Efficacy and Safety Comparison between U-100 Regular Human Insulin and Rapid Acting Insulin when Delivered by V-Go® Wearable Insulin Delivery in Type 2 Diabetes

Coordinating Investigator

Pablo Mora, MD, FACE, CDE
Dallas Diabetes Research/UTSW
4800 Stranz Lane
Plano, TX 75093
469.585.0000
pf_mora@yahoo.com

Investigators

David Sutton, MD, FACE- Principal Investigator, NEFEDA
Northeast Florida Endocrine and Diabetes Associates
915 W. Monroe Street, Suite 200
Jacksonville, FL 32204
904.304.8101
davidsutton5@me.com

Ashwini Gore, MD- Principal Investigator, The Jones Center
The Jones Center for Diabetes and Endocrine Wellness
265 Sheraton Blvd, Suite 100
Macon, GA 31210
478-746-8626
goreash@gmail.com

Rebecca Goldfaden, PharmD, CCRP
East Coast Institute for Research, LLC
3550 University Blvd. South, Suite 101
Jacksonville, FL 32216
904-854-1354
Rebecca.goldfaden@ecirmed.com

Rushab Choksi, PharmD
East Coast Institute for Research, LLC
3550 University Blvd. South, Suite 101
Jacksonville, FL 32216
904-854-1354
Rushab.choksi@eastcoastresearch.net

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Short Title: Regular Insulin vs Rapid Insulin Delivered by V-Go

Protocol Date: October 29, 2018

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ABBREVIATIONS USED in the protocol

Abbreviation	Term
ADA	American Diabetes Association
AE	Adverse Event
A1C	Glycosylated Hemoglobin A1C
BID	Twice a Day
BMI	Body Mass Index
CSII	Continuous Subcutaneous Insulin Infusion
ECIR	East Coast Institute for Research
HCP	Health Care Professional
GCP	Good Clinical Practice
ICF	Informed Consent Form
MDI	Multiple Daily Injections
NEFEDA	Northeast Florida Endocrine and Diabetes Associates
NIGLM	Non-insulin Glucose Lowering Medications
QD	Once a Day
RAI	Rapid Acting Insulin
RHI	Regular Human Insulin
SAE	Serious Adverse Event
SMBG	Self-monitored Blood Glucose
TDD	Total Daily Dose of Insulin
T2D	Type 2 Diabetes
V-Go	V-Go Wearable Insulin Delivery Device

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1 BACKGROUND AND SIGNIFICANCE

According to the American Diabetes Association the cost to treat diabetes has risen to $245 billion of which antidiabetic medications including insulin accounts for 12% of the total costs.[1] People with diagnosed diabetes incur average medical expenditures of approximately $13,700 per year creating a high cost burden carried by themselves and insurers.[1] As the population ages and as disease progresses, the amount of medications prescribed will increase which can further escalate the financial burden to both the subject and health care system.

With the progression of diabetes, insulin therapy is warranted for most subjects and many require both fasting and prandial insulin due to inadequate insulin secretion and insulin resistance in type 2 diabetes. Different types of insulin are available with new analogue insulins typically preferred over RHI (RHI) due to improved insulin profiles and a more predictable glucose response when given via subcutaneous injection. [2] Ninety-six percent (96%) of subjects with type 2 diabetes who take insulin in the United States use analog insulin(s). This is an increase from 19% in the year 2000. [3,4] In subjects prescribed basal-bolus or bolus-only therapy, rapid acting insulin (RAI) analogs have surpassed usage of RHI. However, the steep increase in the cost of RAI has led to rationing of insulin or the total discontinuance of therapy by many subjects due to cost. [5] The lack of affordability of RAI has forced the clinical and economic benefits of RAI to be reconsidered in clinical practice and in literature. For many subjects, RHI provides a more affordable option for insulin therapy when compared to RAIs, especially if the limitations of the insulin profile can be overcome by delivering RAI through continuous subcutaneous insulin infusion (CSII) using a wearable insulin delivery device.

V-Go (Valeritas, Inc. Bridgewater, NJ) is worn like a patch, and insulin is initiated when the subject presses a button to insert a small needle subcutaneously. Once the needle is inserted, a continuous basal rate of insulin is delivered for 24 hours, and on-demand bolus dosing of insulin can be administered in 2-unit increments to meet prandial (mealtime) insulin needs by pressing two buttons.[6] Tubing, programming, or batteries are not required with V-Go, unlike other CSII devices. V-Go is cleared by the FDA for use with a U-100 fast-acting insulin (e.g. insulin lispro, insulin aspart) and has been proven to improve clinical outcomes with less insulin.

Research has demonstrated as the cost of treatment increases the patient adherence decreases, which can be associated with poor health outcomes.[7,8,9] Based on the rising costs for insulin analogs, investigating the prospective use of RHI delivered with V-Go could be a viable option

to decrease costs while improving glycemic control. The utilization of RHI addresses the issue of affordability and cost challenges for many subjects and insurance plans.

2 ETHICS

2.1 Good Clinical Practice (GCP)

This study will be conducted in accordance with Good Clinical Practice (GCP), in accordance with the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). The study will be conducted in compliance with the protocol.

All potential protocol deviations or violations must be reported to the IRB immediately. A protocol deviation or violation is defined as a violation of the GCP guidelines regarding the study protocol, which is likely to significantly affect the safety of the subjects in the study or the scientific validity of the study. Study staff involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks and this study will not use study staff where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board (IRB)

Before initiation of the study, the investigator must have received IRB approval for the protocol, ICF, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects.

