Osavampator (NBI-1065845/TAK-653) demonstrates statistically significant and clinically meaningful improvements in depression severity and is well tolerated in adults with major depressive disorder: phase 2 SAVITRI results

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Background

- Major depressive disorder (MDD) is characterized by a pervasive depressed mood, or a loss of interest or pleasure in activities in discrete episodes of at least 2 weeks.[1]
- Currently available antidepressant treatments have low response rates, and >60% of adults with MDD do not achieve remission after treatment with their first antidepressant medication.[2] As a result, patients with an inadequate response to antidepressants may also be treated with adjunctive medications.
- Osavampator (NBI-1065845/TAK-653) is an investigational selective positive allosteric modulator of the AMPA[a] receptor (AMPA-PAM) under development as a treatment for MDD, with initial studies evaluating its use in combination with oral antidepressants[3] (see **Poster #34** to learn more about the novel mechanism of action of osavampator).
- In preclinical studies, osavampator increased brain-derived neurotrophic factor levels and activated mammalian target of rapamycin signaling pathways associated with synaptic plasticity and antidepressant-like efficacy.[3]
- In phase 1 studies, osavampator had an acceptable safety profile and was well tolerated by healthy volunteers, supporting further investigation of osavampator for the treatment of MDD.[4,5]

[a] Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid.

Objective

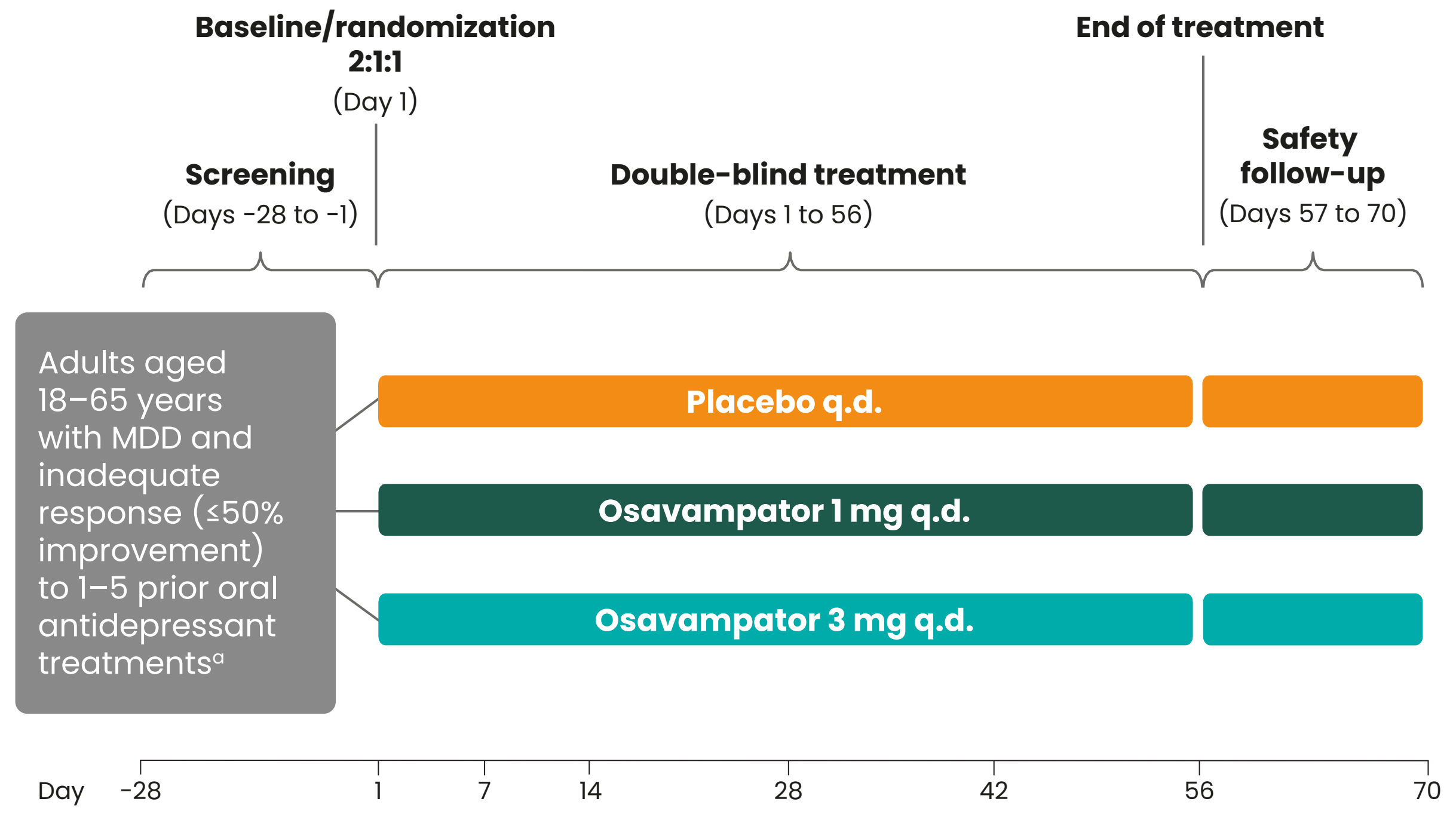
- The SAVITRI study (NCT05203341) evaluated the efficacy and safety of osavampator compared with placebo in individuals with MDD.

