Clinical Study Report Synopsis	
Drug Substance	Not applicable
Study Code	D1841C00004
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A real-world, point-of-care, randomized, parallel group, open, 6-month clinical study to evaluate the effect of a digital disease management tool in patients with type 2 diabetes mellitus

Study dates: First patient enrolled: 10 May 2017
Last patient last visit: 21 May 2018

Phase of development: Not applicable

Sponsor's Responsible Medical Officer: [redacted]

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centers

This study was conducted at 48 sites in the United States.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome measures

Objective		Outcome Measure
Priority	**Description**	**Description**
Primary	To evaluate the effect of a smart phone- and web portal-based digital disease management tool added to Standard of Care, compared to Standard of Care alone, on glycemic control in patients with T2DM.	Change from baseline to the End of Study (Month 6) in HbA1c levels
Secondary	To evaluate the effect of a digital disease management tool on glycemic control and other risk-related treatment goals in patients with T2DM (assessed between the Standard of Care + digital disease management cohort and the Standard of Care cohort).	Percentage of patients who achieved HbA1c levels <7.0% at Month 6
		Mean change in body weight (kg) from baseline to Month 6
		Proportion of patients in both cohorts who intensified antihyperglycemic treatment from Visit 1, defined as an increase in dose or addition of a new antihyperglycemic agent not received at baseline
Exploratory	To evaluate the use of a digital disease management tool in patients with T2DM.	Number of times the smart phone- and/or web portal-based tool was accessed per patient
		Length of time from first to last usage of smart phone- and/or web portal-based tool across the course of the study
		Mean patient satisfaction with the digital disease management tool as assessed by the User Satisfaction Survey
Exploratory	To evaluate the effect of a digital disease management tool on additional clinical measures.	Mean percent change from baseline to Month 6 in systolic blood pressure
		Percentage of patients who achieved blood pressure <140/90 mmHg at Month 6
		Mean percent change from baseline to Month 6 in LDL-C
		Percentage of patients who achieved LDL-C <100 mg/dL at Month 6

Objective		Outcome Measure
Priority	**Description**	**Description**
Exploratory	To evaluate the effect of a digital disease management tool on certain measures of healthcare resource utilization.	Difference in primary care office visits between active and control group during the 6-month study period as reported in patient records *(to examine potential differences in resource utilization)*
		Difference in Emergency Room visits between active and control group during the 6-month study period as reported by patients at the end of the study *(to examine potential differences in resource utilization)*
Exploratory	To evaluate the effect of digital disease management tool on patient-reported outcomes in patients with T2DM (assessed between the Standard of Care + digital disease management cohort and the Standard of Care cohort).	Change from baseline to Month 6 in Diabetes Treatment Satisfaction Questionnaire – Status version score (8-question) (treatment satisfaction)
		Change from baseline to Month 6 in Diabetes Self-Management Questionnaire score (16-question) (patient perception on ability to manage their disease)
		Change from baseline to Month 6 in Morisky Medication Adherence Scale score (8-item) (adherence)

HbA1c = glycosylated hemoglobin; LDL-C = low-density lipoprotein-cholesterol; T2DM = type 2 diabetes mellitus.

Study design

This was a real-world, point-of-care, randomized, parallel group, open, 6-month clinical study to evaluate if the provision of a digital disease management tool improved glycemic control in patients with type 2 diabetes mellitus (T2DM), as measured from baseline to End of Study (Month 6) by change in glycosylated hemoglobin (HbA1c) levels. Clinical assessments for this study were conducted as part of normal Standard of Care.

Patients in the Standard of Care cohort were taken through their T2DM management plan by their healthcare provider per Standard of Care. Patients in the Standard of Care + digital disease management cohort were taken through their standard T2DM management plan by their healthcare provider and trained in the use of the digital disease management tool. This tool did not make treatment decisions. It was not anticipated that the use of this patient tool would be associated with any increase in risk to participating patients. While participating in this study, patients continued to be treated with medications prescribed and obtained as part of Standard of Care. No medications were provided by participating in this study.

All Investigators were encouraged to report any observed adverse event (AE) or serious adverse event (SAE) according to local requirements (health authority and/or manufacturer) through the spontaneous AE reporting system.

Target subject population and sample size

Females or males aged 18 years or older with T2DM, who were on 1 or more non-insulin antihyperglycemic medications for at least 6 months prior to enrollment, who had HbA1c levels ≥7.5% and ≤11.0%, and who owned/had access to and used a smart phone and had access to the internet via a tablet or personal computer.

Assuming an 8% dropout rate for a 6-month study and a 5% dropout rate for people who initiated insulin, a sample size of 328 randomized patients (164 per patient cohort) for a 6-month study yielded 80% power to detect a difference of 0.5% in the mean change from baseline in HbA1c. This calculation assumed a standard deviation of 1.5 and a 2-sided test for the difference between the Standard of Care + digital disease management cohort and Standard of Care cohort at the 0.05 significance level.

Investigational product and comparator(s): dosage, mode of administration, and batch numbers

No investigational product was administered or provided as part of this study.

Duration of treatment

No investigational product was administered or provided as part of this study.

Statistical methods

The primary outcome measure, the mean change from baseline to Month 6 in HbA1c, was analyzed using an analysis of covariance model to compare mean changes in HbA1c between the patient cohorts.

