SUPPLEMENTARY DATA

Improved Glycemic Variability and Increased Time in Range with Sotagliflozin in Combination with Insulin in Adults with Type 1 Diabetes: A Pooled Analysis of 24-Week Continuous Glucose Monitoring Data from the inTandem Program

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SUPPLEMENTARY DATA

Procedure for Assessment of Postprandial Glucose

A 2-hour postprandial glucose (PPG) sample was obtained after a standardized mixed meal (1; 2) on day 1 and at the week 24 visit (or earlier for patient terminating study participation before week 24) in continuous glucose monitoring (CGM) substudy participants. Patients with hypersensitivity or dietary restrictions to the contents of the standardized mixed meal omitted it, and the reason for omission was recorded in source documents.

For both the day 1 and week 24 scheduled mixed meal, patients took their usual/prescribed basal insulin before coming to the site for the visit. Patients did not to take any short-acting (bolus) insulin on the day of the mixed meal until instructed to do so by study staff.

The last dose of single-blind placebo was administered on the day prior to day 1. The first dose of double-blind study drug on day 1 of the standardized mixed meal was given after completion of the 2-hour PPG collection. For the week 24 standardized mixed meal, the patient took the dose of double-blind study drug immediately after the fasting blood samples were obtained and bolus insulin was administered, and approximately 15 minutes before ingestion of the standardized mixed meal began.

Standard Meal for Mixed Meal

The standard (breakfast) meal was provided as a liquid nutrition drink (Boost®, Ensure®, or similar), with ~40 g carbohydrate and ~240 calories per bottle (~8 ounces). The caloric composition of the meal was ~65% carbohydrate, ~15% protein, and ~20% fat. The amount given was 6 mL/kg body weight up to a maximum of 360 mL. Therefore, for patients ≥60 kg, the standard meal consisted of ~60 g carbohydrate and 360 calories. Efforts were made to provide the same mixed meal product for the baseline and week 24 standardized mixed meal.

Fasting plasma glucose (FPG) and other fasting blood samples were collected at time zero. Immediately after this, the patient was instructed to take the meal-time amount of bolus insulin appropriate for the carbohydrate content of the standard meal. Because the endpoint is 2-hour glucose change from time zero glucose, no additional high blood glucose correction (sliding scale) insulin was given at this meal. Patients were instructed to completely consume the meal within 15-20 minutes. Water or noncaffeinated, zero-calorie beverages were allowed ad libitum. No other food could be consumed until the 2-hour PPG sample was collected. If the patient was unable to consume at least 50% of the standard meal at baseline, the standardized mixed meal was not completed, and the subsequent 24-week standardized mixed meal was not be performed. If the patient consumed >50% of the standardized mixed meal, the approximate amount was recorded and an equivalent amount consumed at the subsequent, 24-week standardized mixed meal.

Staff at study centers received the following instructions for the standardized mixed meal:

Baseline Visit (Day 1)

1. Record the amount and brand name of the standard meal liquid nutrition drink the patient is instructed to consume in the source documents.
2. Fasting blood samples are obtained, including FPG.
3. Record the time of blood sample collection in the source documents.
4. Immediately after the fasting blood samples are collected, the patient takes the meal-time amount of bolus insulin appropriate for the carbohydrate content of the standard meal. Because the endpoint is glucose change from time zero glucose, no additional “high blood glucose correction” (sliding scale) insulin should be given at this meal. The amount of insulin and time of administration are recorded in

the source documents.

5. 15 minutes after the bolus insulin is administered, the patient starts consuming the standard meal.
6. Record the time the meal ingestion starts in the source documents.
7. The 2-hour countdown for the 2-hour plasma PPG starts immediately after the patient begins ingestion of the standard meal.
8. The patient is instructed to ingest the prescribed amount of the standard meal within 15 to 20 minutes.
9. Record the time ingestion is completed, measure the portion of the meal not ingested (if any) and record the assessed percent of prescribed amount ingested in the source documents.
10. No blood samples for PK are collected at this visit.
11. 2-hours after the meal ingestion starts, the 2-hour plasma PPG is collected.
12. Record the time the 2-hour plasma PPG is collected in the source documents.
13. Double-blind study drug is administered AFTER the blood sample is drawn at 120 minutes.
14. Record the time the double-blind study drug is administered in the source documents

