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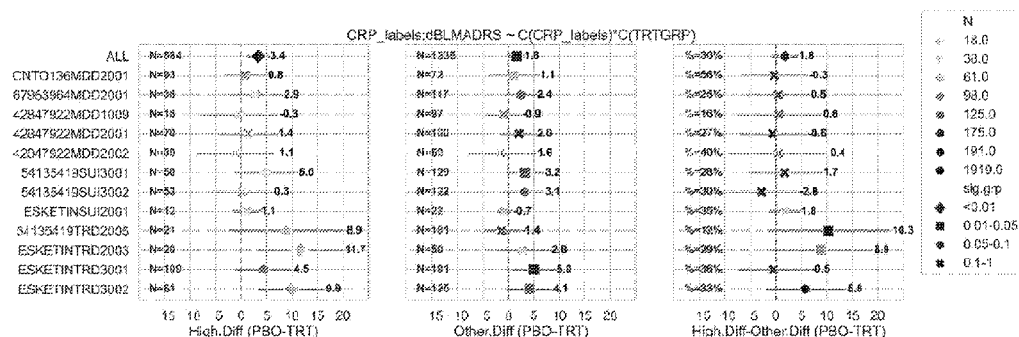
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- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

(54) Title: COMPOSITIONS AND METHODS FOR THE TREATMENT OF DEPRESSION

FIG. 38



(57) Abstract: The disclosure provides methods for treating major depressive disorder in a human patient, wherein the patient is identified as biomarker signature positive. The methods comprise administering to the patient in need thereof an effective amount of an antidepressant.

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COMPOSITIONS AND METHODS FOR THE TREATMENT OF DEPRESSION

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application 63/298,060, filed on January 10, 2022, which is incorporated by reference herein in its entirety.

TECHNICAL FIELD

[0002] The present disclosure relates to methods for treating depression using an antidepressant wherein the patient is identified as biomarker signature positive.

BACKGROUND

[0003] Major depressive disorder (MDD) affects about 7-15% of the general population. MDD is associated with significant morbidity and mortality and the leading cause of disability worldwide. About one third of patients fail to achieve remission despite treatment with multiple antidepressant medications and are considered to have treatment resistant depression (TRD). Such patients who do benefit with oral ADs have high rates of relapse even with continuation of treatment.

[0004] The impact of TRD on patient's lives is difficult to adequately describe. Many patients have depressive episodes lasting years. Severely depressed patients lose the will to carry on with their lives, there is a 7-fold increase in suicide attempts. Life expectancy is lowered by 10 years. In extreme cases they cannot even engage in basic self-care activities such as bathing or eating, or taking care of themselves, leave alone those in their care as a parent, spouse etc. This impacts not only the patient themselves, but also the family and those dependant on them. They also lose the ability to experience pleasure in doing the things that used to enjoy, which robs people of the essence of life and what drives it. In effect their lives are taken away from them by TRD.

[0005] There remains a need for improved treatments for patients having depression, in particular patients having TRD.

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SUMMARY

[0006] In some aspects, the present disclosure is directed to methods for treating depression in a human patient, comprising administering to the patient in need thereof an effective amount of an antidepressant, wherein the patient is identified as biomarker signature positive, and wherein the patient is identified as biomarker signature positive if a biological sample obtained from the patient is identified as having a level of at least one biomarker that is greater or less than a reference biomarker level.

[0007] In still further aspects, the patient is identified as biomarker signature positive. In certain aspects, the patient is identified as biomarker signature positive if the biological sample obtained from the patient is identified as having: (a) a level of CRP greater than a reference CRP level, and (b) at least one of: (i) a level of TNF-alpha that is greater than a reference TNF-alpha level, and (ii) a level of sIL6R that is greater than a reference sIL6R level.

[0008] In certain aspects, the antidepressant is selected from esketamine and aticaprant, or a pharmaceutically acceptable salt thereof.

[0009] In further aspects, the antidepressant is aticaprant, or a pharmaceutically acceptable salt thereof. In certain aspects, the patient had an inadequate response to other antidepressant therapy prior to treatment with aticaprant or a pharmaceutically acceptable salt thereof. In further aspects, the other antidepressant therapy comprised one or more second antidepressants. In certain aspects, the one or more second antidepressants comprised a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI) treatment, or a combination thereof.

[0010] In further aspects, the patient has anhedonia, for example, the patient has high anhedonia as measured by a total score of ≥ 32 on the Snaith Hamilton Pleasure Scale (SHAPS).

[0011] In still further aspects, the antidepressant is esketamine. In certain aspects, the method has an induction phase and, optionally, a subsequent maintenance phase, wherein the induction phase comprises induction phase treatment sessions at a given frequency, and the maintenance phase comprises maintenance phase treatment sessions administered to the patient less frequently.

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[0012] In certain aspects, the depression comprises major depressive disorder. In some aspects, the major depressive disorder is major depressive disorder with suicidal ideation or behavior. In further aspects, the major depressive disorder is treatment resistant depression.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] Fig. 1 is the trial design of Example 1.

[0014] Fig. 2 is a line graph showing the MADRS (Montgomery–Åsberg Depression Rating Scale) total score: least squares mean changes from baseline ($\pm$ SE) during the treatment period for the enriched intent-to-treat (eITT) analysis set.

[0015] Fig. 3 is a plot showing MADRS total score changes at treatment week 6 for enriched and full population: MMRM results – estimated LS means and comparison versus placebo.

[0016] Fig. 4 is a line graph showing SHAPS (Snaith-Hamilton Pleasure Scale) total score: least squares mean changes from baseline ($\pm$ SE) during the treatment period for the eITT analysis set.

[0017] Fig. 5 is a plot showing SHAPS total score changes at treatment week 6 for enriched and full population: MMRM (Mixed-effects Model for Repeated Measures) Results – estimated LSMeans and comparison versus placebo

[0018] Fig. 6 is a line graph showing MADRS total score: mean values ($\pm$ SE) over time for the eITT analysis set.

[0019] Fig. 7A is a line graph showing MADRS total score: mean values ($\pm$ SE) over time for the full intent-to-treat (fITT) analysis set. Fig. 7B is an excerpt from Fig. 7A for treatment weeks 0-6.

[0020] Fig. 8 is a line graph showing MADRS total score: percentage of subjects with remission of depressive symptoms (total score ≤ 10) during the treatment period for the eITT analysis set.

[0021] Fig. 9 is a line graph showing MADRS total score: percentage of subjects with remission of depressive symptoms (total score ≤ 10) during the treatment period for the fITT analysis set.

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[0022] Fig. 10 is a line graph showing MADRS total score: percentage of responders ($\geq 30\%$ improvement from baseline) during the treatment period for the eITT analysis set.

[0023] Fig. 11 is a line graph showing MADRS total score: percentage of responders ($\geq 30\%$ improvement from baseline) during the treatment period for the fITT analysis set.

[0024] Fig. 12 is a line graph showing MADRS total score: percentage of responders ($\geq 50\%$ improvement from baseline) during the treatment period for the eITT analysis set.

[0025] Fig. 13 is a line graph showing MADRS total score: percentage of responders ($\geq 50\%$ improvement from baseline) during the treatment period for the fITT analysis set.

[0026] Fig. 14 is a line graph showing SHAPS total score: mean values ($\pm$ SE) over time for the eITT analysis set.

[0027] Fig. 15 is a line graph showing SHAPS total score: mean values ($\pm$ SE) over time for the fITT analysis set.

[0028] Fig. 16 illustrates the MADRS change from baseline by anhedonia severity.

[0029] Fig. 17A is a line graph showing MADRS change from baseline for patients with high anhedonia, *i.e.*, SHAPS ≥ 38 . Fig. 17B is a line graph showing MADRS change from baseline for patients with low anhedonia, *i.e.*, SHAPS < 38 .

[0030] Fig. 18 is bar graph showing the comparison of MADRS in patients having low and high anhedonia.

[0031] Fig. 19 is a line graph showing the ASEX total score mean change from baseline.

[0032] Fig. 20 is a bar graph showing ASEX item level change total score mean change from baseline.

[0033] Fig. 21 is the study scheme for Example 2. All patients will continue their oral antidepressant SSRI/SNRI during the entire study. Approximately an additional 34 elderly participants will be randomized.

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[0034] Fig. 22 is the study scheme for Example 3. All patients will continue their oral antidepressant SSRI/SNRI during the entire study. Approximately an additional 68 elderly participants will be randomized.

[0035] Fig. 23 is a bar graph showing the SHAPS items: LS means for change from baseline at week 6 by baseline SHAPS total score for the fITT analysis set. In this figure and going from top to bottom, the bars alternatively refer to placebo or aticaprant. For example, the first bar refers to aticaprant, the second bar refers to placebo, the third bar refers to aticaprant, etc.

[0036] Fig. 24 is a plot showing MADRS total score: difference of LSMeans (60% at Weeks 6 by different subgroups for the fITT analysis set. In this plot, <17 indicates mild severity; 18-24 indicates mild to moderate severity, and 25-30 indicates moderate to severe.

[0037] Fig. 25 shows two-panel box plots of the effect of biomarker signatures on patient response to treatment. 3MM biomarker signature positive patients (21% of MDD) respond with 6.3 MADRS points difference at end DB relative to placebo, a 4.7 points improvement compared to biomarker signature negative counterpart.

[0038] Figs. 26A-26D are plots summarizing the outcome of patient subtyping using a biomarker signature composed only of dynorphin levels. Fig. 26A is a graph of treatment effect in the biomarker signature positive group and the signature advantage. Fig. 26B shows the signature effects at δ levels of 19.9 pg/mL (SigPos=DYN > 19.9, 64% of cohort). Fig. 26C shows the signature effects at δ levels of 30 pg/mL (SigPos=DYN > 29.5, 48% of cohort). Fig. 26D shows that at higher levels of dynorphin, the signature effect is more variable (SigPos=DYN > 48.7, 30% of cohort).

[0039] Figs. 27A-27D are plots summarizing the outcome of patient subtyping using a biomarker signature using the union of high dynorphin and 3MM subtypes. Fig. 27A is a graph of treatment effect in the biosgnature positive group and the signature advantage. One caveat is that signature advantage defined by SigPos and SigNeg is not stable a higher cutoffs. Fig. 27B shows the interaction effect is considerably more pronounced due to an average aticaprant response that is worse than that of placebo for biomarker signature negative patients (SigPos= 3MM or DYN > 19.9, 73% of cohort). Figs. 27C and 27D shows that the effects of the biomarker signature are more stable at higher dynorphin cut points. For

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Fig. 27C, SigPos= 3MM or DYN > 29.5, 61% of cohort. For Fig. 27D, SigPos= 3MM or DYN > 48.7, 48% of cohort.

[0040] Figs. 28A and Fig. 28B are plots showing the outcome of patient subtyping using a biomarker signature using the union of high dynorphin and 3MM subtypes. Fig. 28B shows large treatment effect in biomarker signature positive patients and the large signature advantage at a wide range of dynorphin levels (SigPos = (CRP > 3 & (IL6R > 25 | TNFa > 4)) & DYN > 11.5).

[0041] Fig. 29A-29C are plots summarizing the outcome of patient subtyping using a biomarker signature using a combination of high dynorphin ($\delta 1$) or 3MM with moderate dynorphin ($\delta 2$) subtypes, specifically: DYN > $\delta 1$ pg/mL or (DYN > $\delta 2$ pg/mL and CRP > 3 mg/L and (TNFa > 4 pg/mL or sIL6R > 25 ng/mL)). Fig. 29A is a graph of the difference in average response (MADRS) at EP for dynorphin levels in pg/mL. For Fig. 29B, SigPos = DYN > 24.0 or (3MM and DYN > 8), 63% of cohort. For Fig. 29C, SigPos = DYN > 50 or (3MM and DYN > 8), 38% of cohort.

[0042] FIG. 30 is the trial design for Example 1. At entry to the trial, transferred entry non-responder subjects continued to receive the same oral antidepressant initiated in the ESKETINTRD3005 study. The new oral AD is for direct entry subjects only.

[0043] FIG. 31 shows means for the MADRS total score over time in the IND and OP/MA phases based on observed case data for Example 1.

[0044] FIG. 32 shows the response for patients having a response with a $\geq 50\%$ reduction from baseline and a remission with a MADRS of ≤ 12 .

[0045] FIG. 33 shows means for the PHQ-9 total score over time in the IND and OP/MA phases based on observed case data for Example 1.

[0046] FIG. 34 shows the 3MM effect across various clinical trials. For ESKETINTRD2003, only subjects with consistent treatment across two phases of double-blind were considered. The ClinicalTrials.gov identifiers for each of the exemplified trials are as follows: 54135419SUI3001 (NCT03039192); 54135419SUI3002 (NCT03097133); ESKETINSUI2001 (NCT02133001); 54135419TRD2005 (NCT02918318); ESKETINTRD2003 (NCT01998958); ESKETINTRD3001 (NCT02417064); and ESKETINTRD3002 (NCT02418585).

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[0047] FIG. 35 shows 3MM biomarker signature positive subjects (TE Sig^{Pos}), biomarker signature negative subjects (TE Sig^{Neg}) and the difference between subtypes (signature advantage) for various clinical trials. Overall, treatment effect in 3MM+ patients at end DB was 7.8 MADRS points, significantly greater ($p < 0.01$) than treatment effect of 2.0 MADRS points in 3MM- patients. An effect was evident in 3 out of 4 TRD studies. In ESKETINTRD2003, only subjects with consistent treatment across two phases of double-blind were considered.

[0048] FIG. 36A is a graph showing the changes in MADRS for placebo (PBO) versus treatment (TRT) biomarker signature positive patients in the ESKETINTRD2003 trial. FIG. 36B is a graph showing the changes in MADRS for placebo (PBO) versus treatment (TRT) biomarker signature negative patients in the ESKETINTRD2003 trial.

[0049] FIG. 37A shows the 2MM effect across various clinical trials. FIG. 37B shows the 3MM effect across various clinical trials. High.Diff (PBO-TRT) refers to TE SigPos subjects, Other.Diff (PBO-TRT) refers to TE SigNeg subjects, and High.Diff-Other.Diff (PBO-TRT) refers to signature advantage. The ClinicalTrials.gov identifiers for each of the exemplified trials are as follows: CNT0136MDD2001 (NCT02473289); 67953964MDD2001 (NCT03559192); 42847922MDD2001 (NCT03227224); 42847922MDD2002 (NCT03321526); 54135419SUI3001 (NCT03039192); 54135419SUI3002 (NCT03097133); ESKETINSUI2001 (NCT02133001); 54135419TRD2005 (NCT02918318); ESKETINTRD2003 (NCT01998958); ESKETINTRD3001 (NCT02417064); and ESKETINTRD3002 (NCT02418585).

[0050] FIG. 38 shows the CRP effect across various clinical trials. High.Diff (PBO-TRT) refers to TE SigPos subjects, Other.Diff (PBO-TRT) refers to TE SigNeg subjects, and High.Diff-Other.Diff (PBO-TRT) refers to signature advantage. The ClinicalTrials.gov identifiers for each of the exemplified trials are as follows: CNT0136MDD2001 (NCT02473289); 67953964MDD2001 (NCT03559192); 42847922MDD2001 (NCT03227224); 42847922MDD2002 (NCT03321526); 54135419SUI3001 (NCT03039192); 54135419SUI3002 (NCT03097133); ESKETINSUI2001 (NCT02133001); 54135419TRD2005 (NCT02918318); ESKETINTRD2003 (NCT01998958); ESKETINTRD3001 (NCT02417064); and ESKETINTRD3002 (NCT02418585).

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DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0051] All individual features (*e.g.*, particular embodiments or specific preferred features) mentioned herein may be taken in isolation or in combination with any other feature (including particular embodiment or preferred feature) mentioned herein; hence, preferred features may be taken in conjunction with other preferred features, or independently of them (and likewise with particular embodiments).

[0052] The disclosure is directed to methods for the treatment of depression (*e.g.*, major depressive disorder), comprising administering to a patient in need thereof, a therapeutically effective amount of an antidepressant. For example, a patient as measured MADRS with a score of 18 or more or on the CGI scale a score of 4 or more. In some embodiments, the methods are for the treatment of treatment refractory depression or treatment resistant depression. In other embodiments, the medicament is for treating suicidal ideation. These methods advantageously permit tailoring an effective regimen to patients who have depression. Such patients include those who have already been diagnosed with MDD, TRD, are suicidal, or have otherwise been untreated for depression. For example, the methods are directed to patients with major depressive disorder with suicidal ideation or behavior.

[0053] In still further aspects, wherein the depression comprises major depressive disorder. In certain aspects, the major depressive disorder is major depressive disorder with suicidal ideation or behavior. In further aspects, the major depressive disorder is treatment resistant depression.

[0054] In one aspect of the present invention, methods are provided for treating depression in a human patient, comprising administering to the patient in need thereof an effective amount of an antidepressant, wherein the patient is identified as biomarker signature positive, and wherein the patient is identified as biomarker signature positive if a biological sample obtained from the patient is identified as having a level of at least one biomarker that is greater or less than a reference biomarker level.

Biomarker Signatures

[0055] In certain embodiments, the patient is identified as biomarker signature positive.

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[0056] In certain embodiments, the biomarker signature is an inflammatory biomarker signature (“3MM”) with positive status defined by: $CRP > 3mg/L$ and $(TNF\alpha > 4 pg/mL \text{ or } sIL6R > 25 ng/mL)$. In the disclosed methods employing the 3MM biomarker signature, the patient is identified as biomarker signature positive if the biological sample obtained from the patient is identified as having: (a) a level of CRP greater than a reference CRP level, and (b) at least one of: (i) a level of TNF-alpha that is greater than a reference TNF-alpha level, and (ii) a level of sIL6R that is greater than a reference sIL6R level. In certain embodiments, a patient identified as biomarker signature positive demonstrates an improvement in MADRS points relative to a comparative population of patients who received treatment with placebo. In certain embodiments, a patient identified as biomarker signature positive demonstrates an improvement of about 6.3 MADRS point relative to a comparative population of patients who received treatment with placebo. In certain embodiments, a patient identified as biomarker signature positive demonstrates an improvement in MADRS points relative to a comparative population of patients who were administered an antidepressant, and are not biomarker signature positive. In certain embodiments, a patient identified as biomarker signature positive demonstrates an improvement in MADRS points relative to a comparative population of patients who were administered aticaprant, or a pharmaceutically acceptable salt thereof, and are not biomarker signature positive. In certain embodiments, a patient identified as biomarker signature positive demonstrates an improvement of about 4.7 MADRS points relative to a comparative population of patients who were administered aticaprant, or a pharmaceutically acceptable salt thereof, and are not biomarker signature positive. In certain embodiments, a patient identified as biomarker signature positive demonstrates an improvement in MADRS points relative to a comparative population of patients who were administered esketamine and are not biomarker signature positive.

[0057] In certain embodiments, the biomarker signature is an inflammatory biomarker signature (“2MM”) with positive status defined by: $CRP > 3mg/L$ and $sIL6R > 25 ng/mL$. In the disclosed methods employing the 2MM biomarker signature, the patient is identified as biomarker signature positive if the biological sample obtained from the patient is identified as having a level of CRP greater than a reference CRP level, and a level of sIL6R that is greater than a reference sIL6R level. In certain embodiments, a patient identified as

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biomarker signature positive demonstrates an improvement in MADRS points relative to a comparative population of patients who received treatment with placebo. In certain embodiments, a patient identified as biomarker signature positive demonstrates an improvement in MADRS points relative to a comparative population of patients who were administered esketamine, and are not biomarker signature positive.

[0058] In certain embodiments, the biomarker signature is an inflammatory biomarker signature (“CRP”) with positive status defined by: $CRP > 3mg/L$. In the disclosed methods employing the CRP biomarker signature, the patient is identified as biomarker signature positive if the biological sample obtained from the patient is identified as having a level of CRP greater than a reference CRP level. In certain embodiments, a patient identified as biomarker signature positive demonstrates an improvement in MADRS points relative to a comparative population of patients who received treatment with placebo. In certain embodiments, a patient identified as biomarker signature positive demonstrates an improvement in MADRS points relative to a comparative population of patients who were administered esketamine, and are not biomarker signature positive.

[0059] In certain embodiments, the biomarker signature is a dynorphin (“DYN”) biomarker signature with positive status identified by: $DYN > \delta \text{ pg/mL}$. In the disclosed methods employing the dynorphin biomarker signature, the patient is identified as biomarker signature positive if the biological sample obtained from the patient is identified as having a level of dynorphin that is greater than a reference dynorphin level. In certain embodiments, a patient identified as biomarker signature positive demonstrates an improvement in MADRS points relative to a comparative population of patients who received treatment with placebo. In certain embodiments, a patient identified as biomarker signature positive demonstrates an improvement in MADRS points relative to a comparative population of patients who were administered an antidepressant, and are not biomarker signature positive. In certain embodiments, a patient identified as biomarker signature positive demonstrates an improvement in MADRS points relative to a comparative population of patients who were administered aticaprant, or a pharmaceutically acceptable salt thereof, and are not biomarker signature positive. In certain embodiments, a patient identified as biomarker signature positive does not demonstrate an improvement in MADRS points at dynorphin levels greater than about 48 pg/mL. In certain embodiments, a patient identified as biomarker signature

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positive demonstrates an improvement in MADRS points relative to a comparative population of patients who were administered esketamine and are not biomarker signature positive.

[0060] In certain embodiments, the biomarker signature is a 3MM positive or DYN positive signature. In the disclosed methods employing the 3MM or DYN biomarker signature, the patient is identified as biomarker signature positive if the biological sample obtained from the patient is identified as having: (a) a level of CRP greater than a reference CRP level, and at least one of: (i) a level of TNF-alpha that is greater than a reference TNF-alpha level, and (ii) a level of sIL6R that is greater than a reference sIL6R level; or (b) a level of dynorphin greater than a reference dynorphin level. In certain embodiments, a patient identified as biomarker signature positive demonstrates an improvement in MADRS points relative to a comparative population of patients who received treatment with placebo. In certain embodiments, a patient identified as biomarker signature positive demonstrates an improvement in MADRS points relative to a comparative population of patients who were administered an antidepressant, and are not biomarker signature positive. In certain embodiments, a patient identified as biomarker signature positive demonstrates an improvement in MADRS points relative to a comparative population of patients who were administered aticaprant, or a pharmaceutically acceptable salt thereof, and are not biomarker signature positive. In certain embodiments, a patient identified as biomarker signature positive does not demonstrate an improvement in MADRS points at dynorphin levels greater than about 48 pg/mL. In certain embodiments, a patient identified as biomarker signature positive demonstrates an improvement in MADRS points relative to a comparative population of patients who were administered esketamine and are not biomarker signature positive.

[0061] In certain embodiments, the biomarker signature is a 3MM positive and DYN positive signature. In the disclosed methods employing the 3MM and DYN biomarker signature, the patient is identified as biomarker signature positive if the biological sample obtained from the patient is identified as having: (a) a level of CRP greater than a reference CRP level, and at least one of: (i) a level of TNF-alpha that is greater than a reference TNF-alpha level, and (ii) a level of sIL6R that is greater than a reference sIL6R level; and (b) a level of dynorphin greater than a reference dynorphin level. In certain embodiments, a patient

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identified as biomarker signature positive demonstrates an improvement in MADRS points relative to a comparative population of patients who received treatment with placebo. In certain embodiments, a patient identified as biomarker signature positive demonstrates an improvement in MADRS points relative to a comparative population of patients who received are not biomarker signature positive. In certain embodiments, a patient identified as biomarker signature positive does not demonstrate an improvement in MADRS points at dynorphin levels greater than about 48 pg/mL.

[0062] In any of the disclosed embodiments, the reference dynorphin level is between about 6.2 pg/mL and about 116.2 pg/mL. In certain embodiments, the reference dynorphin level is between about 6 pg/mL and about 116 pg/mL. In certain embodiments, the reference dynorphin level is between about 11.4 pg/mL and about 116.2 pg/mL. In certain embodiments, the reference dynorphin level is between about 11 pg/mL and about 116 pg/mL. In certain embodiments, the reference dynorphin level is between about 24 pg/mL and about 116 pg/mL. In certain embodiments, the reference dynorphin level is between about 19.9 pg/mL and about 30 pg/mL. In certain embodiments, the reference dynorphin level is between about 20 pg/mL and about 30 pg/mL. In certain embodiments, the reference dynorphin level is between about 6.2 pg/mL and about 19.9 pg/mL. In certain embodiments, the reference dynorphin level is between about 6.2 pg/mL and about 30 pg/mL. In certain embodiments, the reference dynorphin level is about 11.4 pg/mL. In certain embodiments, the reference dynorphin level is about 11 pg/mL. In certain embodiments, the reference dynorphin level is about 19.9 pg/mL. In certain embodiments, the reference dynorphin level is about 20 pg/mL. In certain embodiments, the reference dynorphin level is about 24 pg/mL. In certain embodiments, the reference dynorphin level is about 30 pg/mL. In certain embodiments, the reference dynorphin level is about 50 pg/mL. In certain embodiments, the reference dynorphin level is less than about 48.7 pg/mL. In certain embodiments, the reference dynorphin level is less than about 50 pg/mL.

[0063] In certain embodiments, the biomarker signature is a 4MM positive signature. In the disclosed methods employing the 4MM biomarker signature, the patient is identified as biomarker signature positive if the biological sample obtained from the patient is identified as having: a level of dynorphin greater than a first reference dynorphin level; or both of (i) and (ii), wherein (i) is a level of CRP greater than a reference CRP level, and at

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least one of: a level of TNF-alpha that is greater than a reference TNF-alpha level and a level of sIL6R that is greater than a reference sIL6R level; and (ii) is a level of dynorphin greater than a second reference dynorphin level. In certain embodiments, a patient identified as biomarker signature positive demonstrates an improvement in MADRS points relative to a comparative population of patients who received treatment with placebo. In certain embodiments, a patient identified as biomarker signature positive demonstrates an improvement in MADRS points relative to a comparative population of patients who received are not biomarker signature positive. In certain embodiments, a patient identified as biomarker signature positive does not demonstrate an improvement in MADRS points at dynorphin levels greater than about 48 pg/mL.

[0064] In any of the disclosed embodiments, the first reference dynorphin level is between about 6.2 pg/mL and about 116.2 pg/mL. In certain embodiments, the first reference dynorphin level is between about 6 pg/mL and about 116 pg/mL. In certain embodiments, the first reference dynorphin level is between about 11.4 pg/mL and about 116.2 pg/mL. In certain embodiments, the first reference dynorphin level is between about 11 pg/mL and about 116 pg/mL. In certain embodiments, the first reference dynorphin level is between about 24 pg/mL and about 116 pg/mL. In certain embodiments, the first reference dynorphin level is between about 19.9 pg/mL and about 30 pg/mL. In certain embodiments, the first reference dynorphin level is between about 20 pg/mL and about 30 pg/mL. In certain embodiments, the first reference dynorphin level is between about 6.2 pg/mL and about 19.9 pg/mL. In certain embodiments, the first reference dynorphin level is between about 6.2 pg/mL and about 30 pg/mL. In certain embodiments, the first reference dynorphin level is about 11.4 pg/mL. In certain embodiments, the first reference dynorphin level is about 11 pg/mL. In certain embodiments, the first reference dynorphin level is about 19.9 pg/mL. In certain embodiments, the first reference dynorphin level is about 20 pg/mL. In certain embodiments, the first reference dynorphin level is about 24 pg/mL. In certain embodiments, the first reference dynorphin level is about 30 pg/mL. In certain embodiments, the first reference dynorphin level is about 50 pg/mL. In certain embodiments, the first reference dynorphin level is less than about 48.7 pg/mL. In certain embodiments, the first reference dynorphin level is less than about 50 pg/mL.

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[0065] In any of the disclosed embodiments, the second reference dynorphin level is about 8 pg/mL.

[0066] In certain embodiments, the first reference dynorphin level is about 50 pg/ml and the second reference dynorphin level is about 8 pg/ml. In further embodiments, the first reference dynorphin level is about 24 pg/ml and the second reference dynorphin level is about 8 pg/ml.

[0067] In any one of the disclosed embodiments, biomarker correlates of any of the biomarkers, e.g., a biomarker correlate of CRP, TNF-alpha, sIL6R, or dynorphin, may be used. As used herein, a “biomarker correlate” of a biomarker is another marker whose level or activity correlates with the level or activity of the biomarker. For example, if the biomarker is X, and the levels of Y correlate with the levels of X, then Y is a biomarker correlate of X.

[0068] As used herein, “CRP” refers to C-reactive protein. In certain embodiments, CRP has UniProtKB/Swiss-Prot number P02741.

[0069] As used herein, “TNF-alpha” refers to Tumor Necrosis Factor alpha. In certain embodiments, TNF-alpha has UniProtKB/Swiss-Prot number P01375.

[0070] As used herein, “IL6R” refers to Interleukin 6 Receptor. In certain embodiments, IL6R has UniProtKB/Swiss-Prot number P08887. As used herein “sIL6R” refers to the soluble form of IL6R.

[0071] As used herein, “DYN” refers to Dynorphin. In certain embodiments, CYN has UniProtKB/Swiss-Prot number P01213.

[0072] In any of the disclosed embodiments, the reference CRP level is about 3 mg/L.

[0073] In any of the disclosed embodiments, the reference TNF-alpha level is about 4 pg/mL.

[0074] In any of the disclosed embodiments, the reference sIL6R level is about 25 ng/mL.

[0075] In any of the disclosed embodiments, the reference CRP, TNF-alpha, sIL6R and/or dynorphin reference levels may be computed according to the methods disclosed in the Examples.

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Certain Terminology

[0076] Some of the quantitative expressions given herein are not qualified with the term “about”. It is understood that whether the term “about” is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including approximations due to the experimental and/or measurement conditions for such given value.

[0077] As used herein, unless otherwise noted, the terms “subject” and “patient” refer to a human, who has been the object of treatment, observation or experiment. Preferably, the patient has experienced and / or exhibited at least one symptom of the disease or disorder to be treated and / or prevented. In some embodiments, the patient is an adult. As used herein, the term “adult” as used herein refers to a human that is about 18 years of age or older. In certain aspects, the patient is an elderly adult, *i.e.*, greater than or equal to 65 years of age.

[0078] In some embodiments, the subject or patient is an adult. As used herein, the term “adult” as used herein refers to a human that is about 18 years of age to about 65 years of age.

[0079] In other embodiments, the subject or patient is geriatric or elderly. As used herein, the terms “geriatric” and “elderly” are used interchangeably to refer to a human subject of about 65 years of age or older. Elderly patients between the ages of ≥ 65 to ≤ 75 appear to be more responsive to treatment than a patient of ≥ 75 .

[0080] In further embodiments, the subject or patient is a pediatric subject. As used herein, the term “pediatric” refers to a human subject of younger than about 18 years of age.

[0081] As used herein, unless otherwise noted, the terms “treating”, “treatment” and the like, shall include the management and care of a subject or patient (preferably mammal, more preferably human) for the purpose of combating a disease, condition, or disorder and includes the administration of a compound described herein to prevent the onset of the symptoms or complications, alleviate one or more of the symptoms or complications, or eliminate the disease, condition, or disorder.

[0082] As used herein, the term “depression” (also referred to as depressive disorder) includes major depressive disorder, persistent depressive disorder, seasonal

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affective disorder, postpartum depression, premenstrual dysphoric disorder, situational depression, anhedonia, melancholic, mid-life depression, late-life depression, bipolar depression, depression due to identifiable stressors, treatment resistant depression, or combinations thereof. In certain embodiments, the depression is major depressive disorder. In other embodiments, the major depressive disorder is with melancholic features or anxious distress. In further embodiments, the depression is treatment-resistant depression. In other embodiments, the depression is major depressive disorder with suicidal ideation.

[0083] As known in the art, a patient is considered to have major depressive disorder if exhibiting five or more symptoms during the same two week period that are a change from previous functioning; depressed mood and/or loss of interest/pleasure must be present; excluding symptoms clearly attributable to another medical condition. See, *e.g.*, Table A.

Table A

1. Depressed mood: Most of the day, nearly every day; may be subjective (*e.g.*, feels sad, empty, hopeless) or observed by others (*e.g.*, appears tearful); in children and adolescents, can be irritable mood
 2. Loss of interest/pleasure: Markedly diminished interest/pleasure in all (or almost all) activities most of the day, nearly every day; may be subjective or observed by others
 3. Weight loss or gain: Significant weight loss (without dieting) or gain (change of >5% body weight in a month), or decrease or increase in appetite nearly every day; in children, may be failure to gain weight as expected
 4. Insomnia or hypersomnia: Nearly every day
 5. Psychomotor agitation or retardation: Nearly every day and observable by others (not merely subjectively restless or slow)
 6. Fatigue: Or loss of energy, nearly every day
 7. Feeling worthless or excessive/inappropriate guilt: Nearly every day; guilt may be delusional; not merely self-reproach or guilt about being sick
 8. Decreased concentration: Nearly every day; may be indecisiveness; may be subjective or observed by others
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9. Thoughts of death/suicide” Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without specific plan, or suicide attempt, or a specific plan for suicide
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[0084] In some embodiments, to be diagnosed with MDD, the following criteria also are met:

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1. Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
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2. Episode not attributable to physiological effects of a substance or another medical condition
-
3. Episode not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders
-
4. No history of manic or hypomanic episode
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[0085] Major depressive disorder may be categorized as mild, moderate, or severe. In some embodiments, the MDD is mild. In other embodiments, the MDD is moderate. In further embodiments, the MDD is severe. As used herein, “mild MDD” applies to a patient having few, if any, symptoms in excess of those required to make the diagnosis, the intensity of the symptoms is distressing but manageable, and the symptoms result in minor impairment in social or occupational functioning. The mild MDD may be a single episode (ICD-10 F32.0) or a recurrent episode (ICD-10 F33.0). “Moderate MDD” applies to a patient having a number of symptoms, intensity of symptoms, and/or functional impairment are between those specified for “mild” and “severe.” The moderate MDD may be a single episode (ICD-10 F32.1) or a recurrent episode (ICD-10 F33.1). “Severe MDD” applies to a patient where the number of symptoms is substantially in excess of that required to make the diagnosis, the intensity of symptoms is seriously distressing and unmanageable, and the symptoms markedly interfere with social and occupational functioning, and urgent symptom control is necessary. In some embodiments, the severe MDD may be a single episode (ICD-10 F32.2) or a recurrent episode (ICD-10 F33.2). In other embodiments, MDD is classified according to the DSM-5 definition of Table B.

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Table B: DSM-5 Criteria for MDD

1. Depressed Mood	At least 1
2. Loss of interest/pleasure (anhedonia)	
1. Weight loss or gain	At least 5
2. Sleep problems	
3. Psychomotor agitation or retardation	
4. Guilt or worthlessness	
5. Decreased concentration	
6. Suicidality	
7. Fatigue	
1. Symptoms cause significant distress or impairment	Must have all 4
2. Not attributable to medical condition	
3. Exclude schizophrenia disorders	
4. No hx of mania or hypomania	

[0086] Several scales are known in the art that may be utilized to diagnose or monitor patients with MDD. Examples of these scales include, without limitation, the Montgomery–Åsberg Depression Rating Scale (MADRS), Clinical Global Impression – Severity (CGI-S) scale, Symptoms of Major Depressive Disorder Scale (SMDDS), Self-Assessment of Treatment Experience (SATE) scale, and Massachusetts General Hospital (MGH) Antidepressant Treatment Response Questionnaire (ATRQ), *i.e.*, MGH-ATRQ.

[0087] In some embodiments, MADRS is utilized to diagnose and/or monitor the patient. MADRS is a 10-item rating scale that is used in antidepressant studies. It is clinician-administered and designed to be used in subjects with MDD to measure the overall severity of depressive symptoms. The MADRS scale is validated, reliable, and acceptable to regulatory health authorities as a primary scale to determine efficacy in major depression. In some embodiments, MADRS is administered using the Structured Interview Guide for the MADRS (SIGMA). The scale consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), summed for a total possible score of 60. Higher scores represent a more severe condition. The MADRS evaluates

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apparent sadness, reported sadness, inner tension, sleep appetite, concentration, lassitude, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts.

[0088] In other embodiments, CGI-S is utilized to diagnose and/or monitor the patient's depression. CGI-S is a scale that rates the severity of the subject's illness at the time of assessment, relative to the clinician's past experience with subjects who have the same diagnosis and improvement with treatment. CGI-S provides an overall clinician-determined summary measure of severity of subject's illness that considers all available information, including knowledge of subject's history, psychosocial circumstances, symptoms, behavior, and impact of symptoms on subject's ability to function. CGI-S evaluates severity of psychopathology on scale of 0 to 7. Subject is assessed on severity of mental illness at time of rating according to: 0=not assessed; 1=normal (not at all ill); 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among most extremely ill patients.

[0089] In further embodiments, SMDDS is utilized to diagnose and/or monitor the patient's depression. SMDDS is a subjective rating of the patient. The SMDDS is a 16-item PRO measure. Each item is rated by the subject according to a 5-point Likert scale. Subjects respond to each question using a rating scale between 0 ("Not at all" or "Never") to 4 ("Extremely" or "Always"). The total score ranges from 0 to 60. The SMDDS uses a 7-day recall period and verbal rating scales. Higher score indicates more severe depressive symptomatology.

[0090] In yet other embodiments, SATE is utilized to diagnose and/or monitor the patient's depression. SATE is a one to three questionnaire administered when the subject is unable to complete other evaluations, *i.e.*, away from the clinical setting such as at home. SATE is useful to evaluate improvement or deterioration of depressive symptoms of the subjects over a short period of time. For rating overall depression, subject selected one option out of Improved, not changed or got worse; for depression improvement, subject selected one option out of slightly improved, much improved, very much improved and for depression worsen subject selected slightly worse, much worse, very much worse. See, Table C.

Table C: SATE Questionnaire

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Question 1: Since starting this study medication, overall would you say your depression is:

- ☐ Improved
- ☐ Got worse
- ☐ Not changed

If the subject selects answer 1 (Improved), following question is asked:

Question 2: How much did your depression improve?

- ☐ Slightly improved
- ☐ Much improved
- ☐ Very much improved

If the subject selects answer 3 (Got worse), following question is asked:

Question 3: How much did your depression worsen?

- ☐ Slightly worse
- ☐ Much worse
- ☐ Very much worse

[0091] The MGH-ATRQ is a self-rated scale used to determine treatment resistance in patient's having MDD. This questionnaire examines the antidepressant treatment history, using specific anchor points to define the adequacy of both dose and duration of each antidepressant trial, and the degree of symptomatic improvement. The MGH-ATRQ permits determining treatment resistance in depression and is known to those skilled in the art.

[0092] As used herein, the term "non-responder" means patients that do not recover fully on an antidepressant medication (*e.g.*, 25% or less change from baseline in total MADRS score).

[0093] As used herein, the term "episode of major depressive disorder" means a continuous period (*e.g.*, about 2 weeks or more) in which a patient has symptoms of a major depressive disorder sufficient to meet criteria for major depression as specified in the Diagnostic and statistical Manual of Mental Disorders, 5th Edition: DSM 5.

[0094] As used herein, "suicide" is the "act of taking one's own life". See, <http://en.wikipedia.org/wiki/Suicide> - cite_note-7. Suicide includes attempted suicide or non-fatal suicidal behavior, which is self-injury with the desire to end one's life that does not

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result in death. Suicide attempt is a self-initiated sequence of behaviors by an individual who, at the time of initiation, expected that the set of actions would lead to his or her own death.

[0095] As used herein, “suicidal ideation” refers to thoughts about or an unusual preoccupation with suicide, or thoughts of ending one's life or not wanting to live anymore but not necessarily taking any active efforts to do so. The range of suicidal ideation varies greatly from fleeting to chronic and progresses to detailed planning, role playing, and unsuccessful attempts, which may be deliberately constructed to fail or be discovered, or may be fully intended to result in death. In some embodiments, a patient is classified as being “suicidal” when the patient has a mean baseline MADRS total score of about 38 or greater. In other embodiments, a patient is classified as being suicidal when the patient has a mean baseline BBSS score of 22 or greater. In further embodiments, a patient is classified as being suicidal when the patient has a score of 6 or greater in the SIBAT clinical global judgement of suicide risk. In yet other embodiments, the patient has one or more combinations of these scores.

[0096] As used herein, the terms “co-therapy”, “combination therapy”, “adjunctive treatment”, “adjunctive therapy”, “combined treatment”, and “co-administration” shall mean treatment of a patient in need thereof by administering esketamine in combination with one or more antidepressant(s), wherein the esketamine and the antidepressant(s) are administered by any suitable means. In some embodiments, esketamine is administered in a regimen with one to five antidepressants. In other embodiments, esketamine is administered in a regimen with one, two, three, four, or five antidepressants. In other embodiments, esketamine is administered in a regimen with one or two antidepressants. In further embodiments, the esketamine is administered in a regimen with the antidepressant currently being administered to the patient. In other embodiments, the esketamine is administered in a regimen with a different antidepressant. In yet further embodiments, the esketamine is administered in a regimen with an antidepressant not previously administered to the patient. In still other embodiments, the esketamine is administered in a regimen with an antidepressant previously administered to the patient. Where the esketamine and the antidepressant(s) are administered in separate dosage forms, the number of dosages administered per day for each compound may be the same or different and more typically different. The antidepressant may be dosed as prescribed by the attending physician and/or by its label and the esketamine is dosed as

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described herein. Typically, a patient is under concurrent treatment with both an antidepressant and esketamine, where both are administered by their prescribed dosing regimens.

[0097] As used herein, unless otherwise noted, the term “antidepressant” shall mean any pharmaceutical agent which can be used to treat depression. Suitable examples include, without limitation, a mono-amine oxidase inhibitor (MAOI), tricyclic, serotonin reuptake inhibitor, serotonin noradrenergic reuptake inhibitor, noradrenergic and specific serotonergic agent, or atypical antipsychotic. Other examples include, but are not limited to mono-amine oxidase inhibitors such as irreversible MAOI (phenelzine, tranylcypromine), reversible MAOI (moclobemide), and the like; tricyclics such as imipramine, amitriptyline, desipramine, nortriptyline, doxepin, protriptyline, trimipramine, clomipramine, amoxapine, and the like; tetracyclics such as maprotiline, and the like; non-cyclics such as nomifensine, and the like; triazolopyridines such as trazodone, and the like; serotonin reuptake inhibitors such as fluoxetine, sertraline, paroxetine, citalopram, escitalopram, fluvoxamine, and the like; serotonin receptor antagonists such as nefazadone, tianeptine and the like; serotonin noradrenergic reuptake inhibitors such as venlafaxine, milnacipran, desvenlafaxine, duloxetine, levomilnacipran and the like; noradrenergic and specific serotonergic agents such as mirtazapine, and the like; noradrenaline reuptake inhibitors such as reboxetine, edivoxetine and the like; anticholinergics *e.g.*, scopolamine; lithium; triple reuptake inhibitors; atypical antipsychotics such as bupropion, and the like; natural products such as Kava-Kava, St. John's Wort, and the like; dietary supplements such as s-adenosylmethionine, and the like; and neuropeptides such as thyrotropin-releasing hormone and the like; compounds targeting neuropeptide receptors such as neurokinin receptor antagonists and the like; and hormones such as triiodothyronine, and the like. In some embodiments, the antidepressant is imipramine, amitriptyline, desipramine, nortriptyline, doxepin, protriptyline, trimipramine, maprotiline, amoxapine, trazodone, bupropion, clomipramine, fluoxetine, duloxetine, escitalopram, citalopram, sertraline, paroxetine, fluvoxamine, nefazadone, venlafaxine, milnacipran, reboxetine, mirtazapine, phenelzine, tranylcypromine, moclobemide, Kava-Kava, St. John's Wort, s-adenosylmethionine, thyrotropin releasing hormone, a neurokinin receptor antagonist, or triiodothyronine. Preferably, the antidepressant is selected from the group consisting of fluoxetine, imipramine, bupropion, venlafaxine and sertraline.

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Preferably, esketamine is administered in combination with one or more compounds selected from the group consisting of mono-amine oxidase inhibitors, tricyclics, serotonin reuptake inhibitors, serotonin noradrenergic reuptake inhibitors, noradrenergic and specific serotonergic agents, atypical antipsychotics, and/or adjunctive therapy with antipsychotic medication (*e.g.*, risperidone, olanzapine, quetiapine, aripiprazole and ziprasidone). More preferably, esketamine is administered in combination with one or more compounds selected from the group consisting of mono-amino oxidase inhibitors, tricyclics, serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors. More preferably, esketamine is administered in combination with one or more compounds selected from the group consisting of serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors. In other embodiments, the antidepressant is phenelzine, tranylcypromine, moclobemide, imipramine, amitriptyline, desipramine, nortriptyline, doxepin, protriptyline, trimipramine, clomipramine, amoxapine, fluoxetine, sertraline, paroxetine, citalopram, fluvoxamine, venlafaxine, milnacipran, mirtazapine, bupropion, thyrotropin-releasing hormone and triiodothyronine. In further embodiments, the antidepressant is lithium, riluzole, phenelzine, tranylcypromine, moclobemide, imipramine, amitriptyline, desipramine, nortriptyline, doxepin, protriptyline, trimipramine, clomipramine, amoxapine, fluoxetine, sertraline, paroxetine, citalopram, fluvoxamine, venlafaxine, milnacipran, levomilnacipran, mirtazapine and bupropion. More preferably, esketamine is administered in combination with one or more compounds selected from the group consisting of phenelzine, tranylcypromine, moclobemide, imipramine, amitriptyline, desipramine, nortriptyline, doxepin, protriptyline, trimipramine, clomipramine, amoxapine, fluoxetine, sertraline, paroxetine, citalopram and fluvoxamine. More preferably, esketamine is administered in combination with one or more compounds selected from the group consisting of fluoxetine, sertraline, paroxetine, citalopram, escitalopram and fluvoxamine.

[0098] Therapeutically effective amounts/dosage levels and dosage regimens for antidepressants (*e.g.*, mono-amine oxidase inhibitors, tricyclics, serotonin reuptake inhibitors, serotonin noradrenergic reuptake inhibitors, noradrenergic and specific serotonergic agents, noradrenaline reuptake inhibitor, natural products, dietary supplements, neuropeptides, compounds targeting neuropeptide receptors, hormones and other pharmaceutical agents disclosed herein), may be readily determined by one of ordinary skill in the art. For example,

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therapeutic dosage amounts and regimens for pharmaceutical agents approved for sale are publicly available, *e.g.*, as listed on packaging labels, in standard dosage guidelines, in standard dosage references such as the Physician's Desk Reference (Medical Economics Company or online at <http://www.pdrel.com>) or other sources.