During the clinical study, any amendment to the clinical trial protocol must be submitted to the IRB before implementation, unless the change is necessary to eliminate an immediate hazard to the subjects, in which case the IRB should be informed as soon as possible. The IRB should also be informed of any event likely to change the safety of subjects in the clinical trial. The investigator must send a progress report to the IRB at least annually, as well as a summary of the clinical trial's outcome at the end of the clinical trial.

2.3 Informed Consent

The investigator will ensure that the ICF includes all elements required by GCP and applicable regulatory requirements, as well as follow the ethical principles within the Declaration of Helsinki. The investigator will ensure that the ICF is reviewed and approved by the IRB prior to use in a clinical trial.

The Investigator, or a person designated by the Investigator, should fully inform the subject of all relevant aspects of the clinical trial including the purpose, potential risks, required procedures, etc. in which they volunteer to participate. All subjects should be informed about the study, in a language and at a level they are able to understand. In circumstances where consent cannot be given to subjects, their legally acceptable representatives must be clearly and fully informed about the purpose, potential risks, required procedures, etc. regarding the clinical trial in which the subject will participate

Prior to a subject's participation in the clinical trial, the written ICF should be signed and dated personally by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written ICF will be provided to the subject.

3 HYPOTHESIS

Subjects administering RAI with V-Go can be safely switched to U-100 RHI delivery with V-Go and maintain similar glycemic control measured by glycated hemoglobin (A1C).

4 PRELIMINARY DATA

V-Go has been previously demonstrated to be safe for use with RAI, and has been shown to allow subjects to achieve improved blood sugar control with a continuous preset basal rate of insulin and on-demand mealtime bolus dosing (10-13). RHI U-100 has been reported to be stable in V-Go devices and clinical findings from two small retrospective studies have demonstrated efficacy and safety using U-100 RHI in V-Go.

Available data for use of RHI U-100 with V-Go (14-16)

Stability Study

For insulin delivery devices it is important to assess the stability of the insulin used within the device, to understand if different types of insulin have differing stability profiles, and to determine if insulin stability is impacted by pre-filling and storage conditions. The purpose of the study was to evaluate the stability (up to 6 days) of RHI U-100 when used with V-Go.

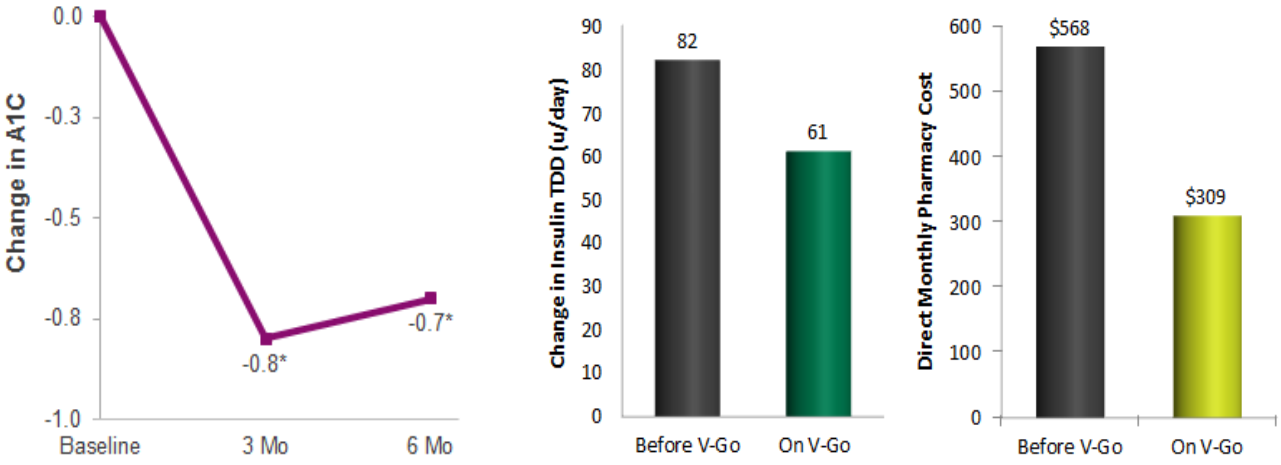
V-Go devices were filled using the EZ Fill™ adapter with RHI and stored at 77°F for 1, 3, and 5 days followed by 1 day (24 hours) at 86°F to simulate potential actual-use.
The data demonstrated 6 days of stability for RHI U-100. All tests performed met specifications at all time-points.

Clinical Retrospective Analyses

A retrospective analysis was conducted by querying an electronic medical records database for subjects administering RHI U-100 with V-Go at a large endocrine practice in Jacksonville, Florida.

Eleven subjects meeting the inclusion criteria were evaluated. At baseline, 7 subjects were on basal-bolus insulin injections, 1 subject was on basal-only insulin, 2 subjects were on pre-mix insulin injections, and 1 subject was naive to insulin therapy prior to RHI delivery via V-Go. Baseline mean A1C was 8.6% (6.0% - 10.7%) and mean insulin total daily dose (TDD) was 82 U/day. After 6 months, A1C was significantly reduced by 0.7% (p=0.029) and mean TDD decreased to 61 U/day reflecting a 26% insulin dose reduction as shown in **Figure 1**. Body weight remained stable. At baseline, the direct pharmacy cost per subject per month for insulin therapy was $568 which was reduced to $309 for V-Go with RHI. Costs were calculated using wholesale acquisition cost and retail pricing**, Figure 1**.