Week 24 Visit

1. Record the amount and brand name of the standard meal liquid nutrition drink the patient is instructed to consume in the source documents.
2. Fasting blood samples are obtained, including FPG and PK samples.
3. Record the time of blood sample collection in the source documents.
4. Immediately after the fasting blood samples are collected, the patient takes the meal-time amount of bolus insulin appropriate for the carbohydrate content of the standard meal. Because the endpoint is glucose change from time zero glucose, no additional “high blood glucose correction” (sliding scale) insulin should be given at this meal. The amount of insulin and time of administration are recorded in the source documents.
5. Double-blind study drug is administered immediately AFTER the bolus insulin is administered.
6. Record the time the double-blind study drug is administered in the source documents.
7. 15 minutes after the meal-time insulin was administered, the patient starts consuming the standard meal.
8. Record the time the meal ingestion starts in the source documents.
9. The 2-hour countdown for the 2-hour PPG starts immediately after the patient begins ingestion of the standard meal.
10. The patient is instructed to ingest the prescribed amount of the standard meal within 15 to 20 minutes.
11. Record the time ingestion is completed, measure the portion of the meal not ingested (if any) and record the assessed percent of prescribed amount ingested in the source documents.
12. 2-hours after the meal ingestion starts, the 2-hour postprandial plasma glucose and PK samples are collected.
13. Record the time the 2-hour postprandial blood samples are collected in the source documents.

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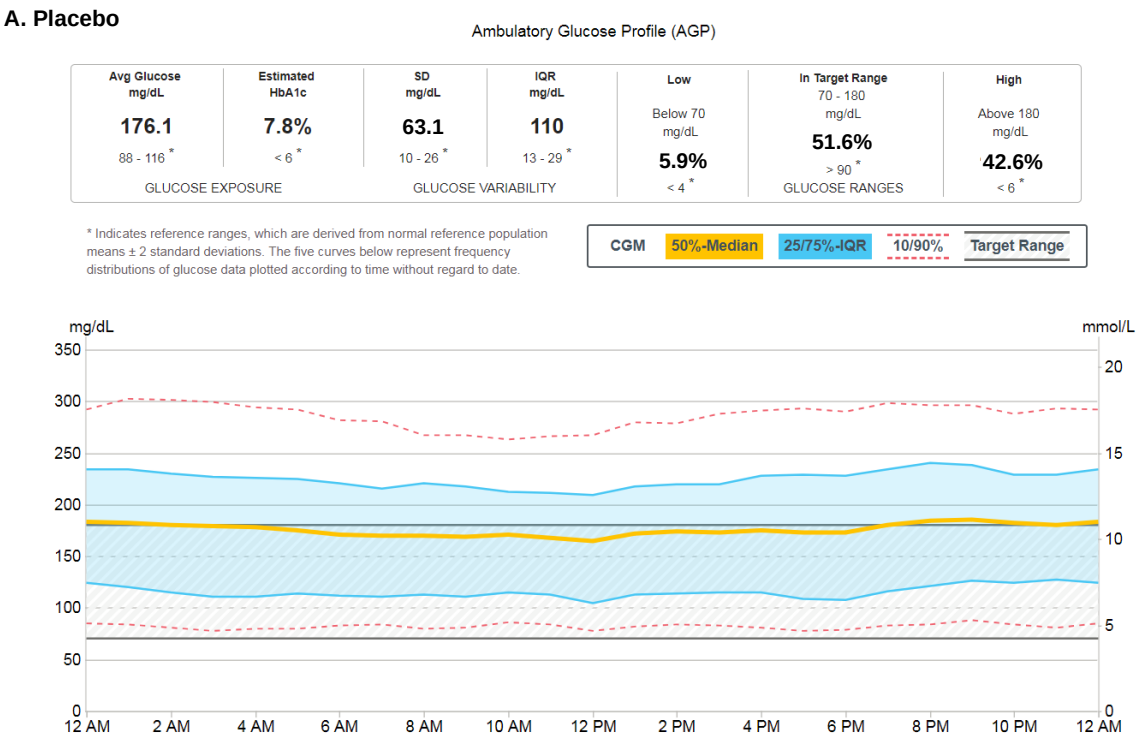
2. Lane JD, Barkauskas CE, Surwitt RS, Feinglos MN. Caffeine impairs glucose metabolism in type 2 diabetes. Diabetes Care 2004; 27:2047-2048.

