DE NOVO CLASSIFICATION REQUEST FOR BT-001

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Diabetes digital behavioral therapeutic device. A diabetes digital behavioral therapeutic device is a prescription use software device that provides digital behavioral therapy to aid in the management of diabetes. This device is intended to provide limited secondary benefit to patients with diabetes mellitus by assisting them in managing their condition. This device is not intended to replace any primary treatment, such as diet/lifestyle changes or medication.

NEW REGULATION NUMBER: 21 CFR 880.5735

CLASSIFICATION: Class II

PRODUCT CODE: QXC

BACKGROUND

DEVICE NAME: BT-001

SUBMISSION NUMBER: DEN220058

DATE DE NOVO RECEIVED: September 21, 2022

SPONSOR INFORMATION:

Better Therapeutics
548 Market Street, #49404
San Francisco, CA 94104

INDICATIONS FOR USE

The BT-001 is indicated as follows:

BT-001 is a prescription-only digital therapeutic device intended to provide cognitive behavioral therapy to patients 18 years or older with type 2 diabetes. The device targets behavior to aid in the management of type 2 diabetes in patients who are under the care of a healthcare provider. BT-001 provides cognitive behavioral therapy as a treatment that should be used adjunctively with standard of care.

LIMITATIONS

The sale, distribution, and use of BT-001 are restricted to prescription use in accordance with 21 CFR 801.109.

The device is not intended for use as a standalone therapy.

The device is not a substitute for a patient's prescribed therapy or medication.

The device should not be used by people with unstable psychiatric disorders.

The device is not intended for use in the treatment of any psychiatric disorder or symptoms.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

BT-001 is a digital diabetes device that delivers cognitive behavioral therapy (CBT) to a patient with Type 2 Diabetes through an application on the patient's personal Android smartphone. BT-001 is prescription use only and is completely self-directed. The device is designed to allow patients to complete CBT without human support or intervention and is intended to be used in 90-day increments adjunctively to standard of care.

The cognitive behavioral therapy delivered by BT-001 is intended to aid users in making behavioral modifications to better adhere to behaviors associated with the management of diabetes. BT-001 focuses on users understanding barriers to their adhering to known diabetes management behaviors such as eating habits, nutrition, and exercise. The device also provides a way for users to self-report their meals, exercise, medications, and biometrics. When relevant, BT-001 will supply additional notifications for users to contact a healthcare provider, such as when a user logs a blood glucose reading.

This medical device has functions subject to FDA premarket review as well as functions that are not subject to FDA premarket review. For this De Novo request, if the product has functions that are not subject to FDA premarket review, FDA assessed those functions only to the extent that they either could adversely impact the safety and effectiveness of the functions subject to FDA premarket review or they are included as a labeled positive impact that was considered in the assessment of the functions subject to FDA premarket review.

SUMMARY OF NONCLINICAL/BENCH STUDIES

SOFTWARE

The device is a software only device accessible through a user's personal Android smartphone. The software of the device consists of the smartphone application (App), Web Server, and Admin. The App is the user interface for the device and features

account management, onboarding, behavioral therapy and program content, biometric entry and tracking, goal setting, and progress visualization, help and support, and user data management. The Web application provides verification of eligibility, registration of their device, and authentication and password retrieval. The Server is a web-based application that provides core functionality to the App and Web via various application programming interfaces (APIs). The Admin is a web-based application that provides administrative functionality for BT-001. Access to the Admin functionality is only available to Administrators of Better Therapeutics.

All of the elements of software and cybersecurity information as outlined in FDA's guidance documents "*Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices*" (issued May 11, 2005) and "*Content of Premarket Submissions for management of Cybersecurity in Medical Devices*" (issued October 2, 2014) were provided.