Figure 1. Change in A1C, Insulin Total Daily Dose and Direct Pharmacy Cost



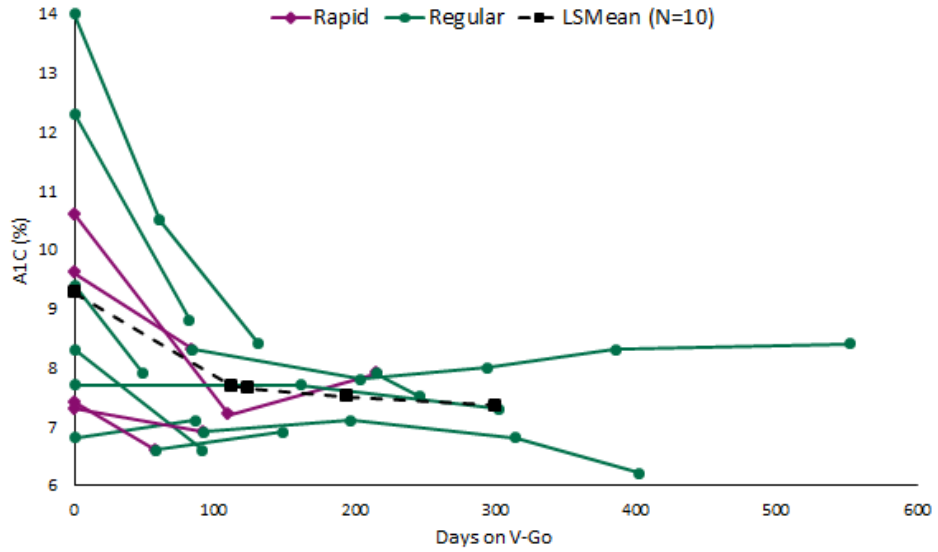
Change in A1C
*N=11 at 3 months, p=0.032, compared to baseline A1C of 8.6%
**N=11 at 6 months with 1 LOCF

Insulin and Direct Pharmacy costs at 6 months
Direct pharmacy pricing per subject/month based on wholesale acquisition costs.
Insulin pricing reflects ReliOn® insulin, manufactured for Walmart Inc.

A second retrospective analysis was conducted by a specialized diabetes system across Texas and evaluated change in A1C, insulin dosing, weight and subject reported severe hypoglycemia when using RHI (RHI) U-100 in V-Go after the cost of insulin was identified as a subject concern. Data was collected using electronic medical records. Ten subjects with T2D (mean age

65 y; duration of diabetes 15 y; A1C 9.3%; weight 96 kg) were evaluated of which 9 were administering insulin (mean TDD 99 U/day) at baseline. V-Go was initiated in 6 subjects using RHI and 4 transitioned to RHI following the use of rapid acting insulin (RAI) first in V-Go. Hierarchical linear models were developed for statistical evaluations. A1C results over time are shown in **Figure 2**. Model adjusted A1C and TDD decreased significantly from baseline ($p<0.001$), with a least squares mean change of -1.8% in A1C and -46 U/day in TDD following a mean of 194 $\pm$ 159 days on V-Go therapy for all subjects. Weight did not significantly change from baseline ($p=0.175$). Regardless of initiating V-Go therapy with RHI or transitioning to RHI from RAI, similar changes in A1C, insulin, and weight were observed over time.

Figure 2. A1C by Insulin Type used in V-Go over Time



A1C over Time
N=10 subjects (6 subjects initiated V-Go with regular insulin, 4 subjects transitioned from using rapid to regular insulin in V-Go).
Solid lines represent mean A1C values by days on V-Go for each subject. Type of insulin is differentiated for 4 subjects transitioned from rapid insulin (purple) use first in V-Go to regular insulin (green) use in V-Go.
Dashed line represents least squares mean A1C values for all 10 subjects calculated using a hierarchical linear model with the baseline A1C and a natural log of days on V-Go as independent variables.

V-Go Wearable Insulin Delivery system was first cleared for use by the FDA in December 2010. V-Go Wearable Insulin Delivery system is considered a non-significant risk device according to the following criteria as defined in 21 CFR 812.3 (m):

- The study is of a device that does not present a potential for serious risk to the health, safety, or welfare of a subject;
- Is not an implant;
- Is not used in supporting or sustaining human life;

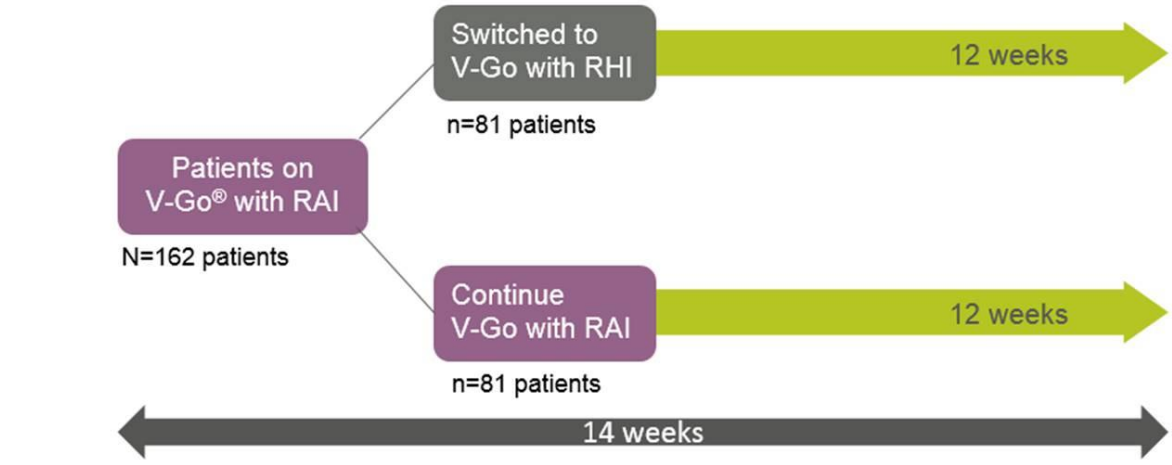
- Is not of substantial importance in diagnosing, curing, mitigating or treating disease or otherwise prevents impairment of human health; and
- Does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

