DE NOVO CLASSIFICATION REQUEST FOR PARALLEL

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Computerized behavioral therapy device for treating symptoms of gastrointestinal conditions. A computerized behavioral therapy device for treating symptoms of gastrointestinal conditions is a prescription device intended to provide a computerized version of condition-specific therapy as an adjunct to standard of care treatments to patients with gastrointestinal conditions.

NEW REGULATION NUMBER: 21 CFR 876.5960

CLASSIFICATION: Class II

PRODUCT CODE: QMY

BACKGROUND

DEVICE NAME: Parallel

SUBMISSION NUMBER: DEN200029

DATE DE NOVO RECEIVED: April 30, 2020

SPONSOR INFORMATION:

Mahana Therapeutics, Inc.
Jean-Noel Courvoisier
230 California Street, Suite 302
San Francisco, California 94111

INDICATIONS FOR USE

The Parallel is indicated as follows:

Parallel is a prescription-only digital therapeutic device intended to provide cognitive behavioral therapy for adults aged 22 years of age and older who have been diagnosed with Irritable Bowel Syndrome (IBS). Parallel is indicated as a 3 month treatment for patients with IBS. Parallel treats IBS by reducing the severity of symptoms and is intended to be used together with other IBS treatments.

LIMITATIONS

The sale, distribution, and use of the Parallel are restricted to prescription use in accordance with 21 CFR 801.109.

In the clinical study, IBS-Symptom Severity Score (IBS-SSS) that exceeded a minimum clinically-important difference (MCID) of 50 points in the Parallel treatment group compared to the Treatment as Usual (TAU) group was limited to 3 months.

Parallel is intended to be used together with the patient's other IBS treatments and is not intended to be used as a stand-alone therapeutic. Parallel does not replace care by a provider and is not a substitute for other IBS treatments the patient may be using.

In order to use Parallel, the patient must be able to read and comprehend English, have a desktop or laptop computer with a web browser and internet connectivity, and be familiar with the use of web applications.

The ability to use Parallel may be limited for patients who are visually impaired.

Users should seek medical care if they have feelings or thoughts of harming themselves or others while using Parallel.

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

DEVICE DESCRIPTION

Parallel is a web-based program designed to deliver Cognitive Behavioral Therapy (CBT) to patients with IBS who continue to have symptoms despite other forms of medical therapy. It is a responsive, web-based application that is intended to be a prescription device for use in the home for patients with IBS under the management of a qualified health care professional for the treatment of their IBS. Parallel is comprised of browser-delivered digital therapy that provides the CBT content. A desktop or laptop computer with a web browser and internet connectivity is required for use.

CBT works by targeting problematic thoughts, feelings, and behaviors, building adaptive coping skills, and interrupting the cycle that is perpetuating the targeted symptoms. CBT can be delivered in-person by a mental health practitioner with adequate training in CBT. A critical component of treatment outcome is the degree to which CBT is administered competently, reliably, and as intended. Parallel treatment uses psychoeducation and teaching behavioral and cognitive skills and techniques to alter patterns of behavior and change unhelpful thoughts.

Parallel is accessed via a secure website. Initially, the patient will receive a secure email containing an access link for the Parallel web application. Upon receiving the email invitation, the user can register electronically to begin their prescription. Once registered, patients are presented with onboarding material that introduces the program. Upon completion of reading the onboarding material, the patient can start the program.

Parallel consists of eight CBT sessions, which include interactive components. The interactive components help patients remember the guidance and concepts, reflect, and engage in the therapeutic processes of CBT. In each session, patients review key points from the previous session and review their homework, thereby reinforcing previous learning. The patient must complete the sessions in sequential order. However, a patient may go back to a previously completed session. The prescription is for 90 days and patients should complete the eight sessions within that 90-day period. After the 90 days, patients can still access the sessions that they have completed.

The eight sessions are described below.

