# A phase 2, multicenter, double-blind, randomized, placebo-controlled study of the safety and efficacy of forvisirvat (SP-624) in the treatment of adults with major depressive disorder

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# A phase 2, multicenter, double-blind, randomized, placebo-controlled study of the safety and efficacy of forvisirvat (SP-624) in the treatment of adults with major depressive disorder

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## ABSTRACT

**Objective:** Forvisirvat (SP-624), an orally-administered epigenetic sirtuin 6 (SIRT6) activator with antidepressant effects in animal models, was well tolerated in three phase 1 trials. This phase 2 study, SP-624-201, evaluated the safety and efficacy of forvisirvat 20 mg daily for 4 weeks in participants with major depressive disorder (MDD).

**Methods:** SP-624-201 (NCT04479852) was a double-blind, placebo-controlled study. Participants were adults who met DSM-5 criteria for moderate to severe MDD and who discontinued psychoactive medications or supplements including antidepressants and mood stabilizers. Primary endpoint was change from baseline to Week 4 in Montgomery Asberg Depression Rating Scale score. Participants were randomized to forvisirvat 20 mg daily ($N = 163$) or placebo ($N = 156$).

**Results:** Of the 317 treated patients, 224 (70.7%) were White and 211 (66.6%) were female. No significant difference in the primary endpoint was observed between treatment groups. However, post-hoc analysis found that women treated with forvisirvat experienced significant overall improvement whereas men did not. The difference between sexes was also consistent for secondary efficacy measures. No serious adverse events were reported for forvisirvat-treated participants. The most frequent treatment-emergent event was headache (forvisirvat: 8.1%, placebo: 11.5%). Six of 161 forvisirvat-treated participants and 5 of 156 participants who received placebo discontinued due to adverse events.

**Conclusions:** The novel epigenetic mechanism of action of forvisirvat, favorable safety profile, and consistent post-hoc efficacy results in women observed in this study support further development of forvisirvat. A phase 2b/3 trial of forvisirvat in MDD (NCT06254612), to confirm these results, is ongoing.

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**PLAIN LANGUAGE SUMMARY**

Forvisirvat increases the amount of Sirtuin 6 in people who take it. Sirtuin 6 may impact depression. In healthy people, forvisirvat had no bad side effects. We looked at how well forvisirvat worked and how safe it was for adults with major depressive disorder (MDD).

About half the people in this study took forvisirvat and half took placebo (capsules that looked the same but did not contain medicine). The Montgomery Asberg Depression Rating Scale (MADRS) is a way to test how depressed people feel. We used it to test if forvisirvat helped people with MDD. We decided that 4 weeks after starting drug would be the best time to test if forvisirvat was working.

About seven of ten people in the study were White. About two-thirds were women. No one had bad side effects. Overall, at 4 weeks the average change in MADRS score was not different between the people who took forvisirvat and those who took placebo. We did a post-hoc analysis (a different way of looking at data from what was originally planned). This is a way to explore new ideas, but not to prove anything. We asked if forvisirvat acted differently in women and men. We found that it did. Women improved more at 4 weeks with forvisirvat than with placebo. Men did not. We saw the same kind of results with other tests of depression included in the study. We are doing another study (NCT06254612) to see whether forvisirvat really does work better in women than in men.

## Introduction

Despite treatment advances for major depressive disorder (MDD), almost a third of patients with MDD are resistant to treatment[1], indicating a need for new targeted treatments to alleviate the burden associated with MDD. Sirtuin 6 (SIRT6) activation has been identified as a potential mechanism for treatment of depression[2]. SIRT6 mRNA is significantly reduced in the brains of patients with MDD during depressive episodes compared with healthy controls, but when patients are in remission concentrations of SIRT 6 mRNA are comparable with those of healthy controls[3].

SIRT6 is a highly conserved chromatin regulatory protein in the sirtuin family of NAD+-dependent enzymes[4,5]. Studies in mice have demonstrated SIRT6 plays a role in promoting organismal health. SIRT6-deficient mice have a shortened lifespan and phenotypes associated with age-related impairments, cancer, and metabolic disorders[6–8]. SIRT6 over-expression in mice protects against metabolic pathologies associated with diet-induced obesity[5,9]. SIRT6 has an epigenetic mechanism of action that includes reduction of inflammation[10], enhancement of mitochondrial health, and DNA repair[11–14]. Each of these may play a role in neurodegeneration, metabolic disorders, and psychiatric disorders such as MDD[15–18].

Forvisirvat, an orally-administered, selective SIRT6 activator, is intended for treatment of MDD and potentially a broad range of other indications. Forvisirvat activates SIRT6 deacetylation of H3K9, H3K18 and H3K27 in intact nucleosomes. Forvisirvat was efficacious in several animal models of treatment-resistant depression, the forced swim test in WKY rats and in an inflammation-induced model, lipopolysaccharide-induced depression.

Forvisirvat also prevented scopolamine (anticholinergic)- and phencyclidine (NMDA antagonist)-induced cognitive deficits in the novel object recognition test. Forvisirvat was also shown to prevent excessive cytokine release in animal models (Data on file, 2025).

Three phase 1 studies examined the pharmacokinetics (PK) and safety of forvisirvat at oral doses of 3 to 80 mg in healthy adults[19]. Forvisirvat was well tolerated with no serious adverse events (AEs). PK parameters showed dose proportionality and reached predicted efficacious concentrations with low inter-subject variability. Here we report results of the SP-624-201 phase 2 clinical study designed to evaluate safety and efficacy of forvisirvat in adults with MDD.

## Methods

Study SP-624-201 (NCT04479852) was a phase 2, multicenter, double-blind, randomized, placebo-controlled study of the safety and efficacy of forvisirvat in adults with MDD. This parallel treatment study was designed to enroll 300 patients to receive forvisirvat 20 mg or placebo daily. The study was conducted from September 30, 2020, to August 9, 2022, at 34 centers in the United States.

