March 30, 2024

Otsuka America Pharmaceutical, Inc.
Nancy Teague
Senior Director, Global Regulatory Affairs
2440 Research Boulevard
Rockville, Maryland 20850

Re: K231209
Trade/Device Name: Rejoyn
Regulation Number: 21 CFR 882.5801
Regulation Name: Computerized Behavioral Therapy Device For Psychiatric Disorders
Regulatory Class: Class II
Product Code: SAP
Dated: March 20, 2024
Received: March 20, 2024

Dear Nancy Teague:

We have reviewed your section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (the Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR Part 803) for devices or postmarketing safety reporting (21 CFR Part 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Pamela D. Scott -S

Pamela D. Scott
Assistant Director
DHT5B: Division of Neuromodulation
   and Rehabilitation Devices
OHT5: Office of Neurological
   and Physical Medicine Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number *(if known)*
K231209

Device Name
Rejoyn™

Indications for Use *(Describe)*

Rejoyn is a prescription digital therapeutic for the treatment of Major Depressive Disorder (MDD) symptoms as an adjunct to clinician-managed outpatient care for adult patients with MDD aged 22 years and older who are on antidepressant medication. It is intended to reduce MDD symptoms.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D)   ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

4   510(k) Summary

4.1   Submitter

Submitted by:	Otsuka America Pharmaceutical, Inc.
Address:	2440 Research Blvd. Rockville, MD 20850
Telephone:	240-263-3560
Fax:	NA
Contact Name:	Nancy F. Teague Senior Director, Global Regulatory Affairs Otsuka Pharmaceutical & Commercialization Development, Inc. (OPDC) nancy.teague@otsuka-us.com
Date Submitted:	27 Apr 2023

4.2   Device

Name of Device:	CT-152
Trade or Proprietary Name:	REJOYN™
Common or Usual Name:	Prescription Digital Therapeutic
Classification Name:	Computerized Behavioral Therapy Device for Psychiatric Disorders (21 CFR 882.5801), Class II (Special Controls)
Regulatory Class:	II
Product Code:	SAP

4.3   Predicate Device(s)

Predicate Device Common Name:	reSET®
Predicate Device Manufacturer:	Pear Therapeutics, Inc.
Predicate Device Premarket Notification #:	DEN160018
Predicate Device Classification:	Computerized Behavioral Therapy Device for Psychiatric Disorders
Predicate Device Product Code:	SAP (21 CFR 882.5801)

4.4 Device Description

Rejoyn (also known as CT-152) is a digital therapeutic smartphone application (app) for the treatment of Major Depressive Disorder (MDD) symptoms. Rejoyn is a prescription smartphone app-based digital therapeutic administered to a user via the user's smartphone device (running Apple iPhone operating system [iOS®] or Android™ operating system [OS]), which delivers a proprietary interactive cognitive-emotional and behavioral therapeutic intervention. The core components of Rejoyn are the Emotional Faces Memory Task (EFMT) exercises, brief cognitive behavioral therapy (CBT)-based lessons to learn and apply key therapeutic skills, and short message service (SMS) text messaging to reinforce CBT-based lesson content and to encourage engagement with the app. It is intended for the treatment of MDD symptoms as an adjunct to clinician-managed outpatient care for adult patients with MDD aged 22 years and older. It is intended to reduce MDD symptoms.

Rejoyn is designed for use as an adjunct to clinician-managed outpatient care over a period of 6 weeks for the treatment of MDD symptoms, followed by a 4-week extension period where CBT-based lesson content will be accessible but no new therapeutic content or EFMT exercises will be available. Rejoyn is not intended to be used as a stand-alone therapy or as a substitution for the patient's clinician prescribed medications.

4.5 Intended Use/Indications for Use

Intended Use: Rejoyn is a prescription digital therapeutic for the treatment of Major Depressive Disorder (MDD) symptoms as an adjunct to clinician-managed outpatient care for adult patients with MDD aged 22 years and older who are on antidepressant medication.

Indications for Use: Rejoyn is a prescription digital therapeutic for the treatment of Major Depressive Disorder (MDD) symptoms as an adjunct to clinician-managed outpatient care for adult patients with MDD aged 22 years and older who are on antidepressant medication. It is intended to reduce MDD symptoms.

Both the Rejoyn and predicate device have the same intended use as computerized behavioral therapy devices for psychiatric disorders, as classified under 21 CFR 882.5801. The Indications for Use statement for Rejoyn is not identical to the predicate device and differ for the psychiatric disorder being treated (ie, MDD for Rejoyn and SUD for reSET). The differences do not alter the intended therapeutic

use of the device. The safety and effectiveness of Rejoyn was demonstrated with compliance to all applicable special controls, consistent with the predicate.

4.6 Comparison of Technological Characteristics with Predicate Device

Rejoyn has similar technological characteristics to reSET, including digital delivery of behavioral therapy through a smartphone application which includes therapeutic content. Additionally, both digital therapies use discrete lessons to deliver CBT. Rejoyn does not include a physician portal whereas reSET does have a physician portal. Both the Patient and Physician Labeling notes that Rejoyn does not monitor the patient's symptoms or clinical status and cannot send or receive alerts or warnings to the prescriber. The data from the Mirai trial reasonably demonstrates that the differences between Rejoyn and the predicate device do not raise new safety and effectiveness questions and Rejoyn is substantially equivalent to the predicate device.

The minor differences in technological characteristics reflect the different clinical needs for the user populations (MDD for Rejoyn and SUD for reSET) and the associated disease-specific content. These differences do not raise new questions of safety and effectiveness.

Table 4.6-1 shows the comparison of characteristics of Rejoyn to the predicate device reSET.

Table 4.6-1	Substantial Equivalence Table Comparing Rejoyn to reSET (Predicate)	
Property or Characteristic	**Rejoyn**	**reSET**
510(k) Number	**K231209**	**DEN160018**
Food and Drug Administration (FDA) Product Code(s)	SAP	PWE
Classification Regulation	Computerized behavioral therapy device for psychiatric disorders (21 CFR 882.5801), Class II (Special Controls)	Computerized behavioral therapy device for psychiatric disorders (21 CFR 882.5801), Class II (Special Controls)

Intended Use	Rejoyn is a prescription digital therapeutic for the treatment of Major Depressive Disorder (MDD) symptoms as an adjunct to clinician-managed outpatient care for adult patients with MDD aged 22 years and older who are on antidepressant medication.	reSET® is a prescription digital therapeutic intended to deliver CBT to adult patients with SUD to increase abstinence from substance use and increase retention in outpatient therapy programs.
Indications for Use	Rejoyn is a prescription digital therapeutic for the treatment of Major Depressive Disorder (MDD) symptoms as an adjunct to clinician-managed outpatient care for adult patients with MDD aged 22 years and older who are on antidepressant medication. It is intended to reduce MDD symptoms.	reSET® is intended to provide CBT, as an adjunct to a contingency management system, for patients 18 years of age and older who are currently enrolled in outpatient treatment under the supervision of a clinician. reSET is indicated as a 12-week (90 days) prescription-only treatment for patients with SUD, who are not currently on opioid replacement therapy, who do not abuse alcohol solely, or who do not abuse opioids as their primary substance of abuse. It is intended to: • increase abstinence from a patient's substances of abuse during treatment, and • increase retention in the outpatient treatment program.

