DE NOVO CLASSIFICATION REQUEST FOR CT-132

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Computerized behavioral therapy device for headache. A computerized behavioral therapy device for headache is a prescription device intended to provide a computerized version of behavioral therapy for the treatment of headache.

NEW REGULATION NUMBER: 21 CFR 882.5806

CLASSIFICATION: Class II

PRODUCT CODE: SEE

BACKGROUND

DEVICE NAME: CT-132

SUBMISSION NUMBER: DEN240064

DATE DE NOVO RECEIVED: November 12, 2024

SPONSOR INFORMATION: Click Therapeutics, Inc.
80 White Street
New York, New York 10013

INDICATIONS FOR USE

CT-132 is indicated as follows:

CT-132 is indicated for the preventive treatment of episodic migraine in patients 18 years of age and older. It is intended for adjunctive use alongside acute and/or other preventive treatments for migraine.

LIMITATIONS

- The benefit of treatment with CT-132 on monthly migraine days (MMDs) was not evaluated beyond 12 weeks of treatment. The ability of CT-132 to prevent migraines after treatment discontinuation has not been studied.
- The sale, distribution, and use of the CT-132 are restricted to prescription use in accordance with 21 CFR 801.109.
- The safety and effectiveness of CT-132 has not been established for the acute treatment of migraines.

- The long-term effects of the chronic use of the CT-132 device have not been evaluated.
- The safety and efficacy of the CT-132 device has not been evaluated for pediatric patients < 18 years old.

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

DEVICE DESCRIPTION

The CT-132 device is a prescription digital therapeutic mobile application (App) designed to provide personalized and accessible preventive treatment based on cognitive behavioral therapy (CBT) to patients with episodic migraine. The CT-132 employs cognitive and behavioral components including behavior modification, risk-factor optimization, and medication and adherence. The App is administered on the user's smartphone device (running Apple iOS or Android operating system (OS)).

The CT-132 active treatment consists of four main treatment components:

- Therapeutic modules and daily lessons: There are 12 weeks of therapeutic content delivered in lessons that introduce users to therapeutic content and skills, and/or reinforce the practice or tracking of previously learned skills or behaviors. These lessons are progressive in nature and grouped together into 12 modules based on therapeutic goals.

- Skills: The device provides App-guided skills that are intended to reduce or prevent stress and migraine symptoms. Skills include Progressive muscle relaxation, Paced breathing, Curiosity mindfulness, Self-compassion meditation, Being with pain, Willing hands, Monitor and accept, Describe what you see, Half smile, and Practice good sleep habits.

- Decision Support Tool: The tool asks the user for 1) an assessment of their emotional state, and 2) how much time they have. Based on the user input, the tool recommends an in-app activity for the user from a list of skills.

- Personalized Messaging: Short Message Service (SMS) text messages that promote CT-132 treatment engagement by reinforcing lesson content, reminding users to complete treatment-related activities, and encouraging completion of the program. The messages are generated using a library of message templates.

The CT-132 also includes a Daily Headache Diary which includes functionality to track headache episodes, track migraine medications, and view the user's previously entered Daily Headache Diary history.

SUMMARY OF NONCLINICAL/BENCH STUDIES

SOFTWARE

The De Novo request provided appropriate software documentation and testing consistent with a "Basic" level of software concern as discussed in the FDA guidance document "Content of Premarket Submissions for Device Software Functions," published June 2023. Software validation and verification testing demonstrated that the device met its design and implementation requirements.

CYBERSECURITY

The De Novo request provided appropriate Cybersecurity testing and documentation according to FDA guidance document "Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions," published September 2023.

SUMMARY OF CLINICAL INFORMATION

Clinical data was provided from two prospective, double-blind, sham-controlled, randomized clinical trials: Pivotal Study (CT-132-R-001) and Bridging Study (CT-132-R-002).

The CT-132-R-001 study recruited patients who experienced at least 4 migraine days per month despite taking a prescription drug for acute treatment and/or prevention of migraine (including first- and second-line preventive medications but excluding calcitonin gene-related peptide (CGRP) inhibitor therapy). CGRP inhibitors were excluded because at time of study they were newer to market and less commonly prescribed. However, clinical guidelines have since recommended CGRP inhibitors for migraines. To address this the sponsor conducted study CT-132-R-002 to evaluate the effectiveness of device in patients taking CGRP inhibitors.

The following study elements were the same for both the CT-132-R-001 and CT-132-R-002 studies:

- Both studies were decentralized trials (DCT) with all activities conducted remotely from a single site (i.e., a 'virtual site'). All study activities for both studies were conducted remotely, with run-in and baseline activities conducted via telemedicine. After completing the study onboarding activities during the study screening period, eligible participants were contacted to schedule a run-in visit conducted remotely via video call (utilizing HIPAA compliant Zoom).

- Both studies utilized two digital health technologies (DHT) mobile applications: an electronic patient reported outcome (ePRO) app and the CT-132 Study App. All assessments in both clinical studies were patient reported. Both apps were developed and validated for each study.

- For both studies, a Digital Control within the CT-132 Study App was used as the comparator group. The Digital Control contained 1) a daily control activity and 2) an

electronic diary (eDiary). The daily control activity required participants to respond to six trials per day of a combination of sentence verification and word categorization prompts. In addition to the daily eDiary, the daily control activity was the only activity available to participants randomized to the Digital Control. The Digital Control was designed as a comparable digital experience with similar daily engagement levels as CT-132.

- Both studies used monthly migraine days (MMD), as collected from the eDiary, as the primary endpoint and migraines were defined according to International Classification of Headache Disorders, 3rd Edition (ICHD-III).

- Both studies had the same Exclusion Criteria, Randomization Scheme, Blinding, Study Protocol/Procedures, Primary and Secondary Effectiveness Endpoints, Exploratory Endpoints, and Safety Analysis.

CT-132-R-001 (Pivotal Study)

Study Overview

The CT-132-R-001 pivotal clinical study was a randomized, double-blind, digital-controlled, parallel-group DCT that evaluated the safety and effectiveness of CT-132 as an adjunct treatment to standard of care (SoC) (including acute treatment and first and second-line preventive medicine treatment), relative to a Digital Control, in participants aged 18 years or older diagnosed with episodic migraine.

Key Inclusion Criteria

A participant was eligible for entry into the study if all of the following criteria were met:

1. Was willing and able to provide written informed consent to participate in the study, attend study visits, and comply with study-related requirements and assessments.
2. Lived in the United States.
3. Adult or late adolescent, 18 years of age or older at the time of informed consent.
4. Fluent in written and spoken English, confirmed by ability to read and understand the informed consent form.
5. The following were to be physician-reviewed: Participant had at least a 1-year history of physician-diagnosed migraine (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition (ICHD-3):

    i. Age of onset of migraines prior to 50 years of age
    ii. Migraine attacks, on average, lasting 4-72 hours if untreated
    iii. Per participant report, four or more migraine days per month within the last three months prior to the Screening Visit (a month was defined as 28 days)
    iv. Four to fourteen migraine days during the Run-In Period

6. Was concurrently managing migraines with ≥ one prescription acute treatment and/or prescription first or second-line preventive medications, as assessed by a physician.

7. Was the sole user of an iPhone with an iPhone operating system (iOS) 14 or later or a smartphone with an Android operating system (OS) 11 or later and was willing to download and use the Study App required by the protocol.
8. Was willing and able to receive SMS text messages and push messages on their smartphone.
9. Was the owner of, and had regular access to, an email address.
10. Had regular access to the Internet via cellular data plan and/or Wi-Fi.