### Study design

Participants completed a screening period of up to 28 days. After screening assessments were completed, participants' antidepressant medications (if any) were discontinued/tapered off according to medication recommendations. Participants were required to wait ≥5 half-lives of their previous medication before initiating study drug. Efficacy and safety assessments were
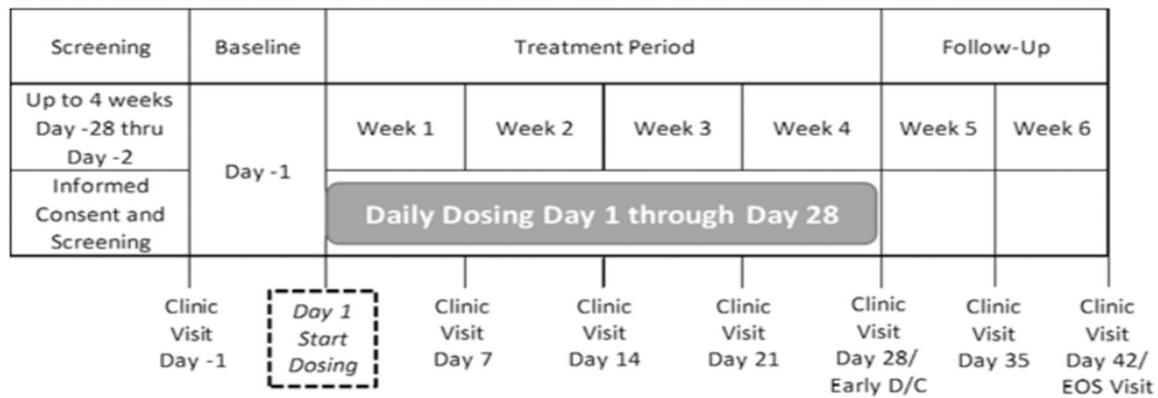
**Figure 1.** Study design.

performed at baseline and Weeks 1, 2, 3, and 4 (Figure 1). Study drug was discontinued at Week 4 visit. Blinded follow-up study visits occurred at Weeks 5 (for both safety and efficacy assessments) and 6 (safety only). Week 5 efficacy evaluations are shown for participants who completed 4 weeks of treatment. For participants who discontinued the trial early, follow-up visits occurred one and two weeks after treatment discontinuation. Participants could receive antidepressant medications according to physician recommendations after the Week 5/1-Week follow-up visit.

### Blinding and randomization

Investigators, staff, participants, and sponsor were blinded to study treatment. Participants were randomized 1:1 to forvisirvat 20 mg or placebo. The study utilized a block randomization plan, and investigators picked the next available kit number from study kits assigned to the site.

### Treatment

Study participants self-administered two 10 mg forvisirvat or inert placebo capsules once daily in the morning for up to 4 weeks. Placebo and forvisirvat capsules were identical in appearance and were dispensed in blister cards. Compliance was measured by patient report and pill count.

### Objectives and endpoints

The primary objective was to evaluate the efficacy of forvisirvat administered once daily for up to 4 weeks compared to placebo in adults with MDD. The primary endpoint was change from baseline to Week 4 in Montgomery Asberg Depression Rating Scale (MADRS) score. Additional efficacy endpoints were change from baseline to Weeks 1, 2, and 3 in MADRS score, change

from baseline to Weeks 1, 2, 3, and 4 in Clinical Global Impressions – Severity of Illness (CGI-S) score, change from baseline to Week 5 and from Week 4 to Week 5 in MADRS and CGI-S, and change from baseline to Week 2 and Week 4 in Hamilton Depression Rating Scale (17 items) (HAM-D-17), Sheehan Disability Scale (SDS), Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR), and Quality of Life Enjoyment and Satisfaction-Questionnaire – Short Form (Q-LES-Q-SF).

Secondary objectives were to evaluate safety and tolerability of forvisirvat compared to placebo and obtain plasma samples for future characterization of the population PK of forvisirvat. Safety endpoints included treatment-emergent adverse events (TEAEs) and change from baseline in standard clinical safety laboratory tests, electrocardiograms, and body weight.

### Study ethics

This study was performed in accordance with ethical principles originating in the Declaration of Helsinki and consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guidance for Good Clinical Practice and applicable regulatory requirements. The protocol was approved by all study site institutional review boards. All participants provided written informed consent.

### Participants

Eligible participants were men and women aged 18 to 65 years with body mass index between 18 and 40 kg/m$^2$ who met DSM-5 criteria for moderate to severe MDD, as confirmed by the Mini International Neuropsychiatric Interview. Participants had to have MADRS scores ≥27 at both screening and baseline and be experiencing an episode of depression with duration between six weeks and two years at screening. Participants could not pose a current or future

suicidal risk, in the Investigator's opinion, have history of suicidal behavior within the past 12 months, or have answered "yes" to "Suicidal Ideation" Items 4 or 5 on the Columbia-Suicide Severity Rating Scale within six months prior to screening or at baseline.

Participants could have a diagnosis of comorbid generalized anxiety disorder if MDD was their primary diagnosis. Participants had to have a history of either inadequate response or non-response to $\geq 1$ adequate antidepressant treatment (an adequate dose for $\geq 6$ weeks) but could not have received $>3$ treatments of the same antidepressant class, nor an adequate treatment regimen of $\geq 2$ antidepressant classes, nor any treatment with antipsychotic medication(s) during their current MDD episode.

Participants receiving psychoactive medications or psychoactive supplements including antidepressants and mood stabilizers, were required to discontinue these medications and wait at least five half-lives of the medications before receiving forvisirvat. Participants could not have depression with peripartum onset, panic disorder, obsessive compulsive disorder, post-traumatic stress disorder, anorexia nervosa, bulimia nervosa, or (within twelve months of screening) moderate or severe substance use disorder (except nicotine or caffeine). They could not have history of or current MDD with psychotic features; any schizophrenia spectrum or other psychotic disorder, bipolar disorder, or personality disorder; or prior treatment with electroconvulsive therapy, vagus nerve stimulation, deep brain stimulation, or transcranial magnetic stimulation within six months of screening. Participants could not, in the Investigator's opinion, require initiation of psychotherapy during the study. They could continue ongoing ($\geq 3$ months) psychotherapy other than cognitive behavioral therapy. Participants could not have history or presence of major bowel resection, total gastrectomy, diabetes, or any clinically significant medical condition, or be pregnant, breastfeeding, or $<6$ months postpartum at screening. Participants had to be sexually abstinent or use adequate and reliable contraception throughout the study and for $\geq 30$ days after the last study drug dose.