PERFORMANCE TESTING - BENCH

Not applicable

PERFORMANCE TESTING - ANIMAL AND/OR CADAVER

Not applicable

SUMMARY OF CLINICAL INFORMATION

Pivotal Study:

The sponsor conducted a controlled, prospective, multicenter pivotal clinical trial consisting of 726 participants where 668 downloaded their assigned digital app and completed the onboarding process. The control group consisted of 343 people with type 2 diabetes who followed their prescribed standard of care therapy and the intervention group consisted of 325 people with type 2 diabetes who used the BT-001 device in addition to their prescribed standard of care therapy. Both groups were allowed to have glycemic control medications changed throughout the study by their healthcare provider.

Study Feature	Description
Title	Open-Label, Randomized, Controlled, Parallel-Group Trial of a Digital Therapeutic for the Treatment of Type 2 Diabetes
Summary	A randomized, open label, controlled trial of 6 months at home BT-001 vs. standard of care (SOC).
Investigational Device	BT-001
Objectives	• The primary objective was to assess the safety and effectiveness of BT-001 as an intervention for type 2 diabetes as measured by a change in HbA1c and the

	occurrence, relatedness and severity of adverse events after 90 days. • The secondary objective was to assess the safety and effectiveness of BT-001 after 180 days.
Study Design	Randomized Open-Label clinical trial with 343 control subjects and 325 intervention subjects
Number of Sites	Fourteen US clinical sites
Population	Eligible subjects were patients aged 18 to 75 years with type 2 diabetes and HbA1c 7.0 – 10.9%. Exclusion criteria included medical conditions or medications likely to affect HbA1c such as active eating disorders, prior bariatric surgery, pregnancy, oral corticosteroids, prandial insulin, weight loss or atypical antipsychotic medications or Patient Health Questionnaire-9 (PHQ-9) scores ≥ 20
Sample Size	The study randomized 726 participants, of whom 668 downloaded their assigned digital app and completed the onboarding process (Control group: 343, BT-001 group: 325)
Treatment Group	Randomized Trial: • Intervention Group: BT-001 use and daily biometric tracking • Control Group: Standard of Care
Study Duration	6 months total
Protocol Overview/Synopsis	• Primary endpoint: difference of control and intervention groups in mean change from baseline of A1c at Day 90 between groups • Secondary endpoint: difference of control and intervention groups in mean change from baseline of A1c at Day 180 between groups

Baseline study demographics are summarized in the table below for the control and intervention (BT-001) groups.

	Control n=313	**BT-001** n=297
Age, years, mean (SD)	58 (9)	58 (9)
Female, n (%)	180 (58)	166 (56)
Race, n (%)		
White	192 (61)	183 (62)
Black or African American	93 (30)	89 (30)
Asian	16 (5)	13 (4)
American Indian or Alaskan Native	6 (2)	3 (1)

Native Hawaiian or another Pacific Islander	2 (1)	1 (0.3)
Other (includes multiple races) or not reported	10 (3)	12 (4)
Hispanic or Latino ethnicity, n (%)	41 (13)	51 (17)
Highest level of education, n (%)		
Less than high school degree	4 (1)	2 (1)
High school degree or equivalent	38 (12)	30 (10)
Some college but no degree	94 (30)	80 (27)
Associate degree	51 (16)	51 (17)
Bachelor's degree	74 (24)	79 (27)
Graduate degree	52 (17)	55 (19)
Median income by ZIP code, $	60441	64778
Body mass index, kg/m2, mean (SD)	35 (7)	34 (7)
HbA1c %, mean (SD)	8.1 (0.9)	8.2 (0.9)
Fasting glucose, mg/dL, mean (SD)	168 (55)	170 (57)
Years since diagnosis of diabetes, mean (SD)	11 (8)	11 (8)

Study Sample Size

The sample size was calculated assuming a two-sided, two-sample t-test would be used to compare the difference in mean change from baseline in HbA1c between the intervention and control arm assuming a common standard deviation for both groups. The assumed common standard deviation of 1.4% and a clinically significant difference in means of 0.4% were used to determine that a nominal sample size, with 90% power, was 259 subjects per treatment group. However, the Applicant also considered a 20% attrition rate and thus calculated a sample size of 324 subjects per group.