Key Exclusion Criteria

A participant was not eligible for study entry if any of the following criteria were met:

1. History of basilar migraine or hemiplegic migraine.
2. Active chronic pain syndromes, such as fibromyalgia, chronic pelvic pain, or complex regional pain syndrome (CRPS).
3. Other pain syndromes (including trigeminal neuralgia), psychiatric conditions (such as major depressive episode, bipolar disorder, major depressive disorder, schizophrenia), dementia, or significant neurological disorders (other than migraine) that, in the investigator's opinion, might interfere with study assessments.
4. History of, treatment for, or evidence of, alcohol or drug abuse within the past 12 months (48 weeks) or having met Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for any significant substance use disorder within the past 12 months (48 weeks) from the date of the Screening Visit.
5. History of use of analgesics (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs] or acetaminophen, including opioids) or butalbital ≥15 days per month during the three months (12 weeks) prior to the Screening Visit or during the Run-In Period.
6. Was concurrently taking a prescription anti-calcitonin gene-related peptide (CGRP) medication for either episodic or chronic migraine.
7. Post-traumatic headache, persistent post-traumatic headache, or post-concussion syndrome.
8. Other significant acute or chronic medical condition(s) that, in the opinion of the investigator, may have confounded the interpretation of findings to inform prescription digital therapeutic (PDT) development.
9. Failure to adhere with or inability to complete Study App inputs and onboarding activities during the Run-In Period. Participants who are not adherent during the Run-In Period were not eligible for study entry.
10. Previous enrollment in any digital therapeutics pilot or pivotal study for a migraine indication.
11. Participation in any other investigational clinical study while participating in this clinical study.

Randomization and Blinding

Subjects were randomized in a 1:1 fashion to treatment with either the CT-123 or the Digital Control. Study participants were blinded to the effectiveness hypothesis of the study. Both treatment arms were presented to the participant as possible treatments for migraine. No references to CT-132 or Digital Control were made to the participant.

Study Procedures

The study objectives were to evaluate the effectiveness and safety of CT-132 in reducing the number of monthly migraine days (MMDs), compared with a Digital Control, among adults 18 years of age and older with episodic migraine.

The study included the following stages (see Figure 1 below.):

- Screening Period (up to 14 days)
- Run-In Period (28 days):
- Intervention Period (12-week double-blind)
- Follow-Up Period for safety assessments (an up-to-7-day)

A participant's baseline MMDs and monthly headache days (MHDs) were the total number of migraine and headache days recorded during the 28-day Run-In Period. The Week 12 MMDs and MHDs were the total number of migraine and headache days recorded over the previous 28 days (Week 9 through Week 12), respectively.

During both the Run-In Period and Intervention Period, participants continued to take their doctor-prescribed acute and first- and second-line preventive medications for the treatment of migraine, while continuing to use the Study App. Participants in the treatment group used the Study App daily for 12 weeks and Participants in the control group used the Digital Control daily for 12 weeks.

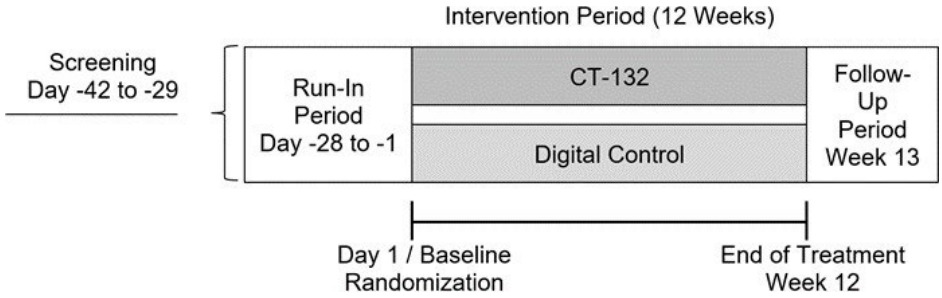

Figure 1: CT-132-R-001 Clinical Study Design

Effectiveness Endpoints

- *Primary Effectiveness Endpoint*
  The primary effectiveness endpoint was change in the number of MMDs from baseline (28-day Run-In Period) to Week 12 (previous 28 days, Week 9 through Week 12).

- *Secondary Effectiveness Endpoints*
  The secondary effectiveness endpoints were:

  - Proportion of participants who have at least a 50% reduction from baseline (28-day Run-In Period) in the number of MMDs to Week 12 (previous 28 days, Week 9 through Week 12)

- Change from baseline (28-day Run-In Period) in the number of MMDs recorded over the previous 28 days at Week 4 (previous 28 days, Week 1 through Week 4) and at Week 8 (previous 28 days, Week 5 through Week 8)
- Reduction from baseline (28-day Run-In Period) in the mean number of MMDs over 12 weeks
- Change in the number of headaches with at least moderate severity from baseline (28-day Run-In Period) to Week 12 (previous 28 days, Week 9 through Week 12)
- Change from baseline (28-day Run-In Period) in the Migraine-Specific Quality-of-Life Questionnaire v2.1 (MSQ) total score over the previous 28 days at Week 4, Week 8, and Week 12
- Change from baseline (28-day Run-In Period) in the Migraine Disability Assessment (MIDAS) to Week 12 (previous 28 days, Week 9 through Week 12)
- Change from baseline (28-day Run-In Period) to Week 12 (previous 28 days, Week 9 through Week 12) in the number of migraines with use of an acute medication
- Change in the number of MHDs from baseline (28-day Run-In Period) to Week 12 (previous 28 days, Week 9 through Week 12)

Safety Analysis

Safety was evaluated by monitoring the frequency and severity of adverse events (AEs), serious AEs (SAEs), and discontinuation from the study due to AEs, as well as the frequency and severity of AEs related to the worsening of migraine.

Statistical Analysis Plan (SAP)

Effectiveness Analysis

The primary effectiveness endpoint was the change in the number of MMDs from baseline (28-day run-in period) to Week 12. The goal of this endpoint is to examine whether there is a difference between the treatment arm and the control in regard to the mean change from baseline to Week 12 in MMDs. The null and alternative hypotheses are defined as follows:

$$H_0: \mu_{-CT123} = \mu_{-DC} \ \ vs. \ \ H_1: \mu_{-CT123} \neq \mu_{-DC}$$

where μ_{-CT123} and μ_{-DC} represented the mean change from baseline to Week 12 in MMDs for treatment and the control arm, respectively. The test was conducted at a two-sided 0.05 alpha level using an analysis of covariance (ANCOVA) model adjusting for treatment, baseline MMDs and concomitant medications. The least squares (LS) mean for the change from baseline along with 95% CI and p-value was used.

The secondary effectiveness endpoints were measured and reported at Week 12, however, they were not used for statistical inference since no multiplicity adjustment was used.

Analysis Population

The primary analysis population for the primary and key secondary endpoints was the intent-to-treat (ITT) population which includes all randomized subjects. In addition, the supportive analyses would also be conducted on the modified ITT (mITT) (including all randomized

subjects who completed at least one of the daily tasks of their assigned digital treatment) and per-protocol (PP) populations (i.e., all participants in the ITT population that do not have protocol deviations that would potentially impact their primary outcomes). Safety data was analyzed by using the Safety Analysis Set, which included all randomized participants who were exposed to the study intervention (completed at least one task).