## Statistics

The power calculation assumed placebo and forvisirvat would yield an approximate 9-unit and 12-unit decrease, respectively, on MADRS score over four weeks with a similar standard deviation (SD) of 9.2 for each treatment group. A sample size of 300 (150 per arm) was estimated to provide 80% statistical power to detect a 3-unit difference between treatment groups.

Participant disposition was determined using the all-participant population. The modified intent-to-treat (mITT) population consisted of all participants who received $\geq 1$ study drug dose and had baseline and $\geq 1$ post-dose efficacy assessments. The safety population consisted of all participants who received $\geq 1$ study drug dose. The primary endpoint, change from baseline in MADRS score at Week 4, was analyzed using a mixed model for repeated measures (MMRM), with change in MADRS score at each visit as the response variable. The MMRM model included fixed effects for treatment, week, and the interaction of week by treatment, and a random effect of subject within treatment. Baseline MADRS total score was included as a covariate in the model. An unstructured covariance matrix was used for within-subject correlation. Kenward-Roger approximation was used to calculate the denominator degrees of freedom. Standard categorical descriptive statistics included count and percentages of participants with level of the variable summarized. Hypothesis tests assessed the null hypothesis that there was no difference between treatment groups. Response was defined as a decrease of at least 50% from baseline in MADRS score. Remission was defined as a MADRS score of $\leq 10$. Two-sided p-values of $\leq 0.05$ were considered statistically significant. No adjustments for multiplicity were performed. The secondary efficacy analyses were performed using a model similar to that used for the primary analysis, reduced if necessary for convergence issues. After database lock and study readout, additional post-hoc analyses stratified by sex were performed. Statistical analyses were completed using Version 9.4 or later of the SAS Statistical Analysis System (SAS Institute, Inc. Cary, NC).

## Results

### Participants

Participants were randomized to receive forvisirvat 20 mg ($N = 163$) or placebo ($N = 156$) daily (Figure 2). Percentages of participants who completed treatment and reasons for treatment discontinuation were similar in the forvisirvat and placebo groups. Mean ages were 41.5 years and 43.9 years for forvisirvat and placebo participants, respectively. Most participants were White and not of Hispanic or Latino ethnicity (Table 1). Both groups were approximately two-thirds women. Depression, current episode history, and number of lifetime depressive episodes were also similar. In both groups, slightly more than one-third of participants were receiving antidepressant treatment at screening.
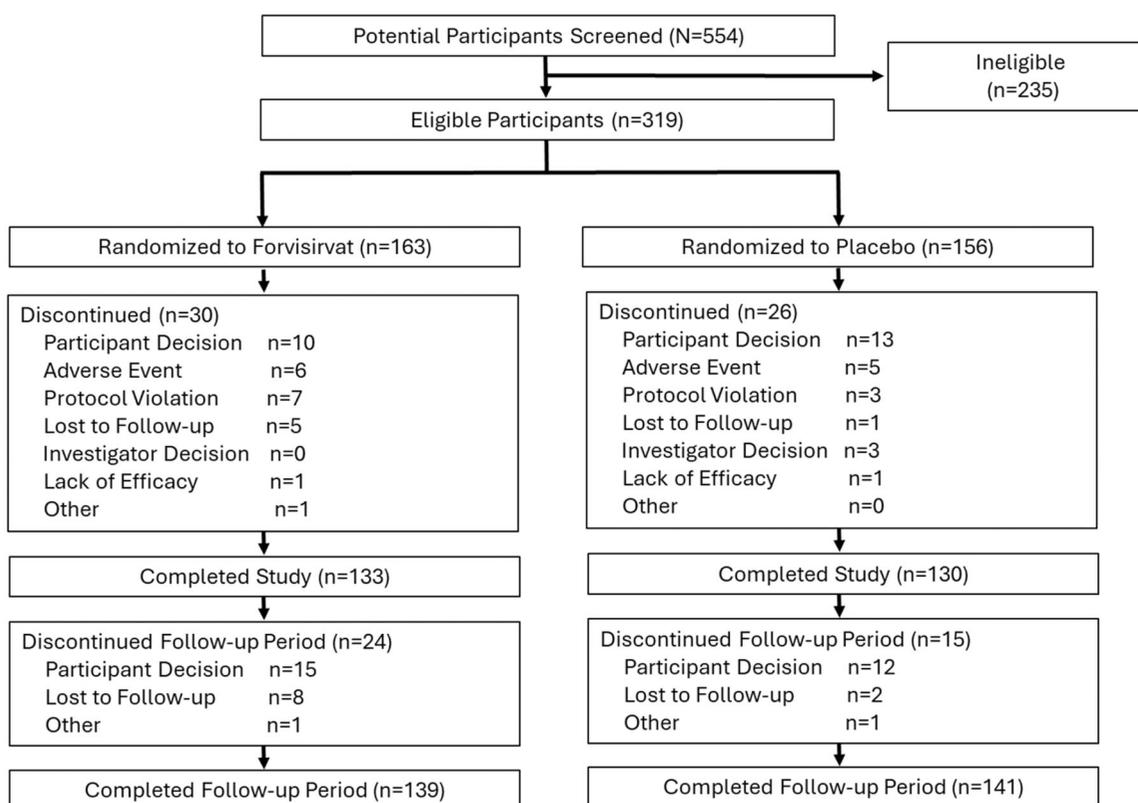
Figure 2. Participant flow diagram. Not all participants who decided to withdraw from the study reported a reason. For those who did, reasons included changes in schedules, burden of study visits or travel, unexpected travel or move, and family issues. Reasons for consent withdrawn by participants were reviewed to ensure accurate categorization.