[0099] As used herein the term “antipsychotic” includes, but is not limited to:

[00100] (a) typical or traditional antipsychotics, such as phenothiazines (*e.g.*, chlorpromazine, thioridazine, fluphenazine, perphenazine, trifluoperazine, levomepromazine), thioxanthenes (*e.g.*, thiothixene, flupentixol), butyrophenones (*e.g.*, haloperidol), dibenzoxazepines (*e.g.*, loxapine), dihydroindolones (*e.g.*, molindone), substituted benzamides (*e.g.*, sulpiride, amisulpride), and the like; and

[00101] (b) atypical antipsychotics and mood stabilizers, such as paliperidone, clozapine, risperidone, olanzapine, quetiapine, zotepine, ziprasidone, iloperidone, perospirone, blonanserin, sertindole, ORG-5222 (Organon), and the like; and others such as sonepiprazole, aripiprazole, nemonapride, SR-31742 (Sanofi), CX-516 (Cortex), SC-111 (Scotia), NE-100 (Taisho), divalproate (mood stabilizer) and the like.

[00102] In an embodiment, the “atypical antipsychotic” is selected from the group consisting of aripiprazole, quetiapine, olanzapine, risperidone and paliperidone. In another embodiment, the atypical antipsychotic is selected from the group consisting of aripiprazole, quetiapine, olanzapine, brexpiprazole, lurasidone, and risperidone; preferably, the atypical antipsychotic is selected from the group consisting of aripiprazole, quetiapine and olanzapine.

[00103] As used herein, the term “treatment-refractory or treatment-resistant depression” and the abbreviation “TRD” shall be defined as major depressive disorder in a patient that does not respond adequately to at least two different antidepressants, preferably between two and five antidepressants, in the current depressive episode. In other embodiments, TRD is defined as major depressive disorder in a patient that has not responded to at least two oral antidepressants of adequate dose and duration in the current depressive episode.

[00104] In other embodiments, the methods for treatment of depression may be combined with adjunctive therapies such as anti-psychotic therapy, electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), or combinations thereof.

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[00105] One skilled in the art will recognize that the failure to respond to an adequate course of a given antidepressant may be determined retrospectively or prospectively. In an embodiment, at least one of the failures to respond to an adequate course of antidepressant is determined prospectively. In another embodiment, at least two of the failures to respond to an adequate course of antidepressant are determined prospectively. In another embodiment, at least one of the failures to respond to an adequate course of antidepressant is determined retrospectively. In another embodiment, at least two of the failures to respond to an adequate course of antidepressant are determined retrospectively in a current depressive episode.

[00106] The “at least two oral antidepressants” or “at least two different oral depressants” has been administered to the patient at an adequate dose which may be determined by the attending physician. Similarly, the antidepressant has been administered for a suitable duration, as determined by the attending physician.

[00107] The term “therapeutically effective amount” as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated. In some embodiments, the antidepressant is utilized in a therapeutically effective amount as determined by the attending physician. In other embodiments, esketamine is utilized in a therapeutically effective amount. In other embodiments, aticaprant or a pharmaceutically acceptable salt thereof is utilized in a therapeutically effective amount.

[00108] As used herein, the term “composition” is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

[00109] As used herein, “stable remission” refers to a patient having a MADRS total score of 12 or less for at least 3 of the last 4 weeks following the patient having achieved a substantially complete response to the esketamine during an induction phase. In certain exemplified embodiments herein, patients in “stable remission” include those having one excursion of a MADRS total score greater than 12 or one missing a MADRS assessment at

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week 13 or 14 following an induction phase. In other embodiments, patients in “stable remission” include those having a MADRS total score at weeks 15 and 16 of 12 or less following an induction phase.

[00110] As used herein, “stable response” refers to a patient having a 50% or greater reduction in the MADRS total score from baseline (Day 1 of induction phase; pre-randomization/prior to the first intranasal dose) in each of the last 2 weeks following the patient having achieved a substantially complete response to the esketamine during the induction phase, but does not meet criteria for stable remission.

Methods and Uses Involving Aticaprant

[00111] In one aspect of the present invention, methods are provided for treating major depressive disorder (MDD) in a human patient, comprising, consisting of, or consisting essentially of administering to the patient in need thereof an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, wherein the patient: (a) has anhedonia, or (b) is identified as biomarker signature positive, wherein the patient is identified as biomarker signature positive if a biological sample obtained from the patient is identified as having a level of at least one biomarker that is greater or less than a reference biomarker level. In a further aspect of the present invention, methods are provided for treating major depressive disorder (MDD) in a human patient, comprising, consisting of, or consisting essentially of administering to the patient in need thereof an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, wherein the patient: (a) has anhedonia, or (b) is identified as biomarker signature positive, wherein the patient is identified as biomarker signature positive if a biological sample obtained from the patient is identified as having a level of at least one biomarker that is greater or less than a reference biomarker level, and wherein the patient has an inadequate response to a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI) treatment, or a combination thereof.

[00112] In a further aspect of the present invention, methods are provided for treating major depressive disorder (MDD) in a human patient, comprising, consisting of, or consisting essentially of administering to the patient in need thereof an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, wherein the patient: (a) has

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anhedonia, and (b) is identified as biomarker signature positive, wherein the patient is identified as biomarker signature positive if a biological sample obtained from the patient is identified as having a level of at least one biomarker that is greater or less than a reference biomarker level. In a further aspect of the present invention, methods are provided for treating major depressive disorder (MDD) in a human patient, comprising, consisting of, or consisting essentially of administering to the patient in need thereof an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, wherein the patient: (a) has anhedonia, and (b) is identified as biomarker signature positive, wherein the patient is identified as biomarker signature positive if a biological sample obtained from the patient is identified as having a level of at least one biomarker that is greater or less than a reference biomarker level, and wherein the patient has an inadequate response to a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI) treatment, or a combination thereof

[00113] In a further aspect of the present invention, methods are provided for treating major depressive disorder (MDD) in a human patient, comprising, consisting of, or consisting essentially of administering to the patient in need thereof an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, wherein the patient: (a) has anhedonia, or (b) is biomarker signature positive, wherein the patient is biomarker signature positive if a biological sample obtained from the patient exhibits a level of at least one biomarker that is greater or less than a reference biomarker level. In a further aspect of the present invention, methods are provided for treating major depressive disorder (MDD) in a human patient, comprising, consisting of, or consisting essentially of administering to the patient in need thereof an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, wherein the patient: (a) has anhedonia, or (b) is biomarker signature positive, wherein the patient is biomarker signature positive if a biological sample obtained from the patient exhibits a level of at least one biomarker that is greater or less than a reference biomarker level, and wherein the patient has an inadequate response to a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI) treatment, or a combination thereof.

[00114] Further described herein is aticaprant, or a pharmaceutically acceptable salt thereof, for use in the treatment of major depressive disorder (MDD) in a human patient,

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comprising, consisting of, or consisting essentially of administering to the patient in need thereof an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, wherein the patient: (a) has anhedonia, or (b) is identified as biomarker signature positive, wherein the patient is identified as biomarker signature positive if a biological sample obtained from the patient is identified as having a level of at least one biomarker that is greater or less than a reference biomarker level. Further described herein is aticaprant, or a pharmaceutically acceptable salt thereof, for use in the treatment of major depressive disorder (MDD) in a human patient, comprising, consisting of, or consisting essentially of administering to the patient in need thereof an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, wherein the patient: (a) has anhedonia, or (b) is identified as biomarker signature positive, wherein the patient is identified as biomarker signature positive if a biological sample obtained from the patient is identified as having a level of at least one biomarker that is greater or less than a reference biomarker level, and wherein the patient has an inadequate response to a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI) treatment, or a combination thereof.

[00115] In another aspect of the present invention, methods are provided for treating major depressive disorder (MDD) in a human patient, comprising administering to the patient in need thereof an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, wherein the patient is identified as biomarker signature positive, and wherein the patient is identified as biomarker signature positive if a biological sample obtained from the patient is identified as having a level of at least one biomarker that is greater or less than a reference biomarker level. In another aspect of the present invention, methods are provided for treating major depressive disorder (MDD) in a human patient, comprising administering to the patient in need thereof an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, wherein the patient is identified as biomarker signature positive, and wherein the patient is identified as biomarker signature positive if a biological sample obtained from the patient is identified as having a level of at least one biomarker that is greater or less than a reference biomarker level, and wherein the patient has an inadequate response to a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI) treatment, or a combination thereof.

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[00116] In another aspect of the present invention, methods are provided for treating major depressive disorder (MDD) in a human patient, comprising administering to the patient in need thereof an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, wherein the patient is biomarker signature positive, and wherein the patient is biomarker signature positive if a biological sample obtained from the patient exhibits a level of at least one biomarker that is greater or less than a reference biomarker level. In another aspect of the present invention, methods are provided for treating major depressive disorder (MDD) in a human patient, comprising administering to the patient in need thereof an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, wherein the patient is biomarker signature positive, and wherein the patient is biomarker signature positive if a biological sample obtained from the patient exhibits a level of at least one biomarker that is greater or less than a reference biomarker level, and wherein the patient has an inadequate response to a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI) treatment, or a combination thereof.

[00117] In a further aspect of the present invention, methods are provided for treating major depressive disorder (MDD) in a human patient, comprising, consisting of, or consisting essentially of evaluating a biological sample obtained from the patient for the presence of a level of at least one biomarker that is greater or less than a reference biomarker level, and administering to the patient an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof. In a further aspect of the present invention, methods are provided for treating major depressive disorder (MDD) in a human patient, comprising, consisting of, or consisting essentially of evaluating a biological sample obtained from the patient for the presence of a level of at least one biomarker that is greater or less than a reference biomarker level, and administering to the patient an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, wherein the patient has an inadequate response to a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI) treatment, or a combination thereof.

[00118] Further described herein is aticaprant, or a pharmaceutically acceptable salt thereof, for use in the treatment of major depressive disorder (MDD) in a human patient, comprising administering to the patient in need thereof an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, wherein the patient is identified as biomarker

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signature positive, and wherein the patient is identified as biomarker signature positive if a biological sample obtained from the patient is identified as having a level of at least one biomarker that is greater or less than a reference biomarker level. Further described herein is aticaprant, or a pharmaceutically acceptable salt thereof, for use in the treatment of major depressive disorder (MDD) in a human patient, comprising administering to the patient in need thereof an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, wherein the patient is identified as biomarker signature positive, and wherein the patient is identified as biomarker signature positive if a biological sample obtained from the patient is identified as having a level of at least one biomarker that is greater or less than a reference biomarker level, and wherein the patient has an inadequate response to a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI) treatment, or a combination thereof.

[00119] In embodiments of any of the foregoing methods of treatment, the patient had an inadequate response to other antidepressant therapy prior to treatment with aticaprant or a pharmaceutically acceptable salt thereof. In certain embodiments, the other antidepressant therapy comprised one or more antidepressants. In certain embodiments, the one or more antidepressants comprised a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI) treatment, or a combination thereof. In certain embodiments, the one or more antidepressants comprised a selective serotonin reuptake inhibitor (SSRI). In certain embodiments, the one or more antidepressants comprised a a serotonin-norepinephrine reuptake inhibitor (SNRI) treatment. In certain embodiments, the one or more antidepressants comprised a selective serotonin reuptake inhibitor (SSRI) and a a serotonin-norepinephrine reuptake inhibitor (SNRI) treatment.

[00120] In certain embodiments, described herein are methods of identifying a patient as a candidate for treatment with aticaprant or a pharmaceutically acceptable salt thereof if the subject is biomarker signature positive, and wherein the patient is identified as biomarker signature positive if a biological sample obtained from the patient is identified as having a level of at least one biomarker that is greater or less than a reference biomarker level. In certain embodiments, said method further comprises administering to said patient an effective amount of aticaprant or a pharmaceutically acceptable salt thereof.

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[00121] For each the methods of treatment described herein, it will be understood that the methods of treatment may also be framed as methods of manufacturing a medicament for the treatment of the described indications or as aticaprant for use in the treatment of the described indications.

[00122] Because MDD alone is difficult to treat, treatment patients having anhedonia are even more problematic since their ability to gauge pleasure is impaired. Thus, such patients often receive inadequate treatment due to ineffective medications, repeated and unnecessary medical appointments, lack of patient compliance, overall patient frustration, among others. Further, antidepressants are known to have a variety of side effects such as weight gain, metabolic side effects, extrapyramidal symptoms, akathisia, cognitive impairment, among others. Thus, patients may choose to refrain from or stop taking antidepressants to avoid or prevent any side-effects.

[00123] The methods described herein are effective in managing the patient's depression and anhedonia using aticaprant. Desirably, the methods successfully permit the patient to manage their depression while simultaneously reducing anhedonia. In particular embodiments, the patients treated according to the described methods have high anhedonia as measured by a total score of ≥ 32 on the Snaith Hamilton Pleasure Scale (SHAPS). The term "anhedonia" as used herein refers to the lack of or decreased ability to experience pleasure in daily activities. The term anhedonia includes loss of pleasure in sensory experiences (*i.e.*, touch, taste, smell), as well as social interactions. In some embodiments, anhedonia and depressed mood are diagnostic criteria for a major depressive episode as part of MDD. Anhedonia also describes deficits in one or more components of reward-related behavior, also known as the pleasure cycle, such as wanting, liking, and learning. The pleasure cycle can be divided into three phases: the appetitive phase (dominated by wanting), the consummatory phase (dominated by liking), and the satiety phase (dominated by learning). The appetitive phase is characterized by the initial energy expenditure to attain a reward; the consummatory phase is enjoyment of the reward; and the satiety phase is characterized by learning and feedback integration.

[00124] To assess a potential effect on anhedonia, an anhedonia scale may be used. For example, the Snaith-Hamilton Pleasure Scale (SHAPS) analysis is a validated scale for the measurement of anhedonia. The SHAPS is a subject completed scale in which subjects

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score whether or not they experience pleasure in performing a list of activities or experiences. The SHAPS is a self-reported 14-item instrument, developed for the assessment of hedonic capacity. Subjects score whether they experience pleasure in performing a list of activities or experiences. Subjects can rate the answers as 1-4 where 1 indicates “Definitely agree”, 2 indicates “Agree”, 3 indicates “Disagree” and 4 indicates “Definitely disagree”. The subject's item responses are summed to provide a total score ranging from 14 to 56. A higher total SHAPS score indicates higher levels of current anhedonia. Physician/clinical judgment can be used to assess anhedonia separately or in conjunction with an anhedonia scale.

[00125] In some embodiments, the patient has anhedonia. In some embodiments, the patient has moderate anhedonia. In other embodiments, the patient has severe anhedonia. An assessment of moderate or severe anhedonia is typically determined physician/clinical judgment and/or by one or more tests that provide insight into whether a patient has anhedonia. For example, the severity of the anhedonia may be determined using the SHAPS method. In some embodiments, a patient with moderate or severe anhedonia is considered to have a high level of anhedonia. For example, a patient with a SHAPS score of 38 or greater is considered to have moderate to severe anhedonia that can be considered a high level of anhedonia. In some embodiments, a high level of anhedonia is reflected by a SHAPS score of at least about 40, about 42, about 44, about 46, about 48, about 50, about 52, about 54, about 56, about 58, or higher. A patient with mild or no anhedonia would be considered to have a low level of anhedonia that is assessed by physician/clinical judgment and/or one or more tests. For example, a patient with a SHAPS score of less than 38 is considered to have low anhedonia. In certain embodiments, a patient with mild anhedonia may have a SHAPS score of 20 to less than 38, for example, a SHAPS score of 20 to about 36, about 22 to about 36, about 24 to about 36, about 26 to about 36, about 26 to about 34, about 26 to about 32, about 26 to about 30, about 26 to about 28, about 28 to about 36, about 28 to about 36, about 30, to about 36, about 32 to about 36, about 34 to about 36, about 20 to about 34, about 22 to about 34, about 24 to about 34, about 26 to about 32, about 26 to about 30, about 26 to about 28, about 28 to about 36, about 28 to about 34, about 28 to about 32, about 28 to about 30, about 30 to about 36, about 30 to about 34, about 30 to about 32, about 32 to about 36, about 32 to about 34, or about 34 to about 36. Typically, a SHAPS score of less than 20 can be

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considered to correspond to normal hedonic functioning, and for purposes of this disclosure, would fall into the low category of anhedonia, *e.g.*, a SHAPS score of less than 38.

[00126] In some embodiments, the patient's anhedonia is reduced from a high level of anhedonia to a low level of anhedonia. In yet other embodiments, the patient's anhedonia is reduced by at least about 40%, as measured by the change from baseline in total score in an anhedonia scale following treatment with aticaprant. In yet other embodiments, the patient's anhedonia is reduced by at least about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or about 95%, as measured by the change from baseline in total score in an anhedonia scale following treatment with aticaprant. In still further embodiments, In yet other embodiments, the patient's anhedonia is reduced by about 40 to about 90%, about 50 to about 90%, about 60 to about 90%, about 70 to about 90%, about 80 to about 90%, about 40 to about 80%, about 50 to about 80%, about 60 to about 80%, about 70 to about 80%, about 40 to about 70%, about 50 to about 70%, about 60 to about 70%, about 40 to about 60%, about 50 to about 60%, or about 50 to about 60%, as measured by the change from baseline in total score in an anhedonia scale following treatment with aticaprant. In other embodiments, the patient's anhedonia is ameliorated, *i.e.*, reduced by 100%, as measured by the change from baseline in total score in an anhedonia scale following treatment with aticaprant.

[00127] Reduction of anhedonia after initiating treatment with aticaprant may be measured relative to the anhedonia of the patient as measured before treatment with aticaprant, *i.e.*, a baseline anhedonia measurement. In doing so, the treating clinician is able to calculate the change of anhedonia from the baseline to the real time anhedonia measurement at any point after treatment with aticaprant. Thus, standard methods for measuring anhedonia may be used, such as an anhedonia scale, *e.g.*, SHAPS.

[00128] Desirably, a baseline anhedonia measurement is obtained no more than about 1 week before initiating treatment with aticaprant. In some embodiments, a baseline anhedonia measurement is obtained about 7 days, about 6 days, about 5 days, about 4 days, about 3 days, about 2 days, or about 1 day before treatment with aticaprant. In further embodiments, a baseline anhedonia measurement is obtained about 24 hours, about 18 hours, about 12 hours, about 8 hours, about 4 hours, about 2 hours, about 1 hours, about 30 minutes, or about 15 minutes before initiating treatment with aticaprant.

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[00129] The patient's change of anhedonia will depend on several factors including, without limitation, anhedonia severity, patient's sensitivity to aticaprant, other pharmaceutical agents being administered, among others. In some embodiments, the patient's anhedonia is reduced after about 3 weeks of aticaprant treatment. In other embodiments, the patient's anhedonia is reduced after about 3 weeks of aticaprant treatment. In further embodiments, the patient's anhedonia is reduced after about 3 weeks to about 6 weeks, and, in certain embodiments, through week 6, of aticaprant treatment. In certain embodiments, the patient's anhedonia is reduced by at least about 40%, as measured by the change from baseline in total score in an anhedonia scale following about 6 weeks of the treatment with aticaprant. In further embodiments, the anhedonia of the patient is reduced within about 3 weeks, and in some embodiments within about 3 weeks to about 6 weeks, as measured by the change from baseline in total score in an anhedonia scale and/or by physician/clinical judgement.

[00130] The methods described herein were found to not only improve the patient's depression and anhedonia symptoms, but resulted in fewer antidepressant side effects. Doing so resulted in less absenteeism (*i.e.*, more visits or interactions with physicians), greater cognitive functioning, improvements in health-related quality of life, more interest and engagement in everyday activities, improvement in family and inter-personal relationships, ability to function in the workplace, fewer hospitalizations, among others.

[00131] In certain embodiments, the patient had an inadequate response to other antidepressant therapy (*i.e.*, antidepressant medication or treatment used to treat depression other than aticaprant). "Inadequate response" as used herein refers to a patient experiencing a less than about 50% reduction in depressive symptom severity from the start of initiating treatment. Typically, the inadequate response is during a current/active episode of the depression. In some embodiments, an inadequate response refers to a patient experiencing about 26 to less than about 50% reduction in depressive symptom severity from the start of initiating treatment. In other embodiments, an inadequate response refers to a patient experiencing about 26 to about 49, about 26 to about 45, about 26 to about 40, about 26 to about 35, about 26 to about 30, about 30 to about 49, about 30 to about 45, about 30 to about 40, about 30 to about 35, about 35 to about 49, about 35 to about 45, about 35 to about 40, about 40 to about 49, or about 40 to about 45% reduction in depressive symptom severity

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from the start of initiating treatment. A patient's response may be measured by one or more scales described herein and/or by physician/clinical judgment. In some embodiments, an inadequate response is measured by MGH-ATRQ, MADRS, or SHAPS. In further embodiments, an inadequate response is measured by MGH-ATRQ.

[00132] To the extent a patient is said to have a partial response to treatment, this refers to some minor to moderate symptomatic improvement since the initiation of treatment, but some of the initial symptoms are still present and troubling to the patient and these persistent symptoms still affect behavior and function. For instance, the patient's motivation, productivity, and interest in his or her usual activities may still be impaired.

[00133] Antidepressant therapy refers to any pharmaceutical agent which can be used to treat depression. Suitable examples include, without limitation, mono-amine oxidase inhibitors, tricyclics, tetracyclics, non-cyclics, triazolopyridines, selective serotonin reuptake inhibitors (SSRI), serotonin receptor antagonists, serotonin noradrenergic reuptake inhibitors (SNRI), noradrenergic and specific serotonergic agents, noradrenaline reuptake inhibitors, or antipsychotics (typical or atypical antipsychotics). Examples of mono-amine oxidase inhibitors include phenelzine, tranylcypromine, moclobemide, and the like. Examples of tricyclics include imipramine, amitriptyline, desipramine, nortriptyline, doxepin, protriptyline, trimipramine, clomipramine, amoxapine, and the like. Examples of tetracyclics include maprotiline, and the like. Examples of non-cyclics include nomifensine, and the like. Examples of triazolopyridines include trazodone, and the like. Examples of SSRIs include fluoxetine, sertraline, paroxetine, citalopram, escitalopram, fluvoxamine, and the like. Examples of serotonin receptor antagonists include nefazadone, and the like. Examples of SNRIs include venlafaxine, milnacipran, desvenlafaxine, duloxetine, levomilnacipran and the like. Examples of noradrenergic and specific serotonergic agents include mirtazapine, and the like. Examples of noradrenaline reuptake inhibitors include reboxetine, edivoxetine and the like. Examples of typical antipsychotics include phenothiazines (*e.g.*, chlorpromazine, thioridazine, fluphenazine, perphenazine, trifluoperazine, levomepromazine), thioxanthenes (*e.g.*, thiothixene, flupentixol), butyrophenones (*e.g.*, haloperidol), dibenzoxazepines (*e.g.*, loxapine), dihydroindolones (*e.g.*, molindone), substituted benzamides (*e.g.*, sulpride, amisulpride), and the like. Examples of atypical antipsychotics include paliperidone, clozapine, risperidone, olanzapine, quetiapine,

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zotepine, ziprasidone, iloperidone, perospirone, blonanserin, sertindole, ORG-5222, sonopiprazole, aripiprazole, nemonapride, SR-31742, CX-516, SC-111, NE-100, divalproate (mood stabilizer) and the like. In further embodiments, the antidepressant therapy includes natural products such as Kava-Kava, St. John's Wort, and the like or dietary supplements such as s-adenosylmethionine, and the like. In yet other embodiments, the antidepressant therapy includes neuropeptides such as thyrotropin-releasing hormone and the like or compounds targeting neuropeptide receptors such as neurokinin receptor antagonists and the like. In still further embodiments, the antidepressant therapy is a hormone such as triiodothyronine, and the like. In other embodiments, the antidepressant therapy is SSRI, SNRI, or a combination thereof. Preferably, the antidepressant is a SSRI that is escitalopram, sertraline, paroxetine, fluoxetine or citalopram. In other embodiments, the antidepressant is a SNRI that is venlafaxine, duloxetine, vortioxetine or desvenlafaxine. There are also non-pharmacologic treatments, such as psychotherapy and transcranial magnetic stimulation, that are also available and options for adjunctive therapy.

[00134] Therapeutically effective amounts/dosage levels and dosage regimens for the other antidepressant therapy may be readily determined by one of ordinary skill in the art. For example, therapeutic dosage amounts and regimens for pharmaceutical agents approved for sale are publicly available, for example as listed on packaging labels, in standard dosage guidelines, in standard dosage references such as the Physician's Desk Reference (Medical Economics Company or online at <http://www.pdrel.com>) or other sources.

[00135] In some embodiments, other antidepressant therapy may include one antidepressant medication. In other embodiments, other antidepressant therapy includes two or more antidepressant medications. In further embodiments, other antidepressant therapy includes two antidepressant medications. In yet other embodiments, other antidepressant therapy includes three antidepressant medications. The attending physician would be able to select suitable antidepressant therapies for use as described herein.

[00136] In certain embodiments, the patient was receiving treatment with other antidepressant therapy prior to receiving aticaprant. In some embodiments, the patient was receiving treatment with other antidepressant therapy that comprised a SSRI, SNRI, or a combination thereof. In other embodiments, the patient stopped treatment with other antidepressant therapy before initiating treatment with aticaprant.

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[00137] Also encompassed by the methods described herein include adjunctive treatment with an effective amount of one or more antidepressants. As used herein, the term “adjunctive treatment” and “adjunctive therapy” shall mean treatment of a patient in need thereof by administering aticaprant in combination with one or more antidepressant(s), wherein aticaprant and the antidepressant(s) are administered by any suitable means, simultaneously, sequentially, separately, or in a single pharmaceutical formulation.

[00138] In some aspects, aticaprant is administered adjunctively with other antidepressant(s) currently being administered to the patient, including current antidepressant(s) to which the patient had an inadequate response. In other embodiments, aticaprant is administered adjunctively with an antidepressant(s) not previously administered to the patient. In still other embodiments, aticaprant is administered in a regimen with an antidepressant(s) previously administered to the patient.

[00139] Where aticaprant and other antidepressant(s) are administered in separate dosage forms, the number of dosages administered per day for each active compound may be the same or different and more typically different. The antidepressant may be dosed as prescribed by the attending physician and/or by its label and aticaprant is dosed as described herein. Typically, a patient is under concurrent treatment with both an antidepressant and aticaprant, where both are administered by their prescribed dosing regimens. The aticaprant and antidepressant(s) may be administered according to simultaneous or alternating regimens, at the same or different times during the course of the therapy, concurrently in divided or single forms.

[00140] Aticaprant and the antidepressant(s) may be administered via the same or different routes of administration. Examples of suitable methods of administration include, but are not limited to, oral, intravenous (iv), intranasal (in) intramuscular (im), subcutaneous (sc), transdermal, buccal, or rectal. In some embodiments, aticaprant is administered orally.

[00141] Treatment with aticaprant as described herein has several advantages over the treatments in the art. In some embodiments, the patient does not experience many of the side effects that are associated with other antidepressants, *i.e.*, antidepressants other than aticaprant. In certain aspects, the patient does not experience weight gain during the treatment with aticaprant. As used herein, the term “weight gain” refers to an increase in the weight of patient, relative to the weight of the patient before taking aticaprant or the weight

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of the patient that is assessed at the time of the initial administration of the aticaprant. In certain embodiments, the patient may actually see a decrease in overall weight, relative to the weight of the patient before taking aticaprant. In further embodiments, the patient's weight is stable, *i.e.*, does not increase or decrease. In certain embodiments, the patient does not experience a clinically relevant weight gain which is characterized as a weight increase of $\geq 7\%$.

[00142] This is contrary to many other antidepressants where weight gain, including clinically relevant weight gain, is a common, but unfortunate, side-effect.

[00143] In certain embodiments, the administration of the aticaprant achieves a maximum plasma concentration ($C_{\max}$) of aticaprant of about 20 to about 45 ng/mL. In further embodiments, the administration of the aticaprant achieves a maximum plasma concentration ($C_{\max}$) of aticaprant of about 25 to about 35 ng/mL. In still further embodiments, the administration of the aticaprant achieves a maximum plasma concentration ($C_{\max}$) of aticaprant of about 30 to about 35 ng/mL.

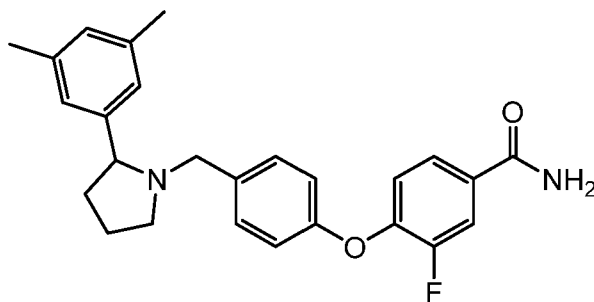
[00144] In further aspects, the patient does not experience a decrease in sexual functioning during the treatment with aticaprant. As used herein, the term "decrease in sexual functioning" refers to reducing or lessening of one or more components of the human sex drive, *i.e.*, sexual functioning. In some embodiments, the sexual functioning comprises one or more of sexual drive, sexual arousal, vaginal lubrication, erection, orgasm achievement, or orgasm satisfaction. In other embodiments, the sexual functioning comprises sexual drive. In further embodiments, the sexual functioning comprises vaginal lubrication satisfaction. In further embodiments, the sexual functioning comprises orgasm achievement. In yet other embodiments, the sexual functioning comprises orgasm satisfaction. Desirably, the patient's sexual functioning is assessed at the time of initial administration of the aticaprant. Thus, the patient's sexual functioning while taking aticaprant can be compared to the patient's sexual functioning before administration of aticaprant. Sexual functioning may be assessed by using standard scales and techniques such as the Arizona Sexual Experience Scale (ASEX). The ASEX is used to investigate whether aticaprant has a further positive or negative effect on sexual function. The ASEX is 5 item rating scale administered to patients that quantifies sexual drive, sexual arousal, vaginal lubrication or penile erection, ability to reach orgasm

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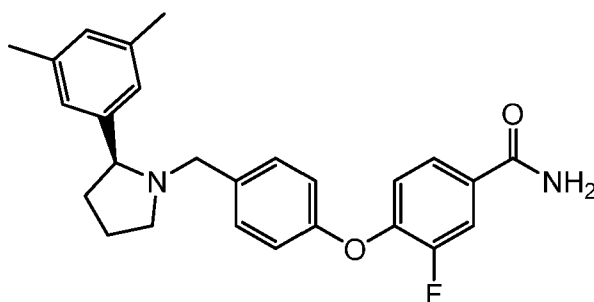
and satisfaction. Scores range from 5 to 30, and two different versions of the scale are available (males and females).

[00145] Other scales may be utilized to determine the effectiveness of the methods used herein to treat the patient. Examples include the Cognitive and Physical Functioning Questionnaire (CPFQ), Karolinska Sleepiness Scale (KSS), and Temporal Experience of Pleasure Scale (TEPS). The CPFQ is a brief self-report scale that provides additional information regarding the impact of adjunctive treatment on aspects of cognitive and executive function including attention, memory and mental acuity. Subjects with MDD are often reported to have difficulties with functioning in this area. The KSS is a subject-reported assessment used to rate sleepiness on a scale of 1 to 9, ranging from “extremely alert” (1) to “very sleepy, great effort to keep awake, fighting sleep” (9). The TEPS includes 18 items, 2 subscales designed to distinguish between anticipatory and consummatory pleasure.

[00146] As used herein, unless otherwise noted, the term “aticaprant” refers to 3-fluoro-4-4-2-(3,5-dimethylphenyl)pyrrolidin-1-yl-methylphenoxybenzamide, *i.e.*, the following compound:

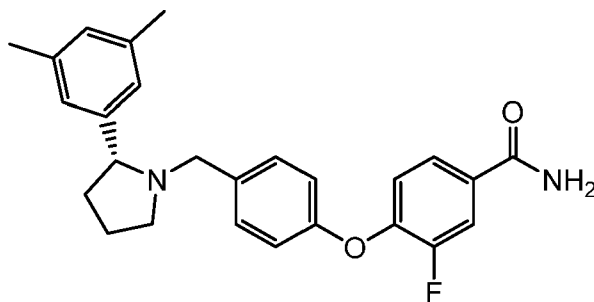


and is also known as JNJ-67953964, CERC-501, and LY-2456302. In some embodiments, “aticaprant” refers to the (S)-enantiomer of aticaprant, *i.e.*, the following compound:



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also known as (S)-aticaprant or (S)-3-fluoro-4-4'-2-(3,5-dimethylphenyl)pyrrolidin-1-yl-methylphenoxybenzamide. In other embodiments, the aticaprant used in the methods described herein is substantially free of the (R)-enantiomer, *i.e.*, (R)-aticaprant or (R)-3-fluoro-4-4'-2-(3,5-dimethylphenyl)pyrrolidin-1-yl-methylphenoxybenzamide having the following structure:



[00147] In other embodiments, the aticaprant contains less than about 10% by weight, based on the weight of the aticaprant, of the (R)-enantiomer of aticaprant. In further embodiments, the aticaprant contains less than about 10, about 9, about 8, about 7, about 6, about 5, about 4, about 3, about 2, about 1, about 0.5, about 0.1, about 0.005, or about 0.001% by weight, based on the weight of the aticaprant, of the (R)-enantiomer of aticaprant. In yet other embodiments, the aticaprant contains about 0.001 to about 10% by weight, based on the weight of the aticaprant, of the (R)-enantiomer of aticaprant. In still further embodiments, the aticaprant contains about 0.001 to about 10%, about 0.001 to about 5%, about 0.001 to about 1, about 0.001 to about 0.5, about 0.001 to about 0.1, about 0.1 to about 5, about 0.1 to about 1, about 0.1 to about 5, or about 0.5 to about 5% by weight, based on the weight of the aticaprant, of the (R)-enantiomer of aticaprant.

[00148] Pharmaceutically acceptable salts of aticaprant are also contemplated by the present invention, which may be readily selected by those skilled in the art. A “pharmaceutically acceptable salt” refers a salt of aticaprant that is non-toxic, biologically tolerable, or otherwise biologically suitable for administration to the subject. See, generally, G.S. Paulekuhn, “Trends in Active Pharmaceutical Ingredient Salt Selection based on Analysis of the Orange Book Database”, *J. Med. Chem.*, 2007, 50:6665-72, S.M. Berge, “Pharmaceutical Salts”, *J. Pharm. Sci.*, 1977, 66:1-19, and *Handbook of Pharmaceutical Salts, Properties, Selection, and Use*, Stahl and Wermuth, Eds., Wiley-VCH and VHCA,

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Zurich, 2002. Examples of pharmaceutically acceptable salts are those that are pharmacologically effective and suitable for administration to patients without undue toxicity, irritation, or allergic response.

[00149] Examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, bromides (such as hydrobromides), iodides (such as hydroiodides), acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrate, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ -hydroxybutyrates, glycolates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

[00150] The methods described herein include administering an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof to the patient. The term “effective amount” as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a human that is being sought by a researcher, medical doctor or other clinician, which includes alleviation of one or more of the symptoms of the disease or disorder being treated. In some embodiments, aticaprant is utilized in an effective amount as determined by the attending physician. In other embodiments, other antidepressant(s) is utilized in an effective amount either separately or in combination with aticaprant.

[00151] The amount of aticaprant for administration according to the methods described herein may be determined by one skill in the art and, unless otherwise noted, are set forth on an aticaprant free base basis. That is, the amounts indicate that amount of the aticaprant molecule administered, exclusive of, for example, solvent (such as in solvates) or counterions (such as in pharmaceutically acceptable salts). In some embodiments, the effective amount of aticaprant is less than about 60 mg. In other embodiments, the effective amount of aticaprant is about 0.5 mg, about 1 mg, about 2 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, or about 60 mg. In further embodiments, the effective amount

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of aticaprant is about 1 to about 50 mg, about 5 to about 50 mg, about 10 to about 50 mg, about 20 to about 50 mg, about 30 to about 50 mg, about 40 to about 50 mg, about 1 to about 45 mg, about 2 to about 45 mg, about 5 to about 45 mg, about 10 to about 45 mg, about 20 to about 45 mg, about 30 to about 45 mg, about 30 to about 40 mg, about 30 to about 35 mg, about 1 to about 40 mg, about 5 to about 40 mg, about 10 to about 40 mg, about 20 to about 40 mg, about 30 to about 40 mg, about 1 to about 35 mg, about 2 to about 35 mg, about 5 to about 35 mg, about 10 to about 35 mg, about 20 to about 35 mg, about 25 to about 35 mg, about 30 to about 35 mg, about 1 to about 30, about 2 to about 30 mg, about 5 to about 30 mg, about 10 to about 30 mg, about 20 to about 30 mg, about 25 to about 30 mg, about 1 to about 20 mg, about 2 to about 20 mg, about 5 to about 20 mg, about 10 to about 20 mg, about 15 to about 20 mg, about 1 to about 15 mg, about 2 to about 15 mg, about 5 to about 15 mg, about 10 to about 15 mg, about 1 to about 10 mg, about 2 to about 10 mg, or about 5 to about 10 mg. In yet other embodiments, the effective amount of aticaprant is about 5 to about 15 mg. In still further embodiments, the effective amount of aticaprant is about 10 mg. In still further embodiments, the effective amount of aticaprant is about 5 mg.

[00152] Advantageously, aticaprant may be administered once daily, or the total daily dosage may be administered in divided doses of two, three or four times daily.

[00153] As described herein, in particular, the patient had an inadequate response to other antidepressant therapy prior to treatment with aticaprant. Thus, in a particular embodiment, the disclosure relates to aticaprant, or a pharmaceutically acceptable salt thereof, for use as described herein, wherein the patient had an inadequate response to other antidepressant therapy prior to treatment with aticaprant. In a further particular embodiment, the disclosure also relates to the use of aticaprant, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, as described herein, wherein the patient had an inadequate response to other antidepressant therapy prior to treatment with aticaprant. In a further particular embodiment, the disclosure further relates to a package or pharmaceutical product as described herein, wherein the patient had an inadequate response to other antidepressant therapy prior to treatment with aticaprant. Such antidepressant therapy can be in particular selected from a selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), or a combination thereof.

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[00154] As described herein, aticaprant may be used as adjunctive treatment, or in other words, in conjunction, as an add-on, or in combination with one or more antidepressants, for example, the patient may be already, or also, administered one or more antidepressants. Thus, in a further particular embodiment, the disclosure relates to aticaprant, or a pharmaceutically acceptable salt thereof, for use as described herein, comprising administration of aticaprant, or a pharmaceutically acceptable salt thereof, as adjunctive treatment with an effective amount of one or more antidepressants. In a further particular embodiment, the disclosure relates to aticaprant, or a pharmaceutically acceptable salt thereof, for use as described herein, comprising administration of aticaprant, or a pharmaceutically acceptable salt thereof, in conjunction with an effective amount of one or more antidepressants. In a further particular embodiment, the disclosure relates to aticaprant, or a pharmaceutically acceptable salt thereof, for use as described herein, comprising administration of aticaprant, or a pharmaceutically acceptable salt thereof, in combination with an effective amount of one or more antidepressants. In a further particular embodiment, the disclosure also relates to the use of aticaprant, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, as described herein, wherein the treatment comprises administration of an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, as adjunctive treatment with an effective amount of one or more antidepressants. In a further particular embodiment, the disclosure also relates to the use of aticaprant, or a pharmaceutically acceptable salt thereof, as described herein, wherein the treatment comprises administration of an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, in conjunction with an effective amount of one or more antidepressants. In a further particular embodiment, the disclosure also relates to the use of aticaprant, or a pharmaceutically acceptable salt thereof, as described herein, wherein the treatment comprises administration of an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, in combination with an effective amount of one or more antidepressants. In a further particular embodiment, the disclosure further relates to a package or pharmaceutical product as described herein, wherein the instructions for treatment direct the administration of an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, as adjunctive treatment with an effective amount of one or more antidepressants. In a further particular embodiment, the disclosure further relates to a

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package or pharmaceutical product as described herein, wherein the instructions for treatment direct the administration of an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, in conjunction with an effective amount of one or more antidepressants. In a further particular embodiment, the disclosure further relates to a package or pharmaceutical as described herein, wherein the instructions for treatment direct administration of an effective amount of aticaprant, or a pharmaceutically acceptable salt thereof, in combination with an effective amount of one or more antidepressants. Such one or more antidepressants can be selected from a selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), or a combination thereof.

[00155] As already described, the disclosure relates to aticaprant, or a pharmaceutically acceptable salt thereof, for use as described herein. In a particular embodiment, aticaprant is S-aticaprant, or a pharmaceutically acceptable salt thereof. In a further embodiment of the disclosure, aticaprant, in particular S-aticaprant, or a pharmaceutically acceptable salt thereof, for use as described herein, is to be administered in an amount of about 2 to about 35 mg, more in particular, of about 10 mg, more in particular, of about 5 mg. In a yet further embodiment, aticaprant, in particular S-aticaprant, or a pharmaceutically acceptable salt thereof, for use as described herein, is administered orally. Furthermore, in a further particular embodiment, the disclosure relates to aticaprant, in particular S-aticaprant, or a pharmaceutically acceptable salt thereof, for use as described herein, administered once daily. The disclosure also relates to the use of aticaprant, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, as described herein. In a particular embodiment, aticaprant is S-aticaprant, or a pharmaceutically acceptable salt thereof. In a further embodiment of the use as described herein, about 2 to about 35 mg aticaprant is to be administered, more in particular, about 10 mg, more in particular, of about 5 mg. In a yet further embodiment of the use, aticaprant is to be administered orally. Furthermore, in a further particular embodiment of the use the aticaprant, in particular S-aticaprant, or a pharmaceutically acceptable salt thereof, is to be administered once daily. In a further particular embodiment, the disclosure further relates to a package or pharmaceutical product as described herein, wherein aticaprant is in particular S-aticaprant, or a pharmaceutically acceptable salt thereof. In a further embodiment of the package or pharmaceutical product as described herein, the instructions for treatment direct

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administration of about 2 to about 35 mg aticaprant, more in particular, about 10 mg, more in particular, of about 5 mg. In a yet further embodiment of the package or pharmaceutical product as described herein, the instructions for treatment direct aticaprant, in particular S-aticaprant, or a pharmaceutically acceptable salt thereof, is for oral administration.

Furthermore, in a further particular embodiment of the package or pharmaceutical product, as described herein, the instructions for treatment direct aticaprant, in particular S-aticaprant, or a pharmaceutically acceptable salt thereof, is for once daily administration.

[00156] Advantageously, administration of aticaprant does not result in weight gain during treatment, including clinically relevant weight gain. Thus, in a further particular embodiment, the disclosure relates to aticaprant, or a pharmaceutically acceptable salt thereof, for use as described herein, wherein the patient does not experience weight gain during the treatment with aticaprant. In a further particular embodiment, the disclosure relates to a use as defined herein, wherein the patient does not experience weight gain during the treatment with aticaprant. In a further particular embodiment, the disclosure further relates to a package or pharmaceutical product as described herein, wherein the patient does not experience weight gain during the treatment with aticaprant. The body weight of the patient can in particular be assessed at the time of the initial administration of aticaprant.

[00157] It was also unexpectedly observed that, based on assessment at the time of initial administration, the patient does not experience a decrease in sexual functioning during the treatment with aticaprant. Thus, in further particular embodiment, the disclosure relates to aticaprant, or a pharmaceutically acceptable salt thereof, for use as described herein, wherein the patient does not experience a decrease in sexual functioning during the treatment with aticaprant. In a further particular embodiment, the disclosure relates to a use as described herein, wherein the patient does not experience a decrease in sexual functioning during the treatment with aticaprant. In a further particular embodiment, the disclosure relates to a package or pharmaceutical product as described herein, wherein the patient does not experience a decrease in sexual functioning during the treatment with aticaprant. Such term “sexual functioning” comprises sexual drive, sexual arousal, vaginal lubrication, erection, orgasm achievement, or orgasm satisfaction. Sexual satisfaction can be assessed by methods known to the skilled person, for example, by applying the Arizona Sexual Experience Scale (ASEX).

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[00158] As already described, the patient has moderate or severe anhedonia. Anhedonia can be measured, through an anhedonia scale, for example, the Snaith Hamilton Pleasure Scale (SHAPS). Thus, in a particular embodiment, the disclosure relates to aticaprant, or a pharmaceutically acceptable salt thereof, for use as described herein, wherein the anhedonia of the patient is reduced by at least 40%, as measured by the change from baseline in total score in an anhedonia scale following 6 weeks of the treatment with aticaprant, more in particular, the anhedonia of the patient is reduced within about 3 weeks to about 6 weeks as measured by the change from baseline in total score in an anhedonia scale. In a further particular embodiment, the anhedonia scale is the Snaith Hamilton Pleasure Scale (SHAPS). Thus, in a particular embodiment, the disclosure relates to the use as described herein, wherein the anhedonia of the patient is reduced by at least 40%, as measured by the change from baseline in total score in an anhedonia scale following 6 weeks of the treatment with aticaprant, more in particular, the anhedonia of the patient is reduced within about 3 weeks to about 6 weeks as measured by the change from baseline in total score in an anhedonia scale. In a further particular embodiment, the anhedonia scale is the Snaith Hamilton Pleasure Scale (SHAPS). In a further particular embodiment, the disclosure relates to the package or pharmaceutical product as described herein, wherein the anhedonia of the patient is reduced by at least 40%, as measured by the change from baseline in total score in an anhedonia scale following 6 weeks of the treatment with aticaprant, more in particular, the anhedonia of the patient is reduced within about 3 weeks to about 6 weeks as measured by the change from baseline in total score in an anhedonia scale. In a further particular embodiment, the anhedonia scale is the Snaith Hamilton Pleasure Scale (SHAPS).

Methods and Uses Involving Esketamine

[00159] In one aspect of the present invention, methods are provided for treating depression comprising, consisting of, or consisting essentially of intranasally administering to a patient in need thereof an effective amount of esketamine, wherein the patient is identified as biomarker signature positive, wherein the patient is identified as biomarker signature positive if a biological sample obtained from the patient is identified as having a level of at least one biomarker that is greater or less than a reference biomarker level.

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[00160] In a further aspect of the present invention, methods are provided for treating depression comprising, consisting of, or consisting essentially of intranasally administering to a patient in need thereof an effective amount of esketamine, wherein the patient is biomarker signature positive, wherein the patient is biomarker signature positive if a biological sample obtained from the patient is identified as having a level of at least one biomarker that is greater or less than a reference biomarker level.

[00161] Further described herein is esketamine for use in the treatment of depression, comprising, consisting of, or consisting essentially of intranasally administering to a patient in need thereof an effective amount of esketamine, wherein the patient is identified as biomarker signature positive, wherein the patient is identified as biomarker signature positive if a biological sample obtained from the patient is identified as having a level of at least one biomarker that is greater or less than a reference biomarker level.