Table 4.6-1	Substantial Equivalence Table Comparing Rejoyn to reSET (Predicate)	

Property or Characteristic	Rejoyn	reSET
Device Type	Software as Medical Device (SaMD)	SaMD
Access	Rx only	Rx Only
Adjunctive Application	Yes – to antidepressant medication in addition to treatment as usual (TAU)[a]	Yes – to Standard of Care (SOC)
Target Conditions	Psychiatric Condition - MDD	Psychiatric Condition - SUD
Mechanis m of Action	Computerized Behavioral Therapy	Computerized Behavioral Therapy
Mobile Platform	Smartphones (iOS and Android)	Smartphones, tablets (iOS and Android)
Validated Form of Behavioral Therapy	A combination of EFMT and CBT-based lessons	Community reinforcement approach
Technology	Digital therapeutic treatment sessions (18 EFMT exercises and 18 brief, CBT-based lessons) over a 6-week period, followed by a 4-week extension period where the Rejoyn smartphone application will remain installed and the CBT-based lessons available for optional reference. The EFMT exercises will not be available during the extension period. Users will receive brief SMS messages in the extension period reminding them of their previously completed Rejoyn treatment course.	Digital therapeutic, with 62 total lessons, including one onboarding lesson, 31 core therapy lessons, and 30 supplemental lessons over a 12-week period.
Labeling	Patient and physician labeling	Patient and physician labeling
Physician Portal	No	Yes

[a]While different terms, it is assumed TAU and SOC have the same meaning in reflecting current clinical practice.
Source: De Novo Classification Request for reSET.

4.7 Performance Data

4.7.1 Summary of Nonclinical Performance Data

Special controls for device types within computerized behavioral therapy device for psychiatric disorders require that the 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.

The software documentation provided in the 510(k) is consistent with the FDA Guidance documents entitled "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" dated 11 May 2005, "Content of Premarket Submissions

for Device Software Functions" issued on 04 Nov 2021, "Off-the-Shelf Software Use in Medical Devices" dated 27 Sep 2019, and "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices" issued on 02 Oct 2014.

Software verification and validation testing was completed, and software documentation was provided in the 510(k) as recommended by the 2005 FDA guidance for a device of Moderate Level of Concern. Software documentation demonstrates that Rejoyn effectively implements the behavioral therapy model.

4.7.2 Summary of Clinical Performance Data

Special Controls for device types within Computerized Behavioral Therapy Device for Psychiatric Disorders require that clinical data must be provided to:

(i) Describe a validated model of behavioral therapy for the psychiatric disorder; and

(ii) Validate the model of behavioral therapy as implemented by the device.

Mirai Trial Design

The Mirai trial was a pivotal, multicenter, remote, double-blinded (patients also blinded to hypothesis), randomized, controlled trial to evaluate the effectiveness and safety of Rejoyn in adult participants diagnosed with MDD who were on antidepressant therapy (ADT) for the treatment of depression (NCT04770285). The primary objective of Mirai was to evaluate the effectiveness of Rejoyn in reducing depressive symptoms compared with Sham which served as a control. Sham consisted of Shapes Memory Task (SMT) exercise which was matched for time and attention to the active EFMT exercise. In order to retain the intended placebo nature of the Sham, it did not include EFMT or CBT-based content.

The primary efficacy endpoint was the change from baseline to Week 6 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score in the Modified Intent-to-Treat (mITT) population. A secondary effectiveness endpoint to evaluate the durability of the effect of Rejoyn was assessed by evaluating changes from baseline to Weeks 8 and 10 in MADRS total score in Rejoyn compared with Sham.

Clinical assessments used to evaluate secondary and exploratory endpoints also included patient-reported outcomes, including the Patient Health Questionnaire-9 (PHQ-9), the clinician-rated Clinical Global Impression-Severity Scale (CGI-S) and the Generalized Anxiety Disorder-7 (GAD-7).

The primary efficacy endpoint was tested at a significance level of 0.049. All other efficacy endpoints, including secondary, exploratory, and post hoc efficacy endpoints, were tested at a nominal 0.05 level (2 sided) without adjusting for multiplicity.

All procedures for the Mirai trial were conducted virtually, either by telephone or by remote visit via telehealth technology; the screening visit could be performed in person at the discretion of the investigator. Participants took part in the trial for up to 13 weeks, which included a screening period of up to 3 weeks, a treatment period for 6 weeks, and an extension period for 4 weeks.

On Day 1, eligible participants were randomized in a 1:1 ratio to Rejoyn or Sham with randomization stratified by trial center. During the treatment period (Day 1 [baseline] to Week 6), participants had remote visits at Weeks 2, 4, and 6 and were contacted by telephone at Weeks 1, 3, and 5. participants were expected to adhere to their digital mobile application exercises, and adherence was monitored during the treatment period. Investigators followed up with participants in both groups who missed sessions and provided reminders to adhere to the session schedule. To evaluate durability of effect after Week 6, participants had remote telehealth visits at Weeks 8 and 10 and were contacted by telephone at Weeks 7 and 9. Participants continued to receive brief text message reminders of the previously completed Rejoyn or Sham treatment course during the extension period (Weeks 7 to 10), retained access to previous CBT-based content and tools (Rejoyn), and continued their ADT. No new digital therapy content was newly introduced or required to be accessed as part of a treatment plan during the extension period. The end of the trial was Week 10.

Participants Disposition

Table 4.7.2-1 summarizes the various analysis sets used in the Mirai Trial. Of the 1034 participants screened, 386 were enrolled and randomized to the Rejoyn (N = 194) or Sham app (N = 192) treatment groups (Intent-To-Treat [ITT]). Demographics characteristics (randomized sample) are shown in Table 4.7.2-2. The mITT population comprised 354 participants (N = 177 from both groups) who had 1 session with either treatment and assessments of MADRS total score at both baseline and at least 1 post-baseline timepoint. The Safety Sample comprised 373 participants (Rejoyn: N = 187; Sham: N = 186) who received at least 1 treatment session with either Rejoyn or Sham. Baseline mean psychiatric evaluation scores for mITT are shown in Table 4.7.2-3.

Table 4.7.2-1: Mirai Trial Analysis Sets			
		Sample Size	
Analysis Set	Description	Rejoyn	Sham
Intent-To-Treat (ITT)	All randomized patients	194	192
Modified Intent-To-Treat (mITT)*	Randomized patients with 1 treatment session (Rejoyn or Sham) and MADRS assessment at baseline and ≥ 1 post-baseline timepoint	177	177
Safety Sample	Randomized patients with ≥ 1 treatment session (Rejoyn or Sham)	187	186

*mITT defined as Full Analysis Set (FAS) in protocol

Table 4.7.2-2: Demographic Characteristics (Randomized Sample)			
Demographic Characterstic	Rejoyn (N=194)	SHAM (N=192)	TOTAL (N=386)
Age (yrs)			
n	194	192	386
Mean (SD)	43.0 (12.1)	42.2 (12.1)	42.6 (12.1)
Median	43.0	41.0	42.0
Min, Max	22,64	22,64	22,64
Sex [n (%)]			
Male	29 (14.9%)	25 (13.0%)	54 (14.0%)
Female	165 (85.1%)	167 (87.0%)	332 (86.0%)
Race [n (%)]			
White	141 (72.7%)	160 (83.3%)	301 (78%)
Black or African American	36 (18.6%)	25 (13.0%)	61 (15.8%)
American Indian or Alaska Native	5 (2.6%)	1 (0.5%)	6 (1.6%)
Asian	5 (2.6%)	4 (2.1%)	9 (2.3%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	7 (3.6%)	2 (1.0%)	9 (2.3%)
Ethnicity			
Hispanic or Latino	20 (10.3%)	16 (8.3%)	36 (9.3%)
Not Hispanic or Latino	173 (89.2%)	174 (90.6%)	347 (89.9%)
Unknown	1 (0.5%)	2 (1.0%)	3 (0.8%)
Cannabis Use [n (%)]			
Yes	11 (5.7%)	24 (12.5%)	35 (9.1%)
No	183 (94.3%)	168 (87.5%)	351 (90.9%)

