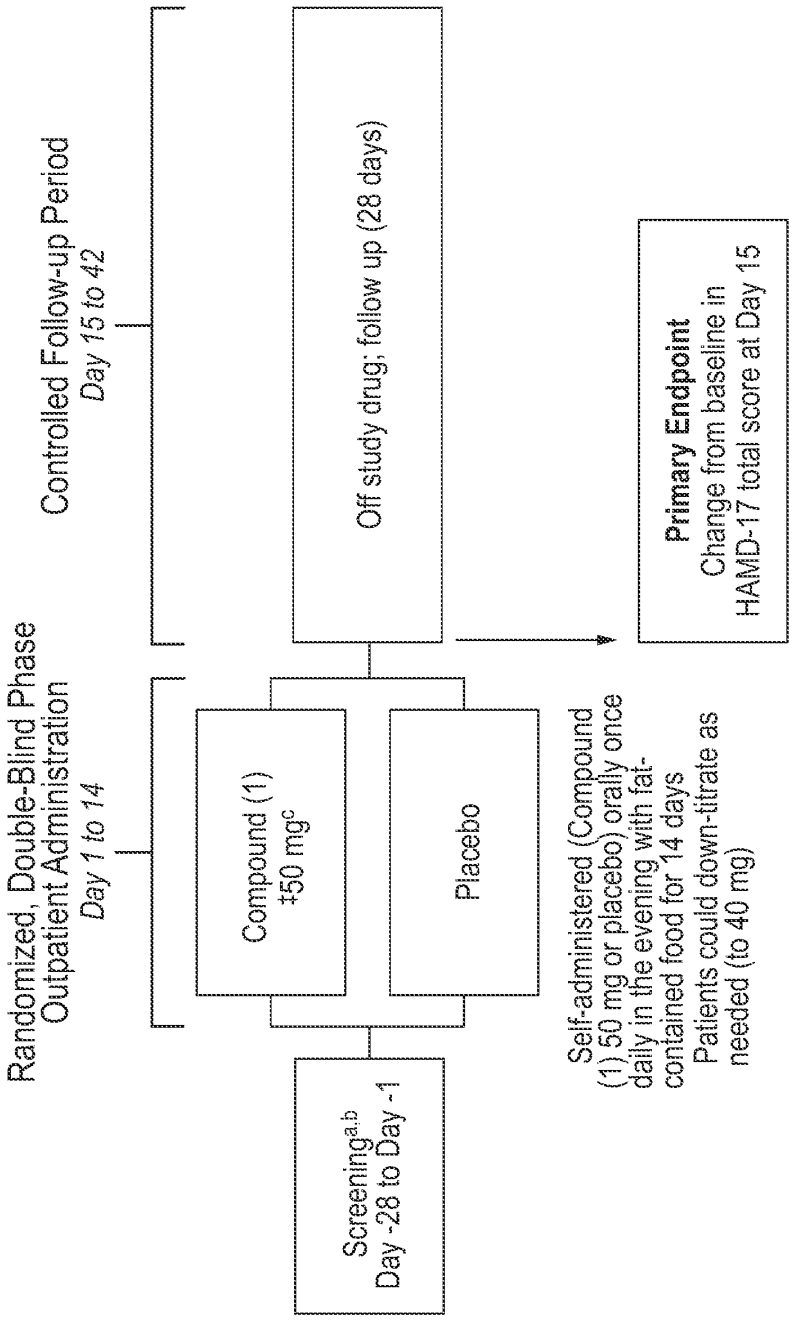


[a]Day -28 to Day -1 refer to timing relative to first day of dosing with Compound (1). [b]Eligible subjects stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥60 days). [c]HAMD-17 = 17-item Hamilton Rating Scale for Depression.

FIG. 1

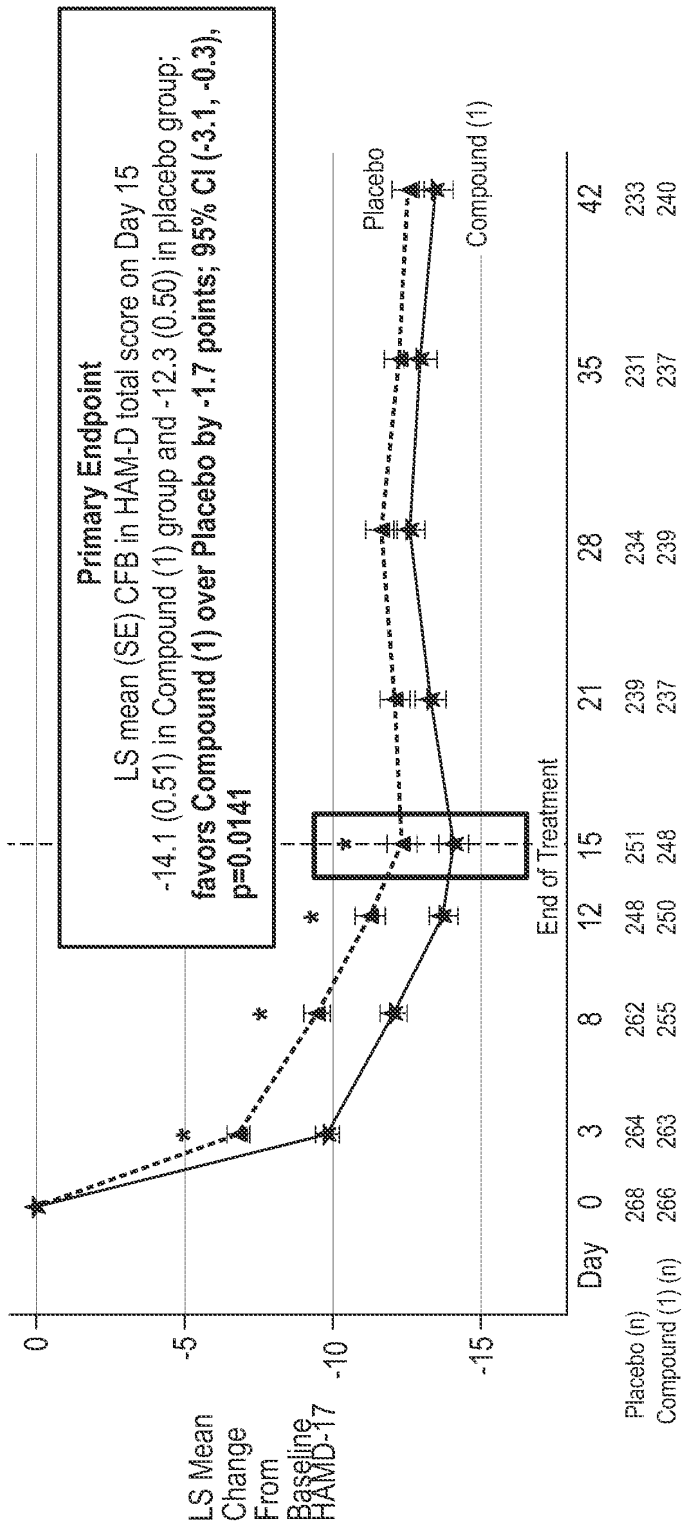

Primary Endpoint
LS mean (SE) CFB in HAM-D total score on Day 15
-14.1 (0.51) in Compound (1) group and -12.3 (0.50) in placebo group;
favors Compound (1) over Placebo by -1.7 points; 95% CI (-3.1, -0.3),
p=0.0141
LS Mean Change From Baseline HAMD-17
0
-5
-10
-15
Placebo
Compound (1)
End of Treatment
Day 0 3 8 12 15 21 28 35 42
Placebo (n) 268 264 262 248 251 239 234 231 233
Compound (1) (n) 266 263 255 250 248 237 239 237 240

FIG. 2

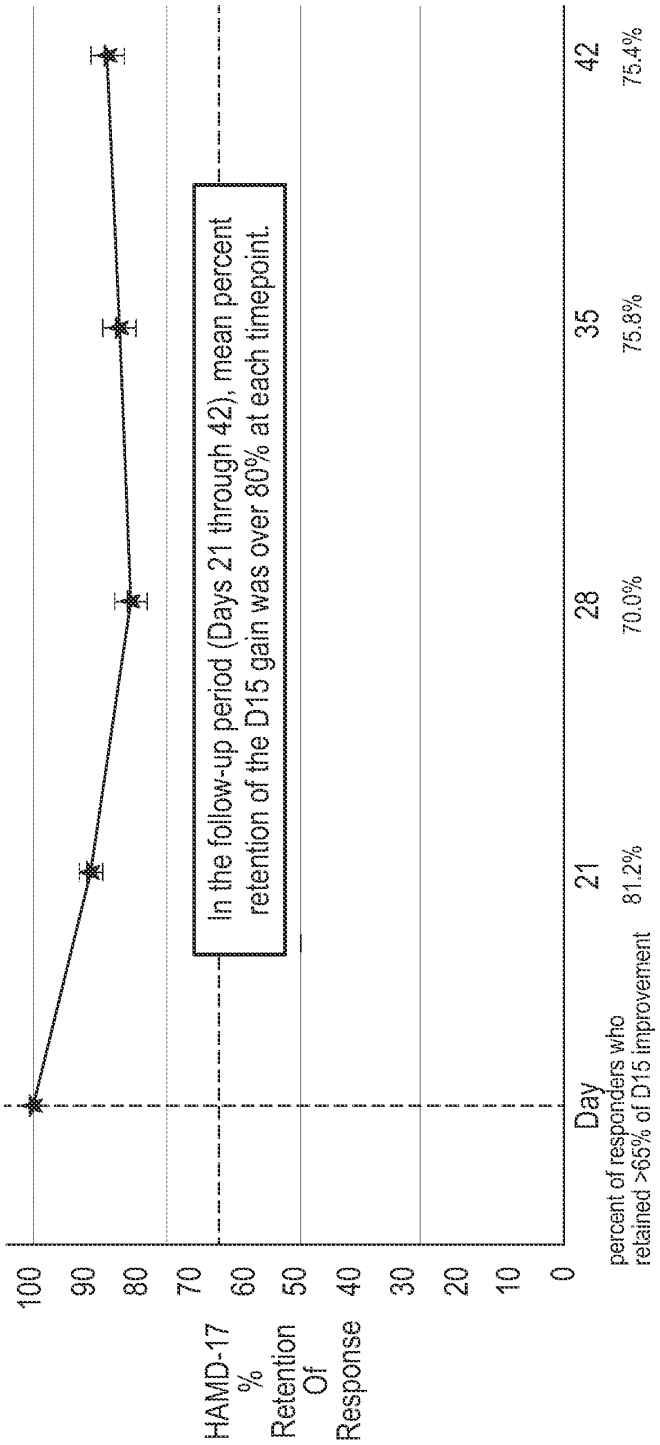

HAMD-17 % Retention Of Response
100
90
80
70
60
50
40
30
20
10
0
In the follow-up period (Days 21 through 42), mean percent retention of the D15 gain was over 80% at each timepoint.
Day
21
28
35
42
percent of responders who retained >65% of D15 improvement
81.2%
70.0%
75.8%
75.4%

FIG. 3

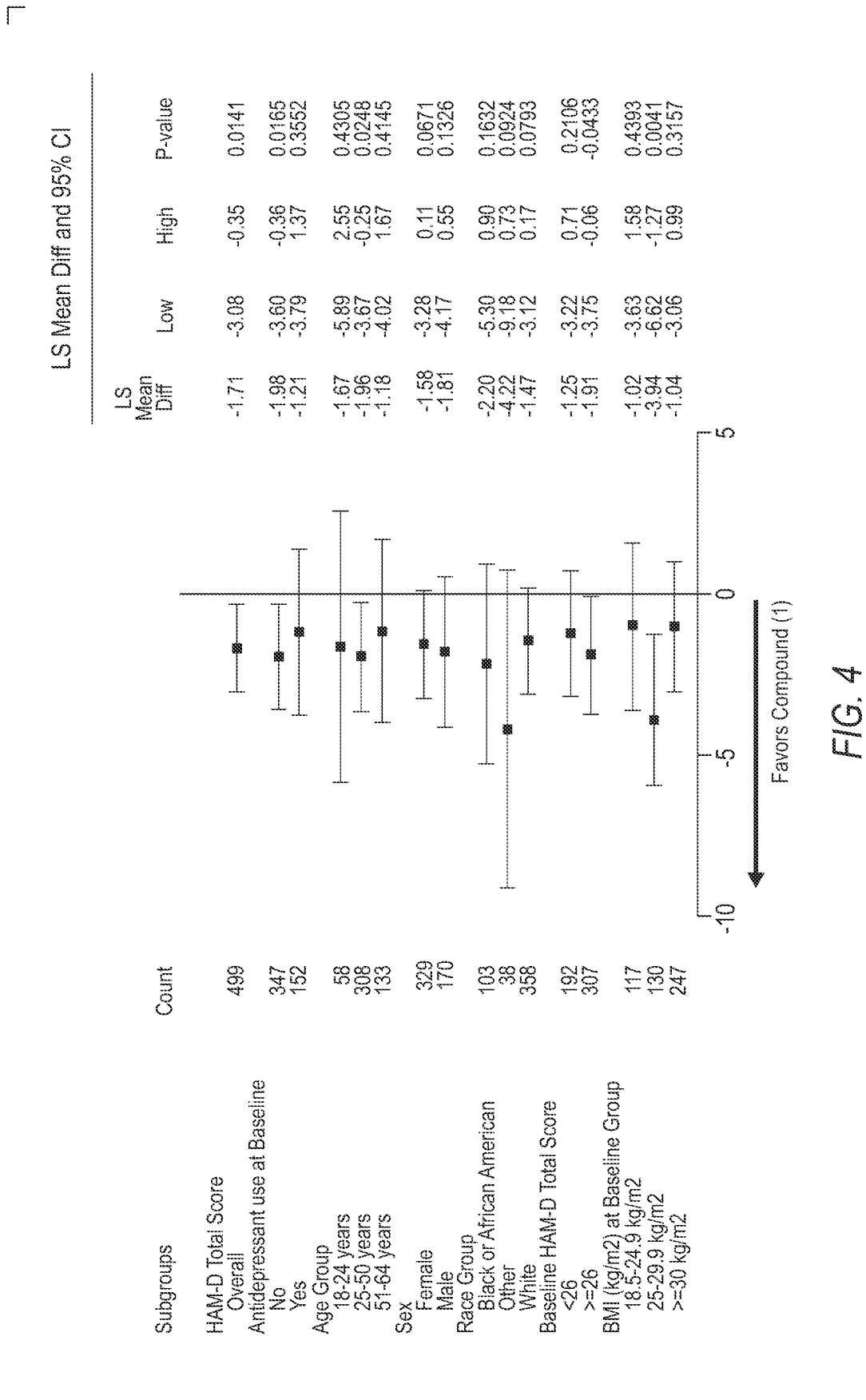

LS Mean Diff and 95% CI
Subgroups
Count
LS Mean Diff
Low
High
P-value
HAM-D Total Score
Overall 499 -1.71 -3.08 -0.35 0.0141
Antidepressant use at Baseline
No 347 -1.98 -3.60 -0.36 0.0165
Yes 152 -1.21 -3.79 1.37 0.3552
Age Group
18-24 years 58 -1.67 -5.89 2.55 0.4305
25-50 years 308 -1.96 -3.67 -0.25 0.0248
51-64 years 133 -1.18 -4.02 1.67 0.4145
Sex
Female 329 -1.58 -3.28 0.11 0.0671
Male 170 -1.81 -4.17 0.55 0.1326
Race Group
Black or African American 103 -2.20 -5.30 0.90 0.1632
Other 38 -4.22 -9.18 0.73 0.0924
White 358 -1.47 -3.12 0.17 0.0793
Baseline HAM-D Total Score
<26 192 -1.25 -3.22 0.71 0.2106
>=26 307 -1.91 -3.75 -0.06 -0.0433
BMI (kg/m2) at Baseline Group
18.5-24.9 kg/m2 117 -1.02 -3.63 1.58 0.4393
25-29.9 kg/m2 130 -3.94 -6.62 -1.27 0.0041
>=30 kg/m2 247 -1.04 -3.06 0.99 0.3157
-10
-5
0
5
Favors Compound (1)

FIG. 4

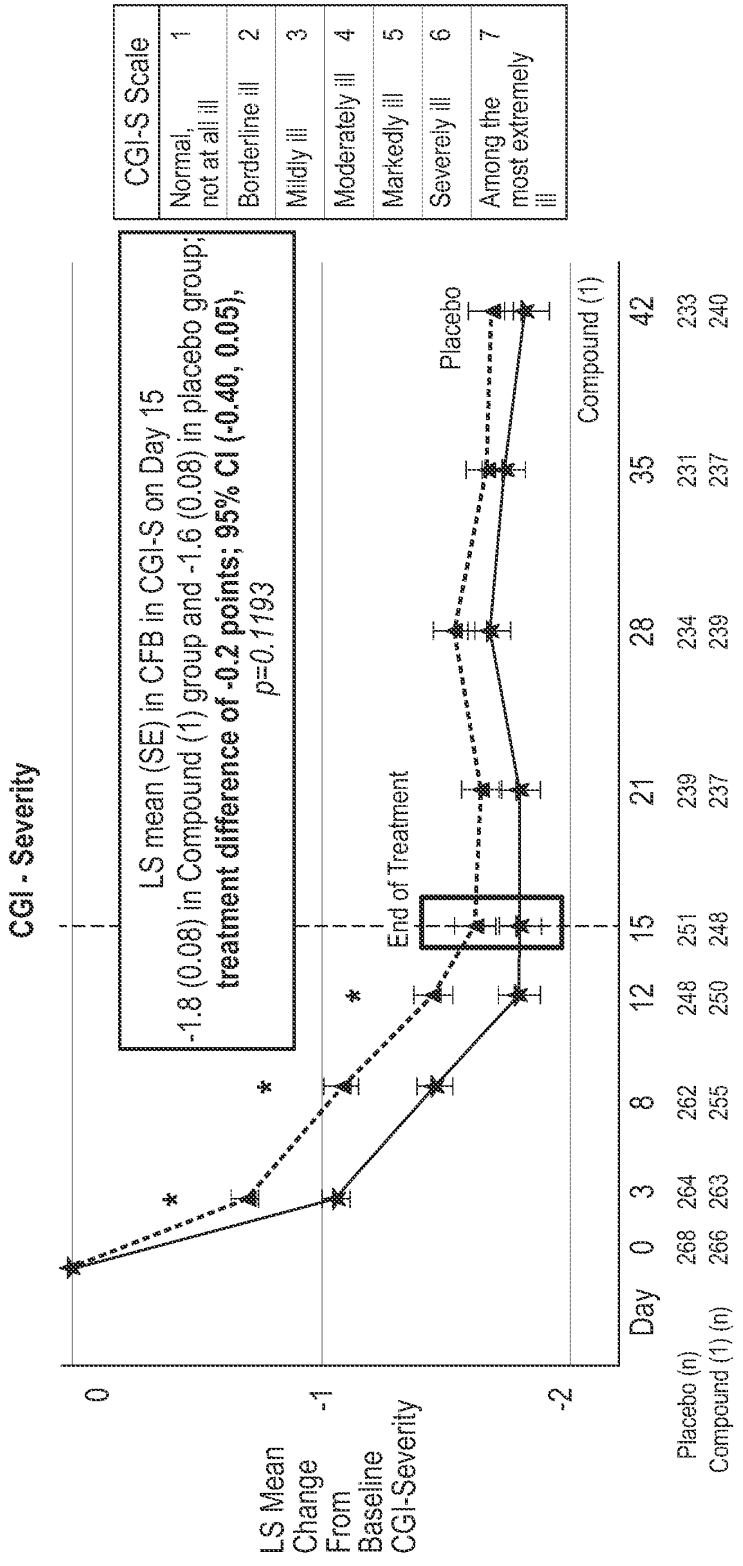

CGI - Severity
LS mean (SE) in CFB in CGI-S on Day 15
-1.8 (0.08) in Compound (1) group and -1.6 (0.08) in placebo group;
treatment difference of -0.2 points; 95% CI (-0.40, 0.05),
p=0.1193
CGI-S Scale
Normal, not at all ill 1
Borderline ill 2
Mildly ill 3
Moderately ill 4
Markedly ill 5
Severely ill 6
Among the most extremely ill 7
LS Mean Change From Baseline CGI-Severity
0
-1
-2
End of Treatment
Placebo
Compound (1)
Day 0 3 8 12 15 21 28 35 42
Placebo (n) 268 264 262 248 251 239 234 231 233
Compound (1) (n) 266 263 255 250 248 237 239 237 240

