Remote Continuous Glycemic Monitoring in Diabetes Drug Development

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Statement of need

Clinical Gold Standard → SBGM / HbA1c

How is this needed in drug development for antidiabetic agents?

- The main goals of early development for a new antidiabetic agent are to characterize the pharmacokinetics, pharmacodynamic response profile and the safety of the new candidate drug
  - **HbA1c**: Is well suited for Phase 2b/3 endpoint where integrated degree of glucose control over an extended period of time is the goal. → Not well suited for early development
  - **Glucose (Analyzer or SMBG)**: Early drug development for diabetes (particularly T1DM) requires dynamic characterization of the acute response to the intervention; direct measurement of glucose is needed.
  - SMBG assumes high level of patient active monitoring and limits volume of data collected (e.g., frequency, timing and total # of samples per day)
Statement of need

Clinical Gold Standard → SBGM / HbA1c

Why take the path of digital measure vs. current modalities?

- Continuous glucose monitoring (CGM) with remote data transmission:
  - **Improve efficiency** in drug development by
    - increasing volume of data collected (more data points with more comprehensive time course sampling; e.g., during sleep), and
    - shortening learning cycles for new data to be integrated into decision making (speed) to select/modify doses
  - **Enhance safety** by making data available almost real-time, with less “active” monitoring burden that can identify dangerously low glucose values
Biomarker classes

- **Susceptibility/Risk**: Indicate potential for developing disease in an individual without clinically apparent disease
- **Diagnostic**: Identify patients with a particular disease or a subset of the disease
- **Monitoring**: Detect a change, over time, in the degree or extent of disease
- **Prognostic**: Indicate likelihood of a clinical event, disease recurrence or progression, in the absence of a therapeutic intervention
- **Predictive**: Identify patients likely to experience a favorable or unfavorable effect from a specific treatment
- **Pharmacodynamic**: Indicate that a biological response has occurred in a patient who has received a therapeutic intervention. May become clinical trial endpoints and for a very small subset, surrogate endpoints.
- **Safety**: Indicate toxicity to a therapeutic intervention

*BEST Resource (Biomarkers, EndpointS, and other Tools)*
Context of Use (COU)

- **What decision is going to be made for drug development?**
  - Characterization of the glucose response to a pharmacologic intervention for the purpose of dose selection
  - By corollary will also be used for identification of glucose values below a safety threshold, i.e., monitor participant safety (early ID and opportunity for intervention for hypoglycemia)

- **What is the population involved?**
  - Patients with diabetes participating in an early development investigational drug trial for a new antidiabetic agent
    - Type 1 diabetes
    - Type 2 diabetes with “brittle” control and/or insulin requiring
  - Adult population (>18 y/o) initially; extended to pediatric based on cumulative evidence

- **What factors will define the limits of the decision?**
  - Degree of correlation of the measure with the true value of glucose in blood
  - Urgency of decision e.g.,
    - Dose modification to optimize Time in Range → sponsor/PI; usually non-urgent
    - Dose modification or other intervention to correct excessive glucose lowering → PI/participant; urgent to preserve safety
  - Speed of availability of the data to the individual (participant or investigator) that can make a decision to modify dose or other intervention
Case scenario COU

[**BEST biomarker category**] to [**drug development use/purpose**] in [**subject population/disease/disease stage**] for [**Intervention type or purpose of treatment**] (any or a specific disease or study population with disease) & **drug development stage**

**Context of Use**

A **Pharmacodynamic biomarker** used for the **purpose of dose selection** [*e.g., determine optimal dose to minimize Time in Hyperglycemia and Hypoglycemia*] in clinical study participants with diabetes receiving an experimental anti-diabetic agent in early drug development [Phase 1-2] studies

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VERKKO: A Practical Example of Remote Glucose Monitoring In Diabetes

Trial Infrastructure-
VERKKO Trial

**Study Title:** EVALUATION OF THE USE OF AN AUTOMATED PROCESS FOR PATIENT RECRUITMENT AND BLOOD GLUCOSE MONITORING IN DIABETES

**Study Objectives:**
- The **primary objective** of VERKKO (developed in collaboration with Langland, Mendor and Sanofi) was to study Mendor’s 3G-enabled wireless structured glucose profiling meter (Mendor Smart) in patients with diabetes.
- The **secondary objective** was to evaluate the feasibility and efficacy of patient engagement and patient-investigator interaction through ClinPal – eClinicalHealth’s fully integrated web-based platform.