Pivotal Study Safety Results:

Better Therapeutics defined adverse events as follows:

- Any abnormal laboratory test result (e.g., hematology, clinical chemistry, or urinalysis) or other abnormal safety assessment (e.g., electrocardiogram, radiological scan, vital sign

measurement), that worsens from baseline and is considered clinically significant in the medical and scientific judgement of the investigator
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition
- New conditions that are identified or diagnosed after the study treatment was administered, even if those conditions may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of a concomitant medication. Overdose per se was not reported as an AE or serious adverse event (SAE) unless it was an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses were to be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected physiological action" per se were not to be reported as an AE or SAE. Such instances were captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae, resulting from lack of efficacy, were reported as an AE or SAE, if they fulfilled the definition of an AE or SAE

Better Therapeutics defined adverse events that occurred after the onboarding of the study as treatment-emergent adverse events (TEAE).

A summary of the number of subjects with reportable TEAEs observed during the study (post-randomization) is provided in the following table:

Table 1. Adverse Events by Study Treatment Group

	Post – Randomization, Days 1-180			
	Control n = 343		**BT-001** n = 325	
	Subjects n (%)	**Events** n	**Subjects** n (%)	**Events** n
TEAE	188 (55)	324	135 (42)	265
Maximum Severity of TEAE				
Mild	117 (34)	219	100 (31)	215
Moderate	55 (16)	87	30 (9)	45
Severe	16 (5)	18	5 (2)	5
Serious TEAE	24 (7)	26	9 (3)	9

The sponsor also provided their assessment of TEAEs that were adjudicated as being possibly or probably associated with intervention. The sponsor reported that four (4) TEAEs in three subjects were adjudicated to be possibly or probably related to use of BT-001 during the study. These events included tachycardia, thirst, pollakiuria, and increasing HbA1c.

PHQ-9 scores were tracked throughout the study to evaluate the risks of worsening depression and suicidal ideation. Participants with scores ≥20 were excluded or discontinued from the study. Table 2 shows PHQ-9 scores that resulted in study discontinuation.

Table 2. PHQ-9 scores ≥20 considered severe, and positive to Question 9 indicates suicidal ideation

	Post – Randomization; Days 1-90		Post – Randomization; Days 90-180	
	Control n = 343	**BT-001** n = 325	**Control** n = 343	**BT-001** n = 325
PHQ-9 ≥20	3	1	2	1
PHQ-9 Positive Question 9	3	1	6	2

Pivotal Study Observed Results:

Overall reduction in % A1c (change from baseline) for the control and intervention groups as measured at Day 90 and Day 180 is shown in Table 3 along with standard deviation.

Table 3. Mean (standard deviation) and range (minimum, maximum) %A1c change from baseline for the intention to treat population and the per protocol population in the control and intervention arms.

Analysis Group and Timepoint (Initial sample size)	**Control (n=343)**	**BT-001 (n=325)**
Intention To Treat - Day 90		
Mean (SD)	0.14 (1.23)	-0.27 (1.11)
(min, max)	(-4.00, 5.95)	(-3.55, 5.50)
Number of subjects	n=313	n=297
Intention To Treat Day - 180		
Mean (SD)	-0.07 (1.19)	-0.37 (1.36)
(min, max)	(-4.20, 3.80)	(-4.40, 5.95)
Number of subjects	n=271	n=244
Per Protocol – Day 90		
Mean (SD)	0.09 (1.16)	-0.38 (1.02)
(min, max)	(-4.00, 4.90)	(-3.55, 3.70)
Number of subjects	n=245	n=159
Per Protocol – Day 180		
Mean (SD)	-0.03 (1.11)	-0.41 (1.10)
(min, max)	(-4.20, 3.80)	(-3.65, 3.15)
Number of subjects	n=217	n=160

For the intervention group the magnitude of A1c reduction was not uniform across the participants. Participants that completed more lessons through device use observed greater reductions in % A1c from baseline at both day 90 and day 180. A post-hoc analysis of the data is shown in Table 4 where a range of completed lessons has a corresponding % A1c reduction.