Missing data handling

Multiple imputation (MI) method was used in the primary analysis for the primary and secondary effectiveness endpoints evaluation. The MI process used 100 repeats in the analysis datasets generated. In addition, sensitivity analyses for the primary endpoints using different missing data imputation strategies were conducted to assess the potential impact from missing data on the study conclusion.

Clinical Study Results

Subject Disposition

The study was initiated on March 28, 2023. Among 1842 patients enrolled, 286 subjects were randomized to the CT-123 arm and 284 were assigned to the Digital Control arm. Seven (9.3%) participants discontinued from the study, among which 3 withdrew consent (1 in CT-132 and 2 in Digital Control), 12 (22.6%) were lost to follow-up (8 in CT-132 and 12 in Digital Control), and 8 (15.1%) subjects were withdrawn by the medical monitor (6 in CT-132 and 2 in Digital Control) due to a significant medication change that constituted a major protocol deviation. The disposition of all study participants is summarized in Table 1. Out of all 570 randomized patients, 568 were included in the ITT analyses.

Table 1 Patient Enrollment and Accountability

	CT-132		**Digital Control**		**Total**	
	n	**%**	**n**	**%**	**n**	**%**
Screened	-		-		14,514	-
Enrolled[a]	-		-		1.842	-
Randomized	286	(100)	284	(100)	54	(100)
ITT Set[a]	285	(99.7)	283	(99.6)	568	(99.6)
Completers	255	(89.2)	262	(92.3)	517	(90.7)
Discontinued	31	(10.8)	22	(7.7)	53	(9.3)

ITT = Intent-to-Treat

[a] 1 potential participant was inadvertently randomized during screening but had no baseline data; 1 was randomized before the Run-in Period was complete.

There was a total of 30 major protocol deviations recorded for the ITT population, including 15 deviations in each group and 1318 (296 subjects) minor deviations. The 30 major deviations included: 16 prohibited medications; 13 subjects had protocol-specified deviation; and one subject had deviation in regard to informed consent.

Baseline Demographics

Baseline demographics are summarized by treatment arms based on the ITT population in Table 2 below. The two study arms were in general balanced regarding baseline characteristics. Most enrolled subjects were female (92.3% in the CT-132 vs 93.6% in the Control). The mean age at

baseline was 38.7 years (38.4 in the CT-132 vs 38.9 in the Control). About 60% of the study population were between the age of 36 to 64 years old. The population was mostly White or Caucasian (93.3%) and not of Hispanic or Latino origin.

Approximately 98% of participants overall used concomitant meds. About 47% of participants had sumatriptan or ibuprofen as a concomitant medication, and almost 31% of participants in each arm had paracetamol or another migraine medication (e.g., acetylsalicylic acid, caffeine) as a concomitant medication.

Table 2: Participant Demographics (ITT Set)

	CT-132 (N=285)	**Digital Control (N=283)**	**Total (N=568)**
Participants with Data (n [%])	285 (100.0)	283 (100.0)	568 (100.0)
Sex (n [%])			
Female	263 (92.3)	265 (93.6)	528 (93.0)
Male	12 (4.2)	13 (4.6)	25 (4.4)
Other	10 (3.5)	5 (1.8)	15 (2.6)
Age (years)			
Mean (SD)	38.4 (±10.4)	38.9 (±10.3)	38.7 (±10.3)
Median	38.0	38.0	38.0
Range	18, 76	18, 73	18, 76
Age Category (n [%])			
18-21	9 (3.2)	11 (3.9)	20 (3.5)
22-35	109 (38.2)	98 (34.6)	207 (36.4)
36-64	166 (58.2)	172 (60.8)	338 (59.5)
65 and older	1 (0.4)	2 (0.7)	3 (0.5)
Ethnicity (n [%])			
Hispanic or Latino	10 (3.5)	13 (4.6)	23 (4.0)
Not Hispanic or Latino	275 (96.5)	270 (95.4)	545 (96.0)
Race (n [%])			
American Indian or Alaska Native	1 (0.4)	3 (1.1)	4 (0.7)
Asian	1 (0.4)	1 (0.4)	2 (0.4)
Black or African American	6 (2.1)	6 (2.1)	12 (2.1)
Multiple	8 (2.8)	12 (4.2)	20 (3.5)
White or Caucasian	269 (94.4)	261 (92.2)	530 (93.3)
Region (n [%])			
Midwest	80 (28.1)	78 (27.6)	158 (27.8)
Northeast	59 (20.7)	49 (17.3)	108 (19.0)
South	94 (33.0)	95 (33.6)	189 (33.3)
West	52 (18.2)	60 (21.2)	112 (19.7)
Unknown	0 (0)	1 (0.4)	1 (0.2)

ITT = Intent-to-Treat; SD = standard deviation

Note: Regions were defined as: Midwest: Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota and Wisconsin; Northeast: Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island and Vermont; South: Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia and West Virginia; West: Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Washington and Wyoming.

Primary Effectiveness Endpoint

Table 3 shows the primary analysis (ANCOVA) using multiple imputation (MI) to account for missing data and/or early termination. This analysis shows that among the 285 CT-132 subjects, the LS mean MMDs change from baseline was -3.04 days; while among the 283 control subjects, the LS mean MMDs change from baseline was -2.14. Both groups showed improvement, however, the CT-132 improved more (-3.04 vs -2.14). The estimated treatment effect between the two study arms (LS mean difference between the CT-132 arm and control arm) was −0.9 day with corresponding 95% CI (-1.53, -0.27). This means that on average the CT-132 experienced 0.9 (as nearly as one day) fewer migraine days per month when compared to the control. At two-sided alpha level of 0.05, the primary effectiveness endpoint at Week 12 was met (p-value=0.005 < 0.05).

Table 3: Primary Effective Analysis: MMDs Change from Baseline (ITT Set)

MMDs Change from Baseline		**CT-132 (N=285)**	**Digital Control (N=283)**	**Difference between Arms**
12 Weeeks	LS Mean	-3.04	-2.14	-0.90
	95% CI	(-3.49, -2.58)	(-2.59, -1.69)	(-1.53, -0.27)
	p-Value	--	--	**0.005**

CI = confidence interval; ITT = Intent-to-Treat; SD = Standard Deviation; LS = Least Squares; MMDs = monthly migraine days

Observed Data: Mean Change in Number of MMDs by Study Period (ITT Set)

Table 4 below shows the change in the number of MDDs by study period for observed data. Due to days with missing reports the overall number of MMDs may be underestimated in this table. The number of MMDs were calculated for periods with one or more diary days. The number of MMDs reduced from baseline in each period, with the largest reduction for the period Week 9 to Week 12. The reduction was larger for the CT-132 arm than in the Digital Control arm for each treatment period.