**Clinical Site:** The Mehiläinen Diabetes Clinic in Helsinki, Finland

**Enrollment target:** 50 patients

**Key event dates:**
- Start date: Nov 2014
- Start online patient outreach: 5 Jan 15
- First patient approved for consenting: 5 Feb 2015
- First patient signed consent: 6 Feb 2015
- First patient enrolled: 8 Feb 2015
- End date: June 2015
VERKKO Trial: Key statistics

74 persons registered through the Facebook campaign

60 persons completed Inform Consent Form (ICF) Online and were sent a *Mendor Smart* blood glucose meter

51 participants started the blood glucose profiling

46 participants completed the glucose profile

59 years old – Average age of participants
VERKKO Trial

Positive Observations

- **Feasibility**: IRB approvals; recruitment through social media; participants self-training → remote patient monitoring of compliance; virtual platform/glucometer worked well
- **Efficiency**: Staff est. 1/3 time of a regular trial
- **Data quality**: Monitor compliance in “real time”; enables immediate corrections
- **Flexibility**: One patient was able to continue the study while on international travel
- **Patient experience**: Remote study was perceived as very convenient and a time saver for patients

CONCLUSION: Currently available technology can support virtual site clinical trials

Gaps

- SMBG *limits the number of measurements* that can be reasonably obtained
  - Depends on memory, patient circumstances to execute on time
  - Req’d minimally invasive self-administered procedure (finger stick) discourage compliance
- **Patient verification** and authentication, data privacy, security around data collection
- Devices and wearables developed for clinical care → validation for clinical trials is needed
- Evolution needed in sponsor infrastructure and regulatory guidance
- **Limited duration of the study** (15 days), doesn’t assess patient’s adherence in a longer study
Context of Use (CoU)

A Pharmacodynamic biomarker used for the purpose of dose selection [e.g., determine optimal dose to minimize Time in Hyperglycemia and Hypoglycemia] in clinical study participants with diabetes receiving an experimental anti-diabetic agent in early drug development [Phase 1-2] studies
Background

Glucose Profile

• HbA1c is a surrogate biomarker that reflects mean glucose levels of the previous 2-3 months
• These values can obscure time in range for glucose as well as frequency, duration and severity of hyper/hypoglycemia and glycemic variability
• Also SMBG are not available for periods when subjects are sleeping, a key time for hypoglycemia awareness
• Patients understand that HbA1c has a relationship with mean glucose but they may not understand the relationship to their symptoms on a day to day basis

Consensus limits of times in range obtained by CGM

<table>
<thead>
<tr>
<th></th>
<th>Target Range</th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time above range</td>
<td></td>
<td>&gt;180 mg/dL</td>
<td>&gt;250 mg/dL</td>
<td>DKA</td>
</tr>
<tr>
<td>Time in range</td>
<td>70-180 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time below range</td>
<td></td>
<td>&lt;70 mg/dL</td>
<td>&lt;54 mg/dL</td>
<td>Need assistance</td>
</tr>
</tbody>
</table>
# Continuous Glucose Monitors