Table 4. Change in %A1c at day 90 and 180 from baseline with more completed lessons from the device

# Lessons Complete	**%A1c Change**	**Standard Deviation**

0 at day 90; n=313	0.14	1.23
<5 at day 90; n=93	-0.11	1.31
6-11 at day 90 n=100	-0.24	1.15
>11 at day 90; n = 104	-0.45	0.86
0 at day 180; n=313	-0.07	1.19
<10 at day 180; n=80	-0.06	1.66
10-20 at day 180; n=77	-0.42	1.20
>20 at day 180; n=87	-0.61	1.14

The second variable that correlated with differences in the magnitude of A1c reduction was whether subjects had additional medical visits outside of the pre-planned visits for the study. The participants in the intervention group who had additional medical visits with a healthcare provider observed greater reductions in A1c compared to intervention group participants who did not have an additional medical visit with a healthcare provider. The data is shown in Table 5 with standard deviations.

Table 5. Change in % A1c (standard deviation) from baseline at days 90 and 180 for the Intention To Treat (ITT) and Per Protocol (PP) populations

	Control	**Intervention**
Additional Medical Visits at day 90 ITT	0.062 (1.16) n=198	-0.40 (0.95) n=189
Additional Medical Visits at day 180 ITT	-0.07 (1.15) n=253	-0.38 (1.31) n=229
No Additional Medical Visits at day 90 ITT	0.27 (1.32) n=115	-0.05 (1.29) n=108
No Additional Medical Visits at day 180 ITT	0.17 (1.60) n=60	0.01 (1.42) n=68
Additional Medical Visits at day 90 PP	0.05 (1.15) n=159	-0.51 (0.93) n=109
Additional Medical Visits at day 180 PP	-0.08 (1.08) n=182	-0.43 (1.13) n=132
No Additional Medical Visits at day 90 PP	0.19 (1.15) n=86	-0.09 (1.15) n=50
No Additional Medical Visits at day 180 PP	0.19 (1.27) n=35	-0.31 (0.97) n=28

Pediatric Extrapolation:

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

Device labeling includes the device indications for use, a description of the device, warnings and precautions, a summary of the clinical testing with the device, and instructions for use of the device. The labeling is sufficient and satisfies the requirements of 21 CFR 801.109 Prescription Devices.

Per the special controls for this generic type of device, labeling includes a summary of the clinical testing with the device and certain limiting statements. The labeling includes the following statements to meet the special controls:

- The device is not intended for use as a standalone therapy.
- The device is not a substitute for a patient's prescribed therapy or medication.
- The device should not be used by people with unstable psychiatric disorders.
- The device is not intended for use in the treatment of any psychiatric disorder or symptoms.
- Among those assigned to the device, the average change in %HbA1c observed in the clinical study was -0.27 compared to baseline after 90 days, and -0.37% compared to baseline after 180 days.
  - After 90 days of device use, while 179 patients (60%) saw numerically improved glycemic control (%HbA1c decreased compared to baseline), there were 118 patients (40%) who saw no change or numerically worsened glycemic control (%HbA1c increased compared to baseline). In comparison, 136 patients (43%) in the control group saw HbA1c improvement and 177 (57%) saw no change or worsened glycemic control. These differences between the device and control group were statistically significant ($p<0.0001$).
  - After 180 days of device use, while 159 patients (65%) saw numerically improved glycemic control after 180 days of device use (%HbA1c decreased compared to baseline), there were 85 patients (35%) who saw no change or numerically worsened glycemic control (%HbA1c increased compared to baseline). In comparison, 122 patients (45%) in the control group saw HbA1c improvement and 149 (55%) saw no change or worsened glycemic control. These differences between the device and control group were statistically significant ($p<0.0001$).