Methods

Study design and participants

- SAVITRI was a phase 2, multicenter, randomized, double-blind, placebo-controlled study conducted across 45 sites between December 6, 2021 and February 21, 2024.
- Following a screening period of ≤4 weeks, participants were randomized 2:1:1 to receive once-daily placebo, osavampator 1 mg, or osavampator 3 mg, administered orally for 8 weeks (**Figure 1**). Randomization was stratified based on region (USA vs non-USA), stable depression symptoms prior to randomization (yes vs no), and use of concomitant antidepressant medication at the time of randomization (yes vs no).

Figure 1. SAVITRI overall study design.



[a] Participants who were receiving stable pharmacological treatment for depression must have been taking their current antidepressant medication for ≥8 weeks prior to randomization, as confirmed by medical/pharmacy records, and must have been willing and able to continue with the same treatment throughout the study.
MDD, major depressive disorder; q.d., once daily.

Study assessments and endpoints

- **Baseline:** Day 1, when participants completed the Montgomery–Åsberg Depression Rating Scale (MADRS) efficacy assessment, after which they were randomized and administered the first dose of study treatment.
- **Primary efficacy endpoint:** change in depression severity from baseline to Day 28 using the MADRS total score.
- **Key secondary efficacy endpoints:**
  - change from baseline in MADRS total score at Day 56
  - response (defined as a decrease of ≥50% in MADRS total score from baseline) at Day 28 and Day 56
  - remission (defined as a MADRS total score ≤10) at Day 28 and Day 56.
- **Safety endpoint:** occurrence of treatment-emergent adverse events (TEAEs).
- **Exploratory *post hoc* analysis:** relationship between osavampator plasma concentration (exposure) and change from baseline in primary and secondary efficacy endpoints (based on MADRS total score; response).

Statistical analysis

- The full analysis set included all randomized participants and was used to summarize the participant demographics, baseline characteristics, and secondary endpoints. The safety analysis set included all randomized participants who took at least 1 dose of study treatment and was used to assess TEAEs.
- The primary endpoint and continuous secondary endpoints were analyzed using an analysis of covariance model with treatment group, region, and concomitant antidepressant use at randomization as stratification factors, and baseline MADRS total score as a covariate. Missing values for the primary endpoint were handled using a control-based multiple imputation approach.
- A nominal 2-sided significance level of 0.05 (no adjustment for multiplicity) was used for the primary and secondary endpoints.