5 STUDY DESIGN

5.1 Description

This is a multi-center prospective, randomized, parallel, non-inferiority 14-week study comparing the efficacy and safety of U-100 RHI to RAI analog in a T2D population already using V-Go Wearable Insulin Delivery device filled with RAI.

Study to be conducted in a real-world practice setting under usual standard of care. All participating subjects must have been prescribed RAI delivered by V-Go as part of their diabetes treatment prior to study enrollment. All subjects agreeing to participate in the study will continue use of V-Go for insulin delivery and will be randomized to either continue with RAI delivered by V-Go or will switch to U-100 RHI delivered by V-Go following enrollment. All subjects will also agree to continue to monitor blood glucose values via their personal glucometer.



Visit	Visit 1	Visit 2	Visit 3	Visit 4
Week	- 2 (±3 days)	0 (±3 days)	2 (±3 days)	12 (±3 days)
Evaluate	HbA1c	7 point SMBG	7 point SMBG	7 point SMBG HbA1c

5.2 Study Population

5.2.1 Study Subjects and Approximate Number of Subjects

This is a multi-center study which will include the participation of approximately 162 subjects (81 subjects per study arm).

5.2.2 Eligibility Criteria

Inclusion Criteria:

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Age ≥ 21 years at time of study enrollment
2. Diagnosed with T2D for at least 6 months prior to screening
3. Screening visit A1C ≥ 6.5% and ≤ 12.5%
   Note: One re-assessment during the screening period is allowed in case the A1c is within 0.2% of the inclusion criteria at the Screening Visit
4. Prescribed a stable (less than 20% change in the past 30 days) of rapid acting U-100 insulin delivered via V-Go insulin delivery device
5. Ability to read and understand English
6. Willing to complete all study related activities
7. Willing and able to understand and sign a written ICF indicating that they agree to participate and have been informed of all pertinent aspects of the study
8. Must be willing to take and record 7 glucose measurements per time period (pre-morning meal (fasting), pre-midday meal, pre-evening meal, and 2-hours after the start of the morning, midday, and evening meals, and at bedtime) three times throughout the study (prior to Visit 2, 3, and 4).
9. Completed a 7-point glucose profile prior to Visit 2
10. Able (by insurance or financial means) to cover the initial investment and ongoing cost of the V-Go insulin delivery device, insulin (current rapid acting insulin or potential new regular human insulin), personal glucometer and supplies for the length of the study.

Exclusion Criteria:

Subjects presenting with any of the following exclusion criteria will not be eligible for enrollment into the study:

1. Subject with confirmed Type 1 diabetes

2. More than 1 episode of severe hypoglycemia (defined as requiring third party assistance) within 3 months of study entry
3. History of hypoglycemia unawareness
4. Require supplemental insulin in addition to V-Go therapy
5. Woman of child-bearing potential who has a positive pregnancy test at screening or plans to become pregnant during the course of the study. Women of childbearing potential are defined as any female who has experienced menarche and who it NOT permanently sterile of postmenopausal. Postmenopausal is defined as 12 consecutive months with no menses without and alternative medical cause.
6. Woman who are lactating.
7. Use of any 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. Stable doses of oral steroids (same daily oral dose for at least 4 weeks) is allowed.
8. A recipient of a solid organ transplant
9. Current use of U-100 RHI in V-Go within 90 days of screening
10. Current use of U-500 RHI in V-Go within 90 days of screening
11. Currently unstable on dialysis, according to investigator's discretion
12. Medical or other problems which in the opinion of the investigator will render study participation unsafe.

5.3 Study Duration

5.3.1 Approximate Duration of Subject Participation

Subjects will actively participate in the study for approximately 14 weeks (including screening) in order for the investigator to collect clinical data from their baseline (Day 0) and scheduled follow-up visits (visit 3 and visit 4).

Discontinuation will be based upon investigator's clinical determination and/or by subject decision. All subjects are free to terminate their participation in the study at any time, and the details regarding discontinuation will be recorded.

5.3.2 Withdrawal documentation

The subject may withdraw consent at will at any time. The subject's request to withdraw from the trial must always be respected. In case of withdrawal, the investigator will record the reason for subject's withdrawal, schedule a clinic visit to capture any glucose

logs after being notified of subject's withdrawal, and continue to follow-up with the subject for a new treatment plan.

- Subject participation in the study may be discontinued for reasons including, but not limited to:
- Withdrawal of subject's consent
- Subject preference
- Subject participation in another study
- Decision of the subject's study physician
- Loss of glycemic control
- Lost to follow-up
- Pregnancy
- Death

5.3.3 Follow-up on Withdrawn Subjects

Early discontinuation does not nullify the need to follow adverse events until resolution or stabilization. Furthermore, respecting the subject's individual choice, the subject should be asked to come in for a last follow-up visit at the projected time of the last visit in the study to complete an end of study visit (visit 4) even if the subject does not continue treatment on product until then.