[00162] Further described herein is esketamine for use in the treatment of depression, comprising, consisting of, or consisting essentially of intranasally administering to a patient in need thereof an effective amount of esketamine, wherein the patient is biomarker signature positive, wherein the patient is biomarker signature positive if a biological sample obtained from the patient is identified as having a level of at least one biomarker that is greater or less than a reference biomarker level.

[00163] In certain embodiments, described herein are methods of identifying a patient as a candidate for treatment with esketamine if the subject is biomarker signature positive, wherein the patient is identified as biomarker signature positive if the biological sample obtained from the patient is identified as having: (a) a level of CRP greater than a reference CRP level, and (b) at least one of: (i) a level of TNF-alpha that is greater than a reference TNF-alpha level, and (ii) a level of sIL6R that is greater than a reference sIL6R level. In certain embodiments, said method further comprises administering to said patient an effective amount of esketamine.

[00164] For each the methods of treatment described herein, it will be understood that the methods of treatment may also be framed as methods of manufacturing a medicament for the treatment of the described indications or as esketamine for use in the treatment of the described indications.

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[00165] Methods of maintaining stable remission or stable response achieved by a patient with depression following administration of a therapeutically effective amount of esketamine during an initial administration phase also are described. Such methods include continuing administration of a therapeutically effective amount of esketamine for at least five months during a subsequent administration phase.

[00166] In embodiments of any of the foregoing methods of treatment, the method has an induction phase and, optionally, a subsequent maintenance phase, wherein the induction phase comprises induction phase treatment sessions at a given frequency, and the maintenance phase comprises maintenance phase treatment sessions administered to the patient less frequently.

[00167] In some embodiments, methods for the long term treatment of depression in a patient are also provided. These methods comprise administering to the patient in need of the treatment a therapeutically effective amount of esketamine for at least six months. Desirably, cognitive performance of the patient remains stable, based on a baseline measurement, following six months of treatment. In some embodiments, the treatment may be a duration of at least about one year, at least about 18 months, or at least about two years. For example, long term treatment may include a duration range of about six months to about two years. Treatment may also be continued for longer periods of time including, without limitation, 4, 5, 6, 7, 8, 9, 10, or longer years, as determined by the attending physician. In some embodiments, the esketamine is initially dosed twice a week for up to four weeks during an induction phase, and, thereafter, dosed less frequently than twice a week.

[00168] In further aspects, the method comprises intranasally administering about 28 mg to about 84 mg of esketamine per induction phase treatment session to said patient, wherein the induction phase treatment session occurs at a frequency of twice weekly during the induction phase; and, optionally intranasally administering about 56 mg to about 84 mg of esketamine per maintenance phase treatment session to said patient, wherein the maintenance phase treatment session occurs at a frequency of once weekly or once every other week. In certain aspects, the induction phase has a duration of about 4 weeks.

[00169] In certain aspects, about 56 or about 84 mg of esketamine is administered per induction phase treatment session. In further aspects, about 56 or about 84 mg of esketamine is administered per maintenance phase treatment session.

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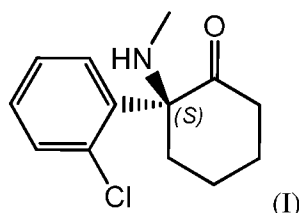
[00170] In certain embodiments, esketamine may be administered in combination with one or more antidepressants, as herein described, preferably in combination with one to three antidepressants, more preferably in combination with one to two antidepressants.

[00171] In certain embodiments, esketamine may be administered in combination with one or more antidepressants, and further in combination with one or more atypical antipsychotics, herein described.

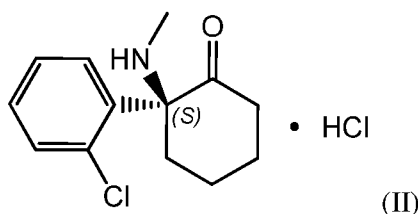
[00172] In further embodiments, the disclosure is directed to combination therapy comprising esketamine and one or more antidepressants; wherein the esketamine is administered as acute treatment. In other embodiments, the disclosure is directed to combination therapy comprising esketamine and one or more antidepressants wherein the esketamine is administered as acute treatment and wherein the one or more antidepressants are administered as chronic treatment.

[00173] In other embodiments, such as during an induction phase, the esketamine may be used as a mono-therapy and not in combination with any other active compounds.

[00174] As used herein, unless otherwise noted, the term “esketaamine” shall mean the (S)-enantiomer of ketamine, *i.e.*, a compound of formula (I):

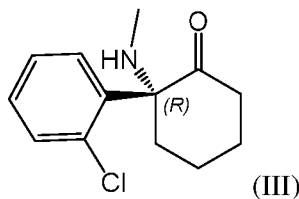


also known as (S)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone. “Esketamine” shall also mean a salt, *e.g.*, a chloride salt such as the hydrochloride salt, of the (S)-enantiomer of ketamine, *i.e.*, a compound of formula (II):



also known as (S)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride.

[00175] In some embodiments, the esketamine is substantially free of the (R)-enantiomer of ketamine, *i.e.*, a compound of formula (III):



[00176] In other embodiments, the esketamine contains less than about 10% by weight, based on the weight of the esketamine sample, of the (R)-enantiomer of ketamine. In further embodiments, the esketamine contains less than about 10, about 9, about 8, about 7, about 6, about 5, about 4, about 3, about 2, about 1, about 0.5, about 0.1, about 0.005, or about 0.001% by weight, based on the weight of the esketamine sample, of the (R)-enantiomer of ketamine. In yet other embodiments, the esketamine contains about 0.001 to about 10% by weight, based on the weight of the esketamine sample, of the (R)-enantiomer of ketamine. In still further embodiments, the esketamine contains about 0.001 to about 10%, about 0.001 to about 5%, about 0.001 to about 1, about 0.001 to about 0.5, about 0.001 to about 0.1, about 0.1 to about 5, about 0.1 to about 1, about 0.1 to about 5, or about 0.5 to about 5% by weight, based on the weight of the esketamine sample, of the (R)-enantiomer of ketamine.

[00177] The term “esketamine” may also include other pharmaceutically acceptable salts thereof, which may readily be selected by those skilled in the art. A “pharmaceutically acceptable salt” is intended to mean a salt of esketamine that is non-toxic, biologically tolerable, or otherwise biologically suitable for administration to the subject. See, generally, G.S. Paulekuhn, “Trends in Active Pharmaceutical Ingredient Salt Selection based on Analysis of the Orange Book Database”, J. Med. Chem., 2007, 50:6665-72, S.M. Berge, “Pharmaceutical Salts”, J Pharm Sci., 1977, 66:1-19, and Handbook of Pharmaceutical Salts, Properties, Selection, and Use, Stahl and Wermuth, Eds., Wiley-VCH and VHCA, Zurich, 2002. Examples of pharmaceutically acceptable salts are those that are pharmacologically effective and suitable for administration to patients without undue toxicity, irritation, or allergic response.

[00178] Examples of other pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, bromides (such as hydrobromides), iodides (such as hydroiodides), acetates, propionates, decanoates, caprylates, acrylates,

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formates, isobutyrate, caproate, heptanoate, propionate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, γ -hydroxybutyrate, glycolate, tartrate, methane-sulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, and mandelate. In particular, the salt of esketamine is a chloride salt such as a hydrochloride salt.

[00179] In certain embodiments, the esketamine is administered intranasally. In other embodiments, the esketamine is administered intranasally as its corresponding hydrochloride salt. In further embodiments, the esketamine is administered intranasally as its corresponding hydrochloride salt in an 16.14% weight/volume solution (equivalent to 14% weight/volume of esketamine base).

[00180] In some embodiments, the esketamine is delivered from an intranasal device in 2 or more sprays during the induction phase and/or the maintenance phase. In certain aspects, said methods further comprise administering a therapeutically effective amount of an oral antidepressant to said patient during the induction and/or maintenance phase. In certain aspects, the esketamine is administered as its corresponding hydrochloride salt during the induction phase and/or the maintenance phase.

[00181] In certain embodiments, the esketamine is administered intranasally as a solution comprising 161.4 mg/mL of esketamine hydrochloride (equivalent to 140 mg/mL of esketamine base), 0.12 mg/mL of ethylenediaminetetraacetic acid (EDTA) and 1.5 mg/mL citric acid, at a pH of 4.5 in water. In other embodiments, the esketamine is administered intranasally, wherein the intranasal delivery administers 100 μ L of a solution comprising 161.4 mg/mL of esketamine hydrochloride (equivalent to 140 mg/mL of esketamine base), 0.12 mg/mL of ethylenediaminetetraacetic acid (EDTA) and 1.5 mg/mL citric acid, at a pH of 4.5 in water. In certain embodiments, the esketamine is delivered intranasally using a nasal spray pump, wherein the pump delivers 100 μ L of a solution comprising 161.4 mg/mL of esketamine hydrochloride (equivalent to 140 mg/mL of esketamine base), 0.12 mg/mL of ethylenediaminetetraacetic acid (EDTA) and 1.5 mg/mL citric acid, at a pH of 4.5 in water.

[00182] In general, a single pump from a nasal spray device may be configured to deliver about 50 μ L to about 200 μ L of an esketamine solution to a nostril of the subject,

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including about 60 μ L, about 70 μ L, about 80 μ L, about 90 μ L, about 100 μ L, about 110 μ L, about 120 μ L, about 130 μ L, about 140 μ L, about 150 μ L, about 160 μ L, about 170 μ L, about 180 μ L, and about 200 μ L. Accordingly, two pumps deliver about 100 μ L to about 400 μ L to the subject.

[00183] In certain embodiments, a patient in need of treatment with a therapeutically effective amount of esketamine, is a patient suffering from an episode of depression (*e.g.*, major depressive disorder). In other embodiments, a patient in need thereof is suffering from an episode of depression (*e.g.*, major depressive disorder), wherein the episode of depression (*e.g.*, major depressive disorder) has not responded to treatment with at least two oral antidepressants (*i.e.*, the patient has not responded to treatment with at least two oral antidepressants). In other embodiments, a geriatric patient in need thereof is suffering from an episode of depression (*e.g.*, major depressive disorder), wherein the episode of depression (*e.g.*, major depressive disorder) has not responded to treatment with two oral antidepressants (*i.e.*, the geriatric patient has not responded to treatment with two oral antidepressants).

[00184] Esketamine and the antidepressant(s) may be administered via the same or different routes of administration. Examples of suitable methods of administration include, but are not limited to, oral, intravenous (iv), intranasal (in) intramuscular (im), subcutaneous (sc), transdermal, buccal, or rectal. In some embodiments, esketamine is administered intranasally.

[00185] The therapeutically effective amount of esketamine and/or antidepressant may be administered during the initial phase(s) and/or subsequent phase(s) as described herein. In some embodiments, the therapeutically effective amount of esketamine is about 20 to about 100 mg. In other embodiments, the therapeutically effective amount of esketamine is about 30 to about 90 mg. In further embodiments, the therapeutically effective amount of esketamine is about 40 to about 80 mg. In yet other embodiments, the therapeutically effective amount of esketamine is about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, about 34, about 35, about 36, about 37, about 38, about 39, about 40, about 41, about 42, about 43, about 44, about 45, about 46, about 47, about 48, about 49, about 50, about 51, about 52, about 53, about 54, about 55,

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about 56, about 57, about 58, about 59, about 60, about 61, about 62, about 63, about 64, about 65, about 66, about 67, about 68, about 69, about 70, about 71, about 72, about 73, about 74, about 75, about 76, about 77, about 78, about 79, about 80, about 81, about 82, about 83, about 84, about 85, about 86, about 87, about 88, about 89, about 90, about 91, about 92, about 93, about 94, about 95, about 96, about 97, about 98, about 99, or about 100 mg. In further embodiments, the therapeutically effective amount is about 28 mg, about 56 mg, or about 84 mg. In other embodiments, the therapeutically effective amount is about 56 mg or about 84 mg. In yet further embodiments, the therapeutically effective amount of esketamine is about 28 mg. In other embodiments, the therapeutically effective amount of esketamine is about 56 mg. In still further embodiments, the therapeutically effective amount of esketamine is about 84 mg. Unless otherwise noted, amounts of esketamine correspond to the free base of esketamine.

[00186] As noted above, methods of treating depression in a patient are described. The methods include administering esketamine in one, two or optionally three phases, *i.e.*, initial and subsequent administration phases. In some embodiments, the phases include an initial induction phase, an extended induction phase, a maintenance phase, or any combination thereof. Accordingly, an effective amount of esketamine is administered in each phase. A physician can assess the patient's condition to determine the most beneficial initiation/induction and maintenance doses for the patient from the dosage range and administration frequencies from those specified herein. The effective amount of esketamine may be the same in each phase or may differ.

[00187] The methods described herein permit optimizing dosages of esketamine for administration to a patient having or being predisposed to depression in an "optimization phase". Optimization may be considered part of the maintenance phase that follows the induction phase. In some embodiments, the methods described herein do not require adjustment of the esketamine dosage. In fact, esketamine may be administered during the phases discussed herein (*e.g.*, induction and maintenance) at the lowest dosing frequency at which an esketamine response is observed and maintained in a patient. An effective amount of esketamine has been found to be from about 28 to about 84 mg.

[00188] As used herein, an "induction phase" or "acute dosing phase" is a period of time that esketamine is initially administered to the patient. In some embodiments, the

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induction phase is sufficiently long as to achieve a robust, stable reduction of depressive symptoms. The induction phase may depend on factors including, without limitation, the particular patient and/or the patient's sex, age, weight, time of administration, administration frequency and concomitant diseases. The induction phase may include an initial induction phase and an extended induction phase. The totality of the induction phase (the initial and extended phases together) may be a period of about 4 to about 12 weeks, about 4 to about 11 weeks, about 4 to about 10 weeks, about 4 to about 9 weeks, about 4 to about 8 weeks, about 4 to about 7 weeks, about 4 to about 6 weeks, about 5 to about 12 weeks, about 5 to about 11 weeks, about 5 to about 10 weeks, about 5 to about 9 weeks, about 5 to about 8 weeks, about 5 to about 7 weeks, about 5 to about 6 weeks, about 6 to about 12 weeks, about 6 to about 11 weeks, about 6 to about 10 weeks, about 6 to about 9 weeks, about 6 to about 8 weeks, about 7 to about 12 weeks, about 7 to about 11 weeks, about 7 to about 10 weeks, about 7 to about 9 weeks, about 8 to about 12 weeks, about 8 to about 11 weeks, or about 8 to about 10 weeks. In some embodiments, the entire induction period is about 4 to about 8 weeks.

[00189] In the initial induction period, a patient is administered a therapeutically effective amount of esketamine at a given frequency of at least twice a week. In some embodiments, a patient is administered a therapeutically effective amount of esketamine at a given frequency of 3 times a week. To the extent that the dosing is 3 times a week, the dosing is on days 1, 3, and 5 of the week ± 1 day. The initial induction phase is typically a period of time in which the patient is shown to be responsive to the treatment, but is not ready to progress to the maintenance phase. At timepoints therein, the patient's response is assessed by one skilled in the art. In some embodiments, the patient's response is assessed daily. In other embodiments, the patient's response is assessed twice weekly. In further embodiments, the patient's response is assessed every other day. In yet other embodiments, the patient's response is assessed at the end of the initial induction phase. Typically, the patient's response may be assessed using techniques and tests known to those skilled in the art. In some embodiments, the patient's MADRS score is determined and used as the determination as to whether the initial induction phase has concluded. The initial induction phase is desirably long as to achieve a reduction of depressive symptoms. In some embodiments, the initial induction phase is a period of about 1 to about 4 weeks. In other embodiments, the induction phase is a period of up to about 1 week, up to about 2 weeks, up to about 3 weeks,

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or up to about 4 weeks. In further embodiments, the initial induction period is about 1 to about 3 weeks, about 1 to about 2 weeks, about 2 to about 4 weeks, about 2 to about 3 weeks, about 3 to about 4 weeks, 1 week, 2 weeks, 3 weeks, 4 weeks, up to 1 week, up to 2 weeks, up to 3 weeks, or up to 4 weeks. The effective amount of esketamine administered during the initial induction phase may be determined by the attending physician. In some embodiments, the effective amount of esketamine administered during the initial induction phase is about 28 mg. In some embodiments, the effective amount of esketamine administered during the initial induction phase is about 56 mg. In other embodiments, the effective amount of esketamine administered during the initial induction phase is about 84 mg.

[00190] The term “twice weekly” as used herein refers to a frequency that is two times in a weekly (7-day) period. For example, “twice weekly” may refer herein to the administration of esketamine. “Twice weekly” may also refer to a frequency of monitoring a patient in one or more phases discussed herein. In some embodiments, twice weekly refers to a frequency that is day 1 and day 2 of a week. In other embodiments, twice weekly refers to a frequency that is day 1 and day 3 of a week. In further embodiments, twice weekly refers to a frequency that is day 1 and day 4 of a week. In still other embodiments, twice weekly refers to a frequency that is day 1 and day 5 of the week. The “day 1” may be any day of the week, including, Sunday, Monday, Tuesday, Wednesday, Thursday, Friday, or Saturday. Typically, with respect to administration of esketamine, twice weekly refers to a frequency that is day 1 and day 4 of a week. To the extent there is a mis-dose, the dose may be taken as soon as possible thereafter and the prescribed regimen thereafter continued.

[00191] In some patient populations (such as the elderly) the reduction of depressive symptoms during the initial induction phase is insufficient, and an extended induction phase is necessary. In an extended initial induction phase, continued administration of a therapeutically effective amount of esketamine at a given frequency of at least twice a week is performed. At timepoints therein, the patient’s response is again assessed by one skilled in the art. In some embodiments, the patient’s response is assessed daily. In other embodiments, the patient’s response is assessed twice weekly. In further embodiments, the patient’s response is assessed every other day. Typically, the patient’s response may be assessed using techniques and tests known to those skilled in the art. In some embodiments, the patient’s MADRS score is determined and used as the determination as to whether the

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extended induction period has concluded. The extended induction phase is desirably long as to achieve a substantial reduction of depressive symptoms, thus achieving a substantially complete response to esketamine.

[00192] The term “substantially complete response to esketamine” as used herein refers to a patient having a reduction of the MADRS score from baseline to at least a 50% improvement from baseline. In some embodiments, a substantially complete response to esketamine refers to a patient having either a MADRS score of at least 50% improvement from baseline or about -20 lower than the patients baseline score. In other embodiments, a substantially complete response includes a MADRS score of a reduction of about -20 or less, -19, or less, -18 or less, -17 or less, -16 or less, -15 or less, -14 or less, -13 or less, -12 or less, -11 or less, or -10 or less. In further embodiments, a substantially complete response results in a patient having a reduction from MADRS baseline score of about -15 to about -20. A substantially complete response to esketamine may also be obtained if the patient’s MADRS scores is reduced by about 50% from the MADRS score at the start of the treatment. Such a substantially complete response may be observed at any point during esketamine treatment. In some embodiments, the substantially complete response is observed when the patient has a reduction of the MADRS total score from the baseline 4 hours following treatment. In other embodiments, the substantially complete response is observed where the patient has a reduction of the MADRS total score from the baseline 2 days following treatment.

[00193] The extended induction phase is a period of time that results in the substantially complete response to esketamine. In some embodiments, extended induction phase is about 1 to about 8 weeks. In other embodiments, the extended induction phase is a period of up to about 1 week, up to about 2 weeks, up to about 3 weeks, up to about 4 weeks, up to about 5 weeks, up to about 6 weeks, up to about 7 weeks, or up to about 8 weeks. In further embodiments, the extended induction period is about 1 to about 8 weeks, about 1 to about 7 weeks, about 1 to about 6 weeks, about 1 to about 5 weeks, about 1 to about 4 weeks, about 1 to about 3 weeks, about 2 to about 8 weeks, about 2 to about 7 weeks, about 2 to about 6 weeks, about 2 to about 5 weeks, about 2 to about 4 weeks, about 3 to about 8 weeks, about 3 to about 7 weeks, about 3 to about 6 weeks, about 3 to about 5 weeks, about 4 to about 8 weeks, about 4 to about 7 weeks, about 4 to about 6 weeks, about 5 to about 8 weeks, about 5 to about 7 weeks, about 1 week, about 2 weeks, about 3

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weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, or about 8 weeks. The effective amount of esketamine administered during the extended induction phase may be determined by the attending physician. In some embodiments, the effective amount of esketamine administered during the extended induction phase is about 56 mg. In other embodiments, the effective amount of esketamine administered during the extended induction phase is about 84 mg.

[00194] The administration may further comprise an optimization/maintenance phase that follows the induction phase and wherein after the patient achieves a substantially complete response to the esketamine during the induction phase, the esketamine is administered at a frequency of less than twice a week during the optimization/maintenance phase. In some embodiments, the frequency of administration during the optimization/maintenance phase is once every week, once every two weeks, once a month, or a combination thereof.

[00195] At any stage during one or more of an induction phase, optimization phase, or maintenance phase, the patient's response to the treatment may be assessed using techniques described herein. This assessment may be performed until the patient is considered by one skilled in the art to have achieved a suitable response to the treatment regimen. In some embodiments, the induction period may be said to have completed when a patient's MADRS score is reduced by $\geq 50\%$ from baseline or from about 20 to about 13. In other embodiments, the patient's MADRS score may be about 19, about 18, about 17, about 16, about 15, about 14, or about 13. Patients with MADRS scores ≤ 12 are considered in remission and if stable for four weeks should be moved to or maintained in the maintenance phase.

[00196] At the end of the induction phase or extended induction phase, the treating physician should evaluate the patient to optimize the dosing amount and frequency for any subsequent administration phases such as the "maintenance phase" or "long-term therapy phase". It is anticipated that the intranasal treatment frequency during the subsequent administration such as the maintenance phase will be reduced from that in the induction phase or extended induction phase (at least twice weekly) to once weekly dosing for at least 4 weeks. In some embodiments, the subsequent administration such as the maintenance phase is at least about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about

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9 week, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, about 11 months, 1 year, or about 2 years. In some embodiments, the continuing administration of the esketamine during the subsequent administration phase is for at least six months. In other embodiments, the continuing administration of the esketamine during the subsequent administration phase is at least one year. In further embodiments, the frequency of administration during the subsequent administration phase is once every week or once every two weeks, or a combination thereof. In yet other embodiments, the dosing frequency and effective amount of esketamine during the subsequent administration phase is the minimum frequency and amount to maintain the stable remission or stable response.

[00197] The subsequent administration, such as in a maintenance period, may include longer periods of time depending on the patient's condition. In some embodiments, those longer periods may be at least about 3 years, about 4 years, about 5 years, about 6 years, about 7 years, about 8 years, about 9 years, about 10 years, or more than about 10 years, including indefinitely. For example, for patients diagnosed with TRD, treatment may be indefinite. In other embodiments, the treatment frequency is reduced to biweekly. In further embodiments, the treatment frequency is reduced to every three weeks. In yet other embodiments, the treatment frequency is reduced to monthly. The patients will be maintained on schedule until the patient achieves remission, maintains a response, or fails treatment. If the patient achieves remission or maintains a response with the once a week treatment for at least 4 weeks, the frequency of intranasal treatment sessions may be decreased to a maintenance dose of once every other week based on the severity of depressive symptoms and for some patient populations the frequency of treatment may be reduced to about once every three or four weeks as discussed above.

[00198] One skilled in the art will recognize that the maintenance phase described herein may continue until further treatment is not required and as indicated by, *e.g.*, prolonged remission of the depression (including *e.g.*, the remission of one or more symptoms associated with depression), social and/or occupational functional improvement to normal or premorbid levels, or other known measures of depression.

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[00199] An effective amount of esketamine is administered to the patient during the maintenance phase. As noted above, the amount of esketamine administered during the maintenance phase is an amount that elicits the biological or medicinal response in a tissue system discussed above for the induction phase. In certain embodiments, the effective amount of esketamine is the amount which maintains a pharmacodynamic steady state of esketamine attained in the induction phase. In other embodiments, if depressed symptoms begin to worsen with treatment every other week, every three weeks or every four weeks, the dosing of esketamine will be increased to stabilize the patient. For example if the patient is being dosed every other week and their symptoms begin to worsen, esketamine can be administered once per week to maintain response during the maintenance phase. Again, at any time during the maintenance phase the patient's response maybe reassessed.

[00200] For elderly patients, the recommended dose of esketamine is about 28 to about 84 mg. The initial dose (at the first treatment session) is recommended to be about 28 mg of esketamine. Based on efficacy and tolerability of the about 28 mg dose, the dose at the next treatment session may remain at about 28 mg or be increased to about 56 mg. Depending on efficacy and tolerability of the about 56 mg dose, the dose at subsequent treatment session may remain at about 56 mg or be increased to about 84 mg, or reduced to about 28 mg. Depending on tolerability of the about 84 mg dose, the dose at subsequent treatment sessions may remain at about 84 mg or be reduced to about 56 mg.

[00201] For hepatically impaired patients, the recommended dose of esketamine is about 28 to about 56 mg. The initial dose (at the first treatment session) is recommended to be about 28 mg of esketamine. Based on efficacy and tolerability of the about 28 mg dose, the dose at the next treatment session may remain at about 28 mg or be increased to about 56 mg. Physicians should regularly monitor the hepatically impaired patients for drug tolerability, because esketamine is extensively metabolized in the liver.

[00202] For the treatment of patients with major depressive disorder with suicidal ideation and at imminent risk for suicide, dosing is more aggressive because of the severity of the condition. The methods include administering esketamine in one or two phases, *i.e.*, an initial induction phase, and optionally in certain circumstances a maintenance phase. Due to the imminent risk to the patient's life the initial dose of esketamine is dosed at the highest effective amount of esketamine that the patient may tolerate twice a week in the induction

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phase. In some embodiments, the patient continues on therapy with the existing (*i.e.*, currently initiated) antidepressant agent simultaneously with the beginning of therapy on esketamine during the induction phase. In other embodiments, the patient is initiated on a new antidepressant agent simultaneously with the beginning of therapy on esketamine during the induction phase. In further embodiments, the patient continues on therapy with a previously administered antidepressant agent simultaneously with the beginning of therapy on esketamine during the induction phase. The antidepressant should be dosed as labeled for the treatment of MDD, in a manner appropriate for the patient's condition/health. The induction phase should be about 4 to about 8 weeks, about 4 to about 7 weeks, about 4 to about 6 weeks, most preferably about 4 weeks. At the end of the induction phase the esketamine dosing should cease if the patient adequately responds to treatment or is in remission. The patient should be monitored to ensure that the patient remains stable/ or in remission on the antidepressant alone. Should the patient fail to stabilize on the first combination of esketamine and antidepressant or fail treatment on the antidepressant that was initiated with esketamine after the dosing with esketamine ceases, a second induction phase may be begun.

[00203] In the second induction phase, the patient would be reinitiated on esketamine at the highest tolerable dose and simultaneously with a second new antidepressant. Alternatively, the patient would be reinitiated on esketamine at the highest tolerable dose and simultaneously with the same antidepressant that was used during the previous induction phase. The esketamine being dosed twice a week. The antidepressant would be dosed as labeled for the treatment of MDD, in a manner appropriate for the patient's condition/health. The second induction phase should be about 4 to about 8 weeks, about 4 to about 7 weeks, about 4 to about 6 weeks, most preferably about 4 weeks. At the end of the second induction phase, if the patient adequately responds to treatment or is in remission the esketamine dosing should cease and the patient should be monitored to ensure that the patient remains stable/ or is in stable remission on the antidepressant alone. Should the patient fail to stabilize or fail treatment on the antidepressant that was initiated with esketamine after the dosing with esketamine ceases, a third induction phase may be begun.

[00204] In the third induction phase the patient would be reinitiated on esketamine at the highest tolerable dose and simultaneously with a third new antidepressant.

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Alternatively, the patient would be reinitiated on esketamine at the highest tolerable dose and simultaneously with the same antidepressant that was used during the second induction phase. The esketamine being dosed twice a week. The antidepressant would be dosed as labeled for the treatment of MDD in a manner appropriate for the patient's condition/health. The third induction phase should be about 4 to about 8 weeks, about 4 to about 7 weeks, about 4 to about 6 weeks, most preferably about 4 weeks. At the end of the third induction phase the patient would proceed to the maintenance phase specified for TRD, since the patient now qualifies as a TRD patient. The methods described herein permit optimizing dosages of esketamine for administration to a patient having or being predisposed to depression. In some embodiments, the methods described herein do not require adjustment of the esketamine dosage.

[00205] In general, the patient may be reinitiated on esketamine at the highest tolerable dose and simultaneously with the same antidepressant that was used during any previous induction phase, including with an antidepressant in which the patient failed to stabilize or otherwise failed treatment. For example, in a method for treating treatment-resistant depression in a patient wherein the patient has not responded to at least two oral antidepressants in the current depressive episode, the patient may be administered esketamine at least twice weekly solely with esketamine or along with a first oral antidepressant that is the same or different than the previously ineffective oral antidepressant in a first induction phase. To the extent the patient fails to achieve a substantially complete response to the esketamine, the patient can be reinitiated at the highest tolerable dose of esketamine alone or simultaneously with a second oral depressant that is the same or different than the first oral antidepressant in a second induction phase. To the extent the patient achieves a substantially complete response to the esketamine during the second induction phase, the patient can then be administered a therapeutically effective amount of esketamine less than twice weekly during a subsequent maintenance phase.

[00206] In the event that one or more (*e.g.*, two) doses of esketamine in any of the phases described herein are missed, the next dose is scheduled when possible based on the dosing frequency regimen. If more than 2 doses are missed, per clinical judgement, adjustment of the dose or frequency of esketamine may be required.

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[00207] Advantageously, esketamine may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily, preferably two times daily. Typically, divided doses should be made closer in time. In some embodiments, divided doses are administered about within 20 minutes, about 15 minutes, about 10 minutes, about 5 minutes, about 4 minutes, about 3 minutes, about 2 minutes, about 1 minute, or less of each other. Additionally, in a flexible dosing regimen a patient could be dosed daily, twice a week, once a week, once every other week or once monthly. For example, one dose of the esketamine is administered on day 1 and another dose of the esketamine is administered on day 2, or one dose of the esketamine is administered on day 1 and another dose of the esketamine is administered on day 3, or one dose of the esketamine is administered on day 1 and another dose of the esketamine is administered on day 4, or one dose of the esketamine is administered on day 1 and another dose of the esketamine is administered on day 5. Furthermore, esketamine is preferably administered in intranasal form via topical use of suitable intranasal vehicles, such as a nasal spray pump.

[00208] A representative nasal spray device is disclosed in U.S. Patent No. 6,321,942, incorporated by reference herein. For example, a disposable atomizer for discharging successive partial discharge amounts as a spray may be utilized to carry out the methods discloses herein. Typically, such devices allow a medicament to be sprayed into both nostrils of a patient in two successive strokes. The device may be ready-to-use wherein the medicament is discharged from a medium container. The device is typically able to separate a first discharge stroke from a second discharge stroke to prevent complete emptying of the medium container in a single motion. The device may take the form of a double-stroke disposable pump, which is disposed of after a single use and enables individual partial discharges with high dosing precision and reliability.

[00209] In one embodiment, the nasal spray device is a single-use device that delivers a total of 28 mg of esketamine in two sprays, one spray per nostril. The device may be operated by the patient under the supervision of a healthcare professional. With respect to dosage amounts, one device may be used for a 28 mg dose, two devices for a 56 mg dose, or three devices for an 84 mg dose. It is also preferable to have a 5-minute interval between the use of each device. As described in Example 1, time 0 is defined as the time of administration of the first intranasal spray to one nostril from the first intranasal device.

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[00210] As used herein, AD = antidepressant; ESK = esketamine nasal spray; PHQ-9 = Patient Adherence Questionnaire; SDS = Sheehan Disability Scale; CGI-S = Clinical Global Impression – Severity; MADRS = Montgomery-Åsberg Depression Rating Scale; SD = standard deviation; C-SSRS = Columbia Suicide Severity Rating Scale; MDD = major depressive disorder; MGH-ATRQ = Massachusetts General Hospital - Antidepressant Treatment History Questionnaire; TRD = treatment resistant depression.

Pharmaceutical Compositions

[00211] Methods of formulating pharmaceutical compositions have been described in numerous publications such as Pharmaceutical Dosage Forms: Tablets, Second Edition, Revised and Expanded, Volumes 1-3, edited by Lieberman et al; Pharmaceutical Dosage Forms: Parenteral Medications, Volumes 1-2, edited by Avis et al; and Pharmaceutical Dosage Forms: Disperse Systems, Volumes 1-2, edited by Lieberman et al; published by Marcel Dekker, Inc.

[00212] In an embodiment, the preferred pharmaceutical composition contains aticaprant as the active ingredient intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for administration. Suitable pharmaceutically acceptable carriers are well known in the art. Descriptions of some of these pharmaceutically acceptable carriers may be found in The Handbook of Pharmaceutical Excipients, published by the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain.

[00213] In a further embodiment, the preferred pharmaceutical composition, S-ketamine hydrochloride as the active ingredient is intimately admixed with a pharmaceutical carrier, preferably water, according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for administration. Suitable pharmaceutically acceptable carriers are well known in the art.

[00214] One suitable aqueous formulation of S-ketamine, comprises water and S-ketamine; wherein the S-ketamine is present in an amount in the range of from about 25 mg/mL to about 250 mg/mL, preferably about 55 mg/mL to about 250 mg/mL or about 100 mg/mL to about 250 mg/mL, or any amount or range therein, based on the total volume of the

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pharmaceutical composition. Preferably, the S-ketamine is present in an amount in the range of from about 150 mg/ml to about 200 mg/mL, or any amount or range therein. More preferably, the S-ketamine is present in an amount in the range of from about 150 mg/mL to about 175 mg/mL, or any amount or range therein. More preferably, the S-Ketamine is present in an amount in the range of from about 160 mg/mL to about 163 mg/mL, *e.g.*, in an amount of about 161.4 mg/mL

[00215] Another suitable aqueous formulation of S-ketamine comprises water and S-ketamine; wherein the S-ketamine is present in an amount in the range of from about eq. 100 mg/mL to about eq. 250 mg/mL, or any amount or range therein, based on the total volume of the pharmaceutical composition. Preferably, the S-ketamine is present in an amount in the range of from about eq. 125 mg/ml to about eq. 180 mg/mL, or any amount or range therein. More preferably, the S-ketamine is present in an amount in the range of from about eq. 140 mg/mL to about eq. 160 mg/mL, or any amount or range therein, *e.g.*, in an amount of about eq. 140 mg/mL.

[00216] Suitable pharmaceutical compositions for use herein are preferably an aqueous formulation. As used herein, unless otherwise noted, the term “aqueous” shall mean that the primary liquid component of the formulation is water. Preferably, water constitutes greater than about 80 wt-% of the liquid component of the pharmaceutical composition, more preferably greater than about 90 wt-%, more preferably greater than about 95 wt-%, more preferably about 98 wt-%.

[00217] In suitable pharmaceutical compositions for use herein, the water content of the composition is within the range of 85±14 wt.-%, more preferably 85±12 wt.-%, still more preferably 85±10 wt.-%, most preferably 85±7.5 wt.-% and in particular 85±5 wt.-%, based on the total weight of the composition.

[00218] In suitable pharmaceutical compositions for use herein, preferably the water content of the composition is within the range of 90±14 wt.-%, more preferably 90±12 wt.-%, still more preferably 90±10 wt.-%, most preferably 80±7.5 wt.-% and in particular 90±5 wt.-%, based on the total weight of the composition.

[00219] In another pharmaceutical composition for use herein, the water content of the composition is within the range of 95±4.75 wt.-%, more preferably 95±4.5 wt.-%, still

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more preferably 95 ± 4 wt.-%, yet more preferably 95 ± 3.5 wt.-%, most preferably 95 ± 3 wt.-% and in particular 95 ± 2.5 wt.-%, based on the total weight of the composition.

[00220] In another pharmaceutical composition for use herein, the water content of the composition is within the range of from 75 to 99.99 wt.-%, more preferably 80 to 99.98 wt.-%, still more preferably 85 to 99.95 wt.-%, yet more preferably 90 to 99.9 wt.-%, most preferably 95 to 99.7 wt.-% and in particular 96.5 to 99.5 wt.-%, based on the total weight of the composition.

[00221] In another pharmaceutical composition for use herein, the composition further comprises one or more buffers and / or buffer systems (*i.e.*, conjugate acid-base-pairs).

[00222] As used herein, the term “buffer” shall mean any solid or liquid composition (preferably an aqueous, liquid composition) which when added to an aqueous formulation adjusts the pH of said formulation. One skilled in the art will recognize that a buffer may adjust the pH of the aqueous formulation in any direction (toward more acidic, more basic or more neutral pH). Preferably, the buffer is pharmaceutically acceptable.

[00223] Suitably examples of buffers which may be used in the aqueous formulations include, but are not limited to citric acid, sodium dihydrogen phosphate, disodium hydrogen phosphate, acetic acid, boric acid, sodium borate, succinic acid, tartaric acid, malic acid, lactic acid, fumaric acid, and the like. Preferably, the buffer or buffer system is selected from the group consisting of NaOH, citric acid, sodium dihydrogen phosphate and disodium hydrogen phosphate.

[00224] In an embodiment, the buffer is selected to adjust the pH of the S-ketamine hydrochloride pharmaceutical compositions (*e.g.*, the aqueous formulations described herein) into a pH in the range of from about pH 3.5 to about pH 6.5, or any amount or range therein. Preferably, the buffer is selected to adjust the pH of the S-ketamine hydrochloride compositions to about in the range of from about pH 4.0 to about pH 5.5, or any amount or range therein, more preferably, in the range of from about pH 4.5 to about pH 5.0, or any amount or range therein.

[00225] Preferably, the concentration of the buffer and buffer system, respectively, preferably NaOH, is adjusted to provide a sufficient buffer capacity.

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[00226] In an embodiment, the disclosure is directed to a pharmaceutical composition comprising S-ketamine hydrochloride, water, and a buffer or buffer system, preferably NaOH; wherein the buffer or buffer system is present in an amount sufficient to yield a formulation with a pH in the range of from about pH 4.0 to about pH 6.0, or any amount or range therein.

[00227] Optionally the pharmaceutical compositions may contain a preservative. As used herein, unless otherwise noted, the terms “antimicrobial preservative” and “preservative” preferably refer to any substance that is usually added to pharmaceutical compositions in order to preserve them against microbial degradation or microbial growth. In this regard, microbial growth typically plays an essential role, *i.e.*, the preservative serves the main purpose of avoiding microbial contamination. As a side aspect, it may also be desirable to avoid any effect of the microbes on the active ingredients and excipients, respectively, *i.e.*, to avoid microbial degradation.

[00228] Representative examples of preservatives include, but are not limited to, benzalkonium chloride, benzethonium chloride, benzoic acid, sodium benzoate, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorbutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, sodium propionate, thimerosal, methyl paraben, ethyl paraben, propyl paraben, butyl paraben, isobutyl paraben, benzyl paraben, sorbic acid, and potassium sorbate.

[00229] The complete absence of preservatives in the pharmaceutical compositions used herein is preferred when the content of S-ketamine hydrochloride is sufficiently high so that due to its preservative property the desired shelf life or in use stability can be achieved by the presence of the drug itself. Preferably, under these circumstances the concentration of S-ketamine hydrochloride is at least eq. 120 mg/mL, preferably in the range of from about eq. 120mg/mL to about eq. 175 mg/ml, or any amount or range therein, more preferably in an amount in the range of from about eq. 125 mg/mL to about eq. 150 mg/mL, or any amount or range therein, *e.g.*, at about eq. 126 mg/mL or at about eq. 140 mg/mL.

[00230] As used herein, the terms “penetration agent”, “penetration enhancer”, and “penetrant” refer to any substance that increases or facilitates absorption and / or bioavailability of the active ingredient (*e.g.*, S-ketamine hydrochloride) of a pharmaceutical

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composition. Preferably, the penetration agents increases or facilitates absorption and / or bioavailability of the active ingredient (*e.g.*, S-ketamine hydrochloride) of a pharmaceutical composition, following nasal administration (*i.e.*, increases or facilitates absorption and / or bioavailability of the active ingredient through the mucosal membrane).

[00231] Suitable examples include, but are not limited to tetradecyl maltoside, sodium glycocholate, tauroursodeoxycholic acid (TUDCA), lecithines, and the like; and chitosan (and salts), and surface active ingredients such as benzalkonium chloride, sodium dodecyl sulfate, sodium docusate, polysorbates, laureth-9, octoxynol, sodium deoxycholate, polyarginine, and the like. Preferably, the penetration agent is tauroursodeoxycholic acid (TUDCA).

[00232] The penetration agent may work via any mechanism, including *e.g.*, by increasing the membrane fluidity, creating transient hydrophilic pores in the epithelial cells, decreasing the viscosity of the mucus layer or opening up tight junctions. Some penetration agents (*e.g.*, bile salts and fusidic acid derivatives) may also inhibit the enzymatic activity in the membrane, thereby improving bioavailability of the active ingredient.

[00233] Preferably, the penetration agent is selected to meet one or more of the following general requirements:

- (a) It is effective at increasing absorption of aticaprant, preferably in a temporary and/or reversible manner;
- (b) It is pharmacologically inert;
- (c) It is non-allergic, non-toxic and / or non-irritating;
- (d) It is highly potent (effective in small amounts);
- (e) It is compatible with the other components of the pharmaceutical composition;
- (f) It is odorless, colorless and / or tasteless;
- (g) It is accepted by regulatory agencies; and
- (h) It is inexpensive and available in high purity.

[00234] In one embodiment, the penetration agent is selected to increase penetration (absorption and / or bioavailability of the S-ketamine hydrochloride) without nasal irritation. In another embodiment, the penetration agent is selected to improve absorption and / or bioavailability of the S-ketamine hydrochloride; and further selected to enhance uniform dosing efficacy.

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[00235] In an embodiment, the disclosure is directed to a pharmaceutical composition comprising S-ketamine and water; herein the pharmaceutical composition does not contain an antimicrobial preservative; and wherein the pharmaceutical compositions further contains a penetration enhancer, preferably TUDCA.

[00236] In another embodiment, the disclosure is directed to a pharmaceutical composition comprising S-ketamine and water; herein the pharmaceutical composition does not contain an antimicrobial preservative; and wherein the pharmaceutical compositions further contains tauroursodeoxycholic acid (TUDCA); wherein the TUDCA is present in a concentration in the range of from about 1.0 mg/mL to about 25.0 mg/mL, or any amount or range therein, preferably in a concentration in the range of from about 2.5 mg/mL to about 15 mg/mL, or any amount or range therein, preferably in a concentration in the range of from about 5 mg/mL to about 10 mg/mL, or any amount or range therein. In another embodiment, the disclosure is directed to pharmaceutical composition wherein the TUDCA is present at a concentration of about 5 mg/mL. In another embodiment, the disclosure is directed to pharmaceutical composition wherein the TUDCA is present at a concentration of about 10 mg/mL.

[00237] The pharmaceutical compositions for use herein may further contain one or more additional excipients *e.g.*, wetting agents, surfactant components, solubilizing agents, thickening agents, colorant agents, antioxidant components, and the like.

[00238] Examples of a suitable antioxidant component, if used, include, but are not limited to one or more of the following: sulfites; ascorbic acid; ascorbates, such as sodium ascorbate, calcium ascorbate, or potassium ascorbate; ascorbyl palmitate; fumaric acid; ethylene diamine tetraacetic acid (EDTA) or its sodium or calcium salts; tocopherol; gallates, such as propyl gallate, octyl gallate, or dodecyl gallate; vitamin E; and mixtures thereof. The antioxidant component provides long term stability to the liquid compositions. Addition of the antioxidant component can help enhance and ensure the stability of the compositions and renders the compositions stable even after six months at 40 °C. A suitable amount of the antioxidant component, if present, is about 0.01 wt.-% to about 3 wt.-%, preferably about 0.05 wt.-% to about 2 wt.-%, of the total weight of the composition.

[00239] Solubilizing and emulsifying agents can be included to facilitate more uniform dispersion of the active ingredient or other excipient that is not generally soluble in

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the liquid carrier. Examples of a suitable emulsifying agent, if used, include, but are not limited to, *e.g.*, gelatin, cholesterol, acacia, tragacanth, pectin, methyl cellulose, carbomer, and mixtures thereof. Examples of a suitable solubilizing agent include polyethylene glycol, glycerin, D-mannitol, trehalose, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, sodium salicylate, sodium acetate, and mixtures thereof.

[00240] Preferably, the solubilizing agent includes glycerin. The solubilizing or emulsifying agent is/are generally present in an amount sufficient to dissolve or disperse the active ingredient, *i.e.*, S-ketamine, in the carrier. Typical amounts when a solubilizing or an emulsifier are included are from about 1 wt.-% to about 80 wt.-%, preferably about 20 wt.-% to about 65 wt.-%, and more preferably about 25 wt.-% to about 55 wt.-%, of the total weight of the composition.

[00241] A suitable isotonizing agent, if used, includes sodium chloride, glycerin, D-mannitol, D-sorbitol, glucose, and mixtures thereof. A suitable amount of the isotonizing agent, when included, is typically about 0.01 wt.-% to about 15 wt.-%, more preferably about 0.3 wt.-% to about 4 wt.-%, and more preferably about 0.5 wt.-% to about 3 wt.-%, of the total weight of the composition.

[00242] A suspending agent or viscosity increasing agent can be added to the pharmaceutical compositions to, *e.g.*, increase the residence time in the nose. Suitably examples include, but are not limited to, hydroxypropyl methylcellulose, sodium carmellose, microcrystalline cellulose, carbomer, pectin, sodium alginate, chitosan salts, gellan gum, poloxamer, polyvinyl pyrrolidone, xanthan gum, and the like.

[00243] The following Examples are set forth to aid in the understanding of the invention, and are not intended and should not be construed to limit in any way the invention set forth in the claims which follow thereafter.