SUPPLEMENTARY DATA

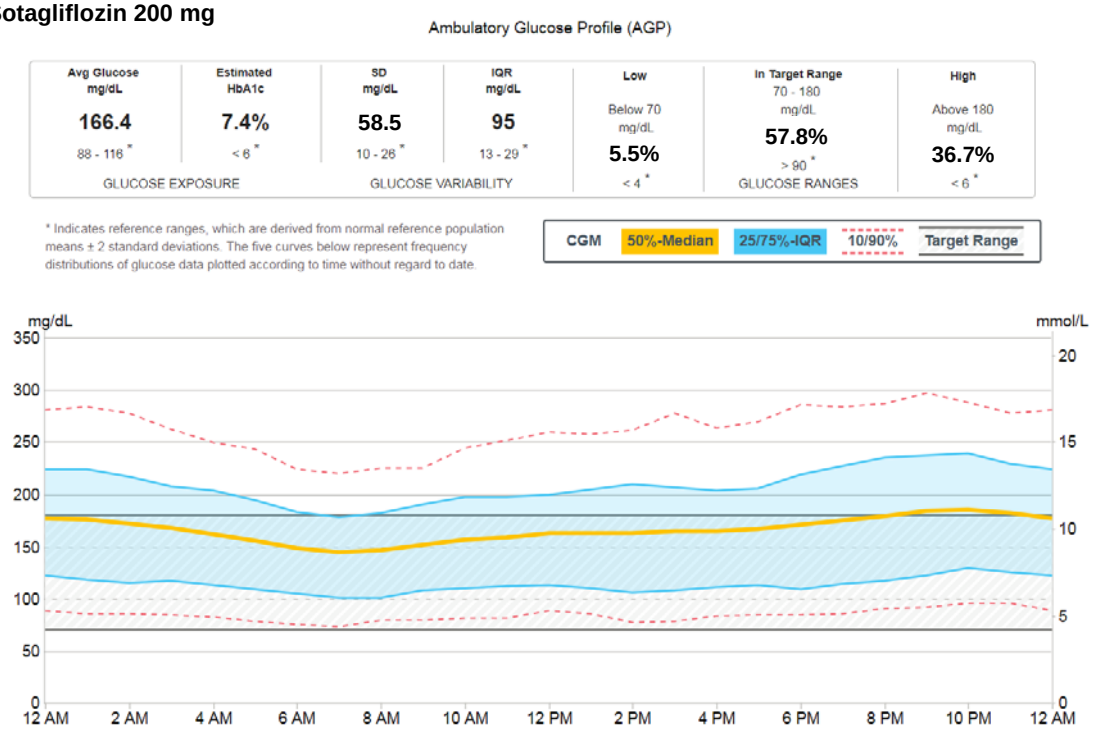
Ambulatory Glucose Profiles for Each Treatment Group

Supplementary Figure S1. Ambulatory glucose profiles (AGP) for each treatment group's CGM data collected in the week prior to week 24 are summarized. Data from the modified intent to treat (mITT) population are presented for standard deviation (SD) and time above, below, and in the target range of 70-180 mg/dL (3.9-10.0 mmol/L), as these analyses were prespecified in the statistical analysis plan. Average glucose, estimated HbA_{1c}, and interquartile range (IQR) were not prespecified and were calculated from CGM datasets collected for AGP analysis, which differed from the mITT dataset summarized in Table 2 of the main paper. *A*: Placebo. *B*: Sotagliflozin 200 mg. *C*: Sotagliflozin 400 mg.