5.3.4 Approximate Duration of Study

This study is anticipated to be completed within approximately seven months after study initiation, including subject enrollment, data collection, and analysis.

5.4 Procedures

The following procedures will be performed at the times shown in the Schedule of Activities.

Demography

Demography will be recorded at Screening (Visit 1) and will consists of:

- Date of birth
- Sex
- Ethnicity
- Race

Medical History

Medical history will be recorded at Screening (Visit 1) and Day 0 (Visit 2). Medical history is a medical event that the subject has experienced in the past, not including past surgeries or procedures. There must be medical records present in the subject's source documents to verify the subject's medical history.

Concomitant Medications

Concomitant medications will be recorded at Screening (Visit 1), Day 0 (Visit 2), Week 2 (Visit 3) and Week 12 (Visit 4). A concomitant medication is any treatment received by the subject concomitantly to any study treatments (RAI or RHI via V-Go). All concomitant medications should be documented in the subject's source documents. This includes all medications that the subject takes at any time during the clinical study, beginning at Screening (Visit 1). Additionally, all medications taken in the 3 months prior to Screening (Visit 1) should be reported.

Body Weight, Height, and Body Mass Index (BMI)

Body weight, height, and BMI will be completed at Screening (Visit 1). Body weight will also be completed at Week 12 (Visit 4). Body weight should be measured without shoes on, wearing only light clothing and is recorded as pounds (lb) to the nearest one decimal place, preferably using the same scale throughout the study. Height should be measured without shoes on, in inches (in) and recorded to the nearest one decimal place. BMI will be calculated once the height and weight are obtained using the National Institute of Health BMI calculator (www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm)

Physical Exam

A complete physical examination will be completed at Day 0 (Visit 2) and Week 12 (Visit 4) and should include general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdomen, lymph nodes, extremities, neurological, skin, and musculoskeletal.

Pregnancy Test

Females who are of child-bearing potential being considered for participation in the trial will be given a pregnancy test at Screening (Visit 1). Childbearing potential will be obtained at Screening (Visit 1).

Hemoglobin A1c (A1c)

A1c will be assessed at Screening (Visit 1) and Week 12 (Visit 4), via the central laboratory for the study.

Vital Signs (Blood Pressure and Pulse)

Systolic and diastolic blood pressure and pulse will be assessed at Screening (Visit 1), Day 0 (Visit 2) and Week 12 (Visit 4) on the non-dominant arm. Blood pressure and pulse should be measured with the subject in a sitting position after the subject has been resting for at least 5 minutes. The subject's legs should be uncrossed with the soles of the feet flat on the ground. Blood pressure must be measured using a calibrated digital blood pressure monitoring device.

V-Go Insulin Dosing Adjustment and Data Collection

Modification of a subject's pre-existing insulin dosing regimen may be required during the study, due to changes in diet, activity, and potential effects of changing insulin from RAI to U-100 RHI. During the trial, subjects will be advised to perform SMBG and document their SMBG results in the paper diary provided by the study. Subjects are to be instructed to document their daily individual insulin doses on their study paper diary. This information will be used to facilitate appropriate insulin dose adjustment and ensure subject safety. Overall glucose control will be reviewed by the investigator at each visit and the insulin dose may be adjusted as deemed appropriate to be consistent with good medical practice and to target glycemic control goals for all subjects similar to those recommended by the American Diabetes Association (ADA).

Table 1: Target Glucose Values for Adjustment of Insulin Therapy

Time of Target Blood Glucose Measurement	**Self-Monitored Blood Glucose (SMBG) Target***
Pre-prandial Plasma Glucose	80 to <130 mg/dL
Peak Postprandial Plasma Glucose	< 180 mg/dL
*More or less stringent glycemic targets may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.	

Prandial hypoglycemia should be addressed by lowering the bolus doses and adjustment to the V-Go option (basal rate) should be made depending on the subject fasting glucose and in the case of hypoglycemia, nocturnal hypoglycemia or severe hyperglycemia. If consistent or repeated blood glucose levels are lower than the target range and/or frequent episodes of post-prandial or pre-prandial hypoglycemia are recorded, then an assessment of the subject to evaluate physical activity and carbohydrate intake prior to considering a reduction in prandial insulin dose, may be required.

Self-Monitoring Blood Glucose (SMBG)

Subjects should bring their glucose meter with them to each study visit to ensure that it is functioning properly and for review of SMBG results. All subjects do not need to utilize the same brand of glucose meter; however, all subjects will use their own glucometer and that meter should remain the same throughout the study. In the event that a glucose meter is changed or replaced by the subject, the investigator will be notified. Subjects will be provided with a paper diary to record all SMBG measurements.

Subjects should be instructed to measure a minimum of 2 SMBG readings daily, which will consist of fasting (pre-morning meal) and either a pre-evening meal or pre-bedtime. Subjects should be informed that checking their blood glucose at additional times throughout the day is recommended. In addition, subjects should obtain additional readings, as needed, in they experience hypoglycemic symptoms, and contact the investigator if they experience unusually high or low blood glucose values.

Seven-Point Self-Monitoring Blood Glucose (SMBG)

Subjects must be instructed to perform required 7-point SMBG profiles prior to 3 visits during the study (Visits 2, Visit 3, and Visit 4). Each 7-point profile should be completed over a 1-day period, within the 3 days prior to each study visit when a 7-point profile is required (Visits 2, Visit 3, and Visit 4). The 7-point profile consists of 7 SMBG measurements on the same day at pre-morning meal (fasting), pre-midday meal, pre-evening meal, and 2-hours after the start of the morning, midday, and evening meals, and at bedtime. Subjects should be urged to eat a morning, midday, and evening meal on the days that the 7-point SMBG is monitored. Pre-meal measurements should be taken before the subject begins eating the meal.