Results

Participant disposition and baseline demographics

- Of the 417 participants screened, 183 were randomized (placebo: n = 91; osavampator 1 mg: n = 45; osavampator 3 mg: n = 47) and 161 participants (88%) completed study treatment (**Table 1**).
- Baseline characteristics were generally similar across treatment groups.
- The use of concomitant medications (those that were continued from before the study or newly started during the study) was high and similar across the treatment groups, with 92.4% of those receiving osavampator (1 mg and 3 mg) and 92.3% of those receiving placebo.

Efficacy

Change in MADRS total score

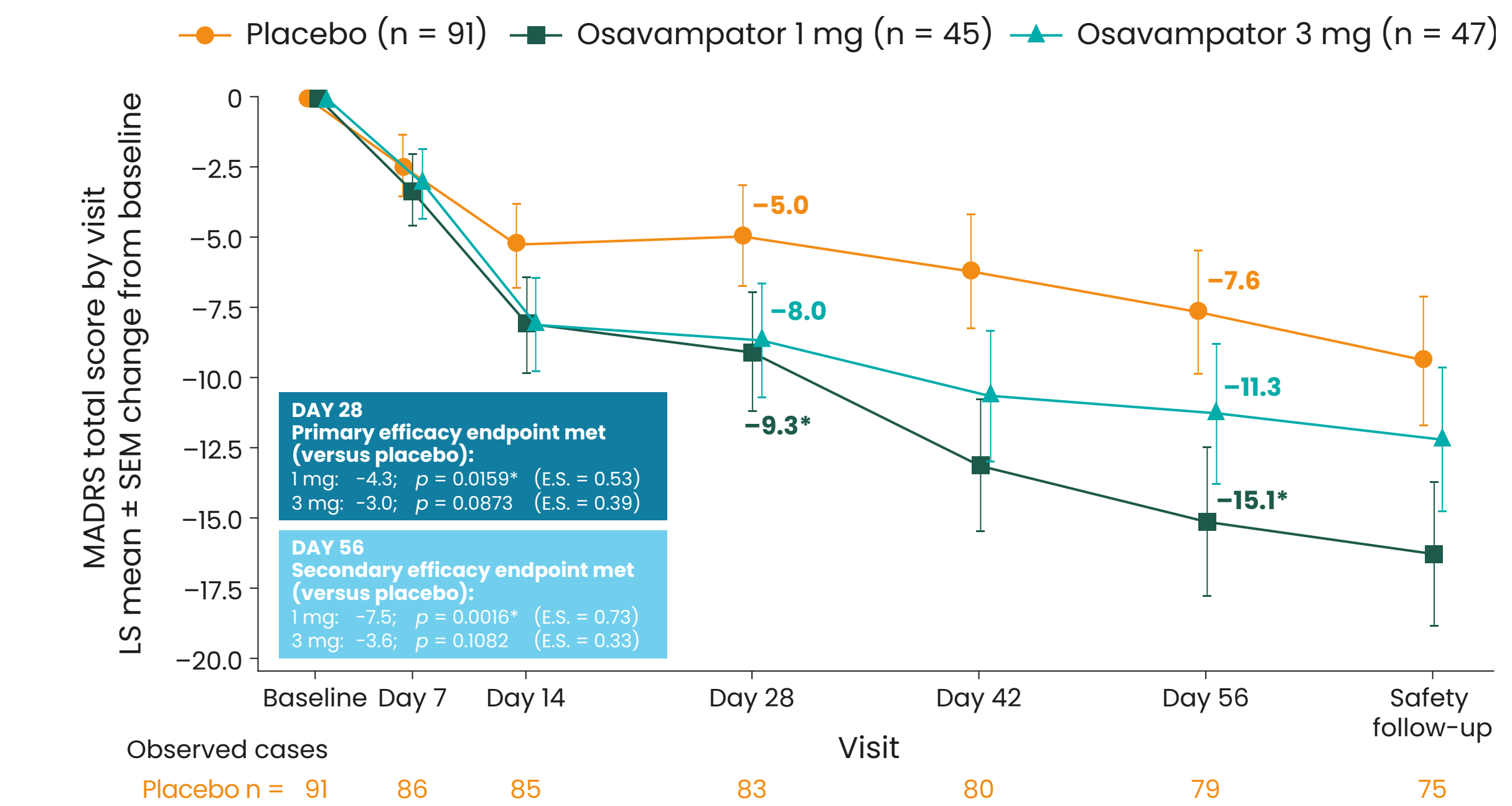
- At Day 28, there was a statistically significant difference in the MADRS total score change from baseline with osavampator 1 mg compared with placebo (least-squares [LS] mean treatment difference [95% confidence interval (CI): -4.3 (-7.8, -0.8)]; nominal *p* = 0.0159; effect size: 0.53) (**Figure 2**).
  - Osavampator 3 mg showed a treatment difference versus placebo (LS mean treatment difference [95% CI]: -3.0 [-6.4, 0.4]; nominal *p* = 0.0873; effect size: 0.39) that did not reach statistical significance.
- At Day 56, osavampator 1 mg showed a statistically significant improvement in MADRS total score versus placebo (LS mean treatment difference [95% CI]: -7.5 [-12.1, -2.9]; nominal *p* = 0.0016; effect size: 0.73).
  - Osavampator 3 mg showed a treatment difference versus placebo (LS mean treatment difference [95% CI]: -3.6 [-8.0, 0.8]; nominal *p* = 0.1082; effect size: 0.33) that did not reach statistical significance.
- Exposures in the 1 mg dose group were associated with the greatest improvement in MADRS total score (change from baseline) across multiple time points. Consistent with the dose response analysis, when compared with the 3 mg dose, the 1 mg dose produced more consistent and robust effects across exposure quartiles over time, most notably at Day 56.
  - These findings substantiate the continued evaluation of the 1 mg once-daily dosing in phase 3 studies in MDD.