FIG. 5

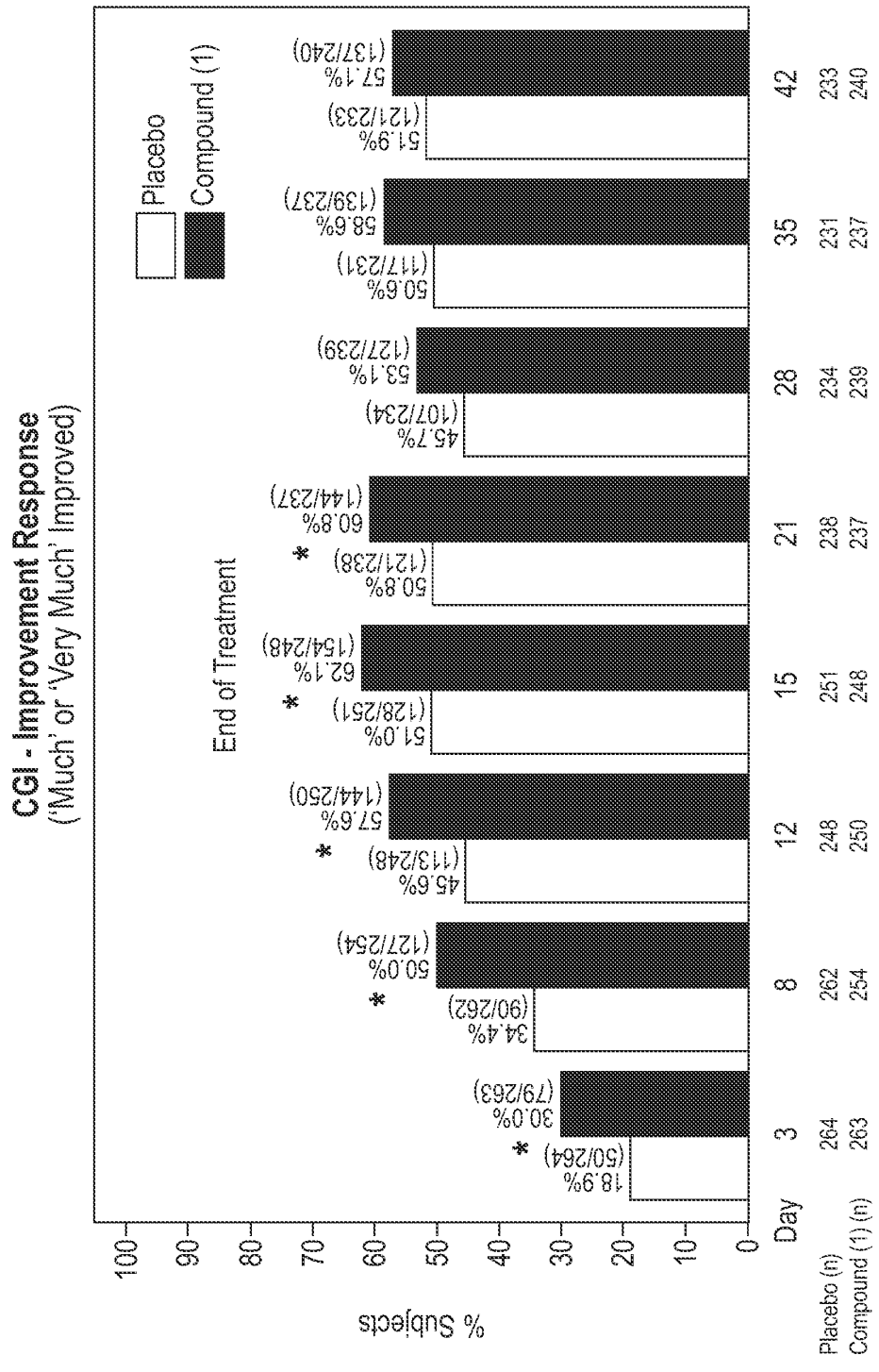
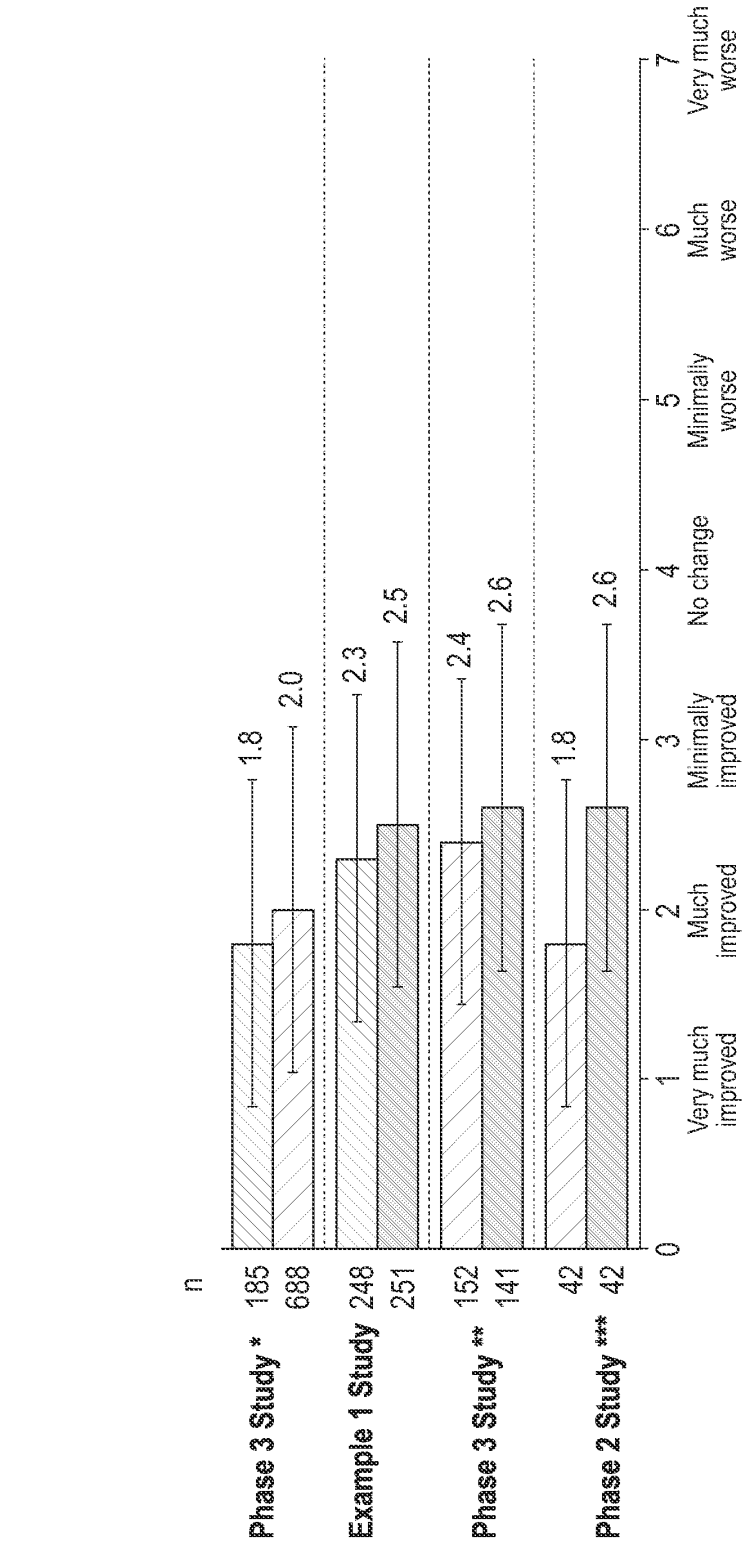

CGI - Improvement Response
('Much' or 'Very Much' Improved)
End of Treatment
Placebo
Compound (1)
% Subjects
100
90
80
70
60
50
40
30
20
10
0
Day 3 8 12 15 21 28 35 42
Placebo (n) 264 262 248 251 238 234 231 233
Compound (1) (n) 263 254 250 248 237 239 237 240
18.9% (50/264)
30.0% (79/263)
34.4% (90/262)
50.0% (127/254)
45.6% (113/248)
57.6% (144/250)
51.0% (128/251)
62.1% (154/248)
50.8% (121/238)
60.8% (144/237)
45.7% (107/234)
53.1% (127/239)
50.6% (117/231)
58.6% (139/237)
51.9% (121/233)
57.1% (137/240)
*
*
*
*
*p<0.05

FIG. 6



CGI-I = Clinical Global Impression-Improvement; MDD = major depressive disorder; n = number of patients on Day 15.

FIG. 7

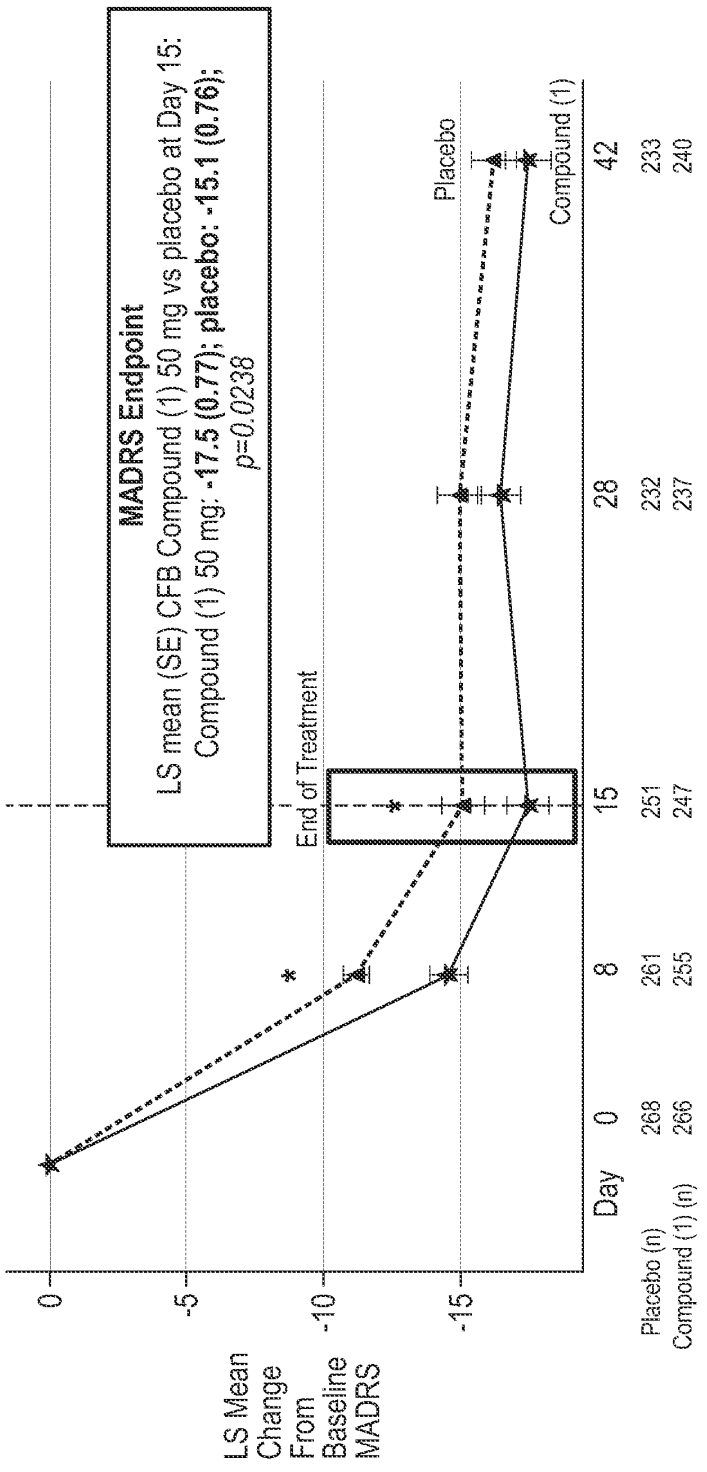

MADRS Endpoint
LS mean (SE) CFB Compound (1) 50 mg vs placebo at Day 15:
Compound (1) 50 mg: -17.5 (0.77); placebo: -15.1 (0.76);
p=0.0238
End of Treatment
Placebo
Compound (1)
LS Mean Change From Baseline MADRS
0
-5
-10
-15
Day 0 8 15 28 42
Placebo (n) 268 261 251 232 233
Compound (1) (n) 266 255 247 237 240
P values pertaining to other secondary endpoints are nominal; CFB = change from baseline; *p<0.05

FIG. 8

Endpoint	LSM Treatment Difference (95% CI)	n	LSM (SE) Compound (1)	LSM (SE) Placebo	p value
CFB HAMD-17 total score		499	-14.1(0.51)	-12.3(0.50)	0.0141
CFB MADRS total score		498	-17.5(0.77)	-15.1(0.76)	0.0238*

P value for CFB MADRS total score is nominal and not adjusted for multiple comparisons.
CFB = change from baseline; HAMD-17 = 17-item Hamilton Rating Scale for Depression; LSM = least squares mean;
MADRS = Montgomery-Åsberg Depression Rating Scale; n = number of patients on that day.

FIG. 9

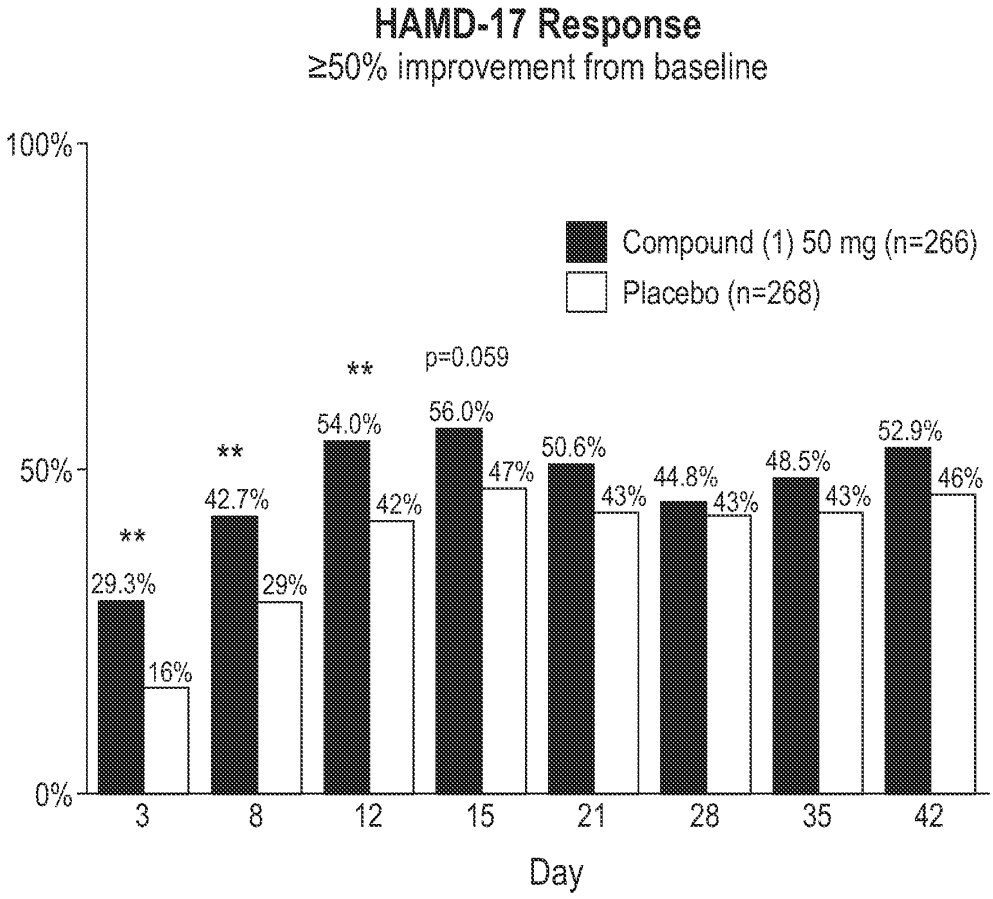

HAMD-17 Response
≥50% improvement from baseline
100%
50%
0%
Compound (1) 50 mg (n=266)
Placebo (n=268)
**
**
**
p=0.059
29.3%
16%
42.7%
29%
54.0%
42%
56.0%
47%
50.6%
43%
44.8%
43%
48.5%
43%
52.9%
46%
3
8
12
15
21
28
35
42
Day