Abbreviations

AE	Adverse Event
AESI	Adverse Event of special interest
ALKS	Alkermes
ALT	Alanine Aminotransferase

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Anti-HEV (IgM)	Anti-hepatitis E Virus (Immunoglobulin M)
ASEX	Arizona Sexual Experiences Scale
AST	Aspartate Transaminase
ATRQ	Antidepressant Treatment History Questionnaire
BMI	Body Mass Index
CBD	Cannabidiol
CERC	Cerecor
CGI-S	Clinical Global Impression – Severity
CI	Confidence Interval
CPFQ	Cognitive and Physical Functioning Questionnaire
C-SSRS	Columbia Suicide Severity Rating Scale
DCS	Direct Current Stimulation
DSM-IV/5	Diagnostic and Statistical Manual of Mental Disorders 4 th /5 th edition
ECG	Electrocardiogram
EQ-5D-5L	European Quality of Life, 5 Dimension, 5-Level
eITT	Enriched Intent-To-Treat (population)
EOT	End-Of-Treatment
FAS	Full Safety Analysis Set
FDA	Food and Drug Administration
fITT	Full Intent-To-Treat (population)
FSH	Follicle Stimulating Hormone
FT4	Free Thyroxine
G17	Gastrin-17
GAD	General Anxiety Disorder
GAD-7	Generalized Anxiety Disorder 7-item Scale
GI	Gastrointestinal
HAM-A	Hamilton Depression Rating Scale
HDRS-17	
HAM-A6	6 Item Subscale from HAM-A
HPA	Hypothalamus Pituitary Adrenal

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Hp IgG	Helicobacter IgG antibodies
KOR	Kappa Opioid Receptor
KSS	Karolinska Sleepiness Scale
LS	Least Squares
MADRS	Montgomery Asberg Depression Rating Scale
MAOI	Monoamine Oxidase Inhibitor
MDMA	Methylenedioxymethamphetamine
MCI	Mild Cognitive Impairment
MDD	Major Depressive Disorder
MDE	Maximum Desired Mean Exposure
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed-effects Model for Repeated Measures
NSAID	Nonsteroidal Anti-Inflammatory Drug
PCP	Phencyclidine
PGI	Pepsinogen I
PGII	Pepsinogen II
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic
PPI	Proton Pump Inhibitor
PRO	Patient Reported Outcome
PWC-20	Physician Withdrawal Checklist 20-items
QD	Once Daily
SAMe	S-Adenosyl Methionine
SCID-CT	Structured Clinical Interview for DSM-5 Axis I Disorders Clinical Trials
SATE	Self-Assessment of Treatment Experience
SD	Standard Deviation
SDS	Sheehan Disability Scale
SHAPS	Snaith-Hamilton Pleasure Scale

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SIGH-A	Structured Interview Guide for the Hamilton Anxiety scale
SIGMA	The Structured Interview Guide for the MADRS
SMDDS	Symptoms of Major Depressive Disorder Scale
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
T3	Thyroxine/triiodothyronine
TEAE	Treatment-Emergent Adverse Event
TMS	Transcranial Magnetic Stimulation
TSH	Thyroid-Stimulating Hormone
ULN	Upper Limit of Normal
WOCBP	Women of Childbearing Potential

EXAMPLE 1

[00244] This was a multi-center, placebo-controlled, randomized, double-blind study in subjects with MDD who have had an inadequate response to SSRI/SNRI treatment. Aticaprant was evaluated as an adjunctive therapy; therefore, eligible subjects were maintained on their SSRI/SNRI treatment without change throughout the study. At least 50% of recruited subjects had to be anhedonic (as measured by SHAPS total score ≥ 20).

A. Objectives

[00245] The primary objective was to evaluate the efficacy of aticaprant compared to placebo when administered as adjunctive treatment in subjects with MDD partially responsive to SSRI / SNRI treatment in terms of reduction of symptoms of depression, as assessed by the change from baseline on the MADRS in non-responders during the placebo lead-in period.

[00246] The secondary objectives are:

- i. To evaluate the efficacy of aticaprant compared to placebo when administered as adjunctive treatment in subjects with MDD partially responsive to SSRI/SNRI treatment in terms of reduction of symptoms of depression, as assessed by the change from baseline on the MADRS in both responders and non-responders during the placebo lead-in period.
- ii. To investigate the overall safety and tolerability of treatment with

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adjunctive aticaprant in subjects with MDD when used in combination with a SSRI or SNRI.

- iii. To investigate the effect of aticaprant versus placebo on depression related anhedonia as assessed by the SHAPS.
 - iv. To investigate the effect of aticaprant on symptoms of depression using the Clinical Global Impression-Severity (CGI-S), the patient reported Symptoms of Major Depressive Disorder Scale (SMDDS) and the self-assessment of treatment experience (SATE).
 - v. To investigate the effect of aticaprant on symptoms of anxiety using the HAM-A and on core symptoms of anxiety using the HAM-A₆ subscale.
 - vi. To assess the plasma PK of aticaprant in subjects with MDD and explore its relationship with efficacy and safety parameters.
- [00247] Secondary exploratory objectives include:
- i. To explore the effect of aticaprant on aspects of cognitive and executive function using the CPFQ.
 - ii. To explore mood-related biomarkers (including but not limited to growth factors, HPA axis markers, immune system activation, metabolic markers) and genetic/epigenetic variation that may be related to clinical response, nonresponse, or safety and tolerability parameters of aticaprant.

B. Study Design

[00248] For each subject, the study consisted of two phases: a screening phase of up to 5 weeks and a double-blind treatment phase lasting 11 weeks. See, Fig. 1.

[00249] Subjects with MDD who have had treatment initiated with a permitted SSRI/SNRI and have had an inadequate or only partial response to this treatment were screened. Assessments include the MINI, Antidepressant Treatment History Questionnaire (TRQ), and MADRS.

[00250] The treatment phase consisted of 3 periods. A placebo lead-in period of concealed duration, after which subjects entered the double-blind treatment period when they were randomly assigned to 10 mg aticaprant (two 5 mg capsules) or continue placebo for 6 weeks. Each capsule contained aticaprant (5 mg), microcrystalline cellulose (94.95 mg), and magnesium stearate (0.05 mg) in a hard gelatin capsule. Subjects who completed the

treatment period, entered the withdrawal period and were treated with placebo for the remaining time of the treatment phase. The total duration for each subject was approximately 16 weeks. There were 11 scheduled visits, including screening. An overall flow diagram is shown in Fig. 1.

[00251] Subjects were screened within 35 to 2 days prior to Day 1 to ascertain their eligibility per the inclusion and exclusion criteria. The symptoms of depression were assessed using the structured interview guide for the MADRS.

Double-Blind Treatment Phase

[00252] The duration of the double-blind treatment phase was 11 weeks divided into 3 periods. The subject received medication after completion of the visit on Day 1. The first dose was taken at home on Day 2. All medication was taken in fasting condition. At Visits 3, 4 and 5, the subjects were re-randomized to blind subjects the duration of the placebo lead-in period. During the double-blind phase, the subjects visited the center for out-patient visits every 1 to 2 weeks. See, Table 1.

[illegible]

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engagement ^k	
Adverse events	continuous
Concomitant medication	continuous
EW = early withdrawal; a. Visits should be conducted $\pm$ 3 days of the scheduled day (based on Visit 2, not based on previous visit). b. If a subject discontinues treatment before the end of the double-blind treatment phase, EW visit should be completed. d. At home: In fasting condition. At clinic visit days: Use blisters dispensed at the previous visit. In fasting condition after completion of predose assessments. e. When Visit 11 is planned up to 3 days later, continue medication. j. During the first screening visit and by telephone up to 4 days before Visit 2, if 2 weeks or more elapse between the MADRS rating at screening and Visit 2. k. Using Q1.6-app on subjects' smartphone. l. Breakfast, lunch or dinner after drug intake at site.	

[00253] *Lead-in period:* Subjects who successfully complete the baseline examination visit at the clinical site/unit, were treated with placebo for the entire duration of the lead-in period.

[00254] *Treatment period:* At the end of the lead-in period both placebo lead-in responders and placebo lead-in non-responders were randomized to receive either placebo or 10 mg aticaprant in a 1:1 ratio for 6 weeks. Subjects remained blinded to exact timing of the randomization, response criterion and drug treatment assignment for each subject.

[00255] *Withdrawal period:* Subjects who completed the double-blind treatment period prior to the end of Week 11 entered the withdrawal period where they were treated with placebo for the remaining time of the treatment phase.

C. Dosage and Administration

[00256] Aticaprant was supplied as 5-mg capsules. Placebo was supplied as matching capsules. All subjects took 2 capsules QD. The capsules were taken daily from Day 2 to Day 78 in fasting condition with some water (fasting for at least 4 hours before dosing). Medication was taken before breakfast. If the subject has forgotten to take the medication before breakfast, this was done before the next following meal, at the latest at dinner of the same day. If the subject remembered later than dinner, the dose of that day was omitted, and the subject took the dose before breakfast on the next day.

[00257] When Visit 11 was planned up to 3 days later, the subject continued medication until Visit 11.

[00258] The capsules were swallowed whole and not chewed, divided, dissolved or crushed. After having taken the medication, subjects did not to eat or drink for at least 30 minutes.

[00259] The first dose was taken in fasting condition on Day 2 of the double-blind phase. The dose of the medication was:

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- 10 mg aticaprant: 2 capsules of 5 mg aticaprant
- Placebo: 2 placebo capsules.

[00260] Medication dose was adjusted as needed to 5 mg QD based on the results of a blinded review of the safety data. When a dose reduction has been decided on, this only applied to new subjects and the dose of medication was:

- 5 mg aticaprant: 1 capsule of 5 mg aticaprant
- Placebo: 1 placebo capsule.

[00261] As used herein, the Enriched ITT Analysis Set (eITT) is defined as all enrolled lead-in placebo non-responders who were randomized into a treatment period, received at least one dose of study medication in the treatment period and have at least one post-baseline MADRS assessment during the treatment period. Similarly, the Full ITT Analysis Set (fITT) is defined as all enrolled subjects who were randomized into a treatment period, received at least one dose of study medication in the treatment period and have at least one post-treatment baseline assessment of MADRS during the treatment period.

D. Clinical assessments

[00262] (i) Depression: Montgomery–Åsberg Depression Rating Scale (MADRS), Clinical Global Impression – Severity (CGI-S), Symptoms of Major Depressive Disorder Scale (SMDDS), and Self-assessment of treatment experience (SATE)

[00263] (ii) Anhedonia: Snaith-Hamilton Pleasure Scale (SHAPS)

[00264] (iii) Anxiety: Structured Interview Guide for the Hamilton Anxiety scale (SIGH-A) and HAM-A6

[00265] (iv) Effects on Cognition: The Cognitive and Physical Functioning Questionnaire (CPFQ)

[00266] (v) Safety Assessments: Standard safety assessments including physical and neurological examination, vital signs, 12-lead ECG, clinical chemistry, hematology, and urinalysis was performed. Based on observations of GI complaints in previous studies, a panel including PGI, PGII, G17 and Hp IgG was added to the clinical laboratory test panel to test for stomach mucosa status.

[00267] (vi) Suicidal ideation: C-SSRS

[00268] (vii) Exploratory: CPFQ

[00269] (viii) Central sedating effects: Karolinska Sleepiness Scale

[00270] (ix) Sexual dysfunction: ASEX

E. Patient Population

[00271] Of 184 subjects, 169 were randomized into the treatment period and included in the safety population, while 166 subjects were considered for the full ITT population. Out of the 166 subjects in the full ITT population, 121 (73%) were lead-in placebo non-responders (enriched ITT population) and the remaining 45 (27%) were lead-in placebo responders. Of the 121 subjects in the enriched population, 112 (92.6%) were white and 84 (69.4%) were female. The mean age was 41.6 years, ranging from 19 to 64 years. All subjects had anhedonia (defined as SHAPS total score ≥ 20) at treatment baseline. A high anhedonia level (defined as SHAPS total score ≥ 38) was observed in 43.8% of the subjects. In general, the treatment groups were similar with respect to the baseline characteristics. Subject demographics for the eITT and safety analysis are provided in Tables 2 and 3.

Table 2: Summary of Demographics and Baseline Characteristics; Full Safety Analysis			
	Placebo (N=84)	aticaprant 10mg (N=85)	Total (N=169)
Age (Years)			
N	84	85	169
Mean (SD)	42.1 (12.54)	43.0 (12.81)	42.6 (12.65)
Median	43.5	43.0	43.0
Range	(19; 64)	(21; 64)	(19; 64)
Gender			
N	84	85	169
Female	62 (73.8%)	60 (70.6%)	122 (72.2%)
Male	22 (26.2%)	25 (29.4%)	47 (27.8%)
Race			
N	84	85	169
American Indian or Alaska Native	1 (1.2%)	0	1 (0.6%)
Asian	2 (2.4%)	2 (2.4%)	4 (2.4%)
Black or African American	2 (2.4%)	5 (5.9%)	7 (4.1%)
White	79 (94.0%)	78 (91.8%)	157 (92.9%)
Ethnicity			
N	84	85	169
Hispanic or Latino	10 (11.9%)	13 (15.3%)	23 (13.6%)
Not Hispanic or Latino	74 (88.1%)	72 (84.7%)	146 (86.4%)
Country			
N	84	85	169
Germany	4 (4.8%)	5 (5.9%)	9 (5.3%)
Moldova	15 (17.9%)	14 (16.5%)	29 (17.2%)

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Russia	25 (29.8%)	21 (24.7%)	46 (27.2%)
Ukraine	9 (10.7%)	7 (8.2%)	16 (9.5%)
United Kingdom	10 (11.9%)	15 (17.6%)	25 (14.8%)
United States	21 (25.0%)	23 (27.1%)	44 (26.0%)
Baseline Height (cm)			
N	84	85	169
Mean (SD)	167.4 (7.91)	168.2 (8.64)	167.8 (8.27)
Median	167.5	167.6	167.6
Range	(150; 183)	(152; 195)	(150; 195)
Baseline Weight (kg)			
N	84	85	169
Mean (SD)	76.2 (14.73)	78.7 (15.23)	77.4 (14.99)
Median	75.3	78.9	77.1
Range	(47; 116)	(42; 119)	(42; 119)
Baseline BMI (kg/m²)			
N	84	85	169
Mean (SD)	27.2 (4.92)	27.7 (4.56)	27.5 (4.73)
Median	26.6	28.1	27.6
Range	(19; 35)	(18; 35)	(18; 35)
Presence of Anhedonia at Baseline			
N	84	85	169
No	0	1 (1.2%)	1 (0.6%)
Yes	84 (100.0%)	84 (98.8%)	168 (99.4%)
Lead-in response status			
N	84	85	169
No	62 (73.8%)	62 (72.9%)	124 (73.4%)
Yes	22 (26.2%)	23 (27.1%)	45 (26.6%)

Table 3: Summary of Demographics and Baseline Characteristics; eITT

	Placebo (N=61)	aticaprant 10mg (N=60)	Total (N=121)
Age (Years)			
N	61	60	121
Mean (SD)	41.6 (12.34)	41.6 (12.78)	41.6 (12.51)
Median	43.0	40.5	42.0
Range	(19; 64)	(21; 64)	(19; 64)
Gender			
N	61	60	121
Female	42 (68.9%)	42 (70.0%)	84 (69.4%)
Male	19 (31.1%)	18 (30.0%)	37 (30.6%)
Race			
N	61	60	121
American Indian or Alaska Native	1 (1.6%)	0	1 (0.8%)

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Asian	2 (3.3%)	1 (1.7%)	3 (2.5%)
Black or African American	2 (3.3%)	3 (5.0%)	5 (4.1%)
White	56 (91.8%)	56 (93.3%)	112 (92.6%)
Ethnicity			
N	61	60	121
Hispanic or Latino	3 (4.9%)	7 (11.7%)	10 (8.3%)
Not Hispanic or Latino	58 (95.1%)	53 (88.3%)	111 (91.7%)
Country			
N	61	60	121
Germany	4 (6.6%)	4 (6.7%)	8 (6.6%)
Moldova	15 (24.6%)	14 (23.3%)	29 (24.0%)
Russia	19 (31.1%)	18 (30.0%)	37 (30.6%)
Ukraine	7 (11.5%)	5 (8.3%)	12 (9.9%)
United Kingdom	6 (9.8%)	10 (16.7%)	16 (13.2%)
United States	10 (16.4%)	9 (15.0%)	19 (15.7%)
Baseline Height (cm)			
N	61	60	121
Mean (SD)	168.1 (8.19)	167.3 (8.10)	167.7 (8.13)
Median	168.0	166.3	167.0
Range	(151; 183)	(152; 186)	(151; 186)
Baseline Weight (kg)			
N	61	60	121
Mean (SD)	74.7 (14.19)	76.8 (15.12)	75.7 (14.63)
Median	74.2	77.1	75.6
Range	(47; 116)	(42; 119)	(42; 119)
Baseline BMI (kg/m²)			
N	61	60	121
Mean (SD)	26.4 (4.67)	27.3 (4.36)	26.9 (4.52)
Median	25.7	27.8	26.7
Range	(19; 35)	(18; 35)	(18; 35)
Presence of Anhedonia at Baseline			
N	61	60	121
No	0	0	0
Yes	61 (100.0%)	60 (100.0%)	121 (100.0%)
Lead-in response status			
N	61	60	121
No	61 (100.0%)	60 (100.0%)	121 (100.0%)
Yes	0	0	0

E. Evaluations of Efficacy

[00272] At the end of the lead-in period, response status of the subjects was assessed according to the double-blind response criteria based on reduction in MADRS relative to lead-in baseline. Both lead-in placebo responders and lead-in placebo non-

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responders were randomly assigned in a 1:1 ratio to either aticaprant or placebo in the treatment period. The randomization was stratified by lead-in response status (non-responders: <30% reduction from baseline in MADRS total score at the end of the lead-in period vs responders: $\geq 30\%$ reduction from baseline at the end of the lead-in period) and presence/absence of anhedonia (presence defined as SHAPS total score ≥ 20).

[00273] Treatment duration: The study consisted of two periods: a screening phase of up to 5 weeks and a double-blind treatment phase of 11 weeks. The double-blind treatment phase of the trial consisted of 3 periods. The first period was a placebo lead-in of 3 weeks, after which subjects entered the treatment period when they were randomly assigned to aticaprant or continuation on placebo for 6 weeks. Subjects who successfully completed the treatment period were treated with placebo during a 2-week withdrawal period, *i.e.*, Period 3. The total duration for each subject was approximately 16 weeks.

[00274] Primary analysis set for efficacy: The efficacy analysis is based on the eITT set defined as all enrolled lead-in placebo non-responders who were randomized into the treatment period, received at least one dose of medication, and have at least one post-baseline MADRS assessment during the treatment period. The primary analysis set is used for all efficacy endpoints.

[00275] Secondary analysis set for efficacy: A secondary analysis set is the fITT set defined as all enrolled subjects who were randomized into the treatment period, received at least one dose of medication, and have at least one post-baseline MADRS assessment during the treatment period. The secondary analysis set is used for all efficacy endpoints to examine the effect in the general population, which may be useful for designing subsequent studies in the development program.

[00276] Analysis set for safety: The safety analysis is based on the full safety analysis set, defined as all enrolled subjects who received at least one dose of medication in the treatment period.

[00277] The efficacy endpoints were presented for both the eITT and the fITT.

[00278] Level of significance: The analysis of primary efficacy endpoint was performed at a significance level of 0.20 (one-sided). The analysis of secondary efficacy endpoints was performed at a significance level of 0.20 (two-sided). No adjustment for multiple comparisons was performed.

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F. Results

[00279] (i) Primary Endpoint: Change from Treatment Baseline in MADRS Total Score at Treatment Week 6 in Non-Responders during Placebo Lead-in Period

Enriched ITT Analysis Set

[00280] The mean (SD) MADRS total score at treatment baseline was 29.0 (4.61), ranging from 19 to 41. See, Fig. 2. The mean change from treatment baseline (SD) in MADRS total score at treatment week 6 was -10.2 (8.44) for aticaprant and -8.2 (8.53) for placebo. The observed effect size was 0.23. See, Tables 4-6 and Fig. 6.

Table 4: Summary of Baseline Psychiatry Rating Scales at the Start of the Lead-in and Treatment Periods; eITT Analysis Set

	MADRS Total Score			SHAPS Total Score		
	N	Mean (SD)	Median (Range)	N	Mean (SD)	Median (Range)
Lead-in Baseline						
Placebo	61	33.4 (4.25)	34.0 (26; 42)	61	38.0 (6.28)	38.0 (22; 55)
aticaprant	60	32.5 (4.18)	32.0 (25; 45)	60	38.3 (5.66)	38.0 (21; 53)
Total	121	32.9 (4.22)	33.0 (25; 45)	121	38.1 (5.96)	38.0 (21; 55)
Treatment Baseline						
Placebo	61	29.2 (5.47)	29.0 (19; 41)	61	36.8 (5.75)	37.0 (23; 50)
aticaprant	60	28.7 (3.58)	28.5 (21; 36)	60	36.4 (5.16)	36.5 (20; 49)
Total	121	29.0 (4.61)	29.0 (19; 41)	121	36.6 (5.45)	37.0 (20; 50)

Table 5: MADRS Total Score: Mean Changes to Placebo During the Treatment Period; eITT Analysis Set

Analysis Treatment	Visit	N	Mean Change from Baseline (SD)	Mean Change to Placebo (SD pooled)	90% CI for Mean Change to Placebo	Effect Size
Treatment Week 1						
Placebo		61	-2.2 (3.73)			
aticaprant		60	-3.3 (5.21)	-1.1 (4.52)	[-2.4,0.3]	-0.24
Treatment Week 3						
Placebo		59	-4.3 (5.99)			
aticaprant		59	-5.7 (6.38)	-1.4 (6.18)	[-3.3,0.5]	-0.22
Treatment Week 4						
Placebo		60	-6.4 (6.66)			
aticaprant		57	-7.3 (7.35)	-0.9 (7.00)	[-3.1,1.2]	-0.14
Treatment Week 5						
Placebo		60	-7.4 (7.15)			
aticaprant		55	-8.4 (7.36)	-1.1 (7.25)	[-3.3,1.2]	-0.14

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[00281] Based on the results of a MMRM model with subject as random effect; country, treatment, time and time-by-treatment interaction as factors; and baseline MADRS total score as continuous covariate a significant positive efficacy signal was detected for aticaprant versus placebo at the one-sided 0.20 significance level. The estimated LS mean difference at treatment week 6 between aticaprant and placebo was -2.1 with 80% 1-sided CI upper limit of -1.09. The corresponding p-value was 0.044. The treatment effect was larger in the fITT than in the eITT population: -3.1 with 80% 1-sided CI upper limit of -2.2 (p=0.002). The effect size was 0.36 and 0.23, respectively. See, Figs. 2 and 3.

Full ITT Analysis Set

[00282] The mean (SD) baseline MADRS total score at treatment baseline was 25.3 (7.86), ranging from 0 to 41. See, Figs. 7A and 7B. The mean changes from treatment baseline in MADRS total score at Treatment Week 6 for fITT were smaller than for eITT: -9.7 (8.02) for aticaprant and -6.6 (8.57) for placebo. The observed effect size was 0.36. These results illustrate a statistical superiority over placebo with a durability of effect with the greatest difference seen at week 6. See, Table 7.

Table 7: Summary of Baseline Psychiatry Rating Scales at the Start of the Lead-in and Treatment Periods; fITT Analysis Set						
	MADRS Total Score				SHAPS Total Score	
	N	Mean (SD)	Median (Range)	N	Mean (SD)	Median (Range)
Lead-in Baseline						
Placebo	83	32.8 (4.25)	33.0 (26; 42)	83	37.8 (6.01)	38.0 (22; 55)
aticaprant	83	32.4 (4.27)	32.0 (21; 45)	83	37.3 (6.23)	38.0 (14; 53)
Total	166	32.6 (4.25)	32.0 (21; 45)	166	37.6 (6.11)	38.0 (14; 55)
Treatment Baseline						
Placebo	83	25.7 (7.73)	26.0 (10; 41)	83	36.3 (5.44)	36.0 (23; 50)
aticaprant	83	24.8 (8.02)	27.0 (0; 36)	83	35.0 (5.85)	36.0 (14; 49)
Total	166	25.3 (7.86)	26.5 (0; 41)	166	35.6 (5.67)	36.0 (14; 50)

[00283] Significant effect for aticaprant versus placebo in fITT population was also detected. The estimated LS mean difference at treatment week 6 between aticaprant and placebo was -3.1 with 80% 1- sided CI upper limit of -2.21. The corresponding p-value was 0.002. See, Tables 8-9 and Fig. 3.

Table 8: MADRS Total Score: MMRM Results - Estimated LS Means and Comparison versus Placebo; fITT Analysis Set

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Analysis Visit Treatment	N	Mean (SD)	Mean (SD)	Change from Baseline			
				LSMean (SE)	LSMean Difference (SE) \ Treatment Placebo	60% Confidence Interval on Difference	p- value ^a
Treatment Week 1							
Placebo	83	24.0 (8.12)	-1.8 (4.00)	-1.7 (0.78)			
aticaprant	83	21.7 (8.78)	-3.1 (4.81)	-3.2 (0.77)	-1.6 (1.03)	[-2.44,- 0.70]	0.0653
Treatment Week 3							
Placebo	81	22.2 (9.28)	-3.4 (6.50)	-3.4 (0.78)			
aticaprant	80	20.0 (8.53)	-5.1 (6.74)	-5.2 (0.78)	-1.9 (1.04)	[-2.74,- 0.99]	0.0368
Treatment Week 4							
Placebo	82	20.8 (9.24)	-4.9 (7.02)	-4.8 (0.78)			
aticaprant	78	17.9 (9.32)	-7.2 (7.02)	-7.3 (0.78)	-2.5 (1.04)	[-3.34,- 1.59]	0.0093
Treatment Week 5							
Placebo	82	19.2 (9.89)	-6.4 (7.16)	-6.3 (0.78)			
aticaprant	76	16.7 (9.47)	-8.3 (7.48)	-8.7 (0.78)	-2.4 (1.05)	[-3.24,- 1.47]	0.0125
Treatment Week 6							
Placebo	81	19.0 (10.35)	-6.6 (8.57)	-6.5 (0.78)			
aticaprant	77	15.9 (9.09)	-9.7 (8.02)	-9.6 (0.79)	-3.1 (1.05)	[-3.97,- 2.21]	0.0017
^a One-sided test for no difference between treatments from a MMRM model with subject as random effect; country, treatment, time and time-by-treatment interaction as factors; and baseline MADRS total score as continuous covariate. An AR(1) variance-covariance matrix was employed							

Table 9: MADRS (Montgomery–Åsberg Depression Rating Scale) Total Score: Mean Changes to Placebo During the Treatment Period; fITT Analysis Set					
Analysis Treatment	Visit	N	Mean Change to Placebo (SD pooled)	90% CI for Mean Change to Placebo	Effect Size
Treatment Week 1					
Placebo		83			

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aticaprant	83	-1.3 (4.43)	[-2.4,-0.2]	-0.29
Treatment Week 3				
Placebo	81			
aticaprant	80	-1.7 (6.62)	[-3.4,0.0]	-0.26
Treatment Week 4				
Placebo	82			
aticaprant	78	-2.3 (7.02)	[-4.1,-0.4]	-0.32
Treatment Week 5				
Placebo	82			
aticaprant	76	-1.9 (7.31)	[-3.9,-0.0]	-0.26
Treatment Week 6				
Placebo	81			
aticaprant	77	-3.0 (8.31)	[-5.2,-0.8]	-0.36
Negative change from baseline indicates improvement. Negative change to Placebo indicates favorable aticaprant effect. Negative effect size favors aticaprant; positive effect size favors Placebo.				

COVID-19 impact on primary efficacy assessment

[00284] Supplementary analysis was conducted using the same MMRM model as described for the primary analysis on all the data collected prior to 15-March-2020 (estimated date of the COVID-19 lockdowns in most of the countries participating in the trial). Seventeen percent of the subjects in fITT and 19% in eITT population had at least one of the MADRS assessment excluded from the model due to COVID-19 impact. Results of the analysis corroborated the findings of the primary efficacy analysis in both: eITT and fITT populations. LSMeans difference estimate was -3.0 (80% 1-sided CI upper limit of -1.88) for eITT and -3.4 (80% 1-sided CI upper limit of -2.51) for fITT.

(ii) Secondary Endpoints

MADRS Remission Rates over Treatment Period

[00285] At Treatment Week 6 the percentage of subjects with MADRS remission (MADRS total score ≤ 10) in the eITT population was 16.9% for aticaprant and 16.9% for placebo. Treatment week 6 remission rates in fITT population were 31.2% for aticaprant and 22.2% for placebo. For both populations (eITT and fITT), no significant treatment differences were detected at treatment week 6 using Chi-square test (2-sided $p=0.999$ and $p=0.203$, respectively). See, Figs. 8 and 9.

MADRS Response Rates (at least 30% improvement) over Treatment Period

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[00286] The percentage of subjects with $\geq 30\%$ improvement in MADRS total score at treatment week 6 in the eITT population was 57.6% for aticaprant and 45.8% for placebo. Treatment week 6 response rates in fITT population were 61.8% for aticaprant and for 44.4% placebo. For both populations, treatment differences at Treatment Week 6 were significant at 20% 2-sided significance level (Chi-square test: $p=0.197$ for eITT and $p=0.029$ for fITT).

MADRS Response Rates (at least 50% improvement) over Treatment Period

[00287] The percentage of subjects with $\geq 50\%$ improvement in MADRS total score at treatment week 6 in the eITT population was 35.6% for aticaprant and 22.0% for placebo. Treatment week 6 response rates in fITT population were 38.2% for Aticaprant and 23.5% for placebo. For both populations, treatment differences at treatment week 6 were significant at 20% 2-sided significance level (Chi-square test: $p=0.104$ for eITT and $p=0.046$ for fITT).

See, Table 10 and Figs. 10-13.

Table 10: Change from Treatment Baseline in MADRS Total Score at Treatment Week 6 in Both Responders and Non-Responders during Placebo Lead-in Period		
End point values	Placebo	aticaprant 10 milligrams (mg)
Number of subjects analyzed	81	77
Units: score on a scale		
Measure Type: Least Squares Mean (Standard Error)	-6.5 ± 0.78	-9.6 ± 0.79
P-value	$= 0.0017$	
Parameter type	Least Squares Mean Difference	
Point estimate	-3.1	
Confidence interval		
level	80%	
sides	1-Sided	
lower limit	-	
upper limit	-2.21	
Variability estimate	Standard Error of the mean	
Dispersion value	1.05	

Changes in SHAPS total score from Treatment baseline to Treatment Week 6

Enriched ITT Analysis Set

[00288] In eITT population, in a subgroup of subjects with high anhedonia level (baseline SHAPS total score ≥ 38), larger differences between aticaprant placebo at

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Treatment Week 6 were observed than in subjects with low anhedonia level ($20 \leq$ baseline SHAPS total score <38). The effect size was 0.38 and 0.11, respectively.

[00289] The mean (SD) SHAPS total score at treatment baseline was 36.6 (5.45), ranging from 20 to 50. The mean change from treatment baseline (SD) in SHAPS total score at treatment week 6 was -4.6 (6.23) for aticaprant and -4.2 (5.04) for placebo. The observed effect size was 0.07. See, Table 11 and Figs. 14 and 23.

Table 11: SHAPS Total Score: Mean Changes to Placebo During the Treatment Period; eITT Analysis Set						
Analysis Treatment	Visit	N	Mean Change from Baseline (SD)	Mean Change to Placebo (SD pooled)	90% CI for Mean Change to Placebo	Effect Size
Treatment Week 1						
Placebo		61	-1.3 (3.17)			
aticaprant		60	-1.9 (4.30)	-0.6 (3.77)	[-1.7,0.6]	-0.15
Treatment Week 3						
Placebo		59	-2.2 (4.65)			
aticaprant		59	-3.4 (5.25)	-1.2 (4.96)	[-2.8,0.3]	-0.25
Treatment Week 4						
Placebo		60	-3.3 (4.47)			
aticaprant		57	-4.5 (5.89)	-1.2 (5.21)	[-2.8,0.4]	-0.23
Treatment Week 5						
Placebo		60	-3.9 (4.88)			
aticaprant		56	-4.3 (6.07)	-0.4 (5.49)	[-2.1,1.3]	-0.08
Treatment Week 6						
Placebo		59	-4.2 (5.04)			
aticaprant		59	-4.6 (6.23)	-0.4 (5.66)	[-2.1,1.3]	-0.07
Negative change from baseline indicates improvement. Negative change to Placebo indicates favorable aticaprant effect. Negative effect size favors aticaprant; positive effect size favors Placebo.						

[00290] Changes in SHAPS total score were analyzed with the same MMRM model used for MADRS total score. The estimated LS Mean difference with 80% 2-sided CI at treatment week 6 between aticaprant and placebo was -0.7 [-1.81, 0.41]. See, Fig. 4 and Tables 12 and 13 and Fig. 15. The corresponding p-value was 0.419.

Table 12: SHAPS Total Score: MMRM Results - Estimated LS Means and Comparison versus Placebo; eITT Analysis Set							
			Change from Baseline				
Analysis Visit	N	Mean	Mean	LSMean	LSMean	60%	p-

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Treatment		(SD)	(SD)	(SE)	Difference (SE) \ Treatment Placebo	Confidence Interval on Difference	value ^a
Treatment Week 1							
Placebo	61	35.5 (6.00)	-1.3 (3.17)	-0.9 (0.63)			
aticaprant	60	34.5 (5.63)	-1.9 (4.30)	-1.7 (0.64)	-0.8 (0.86)	[-1.90,0.31]	0.3542
Treatment Week 3							
Placebo	59	34.9 (6.09)	-2.2 (4.65)	-1.8 (0.64)			
aticaprant	59	33.0 (6.39)	-3.4 (5.25)	-3.2 (0.64)	-1.4 (0.86)	[-2.53,-0.31]	0.1005
Treatment Week 4							
Placebo	60	33.7 (5.89)	-3.3 (4.47)	-2.9 (0.63)			
aticaprant	57	32.0 (6.24)	-4.5 (5.89)	-4.3 (0.64)	-1.4 (0.86)	[-2.48,-0.26]	0.1131
Treatment Week 5							
Placebo	60	33.1 (5.88)	-3.9 (4.88)	-3.5 (0.64)			
aticaprant	56	32.4 (6.61)	-4.3 (6.07)	-4.0 (0.64)	-0.5 (0.87)	[-1.65,0.57]	0.5332
Treatment Week 6							
Placebo	59	32.9 (6.04)	-4.2 (5.04)	-3.7 (0.64)			
aticaprant	59	31.9 (6.60)	-4.6 (6.23)	-4.4 (0.64)	-0.7 (0.87)	[-1.81,0.41]	0.4188
^a two-sided test for no difference between treatments from a MMRM model with subject as random effect; country, treatment, time and time-by-treatment interaction as factors; and baseline SHAPS total score as continuous covariate. An AR(1) variance-covariance matrix was employed.							

Table 13: SHAPS Total Score: MMRM Results - Estimated LS Means and Comparison versus Placebo; fITT Analysis Set

			Change from Baseline				
Analysis Visit	N	Mean (SD)	Mean (SD)	LSMean (SE)	LSMean Difference (SE) \ Treatment Placebo	60% Confidence Interval on Difference	p-value ^a
Treatment Week 1							
Placebo	83	34.8 (5.86)	-1.5 (3.57)	-1.0 (0.54)			

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aticaprant	83	32.9 (6.09)	-2.0 (4.05)	-1.9 (0.54)	-1.0 (0.72)	[-1.88,- 0.02]	0.1888
Treatment Week 3							
Placebo	81	34.3 (6.36)	-2.2 (5.11)	-1.7 (0.54)			
aticaprant	80	31.9 (6.54)	-3.2 (5.07)	-3.1 (0.54)	-1.4 (0.73)	[-2.32,- 0.45]	0.0580
Treatment Week 4							
Placebo	82	33.4 (5.70)	-3.0 (4.41)	-2.5 (0.54)			
aticaprant	78	30.8 (6.37)	-4.2 (5.70)	-4.1 (0.55)	-1.6 (0.73)	[-2.51,- 0.63]	0.0321
Treatment Week 5							
Placebo	82	32.6 (5.63)	-3.8 (4.76)	-3.3 (0.55)			
aticaprant	77	30.9 (6.76)	-4.3 (5.70)	-4.1 (0.55)	-0.8 (0.73)	[-1.71, 0.17]	0.2912
Treatment Week 6							
Placebo	81	32.2 (5.81)	-4.2 (4.98)	-3.7 (0.55)			
aticaprant	77	30.5 (6.98)	-4.7 (5.91)	-4.5 (0.55)	-0.8 (0.73)	[-1.79, 0.10]	0.2503
^a two-sided test for no difference between treatments from a MMRM model with subject as random effect; country, treatment, time and time-by-treatment interaction as factors; and baseline SHAPS total score as continuous covariate. An AR(1) variance-covariance matrix was employed							

[00291] The estimated LS mean differences with 80% 2-sided CI at treatment week 6 between aticaprant and placebo was -0.8 [-1.79, 0.10]. The corresponding p-value was 0.250. See, Figs. 4 and 5.

Full ITT Analysis Set

[00292] Similar trend was observed in fITT population and differences were larger in magnitude than those observed in eITT population. The effect size was 0.51 and 0.29, respectively. The mean (SD) baseline SHAPS total score at treatment baseline was 35.6 (5.67), ranging from 14 to 50. The mean changes from treatment baseline in SHAPS total score at treatment week 6 for fITT population were similar to changes in eITT: -4.7 (5.91) for aticaprant and -4.2 (4.98) for placebo. The observed effect size was 0.08. See, Table 14.

Table 14: SHAPS Total Score: Mean Changes to Placebo During the Treatment Period; fITT Analysis Set

Analysis	Visit	N	Mean	Mean	90%CI for	Effect
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Treatment		Change from Baseline (SD)	Change to Placebo (SD pooled)	Mean Change to Placebo	Size
Treatment Week 1					
Placebo	83	-1.5 (3.57)			
aticaprant	83	-2.0 (4.05)	-0.6 (3.82)	[-1.5,0.4]	-0.15
Treatment Week 3					
Placebo	81	-2.2 (5.11)			
aticaprant	80	-3.2 (5.07)	-1.0 (5.09)	[-2.4,0.3]	-0.20
Treatment Week 4					
Placebo	82	-3.0 (4.41)			
aticaprant	78	-4.2 (5.70)	-1.2 (5.08)	[-2.5,0.1]	-0.23
Treatment Week 5					
Placebo	82	-3.8 (4.76)			
aticaprant	77	-4.3 (5.70)	-0.5 (5.24)	[-1.8,0.9]	-0.09
Treatment Week 6					
Placebo	81	-4.2 (4.98)			
aticaprant	77	-4.7 (5.91)	-0.5 (5.45)	[-1.9,1.0]	-0.08
Negative change from baseline indicates improvement. Negative change to Placebo indicates favorable aticaprant effect. Negative effect size favors aticaprant; positive effect size favors Placebo.					

Changes in MADRS total score from Treatment baseline to Treatment Week 6 by anhedonia level at baseline

Enriched ITT Analysis Set

[00293] In subgroup of subjects with high anhedonia level (SHAPS total score ≥ 38) at treatment baseline, $n=53$, larger differences between aticaprant and placebo at treatment Week 6 were observed than in subjects with low anhedonia level ($20 \leq$ baseline SHAPS total score <38), $n=65$: -3.4 with 90% 2-sided CI of [-7.5, 0.7] and -0.9 with 90% 2-sided CI of [-4.2, 2.5], respectively (Table 15). The observed effect size was 0.38 and 0.11, respectively.

Table 15: MADRS (Montgomery–Åsberg Depression Rating Scale) Total Score: Mean Changes to Placebo During the Treatment Period by Anhedonia Level at Treatment Baseline; eITT Analysis Set						
Analysis Treatment	Visit	N	Mean Change from Baseline (SD)	Mean Change to Placebo (SD pooled)	90% CI for Mean Change to Placebo	Effect size
<u>Low anhedonia</u>						
Treatment Week 1						
Placebo		34	-1.8 (3.43)			

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aticaprant	34	-2.3 (5.03)	-0.5 (4.30)	[-2.2,1.2]	-0.12
Treatment Week 3					
Placebo	32	-4.8 (5.70)			
aticaprant	33	-4.9 (5.99)	-0.1 (5.85)	[-2.5,2.4]	-0.01
Treatment Week 4					
Placebo	33	-6.5 (6.16)			
aticaprant	32	-6.4 (7.40)	0.0 (6.80)	[-2.8,2.9]	0.01
Treatment Week 5					
Placebo	33	-7.6 (6.80)			
aticaprant	29	-7.2 (6.46)	0.3 (6.65)	[-2.5,3.2]	0.05
Treatment Week 6					
Placebo	32	-8.3 (8.25)			
aticaprant	33	-9.2 (8.01)	-0.9 (8.13)	[-4.2,2.5]	-0.11
<u>High anhedonia</u>					
Treatment Week 1					
Placebo	27	-2.7 (4.08)			
aticaprant	26	-4.6 (5.25)	-1.8 (4.69)	[-4.0,0.3]	-0.39
Treatment Week 3					
Placebo	27	-3.6 (6.35)			
aticaprant	26	-6.7 (6.83)	-3.0 (6.59)	[-6.1,0.0]	-0.46
Treatment Week 4					
Placebo	27	-6.3 (7.34)			
aticaprant	25	-8.5 (7.26)	-2.2 (7.30)	[-5.6,1.2]	-0.30
Treatment Week 5					
Placebo	27	-7.1 (7.67)			
aticaprant	26	-9.7 (8.18)	-2.6 (7.93)	[-6.3,1.0]	-0.33
Treatment Week 6					
Placebo	27	-8.1 (9.01)			
aticaprant	26	-11.5 (8.95)	-3.4 (8.98)	[-7.5,0.7]	-0.38
Low Anhedonia level (SHAPS Total Score at Treatment Baseline ≥ 20 and < 38), High Anhedonia level (SHAPS Total Score at Treatment Baseline ≥ 38). The MADRS Total Score ranges from 0 to 60, with higher scores indicating greater severity of depression.					

Full ITT Analysis Set

[00294] A similar trend was observed in fITT population. The differences were larger in magnitude compared to eITT population: -4.6 with 90% 2-sided CI of [-8.4, -0.8] for subjects with high anhedonia level (n=63) and -2.3 with 90% 2-sided CI of [-5.0, 0.4] for subjects with low anhedonia level (n=94). See, Table 16. The observed effect size was 0.51 and 0.29, respectively.

Table 16: MADRS (Montgomery–Åsberg Depression Rating Scale) Total Score: Mean Changes to Placebo During the Treatment Period by Anhedonia Level at Treatment Baseline; fITT Analysis Set

Analysis Treatment	Visit	N	Mean Change from Baseline (SD)	Mean Change to Placebo (SD pooled)	90% CI for Mean Change to Placebo	Effect size
<u>Low anhedonia</u>						
Treatment Week 1						
Placebo		49	-1.3 (4.17)			
aticaprant		52	-2.4 (4.59)	-1.0 (4.39)	[-2.5,0.4]	-0.24
Treatment Week 3						
Placebo		47	-3.6 (6.04)			
aticaprant		49	-4.1 (6.67)	-0.5 (6.37)	[-2.7,1.7]	-0.08
Treatment Week 4						
Placebo		48	-4.9 (6.53)			
aticaprant		48	-6.4 (6.77)	-1.5 (6.65)	[-3.8,0.8]	-0.23
Treatment Week 5						
Placebo		48	-6.6 (6.82)			
aticaprant		45	-7.3 (6.90)	-0.7 (6.86)	[-3.1,1.7]	-0.10
Treatment Week 6						
Placebo		47	-6.5 (8.11)			
aticaprant		47	-8.8 (7.48)	-2.3 (7.80)	[-5.0,0.4]	-0.29
<u>High anhedonia</u>						
Treatment Week 1						
Placebo		34	-2.4 (3.71)			
aticaprant		30	-4.4 (5.04)	-2.0 (4.38)	[-3.8,-0.1]	-0.45
Treatment Week 3						
Placebo		34	-3.1 (7.17)			
aticaprant		30	-6.9 (6.66)	-3.8 (6.94)	[-6.7,-0.9]	-0.54
Treatment Week 4						
Placebo		34	-4.8 (7.75)			
aticaprant		29	-8.6 (7.32)	-3.8 (7.56)	[-7.0,-0.6]	-0.50
Treatment Week 5						
Placebo		34	-6.2 (7.72)			
aticaprant		30	-10.2 (8.04)	-4.0 (7.87)	[-7.3,-0.7]	-0.51
Treatment Week 6						
Placebo		34	-6.8 (9.30)			
aticaprant		29	-11.3 (8.69)	-4.6 (9.03)	[-8.4,-0.8]	-0.51
Low Anhedonia level (SHAPS Total Score at Treatment Baseline ≥ 20 and < 38), High Anhedonia level (SHAPS Total Score at Treatment Baseline ≥ 38). The MADRS Total Score ranges from 0 to 60, with higher scores indicating greater severity of depression.						

[00295] This data illustrates that segmentation into high vs low anhedonia had a benefit for treating MDD: higher treatment effect for Aticaprant. Further, the placebo response was lower in patients with high anhedonia, as compared to low anhedonia.

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Change from Treatment Baseline in CGI-S Total Score at Treatment

Table 17: Change from Treatment Baseline in CGI-S Total Score at Treatment		
End point values	Placebo	aticaprant 10 milligrams (mg)
Number of subjects analyzed	59	59
Units: Scores on a scale		
Measure Type: Arithmetic Mean (SD)	-0.76 ± 0.858	-0.92 ± 1.039

Change from Treatment Baseline in SMDDS Total Score at Treatment Week 6

Table 18: Change from Treatment Baseline in SMDDS Total Score at Treatment Week 6		
End point values	Placebo	aticaprant 10 milligrams (mg)
Number of subjects analyzed	59	59
Units: Scores on a scale		
Measure Type: Arithmetic Mean (SD)	-8.49 ± 9.567	-8.03 ± 9.957

Number of Subjects with SATE Score at Treatment Week 6

Table 19: Number of Subjects with SATE Score at Treatment Week 6		
End point values	Placebo	aticaprant 10 milligrams (mg)
Number of subjects analyzed	61	60
Units: subjects		
Overall Depression (Got worse) (n= 40, 30)	1	0
Overall Depression (Not changed) (n= 40, 30)	12	9
Overall Depression (Improved) (n= 40, 30)	27	21
Depression Worsened (Slightly worse) (n= 1, 0)	1	0
Depression Worsened (Much worse) (n= 1, 0)	0	0
Depression Worsened (Very much worse) (n=1,0)	0	0
Depression Slightly improved (n=27, 21)	13	15
Depression Much improved (n=27, 21)	11	6
Depression Very Much Improved (n=27, 21)	3	0

Change from Treatment Baseline in HAM-A6 Total Score at Treatment Week 6

Table 20: Change from Treatment Baseline in HAM-A6 Total Score at Treatment Week 6		
End point values	Placebo	aticaprant 10 milligrams (mg)
Number of subjects analyzed	59	59
Units: scores on a scale		
Measure Type: Arithmetic Mean (SD)	-2.19 ± 2.837	-2.73 ± 2.651

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[00296] These data show a greater improvement in HAMA6 score in aticaprant treated patients vs. placebo.