Session	*Mechanism of Action*	*Session Targets (What do patients learn/do in the session?)*
Session 1: Understanding your IBS	Knowledge Psychoeducation of treatment model Personalized feedback:	Learn possible causes of IBS and physiology of the digestive system along with the functional changes that occur in the gut as a result of IBS and how these relate to specific symptoms. Learn how the autonomic nervous system ('fight-or-flight' stress system) may interact with the enteric nervous system. Complete IBS-SSS; receive a score and explanation of what that score means.
Session 2: Assessing your symptoms	Awareness Beliefs about consequences	Complete a self-assessment of the interaction between thoughts, emotions, and behaviors, and how these impact stress levels and GI symptoms. Develop a personal model of IBS that incorporates these elements. Learn how to complete the symptom diary. Homework: Complete daily diaries of the severity and experience of IBS symptoms, in conjunction with stress levels and eating routines/behaviors.
Session 3: Managing symptoms and eating	Beliefs about consequences and perceived susceptibility Attentional processes Behavioral regulation Building accurate awareness and reinterpretation of symptoms Decreasing hypervigilance to IBS symptoms Reducing avoidance and safety behaviors	Review the symptom diary. Learn behavioral management of the symptoms of diarrhea and constipation, and resolve common myths in this area. Learn effective goal setting, the importance of healthy, regular eating, and not being overly focused on elimination of foods. Homework: Set goals for managing symptoms and regular/healthy eating.

Session	*Mechanism of Action*	*Session Targets (What do patients learn/do in the session?)*
Session 4: Exercise and activity	Behavioral cueing Behavioral regulation Changing behavioral responses Attention & decisional processes Reducing avoidance and safety behaviors	Learn the importance of exercise in symptom management; Identify problematic activity patterns (*e.g.*, resting too much in response to symptoms or an all-or-nothing style of activity). Begin graded exposure to avoided situations in which IBS sensations are anticipated (*e.g.*, eating at restaurants, long road trips) while decreasing and ultimately discontinuing safety behaviors (*e.g.*, additional clothing in case of an accident). Homework: Set goals for regular exercise and manage unhelpful activity patterns, if relevant.
Session 5: Identifying your thought patterns	Awareness Attention to threat appraisals Reinterpretation Tolerance of uncertainty	Identify unhelpful thoughts (negative automatic thoughts) in relation to high personal expectations and IBS symptoms. Link between these thoughts, feelings, behaviors and symptoms is reinforced. Homework: Goal setting plus daily thought records of unhelpful thoughts related to personal expectations and patterns of over activity.
Session 6: Alternative thoughts	Change IBS-specific cognitions Challenge threat-laden appraisals Decrease attentional biases towards threat	Introduce steps for generating alternatives to unhelpful thoughts using the patient's personal examples. Homework: Goal setting plus daily thought records including coming up with realistic alternative thoughts.
Session 7: Learning to relax, improving sleep, managing stress and emotions	Behavioral regulation Emotion regulation Attentional & decision-making processes Reducing avoidance behaviors with new adaptive behavioral responses	Learn basic stress management and sleep hygiene; Instructional audio and videos teach diaphragmatic breathing, progressive muscle relaxation and guided imagery relaxation; Learn to identify common positive and negative emotions, and the patient's ways of dealing with these; Introduce new strategies to facilitate expression of emotion as well as coping with negative or difficult emotions. Homework: Goal setting for stress management, good sleep habits and emotional processing.
Session 8: Processing emotions, managing flare-ups and the future	Skills generalization Proactive problem-solving Acceptance of slips	Learn to accept and manage emotions; complete interactive tasks to reflect on these concepts. The probability of flare-ups is discussed. Patients are encouraged to develop achievable, long-term goals, and to continue employing learned skills to manage flare-ups and ongoing symptoms.

SUMMARY OF NONCLINICAL/BENCH STUDIES

SOFTWARE AND CYBERSECURITY

Parallel is Software as a Medical Device (SaMD). The software was reviewed according to the "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," dated May 11, 2005. The De Novo request provided appropriate

software documentation consistent with a "Minor" level of software concern. Parallel supports the following browsers: Chrome, Firefox, and Safari and the following Operating systems: Windows and Mac.

Cybersecurity was reviewed according to FDA guidance document "Content of Premarket Submission for Management of Cybersecurity in Medical Devices" dated October 2, 2014. Appropriate cybersecurity documentation was provided.

HUMAN FACTORS

Parallel was evaluated per FDA Guidance "Applying Human Factors and Usability Engineering to Medical Devices." The usability assessment identified that there are no critical tasks associated with the use of the Parallel software application. Therefore, a human factors study was not required to support safe use by the intended user population.