FIG. 10A

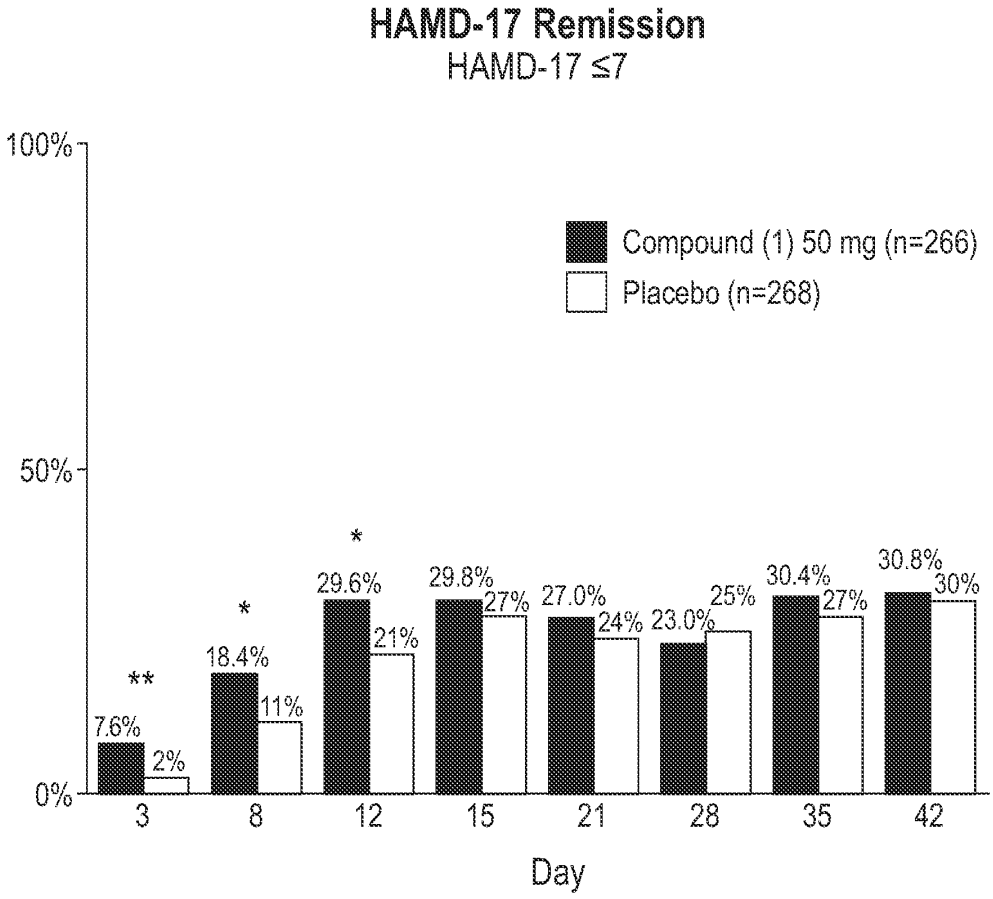
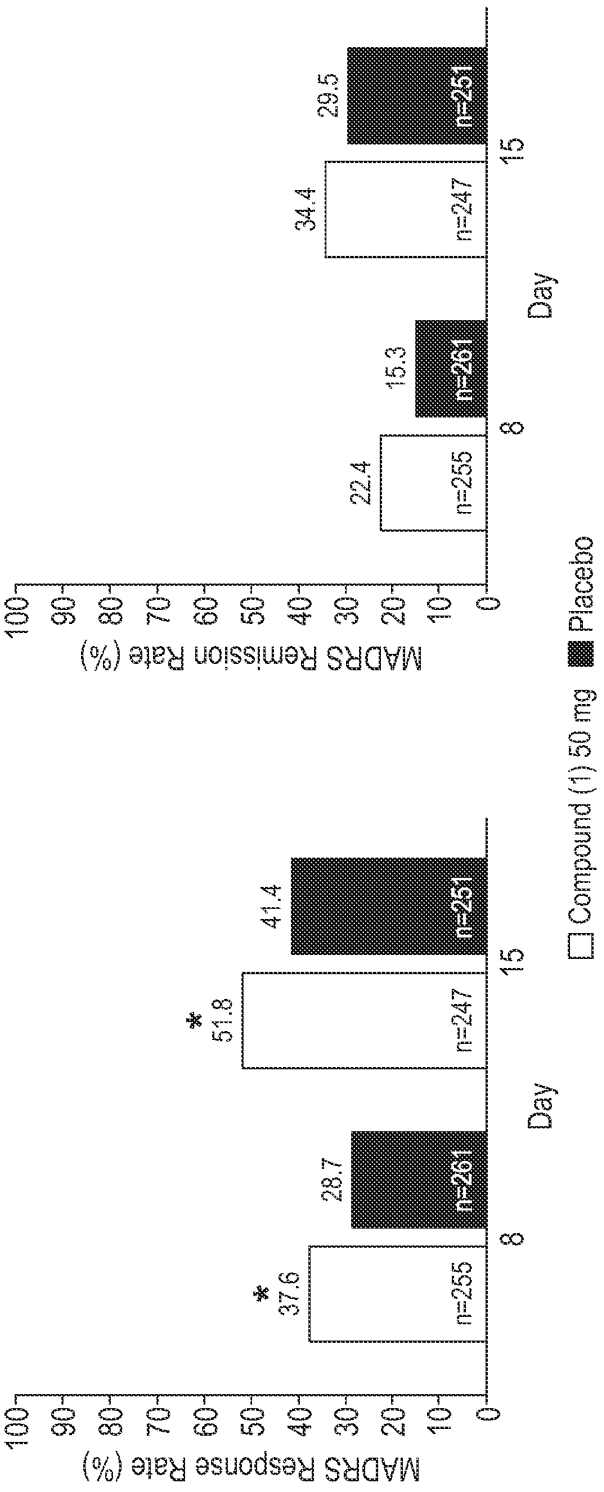

HAMD-17 Remission
HAMD-17 ≤7
100%
50%
0%
Compound (1) 50 mg (n=266)
Placebo (n=268)
**
*
*
7.6%
2%
18.4%
11%
29.6%
21%
29.8%
27%
27.0%
24%
23.0%
25%
30.4%
27%
30.8%
30%
3
8
12
15
21
28
35
42
Day

FIG. 10B



*p<0.05, p values are nominal and not adjusted for multiple comparisons.
MADRS Response is defined as ≥50% reduction in MADRS total score from baseline; MADRS Remission is defined as MADRS total score ≤10.
MADRS = 10-item Montgomery-Asberg Depression Rating Scale; n = number of patients that day.

FIG. 11

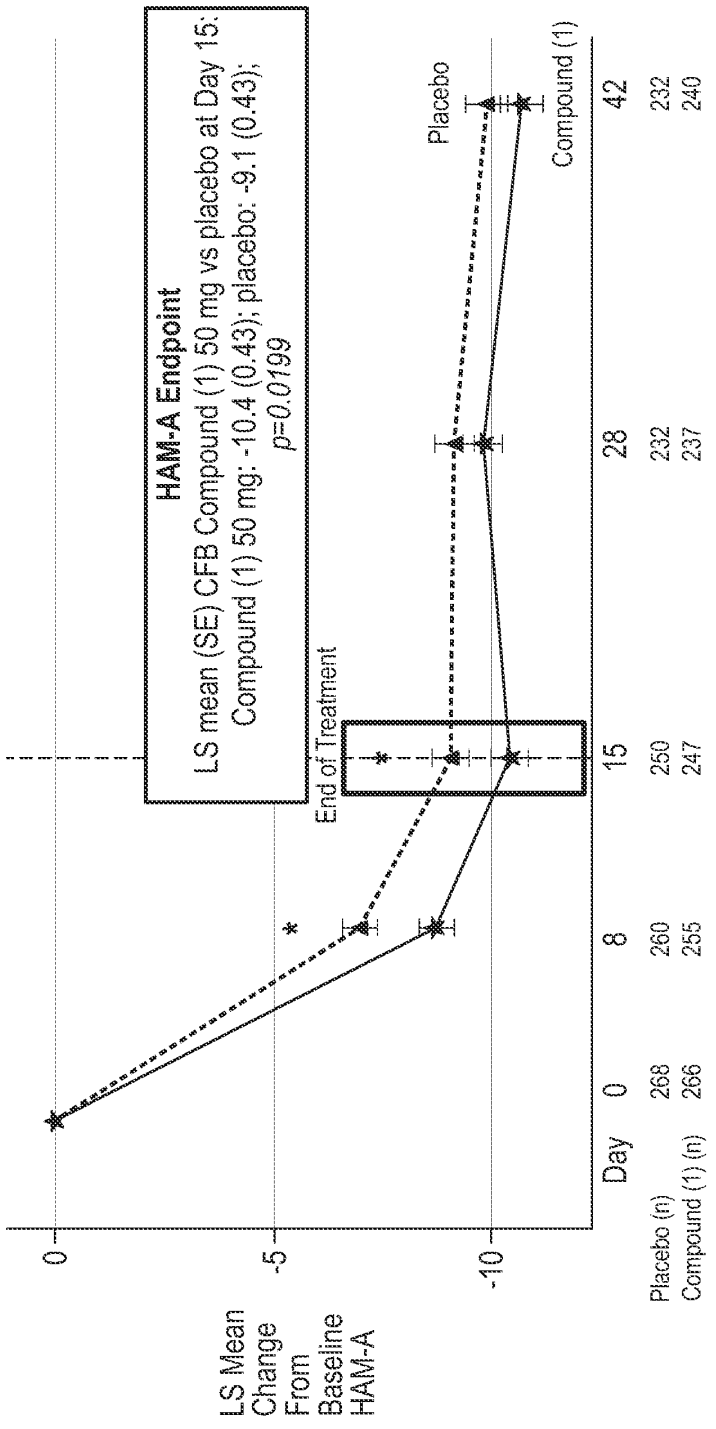

HAM-A Endpoint
LS mean (SE) CFB Compound (1) 50 mg vs placebo at Day 15:
Compound (1) 50 mg: -10.4 (0.43); placebo: -9.1 (0.43);
p=0.0199
End of Treatment
Placebo
Compound (1)
LS Mean Change From Baseline HAM-A
0
-5
-10
Day 0 8 15 28 42
Placebo (n) 268 260 250 232 232
Compound (1) (n) 266 255 247 237 240
P values pertaining to other secondary endpoints are nominal; CFB = change from baseline; *p<0.05

FIG. 12

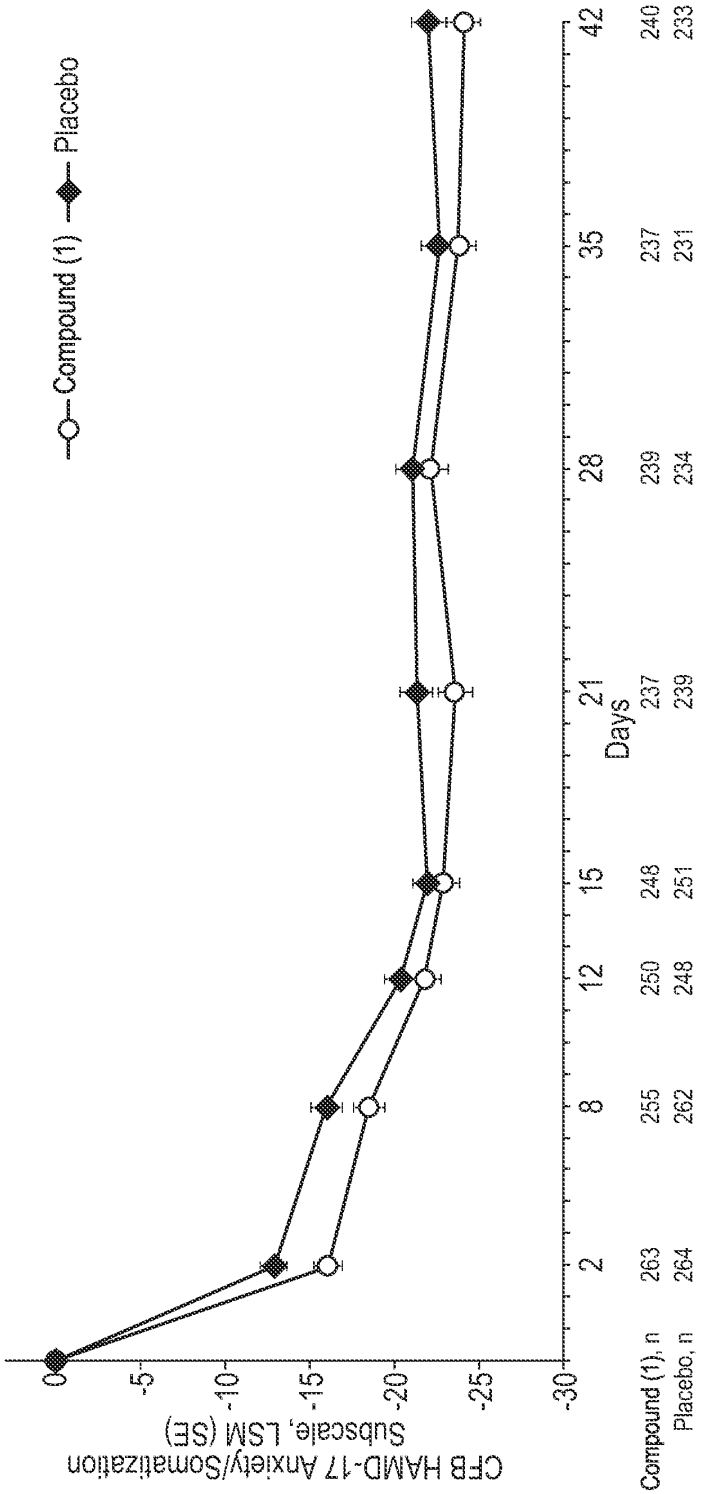

Compound (1)
Placebo
CFB HAMD-17 Anxiety/Somatization Subscale, LSM (SE)
0
-5
-10
-15
-20
-25
-30
2
8
12
15
21
28
35
42
Days
Compound (1), n 263 255 250 248 237 239 237 240
Placebo, n 264 262 248 251 239 234 231 233
*p<0.01, †p<0.05 (p values are nominal and not adjusted for multiple comparisons).

FIG. 13

p values are nominal and not adjusted for multiple comparisons.
The Full Analysis Set was defined as all randomized patients administered **Compound (1)** or placebo with valid baseline HAMD-17 total score and at least 1 valid post-baseline HAMD-17 total score.
HAM-A = Hamilton Anxiety Rating Scale; HAMD-17 = 17-item Hamilton Rating Scale for Depression; CI - confidence interval; LSM = least squares mean; n = number of patients at Day 8.

FIG. 14A

Except for HAMD-17 total score at Day 15 (primary endpoint), p values are nominal and not adjusted for multiple comparisons.
The Full Analysis Set was defined as all randomized patients administered **Compound (1)** or placebo with valid baseline HAMD-17 total score and at least 1 valid post-baseline HAMD-17 total score.
HAM-A = Hamilton Anxiety Rating Scale; HAMD-17 = 17-item Hamilton Rating Scale for Depression; CI - confidence interval; LSM = least squares mean; n = number of patients at Day 15.

FIG. 14B

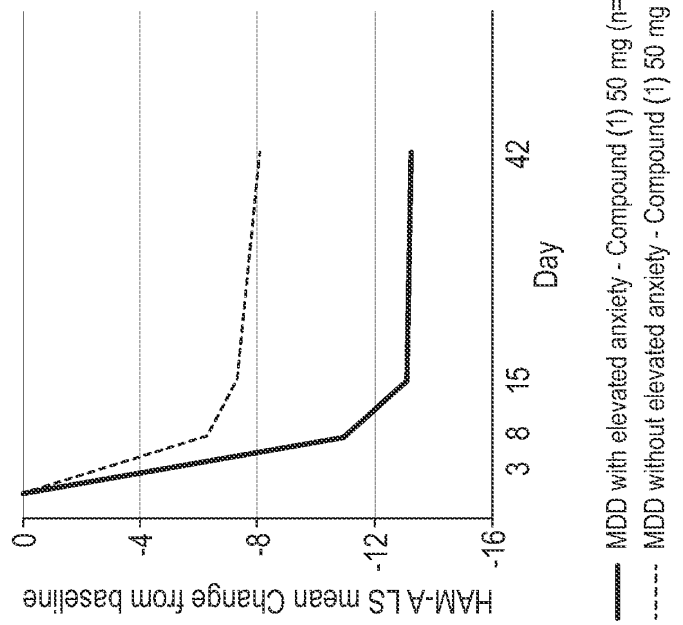


FIG. 15B

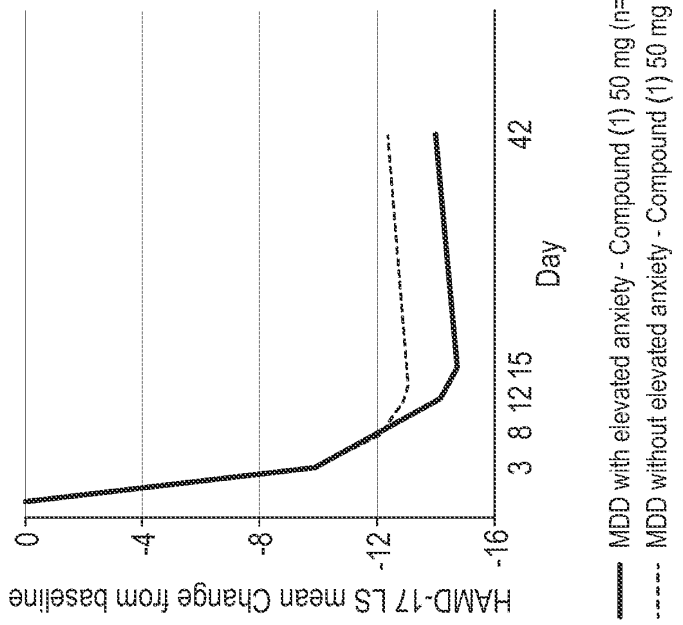


FIG. 15A

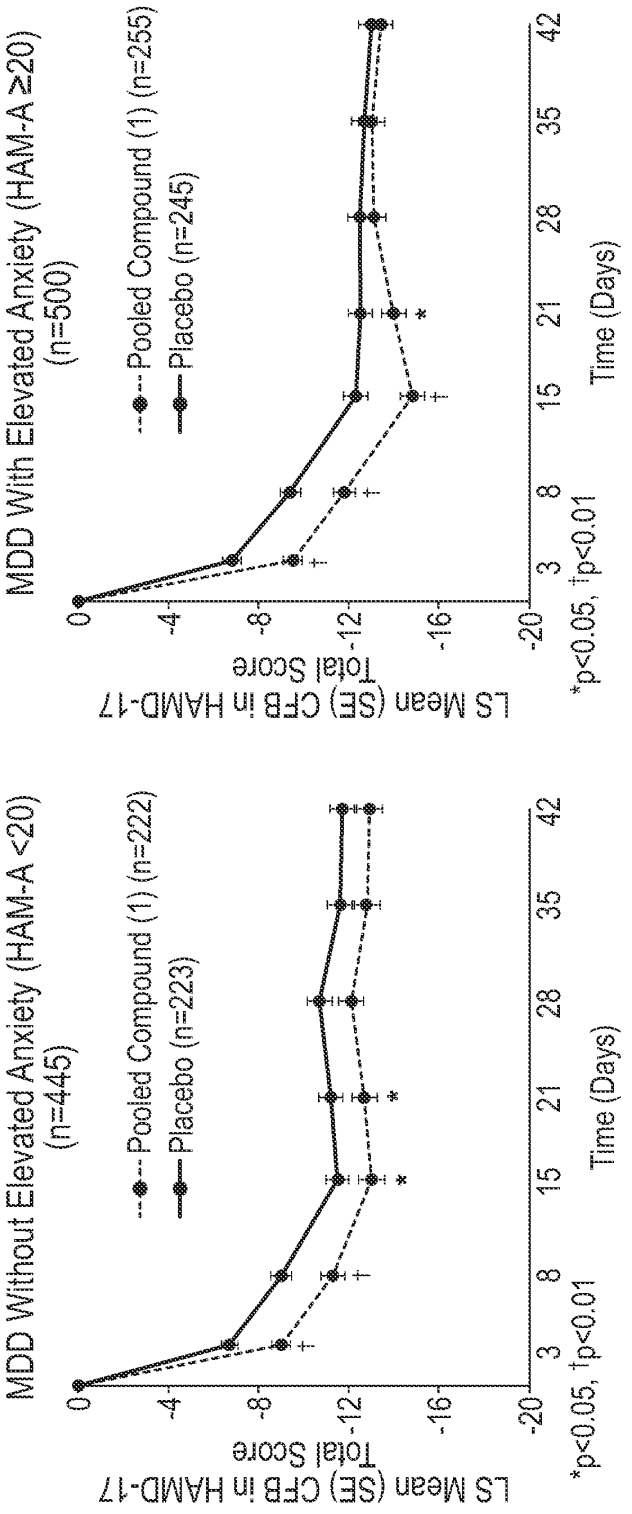

MDD With Elevated Anxiety (HAM-A ≥20)
(n=500)
Pooled Compound (1) (n=255)
Placebo (n=245)
LS Mean (SE) CFB in HAMD-17 Total Score
0
-4
-8
-12
-16
-20
3
8
15
21
28
35
42
Time (Days)
*p<0.05, †p<0.01
MDD Without Elevated Anxiety (HAM-A <20)
(n=445)
Pooled Compound (1) (n=222)
Placebo (n=223)
LS Mean (SE) CFB in HAMD-17 Total Score
0
-4
-8
-12
-16
-20
3
8
15
21
28
35
42
Time (Days)
*p<0.05, †p<0.01