Change from Treatment Baseline in Structured Interview Guide for the SIGH-A Score at Treatment Week 6

Table 21: Change from Treatment Baseline in Structured Interview Guide for the SIGH-A Score at Treatment Week 6		
End point values	Placebo	aticaprant 10 milligrams (mg)
Number of subjects analyzed	59	59
Units: scores on a scale		
Measure Type: Arithmetic Mean (SD)	-5.37 ± 6.549	-5.85 ± 5.369

Maximum Plasma Concentration ($C_{\max}$) of Aticaprant

[00297] $C_{\max}$ is defined as maximum plasma concentration of aticaprant. The eITT population included all enrolled lead-in placebo non-responders who were randomized into a treatment period, received at least 1 dose of study medication, and had at least 1 post-baseline MADRS assessment during the treatment period. Here 'N' (number of subjects analyzed) includes the number of subjects evaluable for this endpoint. Here 'n' (number analyzed) included all subjects evaluable for specified time point categories.

Table 22: $C_{\max}$ of Aticaprant (10 mg)	
Number of subjects analyzed	58
Units: nanograms per milliliter (ng/mL)	
Measure Type: Arithmetic Mean (SD)	
Week 1 (n = 56)	32.7 ± 10.9
Week 3 (n = 56)	33.5 ± 11.1
Week 6 (n = 56)	34.3 ± 11.1
No statistical analyses of this end point.	

(iii) Safety Endpoints

[00298] Overall, in full safety analysis set 40/85 (47.1%) of subjects in the aticaprant group and 30/84 (35.7%) of subjects in the placebo group experienced at least one TEAE during the treatment period. See, Table 23.

Table 23: Overall Summary of Treatment-Emergent Adverse Events During the Treatment Period; Full Safety Analysis Set			
	Placebo (N=84) n (%)	aticaprant 10mg (N=85) n (%)	Overall (N=169) n (%)
Subjects with 1 or more TEAE	30 (35.7)	40 (47.1)	70 (41.4)

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Total subjects affected by non-serious adverse events	9 (10.7%)	23 (27.1%)	
Subjects with drug-related TEAE ^a	13 (15.5)	20 (23.5)	33 (19.5)
Subjects with TEAE leading to death	0	0	0
Subjects with 1 or more serious TEAE	1 (1.2)	0	1 (0.6)
Subjects with TEAE leading to discontinuation of agent	1 (1.2)	1 (1.2)	2 (1.2)
^a Drug relationships of possible, probable, and very likely are included in this category. Subjects are presented by the treatment received during the Treatment period.			

[00299] The most common TEAEs during the treatment period were headache (experienced by 10/85 subjects – 11.8% in the aticaprant group and by 6/84 subjects – 7.1 % in the placebo group) and diarrhea (experienced by 7/85 subjects – 8.2% in the aticaprant group and by 2/84 subjects – 2.4 % in the placebo group). See, Table 24.

Table 24: Treatment-Emergent Adverse Events by Body System or Organ Class and Dictionary-Derived Term in >=5% of Subjects in Either Treatment Group During the Treatment Period; Full Safety Analysis Set				
	Placebo (N=84)	aticaprant 10mg (N=85)	Overall (N=169)	
Body System Preferred Term	n (%)	n (%)	n (%)	
Total no. Subjects with Adverse Events	30 (36)	40 (47)	70 (41)	
Infections And Infestations	9 (11)	13 (15)	22 (13)	
Nasopharyngitis	2 (2)	5 (6)	7 (4)	
Nervous System Disorders	9 (11)	13 (15)	22 (13)	
Headache	6 (7)	10 (12)	16 (10)	
Gastrointestinal Disorders	9 (11)	12 (14)	21 (12)	
Diarrhea	2 (2)	7 (8)	9 (5)	
Skin And Subcutaneous Tissue Disorders	3 (4)	6 (7)	9 (5)	
Pruritus	0	5 (6)	5 (3)	
Percentages calculated with the number of subjects in each group as denominator. Reported dictionary version: MedDRA 22.1. Subjects are presented by the treatment received during the Treatment period.				

[00300] There were 2 subjects in total who discontinued during the treatment period due to treatment-emergent adverse events: 1 subject in the aticaprant 10 group due to diarrhea, nausea, vomiting and headache, and another subject in placebo group due to acute calculous cholecystitis.

[00301] Overall, 17/169 subjects experienced TEAEs of special interest during the treatment period: 13/85 (15.3%) in the aticaprant group and 4/84 (4.8%) in the placebo group.

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The most common treatment-emergent adverse events during the treatment phase were headache and diarrhea. The most common TEAE of special interest during the treatment period were diarrhea and pruritus (experienced by 5/85 subjects –5.9% in the aticaprant group and by 0/84 subjects in the placebo group). Further 1 patient in the placebo group (1.19%) experienced acute cholecystitis, as compared to 0 patients receiving aticaprant. See, Table 25.

Table 25: Treatment-Emergent Adverse Events of Special Interest During the Treatment Period; Full Safety Analysis Set

	Placebo (N=84)	aticaprant 10mg (N=85)	Overall (N=169)
Body System Preferred Term	n (%)	n (%)	n (%)
Total no. Subjects with Adverse Events of Special Interest	4 (4.8)	13 (15.3)	17 (10.1)
Gastrointestinal Disorders	4 (4.8)	9 (10.6)	13 (7.7)
deaths causally related to treatment / all			
Diarrhea	2 (2.4)	7 (8.2)	9 (5.3)
Abdominal Pain Upper	2 (2.4)	0	2 (1.2)
Dyspepsia	1 (1.2)	1 (1.2)	2 (1.2)
Abdominal Pain	0	1 (1.2)	1 (0.6)
Skin And Subcutaneous Tissue Disorders	0	5 (5.9)	5 (3.0)
Pruritus	0	5 (5.9)	5 (3.0)
Percentages calculated with the number of subjects in each group as denominator. Reported dictionary version: MedDRA 22.1. Subjects are presented by the treatment received during the Treatment period.			

[00302] Two serious adverse events occurred. One subject in the placebo group experienced acute calculous cholecystitis during the treatment period and other subject suicidal ideation during the lead-in period. Both subjects discontinued due to these AEs.

[00303] No deaths were reported.

(iv) Anhedonia Analysis

[00304] Patients in the larger fITT group maintained baseline level of depression and anhedonia severity consistent with the eITT group. See, Tables 26-28.

Table 26: Frequency of Subjects with Anhedonia at Treatment Baseline; fITT Analysis Set

	N	No Anhedonia (SHAPS Total Score	Anhedonia (SHAPS Total Score
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		<20)	>=20)
Baseline / Day 22			
Placebo	83	0	83 (100%)
aticaprant	83	1 (1.2%)	82 (98.8%)
Total	166	1 (0.6%)	165 (99.4%)
Anhedonia classification is based on calculated SHAPS total score at Visit Day 22			

[00305] The results illustrate that treatment effect is larger in patients with more anhedonia at baseline. See, Fig. 16.

Table 27: Frequency of Subjects with Different Level of Anhedonia at Treatment Baseline and Treatment Week 6; eITT Analysis Set				
	N	No Anhedonia (SHAPS Total Score <20)	Low Level of Anhedonia (20<=SHAPS Total Score<38)	High Level of Anhedonia (SHAPS Total Score >=38)
Treatment Baseline				
Placebo	61	0	34 (55.74%)	27 (44.26%)
aticaprant	60	0	34 (56.67%)	26 (43.33%)
Total	121	0	68 (56.2%)	53 (43.8%)
Treatment Week 6				
Placebo	59	0	46 (77.97%)	13 (22.03%)
aticaprant	59	3 (5.08%)	48 (81.36%)	8 (13.56%)
Total	118	3 (2.54%)	94 (79.66%)	21 (17.8%)
Anhedonia classification is based on re-calculated SHAPS total score at analysis visits Treatment Baseline and Treatment Week 6.				

Table 28: Frequency of Subjects with Different Level of Anhedonia at Treatment Baseline and Treatment Week 6; fITT Analysis Set				
	N	No Anhedonia (SHAPS Total Score <20)	Low Level of Anhedonia (20>=SHAPS Total Score<38)	High Level of Anhedonia (SHAPS Total Score >=38)
Treatment Baseline				
Placebo	83	0	49 (59.04%)	34 (40.96%)
aticaprant	83	1 (1.2%)	52 (62.65%)	30 (36.14%)
Total	166	1 (0.6%)	101 (60.84%)	64 (38.55%)
Treatment Week 6				
Placebo	81	0	66 (81.48%)	15 (18.52%)
aticaprant	77	7 (9.09%)	62 (80.52%)	8 (10.39%)
Total	158	7 (4.43%)	128 (81.01%)	23 (14.56%)
Anhedonia classification is based on re-calculated SHAPS total score at analysis visits Treatment Baseline and Treatment Week 6.				

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[00306] The results illustrate that the treatment effect is larger in patients with more anhedonia at baseline. See, Figs. 17A and 17B. In Fig. 17A, *i.e.*, the high anhedonia group, the placebo + oral antidepressant group shows less placebo response as compared to the low anhedonia group in Fig. 17B. Similarly the treatment effect of the aticaprant + oral antidepressant group is higher in the high anhedonia group as compared to the low anhedonia group. Overall the effect size is larger at every single time point (from week 1 onwards) in the high anhedonia group. The LSMD in the high anhedonia group is more than double that of the low anhedonia group at week 6. Further, when looking at the symptom level, greater improvement in items related to anhedonia and dysphoria in subgroup with high anhedonia vs low anhedonia. See, Fig. 18.

(v) Weight Change

[00307] At the lead-in baseline timepoint, the mean weight for subjects in the placebo group was 76.17 kg compared to 78.66 in the aticaprant group. After 6 weeks in the double-blind treatment phase, the mean weight in the placebo group was 75.75 kg compared to 78.57 kg in the aticaprant group. This indicates that the weight in both groups remained relatively stable over the 6-week double blind treatment period. This is unexpected because other adjunctive treatments for MDD result in a mean weight increase. See, Thase M, et al. *J Clin Psych.* 2015; 76(9), 1224-1231; Thase, *J Clin Psych.* 2015, 76(9):1232-1240; El Khalili, *Int J Neuropsychopharmacol.* 2010, 13, 917-932; Marcus, *J. Clin. Psychopharmacol.* 2008, 28:156–165; Berman, *J. Clin. Psychiatry* 2007; 68:843–853; Berman, American College of Neuropsychopharmacology, 2008, Annual Meeting Abstracts (Scottsdale, Ariz, Dec 7–11, 2008). Nashville, Tenn, ACNP, 2008; Earley, American College of Neuropsychopharmacology, 2007, Annual Meeting Abstracts (Boca Raton, Fla, Dec 9– 13, 2007). Nashville, TN, ACNP, 2007). See, Table 29.

Table 29: Mean weight by treatment group (kg)		
	Placebo n = 84	Aticaprant n = 85
Screening, mean (SE)	76.39 (1.61)	78.42 (1.65)
Lead-in Baseline, mean (SE)	76.17 (1.61)	78.66 (1.65)
Withdrawal Baseline, mean (SE)	75.75 (1.62)	78.57 (1.71)
Absolute Change (Withdrawal – Lead-in)	-0.42	-0.09
Relative % Change	-0.55%	-0.11%

(vi) Completion Rate

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[00308] Patients who passed the screening phase entered a lead in phase followed by a double-blind phase. Patients who responded to placebo during the lead in phase were labelled as non-responders. Patients who did not respond to placebo were labelled as non-responders. The double-blind treatment phase then continued for an additional 6 weeks, after which patients entered a withdrawal period.

[00309] Of the 121 subjects in the enriched population (60 in aticaprant and 61 in placebo group), 117 (96.7%) completed the study. The overall completion rate for the full ITT analysis set is 95%. This contrasts with completion rates of approximately 85% for studies of adjunctive aripiprazole (Pae, CNS Drugs, 2011; 25, 109-127) and 45-62% for adjunctive quetiapine (El Khalili cited above). In total 4 subjects (3.3%) discontinued the study: 2 subjects in placebo and 2 subjects in aticaprant treatment group. See, Tables 30 and 31.

Table 30: Completion/Early Withdrawal Information; eITT Analysis Set			
	Placebo (N=61)	aticaprant 10mg (N=60)	Total (N=121)
Subject Completed Treatment/Trial			
Completed	59 (96.7%)	58 (96.7%)	117 (96.7%)
Withdrawn	2 (3.3%)	2 (3.3%)	4 (3.3%)
Reason For Withdrawal / Termination			
Lack of Efficacy	0	1 (1.7%)	1 (0.8%)
Non-compliance with drug	0	1 (1.7%)	1 (0.8%)
Withdrawal by subject	1 (1.6%)	0	1 (0.8%)
Other	1 (1.6%)	0	1 (0.8%)
Percentages calculated with the number of subjects in each group as denominator.			

Table 31: Completion/Early Withdrawal Information; Full Safety Analysis Set			
	Placebo (N=84)	aticaprant 10mg (N=85)	Total (N=169)
Subject Completed Treatment/Trial			
Completed	81 (96.4%)	79 (92.9%)	160 (94.7%)
Withdrawn	3 (3.6%)	6 (7.1%)	9 (5.3%)
Reason For Withdrawal/Termination			
Adverse event	1 (1.2%)	1 (1.2%)	2 (1.2%)
Lack of Efficacy	0	2 (2.4%)	2 (1.2%)
Non-compliance with drug	0	1 (1.2%)	1 (0.6%)
Protocol deviation	0	1 (1.2%)	1 (0.6%)
Withdrawal by subject	1 (1.2%)	0	1 (0.6%)

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Other	1 (1.2%)	1 (1.2%)	2 (1.2%)
Percentages calculated with the number of subjects in each group as denominator.			

(vii) Sexual Functioning

[00310] Impairments in sexual functioning is a common side effect of antidepressant treatment and can be very upsetting to patients and their sexual partners. Major depression itself is associated with increased sexual dysfunction, and many of the pharmacological treatments are known to worsen sexual functioning even further. In a large survey of nearly 5000 patients in France, it was estimated that in untreated patients with MDD, the prevalence of sexual dysfunction was 65%. The prevalence of sexual dysfunction increased to 71% for patients treated with antidepressant therapy.

[00311] Sexual pleasure is an important component of hedonic tone. The brain reward circuitry is controlled by several areas: nucleus accumbens, ventral tegmental area and the amygdala. It is hypothesized that treatment with kappa opioid receptors may restore the normal homeostatic balance in patients with overactivation. Treatment with aticaprant could potentially improve symptoms of anhedonia. Other symptoms associated with the reward circuitry includes: sexual pleasure, lack of interest and lack of enjoyment.

[00312] Patients had their sexual functioning measured using a standard, well accepted rating scale: ASEX. See, Table 32.

Table 32: ASEX scores by treatment group		
	Placebo n = 84	Aticaprant n = 85
Baseline	22.04	21.26
Endpoint	21.36	19.79
Absolute Change	-0.68	-1.47
Relative % Change	-3.09%	-6.91%

[00313] The mean change from treatment baseline (SD) in ASEX total score to week 6 was -1.5 (4.02) points for aticaprant compared to -0.7 (2.98) points for placebo. A lower score on the ASEX indicates improvement. The score reduction at week 6 was greater in the aticaprant group compared to placebo. This is unexpected because adjunctive treatments with other agents are expected to worsen sexual functioning, *i.e.*, increase in ASEX score over time. See, Fig. 19.

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[00314] Patients receiving aticaprant had notable improvements in sexual functioning. An examination of individual item level changes was also conducted and revealed that the greatest changes were seen in items related to consummatory pleasure: orgasm satisfying, reach orgasm and vaginal lubrication/erection. Most of the improvements seen in items 3, 4 and 5 of Fig. 20.

(viii) Onset of Effect

[00315] The onset of effect for aticaprant can be estimated from the study. Fig. 7B depicts the least squares mean change from baseline. A significant treatment effect favoring aticaprant was seen as early as week 3. At this point, aticaprant showed a statistically superior effect compared to placebo.

EXAMPLE 2: Single Dose Aticaprant as Adjunctive Antidepressant Therapy

[00316] Study Design: A 6-week, multicenter, double-blind, randomized, placebo-controlled study to assess the efficacy, safety, and tolerability of aticaprant in adult and elderly subjects (18 to 74 years) who have MDD with prominent anhedonia (MDD ANH+), and who have had an inadequate response to a SSRI or a serotonin and SNRI in the current depressive episode. See, Fig. 21.

[00317] For all subjects, this study will consist of 3 phases: an eligibility screening phase (up to 4 weeks prior to first dose administration), a double-blind treatment phase of 6 weeks, and a follow-up of 1-2 weeks. Subjects who have completed the double-blind phase may participate in an open-label long-term safety study.

[00318] Sample Size and Randomization: Approximately 544 subjects with MDD with prominent anhedonia (MDD ANH+) and without prominent anhedonia (MDD ANH-) will be randomized in a 1:1 ratio to adjunctive placebo or aticaprant to achieve a minimum of 314 adult subjects meeting predefined criteria for MDD ANH+ eligible to be included in the primary analysis. Randomization will be stratified by study site, age group (adults [<65 years], elderly [≥ 65 years]), baseline anhedonia, and baseline MADRS total score. All subjects will continue their baseline antidepressant (SSRI/SNRI) during the entire study.

[00319] Doses and Administration All eligible subjects will receive aticaprant or placebo in addition to their baseline SSRI/SNRI which will be continued during the entire study. Study medication will be taken daily.

[00320] Inclusion Criteria:

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1. Age of 18 to 74 years (inclusive).
2. Be medically stable on the basis of physical examination (including a brief neurological examination), medical history, vital signs (including blood pressure), and 12-lead ECG performed at screening and baseline. If there are any abnormalities that are not specified in the inclusion and exclusion criteria, their significance must be determined.
3. Be medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, retesting of an abnormal lab values that may lead to exclusion will be allowed once during the screening phase.
4. Meet DSM-5 diagnostic criteria for recurrent or single episode MDD, without psychotic features (DSM-5 296.22, 296.23, 296.32, or 296.33), based upon clinical assessment and SCID-CT. Subjects 65 years of age or older must have had the first onset of depression prior to 55 years of age. The length of the current depressive episode must be ≤ 18 months.
5. Have had an inadequate response to at least 1 but no more than 2 antidepressants (SSRI/SNRI), administered at an adequate dose and duration in the current episode of depression. An inadequate response is defined as 26% to $<50\%$ reduction in depressive symptom severity and overall good tolerability, as assessed by the MGH-ATRQ. An adequate trial is defined as an antidepressant treatment for at least 6 weeks (and no greater than 12 months in the current episode) at or above the stable therapeutic dose specified in the MGH-ATRQ, must include the subject's current antidepressant treatment. If the subject has received 2 SSRI/SNRI treatments of sufficient dose and duration in the current episode, and has shown $\leq 25\%$ improvement to both, then the subject would not qualify based on exclusion criterion (first exclusion criterion).
6. Current major depressive episode, depression symptom severity, presence of anhedonia and antidepressant treatment response in the current depressive episode must be confirmed. Is receiving and tolerating well any one of the following SSRI or SNRI for depressive symptoms, in any formulation and available in the

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participating country: citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, desvenlafaxine at a stable dose (at therapeutic dose level) for at least 6 weeks, and for no greater than 12 months in the current episode, at screening. The above SSRI/SNRI needs to be approved for the treatment of MDD. Subjects using fluvoxamine as baseline SSRI and have normal renal and hepatic function are admitted.

7. HDRS-17 total score ≥ 22 at start of the screening and must not demonstrate a clinically significant improvement (which is defined as an improvement of $>20\%$ on their HDRS-17 total score) from the start to end of screening (from the first to the last independent HDRS-17 rating).

8. Symptoms of anhedonia based on clinical assessment and confirmed by a positive response for anhedonia (MDE symptoms Item 2) on the SCID-CT at screening and baseline (Day 1 prior to randomization).

9. BMI between 18 and 40 kg/m² (inclusive).

10. Outpatient at screening.

11. A woman of childbearing potential must have a negative highly sensitive serum (β -hCG) pregnancy test at screening and a negative urine pregnancy test predose on Day 1 of the double-blind phase prior to randomization.

12. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.

13. A woman must be either:

- Postmenopausal
 - Permanently sterile
 - Of childbearing potential and practicing a highly effective method of contraception (failure rate of $<1\%$ per year when used consistently and correctly).
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14. A woman must not to donate eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction during the study and for a period of at least 1 month after receiving the last dose of study medication.

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15. During the study and for a minimum of 1 spermatogenesis cycle (defined as approximately 3 months) after receiving the last dose of study medication, a man:
- who is sexually active with a woman of childbearing potential must use a barrier method of contraception (*e.g.*, condom with spermicidal foam/gel/film/cream/suppository) and his female partner must use a highly effective method of contraception.
 - who is sexually active with a woman who is pregnant must use a condom.
 - must not to donate sperm.
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Exclusion Criteria:

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1. History of treatment-resistant MDD, defined as a lack of response to 2 or more adequate antidepressant treatments in the current episode, as indicated by no or minimal improvement ($\leq 25\%$ improvement) when treated with an antidepressant of adequate dose (per MGH-ATRQ) and duration (at least 6 weeks).
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2. Current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychotic features, bipolar or related disorders (confirmed by the SCID-CT), intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319), autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, narcissistic personality disorders or somatoform disorders.
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3. Current active DSM-5 diagnosis of obsessive-compulsive disorder, post-traumatic stress disorder, anorexia nervosa, or bulimia nervosa.
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4. Primary DSM-5 diagnosis of panic disorder, generalized anxiety disorder, social anxiety disorder, or specific phobia which has been the primary focus of psychiatric treatment within the past 2 years. These are allowed as secondary diagnoses if MDD is the primary focus of treatment.
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5. History or evidence of clinically meaningful noncompliance with current antidepressant therapy.
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6. History of moderate to severe substance use disorder including alcohol use disorder according to DSM-5 criteria within 6 months before screening or positive test results for alcohol and/or drugs of abuse (*e.g.*, opiates [including methadone], cocaine,
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amphetamines, methamphetamines, cannabinoids, CBD, barbiturates, MDMA) at screening or at baseline. One retest during screening is allowed. Tobacco and caffeine use are not exclusionary.

7. Has within the last 5 years received any prior antidepressant treatment with ketamine/esketamine, electroconvulsive therapy, vagal nerve stimulation, or a deep brain stimulation device. Subjects who previously had taken up to 2 doses of ketamine/esketamine and did not continue (*e.g.*, did not benefit from the treatment or experienced tolerability issues) can be considered for enrollment.
8. Homicidal ideation/intent or has suicidal ideation with some intent to act within 3 months prior to the start of the screening phase, per clinical judgment or based on the C-SSRS, corresponding to a response of “Yes” on Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) for suicidal ideation on the C-SSRS, or a history of suicidal behavior within the past year prior to the start of the screening phase. Subjects reporting suicidal ideation with intent to act or suicidal behavior prior to the start of the double-blind treatment phase should be excluded.
9. Cognitive impairment that would render the informed consent invalid or limit the ability of the subject to comply with the study requirements. Subject has neurodegenerative disorder (*e.g.*, Alzheimer’s disease, vascular dementia, Parkinson’s disease with clinical evidence of cognitive impairment) or evidence of MCI. Subjects of age ≥ 65 years: has a MMSE < 25 or < 23 for those subjects with less than high school equivalent education.
10. Current or history of seizures (uncomplicated childhood febrile seizures with no sequelae are not exclusionary).
11. Clinically significant ECG abnormalities at screening or Day 1 prior to randomization that may jeopardize the subjects’ safety or the integrity of the study defined as:
 - During screening and/or Day 1, a QT interval corrected according to Fridericia’s formula (QTcF): ≥ 450 msec (males); ≥ 470 msec (females).
 - Evidence of second- and third-degree atrioventricular block.

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- Features of new ischemia.
 - Other clinically important arrhythmia or cardiac abnormalities.
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12. History of, or symptoms and signs suggestive of, liver cirrhosis (*e.g.*, esophageal varices, ascites, and increased prothrombin time) OR ALT or AST values $\geq 3 \times$ the ULN or total bilirubin $> 1.5 \times$ the ULN in the screening phase. Repeat of screening test for abnormal ALT and AST is permitted during the screening period there is an alternative explanation for the out of range value.

13. For elevations in bilirubin if the elevation in bilirubin is consistent with Gilbert's disease, the subject may participate.

14. Positive test result for drugs of abuse (*e.g.*, barbiturates, methadone, opiates, cocaine, PCP, MDMA, and amphetamine/methamphetamine) at the start of the screening phase or Day 1 of the double-blind treatment phase prior to randomization.

15. Subjects who have a positive test result at screening due to prescribed psychostimulants taken for any indication must discontinue the medication at least 2 weeks before Day 1 of the double-blind treatment phase (prior to randomization). The result of the Day 1 (prior to randomization) test for drugs of abuse must be negative for the subject to be randomized. Subjects who have a positive test result at screening due to prescribed/over-the-counter opiates or barbiturates may be permitted to continue in the screening phase if the medication is discontinued at least 1 week or 5 half-lives, whichever is longer, before Day 1 of the double-blind treatment phase (prior to randomization). The result of the Day 1 (prior to randomization) test for drugs of abuse must be negative for the subject to be randomized.

- Intermittent use of cannabinoids prior to the start of the screening phase is not exclusionary as long as the subject does not meet the criteria for substance use disorder.
 - A positive test for cannabinoids at the start of the screening phase is not exclusionary; however, a positive test result for cannabinoids predose on Day 1 of the double-blind treatment phase is exclusionary.
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16. Taking a total daily dose of benzodiazepines greater than the equivalent of 6 mg/day of lorazepam at the start of the screening phase.

17. Recent (last 3 months) history of, or current signs and symptoms of:

- Severe renal insufficiency (creatinine clearance <30mL/min)
 - Clinically significant or unstable cardiovascular, respiratory, gastrointestinal, neurologic, hematologic, rheumatologic, immunologic or endocrine disorders.
 - Uncontrolled Type 1 or Type 2 diabetes mellitus. Subjects with Type 1 or Type 2 diabetes mellitus who are controlled (hemoglobin A1c $\leq$ 8.0% and glucose $\leq$ 150 mg/dL at screening) may be eligible to participate if otherwise medically healthy, and if on a stable regimen of glucose-lowering medications for at least 2 months prior to screening).
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18. Current signs/symptoms of hypothyroidism or hyperthyroidism. For subjects with a history of thyroid disease and for subjects who, regardless of thyroid history have the TSH value out of range, a FT₄ test will be conducted. If the FT₄ value is abnormal and considered to be clinically significant the subject is not eligible.

19. Subjects with a pre-existing history of thyroid disease/disorder who are treated with thyroid hormones need to be on a stable dosage for 3 months prior to the start of the screening phase. Subjects taking thyroid supplementation for antidepressant purposes are not allowed. Has Cushing's Disease, Addison's Disease, primary amenorrhea, or other evidence of significant medical disorders of the hypothalamic-pituitary-adrenal axis.

20. Significant medical illness, particularly unstable medical problem.

21. Ongoing psychological treatments (*e.g.*, Cognitive Behavior Therapy, Interpersonal Psychotherapy, Psychodynamic Psychotherapy etc.), initiated within 6 weeks prior to start of screening. A subject who has been receiving ongoing psychological treatment for a period of greater than 6 weeks is eligible, if psychological treatment to be of stable duration and frequency.

22. Significant medical illness, particularly unstable medical problem.

23. Clinically-relevant GI complaints per clinical judgment (unless symptoms of Axis I disorder) at screening or baseline or history of documented gastric disease

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(including but not limited to documented peptic ulcer disease, gastritis [including atrophic gastritis], upper GI bleeding, Barret's esophagus, Crohn disease, ulcerative colitis, GI precancerous conditions or any other clinically-relevant GI disease irritable bowel syndrome).

24. Requires chronic use of a PPIs. A history of chronic NSAID or aspirin use. (Low dose aspirin *e.g.*, in cardiovascular disease prevention is allowed).

25. History of malignancy within 5 years before the start of the screening phase (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that is considered cured with minimal risk of recurrence).

26. Known allergies, hypersensitivity, intolerance, or contraindications to aticaprant and/or its excipients.

27. Taken any prohibited therapies that would not permit dosing on Day 1.

28. Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 60 days before the start of the screening phase, or has participated in 2 or more MDD or other psychiatric condition clinical interventional studies (with different investigational medication) in the previous 1 year before the start of the screening phase, or is currently enrolled in an investigational interventional study.

29. A woman who is pregnant, breastfeeding, or planning to become pregnant while enrolled or within 6 weeks after the last dose of the study medication.

30. Plans to father a child while enrolled or within 90 days after the last dose of study intervention.

31. Diagnosis of acquired immunodeficiency syndrome. Human immunodeficiency virus testing is not required.

32. Any condition or situation/circumstance for which participation would not be in the best interest of the subject (*e.g.*, compromise the well-being) or that could prevent, limit, or confound the protocol specified assessments.

A. Efficacy Objectives and Endpoints

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[00321] The assessment of primary and secondary (key and other) endpoints will be conducted on the FAS which includes adult (not elderly) subjects with MDD ANH+ who took at least 1 dose of study medication.

[00322] Primary: To evaluate the efficacy of aticaprant compared with placebo as adjunctive therapy to an antidepressant (SSRI or SNRI) in improving depressive symptoms in adult subjects with MDD ANH+ and inadequate response to the current antidepressant, as assessed by the change from baseline in the MADRS total score from Day 1 (pre-randomization) to end of the 6-week double-blind treatment phase (Day 43):

- Change from baseline to Day 43 in the MADRS total score.

[00323] Key Secondary: To assess efficacy of aticaprant compared with placebo in adult subjects with MDD ANH+ as adjunctive therapy to an antidepressant on patient-reported assessment of anhedonia outcomes:

- Change from baseline to Day 43 in the Dimensional Anhedonia Rating Scale (DARS) total score.

[00324] Other Secondary: To assess the efficacy of aticaprant compared with placebo in adult subjects with MDD ANH+ as adjunctive therapy on the following:

- Proportion of responders at Day 43 ($\geq 50\%$ reduction in MADRS total score).
- Proportion of subjects with remission of depressive symptoms, defined as a MADRS total score ≤ 12 at Day 43.
- Change from baseline to Day 43 in MADRS 6
- Change from baseline to Day 43 in PHQ-9 total score.
- Change from baseline to Day 43 in SHAPS total score.
- Change from baseline to Day 43 in symptoms of anxiety using the GAD-7.

[00325] Exploratory: To assess the efficacy of aticaprant compared with placebo in adult subjects with MDD ANH+, and all MDD subjects (adult and elderly subjects with MDD ANH+ and MDD ANH-) as adjunctive therapy on the following:

- Change from baseline over time in the MADRS total score.
- Change from baseline over time in MADRS anhedonia items factor score.
- Change from baseline over time in patient-reported outcomes of anhedonia (SHAPS, DARS).

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- Change from baseline over time in PHQ-9 total score.
- Change from baseline to Day 43 in health-related quality of life and health status, as assessed by the EQ-5D-5L questionnaire.
- Change from baseline to Day 43 in the SDS total score.
- Change from baseline over time in the CGI-S score.
- Change from baseline over time in symptoms of anxiety using the GAD-7.
- Change from baseline over time in depressive symptoms using the PGI-S.
- Change from baseline to Day 43 in patient-reported sexual functioning using the ASEX.

[00326] To assess the efficacy of aticaprant compared with placebo in adult subjects with MDD ANH- as adjunctive therapy on the following:

- Change from baseline over time in MADRS total score.
- Change from baseline over time in DARS total score.

[00327] Safety Objectives (All): The following safety endpoints will be assessed separately for the adult and elderly subjects; the safety analysis set for each age group will include all randomized subjects who have received at least one dose of study medication:

- AEs including AESI. An AE can be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. TEAEs were AEs with onset during the treatment phase that has worsened since baseline. The full safety analysis set included all enrolled subjects who received at least 1 dose of study medication in the treatment period.
- Vital signs
- ECG, Laboratory Values
- Weight/BMI
- Suicidality assessment using the C-SSRS
- Withdrawal symptoms assessment using the PWC-20

B. Concomitant Therapies and Prohibited Therapies

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[00328] Background therapy: All subjects will continue their baseline antidepressant (SSRI/SNRI) during the entire study. The following antidepressants are permitted: citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, and desvenlafaxine. Subjects will only continue one of these allowed antidepressants at an adequate and tolerated dose (*i.e.*, monotherapy) during the study. No changes in antidepressant or dose are permitted from screening until the end of the study.

[00329] Prohibited therapies: Subjects must not use the following medications or food supplements prior to or during the study, as indicated, except to treat an AE or breakthrough symptoms, preferably after the EOT visit:

- MAOIs within 4 weeks before screening until the first follow-up visit.
- Antipsychotic drugs from at least 14 days before Day 1 until the first follow-up visit.
- Hypnotic drugs or food supplements (from at least 7 days prior to Day 1 until the first follow-up visit), including but not limited to benzodiazepines, non-benzodiazepine hypnotics (*e.g.*, zolpidem, zopiclone, zaleplon, eszopiclone, suvorexant and ramelteon), sedating antihistamines including over-the-counter hypnotics (*e.g.*, diphenhydramine, doxylamine, and hydroxyzine), and melatonin / agomelatine.

Subjects who were taking benzodiazepines and/or permitted non-benzodiazepine sleep medications during the screening phase can continue these medications (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) during the double-blind treatment phase. No dose increases beyond the equivalent of 6 mg/day of lorazepam, or new benzodiazepine medications are permitted during the double-blind treatment phase.

- Non-SSRI/SNRI antidepressants (*e.g.*, doxepin, trazodone, mirtazapine, bupropion, tricyclic antidepressants, agomelatine, and SAMe) from at least 7 days before Day 1 until the first follow-up visit.
- Any form of new psychotherapy or change in current psychotherapy is prohibited during the screening and double-blind phase.

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- Opiates and mood stabilizers (*e.g.*, lithium and anticonvulsants) from at least 7 days prior to Day 1 until the first follow-up visit.
- Stimulants (*e.g.*, dexamphetamine, methylphenidate, dexamethylphenidate), oral systemic steroids, and appetite suppressants (ephedrine), and isoxsuprine from at least 7 days before Day 1 until EOT.
- Magnetic and electrical stimulation therapies: electroconvulsive therapy, vagal nerve stimulation, deep brain stimulations, TMS of any type, or DCS or electrical stimulation, from screening to End-of-Study visit. TMS or DCS or electrical stimulation use prior to screening is not exclusionary.
- T3, thyroid hormone or other thyroid function supplementation prescribed for depression.

These medications are allowed when given to control pre-existing thyroid disease/disorder.

- Ketamine or esketamine within 5 years prior to and during the study (up to 2 doses are allowed in lifetime prior to screening).
- Psychedelics (*e.g.*, psilocybin).
- Memantine.
- Other investigational drugs within 30 days prior to and during the study.

EXAMPLE 3: A Randomized, Double-blind, Multicenter, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Fixed Doses of Aticaprant 5 mg and 10 mg as Adjunctive Therapy in Adult and Elderly Subjects with MDD with Prominent Anhedonia and Inadequate Response to Current Antidepressant Therapy

[00330] Study Design: An 8-week, multicenter, double-blind, randomized, placebo-controlled study to assess the efficacy, safety, and tolerability of aticaprant in adult and elderly subjects (18 to 74 years) who have MDD with prominent anhedonia and who have had an inadequate response to a SSRI or a SNRI in the current depressive episode. See, Fig. 22.

[00331] For all subjects, this study will consist of 3 phases:

- an eligibility screening phase (up to 4 weeks prior to first dose administration),
- a double-blind treatment phase of 8 weeks,
- and a follow-up phase of 1-2 weeks.

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[00332] Approximately 624 subjects (randomized in a 2:1:1 ratio to placebo, aticaprant 5 mg, and aticaprant 10 mg) will be enrolled in the study. This enrolment is targeted to achieve a minimum of 556 adult subjects with MDD with prominent anhedonia and approximately 68 elderly subjects (≥ 65 years) with MDD with prominent anhedonia.

[00333] Subjects who have completed the double-blind treatment phase may participate in an open-label long-term safety study.

[00334] Sample Size and Randomization: Approximately 624 adult (< 65 years) and elderly (≥ 65 years) subjects with MDD with prominent anhedonia will be randomized in a 2:1:1 ratio to adjunctive placebo, 5-mg aticaprant, or 10-mg aticaprant to achieve a minimum of 556 adult subjects meeting predefined criteria for MDD with prominent anhedonia eligible to be included in the primary efficacy analysis set. Randomization will be stratified by study site, age group (adult, elderly) and baseline MADRS total score. All subjects will continue their baseline antidepressant (SSRI/SNRI) during the entire study.

[00335] Doses and Administration: All eligible subjects will receive aticaprant 5 mg, aticaprant 10 mg or placebo in addition to their baseline SSRI/SNRI which will be continued during the entire study. Study medication will be taken daily.

[00336] Inclusion Criteria:

1. Age of 18 to 74 years (inclusive).
2. Medically stable on the basis of physical examination (including a brief neurological examination), medical history, vital signs (including blood pressure), and 12-lead ECG performed at screening and baseline.
3. Medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, retesting of an abnormal lab values that may lead to exclusion will be allowed once during the screening phase.
4. Meet DSM-5 diagnostic criteria for recurrent or single episode MDD, without psychotic features (DSM-5 296.22, 296.23, 296.32, or 296.33), based upon clinical assessment and confirmed by the SCID-CT. Subjects 65 years of age or older must have had the first onset of depression prior to 55 years of age. The length of the current depressive episode must be ≤ 18 months.

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5. Symptoms of anhedonia based on clinical assessment and confirmed by a positive response for anhedonia (MDE symptoms Item 2) on the SCID-CT at screening and baseline (Day 1 prior to randomization).
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6. SHAPS total score of ≥ 38 at screening and baseline (Day 1 prior to randomization) corresponding to prominent (high level) of anhedonia.
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7. Inadequate response to at least 1 but no more than 2 antidepressants (SSRI/SNRI), administered at an adequate dose and duration in the current episode of depression. An inadequate response is defined as 26% to <50% reduction in depressive symptom severity and overall good tolerability, as assessed by the MGH-ATRQ. An adequate trial is defined as an antidepressant treatment for at least 6 weeks (and no greater than 12 months in the current episode) at or above the stable therapeutic dose specified in the MGH-ATRQ, must include the subject's current antidepressant treatment. If the subject has received 2 SSRI/SNRI treatments of sufficient dose and duration in the current episode, and has shown $\leq 25\%$ improvement to both, then the subject would not qualify based on exclusion criterion (first exclusion criterion).
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8. The current major depressive episode, depression symptom severity, presence of anhedonia and antidepressant treatment response in the current depressive episode, must be confirmed. Is receiving and tolerating well any one of the following SSRI or SNRI for depressive symptoms, in any formulation and available in the participating country citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, desvenlafaxine at a stable dose (at therapeutic dose level) for at least 6 weeks, and for no greater than 12 months in the current episode, at screening. The SSRI/SNRI needs to be approved for the treatment of MDD.
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9. HDRS-17 total score ≥ 22 at start of the screening and must not demonstrate a clinically significant improvement (which is defined as an improvement of >20% on their HDRS-17 total score) from the start to end of screening (from the first to the last independent HDRS-17 rating).
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10. BMI between 18 and 40 kg/m² (inclusive).
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11. Outpatient at screening.

12. A woman of childbearing potential must have a negative highly sensitive serum (β human chorionic gonadotropin [β -hCG]) pregnancy test at screening and a negative urine pregnancy test predose on Day 1 of the double-blind phase prior to randomization.

13. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.

14. A woman must be either:

- Postmenopausal: A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range based on the reference range of the central laboratory may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
 - Permanently sterile
 - Of childbearing potential and practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly).
 - Remains on a highly effective method and for at least 1 month after the last dose of study medication.
 - A woman must not donate eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction during the study and for a period of at least 1 month after receiving the last dose of study medication.
 - During the study and for a minimum of 1 spermatogenesis cycle (defined as approximately 3 months) after receiving the last dose of study medication, a man (a) who is sexually active with a woman of childbearing potential must use a barrier method of contraception and his female partner must use a highly effective method of contraception; (b)
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who is sexually active with a woman who is pregnant must use a condom;
 (c) must not donate sperm.

Exclusion Criteria:

1. History of treatment-resistant MDD, defined as a lack of response to 2 or more adequate antidepressant treatments in the current episode, as indicated by no or minimal improvement ($\leq 25\%$ improvement) when treated with an antidepressant of adequate dose (per MGH-ATRQ) and duration (at least 6 weeks).
2. Current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychotic features, bipolar or related disorders (confirmed by the SCID-CT), intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319), autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, narcissistic personality disorders or somatoform disorders.
3. Current active DSM-5 diagnosis of obsessive-compulsive disorder, post-traumatic stress disorder, anorexia nervosa, or bulimia nervosa.
4. Primary DSM-5 diagnosis of panic disorder, generalized anxiety disorder, social anxiety disorder, or specific phobia which has been the primary focus of psychiatric treatment within the past 2 years. These are allowed as secondary diagnoses if MDD is the primary focus of treatment.
5. History or evidence of clinically meaningful noncompliance with current antidepressant therapy.
6. History of moderate to severe substance use disorder including alcohol use disorder according to DSM-5 criteria within 6 months before screening or positive test results for alcohol and/or drugs of abuse (*e.g.*, opiates [including methadone], cocaine, amphetamines, methamphetamines, cannabinoids, CBD, barbiturates, MDMA) at screening or at baseline. One retest during screening is allowed. Tobacco and caffeine use are not exclusionary.
7. Has within the last 5 years received any prior antidepressant treatment with ketamine/esketamine, electroconvulsive therapy, vagal nerve stimulation, or a deep brain stimulation device. Subjects who previously had taken up to 2 doses of

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ketamine/esketamine and did not continue (*e.g.*, did not benefit from the treatment or experienced tolerability issues) can be considered for enrollment.

8. Homicidal ideation/intent or has suicidal ideation with some intent to act within 3 months prior to the start of the screening phase, per clinical judgment or based on the C-SSRS, corresponding to a response of “Yes” on Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) for suicidal ideation on the C-SSRS, or a history of suicidal behavior within the past year prior to the start of the screening phase. Subjects reporting suicidal ideation with intent to act or suicidal behavior prior to the start of the double-blind treatment phase should be excluded.
9. Cognitive impairment that would render the informed consent invalid or limit the ability of the subject to comply with the study requirements. Subject has neurodegenerative disorder (*e.g.*, Alzheimer’s disease, vascular dementia, Parkinson’s disease with clinical evidence of cognitive impairment) or evidence of MCI. Subjects of age ≥ 65 years: has a MMSE < 25 or < 23 for those subjects with less than high school equivalent education.
10. Current or history of seizures (uncomplicated childhood febrile seizures with no sequelae are not exclusionary).
11. Clinically significant electrocardiography (ECG) abnormalities at screening or Day 1 prior to randomization that may jeopardize the subjects’ safety or the integrity of the study defined as:
 - During screening and/or Day 1, a QT interval corrected according to Fridericia’s formula (QTcF): ≥ 450 msec (males); ≥ 470 msec (females).
 - Evidence of second- and third-degree atrioventricular block.
 - Features of new ischemia.
 - Other clinically important arrhythmia or cardiac abnormalities.
12. History of, or symptoms and signs suggestive of, liver cirrhosis (*e.g.*, esophageal varices, ascites, and increased prothrombin time) OR ALT or AST values $\geq 3 \times$ the ULN or total bilirubin $> 1.5 \times$ the ULN in the screening phase. Repeat of screening

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test for abnormal ALT and AST is permitted during the screening period provided there is an alternative explanation for the out of range value.

13. For elevations in bilirubin if the elevation in bilirubin is consistent with Gilbert's disease, the subject may participate in the study.

14. Positive test results for drugs of abuse (*e.g.*, barbiturates, methadone, opiates, cocaine, PCP, MDMA, and amphetamine/methamphetamine) at the start of the screening phase or Day 1 of the double-blind treatment phase prior to randomization.

15. Subjects who have a positive test result at screening due to prescribed psychostimulants taken for any indication must discontinue the medication at least 2 weeks before Day 1 of the double-blind treatment phase (prior to randomization). The result of the Day 1 (prior to randomization) test for drugs of abuse must be negative for the subject to be randomized. Otherwise, subjects who have a positive test result at screening due to prescribed/over-the-counter opiates or barbiturates may be permitted to continue in the screening phase if the medication is discontinued at least 1 week or 5 half-lives, whichever is longer, before Day 1 of the double-blind treatment phase (prior to randomization). The result of the Day 1 (prior to randomization) test for drugs of abuse must be negative for the subject to be randomized.

16. Intermittent use of cannabinoids prior to the start of the screening phase is not exclusionary as long as the subject does not meet the criteria for substance use disorder. A positive test for cannabinoids at the start of the screening phase is not exclusionary; however, a positive test result for cannabinoids predose on Day 1 of the double-blind treatment phase is exclusionary.

17. Taking a total daily dose of benzodiazepines greater than the equivalent of 6 mg/day of lorazepam at the start of the screening phase.

18. Recent (last 3 months) history of, or current signs and symptoms of:

- Severe renal insufficiency (creatinine clearance <30mL/min)
 - Clinically significant or unstable cardiovascular, respiratory, gastrointestinal, neurologic, hematologic, rheumatologic, immunologic or endocrine disorders.
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- Uncontrolled Type 1 or Type 2 diabetes mellitus. Subjects with Type 1 or Type 2 diabetes mellitus who are controlled (hemoglobin A1c $\leq 8.0\%$ and glucose ≤ 150 mg/dL at screening) may be eligible to participate if otherwise medically healthy, and if on a stable regimen of glucose-lowering medications for at least 2 months prior to screening).
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19. Current signs/symptoms of hypothyroidism or hyperthyroidism. For subjects with a history of thyroid disease and for subjects who, regardless of thyroid history have the TSH value out of range, a FT₄ test will be conducted. If the FT₄ value is abnormal and considered to be clinically significant the subject is not eligible.

20. Subjects with a pre-existing history of thyroid disease/disorder who are treated with thyroid hormones need to be on a stable dosage for 3 months prior to the start of the screening phase. Subjects taking thyroid supplementation for antidepressant purposes are not allowed.

21. Cushing's Disease, Addison's Disease, primary amenorrhea, or other evidence of significant medical disorders of the hypothalamic-pituitary-adrenal axis.

22. Significant medical illness, particularly unstable medical problem

23. Ongoing psychological treatments (*e.g.*, Cognitive Behavior Therapy, Interpersonal Psychotherapy, Psychodynamic Psychotherapy etc.), initiated within 6 weeks prior to start of screening. A subject who has been receiving ongoing psychological treatment for a period of greater than 6 weeks is eligible.