Table 4: Observed Data - Change in Number of MMDs by Study Period (ITT Set)

Treatment Period	**CT-132 (N=285)**		**Digital Control (N=283)**	
	Actual	**Change from Baseline**	**Actual**	**Change from Baseline**
Baseline (Run-In Period)				
Participants with data (n)	285	--	283	--
Mean (SD)	7.82 (2.85)	--	7.45 (2.78)	--
Week 1 to Week 4				
Participants with data (n)	280	280	278	278
Mean (SD)	6.27 (4.25)	-1.58	6.29 (3.95)	-1.20
Week 5 to Week 8				
Participants with data (n)	277	277	275	275
Mean (SD)	5.59 (4.36)	-2.24	5.64 (4.09)	-1.87
Week 9 to Week 12				
Participants with data (n)	266	266	264	264

Treatment Period	CT-132 (N=285)		Digital Control (N=283)	
	Actual	Change from Baseline	Actual	Change from Baseline
Mean (SD)	4.49 (3.95)	-3.35	5.30 (4.06)	-2.26

ITT = Intent-to-Treat; MMDs = monthly migraine days; SD = standard deviation

Observed Data: Monthly Migraine Days (MMDs) by Range of Change

Table 5 summarizes the change in MMDs from baseline to Week 12. The data presented is based on observed data, using no proration or multiple imputation. In the CT-132 arm, 18.4% of participants saw improvement by more than 6 MMDs, as opposed to 11.7% in the Digital Control arm. At 3-6 MMDs improvement, there were 32.4% of participants in the CT-132 arm and 25.4% in the Digital Control arm. There were approximately 28.9% of participants in the CT-132 arm who experienced only a small improvement by 0-3 MMDs, as opposed to 34.1% in the Digital Control Arm. About 28.8% of participants in the Digital Control arm deteriorated compared to baseline (meaning their change from baseline was ≥0), while only about 20.3% of participants in the CT- 132 deteriorated.

Table 5: Observed Data - MMDs by Range of Change (ITT Set)

Change in MMDs from Baseline	CT-132 (N=285)	Digital Control (N=283)
	n (%)	n (%)
All	266 (100.0)	264 (100.0)
Change from Baseline ≥ 0 (increase in Migraines)	54 (20.3)	76 (28.8)
-3 to 0 Change from Baseline	77 (28.9)	90 (34.1)
> -3 to -6 Change from Baseline	86 (32.4)	67 (25.4)
> -6 Change from Baseline	49 (18.4)	31 (11.7)

ITT = Intent-to-Treat; MI = multiple imputation; MMDs = monthly migraine days Note: This table is based on observed data, using no proration and no MI.

Key Secondary Effectiveness Endpoints

In general, beneficial treatment effect trend was observed regarding key secondary endpoints (Table 6 to Table 13 below), however, *no multiplicity adjustment was used, no hypothesis testing for all secondary endpoints*.

MMD Responders

The primary analysis result of the first secondary effectiveness endpoint was the responder rate, i.e., the proportion of subjects who had at least a 50% reduction in the number of MMDs. Over the 12-week treatment period, the proportion of subjects who had at least 50% reduction in the MMD was 47.9% (136/258) in CT-132 and 39.9% (113/283) in the control arm (Table 6).

Table 6: Proportion of MMD Responders at Week 12 (ITT Set)

ITT Set MMD Responders	CT-132 (N=285)	Digital Control (N=283)	Difference between Arms
ITT Set Responders (estimate using MI)	47.89%	39.99%	7.9%

ITT = Intent-to-Treat; MI = multiple imputation; MMDs = monthly migraine days

MMD Change from Baseline

The change from baseline (28-day Run-in Period) in the number of MMDs recorded over the previous 28 days at Week 4 and at Week 8 is shown in Table 7. Participants in the CT-132 arm showed a greater reduction in MMDs.

Table 7: Change from Baseline in the Number of MMD Recorded over the Previous 28 Days at Week 4 and Week 8 (ITT Set)

MMD Change from Baseline		**CT-132 (N=285)**	**Digital Control (N=283)**	**Difference between Arms**
Week 4	LS Mean	-1.51	-1.25	-0.26
Week 8	LS Mean	-1.90	-1.79	-0.12

ITT = Intent-to-Treat; LS = Least Squares; MMDs = monthly migraine day

Reduction from Baseline in the Mean Number of MMDs over 12 Weeks

The reduction in the CT-132 arm continued over the full 12 weeks, with increasing reduction in MMDs and an increasing difference with the Digital Control arm as treatment progressed (Table 8).

Table 8: MMD Change from Baseline over Week 12 (ITT Set)

MMD Change from Baseline (Over 12 Weeks (ITT Set)	**CT-132 (N=285)**	**Digital Control (N=283)**	**Difference between Arms**
n	285	283	--
LS Mean	-2.15	-1.72	-0.42

ITT = Intent-to-Treat; LS = Least Squares; MMD = monthly migraine days

Change in the Number of MHDs with at Least Moderate Severity from Baseline (28-Day Run-In Period) to Week 12 (Previous 28 Days, Week 9 Through Week 12)

A difference in favor of the CT-132 arm was observed in the reduction of MHDs with at least moderate severity (Table 9). This indicates that CT-132 may reduce the severity of headaches, in addition to reducing the total number of headaches.

Table 9: MHDs with at Least Moderate Severity at Week 12 (ITT Set)

MHDs Change from Baseline		**CT-132 (N=285)**	**Digital Control (N=283)**	**Difference between Arms**
Baseline	**Mean**	6.21	5.98	--
	SD	2.75	2.80	
	Median	6.00	5.00	
	Range (min, max)	0, 18.0	1.0, 17.0	
Week 12 (ITT Set)	**n**	285	283	--
	LS Mean	-3.44	-2.91	-0.53

ITT = Intent-to-Treat; LS = Least Squares; max = maximum; MHDs = monthly headache days; min = minimum; SD = standard deviation

Change from Baseline in the Migraine-Specific Quality-of-Life Questionnaire v2.1 (MSQ) at Week 4, Week 8 and Week 12 (ITT Set)

A higher MSQ number indicates a better quality of life (QoL). The change from baseline was consistently higher for the CT-132 arm than for the Digital Control arm. Both the improvement in MSQ and the difference between arms increased at each subsequent timepoint (Table 10).

Table 10: Change from Baseline in the Migraine-Specific Quality-of-Life Questionnaire v2.1 (MSQ) at Week 4, Week 8 and Week 12 (ITT Set)

MSQ Change from Baseline		CT-132 (N=285)	Digital Control (N=283)	Difference between Arms
Baseline	**Mean**	57.88	56.49	--
	SD	16.08	17.37	--
	Median	58.57	58.57	--
	Range (min, max)	8.6, 98.6	2.9, 92.9	--
Week 4	**LS Mean**	6.37	1.91	4.46
Week 8	**LS Mean**	9.32	4.10	5.22
Week 12	**LS Mean**	12.30	4.68	7.62

ITT = Intent-to-Treat; LS = Least Squares; max = maximum; min = minimum; MSQ = Migraine-Specific Quality-of-Life Questionnaire; SD = standard deviation

Change from Baseline in the Migraine Disability Assessment (MIDAS) at Week 12

A lower score on the MIDAS indicates lower disability. A reduction in total MIDAS score is thus a better outcome. The distribution of MIDAS was skewed; examination of the means and medians favored the CT-132 arm (Table 11).

Table 11: Change from Baseline in the Migraine Disability Assessment (MIDAS) at Week 12 (ITT Set)

MIDAS Descriptive Statistics	CT-132 (N=285)	Change from Baseline	Digital Control (N=283)	Change from Baseline
Median	26.00	-8.00	34.50	-0.50
Range (Min, Max)	0, 220.0	-131.0, 98.0	0, 245.0	-112.0, 122.0

ITT = Intent-to-TreatMIDAS = Migraine Disability Assessment

Change from Baseline in the Number of Migraines with Use of an Acute Medication

There was a reduction in use of acute medications for migraine that favored the CT-132 arm (Table 12). For the ITT Set, this reduction was greater at each measured time point (Week 4, Week 8 and Week 12).