<table>
<thead>
<tr>
<th>Device</th>
<th>Type sensor life time</th>
<th>Accuracy % MARD</th>
<th>Minimum calibration requirement/day</th>
<th>Smart device compatibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medtronic® Paradigm Minimed Veo (530 G)</td>
<td>RT-CGM Enlite, 6 days</td>
<td>13.6</td>
<td>2/day</td>
<td>MiniMed connect</td>
</tr>
<tr>
<td>Medtronic® 630 G with SmartGuard</td>
<td>RT-CGM Enlite, 6 days</td>
<td>14.2</td>
<td>2/day</td>
<td>MiniMed connect</td>
</tr>
<tr>
<td>Medtronic® 670 G</td>
<td>RT-CGM, Guardian 3, 7 days</td>
<td>9.64</td>
<td>2/day</td>
<td></td>
</tr>
<tr>
<td>iPro 2</td>
<td>Professional, Enlite and SofSensor, 6 days</td>
<td>11.0 for Enlite and 9.9 for SofSensor</td>
<td>4/day</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Dexcom G4/G5/G6</td>
<td>RT-CGM, 7 day wear, 10 days for Dexcom G6</td>
<td>13 for G4, 9.0 for G5, 9.3 for G6</td>
<td>2/day</td>
<td>No calibration needed for G6</td>
</tr>
<tr>
<td>Abbott® Freestyle Libre Flash</td>
<td>RT-CGM, 14 days</td>
<td>9.4</td>
<td>NO</td>
<td>LibreLink</td>
</tr>
<tr>
<td>Abbott® Freestyle Libre Pro</td>
<td>Professional, 14 days</td>
<td>11.1</td>
<td>NO</td>
<td>Not available</td>
</tr>
<tr>
<td>Eversense</td>
<td>RT-CGM, 90 days</td>
<td>8.8</td>
<td>2/day</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

Abbreviation: RT-CGM, real-time continuous glucose monitoring.

- Medtronic and Dexcom devices measure the interstitial glucose trend every 5 min.
- In Abbott devices, the interstitial glucose readings are generated every minute.
- Mean Absolute Relative Difference (MARD) is the percentage difference between CGM sensor reading and a value measured at the same time using a reference method. Derived as |(sensor−reference)/reference| \times 100\%. Lesser the number, the better the accuracy.
Sources of Variability

- Differences in glucose concentrations across compartments (Capillary vs Interstitial)
  - Lag time of approximately 10 minutes between the blood and interstitial fluid glucose readings
  - The difference in reading between blood and interstitial fluid can be about 10-20% greater, being more pronounced at lower glucose levels
- Differences in CGM vs the reference (YSI or SMBG)
  - Sensor accuracy is usually measured as Mean Absolute Relative Difference, the percentage difference between a CGM sensor interstitial fluid glucose reading and a blood glucose value measured at the same time using a reference method
- Insertion site
- Glucose range (e.g., accuracy/precision may be different across the claimed measuring range)
- Sensor design/technology

Modified from presentation by F.R. Kaufman

Standardized CGM Metrics for Clinical Practice

Correlation of TIR70-180 with HbA1c is moderate
- Can reflect many different daily profiles
- May be affected by individual variability in RBC lifespan

Batellino et al, Diabetes Care. 2019
Beck et al, J of Diabetes Sci & Tech. 2019
HbA1C of 7% can reflect a wide range of overall glycemic control

Vigersky, J of Diabetes. 2019
Correlation of time in range with development of microvascular complications

Frequency of development of microvascular complications according to level of TIR (70-1280 mg/dL) computed from quarterly seven point glucose testing from DCCT study

Beck et al, Diabetes Care. 2019
Hypothetical CGM Profile in a Phase 1/2 Study

- Rich sampling of glucose 24/7 enabled by CGM
- Use of **Time in Range** as biomarker
- Immediate access for analysis made possible by real-time remote transmission of data; enables continuous feeding of data to pharmacometric models and continuously improving predictions
- Allows implementation of learning into subsequent cohorts in same study → continuous improvement

Technology Verification & Validation

Technology = sensor + algorithm

• What is the sensor type (wearable, implantable, other)
  o **Wearable device**: adhere to skin x several days; use of Transcutaneous electrochemical sensor
  o **Implantable** (implanted in the subcutaneous space)
  o Multiple manufacturers; proprietary technology

• How does the algorithm produce the measurement?
  o **Proprietary algorithms** from each manufacturer

• Novel or Existing measure?
  o **Existing** measures
    o **Time in Range | Time Below Range | Time Above Range | Mean Glucose**

• Regulatory Pathway (Commercial, FDA cleared, etc.)
  o **FDA Cleared**

• Is the relationship of the remote measure to the clinical participant or investigator) that can make a decision to modify dose or other intervention
Benefit Assessment

- What is the relative perceived benefit of the new measure vs. the current standard (if there is one)?
  - Provide richer data sets than SMBG, with more timepoints measured more frequently, with better characterization of 24 hrs profile (e.g., nocturnal measures, pre and post-meals)

