STUDY DESIGN OF RANDOMIZED, ADAPTIVE TRIAL IN ADULT AND PEDIATRIC PATIENTS WITH TYPE 1 DIABETES USING HYBRID CLOSED LOOP VS CONTROL (CSII, MDI OR SAP)

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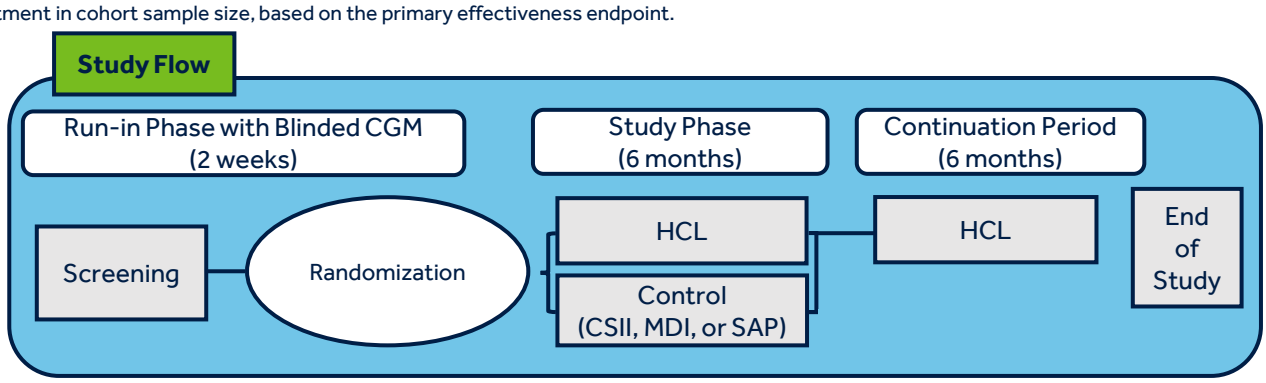
Introduction

The MiniMed™ 670G system with SmartGuard™ technology that automates basal insulin delivery has been studied in adult,[1] adolescent,[1] and pediatric[2] populations and is, commercially available in United States. A prospective randomized trial[3] comparing outcomes of T1D patients using the MiniMed™ 670G hybrid closed-loop (HCL) system to those of patients using other T1D therapies: continuous subcutaneous insulin infusion (CSII), multiple daily injections (MDI) of insulin, or sensor-augmented pump (SAP) has started. The design of this prospective randomized trial is presented here.

Methods

This 6-month randomized, adaptive study in T1D patients aged 2-80 years targets enrollment of approximately 1120 subjects in over 70 investigational centers (United Sates and International). Patient outcomes after use of the MiniMed™ 670G system, CSII, MDI, or SAP will be compared, and patients will have the option to continue using the MiniMed™ 670G system through a voluntary continuation access period. After blinded continuous glucose monitoring (CGM) and current therapy during a 2-week run-in phase, participants will be randomized to use the MiniMed™ 670G system or remain on their current therapy (control). The co-primary effectiveness endpoints are change in HbA1c among Group 1 (Baseline HbA1c > 8%) and time in hypoglycemic range among Group 2 (Baseline HbA1c ≤ 8%). If superiority is established, key secondary endpoints including time in range for Group 1 and change in HbA1c for Group 2 will be further evaluated with non-inferiority tests. Safety endpoints include diabetic ketoacidosis (DKA), severe hypoglycemia, severe hyperglycemia, serious adverse events (SAEs), and unanticipated adverse device effects (UADEs). A Data Safety Monitoring Board has been established to review safety data and an interim analysis will be performed to allow for adjustment in cohort sample size, based on the primary effectiveness endpoint.



Primary Effectiveness Endpoints:

Group 1: Baseline HbA1c >8%: Change in HbA1c

Change in HbA1c, defined as HbA1c measured at the 6-month treatment visit minus that measured at the randomization visit, will be analyzed. The goal is to show superiority of the HCL treatment arm compared to the control arm in reducing HbA1c.

Group 2: Baseline HbA1c ≤8%: Time in Hypoglycemic Range

Time with SG spent <70 mg/dL (<3.9 mmol/L) during the 6-month study period will be analyzed. The goal is to show superiority of the HCL arm compared to the control arm in reducing time spent in hypoglycemic range.

Key Secondary Effectiveness Endpoints:

Group 1: Baseline HbA1c >8%: Time in Hypoglycemic Range

Time with SG spent <70 mg/dL (<3.9 mmol/L) during the 6-month study period will be analyzed. The goal is to show non-inferiority of the HCL treatment arm compared to the control arm in reducing time spent in hypoglycemic range.

Group 2: Baseline HbA1c ≤8%: Change in HbA1c

Change in HbA1c, defined as HbA1c measured at the 6-month treatment visit minus that measured at the randomization visit, will be analyzed. The goal is to show non-inferiority of the HCL arm compared to the control arm in reducing HbA1c.

Additional Secondary Effectiveness Endpoints:

Hierarchically ordered endpoints that will be evaluated in a fixed sequence from endpoint 1 to 5, during the first 6 months of the study phase, are listed below.

1. Group 1 + Group 2: Time in Hypoglycemic Range during the Night

Time with SG <70 mg/dL (<3.9 mmol/L) during the night will be evaluated in the combined Groups. The goal is to show superiority of the HCL arm compared to the control arm in reducing night time hypoglycemia.

2. Group 1 + Group 2: Time in Hypoglycemic Range during the Day and Night

Time in hypoglycemic range below 70 mg/dL (3.9 mmol/L) will be evaluated in the combined Groups. The goal is to show superiority of the HCL arm compared to the control arm in reducing day and night time hypoglycemia.

Additional Secondary Effectiveness Endpoints (cont.):

3. Group 1 + Group 2: Time in Target Range during the Night

Time with SG in target range (70 mg/dL-180 mg/dL, 3.9 mmol/L-10.0 mmol/L) during the night time will be analyzed. The goal is to show superiority of the HCL arm compared to the control arm in improving the time in target range during the night time.

4. Group 1 + Group 2: Time in Target Range during the Day and Night

Time with SG in target range 70 mg/dL-180 mg/dL (3.9 mmol/L-10.0 mmol/L) during the day and night time will be analyzed. The goal is to show superiority of the HCL arm compared to the control arm in improving the time in target range during the day and night time.

5. Group 1 + Group 2: Change in HbA1c

Change in HbA1c will be evaluated for superiority in the combined groups. The goal is to show superiority of the HCL arm compared to the control arm in reducing HbA1c from baseline to the end of the 6-month treatment period.

Status Update

- **CSII/HCL Cohort**: There have been 241 subjects enrolled in over 16 investigational sites.
- **SAP/HCL Cohort**: Initiated the end of January, 2018.
- **MDI/HCL Cohort**: Initiated the end of January, 2018.

Conclusions

This study will assess the safety and effectiveness of the MiniMed™ 670G HCL insulin delivery system compared to CSII, MDI, and SAP in a wide age range of T1D patients.

References

1. Garg SK, et al. *Diabetes Technol Ther.*2017;19:155-163.
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