Re-screening

If a subject does not meet inclusion and/or exclusion criteria at the Screening Visit or Randomization Visit, the subject may be re-screened at a later time.

The following conditions are pre-requisites of re-screening:

- Before re-screening, new written informed consent must be obtained
- Allocation of a new subject identification number
- All assessments for the study must be repeated
- A minimum of 1 month between the initial Screening Visit and re-screening

Randomization

Randomization will occur at the second visit (7-14 days from visit 1-screening). The study statistician will generate a blocked randomization scheme (1:1 treatment allocation ratio),, stratified by study site and A1c (<9%, ≥9%). The randomization assignments will be concealed and will revealed only after the enrolled participant has completed all baseline assessments, including the 7-point glucose profile, and it is time to allocate the intervention to the study subject. Opaque envelopes labeled for each HbA1c stratum will sent to each study site to be opened in enrollment order within each stratum. Authorized study personnel will then obtain the randomization assignment after providing the Subject ID and corresponding stratification information. Eligible subjects will be randomized to either stay on RAI delivered by V-Go (RAI cohort) or randomized to switch to U-100 RHI delivered by V-Go (RHI cohort) at Day 0 (Visit 2).

NIGLM will remain stable with the exception of the removal of a medication due to documented clinically significant hypoglycemia during the screening process.
Subjects switched from RAI to U-100 RHI in their V-Go will be expected to fill the new U-100 RHI prescription within 48 hours of Day 0 (Visit 2) and obtain the U-100 RHI through standard pharmacy channels. Subjects will also be educated on potential risks associated with U-100 RHI.

Subjects randomized to U-100 RHI in V-Go will be instructed to dose (click) 20 minutes before meals and snacks. Subjects randomized to continue RAI will be instructed to dose (click) 5 minutes before meals and snacks.

Study Schematic

Procedure	Screening Visit 1 (-2 week)	Baseline[a] (Day 0) Visit 2 Switch	Visit 3 Week 2	Visit 4 Study End Week 12
Visit Windows	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
Informed consent	X			
Inclusion/Exclusion criteria	X	X		
Randomization		X		
Demography	X			
Complete medical history	X	X		
Vital Signs	X	X		X
Height and BMI	X			
Body Weight	X			X
Physical examination [b]		X		X
Concomitant medications	X	X	X	X
Adverse events		X	X	X
Pregnancy test	X			
A1c: Blood draw, lab handling and/or shipping of samples	X			X
7-point SMBG		X	X	X
Provide subject log to subject	X	X	X	
Collect and review subject log[c] (SMBG values, hypoglycemia, and insulin doses) and download glucometer		X[c]	X[c]	X[c]
Switch RAI to RHI in subjects randomized to RHI Cohort		X		
Titrate insulin as applicable		X	X	X
Pharmacy- Per IP dispensation		X		

a: Enrollment visit should occur within 14 days of the screening visit
b: Physical exam will include brief evaluation of general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdomen, lymph nodes, extremities, neurological, skin, and musculoskeletal to determine health status.
c: Log sheets should include SMGBs, 7-point SMBGs (pre-morning meal [fasting], pre-midday meal, pre-evening meal, and 2-hours after the start of the morning, midday, and evening meals, and at bedtime) and insulin dosing

5.5 Study Endpoints

5.5.1 Primary Endpoints

- To demonstrate that RHI delivered by V-Go is non-inferior to RAI delivered by V-Go as measured by A1C after 12 weeks of treatment.

5.5.2 Secondary Endpoints

- Evaluate the change in prevalence and incidence of hypoglycemic events based on 7-point glucose profiles between groups
- Compare change in TDD of insulin (units/day and units/kg) between groups
- Compare direct pharmacy insulin costs to insurance payor using wholesale acquisition costs between groups

5.5.3 Exploratory Endpoint

- Evaluate 7-point glucose profiles for glucose patterns

5.6 Data Analysis

5.6.1 Statistical Analysis Plan

All statistical analyses will be performed by the study statistician (Beverley Huet), who has extensive experience in clinical trials analysis.

Primary analysis: The primary analysis will be the per-protocol analysis comparing HbA1c response because, in non-inferiority hypothesis testing, the intention-to-treat analysis may be biased toward the null hypothesis. The per-protocol population is defined as the population who continued the assigned intervention as randomized for the duration of the study period, completing the end of study week 12 visit (V4). The non-inferiority of U-100 RHI treatment strategy compared to rapid acting insulin regimen will be assessed using a 95% confidence interval for the between treatment group net difference (Visit 4 minus Visit 1) in HbA1c at end of study. This 95% confidence interval will be derived from the differences of least square means estimated from a mixed-effects model repeated measures analysis. The study subject will be modelled as a random effect. Non-inferiority of U-100 RHI treatment will be concluded if the upper limit of the 95% confidence interval is less than the non-inferiority margin of 0.4%.