FIG. 16

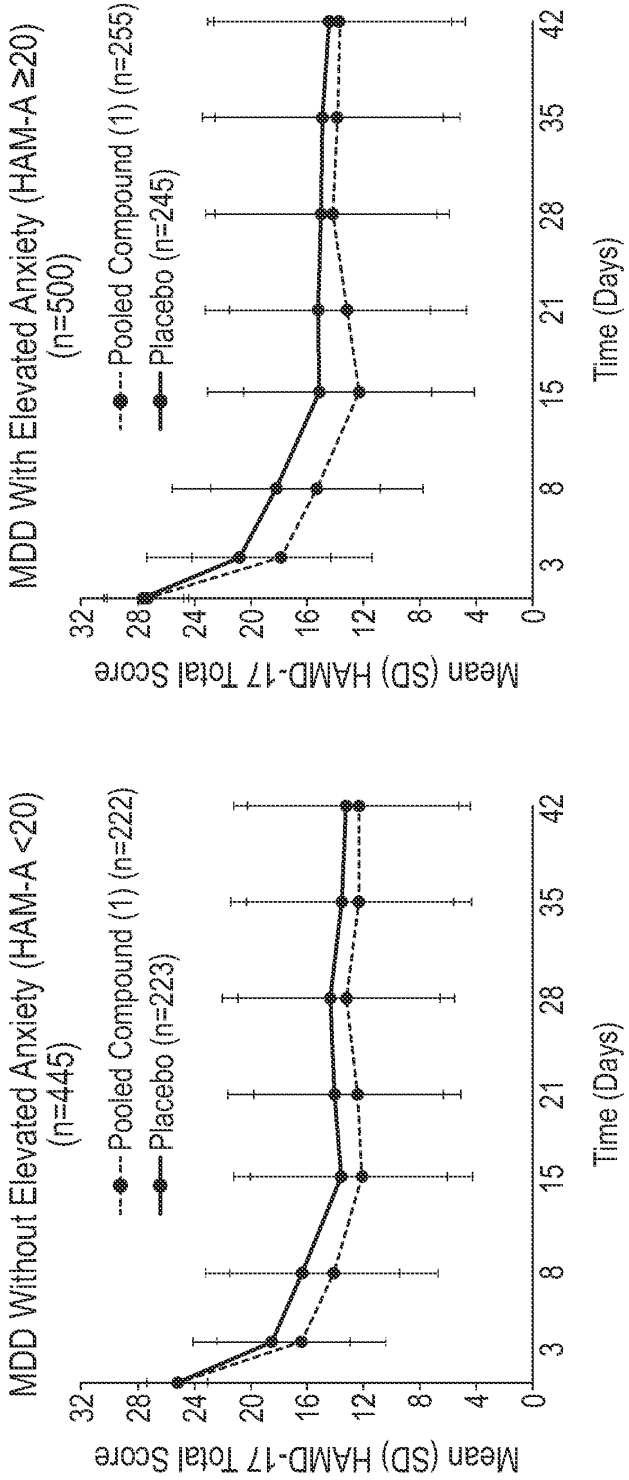

MDD With Elevated Anxiety (HAM-A ≥20)
(n=500)
Pooled Compound (1) (n=255)
Placebo (n=245)
Mean (SD) HAMD-17 Total Score
Time (Days)
MDD Without Elevated Anxiety (HAM-A <20)
(n=445)
Pooled Compound (1) (n=222)
Placebo (n=223)
Mean (SD) HAMD-17 Total Score
Time (Days)

FIG. 17

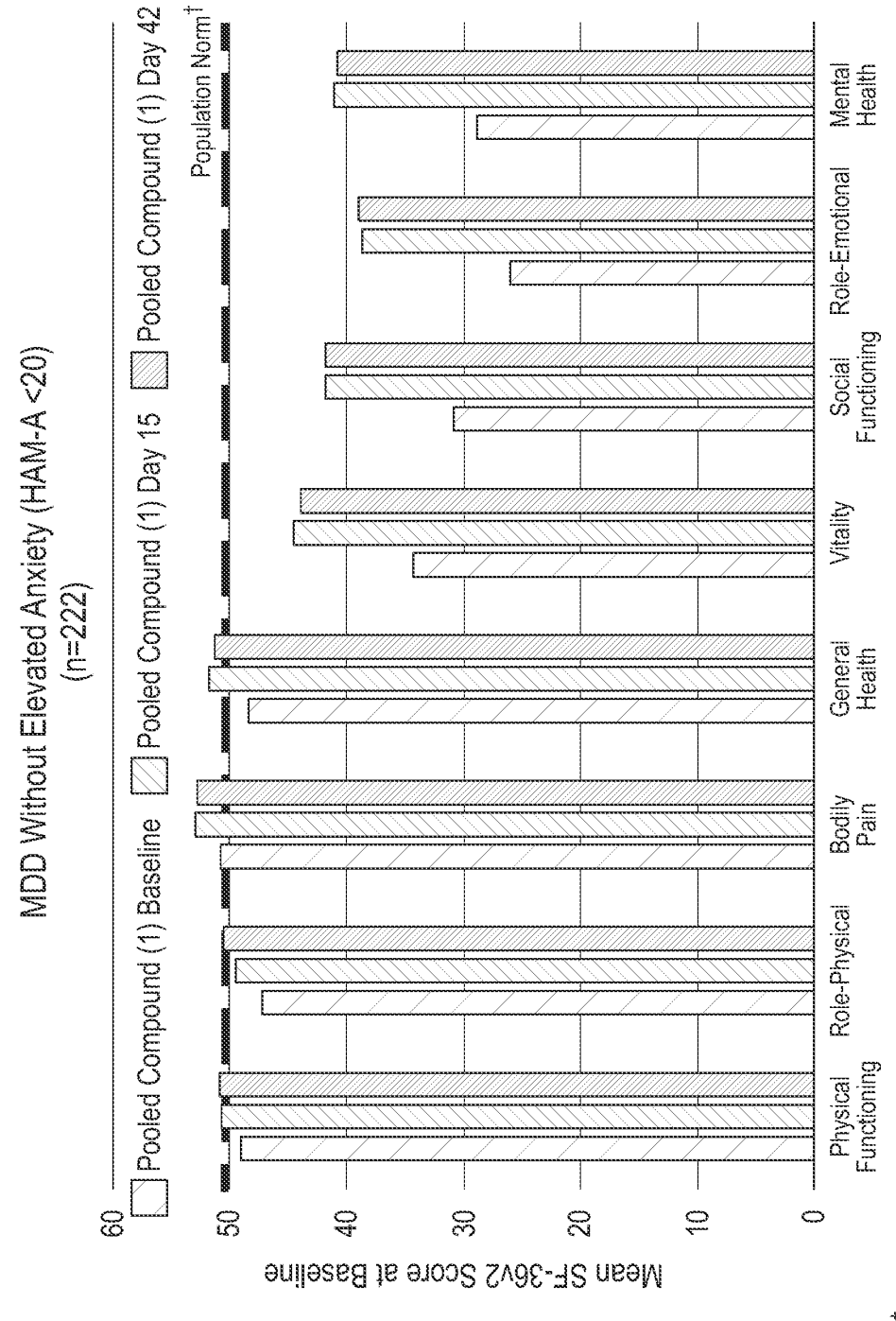

MDD Without Elevated Anxiety (HAM-A <20)
(n=222)
Pooled Compound (1) Baseline
Pooled Compound (1) Day 15
Pooled Compound (1) Day 42
Population Norm†
Mean SF-36v2 Score at Baseline
60
50
40
30
20
10
0
Physical Functioning
Role-Physical
Bodily Pain
General Health
Vitality
Social Functioning
Role-Emotional
Mental Health
†Population norm was defined as scale score of ≥50 on the SF-36

FIG. 18A

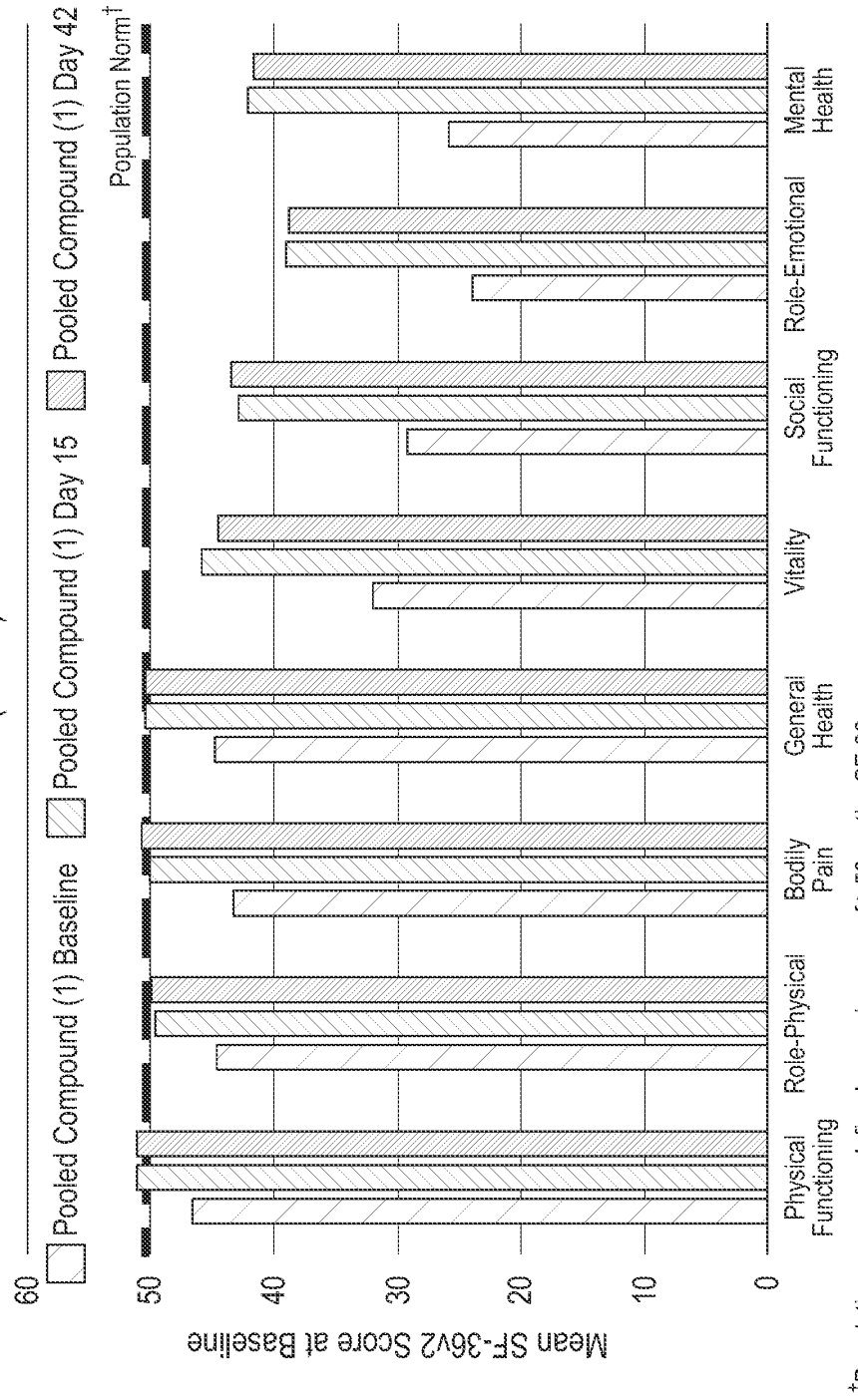

MDD With Elevated Anxiety (HAM-A ≥20)
(n=255)
Pooled Compound (1) Baseline
Pooled Compound (1) Day 15
Pooled Compound (1) Day 42
Population Norm†
Mean SF-36v2 Score at Baseline
60
50
40
30
20
10
0
Physical Functioning
Role-Physical
Bodily Pain
General Health
Vitality
Social Functioning
Role-Emotional
Mental Health
†Population norm was defined as scale score of ≥50 on the SF-36

FIG. 18B

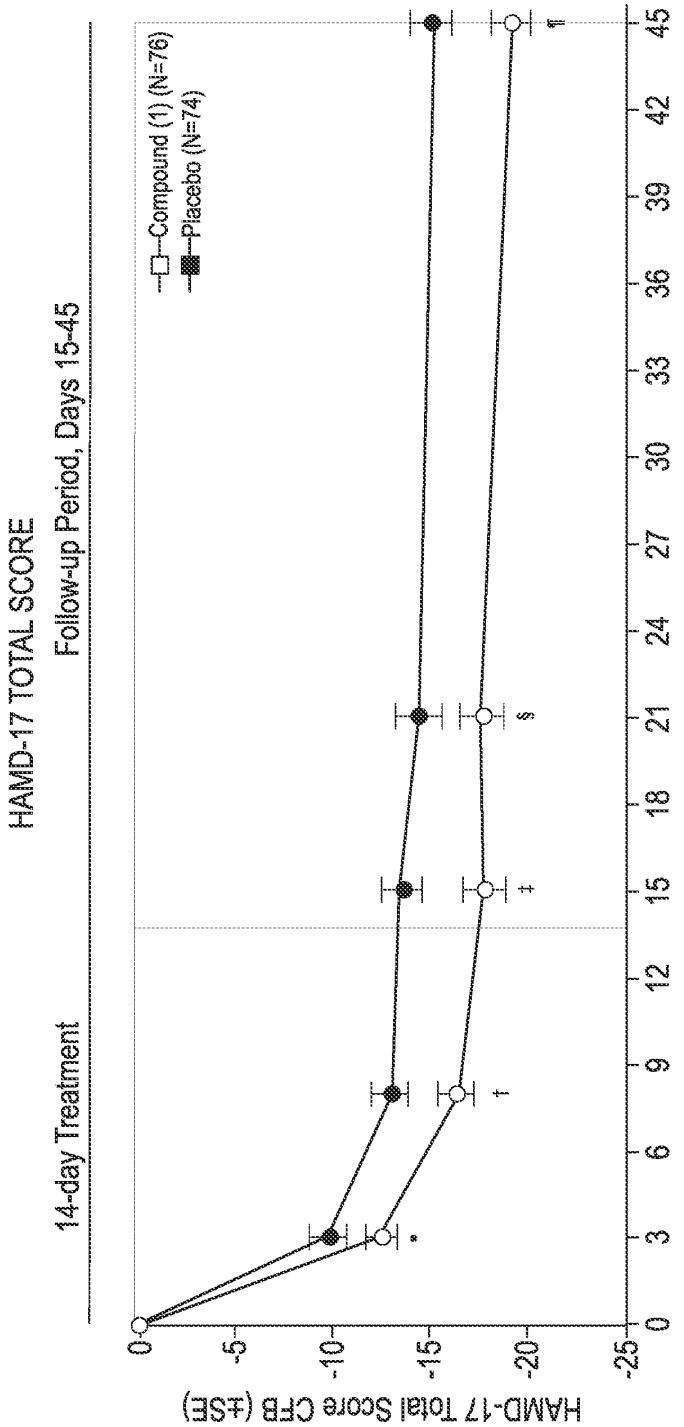

HAMD-17 TOTAL SCORE
14-day Treatment
Follow-up Period, Days 15-45
Compound (1) (N=76)
Placebo (N=74)
HAMD-17 Total Score CFB (±SE)
0
-5
-10
-15
-20
-25
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
Time (Days)
*
†
‡
§
¶
*p=0.0252; †p=0.0106; ‡p=0.0028; §p=0.0321; ¶p=0.0027; vs placebo.