Max = maximum; Min = minimum

Table 4.7.2-3: Baseline Mean Psychiatric Evaluation Scores (ITT and mITT)						
	ITT			mITT		
	Rejoyn	Sham	Total	Rejoyn	Sham	Total
MADRS	28.4	28.5	28.4	28.5	28.4	28.4
GAD-7	9.5	9.7	9.6	9.6	9.6	9.6
CGI-S	4.3	4.3	4.3	4.3	4.3	4.3
PHQ-9	15.4	15.2	15.3	15.3	15.1	15.2
HAM-D17	22.7	22.4	22.5	22.8	22.3	22.6

Safety

Adverse events were directly assessed via phone or video based on the trial being conducted remotely. Adverse events were determined to be related or unrelated to Rejoyn by the investigator. No Treatment Emergent Adverse Event (TEAE) was assessed as related to Rejoyn during the trial. There were no discontinuations due to TEAEs. There was one discontinuation due to lack of efficacy in the Sham group. No serious TEAEs occurred during the treatment period. One serious TEAE of transient ischemic attack (assessed as not related to Rejoyn) was reported during the extension period.

The most common TEAEs during the treatment period (all nonserious and not related to Rejoyn) were upper respiratory tract infection (1.1% [n = 2] and 3.2% [n = 6] in Rejoyn and Sham, respectively), nasopharyngitis (1.1% [n = 2] and 2.7% [n= 5] in Rejoyn and Sham, respectively), and headache (2.1% [n = 4] and 1.6% [n = 3] in Rejoyn and Sham, respectively). Headache was the only TEAE that was experienced by at least 2% of subjects in the Rejoyn group at an incidence rate greater than Sham.

During the treatment period, one subject in the Rejoyn group experienced worsening depressive symptoms (based on predefined protocol criteria). In the Rejoyn group, 3.21% (n = 6) of subjects reported clinically important suicidality (based on predefined protocol criteria), compared to 4.84% (n = 9) of subjects in the Sham group. During the extension period, 0.53% (n = 1) of subjects in the Rejoyn group and 1.08% (n = 2) of subjects in the Sham group had clinically important suicidality.

<u>Summary of Efficacy Results</u>

Overall data from the Mirai Trial indicate that Rejoyn provides benefit to participants with MDD as an adjunct to antidepressant medication. The effectiveness endpoints for both the ITT and mITT populations showed consistent results across patient and clinician-rated scales (see Table 4.7.2-4). More detailed results can also be found in the Clinician Brief Summary.

Table 4.7.2-4: Efficacy Endpoints in ITT and mITT Populations

Outcome Measure	ITT				mITT*			
	Rejoyn	**Sham**	**Between-Group Δ**	**P-value**	**Rejoyn**	**Sham**	**Between-Group Δ**	**P-value**
MADRS								
Change in Total Score from Baseline to Week 6	-8.78	-6.66	-2.12	0.0211[†]	-9.03	-7.25	-1.78	0.0568
Full or Partial Response[‡]	51.3%	38.7%	1.32 RR	0.0191[†]	48.3%	37.5%	1.27 RR	0.0485[†]
Full Response[§]	30.4%	20.2%	1.49 RR	0.0331[†]	28.4%	20.4%	1.38 RR	0.0884
Partial Response[¶]	20.9%	18.6%	1.14 RR	0.5619	19.9%	17.0%	1.15 RR	0.5342
Remission[#]	18.2%	13.0%	1.39 RR	0.1934	17%	13.6%	1.24 RR	0.3901
PHQ-9	-6.93	-5.15	-1.78	0.0012[††]	-6.68	-5.10	-1.58	0.0029[††]
CGI-S	-1.03	-0.74	-0.29	0.0037[††]	-1.06	-0.80	-0.26	0.0098[††]

*mITT defined as Full Analysis Set (FAS) in protocol and used for the primary efficacy endpoint analysis
[†] P-value < 0.05
[††] P-value < 0.01
[‡] ≥30% Reduction from baseline at Week 6
[§] ≥50% Reduction from baseline at Week 6
[¶] ≥30%-50% Reduction from baseline at Week 6
[#] ≥50% Reduction from baseline and MADRS <10 at Week 6

Primary Efficacy Endpoint: MADRS

Data from the Mirai Trial indicate that Rejoyn provides benefit to participants with MDD as an adjunct to antidepressant medication. In the ITT analysis performed on the randomized population using the multiple imputation method, the mean change from baseline to Week 6 in the MADRS total score in the ITT was -8.78 in the Rejoyn group compared with -6.66 in the Sham group, which yielded a group difference of -2.12 (p = 0.0211, 95% CI [-3.93, -0.32]) (see Figure 4.7.2-1). The mean MADRS total score at baseline and scheduled visits during the treatment period for the ITT population is presented in Figure 4.7.2-2. The mean change from baseline to Week 6 in the MADRS total score in the mITT was - 9.03 in the Rejoyn group compared with -7.25 in the Sham group, which yielded a group difference of -1.78 (p = 0.0568, 95% CI [-3.60, 0.05]), which was not statistically significant because the final p-value did not meet the pre-specified threshold of 0.049 (see Figure 4.7.2-3).[1,2] The mean MADRS total score at baseline and scheduled visits during the treatment period for the mITT population is represented in Figure 4.7.2-4.