Table 1. Participant baseline demographics and disease characteristics.

| | All participants | | Women | | Men | |
|---|---|---|---|---|---|---|
| | Forvisirvat (N = 161) | Placebo (N = 156) | Forvisirvat (N = 101) | Placebo (N = 110) | Forvisirvat (N = 60) | Placebo (N = 46) |
| Age, years, mean (SD) | 41.5 (13.95) | 43.9 (14.11) | 41.4 (14.45) | 44.4 (14.30) | 41.7 (13.19) | 42.7 (13.70) |
| Race, n (%) | | | | | | |
| American Indian or Alaskan Native | 2 (1.2) | 2 (1.3) | 1 (1.0) | 1 (0.9) | 1 (1.7) | 1 (2.2) |
| Asian | 8 (5.0) | 12 (7.7) | 5 (5.0) | 9 (8.2) | 3 (5.0) | 3 (6.5) |
| Black or African American | 41 (25.5) | 34 (21.8) | 24 (23.8) | 20 (18.2) | 17 (28.3) | 14 (30.4) |
| Native Hawaiian or other Pacific Islander | 2 (1.2) | 2 (1.3) | 1 (1.0) | 2 (1.8) | 1 (1.7) | 0 (0.0) |
| White | 113 (70.2) | 111 (71.2) | 74 (73.3) | 82 (74.5) | 39 (65.0) | 29 (63.0) |
| Ethnicity, n (%) | | | | | | |
| Hispanic or Latino | 16 (9.9) | 21 (13.5) | 10 (9.9) | 14 (12.7) | 6 (10.0) | 7 (15.2) |
| Non-Hispanic/ Non-Latino | 142 (88.2) | 135 (86.5) | 88 (87.1) | 96 (87.3) | 54 (90.0) | 39 (84.8) |
| Unknown or not reported | 3 (1.8) | 0 (0.0) | 3 (3.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Body Mass Index, kg/m$^2$, mean (SD) | 29.3 (5.47) | 29.1 (5.69) | 30.0 (5.63) | 28.5 (5.44) | 28.1 (5.02) | 30.6 (6.05) |
| Age of onset of first depressive episode, years, mean (SD) | 25.5 (12.02) | 27.6 (13.55) | 24.9 (12.23) | 27.4 (13.96) | 26.5 (11.71) | 28.1 (12.71) |
| Lifetime depressive episodes, n, mean (SD) | 5.3 (4.56) | 5.9 (6.37) | 5.8 (5.20) | 5.6 (6.42) | 4.5 (3.15) | 6.7 (6.25) |
| Duration of current depressive episode, months, mean (SD) | 11.9 (6.11) | 12.5 (6.11) | 11.8 (6.39) | 12.6 (6.15) | 12.1 (5.66) | 12.4 (6.06) |
| Current episode is recurrent depression, n (%) | 146 (93.0) | 150 (98.0) | 93 (94.9) | 104 (97.2) | 53 (89.8) | 46 (100.00) |
| Receiving treatment for current episode at screening, n (%) | 60 (38.5) | 54 (35.3) | 43 (44.3) | 39 (36.4) | 17 (28.8) | 15 (32.6) |

## Efficacy

Overall, least squares mean (LSM) (standard error [SE]) change in MADRS score from baseline to Week 4 was not significantly different between forvisirvat (−12.6 [0.83]) and placebo groups (−10.8 [0.84], p = 0.133; Figure 3A). Both groups appeared to improve from baseline. At 4 weeks, 48 (36.4%) forvisirvat-treated participants achieved response (≥50% decrease from

baseline in MADRS score), compared with 37 (29.6%) participants who received placebo ($p = 0.277$; Figure 4). At 4 weeks, 29 (22.0%) forvisirvat-treated participants achieved remission (MADRS $\leq 10$), compared with 21 (16.8%) participants who received placebo ($p = 0.297$; Figure 4).

All subsequent analyses by sex were post-hoc and not controlled for multiple comparisons. LSM change from baseline to Week 4 in MADRS scores indicated that forvisirvat-treated women had significantly greater change ($-13.4$ [1.05]) than women who received placebo ($-9.4$ [1.02], $p = 0.008$; Figure 3B). In the forvisirvat treatment group, women experienced greater improvement than men ($-13.4$ [1.05] vs. $-11.3$ [1.21]). Among participants who received placebo, women had less improvement than men ($-9.4$ [1.02] vs. $-14.0$ [1.35]). In men, the forvisirvat group showed numerically less improvement in MADRS score at Weeks 3 and 4 compared to placebo ($p \geq 0.134$; Figure 3C). In women at Week 4, individual changes from baseline in MADRS total scores in the $-10$ to $-40$ range (indicating improvement) were more common in the forvisirvat group than the placebo group, whereas scores in the placebo group clustered more in the 10 to $-10$ range (indicating minimal change). In men at Week 4, individual changes from baseline in MADRS total score in the forvisirvat group were generally in the same range as placebo, with no efficacy of forvisirvat observed. Neither the positive treatment effect in women nor the lack of treatment effect in men was driven by outliers (Supplemental Figure 1A and B).

At 4 weeks, 32 (38.1%) forvisirvat-treated women experienced response, compared with 20 (23.3%) of women who received placebo ($p = 0.034$). However, the difference in remission rates (21 [25.0%] forvisirvat-treated women vs. 12 [14.0%] who received placebo) was not significant ($p = 0.067$). For men, no significant differences were seen for response (forvisirvat, $n = 16$ [33.3%], placebo, $n = 17$ [43.6%], $p = 0.327$) or remission (forvisirvat, $n = 8$ [16.7%], placebo, $n = 9$ [23.1%], $p = 0.458$).