FIG. 19

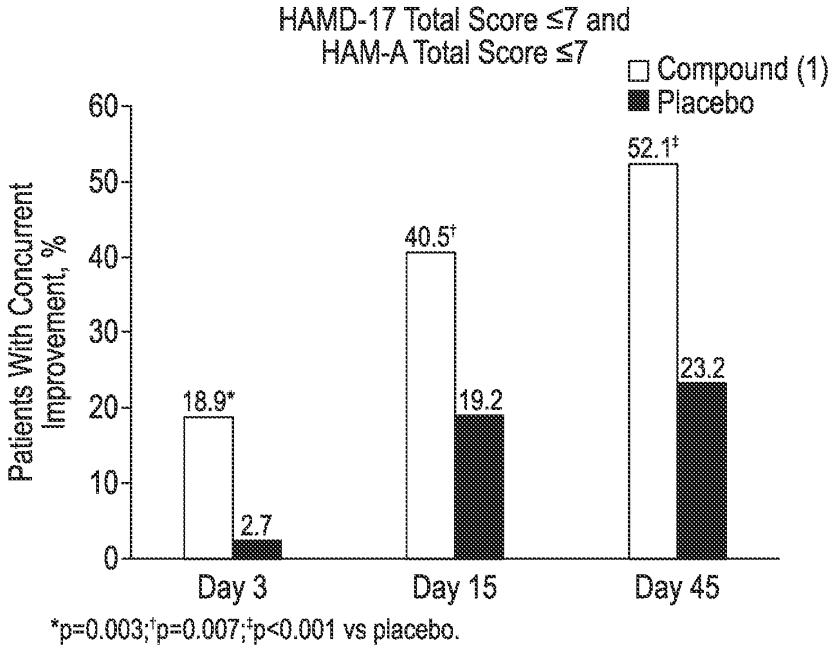


FIG. 20A

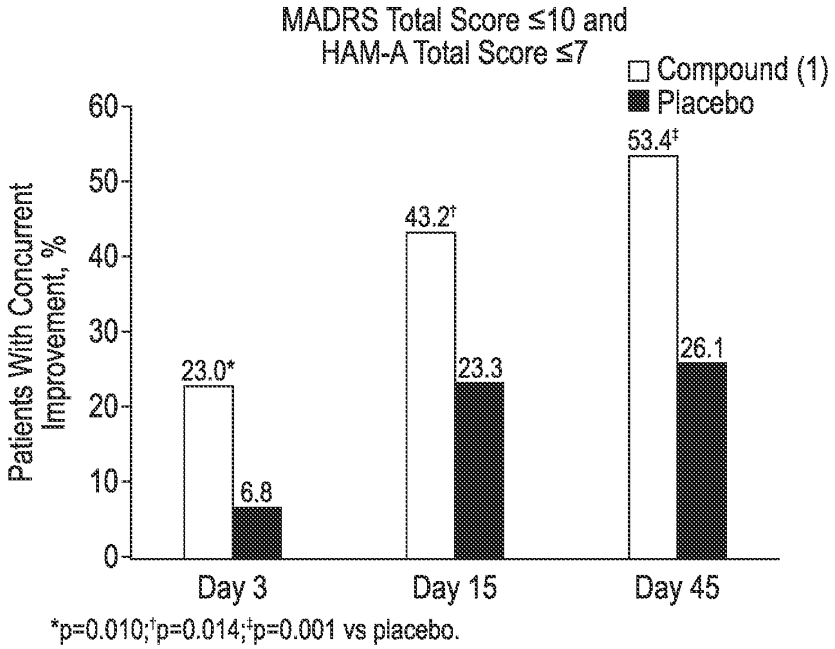
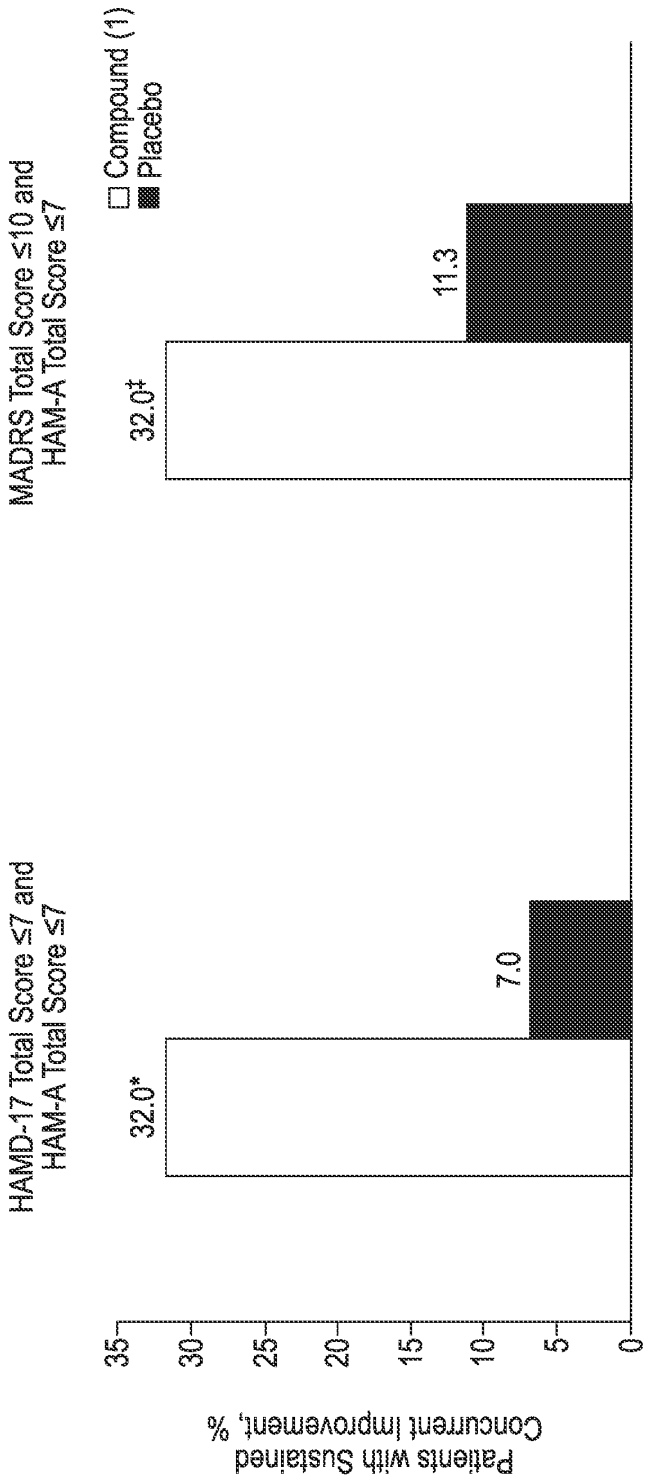


FIG. 20B



*p=0.001; ‡p=0.003.
Significant differences were maintained for sustained response across Day 15 and 45; p-values are from Fisher's exact test for 2-level categorical variables.

FIG. 21

NNTS FOR RESPONSE AND REMISSION, DAY 15

HAMD-17 Measure	NNT(95% CI)
HAMD-17 Response	5(3,13)
HAMD-17 Remission	5(3,17)

Placebo n=73 at Day 15; Compound (1) n=74 at Day 15

- Single-digit NNTs for the outcome support the robustness of the observed Compound (1) effect.

Compound (1): RATES OF RESPONSE AND REMISSION AT DAY 15

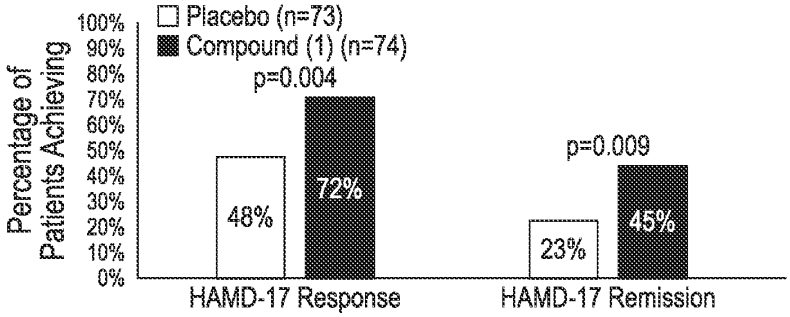


FIG. 22A

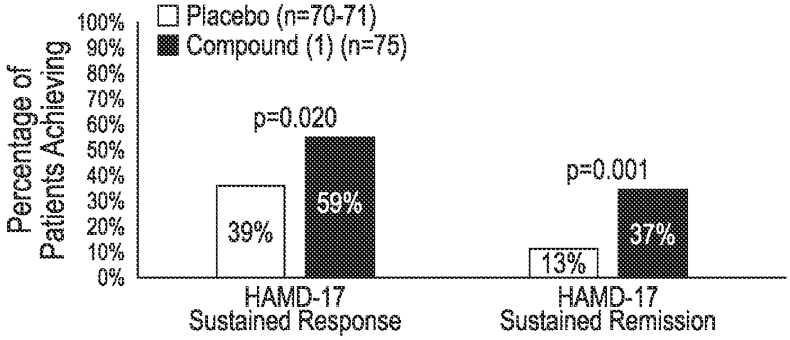
NNTS FOR SUSTAINED RESPONSE AND REMISSION, FROM DAY 15 THROUGH DAY 45

HAMD-17 Measure	NNT(95% CI)
HAMD-17 Response	5(3,27)
HAMD-17 Remission	5(3,10)

Placebo n=70-71 at Day 15-45; Compound (1) n=75 at Day 15-45

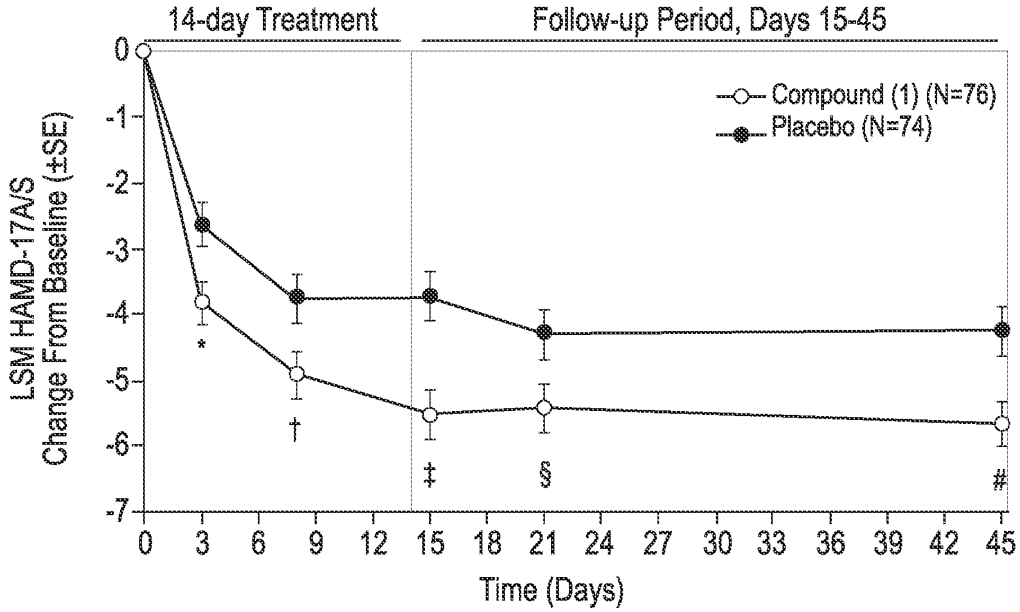
- The NNTs for sustained Response and Remission were similar to those observed at Day 15.

Compound (1): SUSTAINED RESPONSE AND REMISSION RATES FROM DAY 15 THROUGH DAY 45



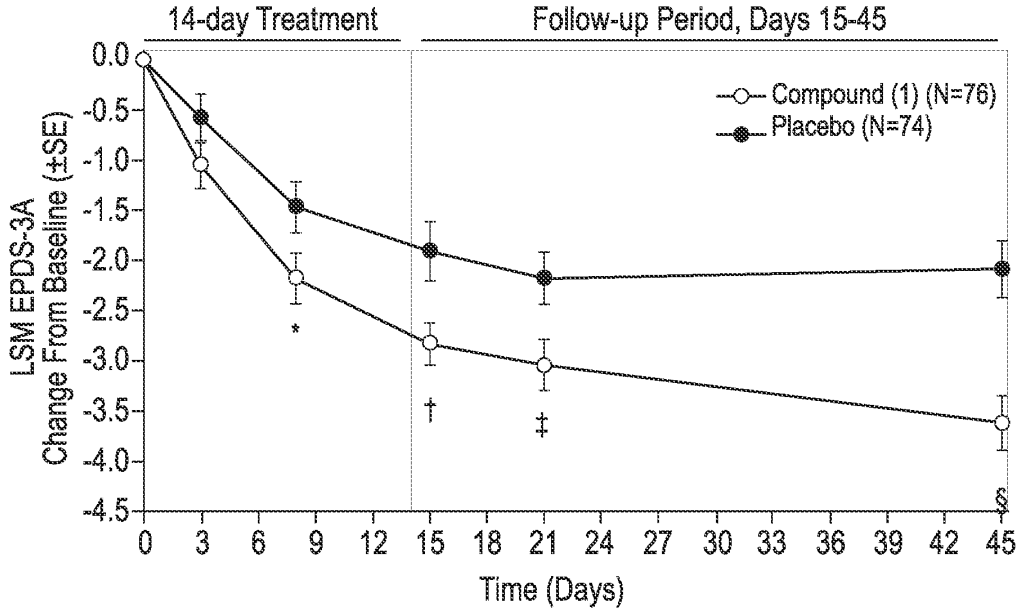
CI = confidence interval; HAMD-17 = 17-item Hamilton Rating Scale for Depression; NNTs = numbers needed to treat.

FIG. 22B



*p=0.0073;†p=0.0147;‡p=0.0004;§p=0.0204;#p=0.0033 versus placebo.

FIG. 23A



*p=0.0015;†p=0.0175;‡p=0.0137;§p=0.0001 versus placebo.

EPDS-3A = Edinburgh Postnatal Depression Anxiety Subscale; HAMD-17 A/S = 17-item Hamilton Rating Scale for Depression - anxiety/somatization; LS = least squares; NNTs = numbers needed to treat; SE = standard error.

FIG. 23B

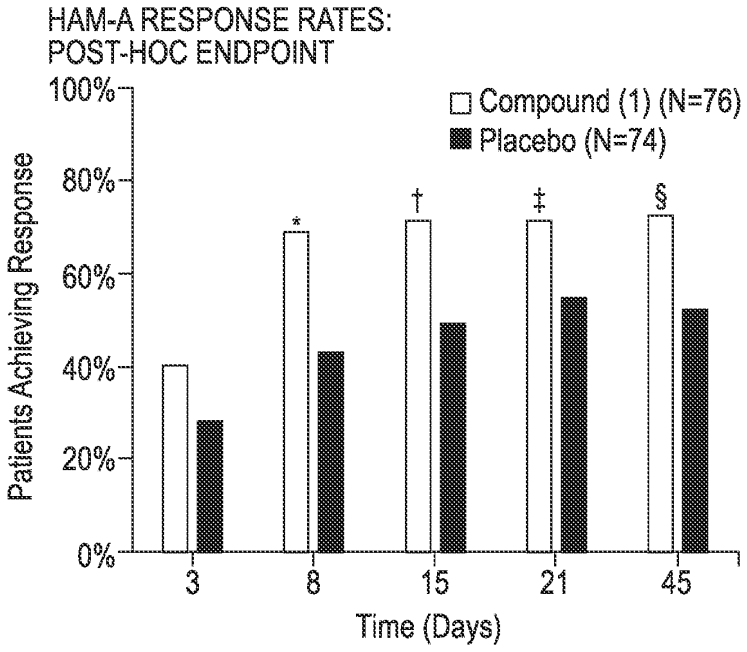


FIG. 24A

*p=0.0016;†p=0.0099;‡p=0.0431;§p=0.0153 versus placebo; p-values compare adjusted rates from the models (not the raw rates presented in the charts); HAM-A Response defined as reduction of ≥50% from baseline.

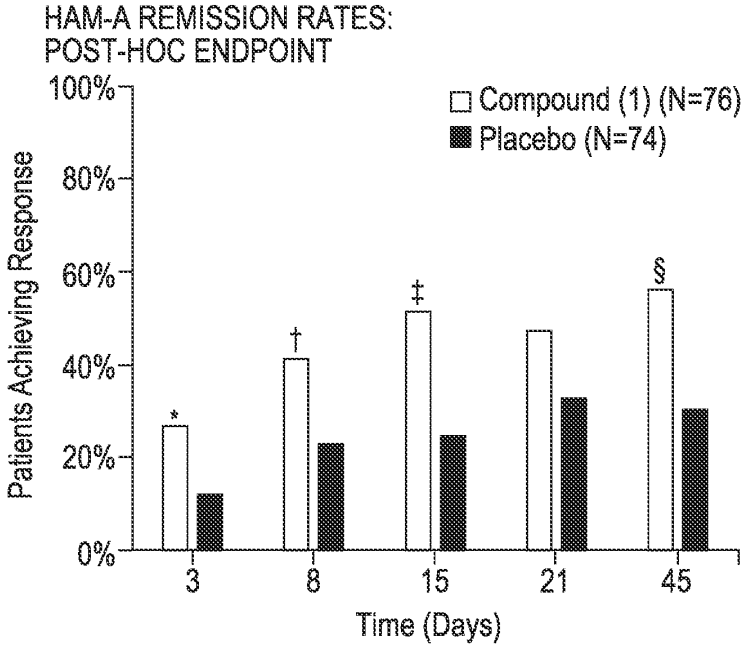


FIG. 24B

*p=0.03340;†p=0.0264;‡p=0.0019;§p=0.0030 vs placebo; p-values compare adjusted rates from the models (not the raw rates presented in the charts); HAM-A Remission defined as total score ≤7.

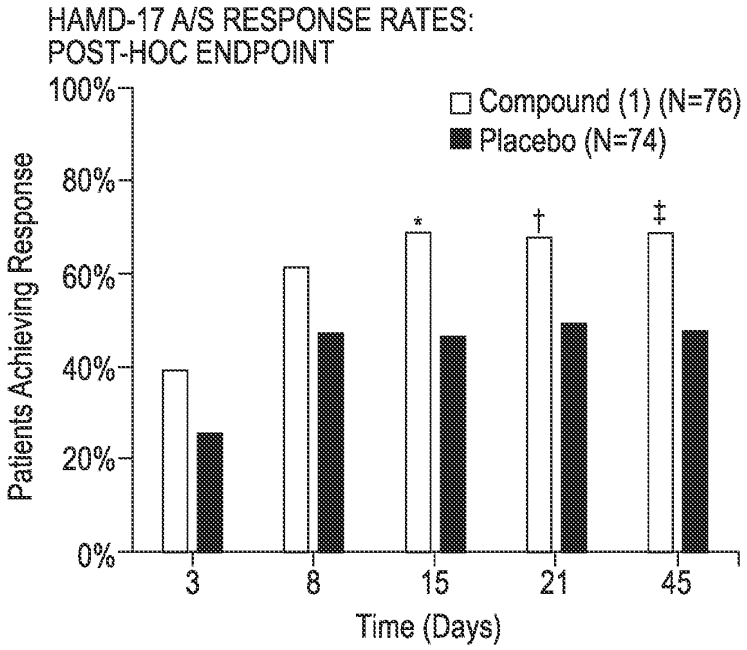


FIG. 24C

*p=0.0086;†p=0.0285;‡p=0.0137 versus placebo; p-values compare adjusted rates from the models (not the raw rates presented in the charts); HAMD-17A/S Response defined as reduction of ≥50% from baseline.

HAM-A = Hamilton Depression Rating Scale - Anxiety; HAMD-17 = 17-item Hamilton Rating Scale for Depression; MADRS = Montgomery - Åsberg Depression Rating Scale; PPD = postpartum depression.

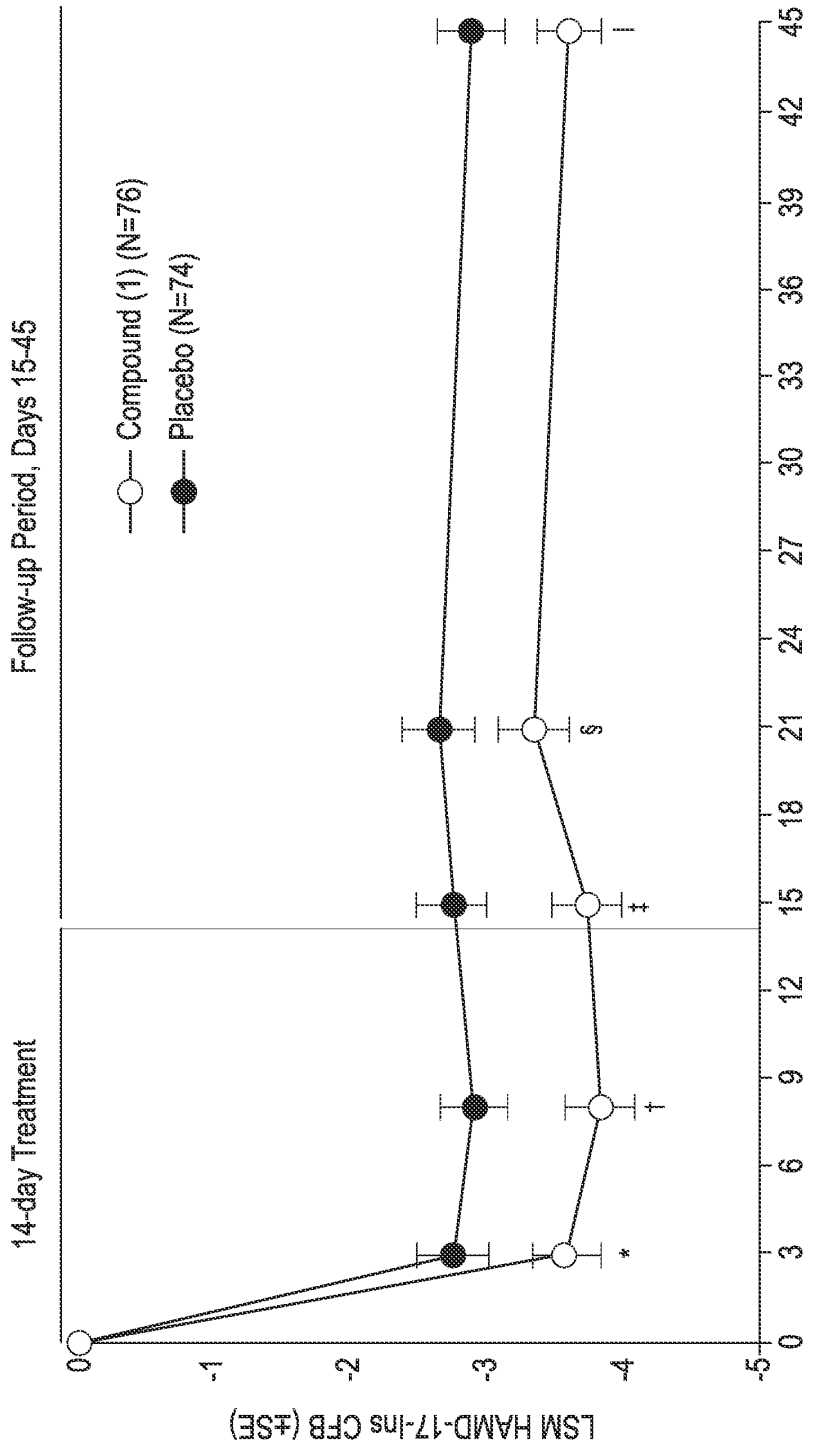

14-day Treatment
Follow-up Period, Days 15-45
Compound (1) (N=76)
Placebo (N=74)
LSM HAMD-17-ins CFB (±SE)
0
-1
-2
-3
-4
-5
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
Time (Days)
*
†
‡
§
‖
*p=0.0142;†p=0.0051;‡p=0.0038;§p=0.0414;‖p=0.0207 vs placebo.
Secondary endpoints were not adjusted for multiplicity.