Table 12: Change from Baseline in the Number of Migraines with Use of an Acute Medication

		CT-132 (N=285)	Digital Control (N=283)	Difference between Arms
Baseline	**Mean**	5.01	5.11	--
	SD	2.35	2.55	
	Median	5.00	5.00	
	Range (min, max)	0, 13.0	0, 13.0	
Week 4 (ITT Set)	**LS Mean**	-1.41	-1.23	-0.18
Week 8 (ITT Set)	**LS Mean**	-2.37	-1.99	-0.38

		CT-132 (N=285)	Digital Control (N=283)	Difference between Arms
Week 12 (ITT Set)	**LS Mean**	-2.75	-2.45	-0.31

ITT = Intent-to-Treat; LS = Least Squares; max = maximum; min = minimum; SD = standard deviation

Change from Baseline to Week 4, Week 8 and Week 12 in Number of MHDs

Change from baseline to Week 12 in number of MHDs was a secondary endpoint. Change from baseline to Week 4 and to Week 8 in number of MHDs were exploratory endpoints. These are shown in Table 13.

The reduction in number of MHDs favored the CT-132 arm over the Digital Control arm. The mean number of MHDs over 12 weeks was calculated as the average of MHDs over each 4-week period (Weeks 1-4, Weeks 5-8 and Weeks 9-12), to get the average number of MHDs. The reduction from baseline was calculated as the mean number of MHDs over 12 weeks minus the baseline MHDs. The results showed reduction favoring the CT-132 arm.

Table 13: Change from Baseline to Week 4, Week 8 and Week 12 in Number of MHDs (ITT Set)

MHDs Change from Baseline		**CT-132 (N=285)**	**Digital Control (n=283)**	**Difference between Arms**
Baseline	**Mean**	11.52	11.13	--
	SD	4.00	3.79	
	Median	11.00	11.00	
	Range (min, max)	4.0, 24.0	4.0, 27.0	
Week 4 (ITT Set)	**LS Mean**	-2.05	-1.68	-0.38
Week 8 (ITT Set)	**LS Mean**	-3.10	-2.70	-0.39
Week 12 (ITT Set)	**LS Mean**	-4.41	-3.57	-0.82

ITT = Intent-to-Treat; LS = Least Squares; max = maximum; MHDs = migraine headache days; min = minimum; SD = standard deviation

Safety Evaluation

Study safety was evaluated by monitoring the frequency and severity of adverse events (AEs), serious adverse events (SAE), and discontinuation from the study due to AEs, as well as the frequency and severity of AEs related to the worsening of migraine. The overall rate of treatment-emergent adverse events (TEAEs) was 6.8%, with 7.9% in the CT-132 arm and 5.8% in the Digital Control arm. Most AEs were mild or moderate, only three TEAEs were severe, and one non-TEAE was severe. No AEs were considered related to treatment intervention. There were no discontinuations or deaths due to AEs. Non-TEAE percentages in each arm were similar, occurring in 3.96% of participants in the CT-132 arm and 2.88% of participants in the Digital Control arm. See Table 14 below.

There was one treatment-emergent SAE of peritonsillar abscess, which occurred in the CT-132 arm but was not related to the investigational product. Three participants (one in the CT-132 arm and two in the Digital Control arm) experienced a TEAE related to worsening of migraines.

Table 14: Overall Summary of Adverse Events (Safety Analysis Set)

	CT-132 (N=278)		Digital Control (N=278)		Total (N=556)	
	n (%)	**m**	**n (%)**	**m**	**n (%)**	**m**
Any TEAE	22 (7.91)	26	16 (5.76)	22	38 (6.83)	48
Any non-TEAE	11 (3.96)	11	8 (2.88)	8	19 (3.42)	19
Any Serious TEAE	1 (0.36)	1	0 (0)	0	1 (0.18)	1

CT-132-R-002 (Bridging Study)

Study Overview

The CT-132-R-002 study was designed as randomized, double blinded, digital-controlled, decentralized trial (DCT) to evaluate the safety and effectiveness at 12 weeks of daily therapy with CT-123 in adults with episodic migraine currently receiving CGRP inhibitor therapy.

This study was intended to explore potential benefits of CT-132 in addition to CGRP inhibitors, which was a relatively new class of migraine preventive treatment when the study was conducted. Furthermore, this study was not powered to test a statistical hypothesis and had no predefined success criteria.

CT-132-R-002 had the same Exclusion Criteria, Randomization Scheme, Blinding, Study Procedures, Primary and Secondary Effectiveness Endpoints, and Safety Analysis as CT-132-R-001.

Key Inclusion Criteria

Inclusion criteria for study CT-132-R-002 were the same as for study CT-132-R-001 except for inclusion criterion #6. Inclusion criterion #6 for the CT-132-R-002 study stated the following: Was concurrently managing migraines with ≥ 1 prescription CGRP inhibitor therapy for the preventative or acute treatment of episodic or chronic migraine during the 3 months prior to screening.

Statistical Analysis Plan (SAP)

This was a bridging study and was not powered. Therefore, one cannot make any statistical claims.

Clinical Study Results

Subject Disposition

In total, 110 participants were randomized in the study from July 2023 to May 2024, among which 54 subjects were enrolled in CT-123 and 56 subjects were enrolled under digital control. The disposition of all study participants is summarized in Table 15. Out of all 305 randomized patients, 110 (54 CT-132 and 56 Digital Control) were included in the ITT analyses.

Table 15: Patient Enrollment and Accountability

	CT-132		Digital Control		Total	
	n	%	n	%	n	%
Screened	-		-		1,354	-
Enrolled[a]	-		-		305	-
Randomized	54	(100.0)	56	(100.0)	110	(100.0)
ITT Set[a]	54	(100.0)	56	(100.0)	110	(100.0)
Completers	53	(98.1)	54	(96.4)	107	(97.3)
Discontinued	1	(1.9)	2	(3.6)	3	(2.7)

ITT = Intent-to-Treat

[a] All enrolled participants who were randomized.

Baseline Demographics

Baseline demographics are summarized by treatment arms based on the ITT population in Table 16 below. Participants were mostly female (94.4% in the CT-132 arm and 96.4% in the Digital Control arm). The mean age at baseline was 36.1 years (36.2 in the CT-132 arm and 36.1 in the Digital Control arm). The population was mostly White or Caucasian and not of Hispanic or Latino origin. Participants were representative of all regions in the US. The two arms were generally balanced.

Table 16: Participant Demographics (ITT Set)

	CT-132 (N=54)	Digital Control (N=56)	Total (N=110)
Sex (n [%])			
Female	3 (5.6)	2 (3.6)	5 (4.5)
Male	51 (94.4)	54 (96.4)	105 (95.5)
Age (years)			
Mean (SD)	36.2 (±10.7)	36.1 (±10.2)	36.1 (±10.4)
Median	32.0	34.5	34.0
Range	19, 63	21, 68	19, 68
Age Category (n [%])			
18-21	1 (1.9)	1 (1.8)	2 (1.8)
22-35	27 (50.0)	30 (53.6)	57 (51.8)
36-64	26 (48.1)	23 (41.1)	49 (44.5)
65 and older	0	2 (3.6)	2 (1.8)
Ethnicity (n [%])			
Hispanic or Latino	10 (3.5)	13 (4.6)	23 (4.0)
Not Hispanic or Latino	275 (96.5)	270 (95.4)	545 (96.0)
Race (n [%])			
American Indian or Alaska Native	0	0	0
Asian	1 (1.9)	1 (1.8)	2 (1.8)
Black or African American	2 (3.7)	3 (5.4)	5 (4.5)
Multiple	0	3 (5.4)	3 (2.7)
White or Caucasian	51 (94.4)	49 (87.5)	100 (90.9)
Region (n [%])			
Midwest	13 (24.1)	15 (26.8)	28 (25.5)
Northeast	14 (25.9)	17 (30.4)	31 (28.2)

	CT-132 (N=54)	Digital Control (N=56)	Total (N=110)
South	18 (33.3)	17 (30.4)	35 (31.8)
West	9 (16.7)	7 (12.5)	16 (14.5)

ITT = Intent-to-Treat; SD = standard deviation

Note: Regions were defined as: Midwest: Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota and Wisconsin; Northeast: Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island and Vermont; South: Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia and West Virginia; West: Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Washington and Wyoming.