Secondary analyses: Intention-to-treat (ITT) which will include all randomized participants who receive at least one dose of a study medication will be performed as a secondary analysis. HbA1c will be compared in a mixed-effects model which can accommodate cases with missing data in the ITT analysis data set, assuming the data are missing at random. After evaluation of the non-inferiority of U-100 RHI hypothesis, the superiority of the HbA1c as a secondary endpoint will be tested in a fixed sequence; if the primary hypothesis of non-inferiority is significant then superiority will be tested. This analysis will be

performed in both the per-protocol and ITT data sets. Secondary analyses will assess baseline covariates and their association with treatment efficacy. Group comparisons and changes from baseline over time (study visits) of continuous secondary outcome variables will be analysed with mixed-effects model repeated measures analysis. Hypoglycemic events, as defined in section 6.3.1.1, will summarized as percent of participants with at least one event and will be compared between treatment groups with Fisher's exact test. Hypoglycemic events will also be summarized as events per person time and analyzed with Poisson or negative binomial regression models. Safety endpoints and other adverse events will be summarized in detail with descriptive statistics. The analysis of safety data will be performed for the ITT population.

Model assumptions regarding normality and covariance structure will be carefully assessed. Nonparametric tests or data transformations will be used if necessary to meet assumptions. Statistical analysis will be performed with SAS software (SAS Institute, Cary NC), particularly Proc Mixed for linear models with both fixed and random effects. A two-sided alpha <5% will be considered significant for all analyses unless otherwise specified.

Interim analysis. After 75% of the participants are randomized, the Data Safety and Monitoring Committee (DMSC) will evaluate a simple analysis for the purpose of reassessment of sample size. The DSMC will be asked to evaluate our initial power and sample size assumptions and estimation based on accumulated HbA1c results. Based on this limited analysis, the final study sample size may be modified and the DSMC will approve the final study sample size. If any subsequent formal efficacy interim analysis is undertaken, the type I error rate will be controlled using a Lan-Demets alpha-spending function with O-Brien-Fleming boundaries for testing the primary non-inferiority HbA1c endpoint. This will include calculation of the confidence interval (and p-value) for testing the non-inferiority hypothesis in relation to the O-Brien-Fleming group sequential boundaries (stopping guideline). The per-protocol analysis is the primary analysis for comparing the HbA1c week 12 change from baseline between the two study groups. The study statistician will perform the interim analysis and the results will be forwarded to the Data Safety and Monitoring Committee for evaluation of study progress. If non-inferiority is demonstrated then the DSMC will advise the study investigators with regard to study continuation without protocol modification, study continuation with protocol modification, or stopping the trial. To ensure trial integrity, efficacy results will not be disclosed to study investigators.

5.6.2 Cost Analysis

Direct diabetes-related pharmacy costs will be calculated to assess cost impact to the pharmacy budget. All insulin costs will be normalized by calculating a 30-day insulin requirement based on the total prescribed TDD and multiplying the monthly insulin dose in units by the unit cost of the prescribed insulin. Costs of insulin will be based on current published wholesale acquisition costs (WAC) and reported in U.S. dollars.

5.6.3 Statistical Power and Sample Size Considerations

To demonstrate that delivery of RHI with V-Go is non-inferior to the delivery or RAI with V-Go with regard to the change in A1C from baseline to end of study with a NIM of 0.4%, 81 completers per treatment cohort (162 in total) are needed. This calculation assumes a SD of 0.9% for A1C at 12 weeks of treatment, a 2-sided significance level of 0.05, and 80% power. PASS 15 Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass. We will need to randomize 180 subjects to test this hypothesis assuming a 10% drop-out rate (estimated drop-out rate based on our extensive prior experience with similar population and length of study). We plan to screen approximately 225 subjects to account for approximately 20% anticipated screen and run-in failures.

5.7 Data Management

5.7.1 Data Collection and Storage

Data required by the protocol will be collected using a data collection form created by the investigative sites. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the data collection form. Excel worksheets will be used create the data repository for the analysis data set which will be de-identified and will employ range checking derived from the study data dictionary. Final data merges for analysis will be performed with SAS software. Electronic data will be stored on encrypted drives and backed up regularly to a secure server. At the end of study completion, all electronic data will be stored on a password protected CD-ROM and archived with study documents.

Subject completed blood glucose and insulin diaries will also be included in the subject source documents. All subject diaries and glucometer downloads will be considered to be source documentation. The data will be transcribed to data collection forms by study personnel, when applicable.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). All physical records will be kept in a locked file cabinet.

5.7.2 Records Retention

The investigator must agree to archive the study documentation (both electronic and paper based records) in an archive after completion or discontinuation of the trial. The investigator should not destroy any documents without prior permission from Valeritas. If the investigator cannot archive the documents at the trial site, they should notify Valeritas. At the conclusion of this study, data from this study will be archived for 15 years for possible use in future research studies.

6 SAFETY MONITORING

6.1 Adverse Event Reporting

Clinical adverse events (AEs) and Serious Adverse Events (SAE) will be monitored throughout the study. All AEs and SAEs will be reported to the Principal Investigator and to Valeritas, Inc regardless of whether they are considered study related. The date and time of onset and outcome, seriousness, intensity, action taken, and causality to study treatment will be assessed by the study PI.

6.2 Definitions

An **adverse event** (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given a test article or in a clinical study. This includes a clinically significant worsening of a concomitant illness and clinical laboratory abnormalities which are clinically significant, i.e. an abnormality that suggests a disease and is of a severity that requires active management. The event does not need to be causally related to the device or clinical study.

The following definitions are used when assessing the intensity of an AE:

- Mild: no or transient symptoms, no interference with the subject's daily activities.
- Moderate: marked symptoms, moderate interference with the subject's daily activities.
- Severe: considerable interference with the subject's daily activities; unacceptable.