SUMMARY OF CLINICAL INFORMATION

A randomized multicenter clinical trial, Assessing Cognitive behavioral Therapy in Irritable Bowel (ACTIB) Pivotal Trial, was conducted to support the intended use of Parallel.[1]

Study Overview

The study included three arms: treatment as usual (TAU), telephone CBT with treatment as usual (telephone), and web-based CBT with treatment as usual (Parallel). The telephone arm received guided therapy provided by a therapist with training in CBT over the telephone. Participants in the Parallel arm were asked to complete the website program at home on their own time. The TAU arm received no CBT. Participants in all three arms of the trial continued treatment as usual, i.e. IBS medications were continued throughout the duration of the study. Prior to randomization, all participants were evaluated for the severity of their IBS using IBS-SSS.

IBS-SSS is a questionnaire that includes five questions with each question having a maximum score of 100 points. The total score range is from 0 to 500. Individuals without IBS have a symptom severity score < 75. Individuals with mild, moderate and severe cases of IBS have scores 75 to 175, 175 to 300, and > 300, respectively. The questionnaire includes an assessment of pain, distention, bowel score, and quality of life. The pain component of the assessment includes the severity and duration of pain. The distention score includes both distention and tightness in the abdomen due to the differences between men and women. The quality of life component includes assessment of global well-being and an overall view on quality of life as it relates specially to irritable bowel syndrome. According to Francis et al. 1997, "a change of 50 was adequate to detect improvement." Therefore, equal to or greater than a 50-point difference defines the MCID for the IBS-SSS. Also, "this scoring system is specifically designed to assess

[1] Everitt, H., et al., *Therapist telephone-delivered CBT and web-based CBT compared with treatment as usual in refractory irritable bowel syndrome: the ACTIB three-arm RCT.* Health Technol Assess, 2019. **23**(17): p. 1-154.

the severity of irritable bowel syndrome in a patient at a particular point in time and is not intended to be used for initial diagnosis of the condition."[2]

Inclusion criteria

- Patient aged 18 years old or over
- Patient had clinically significant symptoms (defined as an Irritable Bowel Syndrome Symptom Severity Scale [IBS-SSS] score $\geq$ 75)
- Patient fulfilled ROME III criteria
  a. ROME III Criteria is defined as recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with 2 or more of the following:
     - Improvement with defecation
     - Onset associated with a change in frequency of stool
     - Onset associated with a change in form (appearance) of stool[3]
- Patient was offered first-line therapies (e.g., anti-spasmodics, antidepressants, or fiber-based medications) but still had continuing IBS symptoms for 12 months or more
- If over 60 years old, patient must have had a medical specialist review in the previous 2 years to confirm symptoms are related to IBS and to exclude other serious bowel conditions

Exclusion Criteria

- Patient had unexplained rectal bleeding or weight loss
- Patient had diagnosis of inflammatory bowel disease, celiac disease, peptic ulcer disease, and/or colorectal carcinoma
- Patient was unable to participate in CBT due to speech or language difficulties
- Patient did not have access to an internet computer to be able to undertake the WCBT
- Patient received CBT for IBS in the last 2 years
- Patient had access to the Parallel software in an earlier pilot trial
- Patient was concurrently participating in an IBS/intervention trial

Treatments

- Telephone: 186 patients received six 60-minute telephone CBT sessions over 9 weeks and two 60-minute booster sessions at 4 and 8 months (8 hours therapist time).

- Parallel: 185 interactive, tailored CBT using Parallel, three 30-minute telephone support calls over 9 weeks and two 30-minute boosters at 4 and 8 months (2.5 hours therapist time). The 30-minute telephone support calls were intended to ensure that participants were adequately using the website resources, and were not equivalent to the therapy sessions provided to the Telephone arm.

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[2] Francis, C.Y., J. Morris, and P.J. Whorwell, *The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress*. Aliment Pharmacol Ther, 1997. **11**(2): p. 395-402.
[3] Longstreth G.F., et al., *Functional Bowel Disorders*. Gastroenterology, 2006. 130 (5): p. 1480-1491.

- Both treatment arms also received TAU. TAU is defined as continuation of current medications, and usual general practitioner follow-up with no psychological therapy for IBS.

Study Population

In total, 558 patients were randomized in the trial: 186 to the Telephone arm, 185 to the Parallel arm,
and 187 to TAU. During the trial, there was a higher than expected drop-out rate (30%). There was a total of 136 complete cases in the Telephone arm, 124 complete cases in the Parallel arm, and 131 complete cases in the in the TAU arm.

