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Enclosure:

- POSTER: Zhang Z, Jiang H, Cochran J, et al. Presented at Psych Congress, September 17-21, 2025; San Diego, CA, USA.

Responders and Participant-Reported Depressive Symptom Clusters That May Benefit From CT-152 Therapy for Major Depressive Disorder

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Poster presented at the 38th Psych Congress 2025
September 17–21, San Diego, CA, USA

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Introduction

- Digital therapeutics (DTx) have the potential to address unmet needs for patients with major depressive disorder (MDD), including increasing access and having fewer side effects than traditional antidepressant medications.[1–7]
- The CT-152 smartphone app is a US FDA-cleared prescription DTx adjunct to antidepressant medication for patients with MDD.
  - In the pivotal Mirai trial (NCT04770285),[8] CT-152 showed benefit over a sham app for the primary outcome on the Montgomery–Asberg Depression Rating Scale (MADRS) and multiple clinician- and patient-reported scales.
  - Post hoc analyses using the clinician-reported MADRS suggested CT-152 may benefit patients with a broad range of symptom profiles.
- In clinical practice, the self-reported Patient Health Questionnaire (PHQ)-9 and Generalized Anxiety Disorder 7-Item scale (GAD-7) are widely used to evaluate symptoms of depression and for comorbid anxiety symptoms, along with the short-form screening rating scales PHQ-2, 4, and 8.
  - In Mirai, CT-152 was favored over sham for PHQ-9 total score from baseline to Week 6 ($P = 0.0029$) and benefited participants with baseline anxiety on both the MADRS ($P = 0.0099$) and GAD-7 ($P = 0.0019$) scores compared with sham.
    - This post hoc analysis assessed the effect of CT-152 on the individual line items of the PHQ-9 and GAD-7, as well as symptom clusters based on the short forms of the PHQ (2,4,8), from baseline to Week 6, versus sham.

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) with inadequate response to their current antidepressant medication were enrolled in the Mirai phase 3 trial, which included a 6-week intervention period to assess treatment efficacy and a 4-week extension to assess treatment durability.[8]
- Participants were randomly assigned 1:1 to either treatment with CT-152 or sham.[8]
  - Delivered via a smartphone app, CT-152 includes 3 components:
    1. Cognitive emotional training (Emotional Faces Memory Task [EFMT])
    2. Brief cognitive behavioral therapy (CBT)-based lessons to reinforce and apply therapeutic skills
    3. Personalized text messages
  - The control group received a sham app which included a Shapes Memory Task, which is a working memory task designed to match the EFMT for time and attention for task completion, but was not intended to be therapeutic, and did not contain CBT-based lessons.
  - All participants continued their current antidepressant medication, and both groups received supportive text messages to encourage treatment completion.
- This analysis explored between-group comparisons for all participants in the CT-152 and sham groups for change from baseline to Weeks 4 and 6 on the individual line items of the PHQ-9, GAD-7, and short forms of PHQ (2,4,8). All scales in this analysis are frequently used in general clinical settings such as primary care (**Table 1**).
  - The PHQ-2 is the briefest version and is used primarily as a screening tool for depression.
  - The PHQ-4 is a screening tool that combines the PHQ-2 (depression) with the GAD-2 (anxiety) to screen for both.
  - The PHQ-8 is almost identical to the PHQ-9, except it omits the final question regarding suicidal ideation. It is often used in research settings in which suicide-related questions might not be appropriate or feasible to address, and is relevant for analysis of the Mirai outcomes because suicidal ideation was one of the exclusion criteria.[8]
- Outcomes were analyzed using mixed models for repeated measures with treatment, visit, treatment by visit interaction, and site as fixed effects.
  - As Mirai was a remote trial, there was not a reason to believe that site would have a significant effect on outcomes.
  - P values for post hoc analyses were not adjusted for multiplicity and are provided solely to help interpret findings.
- Response rates for the PHQ-9 (including full response, defined as ≥ 50% improvement from baseline; and meaningful within-patient change [MWPC] response, defined as ≥ 6-point reduction in total score) were compared between groups from baseline to Week 6.
  - The number needed to treat (NNT), when CT-152 was beneficial compared with sham, was also reported.