24. Significant medical illness, particularly unstable medical problem.

25. Clinically-relevant GI complaints (unless symptoms of Axis I disorder) at screening or baseline or history of gastric disease (including but not limited to documented peptic ulcer disease, gastritis [including atrophic gastritis], upper GI bleeding, Barrett's esophagus, Crohn's disease, ulcerative colitis, GI precancerous conditions or any other clinically-relevant GI disease irritable bowel syndrome).

26. Requires chronic use of a PPIs. A history of chronic NSAID or aspirin use. (Low dose aspirin *e.g.*, in cardiovascular disease prevention is allowed).

27. History of malignancy within 5 years before the start of the screening phase (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in

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situ of the cervix, or malignancy that is considered cured with minimal risk of recurrence).

28. Known allergies, hypersensitivity, intolerance, or contraindications to aticaprant and/or its excipients.

29. Has taken any prohibited therapies that would not permit dosing on Day 1.

30. Taking a total daily dose of benzodiazepines greater than the equivalent of 6 mg/day of lorazepam at the start of the screening phase.

31. Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 60 days before the start of the screening phase, or has participated in 2 or more MDD or other psychiatric condition clinical interventional studies (with different investigational medication) in the previous 1 year before the start of the screening phase, or is currently enrolled in an investigational interventional study.

32. A woman who is pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 6 weeks after the last dose of the study medication.

33. Plans to father a child while enrolled in this study or within 90 days after the last dose of study intervention.

34. Diagnosis of acquired immunodeficiency syndrome. Human immunodeficiency virus testing is not required for this study.

35. Any condition or situation/circumstance for which participation would not be in the best interest of the subject (*e.g.*, compromise the well-being) or that could prevent, limit, or confound the protocol specified assessments.

A. Efficacy Objectives and Endpoints

[00337] The assessment of primary and secondary (key and other) endpoints will be conducted on the full analysis set (FAS) which includes adult (not elderly) subjects with MDD with prominent anhedonia who took at least 1 dose of study medication.

[00338] Primary: Evaluate the efficacy of 2 fixed doses of aticaprant (5 mg and 10 mg) compared with placebo as adjunctive therapy to an antidepressant (SSRI or SNRI) in improving depressive symptoms in adult subjects (18-64 years) with MDD with prominent anhedonia and inadequate response to the current antidepressant

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- Change from baseline to Day 43 in the MADRS total score.

[00339] Key Secondary: To assess efficacy of aticaprant 10 mg compared with placebo in adult subjects with MDD with prominent anhedonia as adjunctive therapy to an antidepressant on patient-reported assessment of anhedonia outcomes:

- Change from baseline to Day 43 in the Dimensional Anhedonia Rating Scale (DARS) total score.

[00340] Other Secondary: Assess the efficacy of aticaprant compared with placebo as adjunctive therapy to an antidepressant (SSRI or SNRI) in adult subjects with MDD with prominent anhedonia:

- Proportion of responders at Day 43 and Day 57 ($\geq 50\%$ reduction in MADRS total score).
- Proportion of subjects with remission of depressive symptoms, defined as a MADRS total score ≤ 12 at Day 43 and Day 57.
- Change from baseline to Day 43 and Day 57 in MADRS-6
- Change from baseline to Day 43 and Day 57 in Patient Health Questionnaire, 9-Item (PHQ-9) total score.

[00341] Exploratory: To assess the efficacy of aticaprant compared with placebo in adult subjects with MDD with prominent anhedonia as adjunctive therapy on the following:

- Change from baseline over time in the MADRS total score.
- Change from baseline over time in MADRS anhedonia items factor score.
- Change from baseline over time in patient-reported outcomes of anhedonia (SHAPS, DARS).
- Change from baseline over time in PHQ-9 total score.
- Change from baseline to Day 43 in health-related quality of life and health status, as assessed by the EQ-5D-5L questionnaire.
- Change from baseline to Day 43 in the Sheehan Disability Scale (SDS) total score.
- Change from baseline over time in the CGI-S score.
- Change from baseline over time in symptoms of anxiety using the GAD-7.
- Change from baseline over time in depressive symptoms using the PGI-S.

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- Change from baseline to Day 43 in patient-reported sexual functioning using the ASEX.

[00342] Safety Objectives (All): The following safety endpoints will be assessed separately for the adult and elderly subjects; the safety analysis set for each age group will include all randomized subjects who have received at least one dose of study medication:

- AEs including AESI
- Vital signs
- ECG
- Laboratory Values
- Weight/BMI
- Suicidality assessment using the C-SSRS
- Withdrawal symptoms assessment using the PWC-20

[00343] Other Objectives (exploratory):

- To identify diagnostic biomarkers and to investigate changes in MDD-related biomarkers in relation to clinical response on depression symptoms and anhedonia upon monotherapy with aticaprant.
- To identify genetic and other factors that may influence the pharmacokinetics (PK), safety, or tolerability of aticaprant.

B. Concomitant Therapies and Prohibited Therapies

[00344] Background therapy: All subjects will continue their baseline antidepressant (SSRI/SNRI) during the entire study. The following antidepressants are permitted: citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, and desvenlafaxine. Subjects will only continue one of these allowed antidepressants at an adequate and tolerated dose (*i.e.*, monotherapy) during the study. No changes in antidepressant or dose are permitted from screening until the end of the study.

[00345] Prohibited therapies: Subjects must not use the following medications or food supplements prior to or during the study, as indicated, except to treat an AE or breakthrough symptoms, preferably after the EOT visit:

- MAOIs within 4 weeks before screening until the first follow-up visit.

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- Antipsychotic drugs from at least 14 days before Day 1 until the first follow-up visit.
- Hypnotic drugs or food supplements (from at least 7 days prior to Day 1 until the first follow-up visit), including but not limited to benzodiazepines, non-benzodiazepine hypnotics (*e.g.*, zolpidem, zopiclone, zaleplon, eszopiclone, suvorexant and ramelteon), sedating antihistamines including over-the-counter hypnotics (*e.g.*, diphenhydramine, doxylamine, and hydroxyzine), and melatonin. Subjects who were taking benzodiazepines and/or permitted non-benzodiazepine sleep medications during the screening phase can continue these medications (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) during the double-blind treatment phase. No dose increases beyond the equivalent of 6 mg/day of lorazepam, or new benzodiazepine medications are permitted during the double-blind treatment phase.
- Non-SSRI/SNRI antidepressants (*e.g.*, doxepin, trazodone, mirtazapine, bupropion, tricyclic antidepressants, agomelatine, and SAME) from at least 7 days before Day 1 until the first follow-up visit.
- Any form of new psychotherapy or change in current psychotherapy is prohibited during the screening and double-blind phase of this study.
- Opiates and mood stabilizers (*e.g.*, lithium and anticonvulsants) from at least 7 days prior to Day 1 until the first follow-up visit.
- Stimulants (*e.g.*, dexamphetamine, methylphenidate, dextmethylphenidate), oral systemic steroids, and appetite suppressants (ephedrine), and isoxsuprine from at least 7 days before Day 1 until EOT.
- Magnetic and electrical stimulation therapies: electroconvulsive therapy, vagal nerve stimulation, deep brain stimulations, TMS of any type, or DCS or electrical stimulation, from screening to End-of-Study visit. TMS or DCS or electrical stimulation use prior to screening is not exclusionary.
- T3, thyroid hormone or other thyroid function supplementation prescribed for depression. These medications are allowed when given to control pre-existing thyroid disease/disorder.

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- Ketamine or esketamine within 5 years prior to and during the study (up to 2 doses are allowed in lifetime prior to screening).
- Psychedelics (*e.g.*, psilocybin).
- Memantine.
- Other investigational drugs within 30 days prior to and during the study.

EXAMPLE 4: Biomarker Assay

[00346] Samples of venous blood were obtained from patients and healthy control subjects from the multi-center, placebo-controlled, randomized, double-blind study in subjects with MDD who have had an inadequate response to SSRI/SNRI treatment described in Example 1. Serum or plasma was prepared from the samples of venous blood. Measurements of human CRP and IL-6-R were performed in serum using an MSD Sector 6000 with the kits# K151STD and K151ALC (MesoScale Discovery, Rockville, MD). Human TNF α was quantified in serum using a Simoa HD-1 analyzer with kit# 143 (Quanterix, Lexington, MA). Human Dynorphin was assayed in plasma using a SpectraMax M plate reader (Molecular devices, San Jose, CA) with kit# CSB-E09128h (Cusabio, Wuhan, China). All measures were performed according to kit manufacturer's recommendations.

[00347] As used in the following biomarker assay analysis, treatment (TRT) refers to treatment with an SSRI/SNRI plus Aticaprant and placebo (PBO) refers to treatment with an SSRI/SNRI plus placebo.

[00348] The following biomarker signatures were employed:

[00349] Treatment Outcome: Change in clinical scale at the of end of the double period. Negative values indicate improvement in depression levels relative to baseline levels. The more negative the change, the greater the improvement.

[00350] Sig^{Pos}: Patient meeting the criteria defined by signature of biomarkers and/or clinical scales.

[00351] 3MM: Inflammatory biomarker signature with positive status defined by CRP > 3 mg/L and (TNF α > 4 pg/mL or sIL6R > 25 ng/mL).

[00352] 4MM: Inflammatory biomarker signature with positive status defined by high dynorphin (δ 1) or 3MM with moderate dynorphin (δ 2) subtypes, specifically: DYN > δ 1 pg/mL or (DYN > δ 2 pg/mL and CRP > 3 mg/L and (TNF α > 4 pg/mL or sIL6R > 25

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ng/mL)). In certain embodiments, the 4MM DYN cutoffs are as follows: Dyn >50 OR (3MM and Dyn > 8); Dyn >24 OR (3MM and Dyn >8), or Dyn > 11.4 and 3MM.

[00353] TE Sig^{Pos}: Treatment Effect in Signature Positive group: (Average mean MADRS change in placebo – Average mean MADRS change in treatment) in Sig^{Pos} group.

[00354] TE Sig^{Neg}: Treatment Effect in Signature Negative group.

[00355] Sig Adv: Signature Advantage (interaction) Difference in TE between signature groups: Sig Adv = TE Sig^{Pos} - TE Sig^{Neg}.

[00356] The effect of biomarker signatures on patient response to treatment is summarized in graphical form using two panel box plots in Fig. 25. The panel on the left of Fig. 25 shows treatment outcomes relative to baseline in the biomarker signature positive group, here defined as subjects whose biomarker profile fits the 3 Marker Model (3MM) (21% of MDD). The panel on the right of Fig. 25 shows treatment outcomes in biomarker signature negative group using tukey box plots in addition to individual patient outcomes marked by circular dots. Red color represents placebo and teal represents aticaprant. Rectangular boxes span Diamonds and error bars represent mean and 95% Confidence Interval (CI) of treatment outcome by treatment arm and biomarker signature status. In the signature positive group, the treatment effect (difference in average treatment outcome between treatment arms) was of 6.29 MADRS points (One sided p=0.07, effect size=0.75). While in the signature negative groups, the treatment effect was 1.59 MADRS points. In other words, subjects who are biomarker signature positive improve by an additional 4.7 points (6.29-4.7) relative to placebo when treated with aticaprant, compared to subjects who are biomarker signature negative. This signature advantage of 4.7 MADRS points represents the interaction of biomarker signature status with treatment effect. Treatment effects, signature advantage, and corresponding p values are assessed using a linear regression model for treatment outcome with independent variables for treatment, biomarker signature status, and their interaction. All p-values are one sided. Significant is defined as nominal one sided p value < 0.05.

[00357] Figs. 26A-26D demonstrate the outcome of patient subtyping using a biomarker signature composed only of dynorphin levels, namely: DYN > δ pg/mL. The biomarker signature effect is shown over a range of values for δ from 6.2 pg/mL to 116.2 pg/mL. At each value tested, treatment effect in the biomarker signature positive group and

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the signature advantage are computed and graphed in Fig. 26A. The percentages shown along the top of the graph show the fraction of subjects who are biomarker signature positive at a particular threshold. Both treatment effect (SigPos:PBO-TRT) and signature advantage (SigPos.DIFF-SigNeg.DIFF) rise with increasing δ reaching a peak around $\delta=19.9$ pg/mL. FIG. 26B and FIG. 26C show the signature effects at δ levels of 19.9 and 30 pg/mL, respectively. At higher levels of dynorphin however (FIG. 26D), the signature effect is more variable.

[00358] Figs. 27A-27D summarize the outcome of patient subtyping using a biomarker signature using the union of high dynorphin and 3MM subtypes, specifically: $DYN > \delta$ pg/mL or $CRP > 3$ mg/L and ($TNF\alpha > 4$ pg/mL or $sIL6R > 25$ ng/mL). As in Figs. 26A-26D, the effect of the biomarker signature is evaluated at a range of dynorphin cut-points (δ). As with the signature with dynorphin alone, treatment effect increases with increasing δ , however the interaction effect is considerably more pronounced (Fig. 26B) due to an average aticaprant response that is worse than that of placebo for biomarker signature negative patients. More importantly, the effects of the biomarker signature are more stable at higher dynorphin cut points (Fig. 27C and Fig. 27D), making this biomarker signature a more reliable identifier of patients who are most likely to benefit from treatment with aticaprant as adjunctive treatment, compared to SOC alone. Targeting both high DYN and 3MM subtypes results in a 3-8 point signature advantage in more than 60% of patients.

[00359] Fig. 28A and Fig. 28B demonstrate the effect of a biomarker signature that captures subjects who are both 3MM positive, and have high dynorphin: $DYN > \delta$ pg/mL and $CRP > 3$ mg/L and ($TNF\alpha > 4$ pg/mL or $sIL6R > 25$ ng/mL). A very large treatment effect in biomarker signature positive patients and the large signature advantage at a wide range of dynorphin levels were observed (Fig. 28B, corresponding to $\delta = 11.5$). This marked improvement with aticaprant in patients with both high dynorphin and high inflammation, suggests that the two identified subtypes reflect different disease etiologies that are both responsive to aticaprant.

[00360] Fig. 29A-29C summarize the outcome of patient subtyping using a biomarker signature using a combination of high dynorphin (δ_1) or 3MM with moderate dynorphin (δ_2) subtypes, specifically: $DYN > \delta_1$ pg/mL or ($DYN > \delta_2$ pg/mL and $CRP > 3$ mg/L and ($TNF\alpha > 4$ pg/mL or $sIL6R > 25$ ng/mL)). The effect of the biomarker signature

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is evaluated at a range of dynorphin cut-points (δ) for δ_1 , but the δ_2 cut point in combination with 3MM is kept constant. These signatures show treatment effects of 4.5 MADRS points or higher and result in a >5 point signature advantage in 38-63% of patients. Fig. 29B corresponds to SigPos= DYN > 24.0 or (3MM and DYN>8), 63% of cohort. Fig. 29C corresponds to SigPos= DYN > 50 or (3MM and DYN>8), 38% of cohort. As shown in Figs. 29A-29C, 4MM biomarker signature positive patients (63% of MDD) respond with 4.6 MADRS points difference at end DB relative to placebo, a 6 points improvement compared to biomarker signature negative counterpart.

EXAMPLE 5

[00361] This is an open-label, multicenter, long-term study to evaluate the efficacy of intranasal esketamine plus a newly initiated oral antidepressant in subjects with TRD (ESKETINTRD3002 / NCT02418585).

Study Drug Information

[00362] Esketamine was supplied as a clear, colorless intranasal solution of esketamine hydrochloride (16.14% weight/volume [w/v]; equivalent to 14% w/v of esketamine base) in a nasal spray pump. The solution consisted of 161.4 mg/mL esketamine hydrochloride (equivalent to 140 mg of esketamine base) formulated in 0.12 mg/mL ethylenediaminetetraacetic acid (EDTA) and 1.5 mg/mL citric acid at a pH of 4.5 in water for injection. It is provided in a nasal spray pump, which delivered 16.14 mg esketamine hydrochloride (14 mg esketamine base) per 100- μ L spray. Each individual nasal spray pump (device) contained a total of 28 mg (*i.e.*, 2 sprays).

[00363] The placebo solution was supplied as a clear, colorless intranasal solution of water for injection, with a bittering agent (denatonium benzoate [Bitrex[®]] at a final concentration of 0.001 mg/mL) added to simulate the taste of the intranasal solution with active drug. The placebo solution was provided in matching nasal spray pump devices. Benzalkonium chloride was added as a preservative at a concentration of 0.3 mg/mL. Each individual nasal spray pump (device) contained 2 sprays.

Intranasal Study Drug

[00364] Table 33 describes how each intranasal treatment session was administered.

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Table 33: Intranasal Treatment Administration during the Double-blind Induction Phase			
Intranasal Treatment	Time of Intranasal Device Administration		
	0^a	5 minutes	10 minutes
Intranasal Device^b	1 st	2 nd	3 rd
Placebo	1 spray of placebo to each nostril	1 spray of placebo to each nostril	1 spray of placebo to each nostril
Esketamine 56 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	1 spray of placebo to each nostril
Esketamine 84 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril
^a Time 0 was defined as the time of administration of the first intranasal spray to one nostril from the first intranasal device. ^b One device was used at each time point. Each individual intranasal device contained 2 sprays. The intranasal devices containing esketamine delivered 14 mg per spray, for a total of 28 mg per individual device (<i>i.e.</i> , 2 sprays).			

[00365] On Day 1, subjects randomized to intranasal esketamine started with a dose of 56 mg. On Day 4, the dose was increased to 84 mg or remained at 56 mg. On Day 8, the dose was increased to 84 mg (if Day 4 dose was 56 mg), remained the same, or was reduced to 56 mg (if Day 4 dose was 84 mg). On Day 11, the dose was increased to 84 mg (if Day 8 dose was 56 mg), remained the same, or was reduced to 56 mg (if Day 8 dose was 84 mg). On Day 15, a dose reduction from 84 mg to 56 mg was permitted, if required for tolerability; no dose increase was permitted on Day 15. After Day 15, the dose remained stable (unchanged).

Oral Antidepressant Medications

[00366] Duloxetine 30 mg, Escitalopram 10 mg, Sertraline 50 mg and 25 mg, and Venlafaxine 75 mg and 37.5 mg were obtained from commercial stock.

Treatment duration/Trial duration

[00367] Each subject participated in up to 4 phases: up to 4-week screening phase (direct-entry subjects only), a 4-week open-label induction (IND) phase (direct-entry subjects and transferred-entry non responder subjects), a 48-week open-label optimization/maintenance (OP/MA) phase (all responder subjects from the open label IND phase of the current study, and transferred-entry responder subjects), and a 4-week follow-up phase. The maximum duration of the subject's participation in ESKETINTRD3004 study was

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60 weeks for direct-entry subjects; 56 weeks for transferred-entry non-responder subjects, and 52 weeks for transferred-entry responder subjects. The sample size of 750 was estimated to have at least 300 subjects received treatment with intranasal esketamine for 6 months and at least 100 subjects for 12 months. In addition, transfer-entry subjects were enrolled from 3005 study to get 100 elderly subjects dosed with esketamine. See, Figure 30 for the trial design.

Analysis sets for efficacy

[00368] The efficacy analyses are based on the full (IND) analysis set and the full (OP/MA) analysis set. The full (IND) analysis set is defined as all subjects who receive at least 1 dose of intranasal study medication or 1 dose of oral antidepressant in the open-label IND phase (for direct-entry and transferred-entry non-responder subjects). The full (OP/MA) analysis is defined as all subjects who receive at least 1 dose of intranasal study medication or 1 dose of oral antidepressant in the OP/MA phase. Efficacy variables include the MADRS which consists of 10 items that cover all the core depressive symptoms: each item is scored from 0 (symptom is not present or is normal) to 6 (severe or continuous presence of the symptom). A total score (0 to 60) is calculated by summing the scores of all 10 items. A higher score represents a more severe condition.

Subject and Treatment Information

[00369] 802 subjects with a DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) diagnosis of MDD were enrolled. Of the 802 enrolled subjects, 691 were direct-entry subjects and 111 were transfer-entry subjects from study ESKETINTRD3005. Out of 779 direct entry or transfer-entry non-responder subjects from the TRD3005 study in the full (IND) analysis set, 580 (74.5%) completed the IND phase. Of the 603 subjects entered in the OP/MA phase, 150 (24.9%) completed the OP/MA phase. A total of 357 subjects entered the follow-up phase and 326 (91.3%) completed the follow-up phase.

[00370] Of the 802 enrolled subjects, one subject did not receive intranasal study drug but did receive oral AD and 1 subject received intranasal study drug but did not receive oral AD. These subjects are included in the all enrolled analysis set. See, Tables 34 and 35.

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Table 34: Number of Subjects Entered from Study ESKETINTRD3005 (By Responder Status) and Direct Entry Subjects (Study ESKETINTRD3004: All Enrolled Analysis Set)	
	Intranasal Esk + Oral AD (N=802)
Direct-entry subjects in study	
ESKETINTRD3004	691 (86.2%)
Transferred-entry subjects from study	
ESKETINTRD3005:	111 (13.8%)
Non-responder subjects	88 (11.0%)
Intranasal esk 28 mg + oral AD	3 (0.4%)
Intranasal esk 56 mg + oral AD	9 (1.1%)
Intranasal esk 84 mg + oral AD	28 (3.5%)
Oral AD + Placebo	48 (6.0%)
Responder subjects	23 (2.9%)
Intranasal esk 28 mg + oral AD	1 (0.1%)
Intranasal esk 56 mg + oral AD	5 (0.6%)
Intranasal esk 84 mg + oral AD	9 (1.1%)
Oral AD + Placebo	8 (1.0%)
The final dose in the TRD3005 study is presented for the Transferred-entry subjects.	

Table 35: Number of Subjects in Each Analysis Set (Study ESKETINTRD3004: All Enrolled Analysis Set)	
	Intranasal Esk + Oral AD (N=802)
Induction phase	
Full (IND)	779 (97.1%)
Optimization/maintenance phase	
Full (OP/MA)	603 (75.2%)
Follow-up phase	
Follow-up	3574.5%)

[00371] Subjects received flexible doses of intranasal ESK for the 1st 2 weeks, followed by fixed doses (28 mg – in elderly subjects only, 56 mg or 84 mg in all age groups) plus a newly initiated oral antidepressant (sertraline, escitalopram, venlafaxine XR or fluoxetine). Esketamine was dosed twice a week during the IND. In the OP/MA, weekly administration occurred from weeks 5 to 8. From weeks 9 to 52 of the OP/MA phase, esketamine was dosed either weekly or every other week depending on the MADRS score with the aim of having the lowest frequency to sustain remission. Switching to every other week treatment (if total MADRS score was ≤ 12) or back to weekly treatment (if total MADRS score was >12) was possible at 4-week intervals, starting at week 8. From day 15

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(patients <65 years) or day 18 (patients $\geq$ 65 years) the dose of esketamine nasal spray remained the same. After an initial period of dose up-titration, the dose of oral antidepressants remained the same. Dose reductions based on tolerability were allowed for both medications. Baseline psychiatric history for the all enrolled analysis set is presented in Table 36.

Table 36: Baseline(IND) Psychiatric History (Study ESKETINTRD3004: All Enrolled Analysis Set)	
	Intranasal Esk + Oral AD (N=802)
Age when diagnosed with MDD (years)	
N	802
Mean (SD)	35.7 (13.75)
Median	35.0
Range	(8; 72)
Baseline MADRS total score	
N	802
Mean (SD)	31.4 (5.39)
Median	31.0
Range	(19; 49)
Baseline CGI-S	
N	802
Mean (SD)	4.8 (0.77)
Median	5.0
Range	(1; 7)
Baseline CGI-S category, n (%)	
N	802
Normal, not at all ill	1 (0.1%)
Borderline mentally ill	3 (0.4%)
Mildly ill	18 (2.2%)
Moderately ill	235 (29.3%)
Markedly ill	409 (51.0%)
Severely ill	130 (16.2%)
Among the most extremely ill patients	6 (0.7%)
Baseline PHQ-9 total score	
N	802
Mean (SD)	17.3 (5.01)
Median	18.0
Range	(0; 27)
Screening C-SSRS lifetime ^a , n (%)	
N	800
No event	474 (59.3%)

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Table 36: Baseline(IND) Psychiatric History (Study ESKETINTRD3004: All Enrolled Analysis Set)	
	Intranasal Esk + Oral AD (N=802)
Suicidal ideation	203 (25.4%)
Suicidal behavior	123 (15.4%)
Screening C-SSRS past 6 or 12 months ^a , n (%)	
N	800
No event	583 (72.9%)
Suicidal ideation (past 6 months)	215 (26.9%)
Suicidal behavior (past 12 months)	2 (0.3%)
Duration of current episode (wks)	
N	802
Mean (SD)	160.5 (261.80)
Median	66.5
Range	(6; 2184)
No. of previous antidepressant medications ^{b c} , n (%)	
N	802
1	17 (2.1%)
2	465 (58.0%)
3	187 (23.3%)
4	84 (10.5%)
5	23 (2.9%)
6	17 (2.1%)
7	4 (0.5%)
8	5 (0.6%)
Family history of depression, n (%)	
N	802
Yes	346 (43.1%)
No	456 (56.9%)
Family history of anxiety disorder, n (%)	
N	802
Yes	61 (7.6%)
No	741 (92.4%)
Family history of bipolar disorder, n (%)	
N	802
Yes	35 (4.4%)
No	767 (95.6%)
Family history of schizophrenia, n (%)	
N	802
Yes	38 (4.7%)
No	764 (95.3%)
Family history of alcohol abuse, n (%)	
N	802

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Table 36: Baseline(IND) Psychiatric History (Study ESKETINTRD3004: All Enrolled Analysis Set)	
	Intranasal Esk + Oral AD (N=802)
Yes	61 (7.6%)
No	741 (92.4%)
Family history of substance abuse, n (%)	
N	802
Yes	24 (3.0%)
No	778 (97.0%)
Number of prior ADs with nonresponse	1 = 2.1% ^d 3 = 23.3% 2 = 58.0% ≥ 4 = 16.6%
Baseline (IND) is the last observation prior to or on the start date of induction phase for direct-entry and transferred-entry non-responder subjects and is baseline (IND) from study 3005 for the transferred-entry responder subjects. ^a C-SSRS category: No event=0; Suicidal ideation = 1, 2, 3, 4, 5; Suicidal behavior = 6, 7, 8, 9, 10. ^b Number of antidepressant medications with non-response (defined as ≤25% improvement or 26%-<50% improvement for direct entry subjects and defined as ≤25% improvement for transfer entry subjects) taken for at least 6 weeks during the current episode as obtained from MGH-ATRQ at the time of the first screening visit. ^c Direct entry subjects are to have to ≥2 oral antidepressant treatments in the current episode of depression and transfer entry subjects are to have ≥1 oral antidepressants in the current episode. ^d Subjects from 3005 who had non-response to 1 AD and showed prospective non-response to 2 nd AD during screening of the 3005 study.	

Extent of Exposure

[00372] The number of doses of intranasal study medication during the IND phase is summarized in Table 37.

Table 37: Number of Days Dosed with Intranasal Study Medication; Induction Phase (Study ESKETINTRD3004: Full (IND) Analysis Set)	
	Intranasal Esk + Oral AD (N=779)
Number of days dosed	
1	29 (3.7%)
2	24 (3.1%)
3	12 (1.5%)
4	11 (1.4%)
5	6 (0.8%)
6	22 (2.8%)
7	52 (6.7%)
8	622 (79.8%)

[00373] A summary of mean, mode and final dose of intranasal study medication during the IND phase is summarized in Table 38. On Day 25 of the IND phase 28/675 (4.1%)

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were receiving the 28 mg dose of esketamine, 298/675 (44.1%) were receiving the 56 mg dose of esketamine and 349/675 (51.7%) were receiving the 84 mg dose of esketamine.

Table 38: Mean, Mode, and Final Daily Dose of Intranasal Study Medication; Induction Phase (Study ESKETINTRD3004: Full (IND) Analysis Set)	
	Intranasal Esk + Oral AD (N=779)
Mean daily dose (mg)	
N	778
Mean (SD)	64.4 (13.15)
Median	63.0
Range	(28; 81)
Mode daily dose (mg)	
N	741
Mean (SD)	68.5 (16.51)
Median	56.0
Range	(28; 84)
Final daily dose (mg)	
N	778
Mean (SD)	68.2 (16.61)
Median	56.0
Range	(28; 84)
The calculation of mean, mode, and final daily dose excludes days off intranasal study medication. The final dose is the last non-zero dose received during the induction phase.	

[00374] The extent of exposure to intranasal study medication during the combined IND and OP/MA phases is summarized in Table 39.

Table 39: Extent of Exposure to Intranasal Study Medication; Induction and Optimization/Maintenance Phases (Study ESKETINTRD3004: All Enrolled Analysis Set)		
	Intranasal Esk + Oral AD	
	Total Duration (N=802)	Cumulative Distribution (N=802)
Duration, weeks		
N	801	801
Category, n (%)		
≤Week 4 (≤ Day 28)	202 (25.2%)	202 (25.2%)
Weeks 4-8 (Days 29-56)	35 (4.4%)	237 (29.6%)
Weeks 8-12 (Days 57-84)	23 (2.9%)	260 (32.4%)
Weeks 12-16 (Days 85-112)	48 (6.0%)	308 (38.4%)
Weeks 16-20 (Days 113-140)	52 (6.5%)	360 (44.9%)
Weeks 20-24 (Days 141-168)	50 (6.2%)	410 (51.1%)
Weeks 24-28 (Days 169-196)	52 (6.5%)	462 (57.6%)
Weeks 28-32 (Days 197-224)	34 (4.2%)	496 (61.8%)

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Table 39: Extent of Exposure to Intranasal Study Medication; Induction and Optimization/Maintenance Phases (Study ESKETINTRD3004: All Enrolled Analysis Set)		
	Intranasal Esk + Oral AD	
	Total Duration (N=802)	Cumulative Distribution (N=802)
Weeks 32-36 (Days 225-252)	30 (3.7%)	526 (65.6%)
Weeks 36-40 (Days 253-280)	32 (4.0%)	558 (69.6%)
Weeks 40-44 (Days 281-308)	45 (5.6%)	603 (75.2%)
Weeks 44-48 (Days 309-336)	35 (4.4%)	638 (79.6%)
Weeks 48-52 (Days 337-364)	155 (19.4%)	793 (98.9%)
>Week 52 (>Day 364)	8 (1.0%)	801 (99.9%)
Mean (SD)	24.9 (18.54)	
Median	22.9	
Range	(0; 56)	
The duration of exposure is defined as the duration between the date of the first exposure and the date of the last exposure to intranasal study medication. It includes days on which subjects did not actually take intranasal study medication.		

[00375] The frequency of subjects with 6 months and 12 months of exposure to esketamine is presented in Table 40.

Table 40: Frequency Distribution of Subjects with 6 Months and 12 Months of Exposure to Intranasal Study Medication (Study ESKETINTRD3004: All Enrolled Analysis Set)	
	Intranasal Esk + Oral AD (N=802)
Subjects with 6 months of exposure	364 (45.4%)
Subjects with 12 months of exposure	136 (17.0%)
6 months is defined as ≥ 180 days and 12 months is defined as ≥ 350 days.	

[00376] A summary of mean, mode and final dose of intranasal study medication during the OP/MA phase is summarized in Table 41.

Table 41: Mean, Mode, and Final Daily Dose of Intranasal Study Medication; Optimization/Maintenance Phase (Study ESKETINTRD3004: Full (OP/MA) Analysis Set)	
	Intranasal Esk + Oral AD (N=603)
Mean daily dose (mg)	
N	603
Mean (SD)	68.8 (15.74)
Median	68.3
Range	(25; 84)
Mode daily dose (mg)	
N	596

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Table 41: Mean, Mode, and Final Daily Dose of Intranasal Study Medication; Optimization/Maintenance Phase (Study ESKETINTRD3004: Full (OP/MA) Analysis Set)	
	Intranasal Esk + Oral AD (N=603)
Mean (SD)	69.1 (15.75)
Median	70.0
Range	(28; 84)
Final daily dose (mg)	
N	603
Mean (SD)	69.0 (16.05)
Median	84.0
Range	(28; 84)
The calculation of mean, mode, and final daily dose excludes days off intranasal study medication. The final dose is the last non-zero dose received during the optimization/maintenance phase.	

[00377] On Week 48 of the OP/MA phase, 7/143 (4.9%), 69/143 (48.3%), 1/143 (0.7%) and 66/143 (46.2%) were receiving the 28 mg dose, 56 mg dose, 70 mg dose, and 84 mg dose of esketamine, respectively. Starting from Week 4 (OP/MA), the intranasal treatment session frequency could be adjusted (if applicable) at fixed, 4-week intervals. Of the 603 subjects treated with intranasal esketamine during the OP/MA phase, 275 (47.6%) subjects switched from weekly dosing to every other week at Week 4 (OP/MA). See, Table 42.

Table 42: Frequency of Subjects who Changed the Dosing Frequency (Weekly to Every Other Week or Every Other Week to Weekly) Over Time Starting From Week 4 (OP/MA) of this Phase; Optimization/Maintenance Phase (Study ESKETINTRD3004: Full (OP/MA) Analysis Set)	
	Intranasal Esk + Oral AD (N=603)
Week 4(OP/MA)	
N	578
Weekly to Every Other Week	275 (47.6%)
Every Other Week to Weekly	0
Did not switch	303 (52.4%)
Week 8(OP/MA)	
N	548
Weekly to Every Other Week	80 (14.6%)
Every Other Week to Weekly	65 (11.9%)
Did not switch	403 (73.5%)
Week 12(OP/MA)	

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Table 42: Frequency of Subjects who Changed the Dosing Frequency (Weekly to Every Other Week or Every Other Week to Weekly) Over Time Starting From Week 4 (OP/MA) of this Phase; Optimization/Maintenance Phase (Study ESKETINTRD3004: Full (OP/MA) Analysis Set)	
	Intranasal Esk + Oral AD (N=603)
N	502
Weekly to Every Other Week	76 (15.1%)
Every Other Week to Weekly	52 (10.4%)
Did not switch	374 (74.5%)
Week 16(OP/MA)	
N	463
Weekly to Every Other Week	58 (12.5%)
Every Other Week to Weekly	43 (9.3%)
Did not switch	362 (78.2%)
Week 20(OP/MA)	
N	405
Weekly to Every Other Week	34 (8.4%)
Every Other Week to Weekly	29 (7.2%)
Did not switch	342 (84.4%)
Week 24(OP/MA)	
N	357
Weekly to Every Other Week	23 (6.4%)
Every Other Week to Weekly	42 (11.8%)
Did not switch	292 (81.8%)
Week 28(OP/MA)	
N	309
Weekly to Every Other Week	28 (9.1%)
Every Other Week to Weekly	22 (7.1%)
Did not switch	259 (83.8%)
Week 32(OP/MA)	
N	287
Weekly to Every Other Week	30 (10.5%)
Every Other Week to Weekly	21 (7.3%)
Did not switch	236 (82.2%)
Week 36(OP/MA)	
N	254
Weekly to Every Other Week	13 (5.1%)
Every Other Week to Weekly	17 (6.7%)
Did not switch	224 (88.2%)
Week 40(OP/MA)	
N	211
Weekly to Every Other Week	13 (6.2%)
Every Other Week to Weekly	14 (6.6%)

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Table 42: Frequency of Subjects who Changed the Dosing Frequency (Weekly to Every Other Week or Every Other Week to Weekly) Over Time Starting From Week 4 (OP/MA) of this Phase; Optimization/Maintenance Phase (Study ESKETINTRD3004: Full (OP/MA) Analysis Set)	
	Intranasal Esk + Oral AD (N=603)
Did not switch	184 (87.2%)
Week 44(OP/MA)	
N	173
Weekly to Every Other Week	9 (5.2%)
Every Other Week to Weekly	6 (3.5%)
Did not switch	158 (91.3%)

[00378] Table 43 displays the dosing regimen changes during the OP/MA phase.

Table 43: Dosing Regimen Changes; Optimization/Maintenance Phase (Study ESKETINTRD3004: Full (OP/MA) Analysis Set)	
	Intranasal Esk + Oral AD (N=603)
Total number of dosing regimen changes per subject	
N	603
0	145 (24.0%)
1	230 (38.1%)
2	85 (14.1%)
3	70 (11.6%)
4	35 (5.8%)
5	28 (4.6%)
6	10 (1.7%) ^a
Dosing Regimen	
N	603
Weekly dose throughout entire OP/MA phase	145 (24.0%)
One change only from weekly to every other week	230 (38.1%)
Change back and forth from weekly to every other week	228 (37.8%)
The denominator is the number of subjects who have dosing $\geq$ Week 4(OP/MA) Regimen: weekly esketamine dosing or every other week esketamine dosing. Number of Changes: 0 = weekly dose throughout OP/MA phase; 1 = 1 change from weekly to every other week (EOW); 2 = change from EOW back to weekly; 3 = 2 changes from weekly to EOW remained on EOW; 4 = 2 changes from weekly to EOW and back to weekly; 5 = 3 changes from weekly to EOW, remaining on EOW; 6 = 3 changes from weekly to EOW and back to weekly. ^a Approximately 22% returned to weekly in total 46% on weekly and 16% returned to every other week (in total 54% on every other week).	

Efficacy Analyses

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[00379] The efficacy analyses were performed on the full analysis sets for the IND and OP/MA phases including all enrolled subjects who received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant study medication in the respective phases.

[00380] Montgomery-Asberg Depression Rating Scale (MADRS)

[00381] The mean change (SD) from Baseline (IND) in MADRS total score to End Point (IND) was -16.4 (8.76) for esketamine + oral AD. The mean change (SD) from Baseline (OP/MA) in MADRS total score to End Point (OP/MA) was 0.3 (8.12) for esketamine + oral AD. See, Figure 31.

[00382] Response ($\geq 50\%$ improvement from Baseline (IND) in the MADRS total score) and Remission (MADRS total score is ≤ 12) rates are presented for the IND and OP/MA phases in Tables 44 and 45, respectively.

[00383] At End Point in the IND phase, the response rate was 78.4% and remission rate was 47.2%; of the responders proceeding to the OP/MA phase, 76.5% were responders and 58.2% were remitters at endpoint. Functional recovery measured by SDS followed with some lag time after mood improvement. At endpoint of the IND, remission rate measured by SDS at endpoint of the IND phase (21.1%, observed case). The remission rate doubled throughout the OP/MA phase (25.2% at week 4 to 51.1% at week 48, observed case). See, Figure 32.

Table 44: Response and Remission Rates Based on MADRS; Induction Phase (Study ESKETINTRD3004: Full (IND) Analysis Set)		
	Response	Remission
	Intranasal Esk +Oral AD	Intranasal Esk +Oral AD
Day 8	86/739 (11.6%)	54/739 (7.3%)
Day 15	185/702 (26.4%)	115/702 (16.4%)
Day 22	312/683 (45.7%)	199/683 (29.1%)
Day 28	581/688 (84.4%)	349/688 (50.7%)
End Point (IND)	593/756 (78.4%)	357/756 (47.2%)
A subject is defined as a responder at a given time point if the percent improvement from baseline (IND) in MADRS total score is at least 50%. A subject is in remission at a given time point if the MADRS total score is ≤ 12 .		

Table 45: Response and Remission Rates Based on MADRS; Optimization/Maintenance Phase (Study ESKETINTRD3004: Full (OP/MA) Analysis Set)		
	Response	Remission
	Intranasal Esk +Oral AD	Intranasal Esk +Oral AD
Week 1	513/583 (88.0%)	325/583 (55.7%)
Week 8	408/530 (77.0%)	277/530 (52.3%)
Week 16	355/446 (79.6%)	273/446 (61.2%)

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Week 24	278/346 (80.3%)	203/346 (58.7%)
Week 32	226/284 (79.6%)	178/284 (62.7%)
Week 40	171/210 (81.4%)	127/210 (60.5%)
Week 48	124/139 (89.2%)	95/139 (68.3%)
End Point (OP/MA)	461/603 (76.5%)	351/603 (58.2%)
A subject is defined as a responder at a given time point if the percent improvement from baseline (IND) in MADRS total score is at least 50%. A subject is in remission at a given time point if the MADRS total score is ≤ 12 .		

Patient Health Questionnaire (PHQ-9) Total Score

[00384] The mean change (SD) from Baseline (IND) in PHQ-9 total score to End Point (IND) was -8.9 (6.67) for esketamine + oral AD. The mean change (SD) from Baseline (OP/MA) in PHQ-9 total score to End Point (OP/MA) was -0.2 (5.65) for esketamine + oral AD. See, Figure 33.

EXAMPLE 6

[00385] Samples of venous blood were obtained from patients and healthy control subjects from subject described in Example 5 and from the other clinical trials referenced herein. Serum or plasma was prepared from the samples of venous blood. Measurements of human CRP and IL-6-R were performed in serum using an MSD Sector 6000 with the kits# K151STD and K151ALC (MesoScale Discovery, Rockville, MD). Human TNF α was quantified in serum using a Simoa HD-1 analyzer with kit# 143 (Quanterix, Lexington, MA). All measures were performed according to kit manufacturer's recommendations.

[00386] As used in the following biomarker assay analysis, treatment (TRT) refers to treatment with intranasal esketamine plus optionally an oral antidepressant and placebo (PBO) refers to treatment with a placebo plus optionally an oral antidepressant.

[00387] The following biomarker signatures were employed:

[00388] 3MM: Inflammatory biomarker signature with positive status defined by CRP > 3 mg/L and (TNF α > 4 pg/mL or sIL6R > 25 ng/mL).

[00389] 2MM: Inflammatory biomarker signature with positive status defined by CRP > 3 mg/L and sIL6R > 25 ng/mL.

[00390] CRP: Inflammatory biomarker signature with positive status defined by CRP > 3 mg/L/

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[00391] The 3MM signature was tested in clinical trials for adjunctive MDD, including treatment-resistant MDD (TRD) and MDD with suicidal ideation (SUI). The effect of 3MM across clinical trials is shown in FIG. 34. Significant was driven by Esketamine (ESK) TRD trials. Esketamine TRD exhibits the most robust effects with respect to high-inflammation biotypes ($(\text{"CRP"} > 3 \text{ mg/L and } (TNF\alpha > 4 \text{ pg/mL or sIL6R} > 25 \text{ ng/mL}))$). In the esketamine trials with suicidal ideation (SUI), 3MM status at baseline did not predict treatment effect. A nominally significant (post-hoc, no correction for multiple testing) differentiation was seen in esketamine TRD trials (see FIG. 35). Colors represent ranges of n 's of subjects and shapes represent p values, the gray shaded area indicates a MADRS change lower than 3 points.

[00392] Across the esketamine TRD trials, a significant greater treatment effect in biomarker signature positive subjects was evident in 3 out of 4 studies: 3MM biomarker signature positive subjects (TE Sig^{Pos}, left panel of FIG. 35) improved by 7.8 MADRS points over placebo at the end of the double blind treatment, a significantly greater ($p < 0.01$) treatment effect than in the biomarker signature negative subjects (TE Sig^{Neg}, middle panel of FIG. 35), who only improved by 2 MADRS points, resulting in a 5.8 point difference between subtypes (Signature advantage, right panel of FIG. 35). A large treatment effect of 11.69 points change in MADRS was also seen in TRD2003 in biomarker signature positive Japanese patients (albeit the n was small, FIG. 36A) compared to 2.83 points in biomarker signature negative Japanese patients (FIG. 36B).

[00393] If the 3MM is reduced to a 2MM by removing TNF α and only taking CRP and sIL6R into account, the same trends were observed across trials. Also included in the 2MM analysis and the CRP analysis, below, are clinical trials CNTO136MDD2001, 67953964MDD2001, 42847922MDD2001, and 42847922MDD2002, which involve administration of sirukumab (CNTO136MDD2001), aticaprant (67953964MDD2001), and seltorexant (42847922MDD2001 and NCT03321526). The overall effect in the biomarker signature positive group (left panels of FIG. 37A and FIG. 37B) is 4.2 points improvement in MADRS across all trials with 2MM (FIG. 37A) versus 4.6 points with 3MM (FIG. 37B), compared to 1.1 points in the biomarker signature negative group (middle panels of FIG. 37A and FIG. 37B) with 2MM and 1.0 with 3MM resulting in a signature advantage (right panel of FIG. 37A and FIG. 37B) of 3 points with 2MM versus 3.6 points with 3MM. Therefore,

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including TNFalpha in the model optimizes the biomarker signature effect and also captures a larger n of patients. In FIG. 37A, TRD2003 and TRD2003 are trending rather than significant due to flipping the identity of one individual in each study.

[00394] When the model is reduced to CRP levels only, the treatment effects observed with 3MM or 2MM are weaker and more variable. The overall effect in the biomarker signature positive group (left panels of FIG. 38) is 3.5 points improvement in MADRS across all trials CRP only (FIG. 38) versus 4.6 points with 3MM (FIG. 37B), compared to 1.2 points in the biomarker signature negative group (middle panel of FIG. 38) with CRP only and 1.0 with 3MM resulting in a signature advantage (right panel of FIG. 38) of only 2.3 points with CRP only versus 3.6 points with 3MM. Therefore, a single marker (CRP) is not as robust as using a combination of markers. In FIG. 38, TRD3002 is trending due to membership differences for 20 subjects relative to 3MM.

[00395] While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

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What is Claimed Is:

1. A method of treating depression in a human patient, comprising administering to the patient in need thereof an effective amount of an antidepressant, wherein the patient is identified as biomarker signature positive, and wherein the patient is identified as biomarker signature positive if a biological sample obtained from the patient is identified as having a level of at least one biomarker that is greater or less than a reference biomarker level.
2. The method of claim 1, wherein the patient is identified as biomarker signature positive if the biological sample obtained from the patient is identified as having:
 - a. a level of CRP greater than a reference CRP level, and
 - b. at least one of:
 - i. a level of TNF-alpha that is greater than a reference TNF-alpha level, and
 - ii. a level of sIL6R that is greater than a reference sIL6R level. The method of claim 2, wherein the reference CRP level is about 3 mg/L.
3. The method of claim 2, wherein the reference TNF-alpha level is about 4 pg/mL.
4. The method of claim 2, wherein the reference sIL6R level is about 25 ng/mL.
5. The method of any one of the preceding claims, wherein the antidepressant is selected from esketamine and aticaprant, or a pharmaceutically acceptable salt thereof.
6. The method of claim 5, wherein the antidepressant is aticaprant, or a pharmaceutically acceptable salt thereof.
7. The method of claim 6, wherein the patient had an inadequate response to other antidepressant therapy prior to treatment with aticaprant or a pharmaceutically acceptable salt thereof.