Efficacy Results

In the clinical study, treatment differences in IBS-SSS were evaluated at 3, 6, and 12 months after therapy. A difference of 35 points between treatment groups and TAU for IBS SSS at 12 months was considered clinically significant in the trial. However, FDA agreed with the previously published[2]MCID for IBS-SSS to be at least a 50-point difference between the treatment group and TAU. For the telephone arm, greater than a 50-point decrease in IBS-SSS,), was observed at each timepoint. The estimated trial arm differences for continuous outcomes of telephone versus TAU was 69 points at 3 months, 58 points at 6 months, and 62 points at 12 months. The estimated trial arm differences for continuous outcomes of Parallel versus TAU was 53 points at 3 months, 35.7 points at 6 months, and 35.5 points at 12 months (See Table 1). Parallel compared to TAU achieved a clinically meaningful benefit of a 50-point difference at 3 months post-randomization. The primary efficacy outcome was treatment differences in IBS-SSS at 12 months. However, only, at 3 months did the device demonstrate a minimum clinical important difference compared to TAU. IBS-SSS score at three months was pre-specified as a secondary outcome measure in the statistical analysis plan (SAP) without pre-specified hypothesis test or suitable multiplicity adjustment to control the overall type I error rate at 2-sided 5%.

Table 1. Estimated trial arm differences for continuous outcomes

	Parallel vs. TAU	Telephone vs. TAU
3 months	53	69
6 months	35.7	58
12 months	35.5	62

Work and Social Adjustment Scale (WASAS) was proposed as a coprimary endpoint in the trial. WASAS is a measure of impairment of functioning specific to the condition being studied. However, WASAS is not a validated measure for improvement of patients undergoing a intervention for IBS. Therefore, WASAS was not considered appropriate for evaluating the benefit of the device.

Uncertainty in these results was contributed to by loss to follow up for study subjects, potential inconsistency in treatment as usual, and post hoc statistical analysis of clinical study results.

Adverse Events

Overall, the proportion of individuals reporting at least one Adverse Event (AE) was similar across the treatment arms, with 27.3% of TAU arm, 30.1% of telephone arm, and 26.5% of Parallel arm reporting at least one AE during the course of the ACTIB trial. The most common AE by System Organ Class (SOCs) included Psychiatric Disorders (6.1% of subjects overall), Gastrointestinal Disorders (5.6% of subjects overall), and Infections and Infestations (5.2% of subjects overall). With respect to the most commonly reported AEs reported by subjects in the Parallel arm (defined as events reported by > 2 subjects and with frequency rate that exceeds the rate observed for said event in the TAU arm), only abdominal pain, generalized pain, diverticulitis, and depression met this definition. The frequency rate of abdominal pain was 2.2% for the Parallel arm compared to 0.5% for the TAU arm; for generalized pain, the rates were 1.6% and 0.0% for the two arms, respectively; diverticulitis was reported by 1.1% and 0.0% of Parallel and TAU patients, respectively; and, for depression, the frequency rates were 2.2% for Parallel and 1.1% for TAU.

The frequency of related treatment-emergent AEs (TEAEs) revealed no notable differences between
treatment groups. The frequency of related TEAEs was 1.1%, 0.5%, and 0.5% in the Telephone, Parallel, and TAU arms, respectively. For the Parallel arm, the only related event was a case of abdominal pain that was considered "remotely" related to treatment with the device. The only AEs that
were deemed possibly related to treatment were reported for the TAU arm (3 subjects, 1.6%). These included abdominal pain (1), abdominal distension (1), and flatulence (1).

Summary

In summary, the study supporting the Parallel device as an adjunct to TAU showed a clinically meaningful benefit of > 50 points with the IBS-SSS in Parallel versus TAU populations at 3 months post randomization.

LABELING

The Sponsor provided labeling that included patient directions for use, a patient information sheet, and a clinician information sheet for Parallel. The patient directions for use addresses the known hazards and risks of the device for the intended use and incorporates safety statements to mitigate these risks. The labeling includes:

- Instructions intended to minimize the risk of improper use of Parallel including a summary of how to navigate the software.

- Contraindications and warnings to ensure the patient continues current medications and treatments under the guidance of a physician or other healthcare professional.

- The browser and hardware requirements to use the device, and language and technology skills needed to use the device.