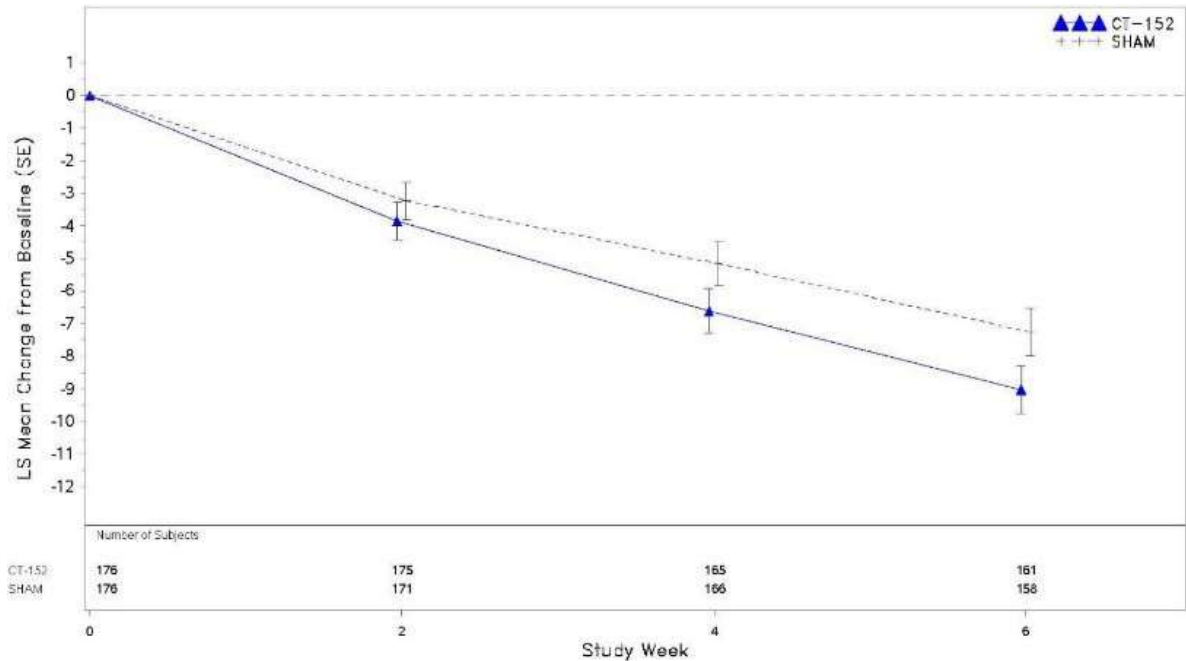**Figure 4.7.2-1: LS Mean Change from Baseline During the Treatment Period in MADRS Total Score, MMRM (ITT)**
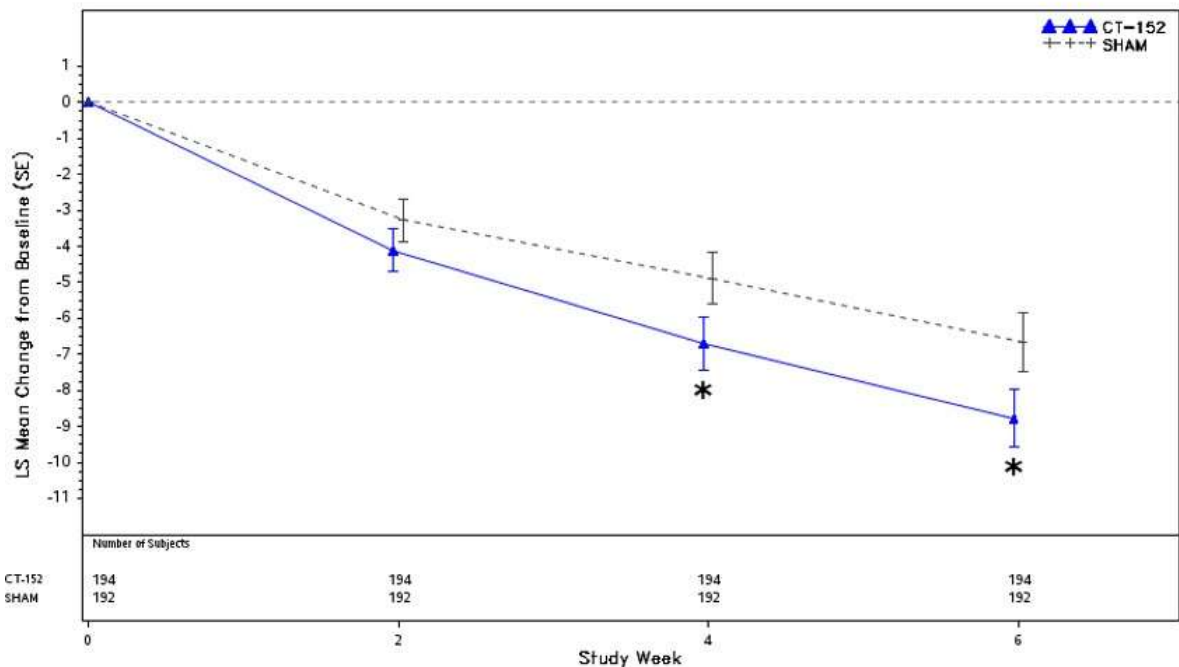
* P-value < 0.05
Note: Error bars are LS Mean +/- one SE.

Figure 4.7.2-2: Mean MADRS Total Score at Baseline and Scheduled Visits During the Treatment Period (ITT)

Figure 4.7.2-3: LS Mean Change from Baseline During the Treatment Period in MADRS Total Score, MMRM (mITT)

Note: Error bars are LS Mean +/- one SE.

Figure 4.7.2-4: Mean MADRS Total Score at Baseline and Scheduled Visits During the Treatment Period (mITT)

PLACEHOLDER

MADRS Response and Remission Rates

In addition to primary and secondary endpoints, the Mirai Trial included exploratory endpoints to determine the percentage of subjects in each group who achieved a: (1) Full or Partial Response (defined as $\geq$ 30% reduction in MADRS total score from baseline to Week 6); (2) Full Response (defined as $\geq$ 50% reduction in MADRS total score from baseline to Week 6); (3) Partial Response (defined as $\geq$ 30% and < 50% reduction in MADRS total score from baseline to Week 6); and (4) Remission (defined as $\geq$ 50% reduction in MADRS total score from baseline to Week 6 and MADRS total score of 10 or less). In the ITT analysis performed on the randomized population using the multiple imputation method, compared with the Sham group, patients in the Rejoyn group demonstrated numerically greater Full or Partial response rate (51.3% compared to 38.7%, respectively; p = 0.0191), Full Response Rate (30.4% compared to 20.2%,

respectively; p = 0.0331), Partial Response Rate (20.9% compared to 18.6%, respectively; p = 0.5619), and Remission Rate (18.2% compared with 13%, respectively, p = 0.1934).

In the mITT analysis performed on the randomized population using the multiple imputation method, compared with the Sham group, patients in the Rejoyn group demonstrated a numerically greater Full or Partial Response rate (48.3% compared with 37.5%, respectively; p = 0.0485), Full Response Rate (28.4% compared with 20.5%, respectively; p = 0.0884), Partial Response Rate (19.9% compared to 17.0%, respectively, p = 0.5342), and Remission Rate (17.0% compared with 13.6%, respectively; p = 0.3901).

<u>Analysis of Within-Patient Changes</u>

A post-hoc analysis was conducted to determine the improvement in the MADRS score that represents meaningful within-patient change (MWPC) thresholds using an anchor-based approach in the mITT population. An anchor-based approach defines a responder by exploring the associations between the primary endpoint instrument, MADRS, and other instruments used in the trial, CGI-S and PHQ-9, for which meaningful differences are more easily/directly interpretable or already known.[3,4] An 8-point and 10-point reduction in MADRS were identified as appropriate MWPC thresholds (see Table 4.7.2-5). From baseline to Week 6, 50.3% of patients in the Rejoyn group met or exceeded the 8-point threshold compared with 44.9% of patients in the Sham group (see Table 4.7.2-5).This 5.4% between-group difference indicates patients in the Rejoyn group were 24% more likely to achieve an 8-point improvement (odds ratio [OR] [95% CI] = 1.24 [0.799, 1.927]) and 12% more likely to experience this improvement (relative risk [RR] [95% CI] = 1.12 [0.889, 1.411]) compared with patients in the Sham group.

When applying the higher MWPC threshold of a 10-point improvement in the MADRS score from baseline to week 6, 44.7% of patients in the Rejoyn group met or exceeded this threshold, compared with 35.4% of patients in the Sham group (see Table 4.7.2- 5). This 9.3% between-group difference indicates patients in the Rejoyn group had 47% greater odds of achieving a 10-point improvement (OR [95% CI] = 1.47 [0.939, 2.312]) and were 26% more likely to experience this improvement (RR [95% CI] = 1.26 [0.962, 1.656]) compared with patients in the Sham group.

When viewed graphically in Figure 4.7.2-5, there is clear separation at the MWPC thresholds of 8-point and 10-point improvement in MADRS and the cumulative proportion of responders is higher across the improvement (negative) values of MADRS for the Rejoyn group relative to Sham. This suggests that a greater proportion of patients in the Rejoyn group observed a beneficial reduction of symptoms compared with the Sham group.

As stated above, this anchor-based MWPC analysis and responder comparisons are part of a post-hoc analysis, and therefore, should be interpreted with caution.