- In the clinical study with the device, observed reduction in HbA1c was correlated with increased usage of the BT-001 app. In addition, for patients that used the BT-001 app, those with additional medical visits to a health care provider had average HbA1c reductions of -0.40% at day 90 and -0.38% at day 180. In comparison, patients in the control group with additional medical visits had an average HbA1c increase of +0.06% at day 90 and average reduction of -0.07% at day 180. The difference between groups was -0.46% at day 90 and -0.31% at day 180. Patients without additional medical visits who used the BT-001 app had average HbA1c reductions of -0.05% at day 90, and an average increase of +0.01% at day 180. In comparison, patients in the control group without additional medical visits had an average HbA1c increase of +0.27% at day 90 and +0.17% at day 180. The difference between groups was -0.32% at day 90 and -0.16% at day 180.

- Patients who used the BT-001 app were financially compensated for taking frequent blood glucose measurements, whereas patients who used a control app were treated according to standard of care. Patients who used a control app did not take study-directed blood glucose measurements, thus their compensation was not associated with blood glucose measurements. Total compensation was equal for subjects who used the BT-001 app and those who did not use the app.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of a diabetes digital behavioral therapeutic device and the measures necessary to mitigate these risks.

Risks to Health	Mitigation Measures
Worsening of condition due to device providing ineffective treatment	Certain design verification and validation activities, including clinical data Certain labeling information, including certain limiting statements
Treatment results in anxiety, depressed mood, depression, mental disorder (unspecified), stress or suicidal ideation	Certain design verification and validation activities, including clinical data Certain labeling information, including certain limiting statements
Ineffective treatment due to use error / improper use of device / device software failure	Certain labeling information, including certain limiting statements

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the diabetes digital behavioral therapeutic device is subject to the following special controls:

(1) Design verification and validation must include documentation of:

(i) Clinical data from a statistically and clinically justified sample size, fulfilling the following:

(A) Appropriately validating the model of therapy as implemented by the device using a clinically defined endpoint, and

(B) Demonstrating that use of the device does not adversely impact the health outcomes or health status of the intended use population. A device hazard analysis must consider all device-related adverse events observed from the clinical data collected and must demonstrate that patient risk from use of the device is minimal.

(ii) Software verification, validation, and hazard analysis must demonstrate that the device performs as intended.

(2) The labeling must include:

(i) A summary of the clinical testing with the device, including a discussion of the limitations of the clinical significance of the results.

(ii) Limiting statements that indicate:

(A) The device is not intended for use as a standalone therapy.

(B) The device is not a substitute for a patient's prescribed therapy or medication.

(C) The device should not be used by people with unstable psychiatric disorders.

(D) The device is not intended for use in the treatment of any psychiatric disorder or symptoms.

BENEFIT-RISK DETERMINATION

Summary of Benefits:

The probable benefits of the device are related to supporting user behaviors to better adhere to known diabetes management skills. The benefits of the device are based on data collected in a clinical study described above. On average, study subjects who used BT-001 experienced a reduction in %A1c of -0.37 compared to an average reduction of -0.07 in the control group at day 180 (ITT population).

Factors that increase uncertainty in determining probable benefits for BT-001 include:

- Improvement in %A1c was not uniform across study subjects who used BT-001. While an average improvement of -0.37 from baseline was observed at day 180 for BT-001 users, the range of %A1c change from baseline was (-4.40, 5.95) with a standard deviation of 1.36. While 159 patients (65%) saw numerically improved glycemic control after 180 days of device use (%HbA1c decreased compared to baseline), there were 85 patients (35%) who saw no change or numerically worsened glycemic control (%HbA1c increased compared to baseline). In comparison, 122 patients (45%) in the control group saw HbA1c improvement and 149 (55%) saw no change or worsened glycemic control. As a result, there is moderate residual uncertainty regarding whether a particular user of BT-001 will experience improvement of glycemic control following device use.