In all participants, LSM change from baseline in CGI-S was significantly greater with forvisirvat than placebo at Week 2 ($-0.9$ [0.08] vs. $-0.6$ [0.08], $p = 0.039$) and Week 3 ($-1.1$ [0.09] vs. $-0.8$ [0.09], $p = 0.026$), but not Week 4 ($-1.2$ [0.10] vs. $-0.9$ [0.10], $p = 0.059$; Supplemental Figure 2A). Numerically greater improvement was observed with forvisirvat compared with placebo at all time points. Post-hoc analyses showed forvisirvat-treated women had significantly greater improvement in CGI-S score at Weeks 2, 3, and 4 than women who received placebo (forvisirvat: $-0.8$ [0.10], $-1.1$ [0.11], and $-1.2$ [0.12]; placebo:

$-0.6$ [0.09], $-0.7$ [0.11], and $-0.8$ [0.11], respectively, all p-values $\leq 0.040$; Supplemental Figure 2B). In contrast, in men, no significant difference between groups was observed at any time point (forvisirvat: $-1.0$ [0.14], $-1.1$ [0.14], and $-1.0$ [0.15]; placebo: $-0.8$ [0.16], $-1.1$ [0.16], and $-1.2$ [0.16], Weeks 2, 3, and 4 respectively, all p-values $\geq 0.437$). In men, the forvisirvat group had numerically greater improvement in CGI-S from baseline compared to placebo only at Week 2 (Supplemental Figure 2C); otherwise, improvement in men with forvisirvat was comparable to or less than with placebo.

No significant differences between treatment groups were observed for change from baseline at Week 2 or Week 4 in HAM-D-17 score, SDS, QIDS-SR, or Q-LES-Q-SF (Supplemental Table 1). In post-hoc analyses, forvisirvat-treated women had significantly larger LSM change from baseline than women who received placebo for HAM-D-17 score at Week 4 ($-8.6$ [0.68] vs. $-6.3$ [0.67], respectively, $p = 0.016$), SDS at Week 2 ($-4.7$ [0.58] vs. $-3.0$ [0.56], respectively, $p = 0.035$) and Week 4 ($-5.9$ [0.65] vs. $-3.9$ [0.64], respectively, $p = 0.029$), and QIDS-SR score at Week 4 ($-5.9$ [0.48] vs. $-3.9$ [0.47], respectively, $p = 0.004$). No significant differences were observed for women for Q-LES-Q-SF score, although improvement was numerically greater with forvisirvat at both timepoints. No statistically significant differences between forvisirvat and placebo were observed for men for HAM-D-17, QIDS-SR, or Q-LES-Q-SF scores. For men, change in SDS score was significantly less with forvisirvat than placebo at Week 2 ($p = 0.025$).

## Persistence of effect

We examined persistence of drug effect on the MADRS and CGI-S scales after one week off drug in participants who had completed treatment. Investigators and participants were aware of study drug discontinuation but remained blinded to previous treatment assignment. In the prespecified analysis of the total study population, we observed a statistically significant LSM difference at Week 5 between forvisirvat vs. placebo (MADRS, $-12.1$ [0.82] vs. $-9.7$ [0.84], $p = 0.045$; [Figure 3A]; CGI-S, $-1.1$ [0.10] vs. $-0.8$ [0.10], $p = 0.015$ [Supplemental Figure 2A]). In post-hoc analyses, we observed a persistence of effect for forvisirvat-treated women while women who received placebo reverted towards baseline values (Figure 3B, Supplemental Figure 2B). In men, both the forvisirvat and placebo groups reverted toward baseline in parallel (Figure 3C, Supplemental Figure 2C).
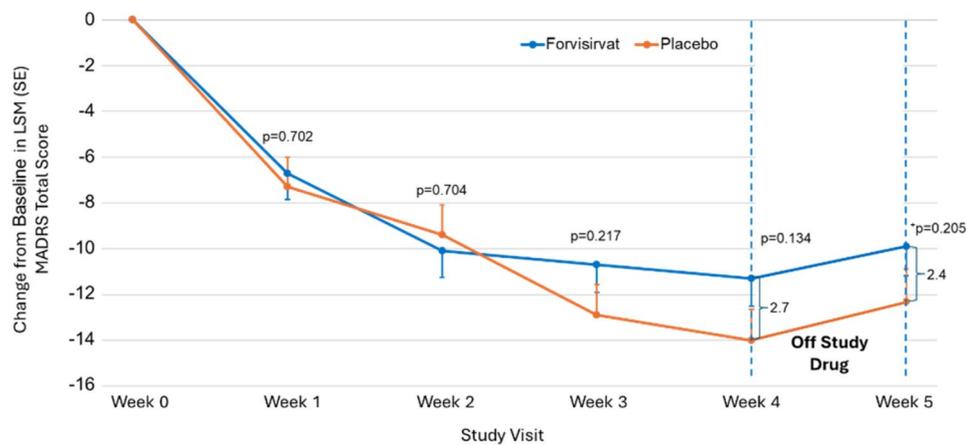
## A. mITT Population, Women and Men
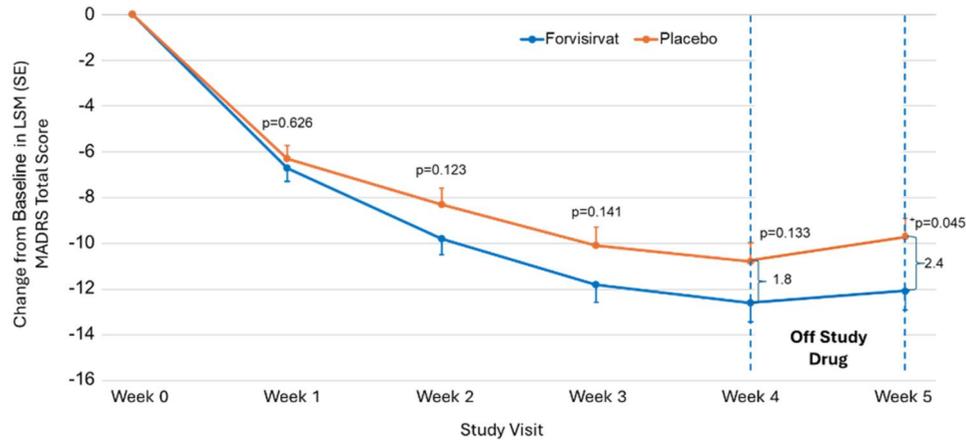