Table 4.7.2-5: Proportions of MADRS Responders at 8-Point and 10-Point Minimum Within-Patient Change Improvement Thresholds by Treatment Group at Week 6 (mITT)

| MWPC MADRS* Improvement Threshold	Status[†]	Statistic	Rejoyn	Sham	Total
8-points		N	161	158	319
	Improved	n (%)	81 (50.31)	71 (44.94)	152 (47.65)
	Not Improved	n (%)	80 (49.69)	87 (55.06)	167 (52.35)
		n missing	16	19	35
		OR (95% CI)[‡]	1.24 (0.799, 1.927)		
		RR (95% CI)[‡]	1.12 (0.889, 1.411)		
10-points		N	161	158	319
	Improved	n (%)	72 (44.72)	56 (35.44)	128 (40.13)
	Not Improved	n (%)	89 (55.28)	102 (64.56)	191 (59.87)
		n missing	16	19	35
		OR (95% CI)[‡]	1.47 (0.939, 2.312)		
		RR (95% CI)[‡]	1.26 (0.962, 1.656)		

MWPC = minimum within-patient change; OR = odds ratio; RR = relative risk

*Higher MADRS scores indicate more severe depressive symptoms; negative change scores indicate improvement.

[†]Improvement was defined as a change in MADRS score from baseline that met or exceeded the defined MWPC threshold in the direction of improvement (negative change from baseline). All other patients were classified as not improved.

[‡]Odds ratio (OR) and relative risk (RR) are calculated for improved versus no change/not improved

Figure 4.7.2-5: Empirical Cumulative Distribution Function (eCDF) of the MADRS Total Score Change from Baseline at Week 6 by Treatment; Population (N=354) (mITT)
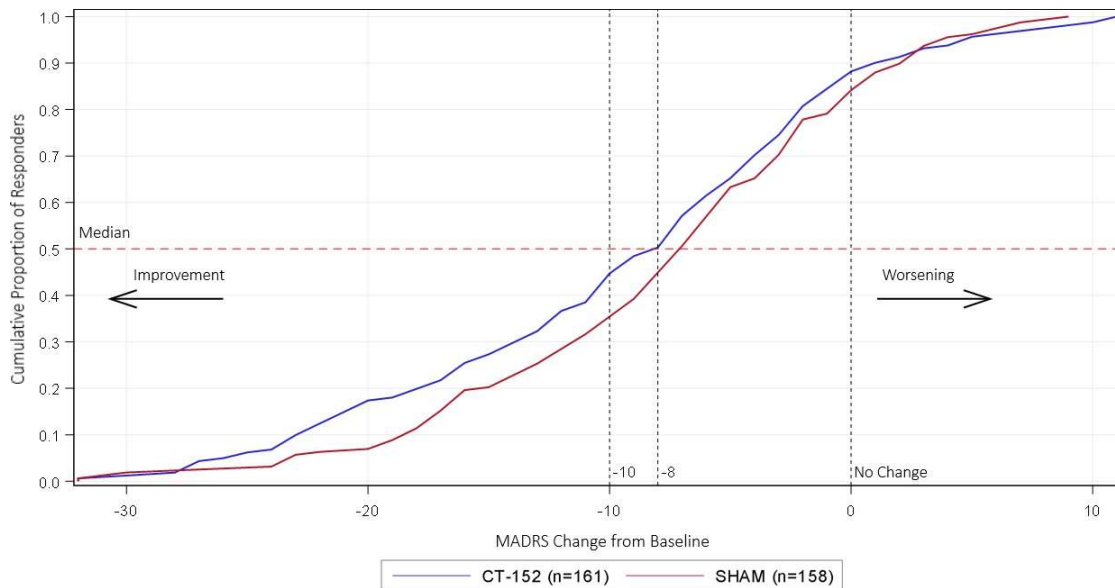
PHQ-9 and CGI-S

MADRS data were supported by a participant-reported outcome scale of depression (PHQ-9) and a clinician assessment of global symptom severity (CGI-S). The mean change from baseline to Week 6 in the PHQ-9 total score in the ITT population was -6.93 in the Rejoyn group compared with -5.15 in the Sham group, which yielded a group difference of -1.78 (p = 0.0012 CI [-2.85, -0.71]) (see Figure 4.7.2-6). The mean change from baseline to Week 6 in the PHQ-9 total score in the mITT population was -6.68 in the Rejoyn group compared with -5.10 in the Sham group, which yielded a group difference of -1.58 (p = 0.0029, CI [-2.62, -0.54]) (see Figure 4.7.2-7). The mean within- group change in the Rejoyn group , in both the ITT and mITT populations represents a clinically meaningful and a categorical improvement from "moderately severe" to "mild".[2,4] In the Sham group, the mean within-group change in both the ITT and mITT populations also represents a clinically meaningful change, associated with a categorical improvement from "moderately severe" to "moderate".[5]
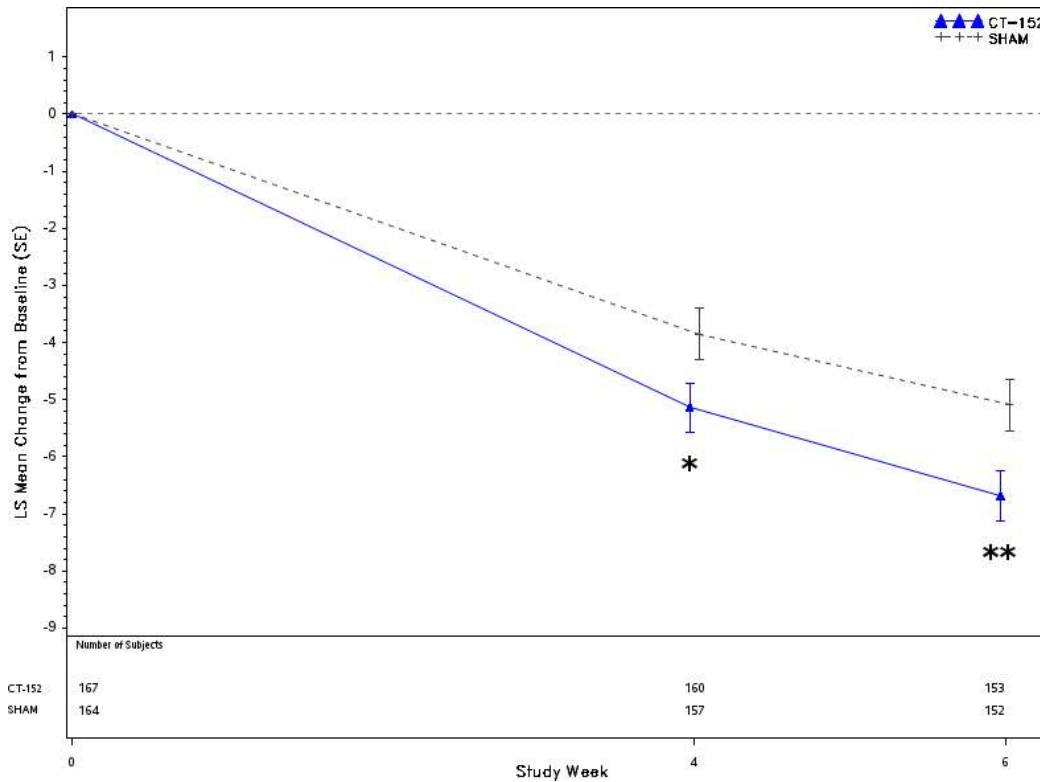
Figure 4.7.2-6: LS Mean Change from Baseline During Treatment Period in PHQ-9 Total Score, MMRM (ITT)
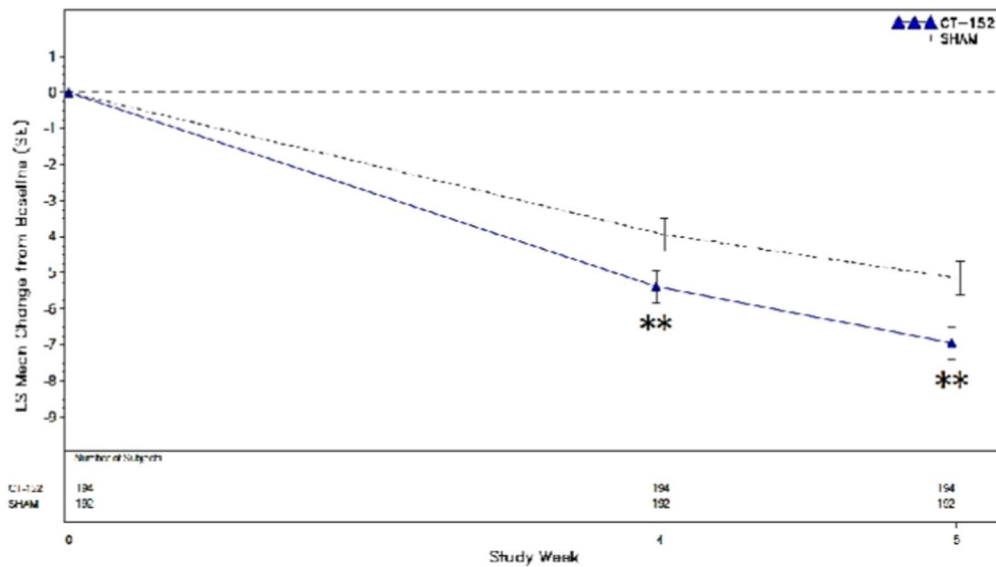
** P-value < 0.01
Note: Error bars are LS Mean +/- one SE.