- When in the drug development lifecycle is the measure intended to be used?
  - Early development (Phase 1 – 2a)

- How will the measure impact drug development and regulatory review?
  - Immediate access of glucose data for analysis made possible by real-time remote transmission of data; enables continuous feeding of data to pharmacometric models and continuously improving predictions. Expected to allow for faster and more accurate dose characterization
  - Allows implementation of learning into subsequent cohorts in same study → continuous improvement. Potential for fewer subjects needed to determine optimum dosing paradigm
Is the benefit of the measure to the individual or society?

- **Benefit to individual**: Permits data collection with *less active monitoring* burden to the patient; technology can serve double-duty as *safety biomarker* (alerts for hypoglycemia) particularly at times that SMBG will not provide information (e.g., sleep).

- **Benefit to society**: Improved ability to accurately ascertain *optimal dose* should translate in *greater safety* for patients, more *efficient use of drug*, and reduction in study timelines that translate into *lower costs* of development. Saved resources can be deployed to other areas of need.
Risk Assessment

- What is the severity of the disease or condition? What are the unmet needs of the population defined in the COU? What are the risks for mortality and morbidity in the absence of treatment?
  - Diabetes is a serious chronic disease with increased risk for cardiovascular events and microvascular complications. Only approx. 50% of patients currently achieve recommended glycemic control targets.

- What is the potential consequence or harm if the measure’s performance is not aligned with expectations based on the COU?
  - Incorrect dose selection leading to:
    - Suboptimal glucose control that fails to maximally reduce risk of chronic complications
    - Hypo or hyperglycemia potentially resulting in acute adverse events
  - Reliance on automatic alerts that, if not working properly, may greater risk of hyper/hypoglycemic events in a trial depending on these alarms for safety, rather than SMBG roving predictions. Expected to allow for faster and more accurate dose characterization.
Is the risk of the measure to the individual or society?

- **Risk to individual:**
  - Risk of adverse events due to overcorrecting or undercorrecting
  - Risk of relaxing SMBG safety monitoring resulting in more hypo/hyperglycemia events
  - Potential increase in adverse events in late development of the wrong dose is advanced to subsequent trials

- **Risk to society:**
  - Additional cost and resources needed to manage acute AEs and “lost opportunity” in not achieving full benefit of therapy due to suboptimal dose selection
  - Potential for advancing a suboptimal dose to late development may result in need for clinical development re-work and increased cost

**Risk Mitigation Strategy**

- Implement/require limited SMBG for safety while relying on CGM for efficacy mostly, and for safety as an upside
- Late development studies should uncover the suboptimal dose, ultimately requiring re-work by the sponsor, but protecting the patients from release of a drug with suboptimal dosing instructions
Characteristics of Types of Evidence

As identified in Evidentiary Criteria Workshop – July 2018

• **Who is informed for decision making by the measure?**
  - COU proposes use for early clinical development so user will be the drug developer
    - Not for regulatory approval
    - Study Sponsor internal decision making for dose selection

• **What is the purpose of the decision?**
  - Enhance ability to inform models with richer data sets faster \(\rightarrow\) accelerate drug development.
  - Select dose that leads to improved HbA1c levels long term with a reduced frequency of **acute AEs** due to glucose hyper or hypoglycemia.
  - **Not** seeking to select a dose that minimizes variability based on hypothesis implicating **glycemic variability** with **long term risk** of microvascular and macrovascular complications.
Proposed biomarker

- **Time in Range** *(for glucose levels), supported by associated measures (Time Below Range; Time Above Range; Mean Glucose, etc.)*
  - **Universality** (to what extent is there evidence across drug mechanisms or across different populations)
  - **Plausibility** (is the biology of the measure so compelling that it adds to the weight of evidence for acceptance)
  - **Causality** (is there a compelling case for it being causal so there is less of a need for evidence of universality)
  - **Proportionality** (to what extent does the measure explain the disease or the change in disease)

Are there data to assess the performance of this measure to optimize dose selection? What additional data are needed?
Thank You

