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Enclosure:

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Efficacy of CT-152 for Major Depressive Disorder Using the Self-Reported 9-Item Patient Health Questionnaire in Participants With Baseline Anxiety Symptoms and/or Difficulty Sleeping

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Introduction

- The CT-152 smartphone app is a US FDA-cleared prescription digital therapeutic adjunct to antidepressant medication for patients with major depressive disorder (MDD).
- CT-152 includes 3 components: cognitive-emotional training (Emotional Faces Memory Task [EFMT]), cognitive-behavioral therapy (CBT)-based lessons, and personalized supportive text messages.[1]
  - EFMT employs a novel mechanism of action designed to enhance cognitive control over emotional information processing by targeting brain regions implicated in MDD.[1,2]
- In the pivotal 10-week Mirai trial (NCT04770285), CT-152 was more effective than a sham app for improving depressive symptoms on the Montgomery–Åsberg Depression Rating Scale and other clinician- and patient-reported instruments, including the Patient Health Questionnaire 9-Item (PHQ-9).[3]
- Effective treatment for MDD is multifaceted; an estimated 50%–60% of patients experience anxiety and up to 90% of patients experience sleeping difficulties, either of which may exacerbate depressive symptoms.[4–6]
  - Generalized anxiety disorder may predict or precede MDD and vice versa, and poor sleep quality has been identified as a potential mediator of this bidirectional relationship.[6]
- In this post hoc analysis, we analyzed the efficacy of CT-152 versus sham in relieving depressive symptoms, assessed using the PHQ-9, for participants with baseline anxiety symptoms and/or sleep difficulties.
  - The efficacy of CT-152 versus sham for improving sleep disturbances in participants with MDD was also assessed.

Methods

- Adults aged 22–64 years with a primary diagnosis of MDD (based on the criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition)[7] with inadequate response to their current antidepressant medication were enrolled in the Mirai phase 3 trial.[1]
  - The trial included a 6-week intervention period to assess treatment efficacy and 4-week extension to assess treatment durability.[1]
- Participants were randomly assigned 1:1 to use CT-152 or a sham app.[1,3]
  - CT-152 included cognitive-emotional training through EFMT and brief CBT-based lessons aimed to teach and apply key therapeutic skills.
  - The sham app included a shapes memory task (a working memory task designed to match the EFMT for time and attention but not intended to be therapeutic) and did not include CBT-based lessons.
  - All participants continued their current antidepressant medication, and both groups received supportive text messages to encourage treatment completion.
- This post hoc analysis evaluated changes from baseline to Week 6 in the PHQ-9 total score and individual line items in participants with anxiety symptoms or sleep disturbances at baseline.
  - The efficacy of CT-152 versus sham in alleviating sleep disturbances was also assessed based on changes from baseline in the sleep line item of the PHQ-9 in the overall Mirai population.
- Different rating scales were used to identify subgroups of participants with anxiety symptoms or sleep disturbances at baseline (**Table 1**).
- A mixed-effects model for repeated measures was used to assess treatment efficacy across subgroups with treatment, visit, and treatment by visit and baseline by visit interactions included as variables. Treatment site was not included as a variable to minimize the potential for confounding due to small centers at the subgroup level.
  - For the PHQ-9 total score and line items, changes were assessed from baseline to Week 4 and Week 6.
  - The rates of participants with a full response (a ≥ 50 percentage point reduction from baseline in PHQ-9 total score) or a meaningful within-patient change (a ≥ 6 point reduction from baseline in PHQ-9 total score) were summarized for all subgroups.
  - All outcomes in this analysis were tested at a nominal 0.05 two-sided significance level, without adjusting for multiplicity.

Results

- Participants (N = 386) were randomly assigned 1:1 to use CT-152 (n = 194) or sham (n = 192).[3]
- Participant demographics were similar between treatment groups. Participants were predominantly White (301/386, 78.0%) and female (332/386, 86.0%); the mean (standard deviation) age was 42.6 (12.1) years.
  - Each of the 4 subgroups included in this analysis had a similar pattern of baseline characteristics to the entire study population.
- Similarly to the trends reported in the Mirai trial,[3] changes from baseline in PHQ-9 total score favored CT-152 over sham in participants with baseline anxiety symptoms, regardless of the screening instrument used (**Figure 1, A–C**).
- Nominal significance ($P < 0.05$) favoring CT-152 over sham was observed for 7 out of 9 (**Figure 1D**), 3 out of 9 (**Figure 1E**), and 5 out of 9 (**Figure 1F**) individual PHQ-9 line items in participants with a baseline total Generalized Anxiety Disorder 7-item scale (GAD-7) score of ≥ 10, a baseline Hamilton Depression Rating Scale - Anxiety/Somatization (HAMD-A/S) score of ≥ 7, and a baseline Hamilton Depression Rating Scale - Anxiety (HAMD-A) score of ≥ 3, respectively.
- Analysis of the sleep-related line item of the PHQ-9 revealed greater improvement from baseline to Week 6 in sleep difficulty for those using CT-152 versus sham in the Mirai overall population (nominal $P < 0.01$; **Figure 2**).
- In the subgroup of participants with a Hamilton Depression Rating Scale - Sleep Disturbance Factor (HAMD-SDF) score of ≥ 3 at baseline, changes from baseline in PHQ-9 total score favored CT-152 over sham at Week 4 and Week 6 (nominal $P < 0.01$ for both time points; **Figure 3A**).
- Nominal significance ($P < 0.05$) versus sham was observed for participants in the "trouble falling or staying asleep" and "feeling tired or little energy" PHQ-9 line items for those with a baseline HAMD-SDF score of ≥ 3 (**Figure 3B**).
- For all subgroups, higher response rates were observed for CT-152 versus sham, with the highest CT-152 response rates observed in those with a baseline GAD-7 score ≥ 10 (**Table 2**).