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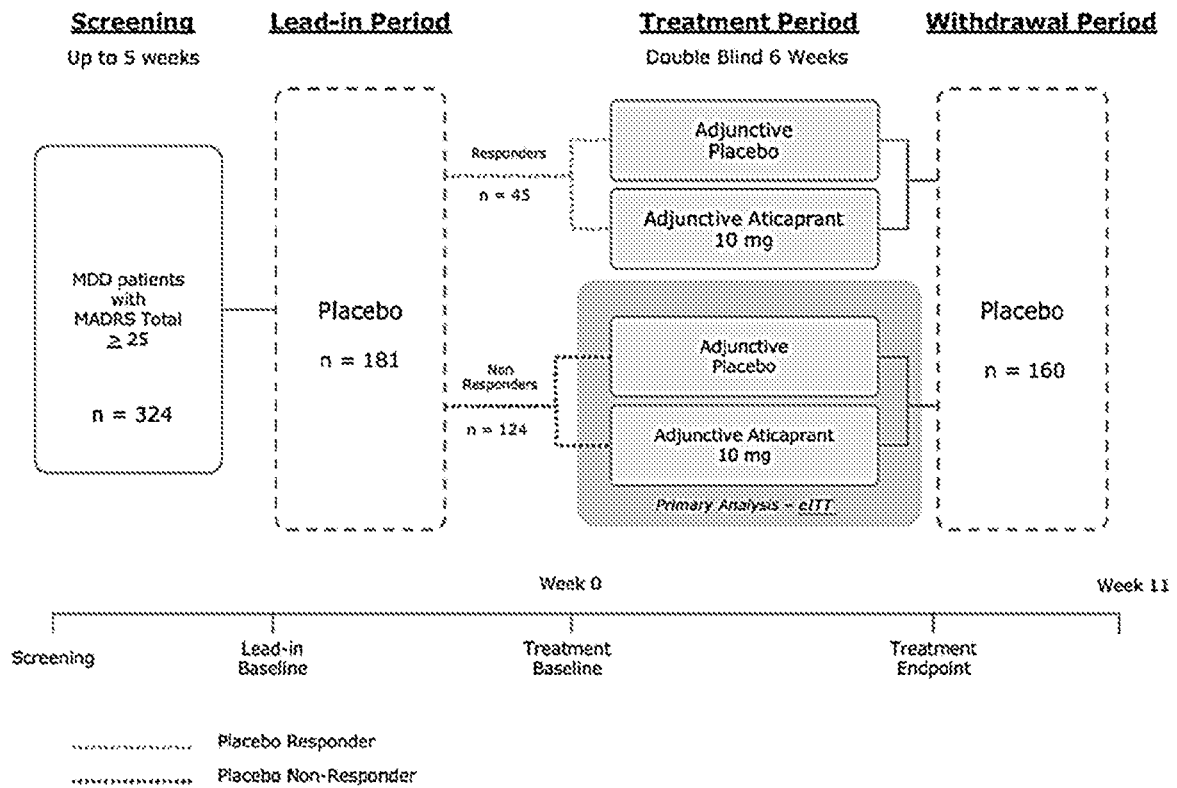
8. The method of claim 7, wherein the other antidepressant therapy comprised one or more second antidepressants.
9. The method of claim 8, wherein the one or more second antidepressants comprised a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI) treatment, or a combination thereof.
10. The method of claim any one of the preceding claims, wherein the patient has anhedonia.
11. The method of claim 10, wherein the patient has total score of ≥ 32 on the Snaith Hamilton Pleasure Scale (SHAPS).
12. The method of any one of the preceding claims, further comprising adjunctive treatment with an effective amount of one or more second antidepressants.
13. The method of claim 12, wherein the one or more second antidepressants is a selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), or a combination thereof.
14. The method of claim 6, wherein the aticaprant is S-aticaprant, or a pharmaceutically acceptable salt thereof.
15. The method of claim 6, wherein the effective amount of aticaprant is about 2 to about 35 mg.
16. The method of claim 15, wherein the effective amount of aticaprant is about 10 mg.
17. The method of claim 15, wherein the effective amount of aticaprant is about 5 mg.
18. The method of claim 6, wherein the aticaprant is administered orally.
19. The method of claim 6, wherein the aticaprant is administered once daily.
20. The method of claim 6, wherein the antidepressant is esketamine.

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21. The method of claim 20, the method having an induction phase and, optionally, a subsequent maintenance phase, wherein the induction phase comprises induction phase treatment sessions at a given frequency, and the maintenance phase comprises maintenance phase treatment sessions administered to the patient less frequently.
22. The method of claim 21, comprising
- a. intranasally administering about 28 mg to about 84 mg of esketamine per induction phase treatment session to said patient, wherein the induction phase treatment session occurs at a frequency of twice weekly during an the induction phase; and, optionally
 - b. intranasally administering about 56 mg to about 84 mg of esketamine per maintenance phase treatment session to said patient, wherein the maintenance phase treatment session occurs at a frequency of once weekly or once every other week.
23. The method of claim 21 or 22, wherein the induction phase has a duration of about 4 weeks.
24. The method of any one of claims 21 to 24, wherein about 56 or about 84 mg of esketamine is administered per induction phase treatment session.
25. The method of claim 24, wherein about 56 or about 84 mg of esketamine is administered per maintenance phase treatment session.
26. The method of any one of claims 21-25, wherein the esketamine is delivered from an intranasal device in 2 or more sprays during the induction phase and/or the maintenance phase.
27. The method of any one of claims 20-26, further comprising administering a therapeutically effective amount of an oral antidepressant to said patient during the induction and/or maintenance phase.

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28. The method of any one of claims 21-27, wherein the esketamine is administered as its corresponding hydrochloride salt during the induction phase and/or the maintenance phase.
29. The method of any one of the preceding claims wherein the depression comprises major depressive disorder.
30. The method of claim 29, wherein the major depressive disorder is major depressive disorder with suicidal ideation or behavior.
31. The method of claim 29, wherein the major depressive disorder is treatment resistant depression.

**Fig. 1**

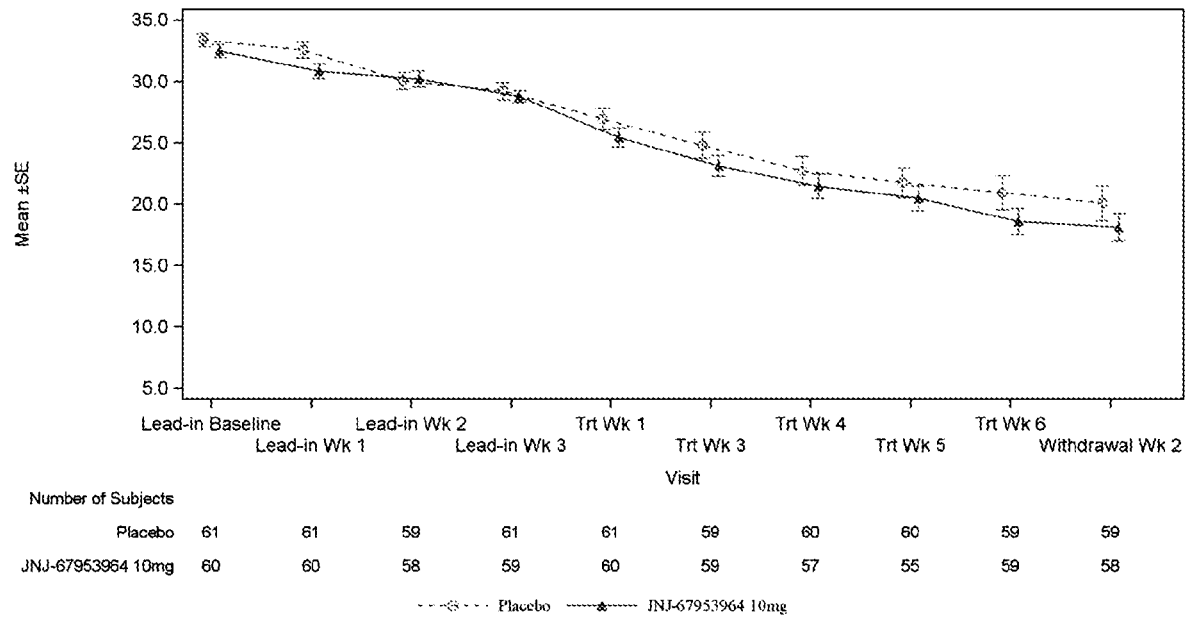


Fig. 2

Population	Treatment		LSMean Diff. (SE)	60% CI	p-value
Enriched	JNJ-67953964 10mg		-2.14 (1.252)	[-3.20, -1.09]	0.0443
Full	JNJ-67953964 10mg		-3.09 (1.049)	[-3.97, -2.21]	0.0017

Legend: --- Favours Active --- Favours Placebo

Fig. 3

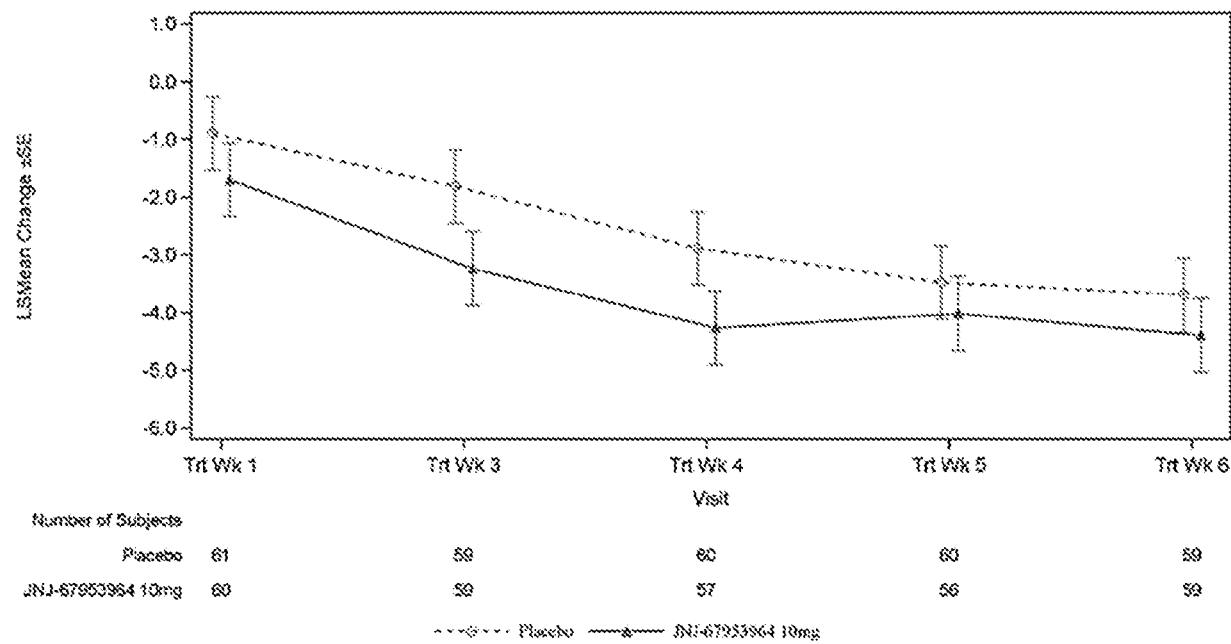


Fig. 4

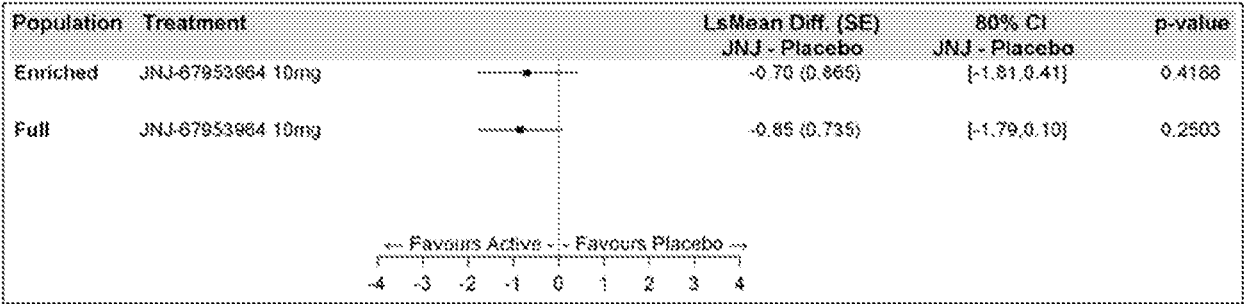


Fig. 5

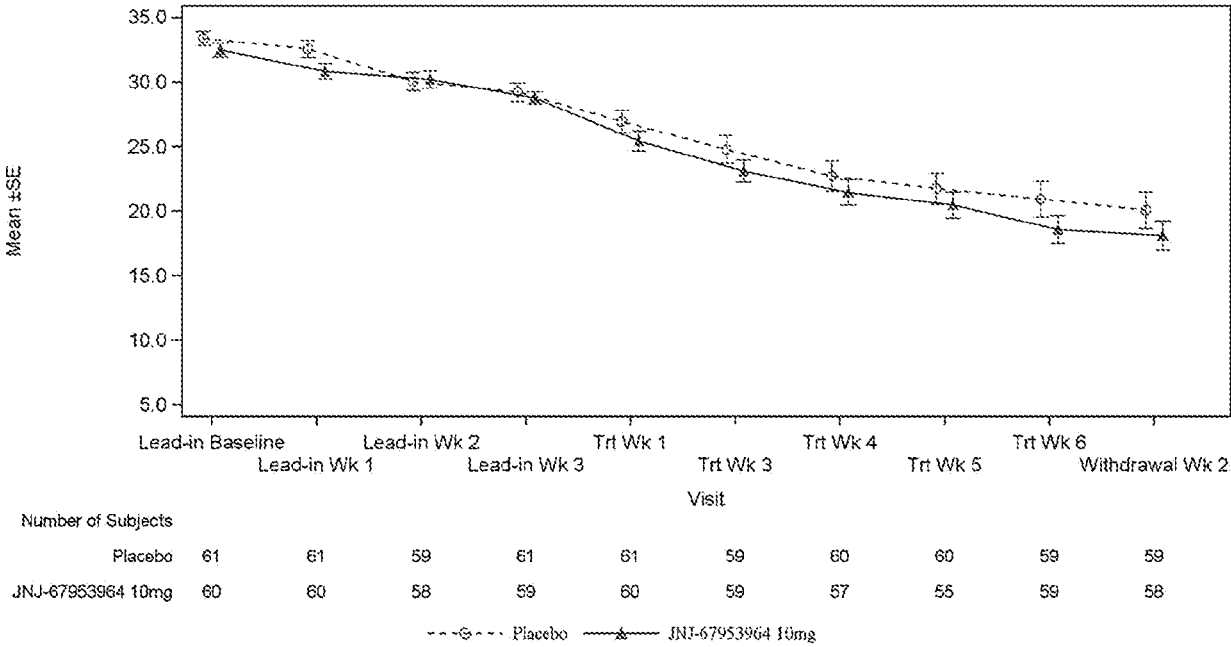


Fig. 6

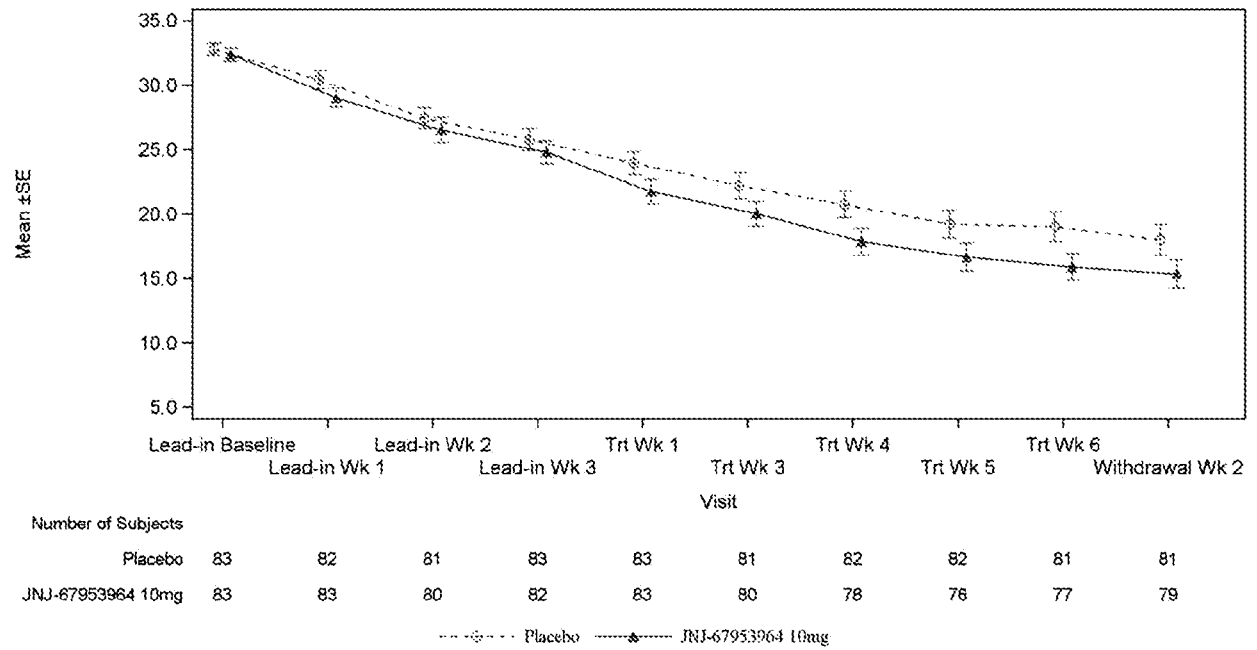


Fig. 7A

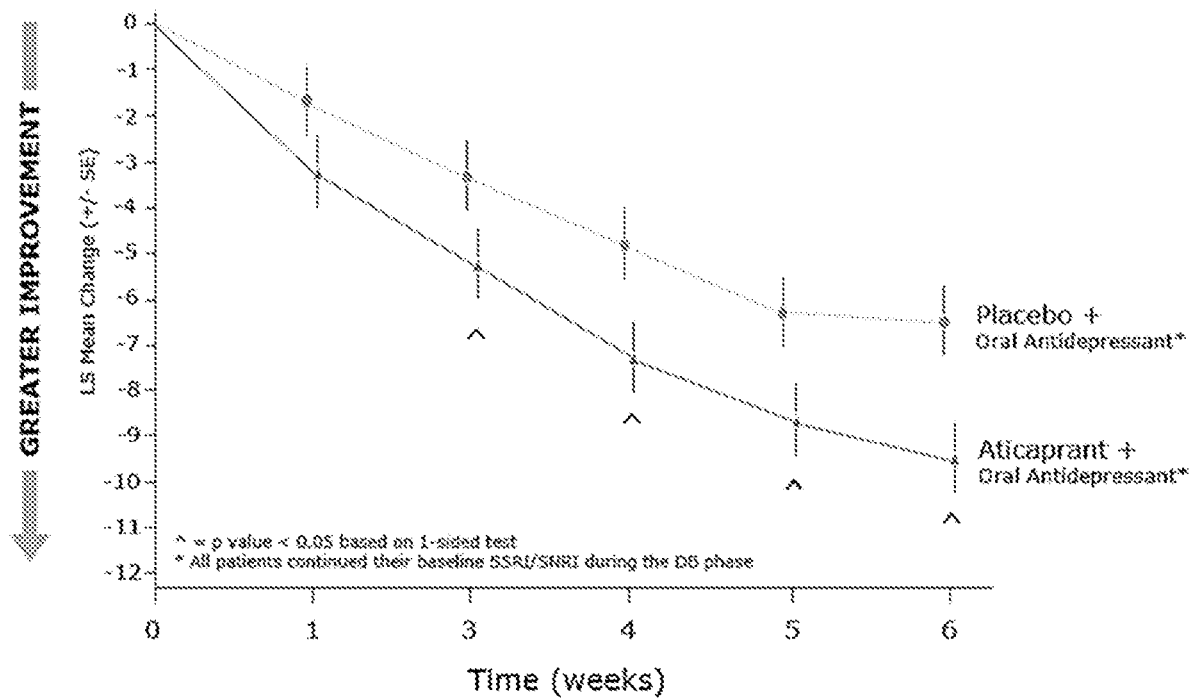


Fig. 7B

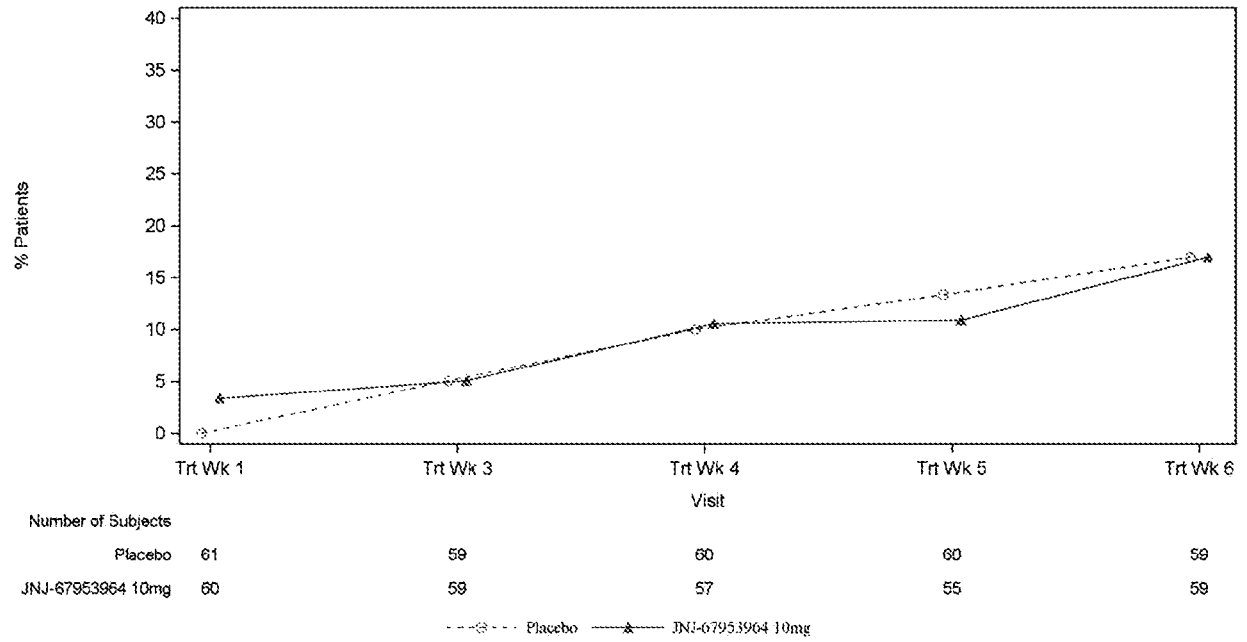


Fig. 8

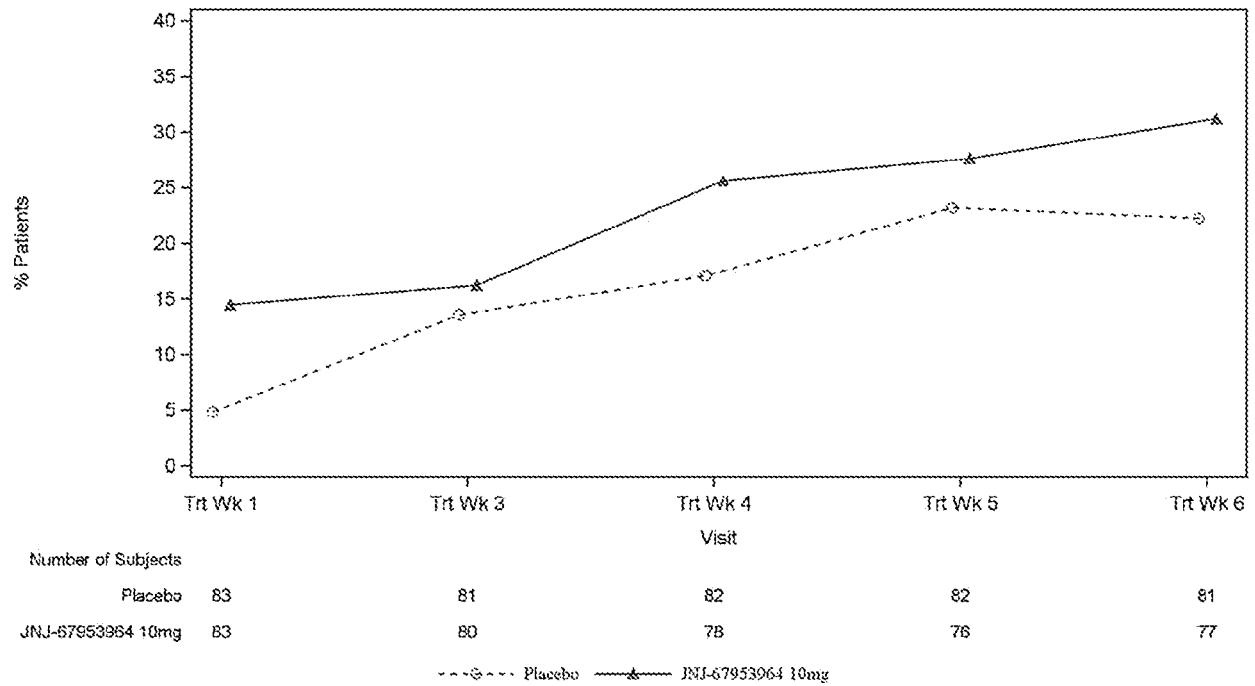
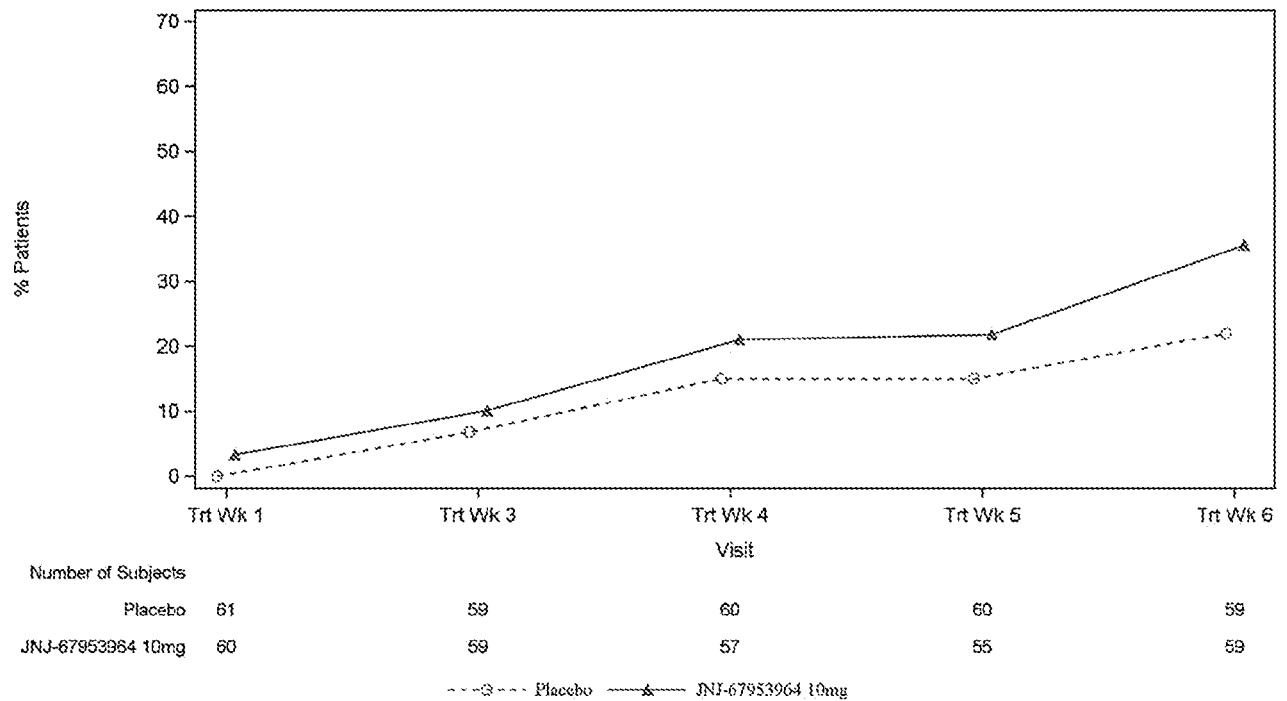
*Fig. 9*

Fig. 10

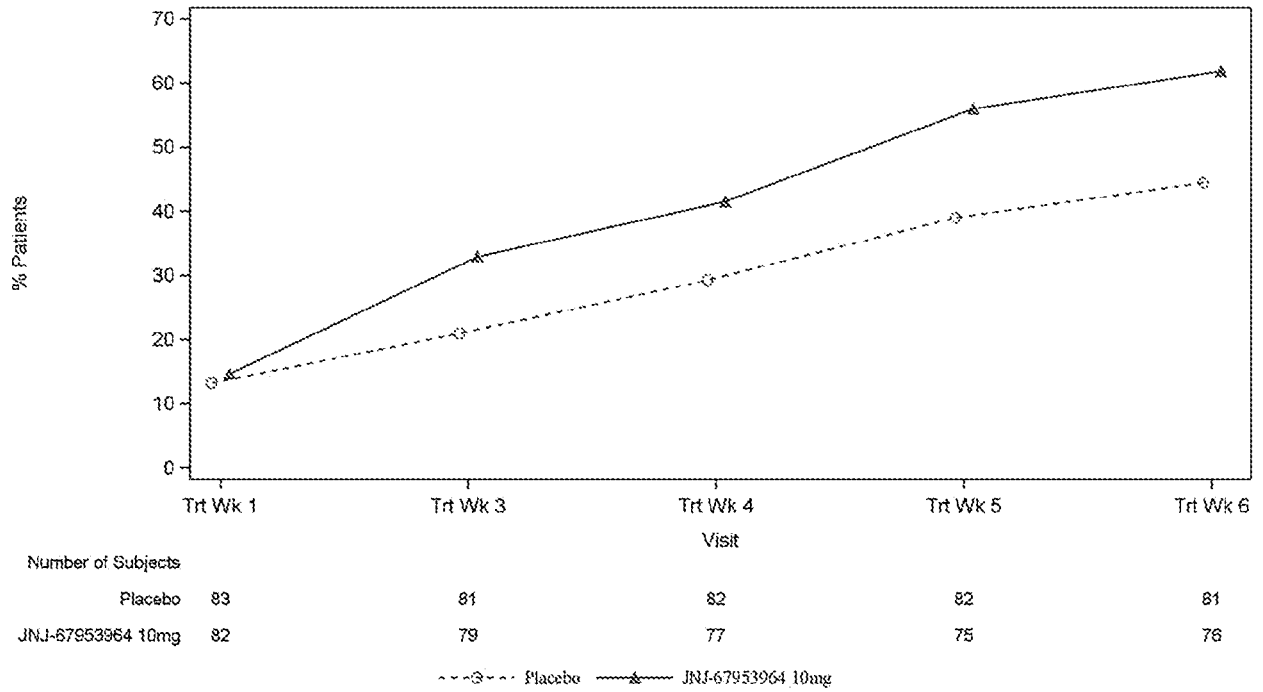


Fig. 11

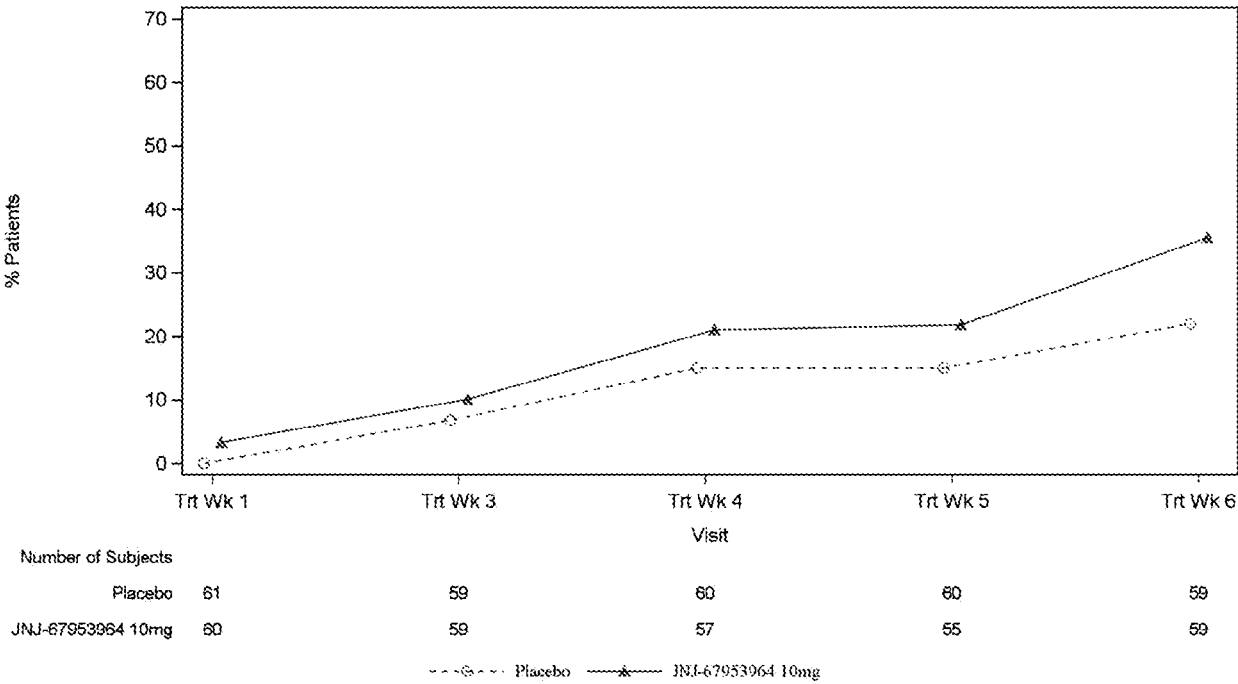


Fig. 12

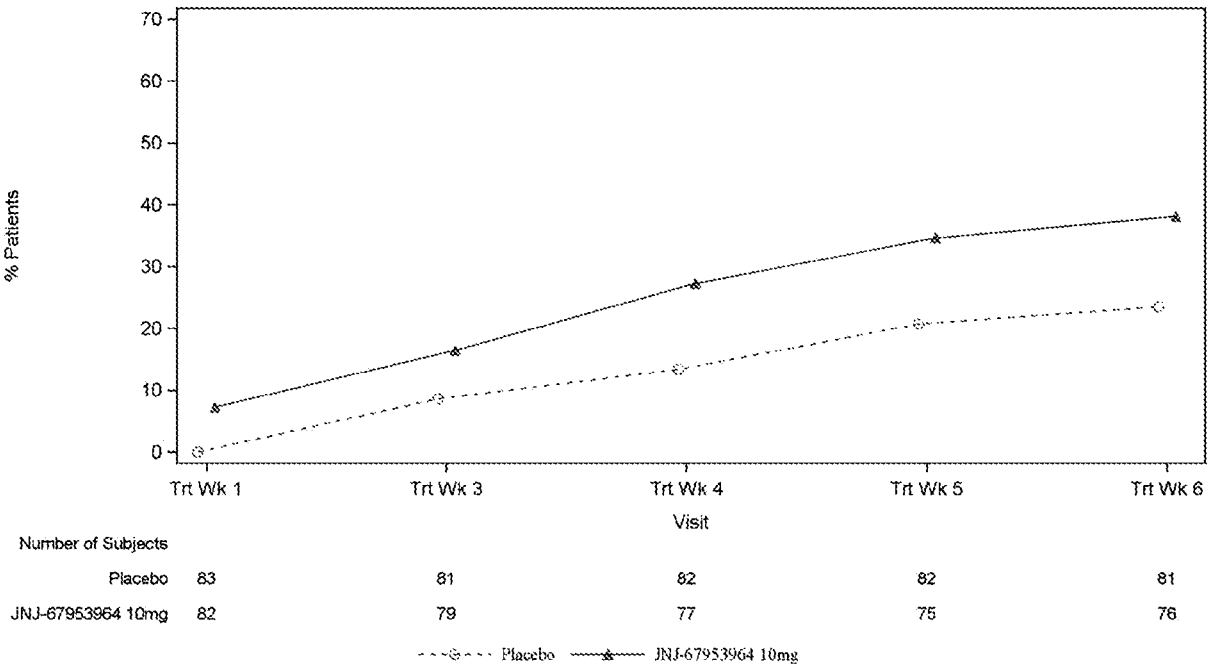


Fig. 13

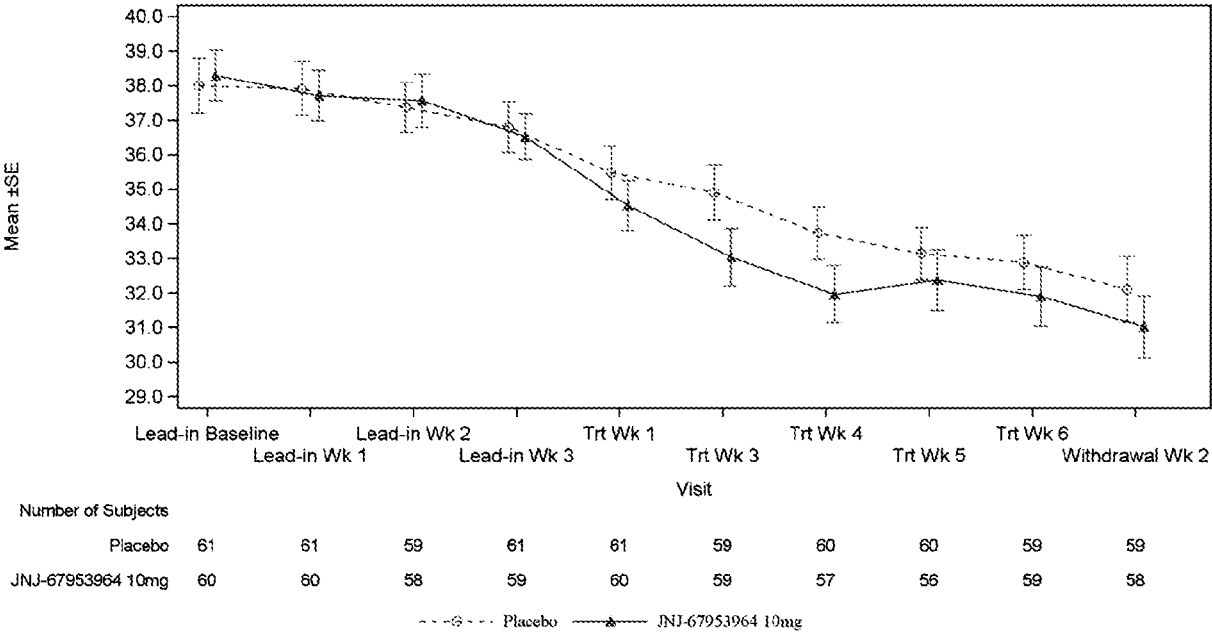


Fig. 14

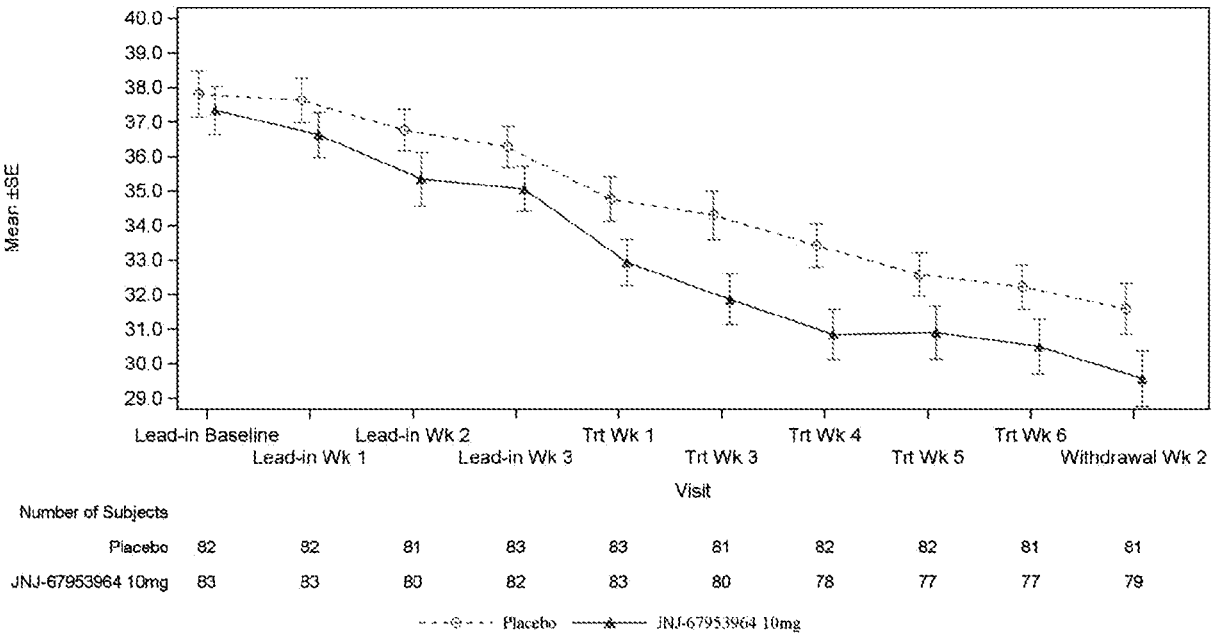


Fig. 15

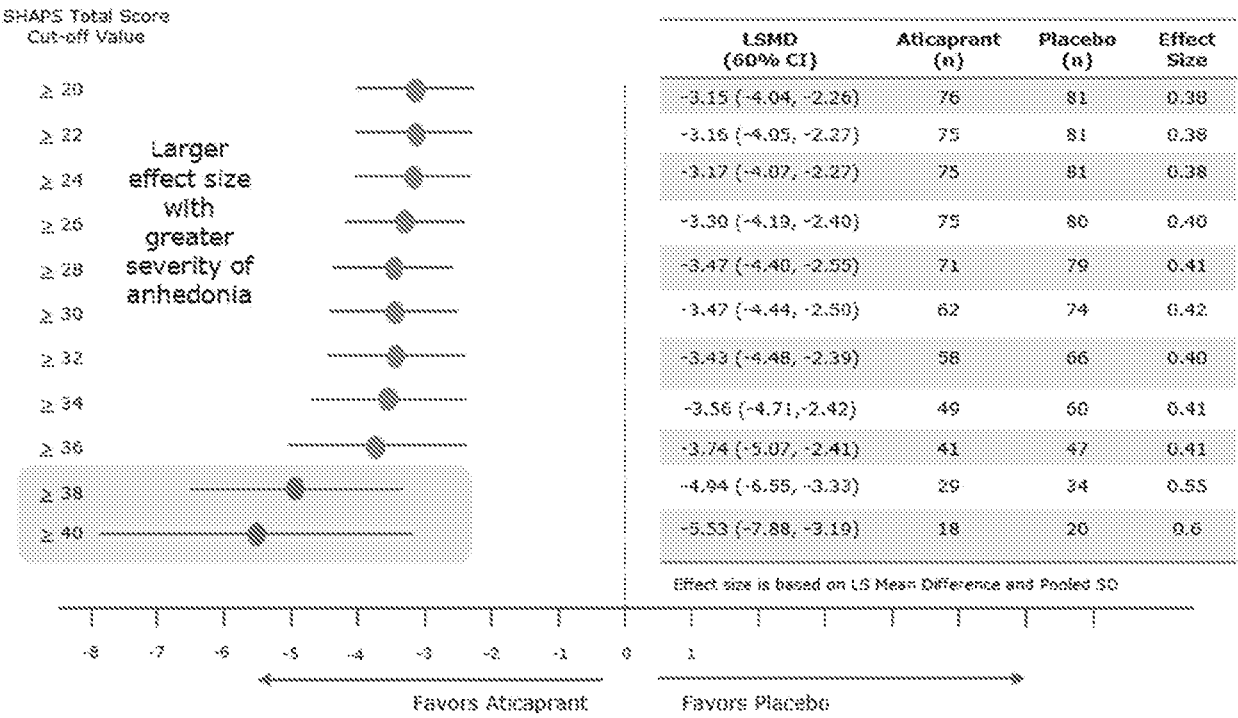
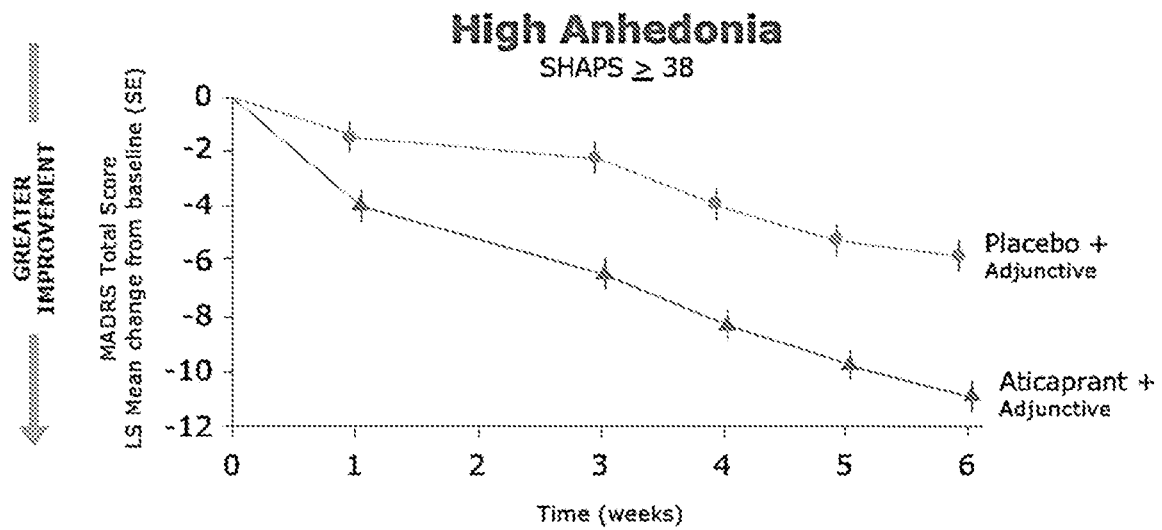
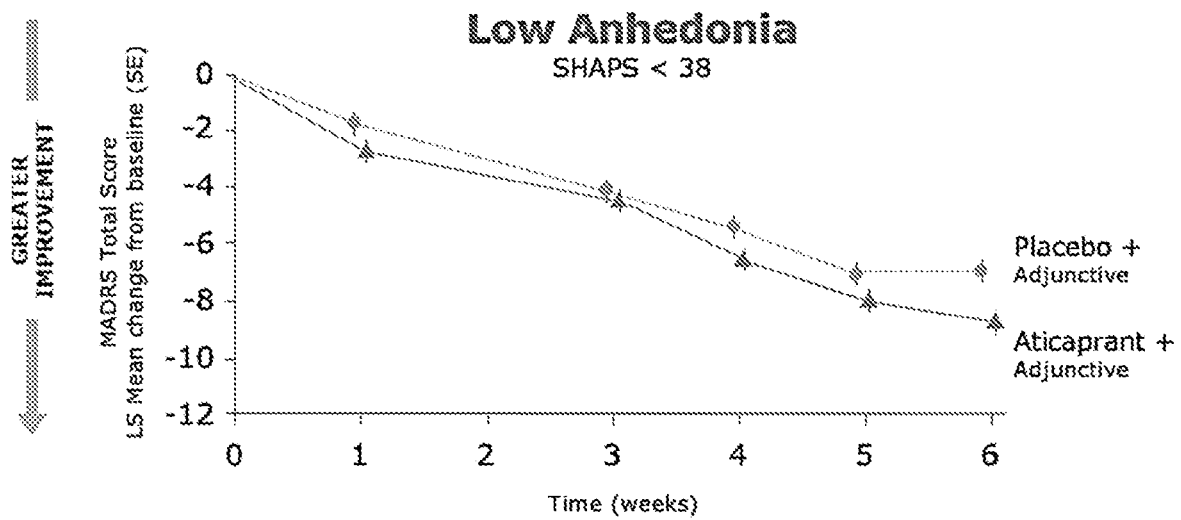