The patient and clinician information sheets include a summary of the clinical data stating a clinically meaningful benefit that included reduction in symptom severity that was observed 3 months after treatment with Parallel compared to the TAU study arm.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of Parallel and the measures necessary to mitigate these risks.

Identified Risks to Health	Mitigation Measures
Worsening of condition due to device providing ineffective treatment.	Clinical data Labeling
Delayed access to treatment due to device software failure.	Software verification, validation, and hazard analysis Labeling
Ineffective treatment due to use error/ improper use of device	Usability assessment Labeling
Treatment results in anxiety, depressed mood, depression, mental disorder (unspecified), stress or suicidal ideation	Clinical data Labeling

In combination with the general controls of the FD&C Act, the Computerized behavioral therapy device for treating symptoms of gastrointestinal conditions is subject to the following special controls:

1. Clinical data must be provided to fulfill the following:
    i. Describe a model of therapy for the indicated gastrointestinal conditions;
    ii. Validate the model of therapy as implemented by the device using a clinically defined endpoint; and
    iii. Evaluate all adverse events.
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. Usability assessment must demonstrate that the intended user(s) can safely and correctly use the device.
4. Labeling must include:
    i. Labeling must include instructions for use, including images that demonstrate how to interact with the device;
    ii. Patient and physician labeling must list the minimum operating system requirements that support the software of the device;
    iii. Patient and physician labeling must include a warning that the device is not intended for use in lieu of a standard therapeutic intervention or represent a substitution for the patient's medication;.
    iv. Patient and physician labeling must include a warning to seek medical care if a patient has feelings or thoughts of harming themselves or others; and.

v. Physician and patient labeling must include a summary of the clinical testing with the device.

BENEFIT-RISK DETERMINATION

The risks of the device are based on data collected in the clinical study described above. The most common AE SOCs included Psychiatric Disorders (6.1% of subjects overall), Gastrointestinal Disorders (5.6% of subjects overall), and Infections and Infestations (5.2% of subjects overall). The risks associated with Parallel were comparable to the treatment as usual group.

With respect to the most commonly reported AEs reported by subjects in the Parallel group (defined as events reported by > 2 subjects and with frequency rate that exceeds the rate observed for said event in the TAU group), only abdominal pain, generalized pain, diverticulitis, and depression met this definition. Of those most commonly reported AEs, the only AE rated as severe was a single case of diverticulitis in the Parallel group. For the Parallel arm, the only related event was a case of abdominal pain that was considered remotely related to treatment with the device. The only AEs that were considered to be possibly related to treatment were reported for the TAU arm, which included abdominal pain, abdominal distension, and flatulence.

The probable benefits of the device are also based on data collected in the clinical study described above.

Several factors, such as significant loss to follow up and post-hoc statistical analysis, contributed to uncertainty in the clinical data. Additionally, an MCID that exceeded 50 points for IBS-SSS was not achieved at 12 months in the trial. However, after 3 months a clinical benefit of greater than 50 points was seen with the IBS-SSS in the Parallel versus TAU populations. Therefore, the labeling includes a summary of the clinical data and includes a statement that a clinically meaningful benefit was observed 3 months.

Given that the device demonstrated clinical benefit with acceptable uncertainty at 3 months and provides increased access to CBT to treat IBS symptoms for patients that do not have access to other forms of CBT and the risks were minimal with little uncertainty and low severity, the probable benefits of the Parallel device outweigh the probable risks.

Patient Perspectives

Patient perspectives considered for the Parallel during the review include:

Several participants assigned to the Parallel intervention during the clinical trial were interviewed immediately upon completion of the treatment period and at the end of the trial.

Participants reported several benefits gained from the use of the product, including improvements in IBS symptoms, enhanced understanding of IBS as a condition, more control over IBS symptoms, and positive impact on their work and social life.

Benefit/Risk Conclusion

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

> Parallel is a prescription-only digital therapeutic intended to provide cognitive behavioral therapy for adults aged 22 years of age and older who have been diagnosed with Irritable Bowel Syndrome (IBS). Parallel is indicated as a 3 month treatment for patients with IBS. Parallel treats IBS by reducing the severity of symptoms and is intended to be used together with other IBS treatments.

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

Product Code: QMY
Device Type: Computerized behavioral therapy device for treating symptoms of gastrointestinal conditions
Regulation Number: 21 CFR 876.5960
Class: II