The following definitions are used when assessing the causality (relationship) of an AE:

- Related: A causal relationship between the study treatment and the AE is a reasonable possibility. The Investigator must further qualify the degree of certainty as "possible" or "probable."
    - Possible: A causal relationship is conceivable and cannot be dismissed.
    - Probable: Good reason and sufficient documentation to assume a causal relationship.
- Not Related: A causal relationship between the study treatment and the AE is not a reasonable possibility.

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment;
- The course of the event, considering especially the effect of the discontinuation of study treatment or the reintroduction of study treatment, as applicable;
- Whether the event is known to be associated with the study treatment or with other similar treatments;
- The presence of risk factors in the study subject known to increase the occurrence of the event; and,
- The presence of non-study treatment-related factors that are known to be associated with the occurrence of the event.

The following definitions are used when assessing the outcome of an AE:

- Recovered/resolved: The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the ICF.
- Recovering/resolving: The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
- Recovered/resolved with sequelae: The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- Not recovered/not resolved: The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known.
- Unknown: This term is only applicable if the subject is lost to follow-up.

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening (i.e., the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Is a medically important event.

6.3 Recording and Reporting

A subject's AEs and SAEs will be recorded and reported from the signing of the informed consent form to the subject's last study visit. All SAEs must be reported to Valeritas by investigative sites. The investigative sites are to report all SAEs by calling Valeritas Customer Care and providing all requested information within 24 hours of becoming aware of the SAEs.

Valeritas contact information for SAE reporting is:

V-Go Customer Care (VCC)
Phone: 1-866-881-1209 **(toll-free)**

6.3.1.1 Hypoglycemic Events

Reported hypoglycemia will be analyzed according to the following definitions according to the International Hypoglycemia Study Group.[13]

Level 1	A glucose alert value of 70mg/dL or less
Level 2	A glucose level of less than 54mg/dL is sufficiently low to indicate serious, clinically important hypoglycemia
Level 3	Severe hypoglycemia, as defined by the ADA, denotes severe cognitive impairment requiring external assistance for recovery.

Hypoglycemia, as defined above, will be reported by both incidence and prevalence: Incidence will be reported as the percentage of subjects in a treatment group reporting at least one event for the duration of the study.

6.4 V-Go Product Complaint Reporting

The V-Go product complaint information includes, but not limited to the following:

- Any type of unusual local or bodily reaction to a device
- Alleged non-sterility
- Alleged product failure-design defect or abnormal functional behavior
- Improper use of the product whether or not physical injury or product failure results
- User error in handling the product regardless of final outcome to the subject
- Packaging or product labeling misunderstandings

6.4.1 Reporting Period of Product Complaints

All Product Complaints must be reported to Valeritas by investigative sites. The investigative sites are to report all Product Complaints by calling Valeritas Customer Care and providing all requested information within 24 hours of becoming aware of the Product Complaint.

Valeritas contact information for V-Go Product Complaint reporting is:

V-Go Customer Care (VCC)
Phone: 1-866-881-1209 **(toll-free)**

7 ADMINISTRATIVE PROCEDURES

7.1.1 Changes to the Protocol

There are to be no changes to the protocol without written approval from the Investigators and sponsors. Protocols will be followed as written.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved before implementation by the sponsor and IRB. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRBs of all investigational sites. These requirements should in no way prevent any immediate action from being taken by the Investigator or by the Sponsor in the interest of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the sponsor and IRB must be notified promptly.

Changes affecting only the administrative aspects of the study do not require formal protocol

amendments or IRB approval, but the IRB must be kept informed of such changes. In these cases, the Principal Investigator will send a letter to the IRB detailing such changes.

7.1.2 Adherence to the Protocol

The Investigators will conduct the study in strict accordance with the protocol, which has been written to enable the Investigator's compliance with Good Clinical Practices.

7.1.3 Monitoring Procedures

7.1.3.1 Responsibilities of the Principal Investigator

The principal investigator is required to ensure compliance with all procedures required by the clinical trial protocol and agrees to provide reliable data requested by the clinical trial protocol in an accurate and legible manner. The principal investigator may delegate other individuals as they may deem appropriate as sub-investigators to assist in the conduct of the clinical trial. The sub-investigators will work under the responsibility of the principal investigator. The principal investigator will provide them with a copy of the clinical trial protocol and all necessary information.

7.1.3.2 Responsibilities of the Monitor

The monitor of this clinical trial is responsible for taking all reasonable steps to ensure the proper conduct of the clinical trial regarding ethics, clinical trial protocol compliance, and integrity and validity of the data recorded. Thus, the main duty of the monitor is to help the principal investigator maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

Throughout the clinical trial, the monitor will contact the site, through monitoring visits or phone calls, to review study progress, investigator and patient compliance with the protocol, and any issues. The monitoring visits will include, but not be limited to, review of the following aspects: patient ICFs, patient recruitment and follow-up, SAE documentation and reporting, AE documentation, patient compliance with the study protocol, and quality of data. The monitor must check the data collected against the source documents.

8 PUBLICATION PLAN

Results from this research (without any subject identifiers) will be submitted for journal publication and presentation at national meetings. Data on the use of V-Go insulin delivery device and results of all clinical and laboratory studies are considered private and confidential. Interim

reports may be prepared periodically and presented to study personnel. Important findings may be submitted to conferences and for publication in peer-reviewed scientific journals. The identity of the subjects may not be disclosed, unless required by law, to any persons not immediately involved in the study or the study procedures.

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