Analysis Sets

Table 17 describes the analysis sets. The primary analysis was conducted on the ITT Set. The Safety Analysis Set was used for safety analyses.

Table 17: Analysis Sets

	CT-132		Digital Control		Total	
	n	(%)	n	(%)	n	(%)
Enrolled Analysis Set	--	--	--	--	305	--
Participants Randomized	54	(100.0)	56	(100.0)	110	(100.0)
ITT Set	54	(100.0)	56	(100.0)	110	(100.0)
Safety Analysis Set	54	(100.0)	56	(100.0)	110	(100.0)

ITT = Intent-to-Treat

Primary Effectiveness Endpoint

Table 18 shows the primary analysis (ANCOVA) using multiple imputation (MI) to account for missing data and/or early termination. The primary effectiveness endpoint showed an absolute difference favoring CT-132, with a mean reduction of 2.13 MMDs from baseline and a mean reduction of 1.34 MMDs reduction for the Digital Control arm. The ITT analysis showed that the LS means of the difference between the treatment groups (CT-132 - Digital Control) was −0.7 with 95% CI (−2.3, 0.9), with LS mean score changes of −1.8 (CI, (−3.1, -0.5)) for the CT-132 group and −1.1 (CI, (−2.2, -0.1)) for the Digital Control group. *Therefore, the primary endpoint data indicated beneficial treatment effect trend. However, note that since the study was not powered, we cannot make any statistical claims even though the primary effectiveness endpoint was not met statistically.*

Table 18: Primary Effective Analysis: MMDs Change from Baseline (ITT Set)

MMDs Change from Baseline		CT-132 (N=54)	Digital Control (N=56)	Difference between Arms
Week 12	Observed Mean	-2.13	-1.34	-0.79
	Standard Deviation	3.29	3.82	-
	LS Mean	-1.8	-1.1	-0.70
	95% CI	(-3.1, -0.5)	(-2.2, -0.1)	(-2.3, 0.9)
	p-Value	--	--	0.3978

CI = confidence interval; ITT = Intent-to-Treat; LS = Least Squares; MMDs = monthly migraine days

Monthly Migraine Days (MMDs) by Range of Change

Table 19 summarizes the change in MMDs from baseline to Week 12. Among those who reported no change in their MMDs from baseline at Week 12, a greater proportion of Digital Control participants (10.7%) was observed than CT-132 participants (5.6%). A greater proportion of CT-132 participants was observed than Digital Control participants for those reporting a reduction between 0 and 3 MMDs (46.3% for CT-132, 41% for Digital Control), between 4 and 6 MMDs (25.9% for CT-132, 21.4% for Digital Control), or more than 6 MMDs (7.4% for CT-132, 3.6% for Digital Control) at Week 12.

Table 19: Primary Analysis of MMDs by Range of Change (ITT Set)

Change in MMDs from Baseline	CT-132 (N=54) n (%)	Digital Control (N=56) n (%)
All	54 (100.0)	56 (100.0)
No change	3 (5.6)	6 (10.7)
-3 to 0 Change from Baseline	25 (46.3)	23 (41.0)
-4 to -6 Change from Baseline	14 (25.9)	12 (21.4%)
> -6 Change from Baseline	4 (7.4)	2 (3.6)

ITT = Intent-to-Treat; MI = multiple imputation; MMDs = monthly migraine days Note: This table is based on observed data, using no proration and no MI.

Secondary Effectiveness Endpoints

In general, beneficial treatment effect trend was observed regarding all the secondary endpoints (Table 20 to Table 26 below), however, *the primary endpoint was not statistically powered and no multiplicity adjustment was used, therefore, there is no hypothesis testing for all secondary endpoints.*

Proportion of Participants Who Had at Least a 50% Reduction from Baseline in the Number of MMDs at Week 12

This endpoint was calculated as the percentage of participants who had at least a 50% response to those who did not. In the CT-132 arm, 39.6% of participants had a 50% or greater reduction in MMDs from baseline to Week 12, while 35.2% of Digital Control participants had a 50% or greater reduction (Table 20).

Table 20: Proportion of Participants with at Least 50% Reduction in Number of MMDs from Baseline to Week 12 (ITT Set)

	CT-132 (N=54)	Digital Control (N=56)
Number of participants with data (n)	53	54
Responders (n[%])[a]	21 (39.6)	19 (35.2)
Non-Responders (n[%])[a]	32 (60.4)	35 (64.8)
Proportion of Responders[b]	0.34	0.35

ITT = Intent-to-Treat; MMDs = monthly migraine days

a Based on observed data

b Based on imputed data

Change from Baseline in the Mean Number of MMDs over 12 Weeks

The change from baseline over 12 weeks was calculated as the difference between the MMD

value for the Run-in Period and the average of the number of MMDs for the three months of the Intervention Period (Table 21). Over 12 weeks, CT-132 participants had an LS Mean reduction of 2.1 MMDs, and Digital Control participants had an LS Mean reduction of 0.8 MMDs. The LS mean treatment difference of 1.3 MMDs favored CT-132.

Table 21: MMD Change from Baseline over 12 Weeks (ITT Set)

MMD Change from Baseline		**CT-132 (N=54)**	**Digital Control (N=56)**	**Difference between Arms**
Over 12 Weeks (ITT Set)	n	54	56	--
	LS Mean	-2.1	-0.8	-1.3

ITT = Intent-to-Treat; LS = Least Squares; MMDs = monthly migraine days

Change in the Number of Headaches with at Least Moderate Severity from Baseline to Week 12

To assess the frequency of more severe headaches over time, an analysis of the change in number of headaches with at least moderate severity from baseline to Week 12 was conducted (Table 22). CT-132 participants had an LS mean reduction of 2.5 headaches of moderate or severe intensity from Baseline to Week 12, while Digital Control participants had a mean reduction of 1.9 moderate-or-severe headaches (LS mean treatment difference of 0.6 favoring CT-132).

