severe hyperglycemic events as defined in CEP298 Section 10.2 will be summarized whether they are device related or not or whether they are associated with infusion set failure or not.

• Descriptive summary of infusion set change at baseline

7.2.5   Device Deficiencies

Descriptive summary will be used to characterize device deficiencies.

7.2.6   Subject Feedback

Descriptive summary will be used to characterize study questionnaire results.

7.3   Center Pooling

Data will be pooled for analysis.

7.4   Handling of Missing, Unused, and Spurious Data and Dropouts

In the case of partially missing day and/or month, the first day of the month will be used for event dates with known year and month but unknown day, unless specified otherwise in the description; similarly,

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the first day of the year will be used for event dates with known year but unknown month and day, unless specified otherwise.

In the case of partially missing time, 12 am will be used for event times with known day but unknown time, if applicable.

No additional imputation will be applied for the missing data.

7.5   Demographic and Other Baseline Characteristics

Subject characteristics, including age, gender, race, ethnicity, medical diagnosis, height, weight, BMI, and baseline HbA1c will be summarized by descriptive statistics (mean, standard deviation, minimum, median, and maximum) for continuous variables and by counts and percentages for categorical variables.

7.6   Treatment Characteristics

Not applicable.

7.7   Interim Analyses

Not applicable.

7.8   Evaluation of Objectives

7.8.1   Primary Safety Endpoint

- Incidence of Serious Adverse Events (SAE)
- Incidence of Serious Adverse Device Effects (SADE)
- Incidence of Unanticipated Adverse Device Effects (UADE)
- Incidence of Severe Hypoglycemia
- Incidence of Severe Hyperglycemia
- Incidence of DKA
- Incidence of skin infections at infusion set insertion site

7.8.2   Primary Effectiveness Endpoint

The primary effectiveness endpoints will be independently evaluated in blocks of 2 in the study. Analysis will be done in the blocks of 2 insulin types as:

- Novolog™*
- Humalog™*

Rate of infusion set failure due to unexplained hyperglycemia (i.e. suspected occlusion) at the end of Day 6. The rate of infusion set failure is defined as the number of infusion set removals associated with unexplained hyperglycemia divided by total number of infusion sets inserted.

The hypothesis is that the overall rate of infusion set failure due to unexplained hyperglycemia (i.e. suspected occlusion) at the end of day 6 is not inferior to 20%, with two sided 0.05 significance level,

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which will ensure the mean rate of infusion set failure due to unexplained hyperglycemia is ≤ 16%. The hypothesis is mathematically expressed as:

H0: μ ≥ 0.20

Ha: μ < 0.20

Where μ is the mean rate of infusion set failure due to unexplained hyperglycemia at the end of day 6.

A generalized estimating equation method model will be used. The one sided 97.5% upper confidence limit of the failure rate will be tested against the threshold of 20%. For the GEE model, Exchangeable (exch) or Auto-regressive (AR1) or Independence (IND) correlation structure will be used, based on quasi-AIC (QIC). Site effect will be evaluated. If it is significant (p-value less than or equal to (≤) 0.1), site will be included in the model so as to obtain the adjusted confidence limit.

7.8.3   Secondary Effectiveness Endpoint

The secondary effectiveness endpoints will be evaluated only when the primary endpoint is met. This analysis will be independently done in blocks of 2 insulin types in the study:

- Novolog™*
- Humalog™*

Rate of infusion set failure due to unexplained hyperglycemia (i.e. suspected occlusion) at the end of Day 7. The rate of infusion set failure is defined as the number of infusion set removals associated with unexplained hyperglycemia divided by total number of infusion sets inserted.

The hypothesis is that the overall rate of infusion set failure due to unexplained hyperglycemia (i.e. suspected occlusion) at the end of day 7 is not inferior to 20%, with two sided 0.05 significance level, which will ensure the mean rate of infusion set failure due to unexplained hyperglycemia is ≤16%. The hypothesis is mathematically expressed as:

H0: μ ≥ 0.20

Ha: μ < 0.20

Where μ is the mean rate of infusion set failure due to unexplained hyperglycemia at the end of day 7.

A generalized estimating equation method model will be used. The one sided 97.5% upper confidence limit of the failure rate will be tested against the threshold of 20%. For the GEE model, Exchangeable (exch) or Auto-regressive (AR1) or Independence (IND) correlation structure will be used, based on quasi-AIC (QIC). Site effect will be evaluated. If it is significant (p-value less than or equal to (≤) 0.1), site will be included in the model so as to obtain the adjusted confidence limit.

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7.8.4   Descriptive Endpoints

- Descriptive summary of all infusion set failures and the day they failed. All causes of infusion set failures, such as removal due to discomfort of site, accidental removals, kinked or bent cannula, leakage, loss of insertion (e.g. patient does not appear to be receiving insulin within 12 hours after infusion set is inserted), mechanical failure, and adhesive issue will be collected and analyzed.

- HbA1c changes from baseline to the end of study.

- All severe hyperglycemic events as defined in CEP298 Section 10.2 will be summarized whether they are device related or not or whether they are associated with infusion set failure or not.

- Descriptive summary of infusion set change at baseline

7.8.5   Device Deficiencies

Descriptive summary will be used to characterize device deficiencies.

7.8.6   Subject Feedback

Descriptive summary will be used to characterize study questionnaire results.

7.9   Safety Evaluation

- Incidence of Serious Adverse Events (SAE)
- Incidence of Serious Adverse Device Effects (SADE)
- Incidence of Unanticipated Adverse Device Effects (UADE)
- Incidence of Severe Hypoglycemia
- Incidence of Severe Hyperglycemia
- Incidence of DKA
- Incidence of skin infections at infusion set insertion site

7.10 Health Outcomes Analyses

Descriptive summary will be used to characterize data from questionnaires that are given to subjects to record feedback.

7.11 Changes to Planned Analysis

The definition of Intention to Treat (ITT) population in the CEP298 has been updated to "subjects who have at least one EWIS Infusion set inserted".

The definition of Per Protocol (PP) population in the CEP298 has been updated to "subjects who have no major deviations (i.e., meet the inclusion/exclusion criteria) and complete 12 sets of infusion set wears".

8.   Validation Requirements

Level I or Level II validation are required for analysis output. Level I requires that the peer reviewer independently programs output and then compares the output with that generated by the original

Statistical Programmer. Level II requires that the peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output.

9.   References

American Diabetes Association. Hyperglycemic Crises in Diabetes. Diabetes Care. 2004; 27(1):S94-S102.

American Diabetes Association Workgroup on Hypoglycemia. Defining and Reporting Hypoglycemia in Diabetes, Diabetes Care. 2005; 28: 1245-1249