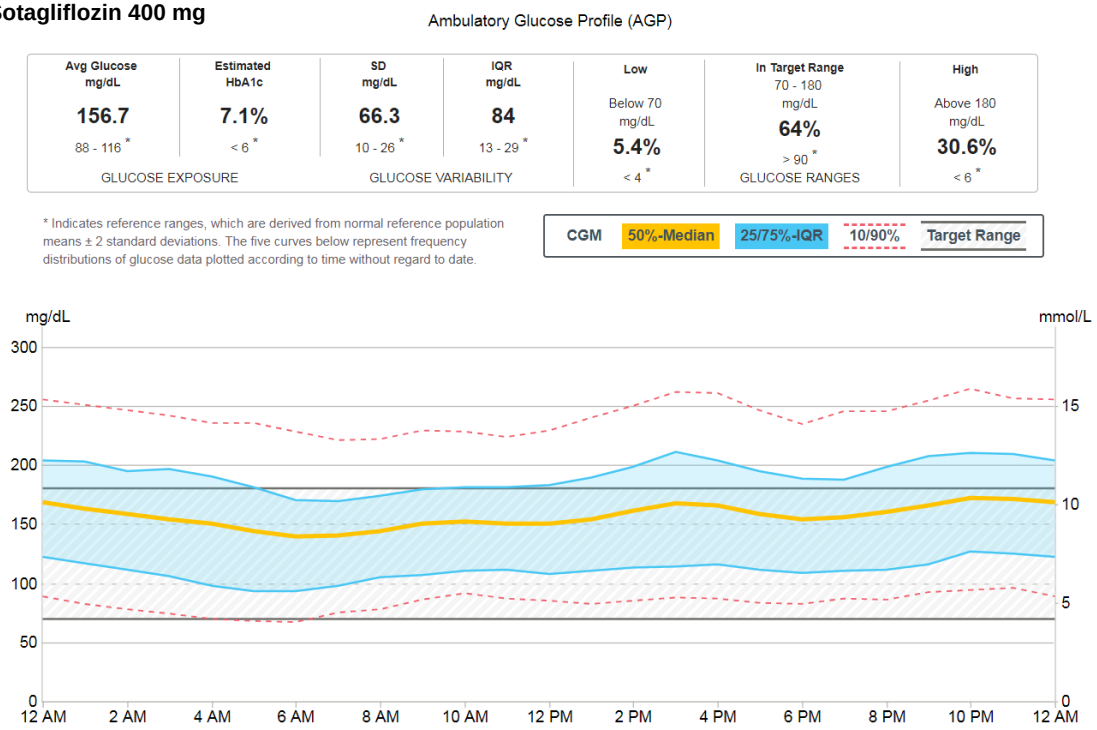


SUPPLEMENTARY DATA

B. Sotagliflozin 200 mg



C. Sotagliflozin 400 mg



SUPPLEMENTARY DATA

CGM Data from Patients with Similar HbA_{1c} Values at Baseline

The following figures show patient-specific CGM data for 1 patient in each treatment group (placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg) with similar HbA_{1c} values at baseline. Three CGM thresholds were selected: 6.5% (Figure 1), 7.0% (Figure 2), and 8.0% (Figure 3).

Method for Patient Selection

The baseline HbA_{1c} was sorted lowest to highest. For each HbA_{1c} threshold value, up to 3 patients (with baseline and week 24 CGM data) with the exact HbA_{1c} value were selected. If the number of patients with the exact value was fewer than 2, then patients with HbA_{1c} immediately above this value were selected until 2 patients total were at or above the HbA_{1c} threshold. The patient with the largest improvement in percent time in range at week 24 compared to baseline was selected. If percent time in range (3.9-10 mmol/L [70-180 mg/dL]) at week 24 was improved by less than 5%, then the patient with the largest decrease in percent time below 3.9 mmol/L (70 mg/dL) was selected.

Visualization Technology

Individual patient and aggregate visualizations of CGM data were generated by Cenduit, LLC (Durham, NC) and any reproductions must acknowledge Cenduit, LLC.

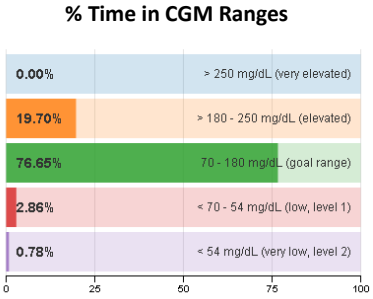
SUPPLEMENTARY DATA

Supplementary Figure S2. Individual patient visualizations at HbA_{1c} threshold of 6.5%. Visualizations provided are based on 1 week of data prior to baseline and the week 24 visit. BL, baseline. *A:* Placebo. *B:* Sotagliflozin 200 mg. *C:* Sotagliflozin 400 mg.