## B. mITT Population, Women
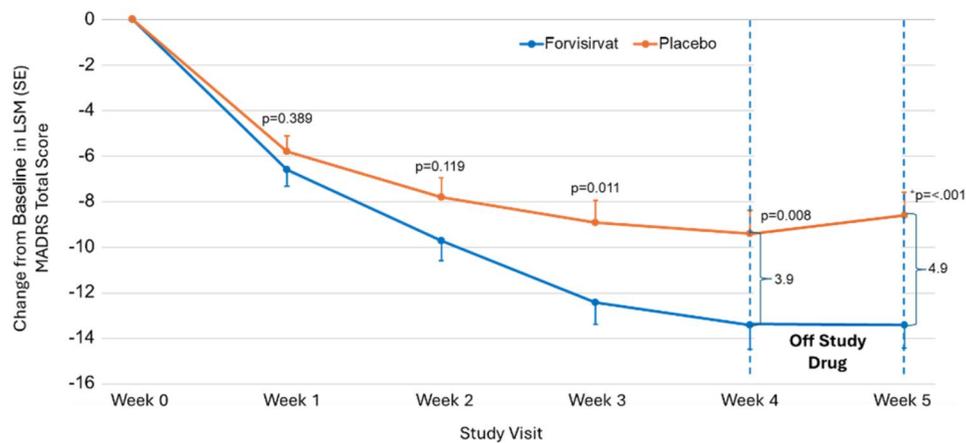


## C. mITT Population, Men



**Figure 3.** Least squares mean (LSM) change from baseline in Montgomery Asberg Depression Rating Scale Total Score. Participants received study drug for 4 weeks. Week 5 values indicate scores 1 week after completing treatment. P-values are for the difference between forvisirvat and placebo in LSM estimate and 95% CI based on mixed model for repeated measures. Error bars represent standard error for LSM estimate.

+The model for the change at Week 5 analysis is different from the change through Week 4 (treatment period) analysis due to the inclusion of data at Week 5 (off-treatment follow-up period).
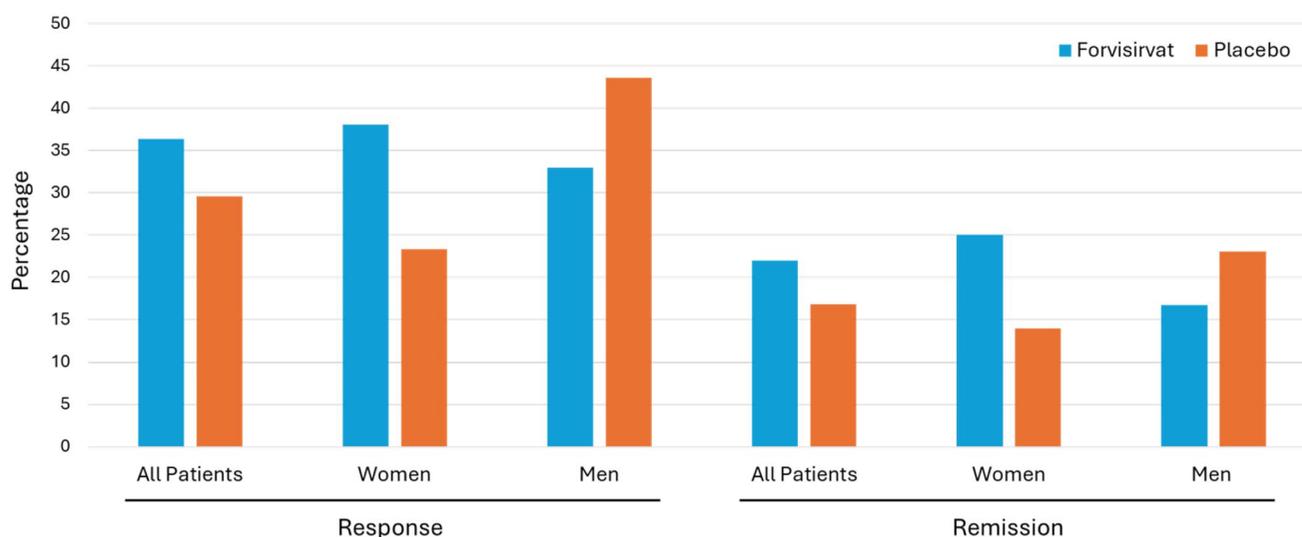
**Figure 4.** Response (50% or greater reduction from baseline in Montgomery Asberg Depression Rating Scale [MADRS]) and Remission (MADRS total score $\leq$ 10) at 4 Weeks.

**Table 2.** Adverse events.

| | All participants | | Women | | Men | |
|---|---|---|---|---|---|---|
| | Forvisirvat (N = 161) | Placebo (N = 156) | Forvisirvat (N = 101) | Placebo (N = 110) | Forvisirvat (N = 60) | Placebo (N = 46) |
| Adverse events, n | 139 | 137 | 95 | 113 | 44 | 24 |
| Participants with $\geq$1 adverse event, n (%) | 73 (45.3) | 67 (42.9) | 47 (46.5) | 52 (47.3) | 26 (43.3) | 15 (32.6) |
| Treatment-emergent adverse events, n | 127 | 129 | 87 | 106 | 40 | 23 |
| Participants with $\geq$1 treatment-emergent adverse event, n (%) | 68 (42.2) | 65 (41.7) | 45 (44.6) | 51 (46.4) | 23 (38.3) | 14 (30.4) |
| Participants with $\geq$1 drug-related treatment-emergent adverse event, n (%) | 40 (24.8) | 38 (24.4) | 27 (26.7) | 29 (26.4) | 13 (21.7) | 9 (19.6) |
| Participants with $\geq$1 treatment-emergent adverse event leading to drug withdrawal, n (%) | 6 (3.7)* | 5 (3.2) | 3 (3.0) | 5 (4.5) | 3 (5.0)* | 0 (0.0) |
| Participants with $\geq$1 serious adverse event, n (%) | 0 (0.0) | 2 (1.3) | 0 (0.0) | 2 (1.8) | 0 (0.0) | 0 (0.0) |
| Treatment-emergent adverse events occurring in $\geq$2% of forvisirvat-treated patients, n (%) | | | | | | |
| Headache | 13 (8.1) | 18 (11.5) | 9 (8.9) | 14 (12.7) | 4 (6.7) | 4 (8.7) |
| Nausea | 9 (5.6) | 13 (8.3) | 8 (7.9) | 10 (9.1) | 1 (1.7) | 3 (6.5) |
| Diarrhea | 9 (5.6) | 7 (4.5) | 7 (6.9) | 7 (6.4) | 2 (3.3) | 0 (0.0) |
| Dizziness | 4 (2.5) | 9 (5.8) | 3 (3.0) | 8 (7.3) | 1 (1.7) | 1 (2.2) |
| Somnolence | 4 (2.5) | 2 (1.3) | 3 (3.0) | 2 (1.8) | 1 (1.7) | 0 (0.0) |
| Anxiety | 4 (2.5) | 1 (0.6) | 2 (2.0) | 1 (0.9) | 2 (3.3) | 0 (0.0) |