Figure 4.7.2-7: LS Mean Change from Baseline During Treatment Period in PHQ-9 Total Score, MMRM (mITT)
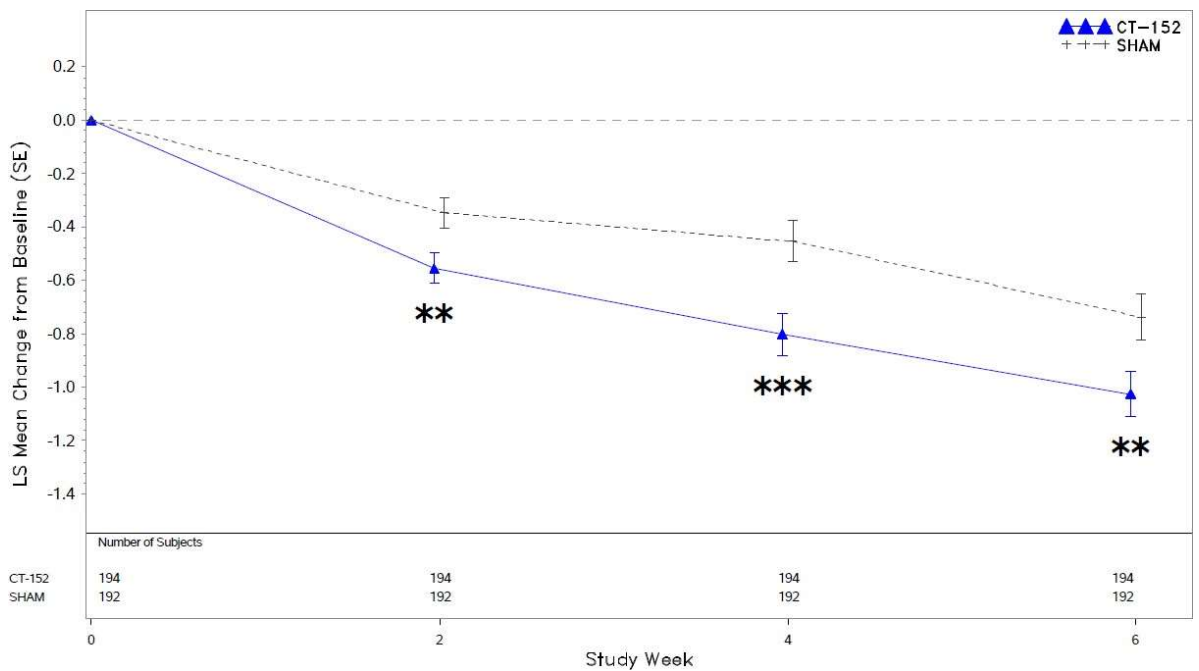

* P-value < 0.05, ** P-value < 0.01

Note: Error bars are LS Mean +/- One SE. Note: The PHQ-9 baseline was obtained at the screening visit.

The mean change from baseline to Week 6 in the CGI-S total score in the ITT population was -1.03 in the Rejoyn group compared with -0.74 in the Sham group, which yielded a group difference of -0.29 (p = 0.0037, 95% CI [-0.48, -0.09]) (see Figure 4.7.2-8). The mean change from baseline to Week 6 in the CGI-S total score in the mITT population was -1.06 in the Rejoyn group compared with -0.8 in the Sham group, which yielded a group difference of -0.26 (p = 0.0098, 95% CI [-0.46, -0.06]) (see Figure 4.7.2-9). The mean within-group change in the CGI-S, in both the ITT and mITT populations represents a clinically meaningful and a categorical improvement from "moderately ill" to "mildly ill".[2]
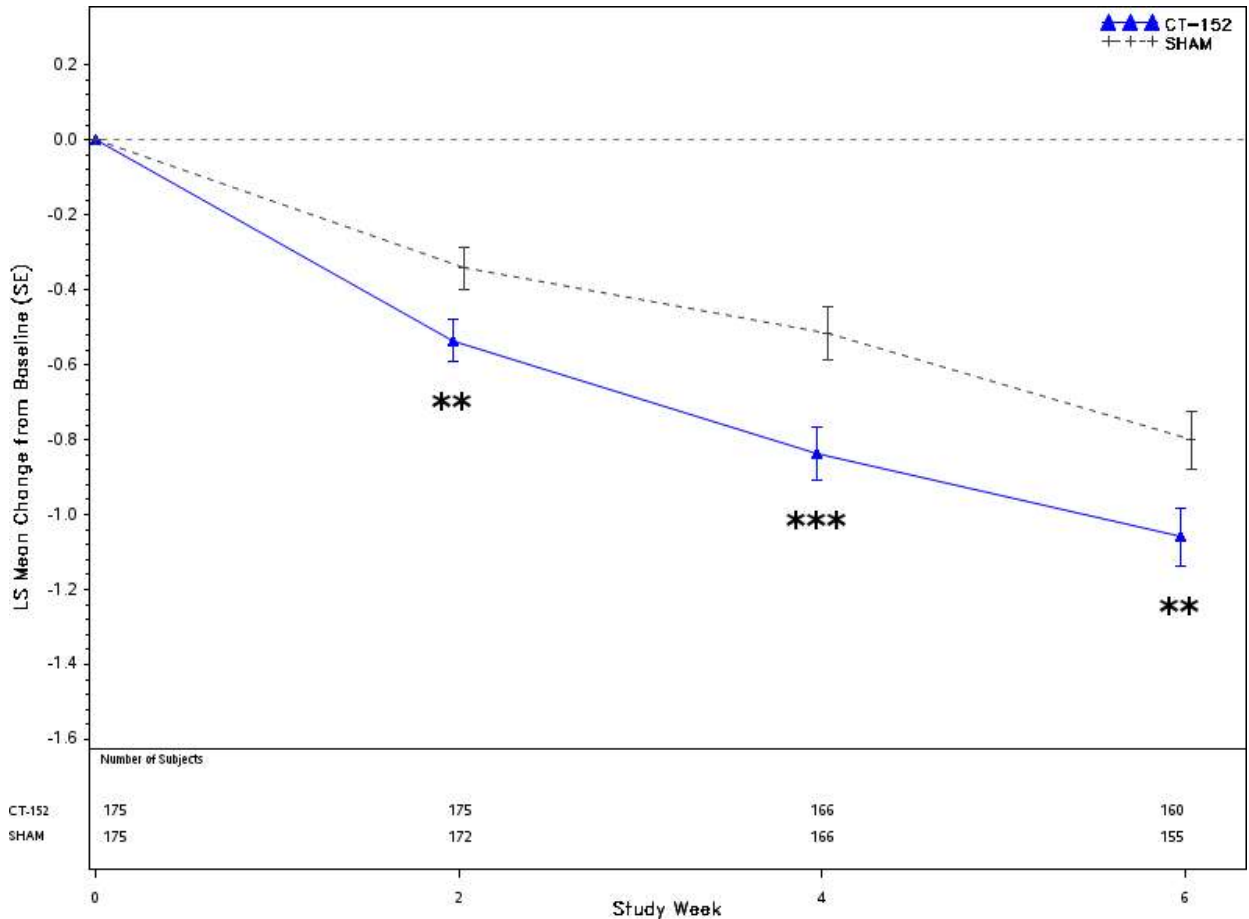
Figure 4.7.2-8: LS Mean Change from Baseline During Treatment Period in CGI-S Score, MMRM (ITT)