Table 1. Scales and criteria used to identify participants with baseline anxiety symptoms and sleep disturbances

	Criterion	Scale description
Baseline anxiety symptoms	GAD-7 score of ≥ 10	A 7-item, participant-reported scale to screen for and assess the severity of GAD (range 0–21; a score of ≥ 10 is indicative of moderate or worse anxiety symptoms)[8]
	HAMD-A/S score of ≥ 7	The sum of 6 anxiety- or somatic-related items of the HAMD-17[a] (range 0–18; a score of ≥ 7 is indicative of "anxious depression"; higher scores indicate worsening symptoms)[9]
	HAMD-A score of ≥ 3	The sum of 2 anxiety-related items (psychic and somatic anxiety) of the HAMD-17[a] (range 0–8; a score of ≥ 3 is indicative of moderate or worse anxiety symptoms)
Baseline sleep disturbances	HAMD-SDF score of ≥ 3	The sum of 3 insomnia-related items of the HAMD-17[a] (range 0–6; a score of ≥ 3 is indicative of sleep disturbance; higher scores indicate worsening symptoms)

[a]The HAMD-17 is a 17-item, observer-reported scale used to evaluate depression severity, anxiety symptoms, and treatment response.[10]

GAD, Generalized Anxiety Disorder; GAD-7, Generalized Anxiety Disorder 7-Item scale; HAMD-17, Hamilton Depression Rating Scale, 17-Item; HAMD-A, Hamilton Depression Rating Scale - Anxiety; HAMD-A/S, Hamilton Depression Rating Scale - Anxiety/Somatization; HAMD-SDF, Hamilton Depression Rating Scale - Sleep Disturbance Factor.

Table 2. Response analysis based on PHQ-9 total score at Week 6 for all subgroups

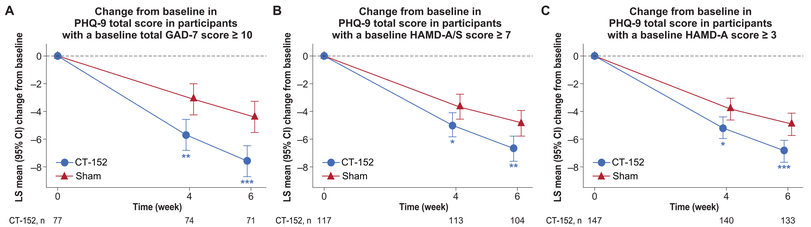
		CT-152 response rate, n/N (%)	Sham response rate, n/N (%)	Relative risk (95% CI)	Nominal *P* value	NNT (95% CI)
Anxiety symptoms	**Baseline GAD-7 score ≥ 10**					
	MWPC response[a]	51/77 (66.2)	39/78 (50.0)	1.3 (1.0, 1.7)	< 0.05	7 (4, 110)
	Full response[b]	43/77 (55.8)	15/78 (19.2)	2.9 (1.8, 4.8)	< 0.0001	3 (2, 5)
	Baseline HAMD-A/S score ≥ 7					
	MWPC response[a]	67/117 (57.3)	53/108 (49.1)	1.2 (0.9, 1.5)	0.2196	13 (5, > 500)
	Full response[b]	62/117 (53.0)	30/108 (27.8)	1.9 (1.4, 2.7)	< 0.01	4 (3, 8)
	Baseline HAMD-A score ≥ 3					
	MWPC response[a]	90/147 (61.2)	66/142 (46.5)	1.3 (1.1, 1.6)	< 0.05	7 (4, 30)
	Full response[b]	79/147 (53.7)	42/142 (29.6)	1.8 (1.4, 2.4)	< 0.0001	5 (3, 8)
Sleep disturbances	**Baseline HAMD-SDF score ≥ 3**					
	MWPC response[a]	80/134 (59.7)	63/124 (50.8)	1.2 (0.9, 1.5)	0.1517	12 (5, > 500)
	Full response[b]	69/134 (51.5)	36/124 (29.0)	1.8 (1.3, 2.4)	< 0.001	5 (3, 10)