*One participant had elevated transaminase concentrations at baseline, leading to withdrawal from the study. This was recorded as a treatment-emergent adverse event in error.

## Safety

No serious AEs occurred in forvisirvat-treated participants; two occurred with placebo: accidental overdose and gastrointestinal hemorrhage. TEAEs were experienced by 42.2% of forvisirvat-treated participants and 41.7% of the placebo group (Table 2). The most frequent TEAEs were headache (forvisirvat: 8.1%, placebo: 11.5%), nausea (forvisirvat: 5.6%, placebo: 8.3%), and diarrhea (forvisirvat: 5.6%, placebo: 4.5%).

Two participants experienced transaminase increase as a TEAE. One had ongoing obesity and hypercholesterolemia as well as alanine transaminase (ALT) slightly above the upper limit of normal (ULN) at screening but normal at baseline. Both ALT and aspartate transaminase (AST) were elevated by Week 2 ($>3 \times$ ULN for ALT, $>2 \times$ ULN for AST) and peaked at Week 3 ($8 \times$ ULN for ALT, $>4 \times$ ULN for AST). The participant continued dosing and completed the study; both parameters reduced markedly through the end of the study (Week 4: ALT $4 \times$ ULN, AST $1.3 \times$ ULN; 3 weeks after last forvisirvat dose: ALT $1.03 \times$ ULN, AST $<$ ULN) and were almost normal at the final follow-up visit 4 weeks after last forvisirvat dose: ALT $1.13 \times$ ULN, AST $<$ ULN). Alkaline phosphatase and bilirubin for this participant remained normal throughout. This participant tested positive for Epstein Barr virus at Week 4, and for cannabinoids at

screening and during follow-up; concomitant medications included progestin intrauterine contraceptive device and atorvastatin. The second participant with transaminases increased had ALT and AST concentrations >1 × ULN by Week 2. ALT concentration peaked at Week 3 (>3 × ULN), but the participant was lost to follow-up after unscheduled Week 3 re-testing. The participant's alkaline phosphatase and bilirubin were normal throughout study participation. Concomitant medications included ibuprofen.

Suicidal ideation was experienced by one (0.6%) forvisirvat-treated participant and two participants (1.3%) in the placebo group. All incidents were considered unrelated to treatment. The forvisirvat-treated participant experienced mild suicidal ideation, lasting 9 days. One participant in the placebo group experienced fleeting thoughts of wishing to be dead, considered to be mild, over the course of one week; the other experienced passive suicidal ideation secondary to worsening depression, considered to be mild, lasting one day. One forvisirvat-treated participant had a TEAE of non-suicidal self-injurious behavior, considered mild and unrelated to treatment, lasting one day. Specifically, the participant engaged in cutting to relieve anxiety, resulting in superficial abdominal cuts. No participants made spontaneous reports of dissociation or sexual dysfunction.

Six participants treated with forvisirvat withdrew due to TEAEs (one each for irritability and metrorrhagia, headache, anxiety, influenza, lethargy, and transaminases increased). However, the incidence of increased transaminases was experienced at baseline and reported as a TEAE in error. The participant was discontinued from the study because of transaminase concentrations outside of defined screening requirements. Five participants in the placebo group withdrew due to TEAEs (one each for headache, accidental overdose, COVID-19, gastrointestinal hemorrhage, and suicidal ideation). No participants in either group experienced TEAEs leading to dose reduction.

Mean weight at baseline was similar in the forvisirvat and placebo groups (85.1 kg and 82.1 kg, respectively). Mean (SD) changes from baseline to Week 4 were also similar 0.1 (1.65) kg and 0.2 (1.60) kg, respectively. No notable changes in ECG values were observed.

## Plasma concentrations

After forvisirvat treatment, plasma concentrations were generally within the expected ranges for both women and men based on comparison of results from the phase 1 multiple dose study, SP-624-102[19]. On visual inspection, plasma concentrations of forvisirvat were not correlated with efficacy as assessed by MADRS score. Concentrations of forvisirvat exceeded by several fold the exposures shown to be efficacious in animal models of depression.

## Target engagement

SIRT6 is a key regulator of glucose homeostasis[17,18]. Therefore, we conducted a post-hoc exploratory analysis of plasma glucose concentrations as a surrogate marker of target engagement. Participants with diabetes were excluded from the study; however, participants with prediabetic fasting glucose concentrations (≥100 mg/dL, $n = 20$) at baseline in the forvisirvat group had decreases in mean fasting glucose at Week 4 (111.7 mg/dL at baseline and 96.8 mg/dL at Week 4 [$n = 11$]), while participants in the placebo group did not (105.4 mg/dL [$n = 19$] and 106.9 mg/dL [$n = 14$], respectively) (Supplemental Figure 3; Supplemental Table 2). Consistent with the involvement of SIRT6 in glucose homeostasis, participants with euglycemia at baseline remained within normal range and there was no evidence of hypoglycemia. Similar results were seen in men and women.