Table 1. Baseline characteristics (FAS, n = 183).

	Placebo (n = 91)	Osavampator 1 mg (n = 45)	Osavampator 3 mg (n = 47)
Age, years			
Mean (SD)	47.8 (12.1)	45.0 (12.1)	48.9 (13.1)
Min, max	19, 65	22, 65	22, 64
Sex, n (%)			
Male	39 (42.9)	12 (26.7)	15 (31.9)
Female	52 (57.1)	33 (73.3)	32 (68.1)
BMI, kg/m²			
Mean (SD)	28.98 (5.60)	28.18 (4.78)	28.23 (5.36)
Min, max	18.00, 39.59	20.11, 39.11	18.17, 39.02
Race, n (%)			
White	81 (89.0)	41 (91.1)	43 (91.5)
Black or African American	6 (6.6)	3 (6.7)	0
Asian	3 (3.3)	1 (2.2)	2 (4.3)
Other	1 (1.1)	0	0
Multiple	0	0	1 (2.1)
American Indian or Alaska Native	0	0	1 (2.1)
Region, n (%)			
USA	42 (46.2)	21 (46.7)	20 (42.6)
Non-USA	49 (53.8)	24 (53.3)	27 (57.4)
Stability of depression symptoms prior to randomization, n (%)			
Yes	76 (83.5)	38 (84.4)	39 (83.0)
No	15 (16.5)	7 (15.6)	8 (17.0)
Antidepressant use at randomization, n (%)			
Yes	85 (93.4)	42 (93.3)	43 (91.5)
No	6 (6.6)	3 (6.7)	4 (8.5)
Number of failed antidepressants in current episode, n (%)			
≥2	32 (35.2)	16 (35.6)	9 (19.1)
Number of failed antidepressants at screening, n (%)			
≥2	16 (17.6)	8 (17.8)	4 (8.5)
MADRS total score			
Mean (SD)	32.3 (4.7)	34.2 (4.2)	32.6 (3.9)
Min, max	18, 42	24, 42	25, 42

BMI, body mass index; FAS, full analysis set; MADRS, Montgomery–Åsberg Depression Rating Scale; max, maximum; min, minimum; n, number of participants; SD, standard deviation.

Figure 2. LS mean (SEM) change from baseline in MADRS total score by visit (FAS).