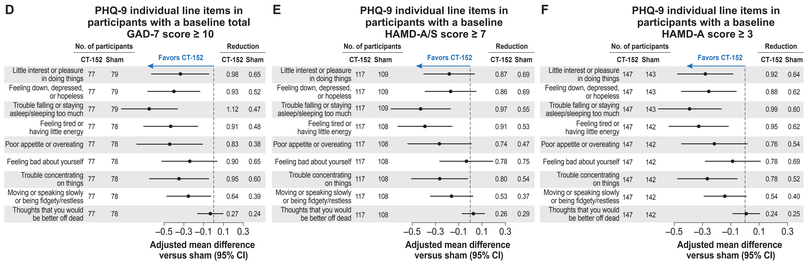
[a]Defined as a ≥ 6 point reduction from baseline in PHQ-9 total score.

[b]Defined as a ≥ 50 percentage point reduction from baseline in PHQ-9 total score.

GAD-7, Generalized Anxiety Disorder 7-Item scale; HAMD-A, Hamilton Depression Rating Scale - Anxiety; HAMD-A/S, Hamilton Depression Rating Scale - Anxiety/Somatization; HAMD-SDF, Hamilton Depression Rating Scale - Sleep Disturbance Factor; MWPC, meaningful within-patient change; NNT, number needed to treat; PHQ-9, Patient Health Questionnaire 9-Item.

Figure 1. Changes from baseline in PHQ-9 total score and individual line items for CT-152 versus sham in participants with baseline anxiety symptoms assessed by different screening instruments

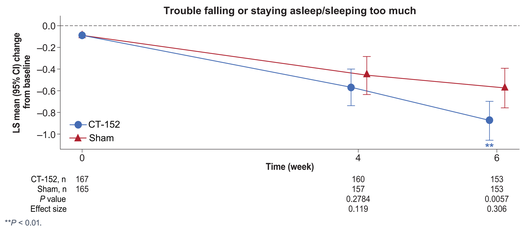




*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

CI, confidence interval; GAD-7, Generalized Anxiety Disorder 7-Item scale; HAMD-A, Hamilton Depression Rating Scale - Anxiety; HAMD-A/S, Hamilton Depression Rating Scale - Anxiety/Somatization; LS, least-squares; No., number; PHQ-9, Patient Health Questionnaire 9-Item.

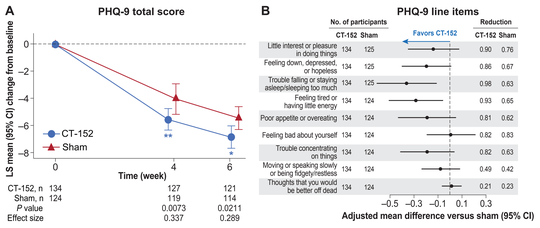
Figure 2. Change from baseline in the PHQ-9 line item for sleep disturbance for CT-152 versus sham in the Mirai overall population



**$P < 0.01$.

CI, confidence interval; LS, least-squares; PHQ-9, Patient Health Questionnaire 9-Item.

Figure 3. Changes from baseline in PHQ-9 total score (A) and individual line items (B) for CT-152 versus sham in participants with sleeping difficulties (HAMD-SDF score ≥ 3) at baseline



*$P < 0.05$; **$P < 0.01$.

CI, confidence interval; HAMD-SDF, Hamilton Depression Rating Scale - Sleep Disturbance Factor; LS, least-squares; No., number; PHQ-9, Patient Health Questionnaire 9-Item.

CONCLUSIONS

We previously demonstrated that CT-152 can reduce symptoms of depression and anxiety in people with MDD.[3] Here, we build on these findings, demonstrating that CT-152 can reduce depressive symptoms in those with baseline anxiety symptoms or sleep difficulties and can reduce sleep disturbances related to MDD.

- Results for participants with baseline anxiety symptoms were consistent regardless of the screening instrument used to assess anxiety at baseline.

Collectively, these findings suggest that CT-152 is effective at alleviating core symptoms of MDD and may provide broad benefits for patients, including those with anxiety symptoms and/or sleep difficulties.

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At Otsuka, we hold a deep respect for the value of every mind. We will not rest until mental illnesses and brain diseases are approached with the same priority and urgency as our physical health and recognized as chronic diseases that warrant early, equitable, and accessible intervention for patients and caregivers everywhere.

Disclosures

ZZ, **HJ**, **JC**, **JA**, **BR**, **TC**, **CM**, **HX**, and **AF** are employees of Otsuka Pharmaceutical Development & Commercialization, Inc. **MP** was an employee of Click Therapeutics, Inc. at the time the study was conducted. **DC** is an employee of Otsuka Precision Health, Inc. **TP** is an employee of Otsuka Pharmaceutical Europe Ltd.