## Discussion

SIRT6 activation represents a novel epigenetic mechanism of action for the treatment of MDD. We believe this work represents the first published clinical study of a SIRT6 activator for any indication. In this phase 2, randomized, double-blind, placebo-controlled trial in MDD, much was learned about the efficacy and safety of forvisirvat. Although statistically significant separation was not seen on the primary study outcome measure (change from baseline at Week 4 in MADRS score), forvisirvat-treated participants showed consistent numerical improvement over time in all efficacy measures compared with placebo. Therefore, we conducted post-hoc analyses examining efficacy by sex, which indicated a positive effect in women but not in men. Nominally significantly greater improvement was observed in women for forvisirvat treatment versus placebo on five of the six efficacy assessments (i.e. the MADRS, CGI-S, HAM-D-17, QIDS-SR, and SDS), and trended on the Q-LES-Q-SF. In addition, women treated with forvisirvat showed persistence of symptom reduction on efficacy measures (MADRS and CGI-S scores) while off forvisirvat (from Week 4 to 5), while women who received placebo showed a return of symptoms toward baseline. While these were post-hoc

analyses and not controlled for multiple comparisons, the consistency of the data suggest that forvisirvat-treated women experienced a true drug effect.

On the six efficacy measures assessed in this study, men who received placebo had similar or greater numerical improvement by the end of the treatment period compared to forvisirvat-treated men. In addition, in men, changes in both the MADRS and CGI-S values during the week following treatment discontinuation (Week 4 to 5) for the forvisirvat and placebo groups appear as parallel lines regressing towards baseline severity (Figure 3 and Supplemental Figure 2). These findings suggest lack of efficacy in men.

Large placebo responses were observed for men on all efficacy measures. The power calculation for this study assumed a mean placebo response at Week 4 of approximately 9 units on the MADRS. However, the actual mean change on placebo was −11.1 among all participants and −9.4 and −14.8, respectively, among women and men. Thus, placebo responses were as predicted for women and larger for men, while the degree of improvement following treatment with forvisirvat was larger in women (approximately 12 units predicted versus actual mean change of −13.4 observed). Traditionally, larger placebo response rates in psychiatric clinical trials are correlated with smaller effect sizes[20–23]. Individual analyses of MADRS change from baseline showed the improvement observed in women and the lack of improvement observed in men with forvisirvat was not driven by outliers. Our confidence in reaching a conclusion regarding the efficacy of forvisirvat in women is higher than in men because the placebo response in women was low and as predicted.

The results in men and in participants overall open the question of whether a different dose would have elicited a greater response. No correlation was observed between plasma concentrations of forvisirvat and efficacy in either men or women. A preliminary indication of target engagement in both men and women at the 20 mg daily dose was seen in the glucose data. Furthermore, in a phase 1 clinical trial (SP-624-102) where doses of forvisirvat ranging from 3 mg to 30 mg were examined, a maximum tolerated dose was not reached[19]. In addition, the maximum concentration ($C_{max}$) in healthy volunteers receiving 30 mg was ~30× greater than the 3 ng/ml plasma concentration that was efficacious in animal studies. Based on these results, a dosage of 20 mg forvisirvat daily was predicted to be well tolerated and sufficient to achieve efficacy.

Incidence of and treatment effects on depression are known to differ based on sex. Globally, depression is 50% to 70% more common in women than in men[24,25].

Men and women also differ in their response to antidepressant treatment [reviewed in[26]]. A recent study found women were more likely to benefit from augmentation strategies for depression despite the fact that men were more likely to receive treatment augmentation[27]. Differential expression of genes in men and women with MDD has also been described. In a study of gene expression in post-mortem brain tissue from people with MDD compared to sex-matched controls, expression of 822 genes differed between women with and without MDD and expression of 776 genes differed between men with and without MDD. However, gene expression in women and men with MDD changed in the same direction for only 21 genes while 52 genes displayed statistically significant expression changes in opposite directions between sexes[28]. These differences could result in epigenetic pharmacological treatments having different or opposite effects in women and men with depression.

Forvisirvat was well tolerated, with no serious AEs or TEAEs leading to dose reduction. The most common TEAEs (headache, nausea, and diarrhea) were reported at the same or lower rates in the forvisirvat arm compared with placebo. Frequency of reported suicidal ideation or self-harm was low with no notable difference between treatment groups. Notable changes in weight were not observed. Safety and tolerability did not differ between men and women and no safety findings occurred that would have potentially unblinded the participants or investigators.

This trial was conducted during the COVID pandemic, which introduced unexpected complications and slowed enrollment. In-person study visits breaking the isolation experienced during the pandemic may have increased response in some patients. In common with most clinical trials, eligibility criteria likely resulted in a study population that is not fully representative of the real world population of people with MDD. Other limitations of the trial include use of only one dose and the comparatively short duration of treatment (4 weeks, without a long-term extension). A short duration was supported by data from animal models and minimized the time that some participants would be receiving placebo. In addition, some participants experienced notable reductions in MADRS score during this period. Although participant weight was collected, no criteria were set regarding clothing, fasting, etc., and menstrual cycle information was not collected from women. Strengths of the study included the requirement that participants received previous adequate antidepressant treatment during their current depressive episode, confirming MDD diagnosis. In addition, we aimed to

decrease the placebo response by minimizing study visit length through the use of a limited number of clinician- and patient-rated mood and functional scales. The lack of substantial AEs in the forvisirvat treatment group suggests that study staff and participants were blind to treatment allocation.

## Conclusions

The novel epigenetic mechanism of action of forvisirvat, consistent efficacy results in women, reassuring safety and tolerability profile, and the large unmet need for new treatments support the continued investigation of forvisirvat for MDD. A phase 2b/3 trial of forvisirvat in MDD (NCT06254612) to confirm and expand the results of this study is ongoing.

## Transparency

## Author contributions

Conceptualization: JR, GR, KA, YP, JH; Data curation: YP, KA, JR, MA, GR, JH; Methodology: JR, KA, YP, JH; Project administration: YP, KA; Supervision: JR, KA, YP, JH, GR; Validation: KA, JR; Visualization: all authors; Writing – review and editing: all authors.

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## Data availability statement

The participants of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of the research, supporting data is not available.

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