Panel Discussion
BACKUP / PANEL SLIDES
Hypothetical Dose-Ranging Study Design

= CGM Data transfer → Modeling → New dose guidance

Cohort #1
Period A → Period B → Period C

Cohort #2
Period A → Period B → Period C

Cohort #3
Period A → Period B → Period C

Improved Dose Guidance

Final Dose Guidance Recommendation
Clarke’s Error Grid: A tool to assess clinical accuracy

http://blog.profil.com/blog/error-grid-analysis


1. Zone A represents glucose values that deviate from the reference by no more than 20%
2. Zone B represents values that deviate from reference by >20% but would lead to benign or no treatment
3. Zone C values would result in overcorrecting acceptable blood glucose levels
4. Zone D represents "dangerous failure to detect and treat" errors
5. Zone E is an "erroneous treatment" zone; values within this zone are opposite to the reference values, and corresponding treatment decisions would therefore be opposite to that needed
Interpretation of CGM Data - Considerations

• **Lag time** of approximately 10 minutes between the blood and interstitial fluid glucose readings

• The **difference in reading** between blood and interstitial fluid can be about 10-20% greater, being more pronounced at lower glucose levels

• **Sensor accuracy** is usually measured as Mean Absolute Relative Difference, the percentage difference between a CGM sensor interstitial fluid glucose reading and a blood glucose value measured at the same time using a reference method

• **Ambulatory glucose profile** is **software derived**, including summary statistics and a glucose profile graph

• **Subject or clinician** is given amount of time the blood glucose is in on target, any hypoglycemic or hyperglycemic episodes and post prandial hyper or hypoglycemia
## Comparison to a Reference Standard

### Concurrence of CGM System Readings and Comparator Values by Comparator Glucose Range (Adults)

<table>
<thead>
<tr>
<th>CGM glucose range</th>
<th>Comparator Glucose Range (mg/dL)</th>
<th>&lt;40</th>
<th>40-60</th>
<th>61-80</th>
<th>81-120</th>
<th>121-160</th>
<th>161-200</th>
<th>201-250</th>
<th>251-300</th>
<th>301-350</th>
<th>351-400</th>
<th>&gt;400</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td></td>
<td>51.9%</td>
<td>5.0%</td>
<td>1.1%</td>
<td>0.1%</td>
<td>0.1%</td>
<td>.</td>
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<tr>
<td>40-60</td>
<td></td>
<td>40.7%</td>
<td>52.7%</td>
<td>11.7%</td>
<td>0.7%</td>
<td>0.1%</td>
<td>0.0%</td>
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</tr>
<tr>
<td>61-80</td>
<td></td>
<td>7.4%</td>
<td>41.0%</td>
<td>63.7%</td>
<td>11.0%</td>
<td>0.2%</td>
<td>0.1%</td>
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</tr>
<tr>
<td>81-120</td>
<td></td>
<td>.</td>
<td>1.3%</td>
<td>24.4%</td>
<td>75.8%</td>
<td>19.7%</td>
<td>1.0%</td>
<td>0.0%</td>
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</tr>
<tr>
<td>121-160</td>
<td></td>
<td>.</td>
<td>.</td>
<td>0.0%</td>
<td>12.2%</td>
<td>66.9%</td>
<td>24.0%</td>
<td>1.4%</td>
<td>0.0%</td>
<td>0.1%</td>
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<tr>
<td>161-200</td>
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<td>.</td>
<td>1.3%</td>
<td>59.9%</td>
<td>23.3%</td>
<td>1.7%</td>
<td>0.4%</td>
<td>0.2%</td>
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<tr>
<td>201-250</td>
<td></td>
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<td>.</td>
<td>14.1%</td>
<td>61.9%</td>
<td>30.0%</td>
<td>5.1%</td>
<td>0.2%</td>
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<tr>
<td>251-300</td>
<td></td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>11.2%</td>
<td>56.2%</td>
<td>35.9%</td>
<td>9.6%</td>
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<tr>
<td>301-350</td>
<td></td>
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<td>.</td>
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<td>.</td>
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<td>.</td>
<td>11.3%</td>
<td>48.0%</td>
<td>38.0%</td>
<td>26.1%</td>
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<tr>
<td>351-400</td>
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<td>.</td>
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<td>.</td>
<td>.</td>
<td>10.5%</td>
<td>46.0%</td>
<td>47.8%</td>
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<tr>
<td>&gt;400</td>
<td></td>
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<td>.</td>
<td>.</td>
<td>.</td>
<td>0.1%</td>
<td>2.9%</td>
<td>26.1%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>27</td>
<td>1,180</td>
<td>2,191</td>
<td>3,503</td>
<td>2,910</td>
<td>2,457</td>
<td>2,755</td>
<td>2,383</td>
<td>1,601</td>
<td>437</td>
<td>23</td>
</tr>
</tbody>
</table>