Table 22: MHDs with at Least Moderate Severity at Week 12 (ITT Set)

MHDs Change from Baseline		**CT-132 (N=54)**	**Digital Control (N=56)**	**Difference between Arms**
Baseline	Mean	5.6	5.4	--
	SD	2.60	1.98	--
	Median	5.0	5.0	--
	Range (min, max)	2, 13	1, 10	--
Week 12 (ITT Set)	n	53	54	--
	LS Mean	-2.5	-1.9	-0.6

ITT = Intent-to-Treat; LS = Least Squares; max = maximum; MHDs = monthly headache days; min = minimum; SD = standard deviation

Change from Baseline (in the Migraine-Specific Quality-of-Life Questionnaire v2.1 (MSQ) Total Score over the Previous 28 Days at Week 4, Week 8 and Week 12

To assess migraine-specific quality of life, changes from baseline to Week 4, Week 8 and Week 12 were analyzed (Table 23). At Week 4, participants in the CT-132 arm reported a LS mean increase from baseline in MSQ total score of 3.6 versus an increase in the Digital Control arm of 2.5 (LS mean treatment difference of 1.1 favoring CT-132). At Week 8, participants in the CT-132 arm reported a LS mean increase from baseline of 7.1 versus an increase in the Digital Control arm of 5.9 (treatment difference of 1.3 favoring CT-132). At Week 12, participants in the CT-132 arm reported a LS mean increase from baseline of 7.8 versus an increase in the Digital Control arm of 6.1 (LS mean treatment difference of 1.7 favoring CT-132).

Table 23: Change from Baseline in the Migraine-Specific Quality-of-Life Questionnaire v2.1 (MSQ) at Week 4, Week 8 and Week 12 (ITT Set)

MSQ Change from Baseline		CT-132 (N=54)	Digital Control (N=56)	Difference between Arms
Baseline	Mean	59.0	56.0	--
	SD	17.26	17.14	--
	Median	60.0	60.0	--
	Range (min, max)	0, 90	17, 90	--
Week 4	LS Mean	3.6	2.5	1.0
Week 8	LS Mean	7.1	5.9	1.3
Week 12	LS Mean	7.8	6.1	1.7

LS = Least Squares; max = maximum; min = minimum; MSQ = Migraine-Specific Quality-of-Life Questionnaire; SD = standard deviation

Change from Baseline in the Migraine Disability Assessment Scale (MIDAS) to Week 12

To assess change in disability from baseline to Week 12, an analysis of MIDAS scores was conducted. Participants in the CT-132 arm had an average MIDAS score reduction of 7.0, and participants in the Digital Control arm had an average MIDAS score reduction of 5.7. (Table 24).

Table 24: Change from Baseline in the Migraine Disability Assessment Scale (MIDAS) at Week 12 (ITT Set)

MIDAS Descriptive Statistics		CT-132 (N=54)	Change from Baseline	Digital Control (N=56)	Change from Baseline
Baseline	n	54	--	55	--
	Mean	46.3	--	47.0	--
	SD	40.7	--	43.56	--
	Median	37.0	--	35.0	--
	Range (min, max)	3, 231	--	0, 229	--
Week 12	n	53	53	54	53
	Mean	39.1	-7.0	42.0	-5.7
	SD	35.99	28.46	37.91	37.43
	Median	26.0	-4.0	29.5	-4.0
	Range (min, max)	0, 160	-101, 55	0, 159	-160, 74

ITT = Intent-to-Treat; LS = Least Squares; max = maximum; MIDAS = Migraine Disability Assessment Scale; min = minimum; SD = standard deviation

Change from baseline (28-day Run-in Period) over the previous 28 days at Week 4 and Week 8 in the number of migraines with use of an acute medication.

The change from baseline over the previous 28 days at Week 4 and at Week 8 in the number of migraines with use of an acute medication was also an endpoint (Table 25). From baseline means of 5.7 and 5.9 migraines with use of an acute medication, respectively, at Week 4, participants in the CT-132 arm (mean = 4.6) had a LS mean reduction of 1.2 such migraines, while participants in the Digital Control arm (mean = 5.4) had a reduction of 0.6 migraines (treatment difference of 0.7 favoring CT-132). At Week 8, participants in the CT-132 arm (mean = 3.6) had a LS mean reduction of 2.2 migraines, while participants in the Digital Control arm (mean = 4.3) had a reduction of 1.6 migraines (treatment difference of 0.6 favoring CT-132).

Table 25: Change from Baseline to Week 4, Week 8 and Week 12 in Number of Migraines with Use of an Acute Medication (ITT Set)

		CT-132 (N=54)	Digital Control (N=56)	Difference between Arms
Baseline	Mean	5.7	5.9	--
	SD	2.69	2.78	--
	Median	6.0	6.0	--
	Range (min, max)	0, 14	0, 12	--
Week 4 (ITT Set)	n	53	55	--
	LS Mean	-1.2	-0.6	-0.7
Week 8 (ITT Set)	n	53	54	--
	LS Mean	-2.2	-1.6	-0.6
Week 12 (ITT Set)	n	53	54	--
	LS Mean	-2.6	-2.0	-0.6

ITT = Intent-to-Treat; LS = Least Squares; max = maximum; min = minimum; SD = standard deviation

Change in the Number of MHDs from Baseline to Week 12

Change in the number of monthly headaches of any severity was assessed by analyzing differences in MHDs from baseline to Week 12 (Table 26). The CT-132 arm averaged 12.25 MHDs at baseline, compared to the Digital Control arm average of 11.28 MHDs. At Week 12, participants in the CT-132 arm had a LS mean reduction of 3.4 MHDs, while participants in the Digital Control arm had a reduction of 2.1 MHDs (treatment difference of 1.3 favoring CT-132). Over 12 weeks, participants in the CT-132 arm had an LS Mean reduction of 3.0 MHDs, while participants in the Digital Control arm had a reduction of 1.8 MHDs (treatment differences of -1.2).

Table 26: Change from Baseline Week 12 in Number of MHDs (ITT Set)

MHDs Change from Baseline		CT-132 (N=54)	Digital Control (n=56)	Difference between Arms
Baseline	Mean	12.25	11.28	--
	SD	4.65	3.80	--
	Median	11.70	11.00	--
	Range (min, max)	5.0, 28.0	5.0, 26.0	--
Week 12 (ITT)	LS Mean	-3.4	-2.1	-1.3
Over 12 Weeks (ITT)	LS Mean	-3.0	-1.8	-1.2

ITT = Intent-to-Treat; LS = Least Squares; max = maximum; MHDs = migraine headache days; min = minimum; SD = standard deviation

Safety Evaluation

Adverse events are summarized in Table 27. The overall rate of TEAE was low (19.1%). In the CT-132 arm, 13% of the participants experienced an AE and 25% of participants in the Digital Control arm experienced an AE. No TEAE were considered related to treatment. All AE were mild or moderate; none were severe. One serious TEAE occurred in the CT-132 arm (postural orthostatic tachycardia syndrome (POTS)). There were no deaths or discontinuations due to AEs. In the CT-132 arm, 16.7% of participants experienced non-TEAE; 5.4% of participants in the Digital Control arm experienced non-TEAE.

Table 27: Overall Summary of Adverse Events (Safety Analysis Set)

	CT-132 (N=54)		Digital Control (N=56)		Total (N=110)	
	n (%)	**m**	**n (%)**	**m**	**n (%)**	**m**
Any TEAE	7 (13.0)	11	14 (25.0)	19	21 (19.1)	30
Any non-TEAE	9 (16.7)	11	3 (5.4)	3	12 (10.9)	14
Any Serious TEAE	1 (1.9)	1	0 (0)	0	1 (0.9)	1
Any TEAE related to worsening of migraine	2 (3.7)	2	5 (8.9)	5	7 (6.4)	7
Any related TEAE	0 (0)	0	0 (0)	0	0 (0)	0
Any TEAE Leading to Death	0 (0)	0	0 (0)	0	0 (0)	0
Any TEAE Leading to Study Discontinuation	0 (0)	0	0 (0)	0	0 (0)	0

AE = adverse event; ICF = informed consent form; m = number of events; n = number of participants; TEAE = treatment-emergent adverse events

Note: AE were recorded from date of signing the ICF and were coded by system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) version 26.0.