FIG. 25A

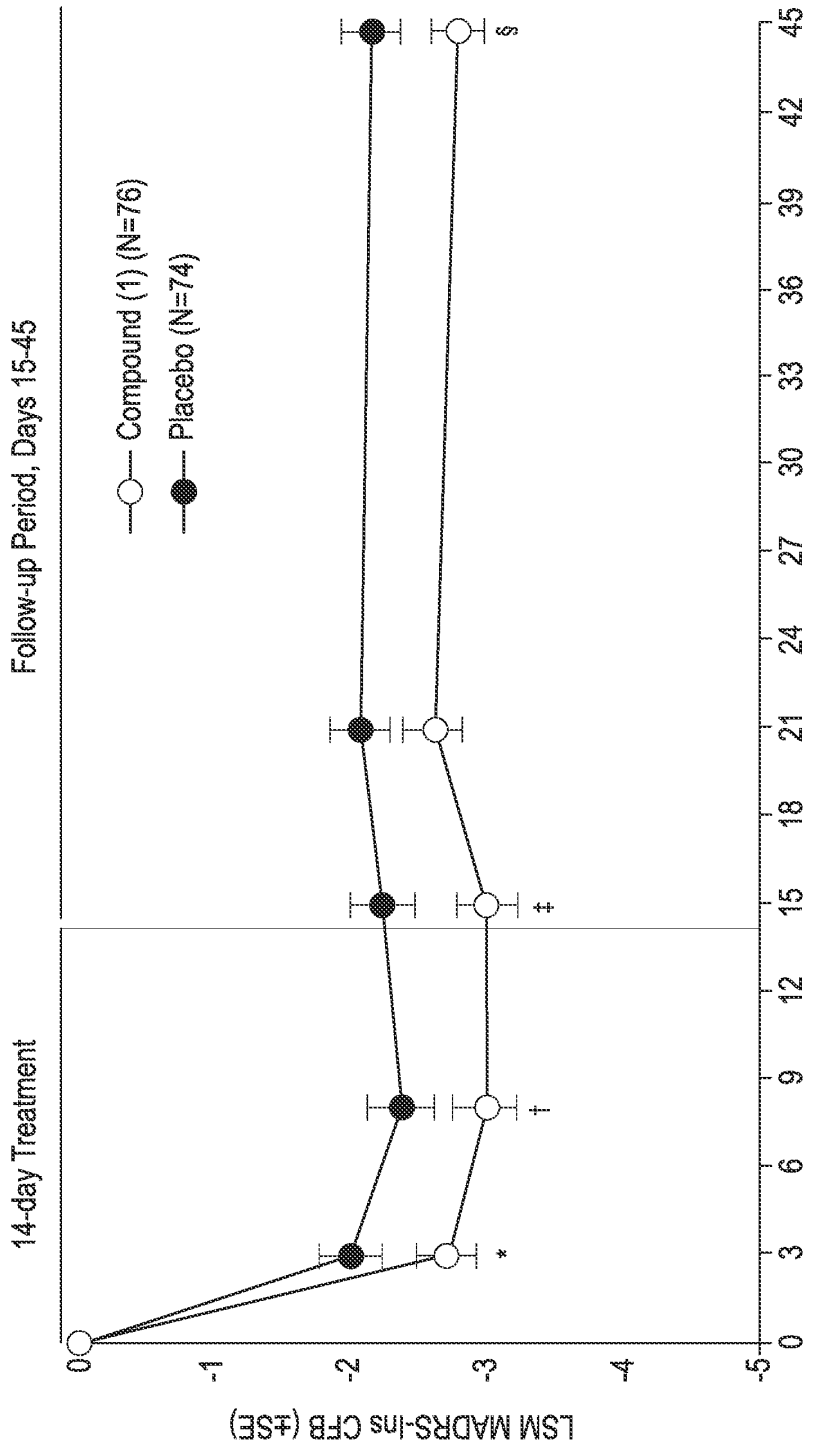

14-day Treatment
Follow-up Period, Days 15-45
Compound (1) (N=76)
Placebo (N=74)
LSM MADRS-ins CFB (±SE)
Time (Days)
0
-1
-2
-3
-4
-5
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
*
†
‡
§
*p=0.0170;†p=0.0366;‡p=0.0116;§p=0.0221 vs placebo.
Secondary endpoints were not adjusted for multiplicity.

FIG. 25B

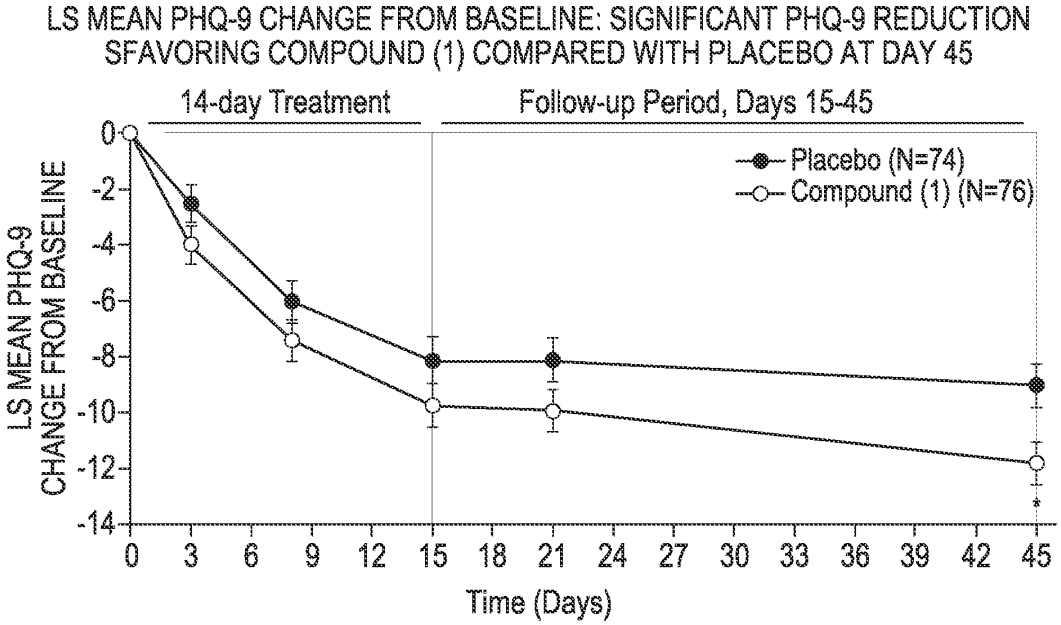


FIG. 26A

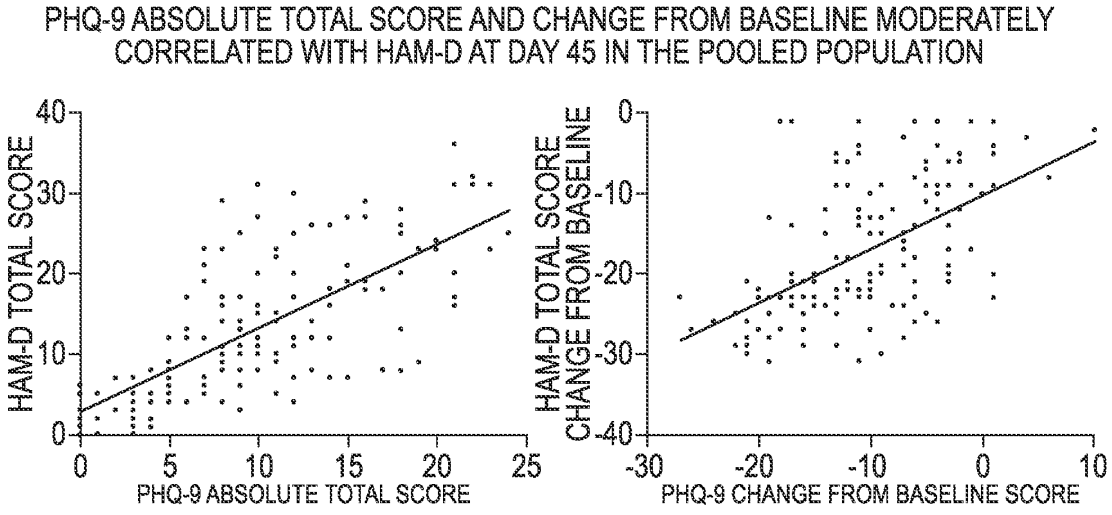
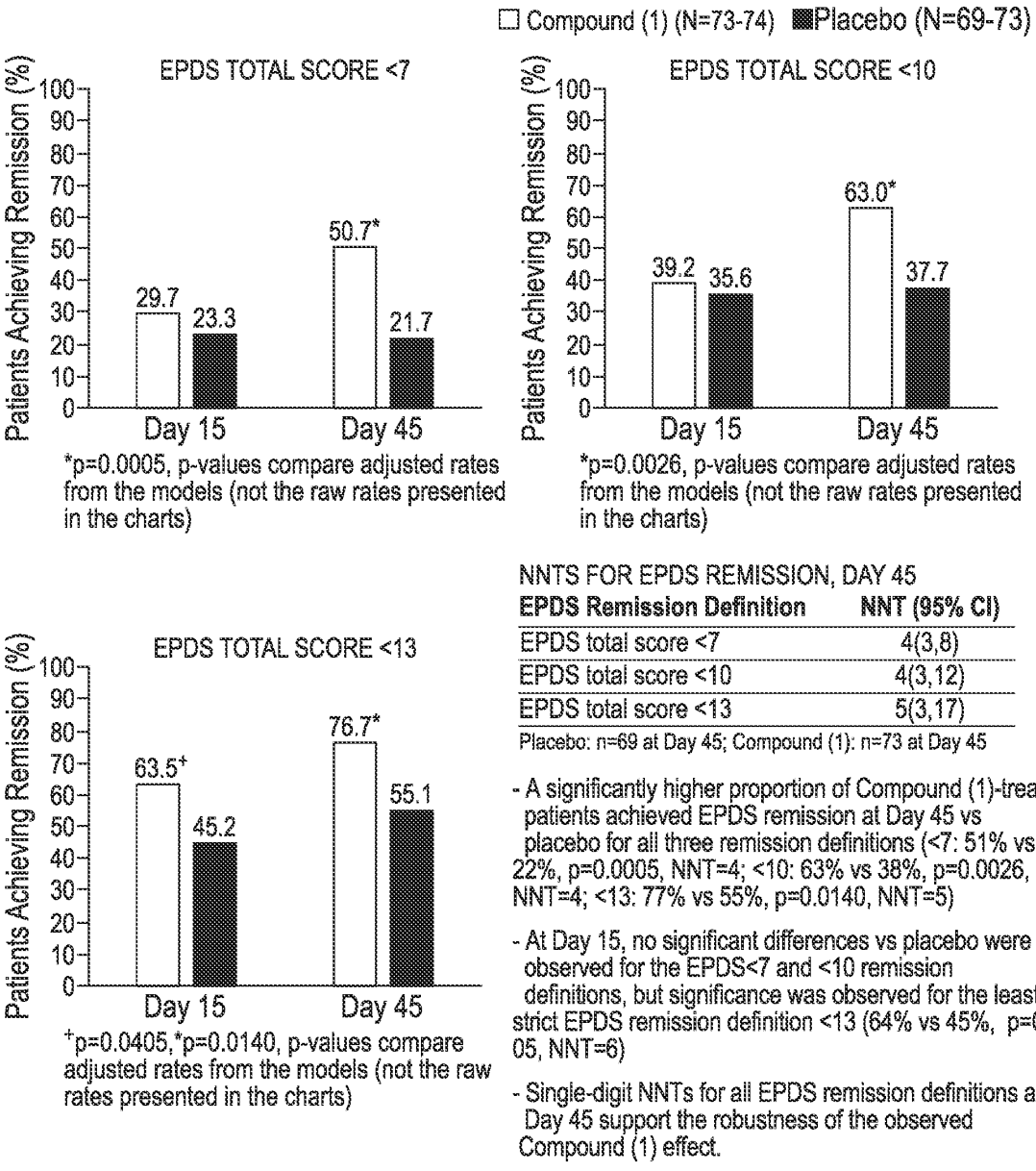


FIG. 26B



NNTS FOR EPDS REMISSION, DAY 45

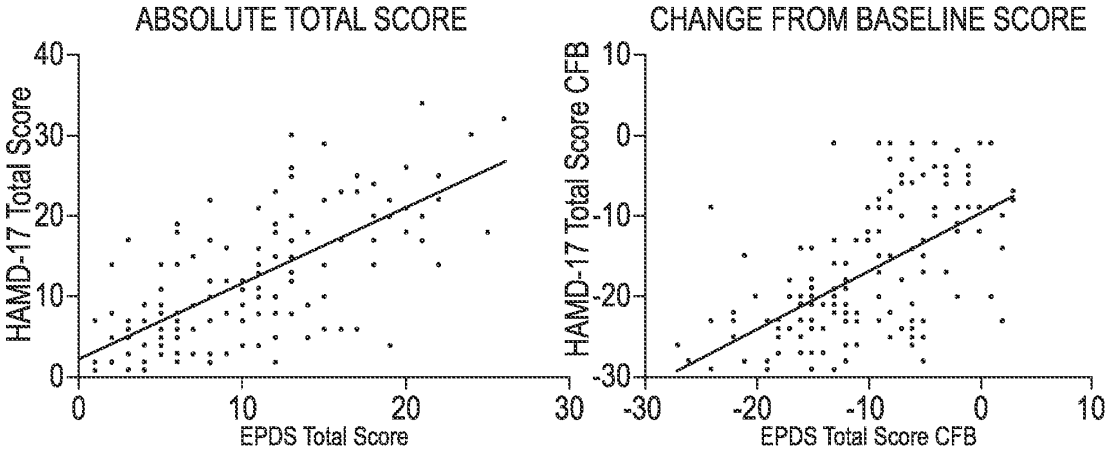
EPDS Remission Definition	NNT (95% CI)
EPDS total score <7	4(3,8)
EPDS total score <10	4(3,12)
EPDS total score <13	5(3,17)

Placebo: n=69 at Day 45; Compound (1): n=73 at Day 45

- A significantly higher proportion of Compound (1)-treated patients achieved EPDS remission at Day 45 vs placebo for all three remission definitions (<7: 51% vs 22%, p=0.0005, NNT=4; <10: 63% vs 38%, p=0.0026, NNT=4; <13: 77% vs 55%, p=0.0140, NNT=5)
- At Day 15, no significant differences vs placebo were observed for the EPDS<7 and <10 remission definitions, but significance was observed for the least strict EPDS remission definition <13 (64% vs 45%, p=0.0405, NNT=6)
- Single-digit NNTs for all EPDS remission definitions at Day 45 support the robustness of the observed Compound (1) effect.

CI = confidence interval; NNT = number needed to treat.

FIG. 27



- HAMD-17 and EPDS total scores were significantly and strongly (≥0.7) correlated at Day 45 ($r=0.72$, $R^2=0.52$, $p<0.001$)

- HAMD-17 and EPDS total score CFB were significantly and moderately (0.5-0.7) correlated at Day 45 ($r=0.58$, $R^2=0.34$, $p<0.001$)

PEARSON CORRELATIONS FROM HAMD-17 AND EPDS SCORES BY VISIT

Visit Day (N)	Absolute Total Score Correlation (95% CI*)	p-value
3(144)	0.38(0.23, 0.51)	<.0001
8(149)	0.56(0.44, 0.66)	<.0001
15(147)	0.70(0.61, 0.78)	<.0001
21(147)	0.72(0.62, 0.79)	<.0001
45(142)	0.72(0.63, 0.79)	<.0001

Visit Day (N)	CFB Score Correlation (95% CI*)	p-value
3(144)	0.41(0.26, 0.54)	<.0001
8(149)	0.53(0.41, 0.64)	<.0001
15(147)	0.63(0.52, 0.72)	<.0001
21(147)	0.66(0.56, 0.74)	<.0001
45(142)	0.68(0.46, 0.68)	<.0001

* Confidence Interval.

- Absolute and CFB in HAMD-17 and EPDS total scores were significantly correlated throughout the study period ($p<0.0001$ for all measured time points).