SUPPLEMENTARY DATA

C. 6.5% Threshold: Sotagliflozin 400 mg Patient

Baseline

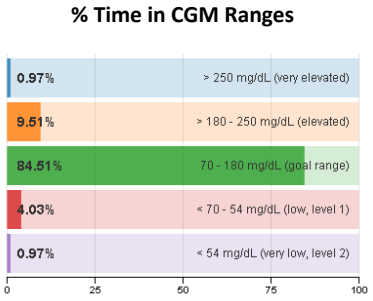


Baseline

A1C=6.6%

Insulin dose:
Basal=25.4 IU/day
Bolus=8.4 IU/day

Week 24



Week 24

A1C=6.4%

Insulin dose:
Basal=26.4 IU/day
Bolus=5.8 IU/day

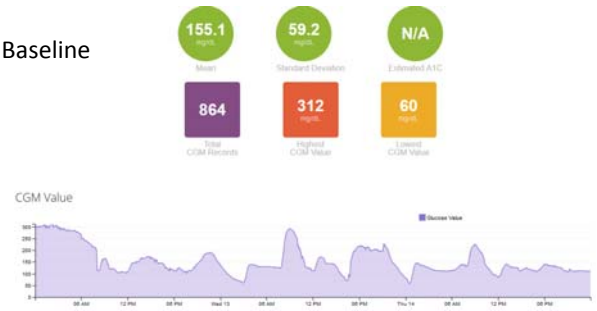
SUPPLEMENTARY DATA

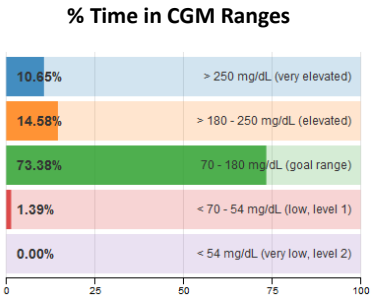
Supplementary Figure S3. Individual patient visualizations at HbA_{1c} threshold of 7.0%. Visualizations provided are based on 1 week of data prior to baseline and the week 24 visit. BL, baseline. *A:* Placebo. *B:* Sotagliflozin 200 mg. *C:* Sotagliflozin 400 mg.