Results

- Participants (N = 386) were randomly assigned to CT-152 (n = 194) or sham (n = 192).
  - Mean age was 43 years, and most participants were female (86%) and White (78%).

PHQ-9 line items and symptom clusters

- All PHQ-9 line items showed a numerically higher reduction in the CT-152 group compared with sham at Week 6 (**Figure 1**).
  - Six line items showed nominal significance: "little interest/pleasure in things", "feeling down, depressed, or hopeless", "trouble falling or staying asleep", "feeling tired or little energy", "trouble concentrating on things" (all $P < 0.05$), and "poor appetite or overeating" ($P < 0.1$).
  - No line items favored sham.
- The CT-152 group showed greater improvement at Weeks 4 and 6 compared with sham on the PHQ-2 (Week 4, $P = 0.0020$; Week 6, $P = 0.0108$), PHQ-4 (Week 4, $P = 0.0116$; Week 6, $P = 0.0098$), and PHQ-8 (Week 4, $P = 0.0091$; Week 6, $P = 0.0025$) (**Figure 2A–C**).

PHQ-9 responder analysis

- CT-152 had higher response rates versus sham for both the full and the MWPC response criteria (**Figure 2D**).
- The estimated NNT was 5 (full response) or 9 (MWPC); thus, for every 100 patients treated, 11–20 additional patients would benefit.

GAD-7 line items

- At Week 6, all GAD-7 line items showed a numerically higher reduction for CT-152 compared with sham; one line item, "feeling nervous, anxious or on edge," showed nominal significance ($P = 0.0260$) (**Figure 3**).
  - No line items favored sham.

Limitations

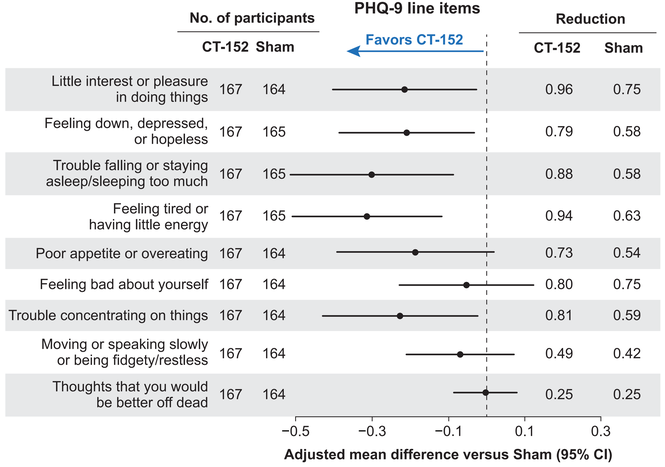
- The analysis of outcomes on the GAD-7 were for the overall population and may not fully reflect efficacy in those with baseline anxiety symptoms.
- The line-item analysis is not powered, thus the reported P values should be considered as nominal, supportive information to help interpret findings. They are not intended to be used for any hypothesis testing.

Table 1. Line items for different PHQ screening tools

	Line items	PHQ-2	PHQ-4	PHQ-8	PHQ-9
PHQ-9	Little interest or pleasure in things	X	X	X	X
	Feeling down, depressed, or hopeless	X	X	X	X
	Trouble falling or staying asleep, or sleeping too much			X	X
	Feeling tired or having little energy			X	X
	Poor appetite or overeating			X	X
	Feeling bad about yourself – or that you are a failure or have let yourself or your family down			X	X
	Trouble concentrating on things, such as reading the newspaper or watching television			X	X
	Moving or speaking so slowly that other people could have noticed, or being so fidgety or restless that you have been moving around a lot more than usual			X	X
	Thoughts that you would be better off dead or of hurting yourself in some way				X
GAD-2	Feeling nervous, anxious, or on edge		X		
	Not being able to stop or control worrying		X		