The key secondary outcome measures were the proportion of patients who achieved HbA1c levels <7.0%, the proportion of patients in both cohorts who intensified antihyperglycemic treatment from Visit 1, and the proportion of patients who initiated a new class of pharmacotherapy not received at baseline. These key secondary outcome measures were analyzed between the 2 patient cohorts by the Cochran-Mantel-Haenszel General Association test. The key secondary outcome measure of mean change from baseline in body weight was analyzed using an analysis of covariance model.

There was no collection or analysis of any AEs or SAEs in this study.

Subject population

A total of 328 patients were randomized at 48 sites in the United States. A total of 251 (76.5%) patients completed the study: 132 (81.5%) patients in the Standard of Care cohort and 119 (71.7%) patients in the Standard of Care + digital disease management cohort. A total of 77 (23.5%) patients discontinued the study: 30 (18.5%) patients in the Standard of Care cohort and 47 (28.3%) patients in the Standard of Care + digital disease management cohort. The most common reasons for study discontinuation were lost to follow up, withdrawal by patient, and protocol deviation.

Summary of efficacy results

Mean HbA1c at baseline was 8.46% for the Standard of Care cohort and 8.57% for the Standard of Care + digital disease management cohort. The adjusted mean change in HbA1c from baseline to Month 6 was -0.42% for the Standard of Care cohort ($p<0.001$) and -0.31% for the Standard of Care + digital disease management cohort ($p=0.028$). The difference in adjusted mean change between the 2 cohorts was 0.11% ($p=0.540$), indicating there was no statistically significant difference between the 2 cohorts in mean HbA1c decrease.

At Month 6, 22/121 (18.2%) patients in the Standard of Care cohort and 12/84 (14.3%) patients in the Standard of Care + digital disease management cohort had HbA1c levels <7.0%. The risk ratio between the 2 cohorts was 1.21 and the p-value from the Cochran Mantel Haenszel General Association test was 0.563, indicating that there was no association (after controlling for sex and age group) between cohort and percentage of patients with HbA1c levels <7.0%.

Mean body weight at baseline was 96.61 kg for the Standard of Care cohort and 99.26 kg for the Standard of Care + digital disease management cohort. The adjusted mean change in body weight from baseline to Month 6 was 0.04 kg for the Standard of Care cohort ($p=0.935$) and -0.92 kg for the Standard of Care + digital disease management cohort ($p=0.094$). The difference in adjusted mean change between the 2 cohorts was -0.95 kg ($p=0.183$), indicating there was no statistically significant difference between the 2 cohorts in mean body weight change.

From Visit 1, 18/139 (12.9%) patients in the Standard of Care cohort and 10/112 (8.9%) patients in the Standard of Care + digital disease management cohort intensified antihyperglycemic treatment. The risk ratio between the 2 cohorts was 1.66 and the p-value from the Cochran-Mantel-Haenszel General Association test was 0.205, indicating that there was no association (after controlling for sex and age group) between cohort and proportion of patients who intensified antihyperglycemic treatment. During the study, 13/139 (9.4%) patients in the Standard of Care cohort and 8/112 (7.1%) patients in the Standard of Care + digital disease management cohort initiated a new class of pharmacotherapy not received at baseline. The risk ratio between the 2 cohorts was 1.45 and

the p-value from the Cochran-Mantel-Haenszel General Association test was 0.414, indicating that there was no association (after controlling for sex and age group) between cohort and proportion of patients who initiated a new class of pharmacotherapy not received at baseline.

Summary of safety results

Safety was not assessed in this study.

Conclusions

- The adjusted mean change in HbA1c from baseline to Month 6 was statistically significant for the Standard of Care cohort (-0.42%; p<0.001) and the Standard of Care + digital disease management cohort (-0.31%; p=0.028); however, the difference in adjusted mean change between the 2 cohorts was 0.11% (p=0.540), indicating there was no statistically significant difference between the 2 cohorts in mean HbA1c decrease.
- At Month 6, 18.2% patients in the Standard of Care cohort and 14.3% patients in the Standard of Care + digital disease management cohort had HbA1c levels <7.0%; there was no association between cohort and percentage of patients with HbA1c levels <7.0% (risk ratio 1.21; p=0.563).
- The adjusted mean change in body weight from baseline to Month 6 was 0.04 kg for the Standard of Care cohort (p=0.935) and -0.92 kg for the Standard of Care + digital disease management cohort (p=0.094). The difference in adjusted mean change between the 2 cohorts was -0.95 kg (p=0.183), indicating there was no statistically significant difference between the 2 cohorts in mean body weight change.
- From Visit 1, 12.9% patients in the Standard of Care cohort and 8.9% patients in the Standard of Care + digital disease management cohort intensified antihyperglycemic treatment; there was no association between cohort and proportion of patients who intensified antihyperglycemic treatment (risk ratio 1.66; p=0.205).
- During the study, 9.4% patients in the Standard of Care cohort and 7.1% patients in the Standard of Care + digital disease management cohort initiated a new class of pharmacotherapy not received at baseline; there was no association between cohort and proportion of patients who initiated a new class of pharmacotherapy not received at baseline (risk ratio 1.45; p=0.414).
- Safety was not assessed in this study. There was no collection or analysis of any AEs or SAEs in this study. No AEs or SAEs were reported to the Sponsor during the study.