- The magnitude of the A1c reduction may be dependent on various factors, including adjustment and adherence to glycemic control medications, adherence to device use, frequency of medical visits, and adherence to other standard of care treatments such as frequent blood glucose monitoring.

- The clinical study was limited to 6 months (180 days) in duration. As a result, the durability of the treatment effect is unclear. Diabetes mellitus is a chronic condition and clinical benefit is only expected from sustained improvement in %A1c over the long term.

- There were patients that missed the day 90 and day 180 study visits where measurements of %A1c were made for evaluation of device efficacy. The number of BT-001 users with missing %A1c measurements was 28/325 (8.6%) at day 90 and 81/325 (25%) at day 180 in the treatment group (ITT population).

- Patients who used the BT-001 app were financially compensated for taking frequent blood glucose measurements, whereas patients who used a control app were treated according to standard of care. Patients who used a control app did not take study-directed blood glucose measurements, thus their compensation was not associated with blood glucose measurements. Total compensation was equal for subjects who used the BT-001 app and those who did not use the app.

Summary of Risks:

The probable risks of the device are based on data collected in a clinical study described above. Specifically:

- Types of adverse events observed during the study were similar between groups, with BT-001 users experiencing numerically fewer events overall compared to the control group.

- There were four (4) adverse events in three (3) subjects reported during the study that were judged to be possibly device-related, one of which was for worsening of glycemic control. In the observed case of worsening glycemic control, the subject only opened 1 lesson in BT-001 prior to day 90, and self-reported non-compliance with prescribed medication. Tachycardia reported by one subject was associated with increased physical activity as part of the BT-001 program. Pollakiuria and thirst were reported by one subject who had completed 26 lessons in BT-001.

- Overall, device-related adverse events were not serious, and the rate and degree of adverse events was not worse than those experienced by subjects in the control group.

- Cognitive behavioral therapy is associated with a class-effect risk of worsening depression and suicidality. BT-001 users experienced numerically fewer of such events overall compared to the control group.

As described above, there were several factors that increased the uncertainty in determining the probable benefits that a patient is expected to experience from using the BT-001 device. Notably, 35% of patients using BT-001 saw either no change or worsening glycemic control after 180

days of use. However, given that the rate of no change or worsening glycemic control was observed to be higher in the control group (where 55% of patients saw no change or worsening control), and there were numerically fewer adverse events in the BT-001 group, it appears that the device may offer limited secondary benefit compared to standard of care alone.

PATIENT PERSPECTIVES

The clinical study described above included use of the Patient Health Questionnaire-9 (PHQ-9) as a patient-reported outcome to evaluate the presence and severity of depression. PHQ-9 scores were evaluated at baseline and throughout the study. PHQ-9 scores of ≥20 or reported suicidal ideation were exclusion criteria for the study and subjects reporting a score of ≥20 or suicidal ideation at days 90 or 180 were removed from the study.

At baseline, PHQ-9 scores were similar between the two treatment arms (2.5 ± 2.9 in the Control group versus 2.6 ± 3.0 in the BT-001 group). At Day 90, 3 subjects in the Control group and 1 subject in the BT-001 group had scores ≥20 and were withdrawn from the study. At Day 180, 2 subjects in the Control group and 1 subject in the BT-001 group had scores ≥20.

BENEFIT/RISK CONCLUSION

In conclusion, given the available information above, for the following indication statement:

> BT-001 is a prescription-only digital therapeutic device intended to provide cognitive behavioral therapy to patients 18 years or older with type 2 diabetes. The device targets behavior to aid in the management of type 2 diabetes in patients who are under the care of a healthcare provider. BT-001 provides cognitive behavioral therapy as a treatment that should be used adjunctively with standard of care.

The probable benefits outweigh the probable risks for the BT-001 device. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the BT-001 is granted and the device is classified as follows:

Product Code: QXC
Device Type: Diabetes digital behavioral therapeutic device
Regulation Number: 21 CFR 880.5735
Class: II