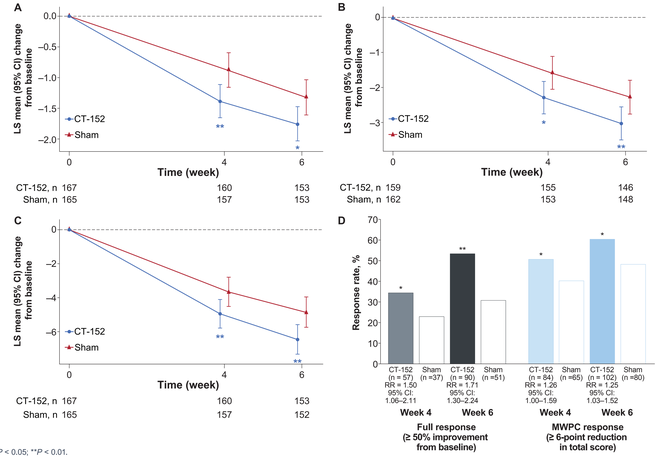
GAD-2, Generalized Anxiety Disorder 2-Item scale; PHQ, Patient Health Questionnaire.

Figure 1. Forest plot of change from baseline in PHQ-9 line items showing the effects of CT-152 treatment versus sham at Week 6



CI, confidence interval; No., number; PHQ-9, Patient Health Questionnaire 9-Item.

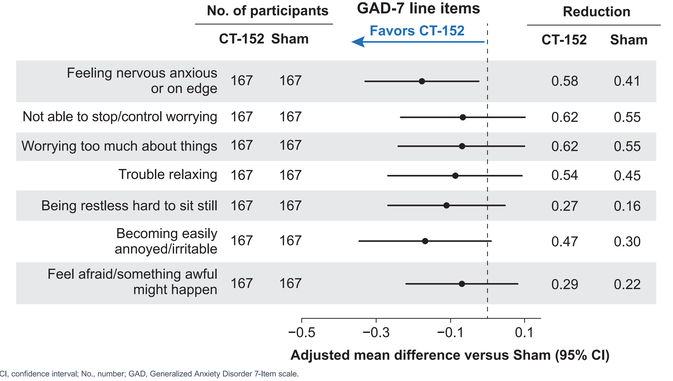
Figure 2. Change from baseline to Weeks 4 and 6 in PHQ-2 (A), PHQ-4 (B), and PHQ-8 (C) scores, and PHQ-9 responders (D)



*$P < 0.05$, **$P < 0.01$.

CI, confidence interval; LS, least-squares; MWPC, meaningful within-patient change; PHQ, Patient Health Questionnaire; RR, relative risk.

Figure 3. Forest plot of change from baseline in GAD-7 line items showing the effects of CT-152 treatment versus sham at Week 6



CI, confidence interval; No., number; GAD, Generalized Anxiety Disorder 7-Item scale.

CONCLUSIONS

These findings are consistent with the Mirai primary results and prior post hoc analyses.

CT-152 was favored over sham for the common patient-reported rating scales (PHQ-9 and GAD-7), associated line items, and short forms.

- The PHQ-9 and GAD-7 are frequently used in clinical practice and assess symptoms that are common for patients with MDD.
- Using these line items and symptom clusters provides a better understanding of the potential for benefit in daily practice.

CT-152 had a higher response rate compared with sham and a low NNT, as measured by the PHQ-9.

These findings support the potential for broad therapeutic benefit of CT-152 for patients with MDD and other comorbid symptomatology.

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Funding source

This study was funded by Otsuka Pharmaceutical Development & Commercialization, Inc. Click Therapeutics, Inc. was a co-development collaborator.

Acknowledgments

Medical writing support was provided by Caroline Leitschuh, PhD of Oxford PharmaGenesis Inc., Wilmington, DE, USA, and was funded by Otsuka Pharmaceutical Development & Commercialization, Inc.

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.