Extracted from public documents of a CGM system’s regulatory submission
Hypothetical Drug Development Scenarios

**Case Scenario #1**
- Development of a new injectable Nano-Network based glucose mediated insulin delivery system
- The product is intended to substitute daily injectable insulin administration; the injected polymeric network provides self-regulated delivery of insulin that responds to circulating glucose levels for up to 10 days

**Case Scenario #2**
- Development of a new short-acting small molecule insulin receptor agonist intended for intranasal administration
- The product is intended to substitute short-acting insulin administration, to be used as adjunct to once-daily basal insulin therapy
<table>
<thead>
<tr>
<th>Analyte</th>
<th>Measurement</th>
<th>Advantages and Limitations</th>
</tr>
</thead>
</table>
| HbA1c    |                        | ▪ Provides an integrated measure of glycemic state over time (previous 12 weeks). ↑  
▪ Does not reflect acute changes that may be of value to improve compliance and maintain safety. ↓  
▪ The same HbA1c measurement can represent substantially different profiles of diurnal glycemia ↓ |
| Glucose  | SMBG (blood from finger stick) | ▪ Its measurement reflects the acute metabolic state. ↑  
▪ Requires a minimally invasive, usually self-administered procedure (finger prick for glucose sample) to measure glucose. Limiting for rich sampling. ↓ |
|          | CGM (interstitial fluid) | ▪ Provides a means of frequent measurement capture with even less invasive means of sample collection. ↑  
▪ Allows for automated data collection and storage thus increasing “compliance” and contributing to data quality. ↑  
▪ Gradients between interstitial and plasma glucose concentrations may vary ↓  
▪ Data is stored locally and is accessed at intervals (clinic visits), limiting real time availability of data to investigators. ↓ |
Key Glycemic Biomarkers

**Glucose:** Thresholds of hyperglycemia diagnostic of diabetes reflect inflections that confer a risk of developing long-term microvascular complications → Prognostic biomarker, diagnostic biomarker and pharmacodynamic biomarker

**HbA1c:** A biomarker for the presence and severity of hyperglycemia, implying diabetes or pre-diabetes, or, over time, as a “biomarker for a risk factor” → Prognostic biomarker and diagnostic biomarker

Ambulatory Glucose Profile (AGP)

AGP Report

GLUCOSE STATISTICS AND TARGETS

<table>
<thead>
<tr>
<th>Period</th>
<th>% Time CGM is Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 Feb 2019-10 Mar 2019</td>
<td>13 days 99.9%</td>
</tr>
</tbody>
</table>

**Glucose Ranges**

- Target Range: 70–180 mg/dL
- Very High: >250 mg/dL
- High: 181–250 mg/dL
- Target Range: 70–180 mg/dL
- Low: 54–89 mg/dL
- Very Low: <54 mg/dL

**Targets [% of Readings (Time/Day)]**

- Target Range: 70–180 mg/dL
- Greater than 70% (16h 48min)
- Below 70 mg/dL: Less than 4% (58 min)
- Below 54 mg/dL: Less than 1% (14 min)
- Above 180 mg/dL: Less than 25% (8 h)
- Above 250 mg/dL: Less than 5% (1 h 12 min)

Each 5% increase in time in range (70–180 mg/dL) is clinically beneficial.

**Average Glucose** 173 mg/dL

**Glucose Management Indicator (GMI)** 7.6%

**Glucose Variability** 49.5%

Defined as percent coefficient of variation (%CV); target ≤36%