DAY 28
Primary efficacy endpoint met (versus placebo):
1 mg: −4.3; *p* = 0.0159* (E.S. = 0.53)
3 mg: −3.0; *p* = 0.0873 (E.S. = 0.39)

DAY 56
Secondary efficacy endpoint met (versus placebo):
1 mg: −7.5; *p* = 0.0016* (E.S. = 0.73)
3 mg: −3.6; *p* = 0.1082 (E.S. = 0.33)

Observed cases	Baseline	Day 7	Day 14	Day 28	Day 42	Day 56	Safety follow-up
Placebo n =	91	86	85	83	80	79	75
Osavampator 1 mg n =	45	44	45	42	44	39	42
Osavampator 3 mg n =	46	42	45	40	42	40	40

Observed data. *$p < 0.05$ versus placebo.
E.S., effect size; FAS, full analysis set; LS, least-squares; MADRS, Montgomery–Åsberg Depression Rating Scale; n, number of participants; SEM, standard error of the mean.

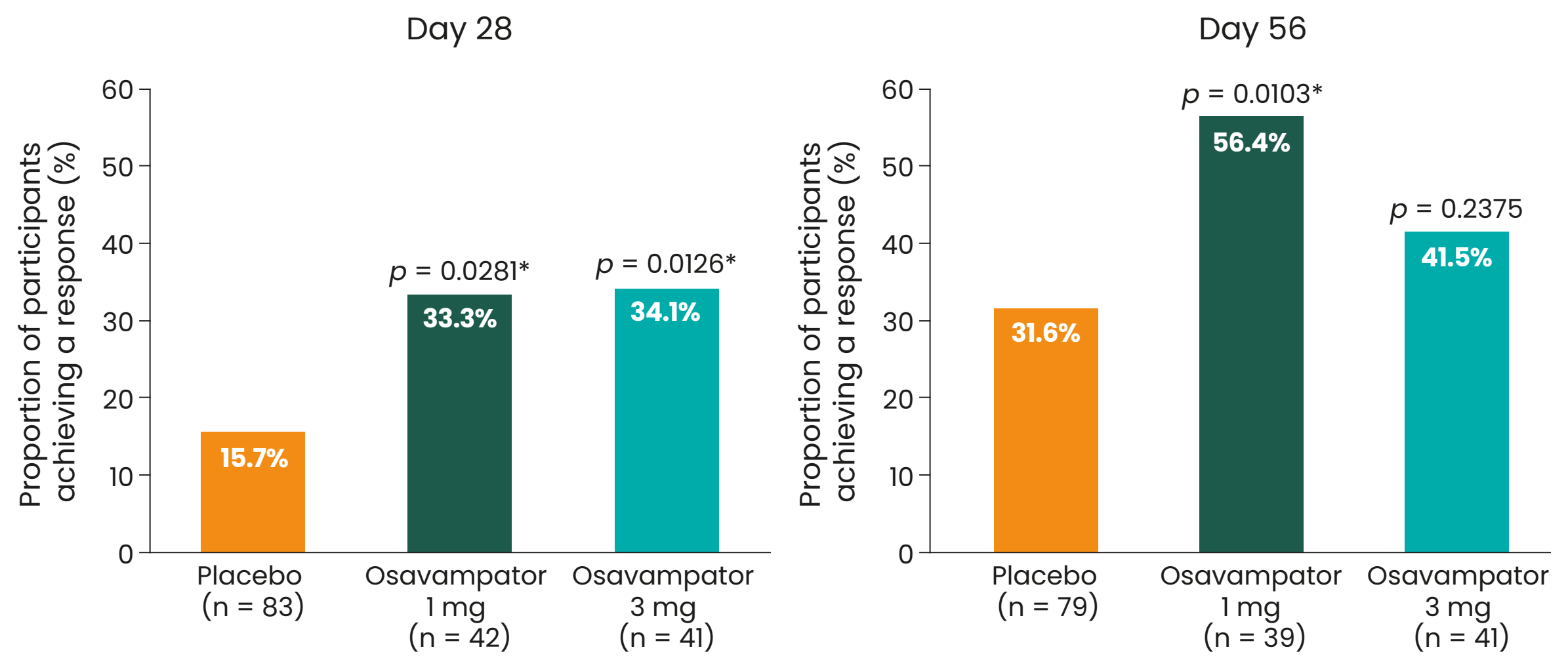
Depression response