SUPPLEMENTARY DATA

C. 7.0% Threshold: Sotagliflozin 400 mg Patient

Baseline



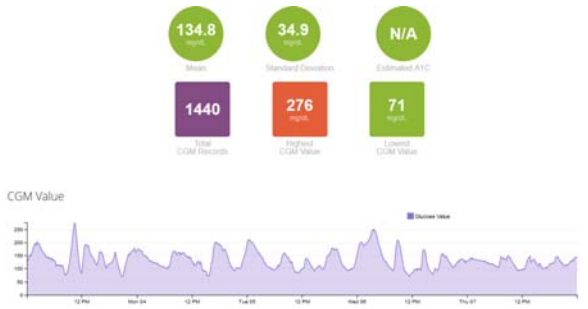


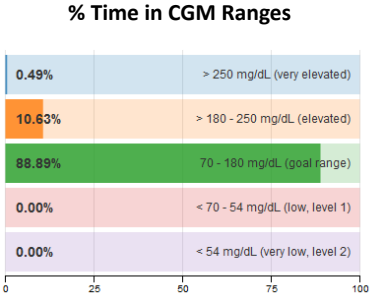
Baseline

A1C=7.0%

Insulin dose:
Basal=26.0 IU/day
Bolus=35.6 IU/day

Week 24





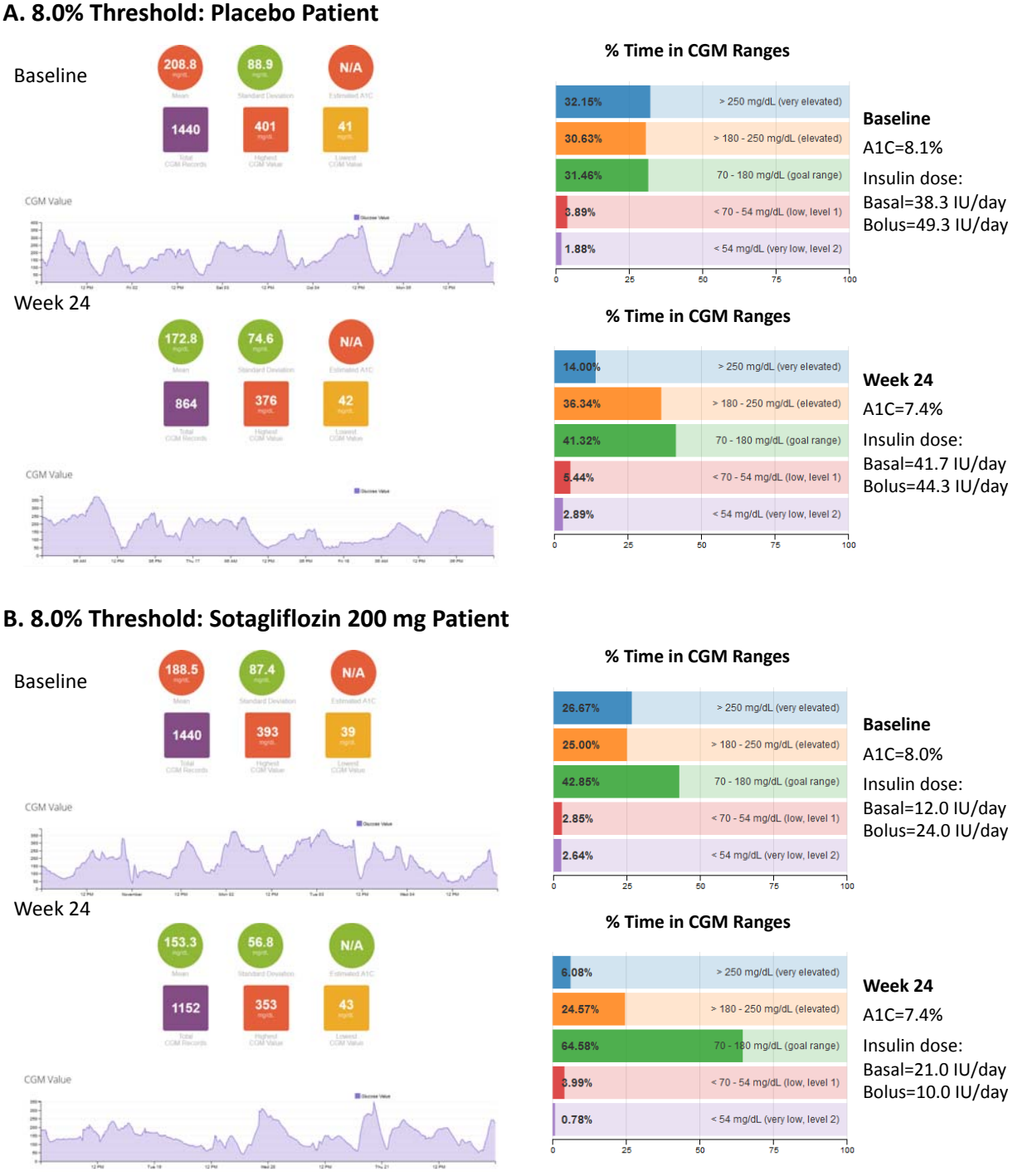
Week 24

A1C=6.6%

Insulin dose:
Basal=21.5 IU/day
Bolus=29.4 IU/day

SUPPLEMENTARY DATA

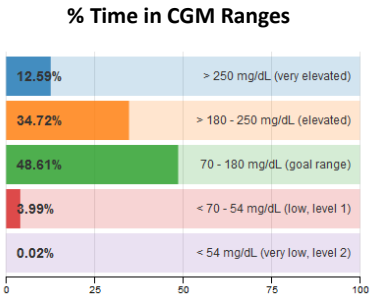
Supplementary Figure S4. Individual patient visualizations at HbA_{1c} threshold of 8.0%. Visualizations provided are based on 1 week of data prior to baseline and the week 24 visit. BL, baseline. *A:* Placebo. *B:* Sotagliflozin 200 mg. *C:* Sotagliflozin 400 mg.



SUPPLEMENTARY DATA

C. 8.0% Threshold: Sotagliflozin 400 mg Patient

Baseline

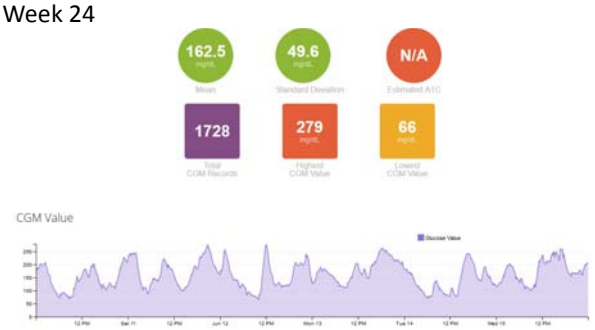


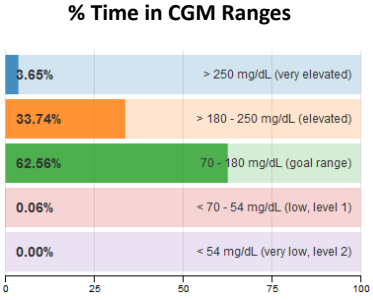
Baseline

A1C=8.0%

Insulin dose:
Basal=21.0 IU/day
Bolus=14.0 IU/day

Week 24





Week 24

A1C=6.8%

Insulin dose:
Basal=19.0 IU/day
Bolus=10.0 IU/day