CI = confidence interval; CFB = change from baseline; EPDS = Edinburgh Postnatal Depression Scale; HAMD-17 = 17-item Hamilton Rating Scale for Depression

FIG. 28

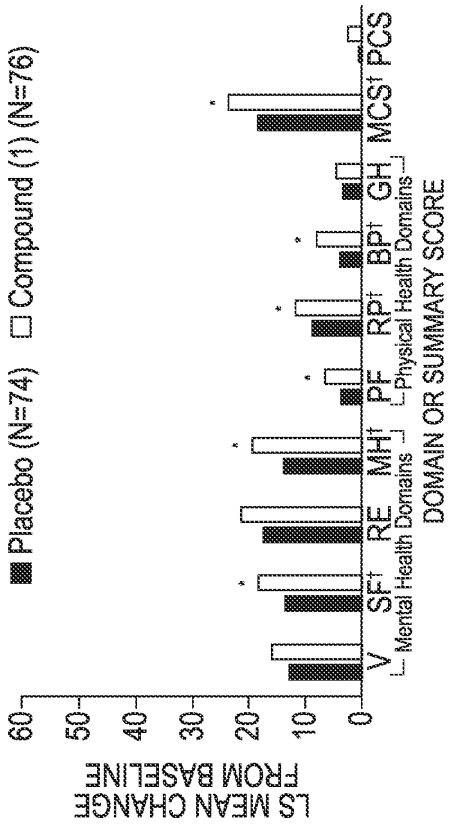


FIG. 29A

FIG. 29B

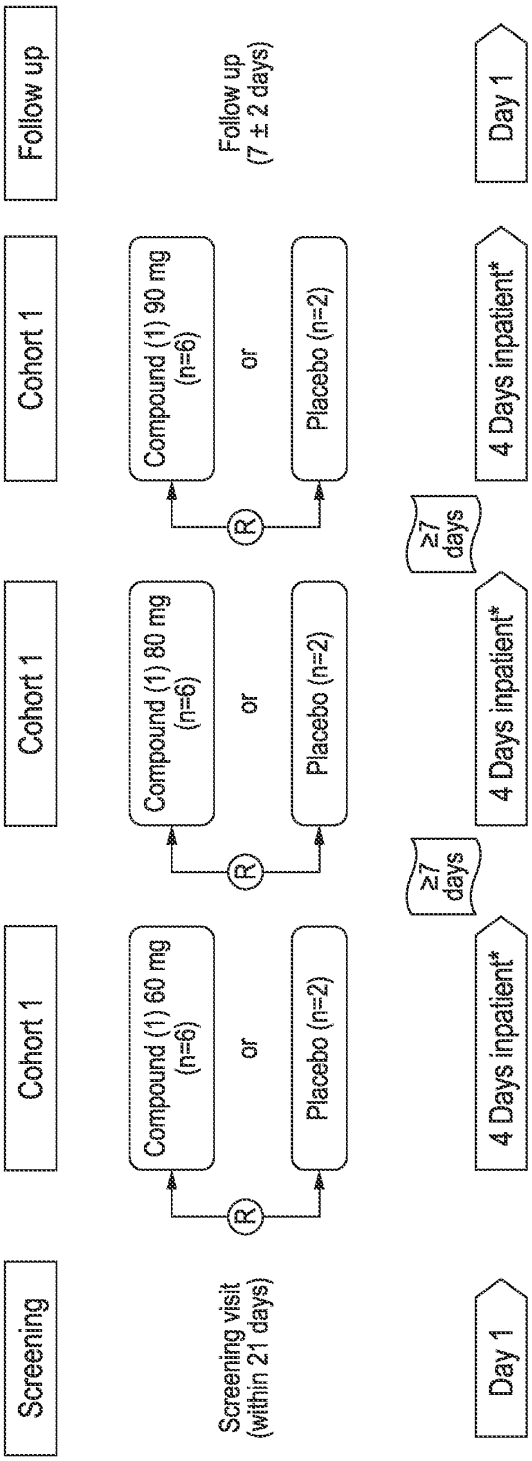

Screening
Cohort 1
Cohort 1
Cohort 1
Follow up
Screening visit (within 21 days)
Compound (1) 60 mg (n=6)
or
Placebo (n=2)
Compound (1) 80 mg (n=6)
or
Placebo (n=2)
Compound (1) 90 mg (n=6)
or
Placebo (n=2)
R
R
R
Follow up (7 ± 2 days)
Day 1
4 Days inpatient*
4 Days inpatient*
4 Days inpatient*
≥7 days
≥7 days
Day 1

FIG. 30A

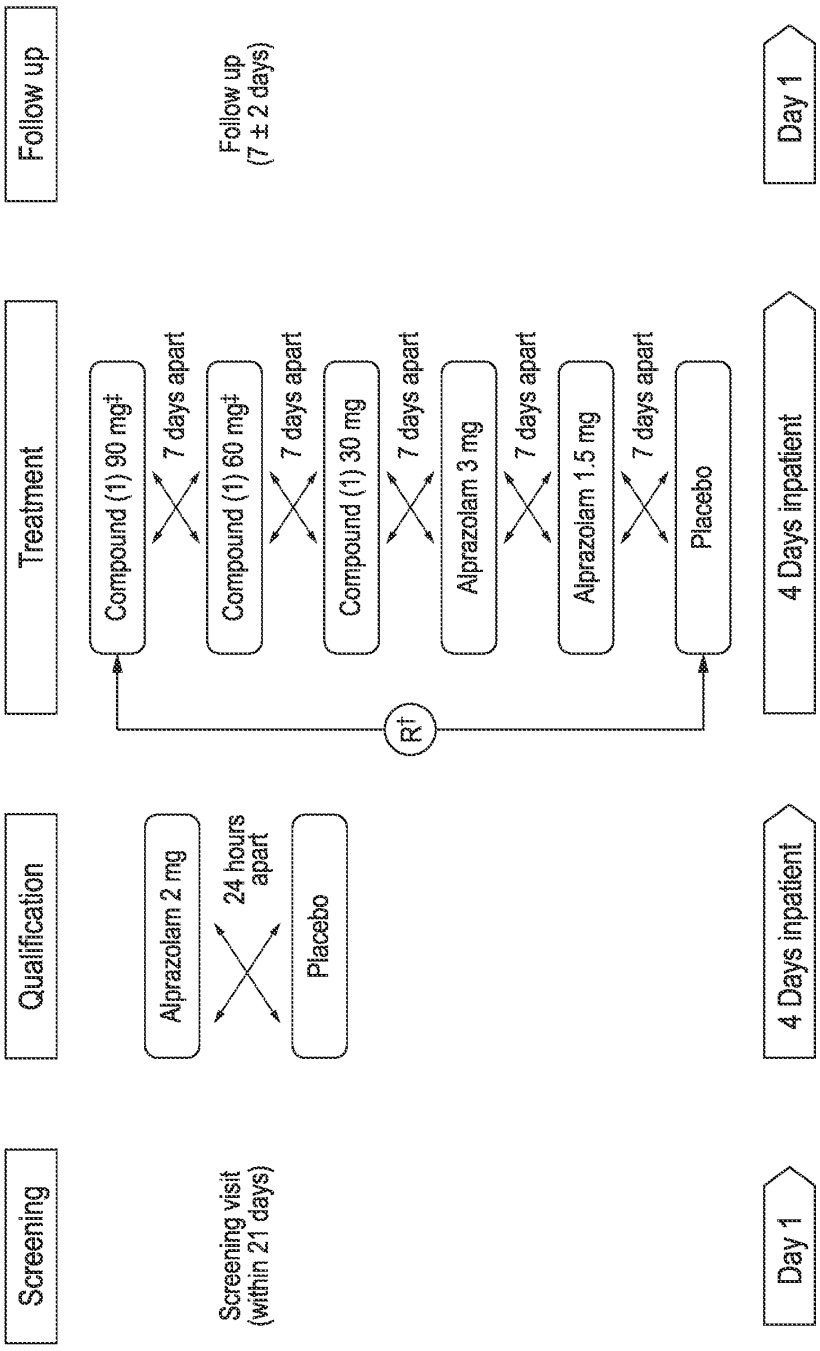

Screening
Qualification
Treatment
Follow up
Screening visit
(within 21 days)
Alprazolam 2 mg
24 hours apart
Placebo
Day 1
4 Days inpatient
R†
Compound (1) 90 mg‡
Compound (1) 60 mg‡
Compound (1) 30 mg
Alprazolam 3 mg
Alprazolam 1.5 mg
Placebo
7 days apart
4 Days inpatient
Day 1
Follow up
(7 ± 2 days)

FIG. 30B

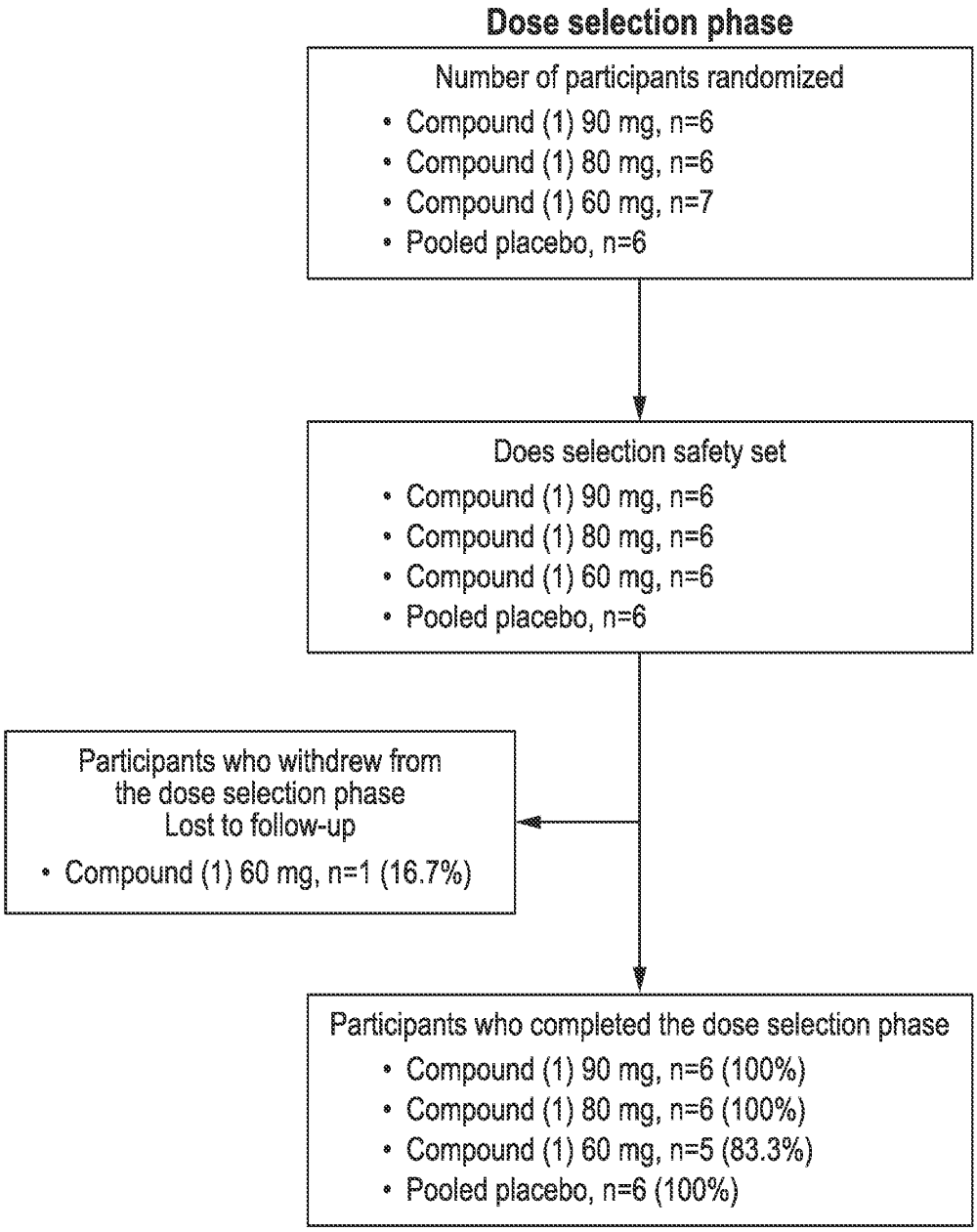
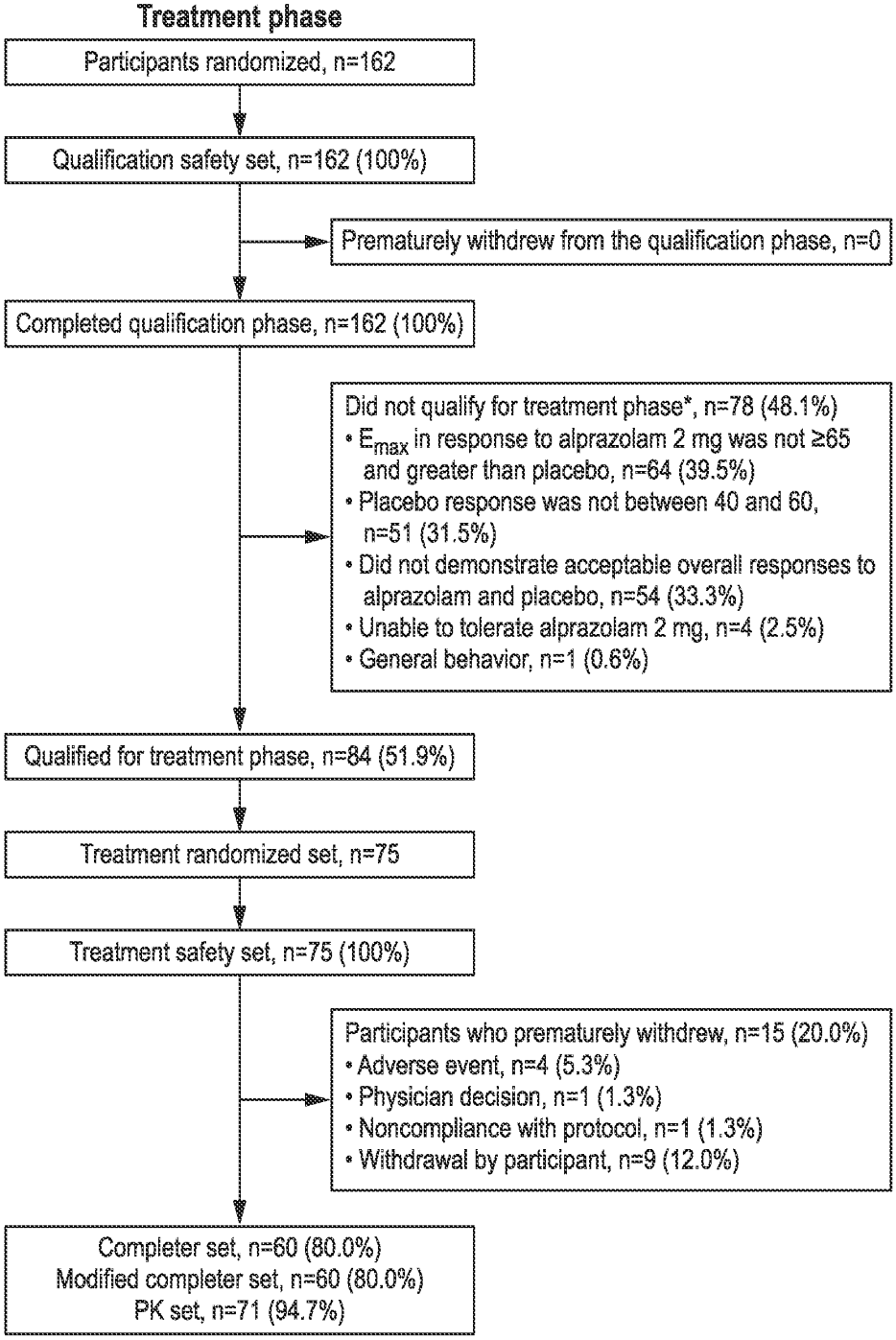

Dose selection phase
Number of participants randomized
• Compound (1) 90 mg, n=6
• Compound (1) 80 mg, n=6
• Compound (1) 60 mg, n=7
• Pooled placebo, n=6
Does selection safety set
• Compound (1) 90 mg, n=6
• Compound (1) 80 mg, n=6
• Compound (1) 60 mg, n=6
• Pooled placebo, n=6
Participants who withdrew from the dose selection phase Lost to follow-up
• Compound (1) 60 mg, n=1 (16.7%)
Participants who completed the dose selection phase
• Compound (1) 90 mg, n=6 (100%)
• Compound (1) 80 mg, n=6 (100%)
• Compound (1) 60 mg, n=5 (83.3%)
• Pooled placebo, n=6 (100%)

FIG. 31A



*Participants may have been excluded for failure to meet more than 1 qualification criterion.

FIG. 31B

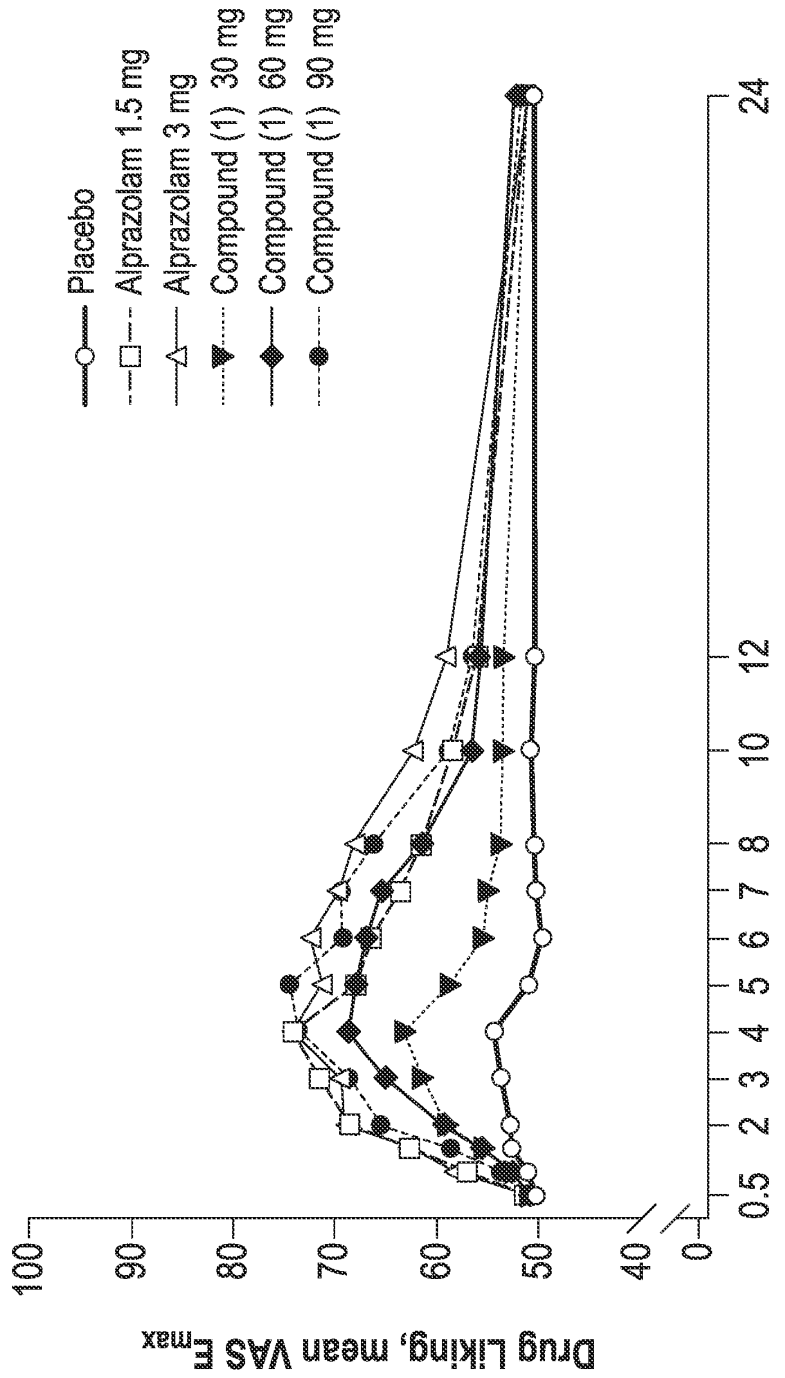
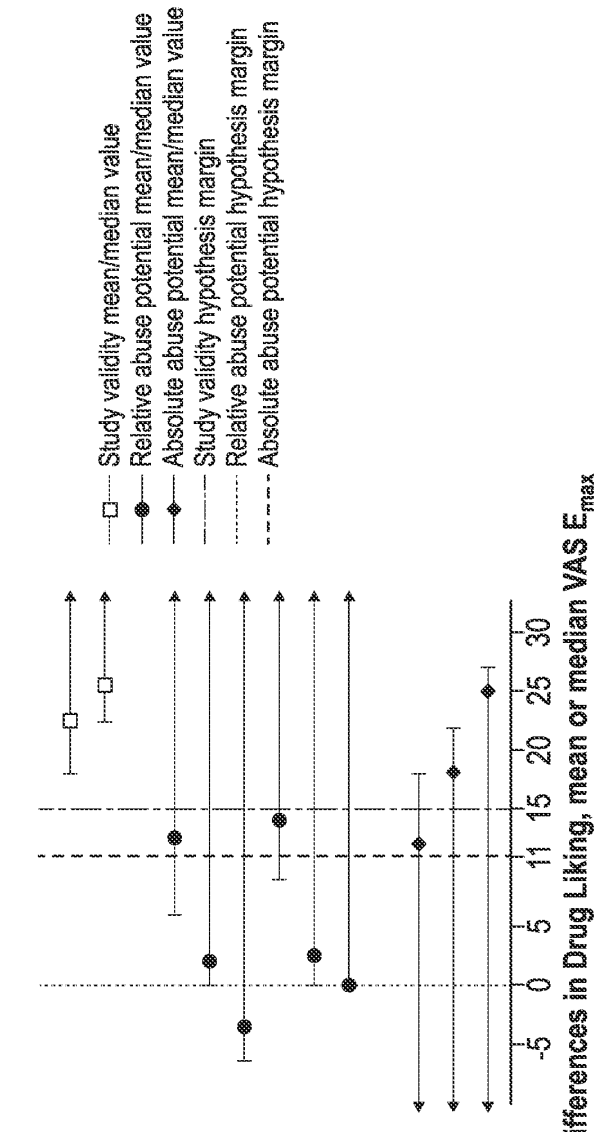