- Response rates with osavampator 1 mg were statistically significantly higher than with placebo at Day 28 and at Day 56 (**Figure 3**).
- Response rates with osavampator 3 mg were statistically significantly higher than with placebo at Day 28; the difference at Day 56 was nominal but favored osavampator (**Figure 3**).

Remission rates

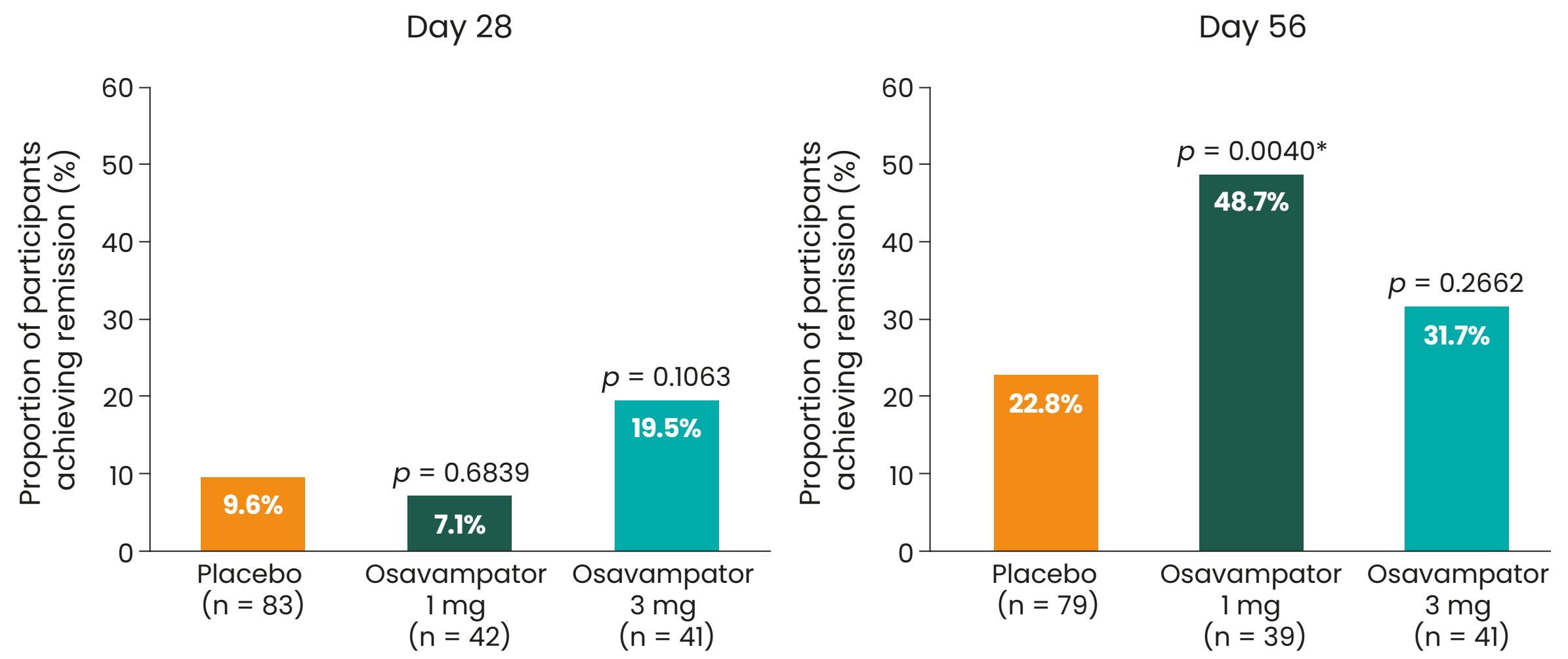
- At Day 28, compared with placebo, remission rates were lower for osavampator 1 mg but higher for osavampator 3 mg (**Figure 4**).
- At Day 56, both osavampator doses showed higher remission rates versus placebo; rates were statistically significantly higher with osavampator 1 mg than with placebo, but not for osavampator 3 mg versus placebo (**Figure 4**).