Pediatric Extrapolation

CT-132 is indicated for patients 18 years of age and older. For medical devices, the FD&C Act defines patients before their 22nd birthday as pediatric patients. In this De Novo request, data from patients between 18-21 were used to support the use of the device in patients over the age of 18. It was appropriate to indicate the device for individuals 18 and older because of this data and patients aged 18 to 21 do not carry additional differences or risks relative to the patient population studied.

LABELING

The labeling meets the requirements of 21 CFR Part 801.109 for prescription devices.

The labeling includes instructions explaining how to use the CT-132 App, identification of compatible devices and operating systems, a warning that the device is not intended as a standalone therapy, and a warning that the device is not intended to substitute for any medications.

The labeling also includes a detailed summaries of the Pivotal Study (CT-132-R-001) and Bridging Study (CT-132-R-002) supporting this De Novo request.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the computerized behavioral therapy device for headache.

Risks to Health	Mitigation Measures
Device provides ineffective treatment, leading to worsening condition	Clinical performance testing Software verification, validation, and hazard analysis Labeling
Device software failure, leading to delayed access	Software verification, validation, and hazard analysis Labeling
Use error / improper device use leading to worsening condition	Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the computerized behavioral therapy device for headache is subject to the following special controls:

(1) Clinical performance testing must be provided to fulfill the following:
   (i) Describe a model of behavioral therapy for the treatment of headache; and
   (ii) Validate the model of behavioral therapy as implemented by the device.

(2) Software must be described in detail in the software requirements specification (SRS) and software design specification (SDS). Software verification, validation, and hazard analysis must be performed. Software documentation must demonstrate that the device effectively implements the behavioral therapy model.

(3) The following labeling must be provided:
   (i) Patient and physician labeling must include instructions for use, including images that demonstrate how to interact with the device;
   (ii) Patient and physician labeling must list compatible devices;
   (iii) Patient and physician labeling must include a warning that the device is not intended for use as a standalone therapy if intended to be used as an adjunct therapy;
   (iv) Patient and physician labeling must include a warning that the device does not represent a substitution for the patient's medication; and
   (v) Physician labeling must include a summary of the clinical testing with the device.

BENEFIT-RISK DETERMINATION

Probable Risks

The risks of the device are based on nonclinical laboratory studies as well as data collected in the clinical studies described above.

The primary risk for this device is ineffective device performance. Other risks include device software malfunction, cyber-security breaches, and use error (e.g., misuse of the device as a replacement for a patient's other migraine treatments). The severity and probability for each of these risks is low and adequate mitigation measures have been included.

In the Pivotal Study (CT-132-R-001), the overall rate of AEs was low (6.8%). Only 7.9% of participants in the CT-132 arm experienced TEAEs, while 5.8% of participants in the Digital Control arm experienced TEAEs. Most AEs were mild or moderate, only 3 TEAE were severe and one non-TEAE was severe. No AEs were considered related to treatment intervention. There were no discontinuations or deaths due to AEs. Non-TEAE percentages in each arm were similar, occurring in 4% of participants in the CT-132 arm and 3.4% of participants in the Digital Control arm.

In Bridging Study (CT-132-R-002), the overall rate of TEAEs was 19.1%, with 13% in the CT-132 arm and 25% in the Digital Control arm. No participants died or discontinued due to AEs. There was only one serious TEAE (postural orthostatic tachycardia syndrome), which was not considered related to treatment. All AE were mild or moderate; none were severe. No TEAE were considered related to treatment.

Probable Benefits

The probable benefits of the device are also based on data collected in the clinical studies as described above. The device provides probable benefits of reduction of monthly migraine days.

CT-132-R-001 (Pivotal Trial)

In the CT-132-R-001 study, there was a statistically significant difference (P=0.005) in the primary endpoint (i.e., the change in the number of MMDs from baseline to Week 12) between the CT-132 group and the Digital Control group. The LSM difference was -0.9 (95% CI: -1.53, -0.27). This demonstrates a decrease of about 1 headache per month in the CT-132 group as compared to the Digital Control.

The observed change in headache frequency in study CT-132-R-001 is also supportive of the primary effectiveness endpoint. There was a greater percentage of subjects experiencing a reduction of greater than 6 MMDs in the CT-132 arm versus the Digital Control (18.4% of participants in the CT-132 arm versus 11.7% of participants in the Digital Control arm) and 32.4% of participants in the CT-132 arm versus 25.4% of participants in the Digital Control arm showed a reduction of 3 to 6 MMDs. Although there was no multiplicity adjustment and no hypothesis testing for all secondary endpoints, secondary end point results also showed a trend for an improvement in CT-132 over the Digital Control.

CT-132-R-002 (Bridging Trial)

The sponsor conducted study CT-132-R-002 to evaluate the effectiveness of device in patients taking CGRP inhibitors. This study was designed similarly to CT-132-R-001 and was intended to explore potential benefits of CT-132 in addition to CGRP inhibitors and was not powered to test a statistical hypothesis and had no predefined success criteria. The primary effectiveness endpoint showed an absolute difference favoring CT-132, with a mean reduction of 2.13 MMDs from baseline and a mean reduction of 1.34 MMDs reduction for the Digital Control arm. The ITT analysis showed that the LS means of the difference between the treatment groups (CT-132 - Digital Control) was −0.7 (or < 1 day) with 95% CI (−2.3, 0.9).

The observed change in headache frequency in study CT-132-R-001 is also supportive of the primary effectiveness endpoint. A greater proportion of CT-132 participants than Digital Control

participants reported a reduction between 0 and 3 MMDs (46.3% for CT-132, 41% for Digital Control), between 4 and 6 MMDs (25.9% for CT-132, 21.4% for Digital Control), or more than 6 MMDs (7.4% for CT-132, 3.6% for Digital Control) at Week 12. Therefore, the primary endpoint data indicated beneficial treatment effect trend. Although there was no multiplicity adjustment and no hypothesis testing for all secondary endpoints, secondary end points also showed changes that trend towards effectiveness.

Patient Perspectives

Patient perspective of improvement in their overall status was assessed in an exploratory endpoint by the Patient Global Impression of Change (PGI-C) score at the end of the treatment period (Week 12). PGI-C data showed greater patient-perceived benefit for CT-132 compared to Digital Control in the pivotal (Table 28). The bridging study showed a directionally similar outcome for PGI-C.

Table 28. Patient Global Impression of Change (PGI-C) Score (Pivotal Study, ITT Set)

	CT-132 (N=285)	**Digital Control (N=283)**	**Difference Between Arms**
PGI-C Score at Week 12	2.78	3.49	-0.71

The PGI-C is scored 1–7, with (1) representing *"Very Much Improved"* and (7) representing "*Very Much Worse."*

Benefit/Risk Conclusion

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

> CT-132 is indicated for the preventive treatment of episodic migraine in patients 18 years of age and older. It is intended for adjunctive use alongside acute and/or other preventive treatments for migraine.

The probable benefits outweigh the probable risks for CT-132. 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 CT-132 is granted and the device is classified as follows:

> Product Code: SEE
> Device Type: Computerized behavioral therapy device for headache
> Class: II
> Regulation Number: 21 CFR 882.5806