** P-value < 0.01, *** P-value < 0.001
Note: Error bars are LS Mean +/- one SE.

**Figure 4.7.2-9: LS Mean Change from Baseline during
Treatment Period in CGI-S Score, MMRM (mITT)**

** P-value < 0.01, *** P-value < 0.001
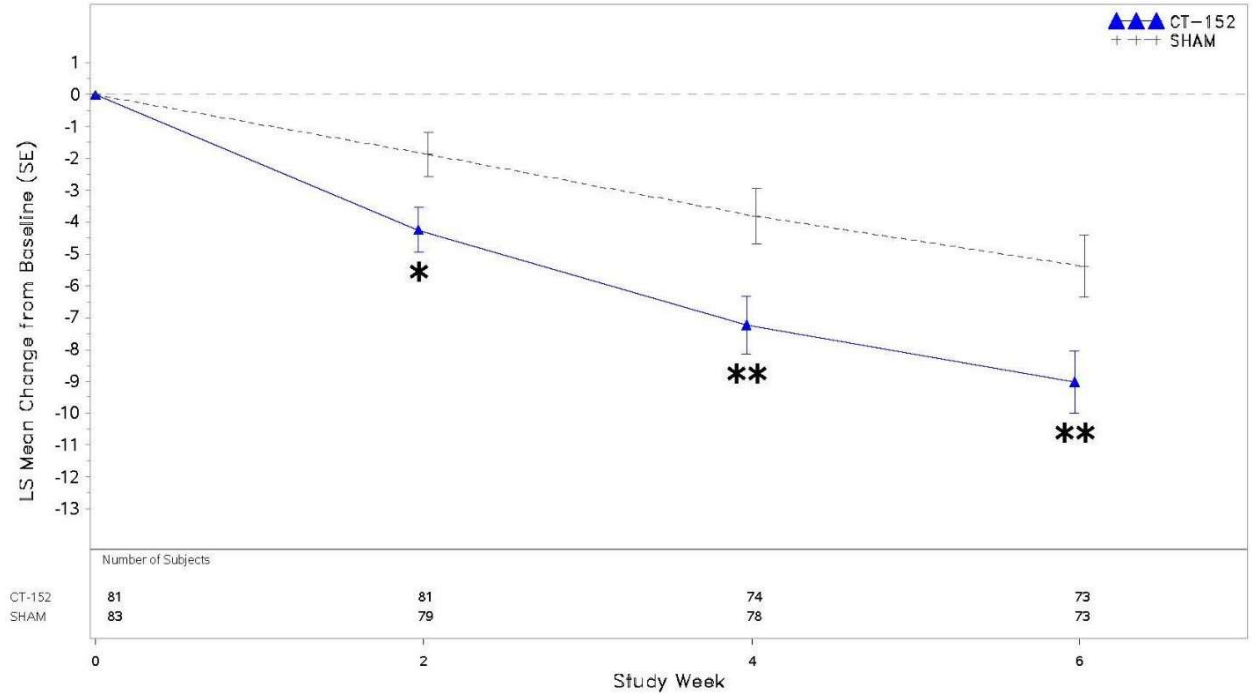Note: Error bars are LS Mean +/- One SE.

GAD-7

An additional analysis was conducted in the mITT population to assess the change from
baseline to Week 6 in GAD-7 total score for Rejoyn versus Sham. The mean change from
baseline to Week 6 in the GAD-7 total score was -3.41 in the Rejoyn group compared
with -2.64 in the Sham group, which yielded a group difference of -0.77 (p = 0.0705,
95% CI [-1.61, 0.07]).

MADRS Anxious Subgroup

Several pre-planned analyses were conducted in the mITT population based on baseline
symptom severity. In an analysis of participants with moderate or higher anxiety
symptoms at baseline, defined as a score of 10 or greater on the GAD-7, early and

sustained treatment effects were observed. The mean change from baseline to Week 6 in the MADRS total score was -9.01 in the Rejoyn group compared with -5.39 in the Sham group, which yielded a treatment group difference of -3.62 (p = 0.0099, 95% CI [-6.36, -0.88]) (see Figure 4.7.2-10).

Figure 4.7.2-10: LS Mean Change from Baseline during Treatment Period in MADRS Total Score in the Subgroup with Baseline GAD-7 Total Score ≥10, MMRM (mITT)

* P-value < 0.05, ** P-value < 0.01
Note: Error bars are LS Mean +/- One SE.

MADRS - Extension Phase

In the mITT, the treatment effect of Rejoyn persisted past Week 6 with a trend favoring continued improvement. The mean change from baseline to Week 10 in MADRS total score was -10.96 in the Rejoyn group compared with -9.93 in the Sham group, which yielded a group difference of -1.03. This between-group difference was not clinically significant.

In the MADRS Anxious Subgroup, the mean change from baseline to Week 10 in MADRS total score was -11.48 in the Rejoyn group compared with -9.31 in the Sham group, which yielded a group difference of -2.18.

MADRS - Adherent Subgroups

Participants were considered adherent to the digital therapy if they completed at least 12 of 18 treatment sessions. In participants who were deemed "adherent", the mean change from baseline to Week 6 in MADRS total score in the mITT was -9.21 in the Rejoyn group compared with -7.47 in the Sham group, which yielded a group difference of -1.74 (p = 0.0721, 95% CI [-3.65, 0.16]). At the end of the extension period, the mean change from baseline to Week 10 in MADRS total score was -12.58 in the Rejoyn group compared with -10.8 in the Sham group, which yielded a group difference of - 1.78. This suggests a durable effect (see Figure 4.7.2-11). A high percentage of participants met this definition of adherence (88.1% for both groups).