Placebo
Alprazolam 1.5 mg
Alprazolam 3 mg
Compound (1) 30 mg
Compound (1) 60 mg
Compound (1) 90 mg
Drug Liking, mean VAS E_{max}
100
90
80
70
60
50
40
0
0.5
2
3
4
5
6
7
8
10
12
24
Time, hours

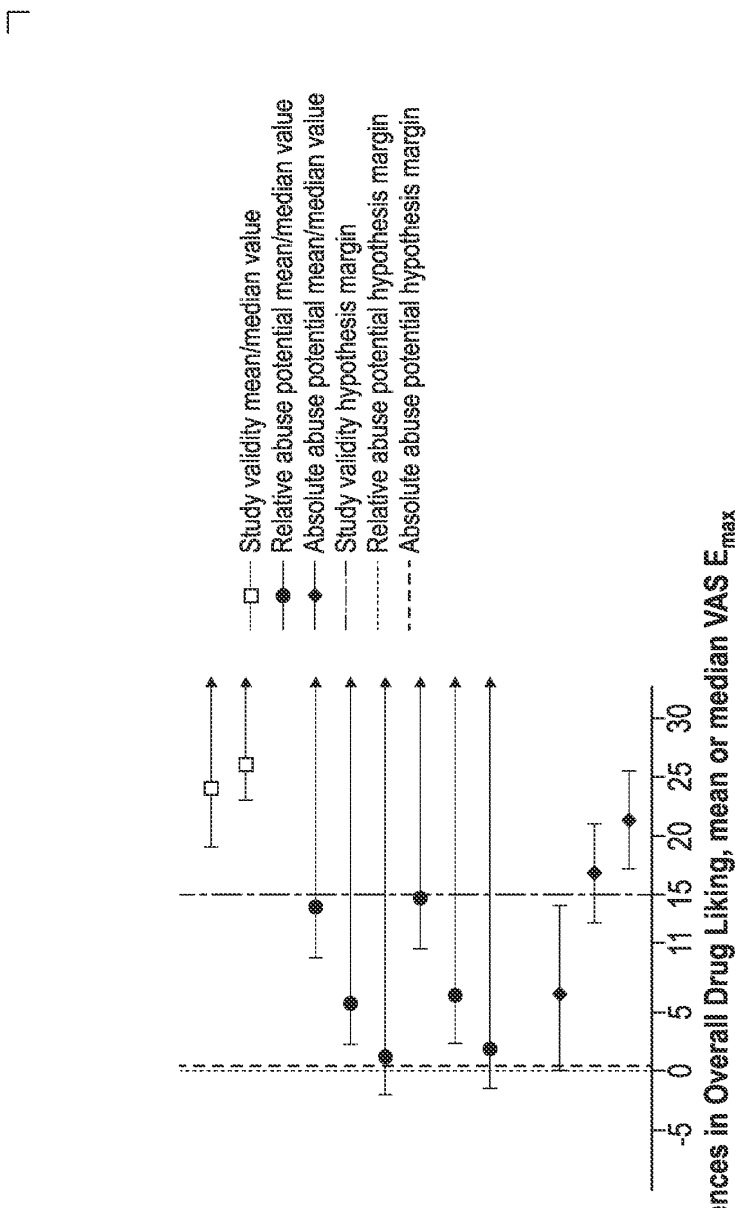
FIG. 32



*Squares, circles, and diamonds represent medians of differences based on sign test, bounded by a distribution-free, 1-sided 95% CI.

†Squares, circles, and diamonds represent means of differences based on paired t-test, bounded by a 1-sided 95% CI.

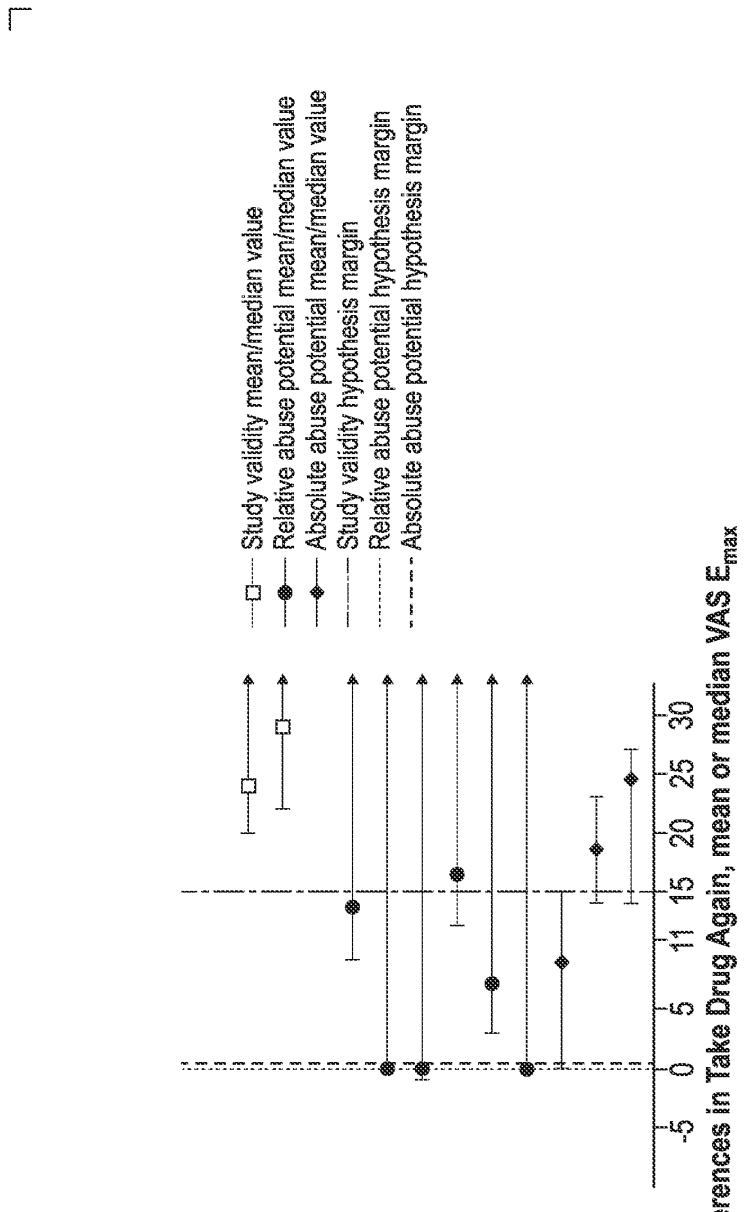
FIG. 33



*Squares, circles, and diamonds represent medians of differences based on sign test, bounded by a distribution-free, 1-sided 95% CI.

†Squares, circles, and diamonds represent means of differences based on paired t-test, bounded by a 1-sided 95% CI.

FIG. 34A



*Squares, circles, and diamonds represent medians of differences based on sign test, bounded by a distribution-free, 1-sided 95% CI.

†Squares, circles, and diamonds represent means of differences based on paired t-test, bounded by a 1-sided 95% CI.

FIG. 34B

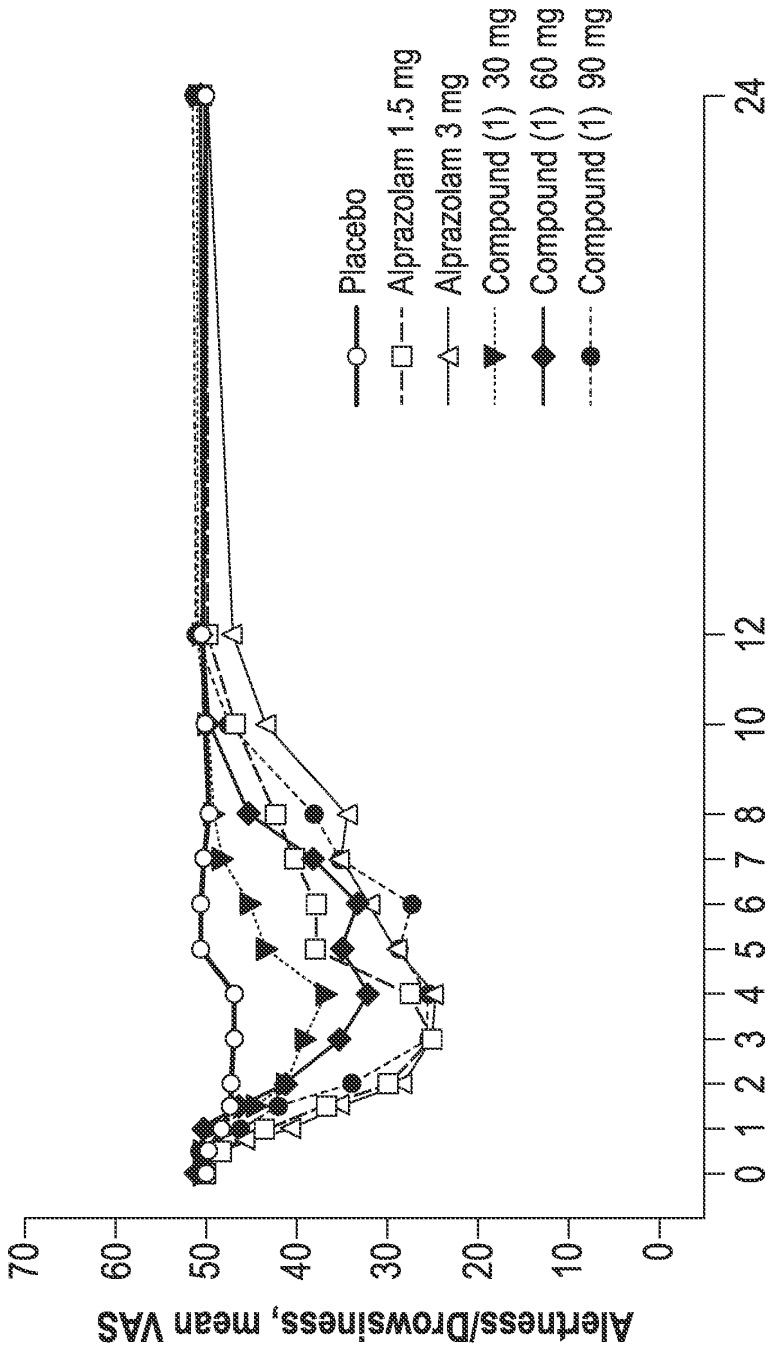

Alertness/Drowsiness, mean VAS
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 10 12 24
Time, hours
Placebo
Alprazolam 1.5 mg
Alprazolam 3 mg
Compound (1) 30 mg
Compound (1) 60 mg
Compound (1) 90 mg

FIG. 35

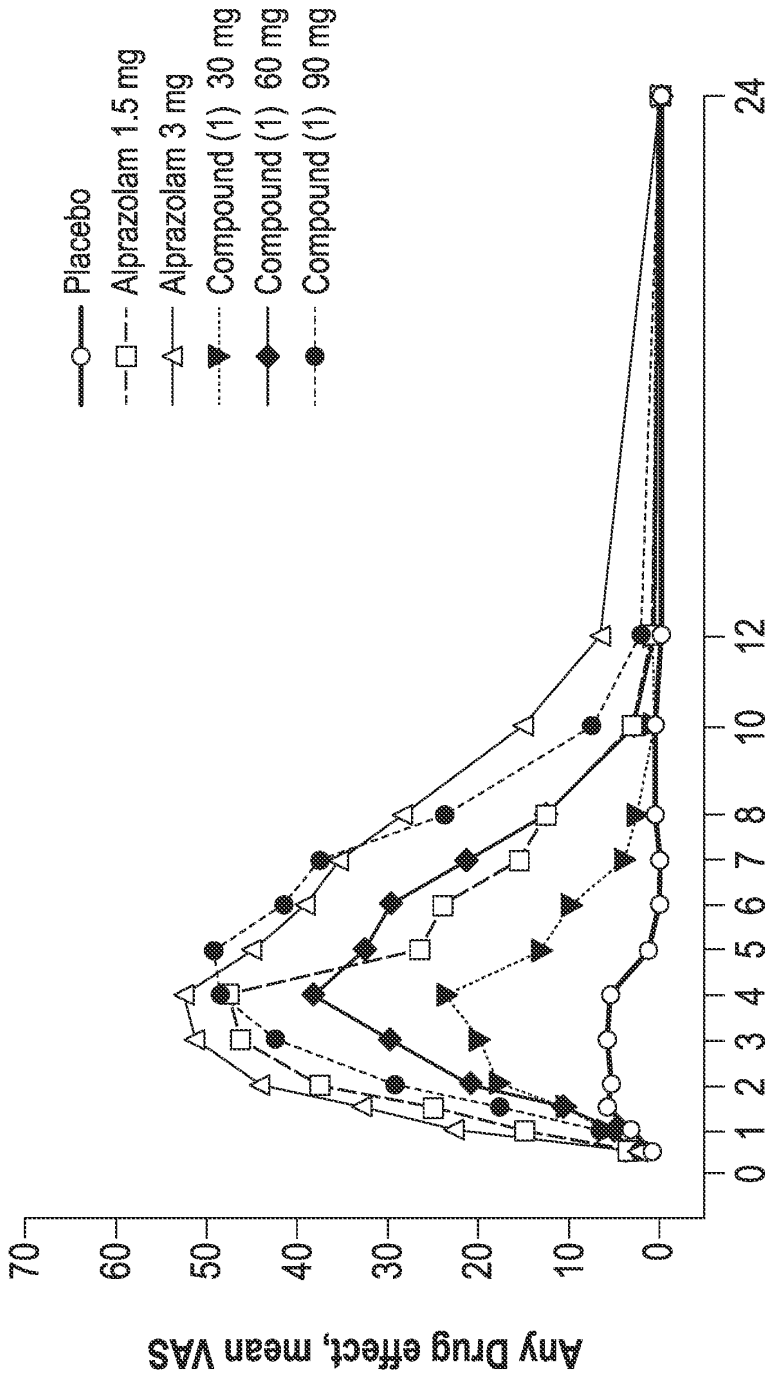

Placebo
Alprazolam 1.5 mg
Alprazolam 3 mg
Compound (1) 30 mg
Compound (1) 60 mg
Compound (1) 90 mg
Any Drug effect, mean VAS
0
10
20
30
40
50
60
70
0 1 2 3 4 5 6 7 8 10 12 24
Time, hours

FIG. 36

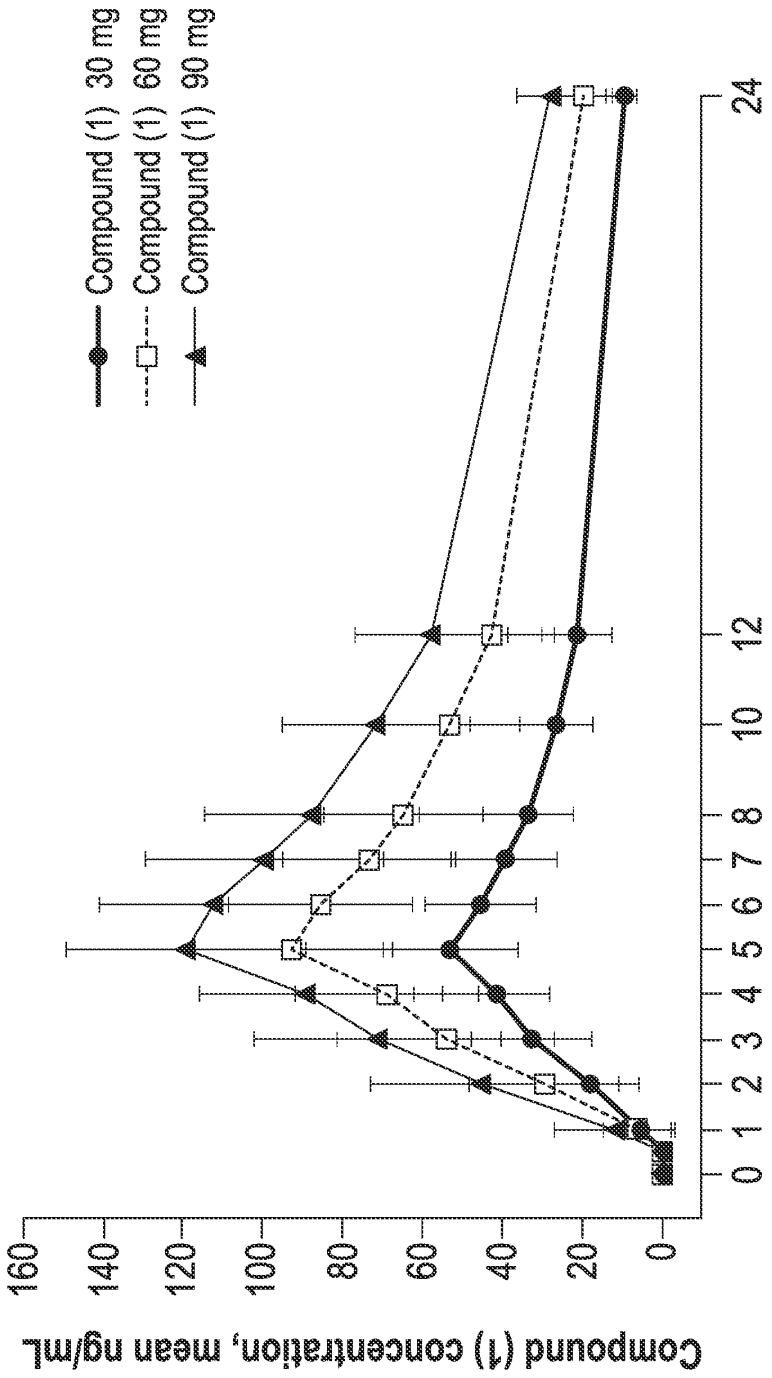

Compound (1) 30 mg
Compound (1) 60 mg
Compound (1) 90 mg
Compound (1) concentration, mean ng/mL
0
20
40
60
80
100
120
140
160
0 1 2 3 4 5 6 7 8 10 12 24
Time, hours

FIG. 37