Figure 3. Participants who achieved a response[a] at Day 28 and Day 56 (FAS).



[a] Response was defined as a decrease of ≥50% in MADRS total score from baseline.
*Achieved significance ($p < 0.05$) versus placebo.
FAS, full analysis set; MADRS, Montgomery–Åsberg Depression Rating Scale; n, number of participants.

Figure 4. Participants who achieved remission[a] at Day 28 and Day 56 (FAS).



[a] Remission was defined as a MADRS total score ≤10.
*Achieved significance ($p < 0.05$) versus placebo.
FAS, full analysis set; MADRS, Montgomery–Åsberg Depression Rating Scale; n, number of participants.

Safety

- Overall, 39 (42.9%), 25 (55.6%), and 21 (44.7%) of the participants receiving placebo, osavampator 1 mg, and osavampator 3 mg, respectively, reported at least 1 TEAE; most TEAEs were mild or moderate in severity (**Table 2**).
- TEAEs leading to drug discontinuation occurred in 3 participants (3.3%) receiving placebo and 2 participants (4.3%) receiving osavampator 3 mg (**Table 2**).
- The most commonly reported TEAEs (occurring in ≥5%) in participants receiving osavampator were headache and nasopharyngitis, which were similar in occurrence to placebo.
- No deaths, serious adverse events, or adverse events of special interest (such as tremors or seizures) were reported across all treatment groups.

Table 2. Summary of TEAEs (SAS; n = 183).

	Placebo (n = 91)	Osavampator 1 mg (n = 45)	Osavampator 3 mg (n = 47)
≥1 TEAE, n (%)	39 (42.9)	25 (55.6)	21 (44.7)
Mild	21 (23.1)	8 (17.8)	9 (19.1)
Moderate	17 (18.7)	17 (37.8)	11 (23.4)
Severe	1 (1.1)	0	1 (2.1)
Serious TEAEs, n (%)	0	0	0
TEAEs resulting in death, n (%)	0	0	0
TEAEs leading to study drug discontinuation, n (%)	3 (3.3)	0	2 (4.3)
Frequent TEAEs,[a] n (%)			
Headache	8 (8.8)	5 (11.1)	2 (4.3)
Nasopharyngitis	5 (5.5)	2 (4.4)	3 (6.4)
Insomnia	2 (2.2)	1 (2.2)	3 (6.4)
Somnolence	3 (3.3)	3 (6.7)	0
Nausea	5 (5.5)	1 (2.2)	0
Dizziness	5 (5.5)	0	0

An adverse event was defined as any sign, symptom, syndrome, or new illness (regardless of relationship to study drug) that occurred after the first dose of double-blind study treatment and ≤30 days after the last dose of double-blind study treatment or early termination. Participants were randomized 2:1:1 to receive once-daily placebo, osavampator 1 mg, or osavampator 3 mg.
[a] Frequent TEAEs were those occurring in ≥5% of participants in any treatment group.
n, number of participants; SAS, safety analysis set; TEAE, treatment-emergent adverse event.

Conclusion

- In the phase 2 SAVITRI study, once-daily oral administration of osavampator 1 mg or 3 mg resulted in improvement in MADRS total scores at Day 28 and at Day 56 when compared with placebo; only the 1 mg dose achieved a clinically meaningful and statistically significant improvement.
- Both dose levels of osavampator were well tolerated, with no clinically significant safety concerns.
- The results from the SAVITRI study are supportive of further investigation of osavampator for the treatment of MDD.

Disclosures

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