Figure 4.7.2-11: LS Mean Change From Baseline in MADRS Total Score for Participants Who Completed 12 or More Treatment Sessions, MMRM (mITT)
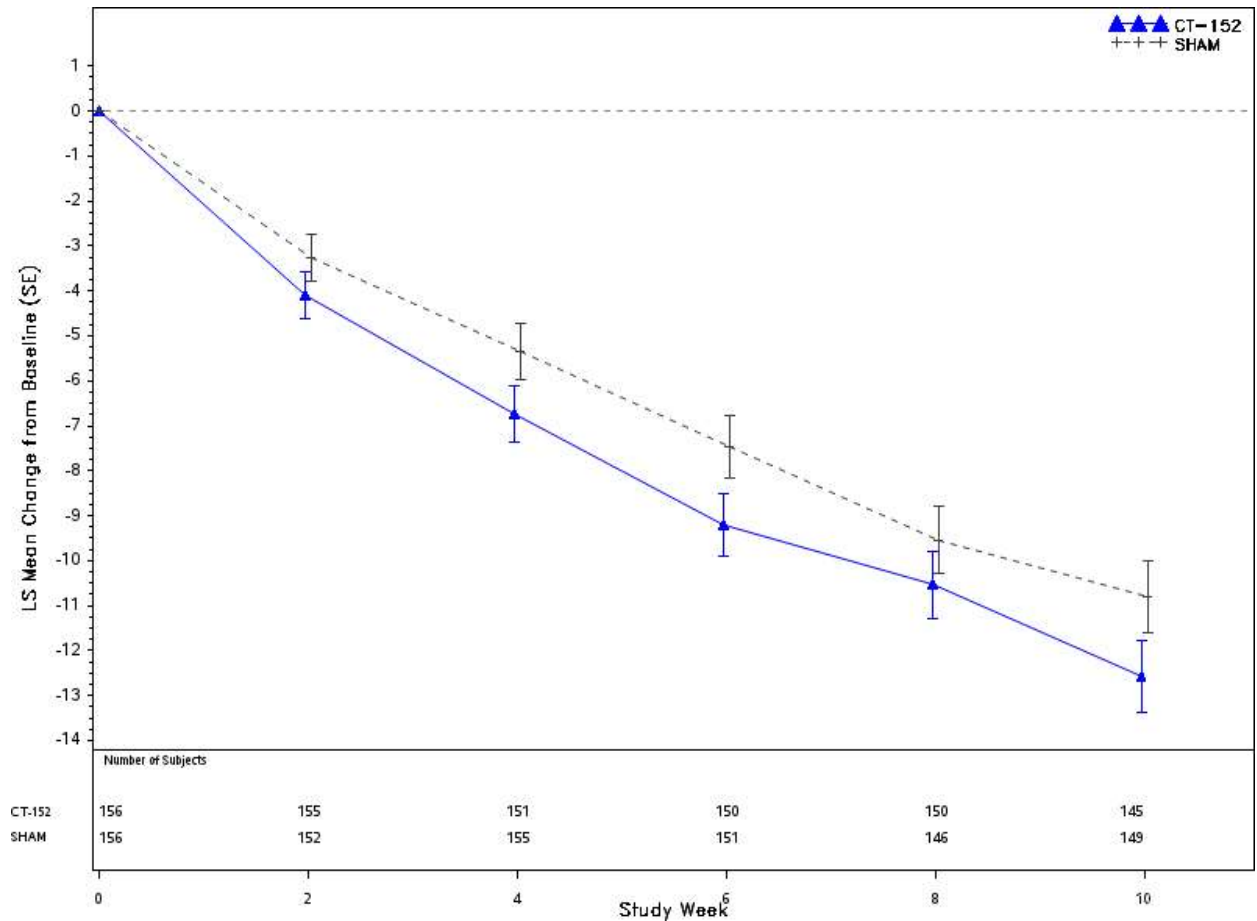
Note: Error bars are LS Mean +/- One SE. (p-values are not available for Weeks 8 and 10)
Weeks 1 through 6 represent the treatment period. Weeks 7 through 10 represent the extension period.

In participants who were fully adherent to the recommended 6-week treatment course, completing 18 out of 18 sessions, the mean change from baseline to Week 6 in MADRS

total score was -9.44 in the Rejoyn group compared with -7.48 in the Sham group, which yielded a group difference of - 1.95 (p = 0.1438, 95% CI [-4.58, 0.67]). At the end of the extension period, the mean change from baseline to Week 10 in MADRS total score was -13.98 in the Rejoyn group compared with -10.61 in the Sham group, which yielded a group difference of -3.37. A considerable percentage of participants were fully adherent (43.5% and 42.4% for Rejoyn and Sham, respectively). In sum, this MADRS adherence subgroup analyses suggest that participants who were adherent to the recommended number of sessions (or adherent per protocol) had a greater therapeutic effect that sustained over time.

Overall, out of the 18 total treatment sessions, the mean number of sessions completed was 15.1 for Rejoyn compared with 15.4 for Sham.

Participant and Healthcare Professional Satisfaction

Participant satisfaction and Healthcare Professional (HCP) satisfaction with Rejoyn were assessed by ratings on the Subject Satisfaction Scale (SSS) and HCP Satisfaction Scale (HCP- SS), respectively, at the end of the treatment period (Week 6). Participants in the Rejoyn group had a favorable impression of the treatment session experience with 85% rating the experience as "extremely satisfied" (37.1%) "satisfied" (38.9%), or "somewhat satisfied" (9%).

Investigators in the Mirai Trial had a favorable impression regarding the convenience of software to deliver treatment with 82.4% rating the convenience as "extremely convenient" (18.7%), "convenient" (49.7%) or "somewhat convenient" (14.0%).

Conclusions from the Mirai Trial

Effectiveness and safety data from the Mirai trial demonstrate that Rejoyn provides a benefit to patients with MDD when added to antidepressant pharmacotherapy. This data extends the findings from two earlier EMFT studies where a reduction in depression symptoms was demonstrated in MDD patients.[6,7] In the Mirai trial, the benefit of Rejoyn over Sham in reducing depressive symptoms was consistently rated by independent assessors via the MADRS, and by study investigators via the CGI-S.

The effects of Rejoyn observed in the Mirai trial were larger and more durable over time for participants who had protocol-defined adherence (ie, completed 12 of 18 treatment sessions) and for participants with full adherence (ie, completed 18 of 18 treatment sessions) to the intervention. Rejoyn also showed benefit in depression symptoms in highly anxious participants with MDD, a subgroup who have been shown to have poorer

outcomes.[8]

These effectiveness data are particularly noteworthy in the context of Rejoyn's safety profile. Adverse events were directly assessed via phone or video based on the trial being conducted remotely. Adverse events were determined to be related or unrelated to Rejoyn by the investigator. Treatment-emergent adverse events were low in frequency, unrelated to Rejoyn, and not appreciably different across treatment groups. Rate of discontinuation from the study was also low. Overall, Rejoyn offers a positive benefit-to-risk profile.

4.8 Conclusions

Rejoyn and its predicate, reSET, both are computerized behavioral therapy devices intended for patients with psychiatric disorders. The differences in their indications for use are due to differences in the primary psychiatric diagnosis of the patient populations in whom the device was studied and for whom the device is intended: Major Depressive Disorder (Rejoyn) and Substance Use Disorder (SUD) (reSET). Rejoyn and reSET have similar technological characteristics, including digital delivery of behavioral therapy through a smartphone application and therapeutic content that addresses a psychiatric disorder. Differences in content delivery sequence and therapy duration are due to the different intended patient populations specific to Rejoyn and reSET (MDD vs SUD, respectively).

Software testing and software documentation demonstrates that the device effectively implements the behavioral therapy model. The pivotal clinical trial shows that Rejoyn has demonstrated safety and effectiveness for the target population, consistent with the predicate device special controls on clinical validation. These data reasonably demonstrate that the differences between Rejoyn and the predicate device do not raise new safety and effectiveness questions and Rejoyn is substantially equivalent to the predicate device. Rejoyn meets all special controls per the regulatory requirements regarding clinical data, software, and labeling for a computerized behavioral therapy device for psychiatric disorders (21 CFR 882.5801). Given the positive benefit-to-risk ratio, these data support a 510(k) clearance for Rejoyn as a treatment option for those suffering from MDD.

4.9   References

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