Fig. 16

*Fig. 17A**Fig. 17B*

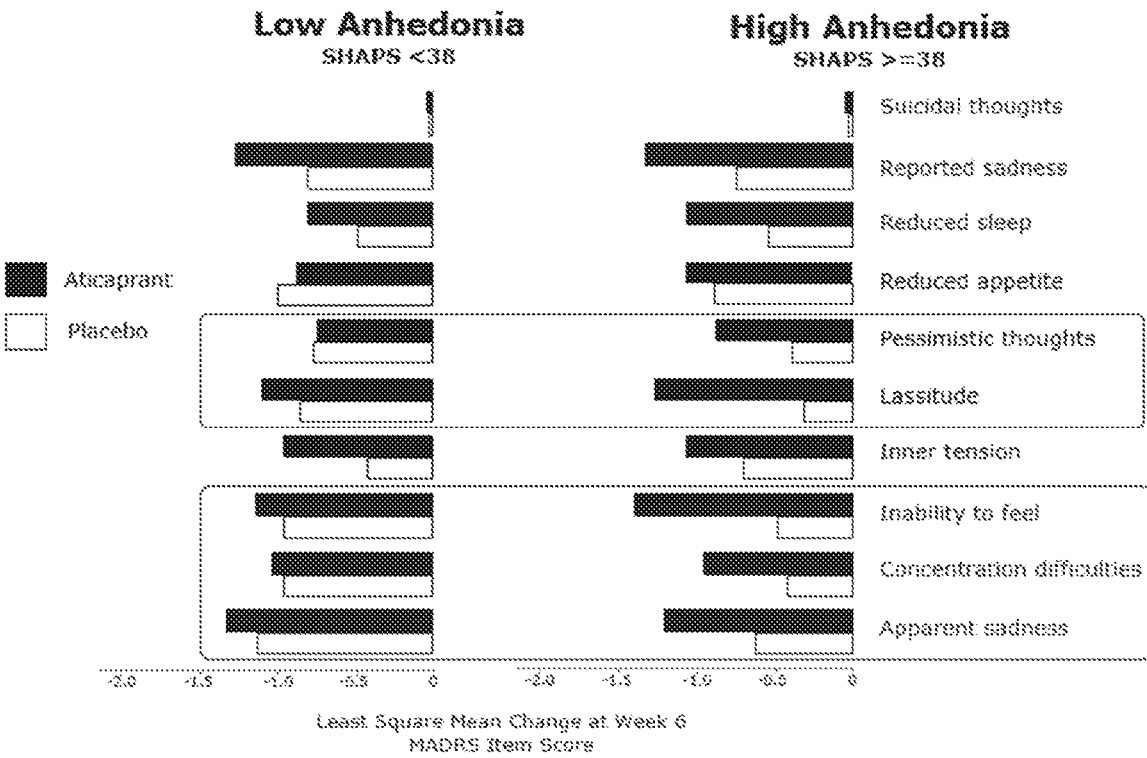


Fig. 18

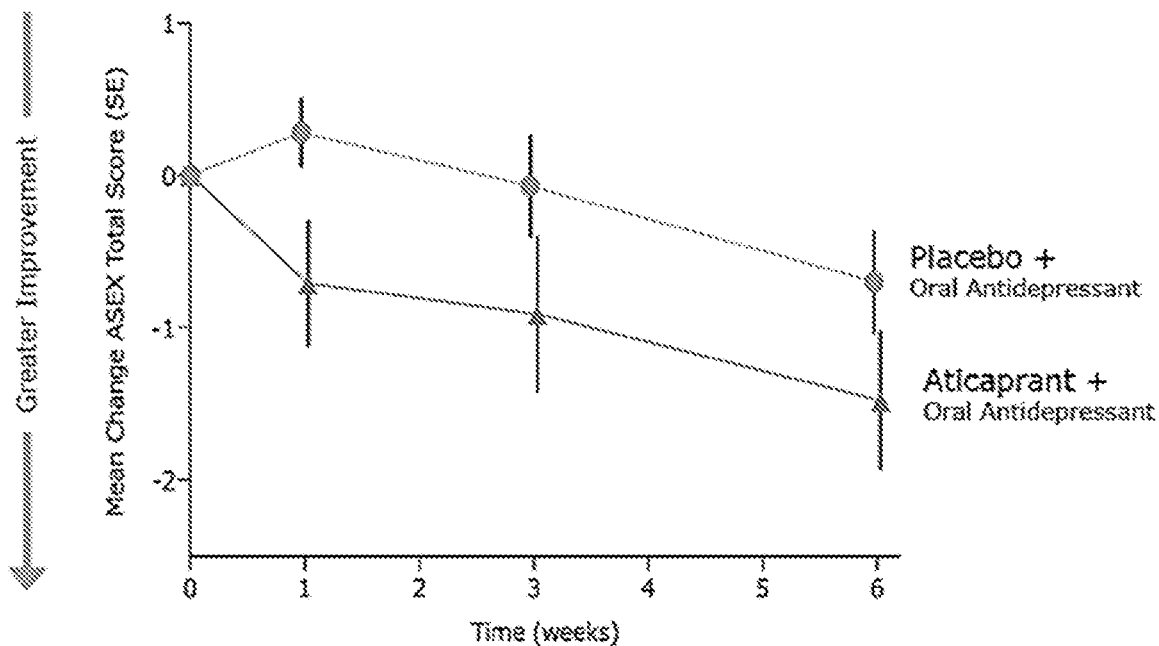


Fig. 19

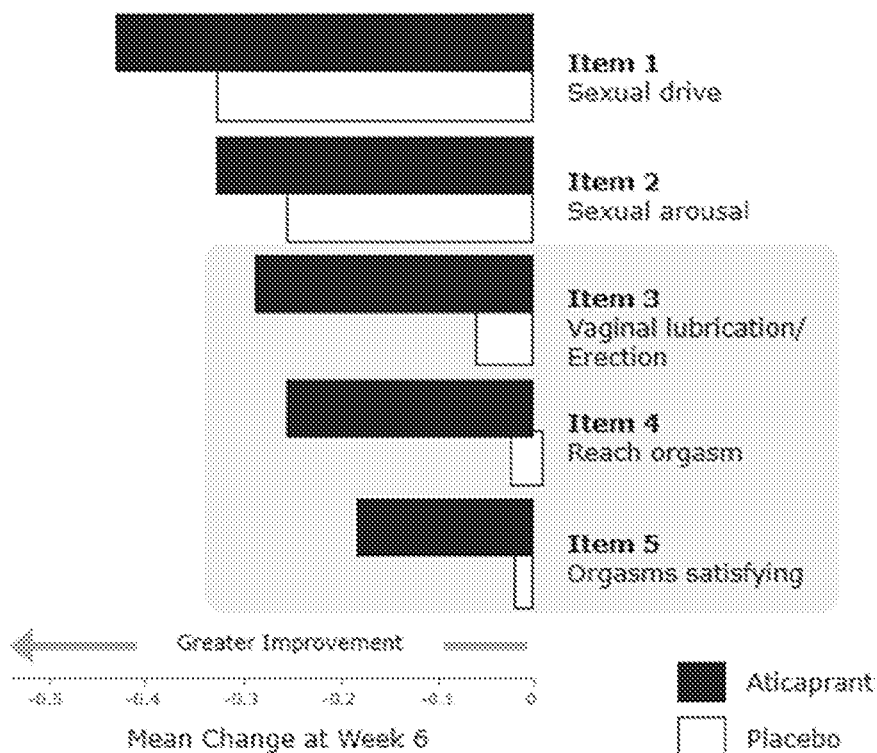
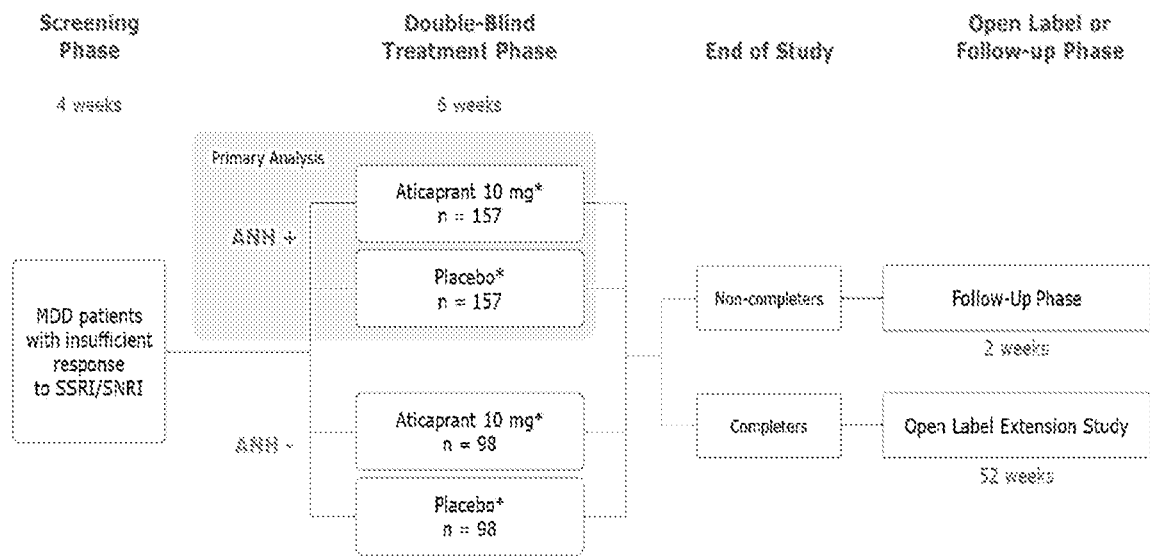
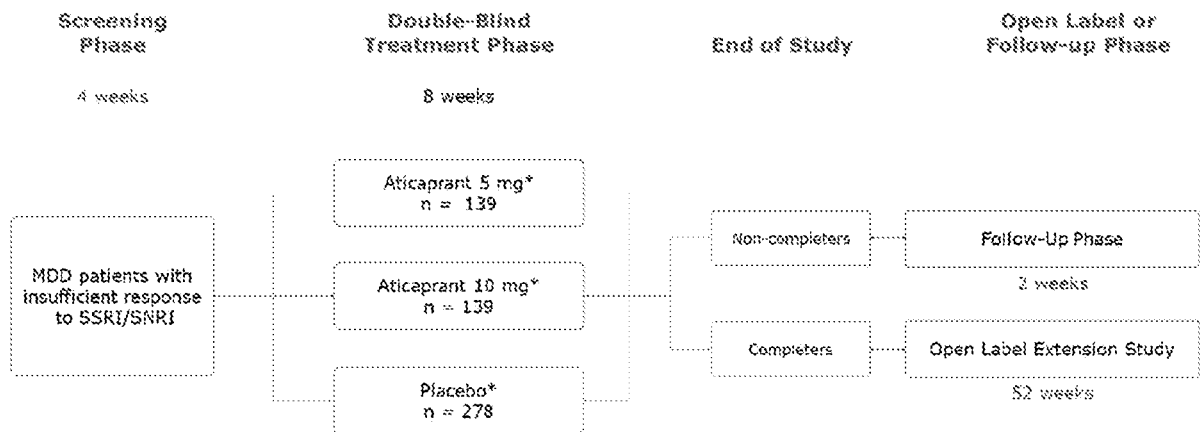


Fig. 20

*Fig. 21**Fig. 22*

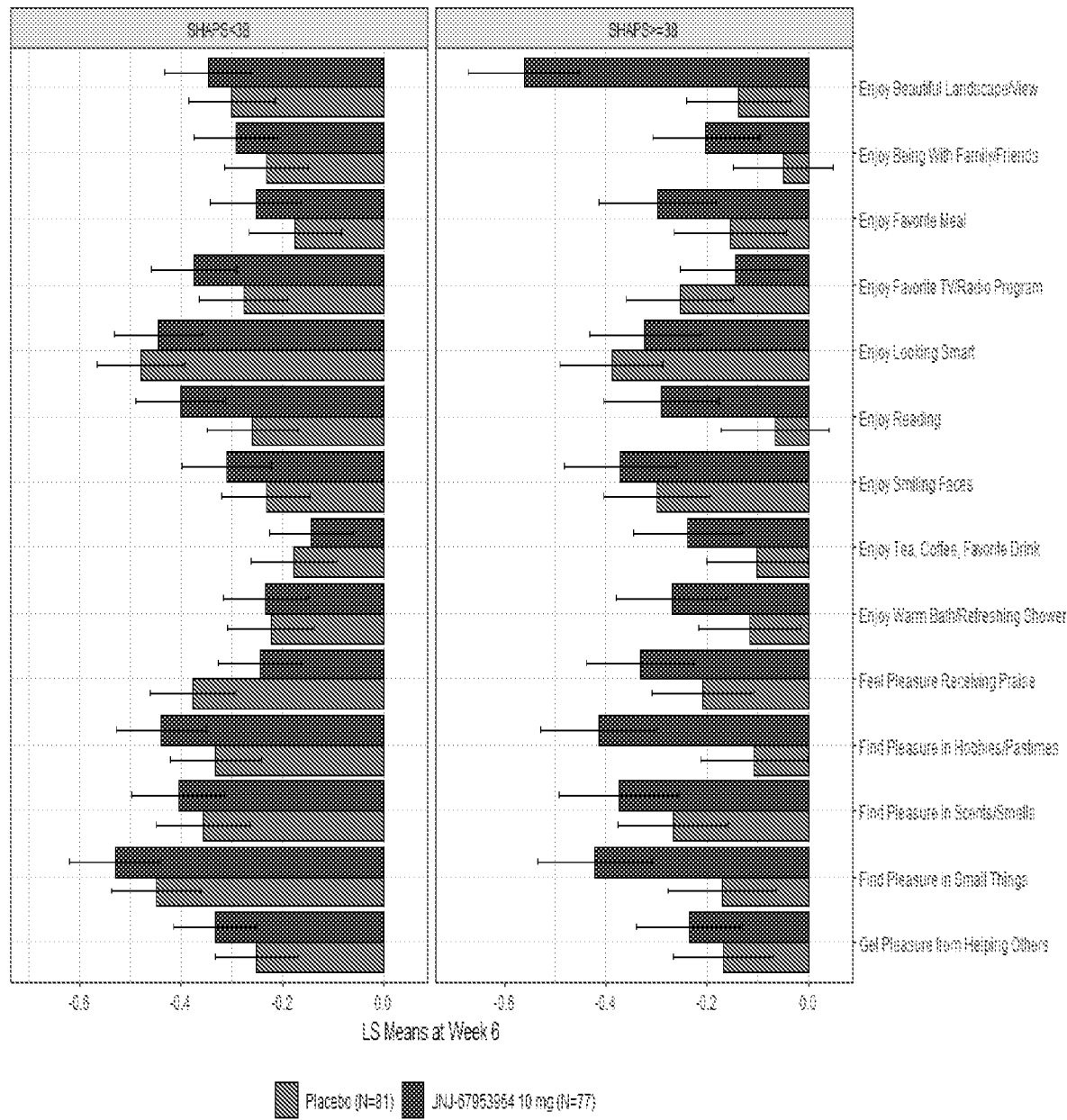


Fig. 23

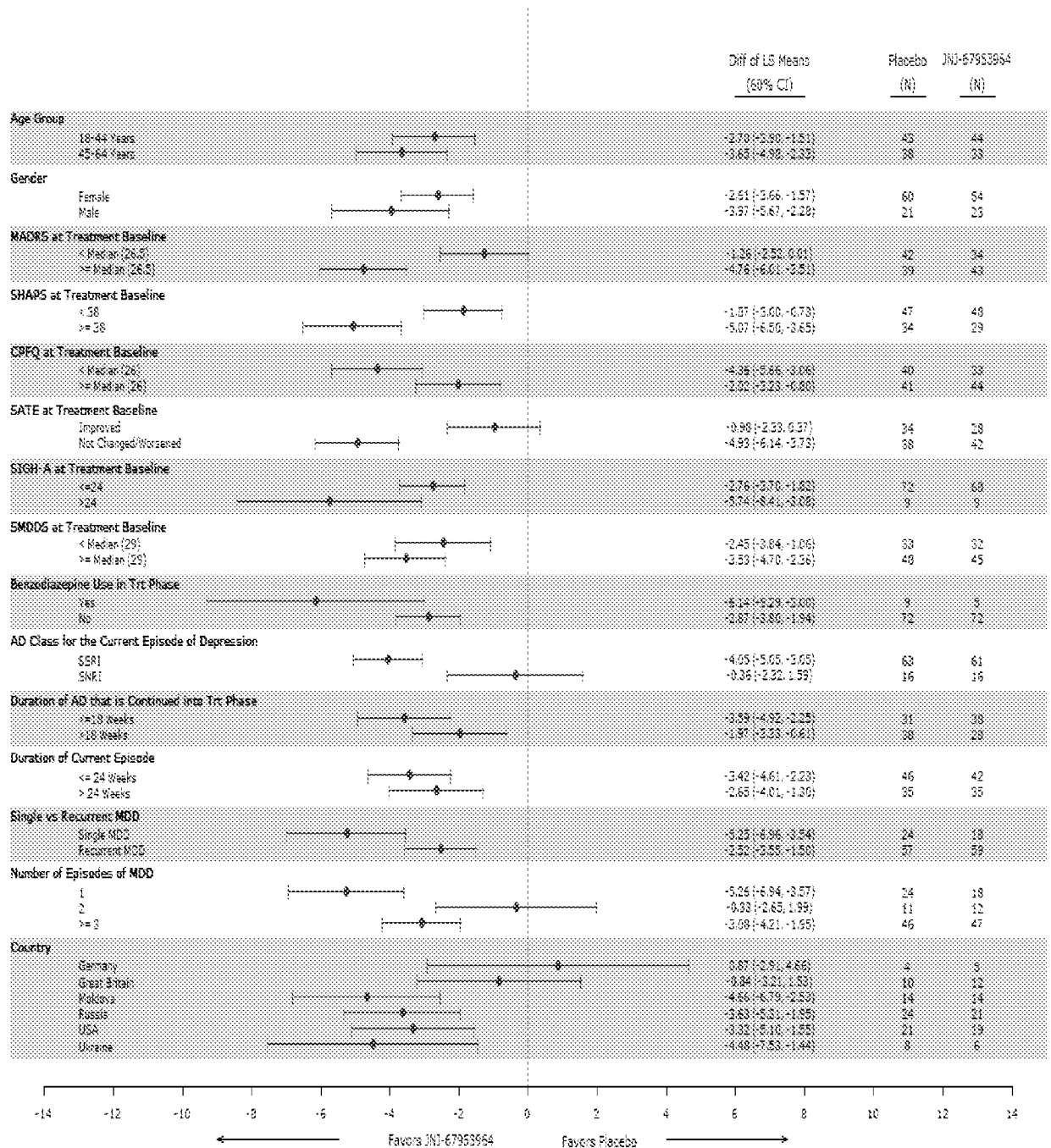


Fig. 24

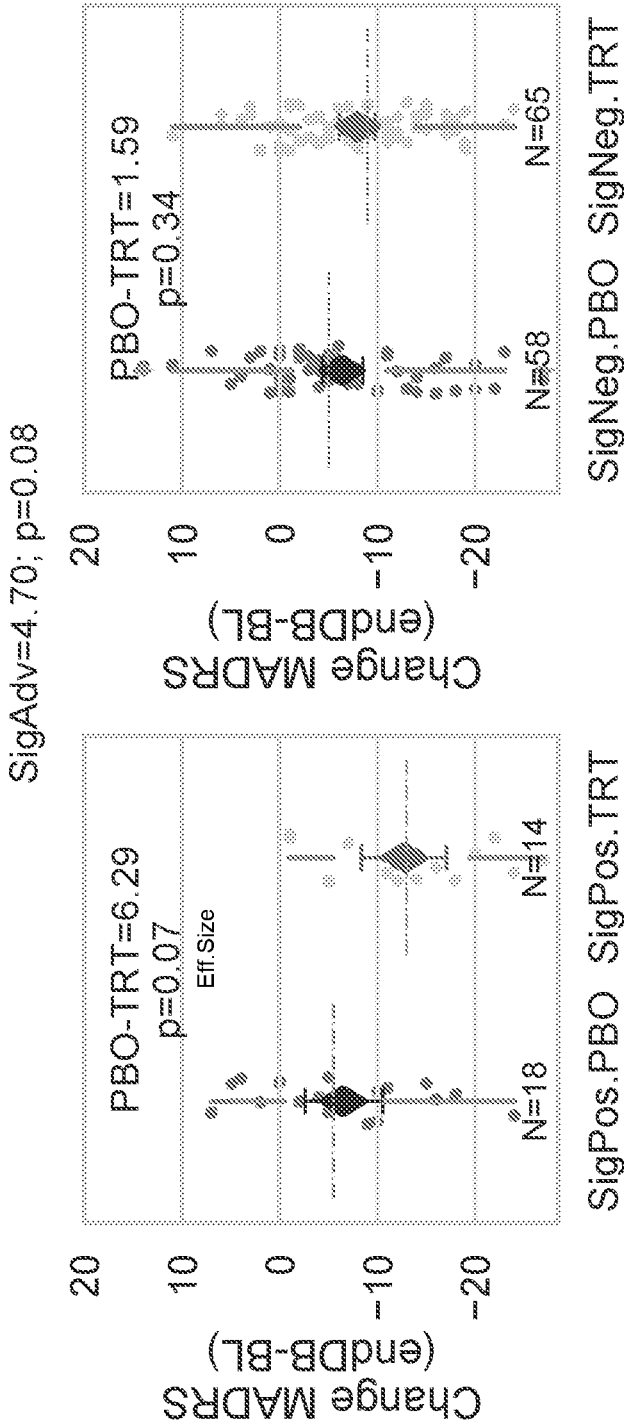


Fig. 25

Fig. 26A

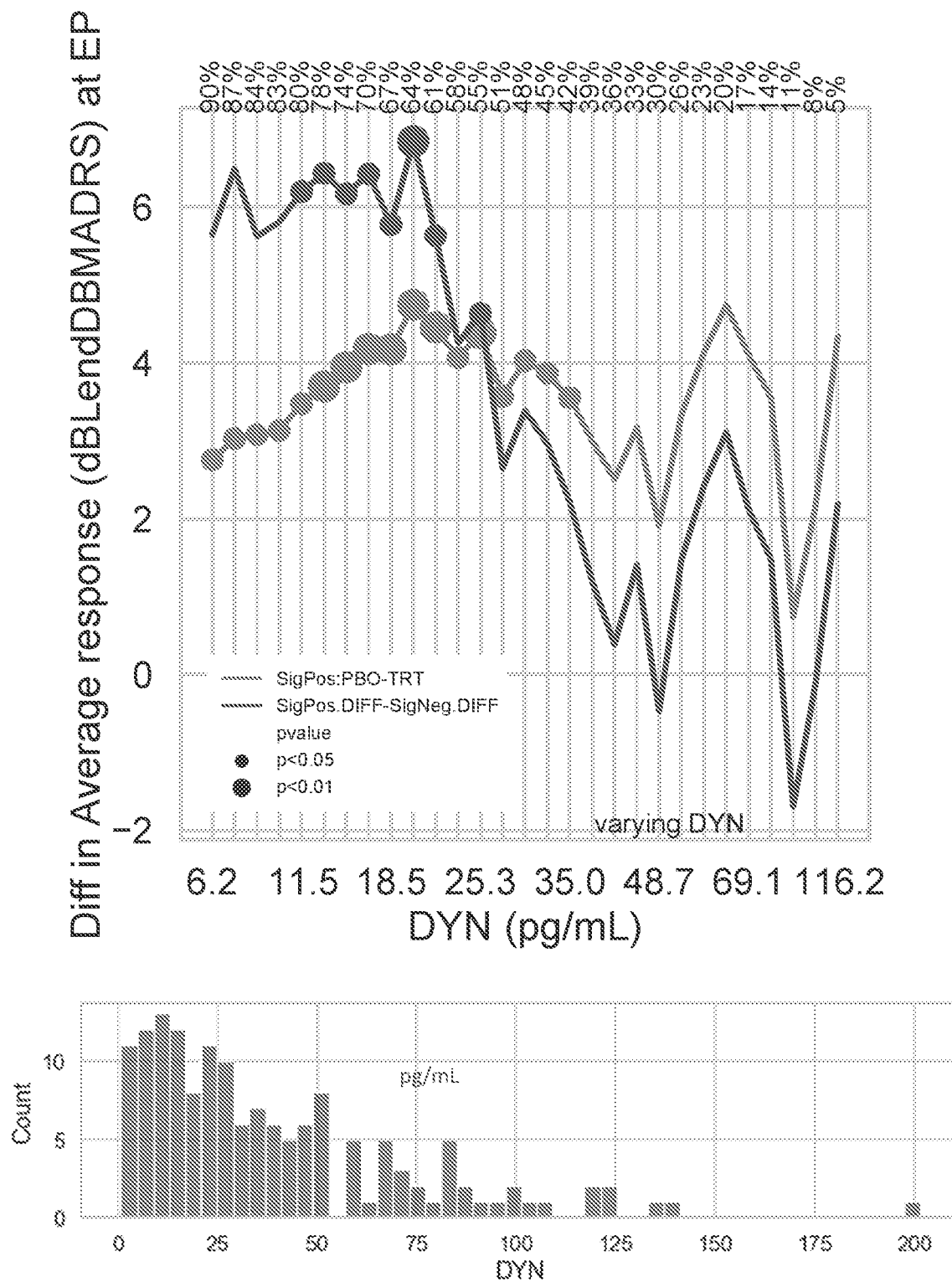


Fig. 26B

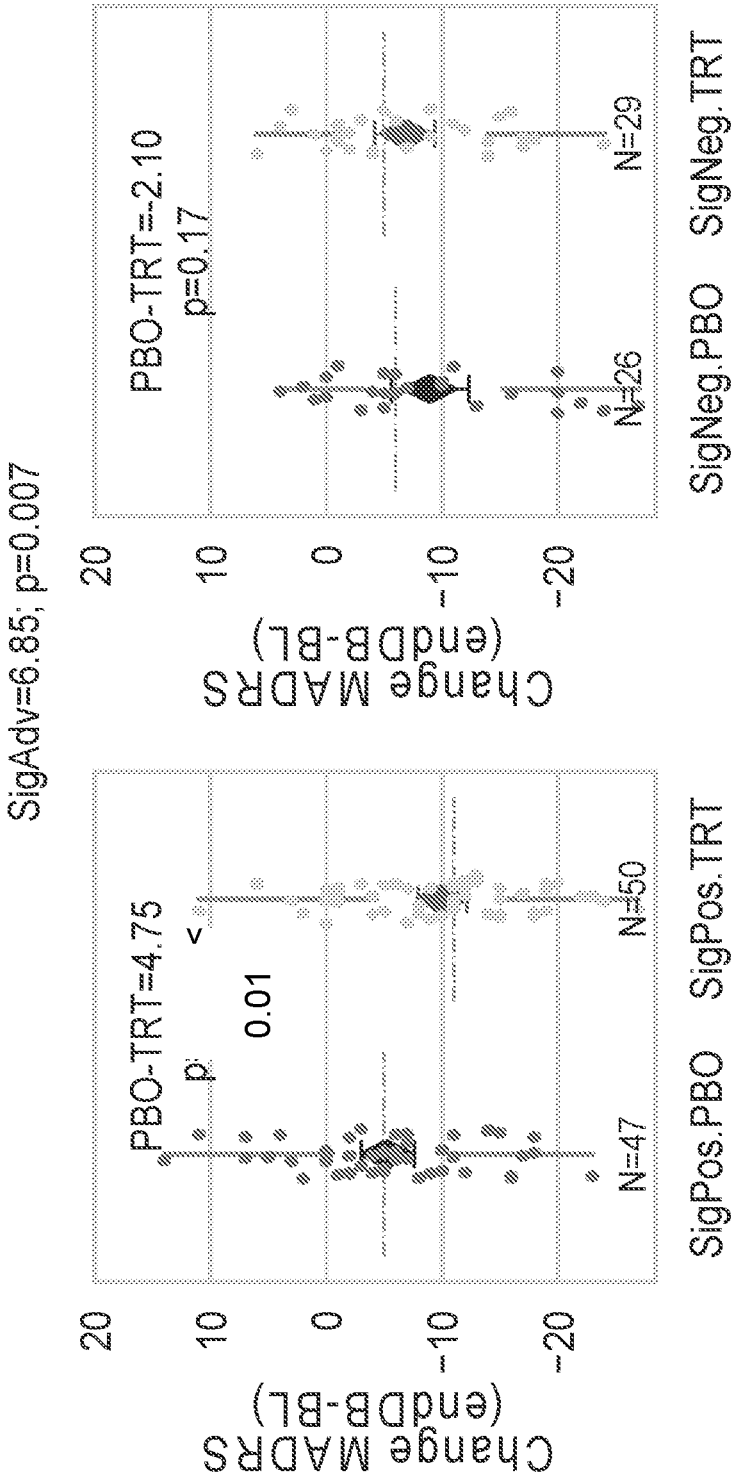


Fig. 26C

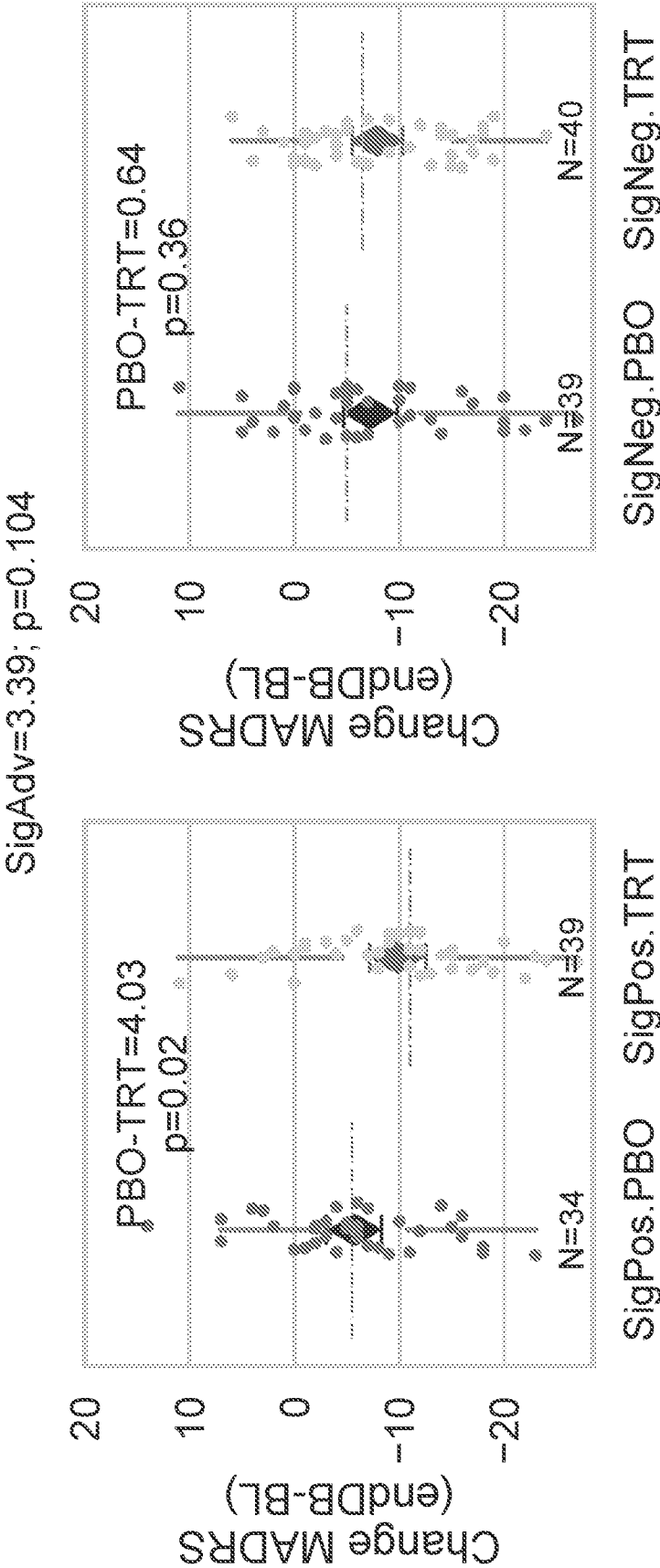


Fig. 26D

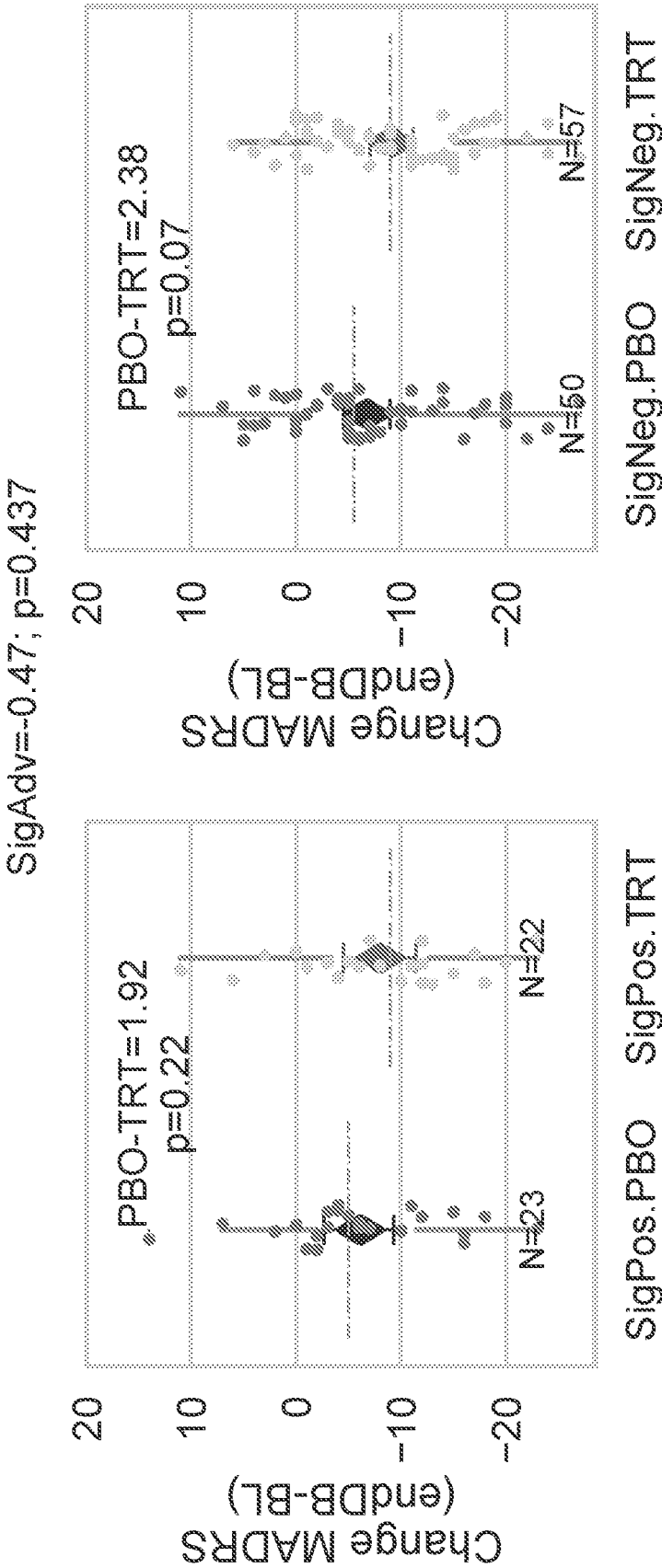


Fig. 27A

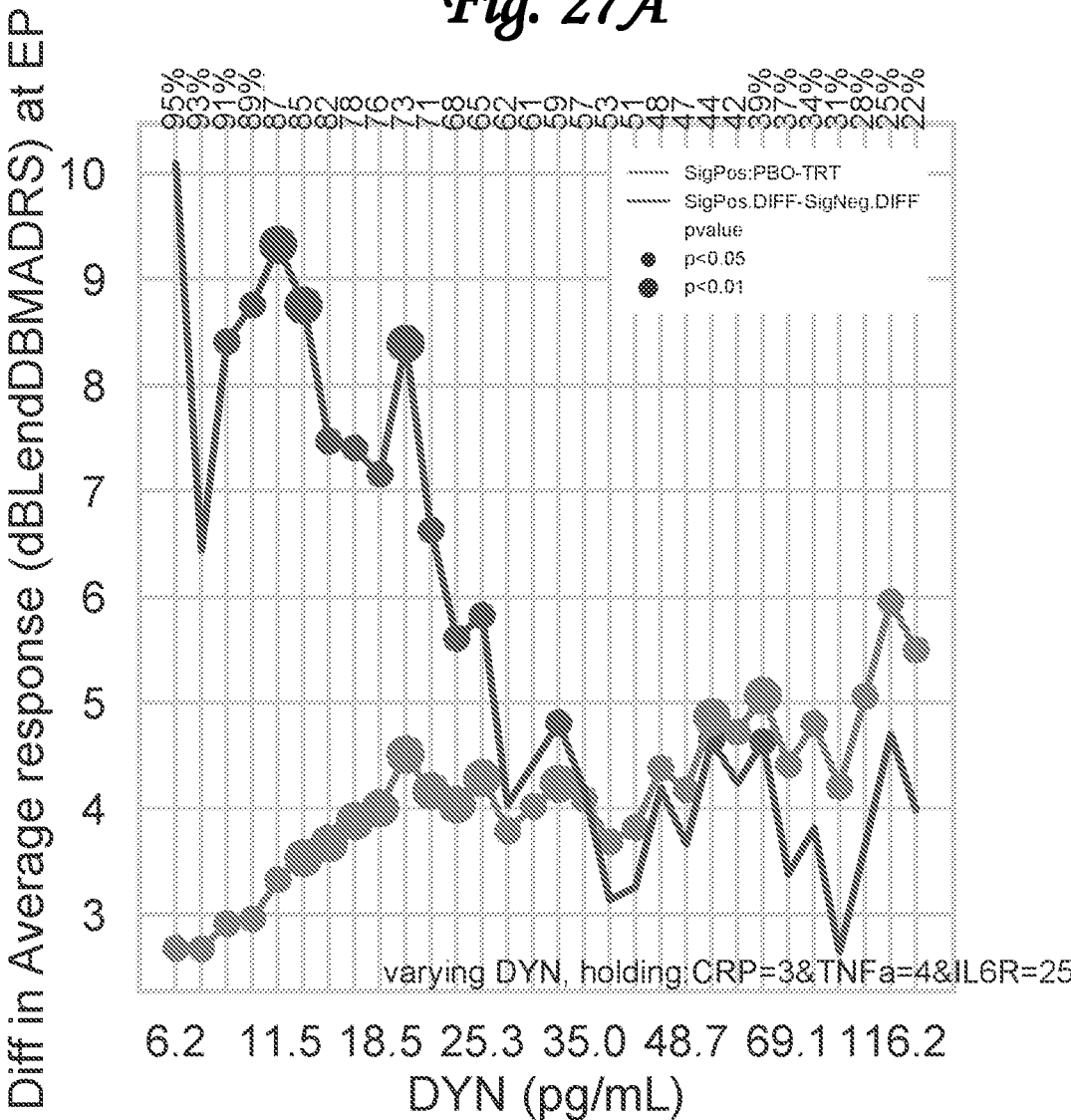


Fig. 27B

SigAdv=8.39; p=0.003

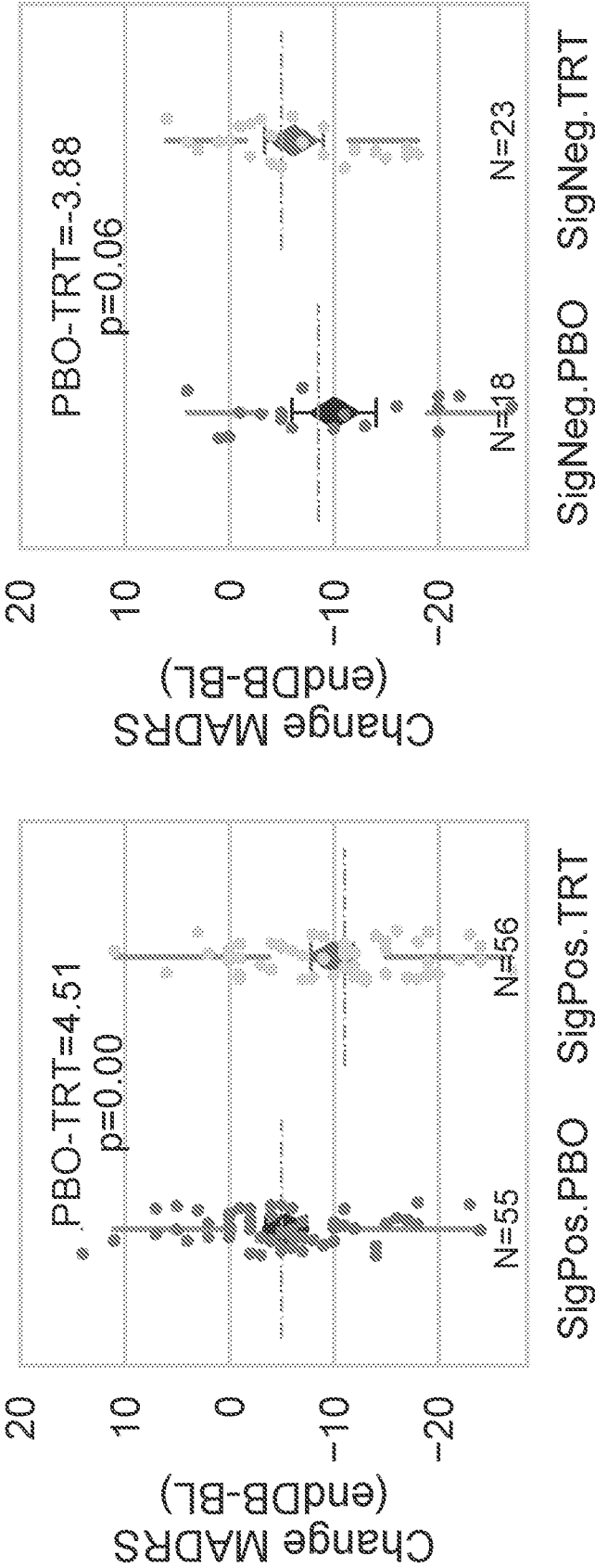


Fig. 27C

SigAdv=4.42; p=0.054

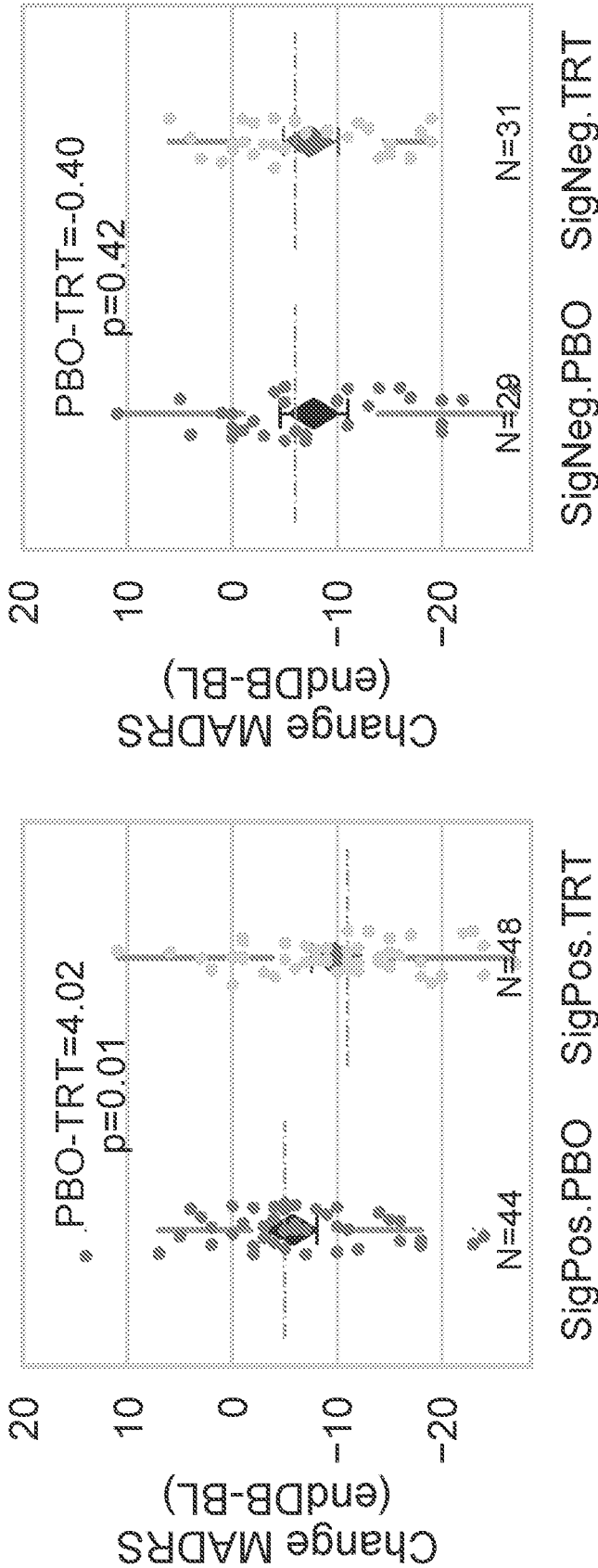


Fig. 27D

SigAdv=3.67; p=0.087

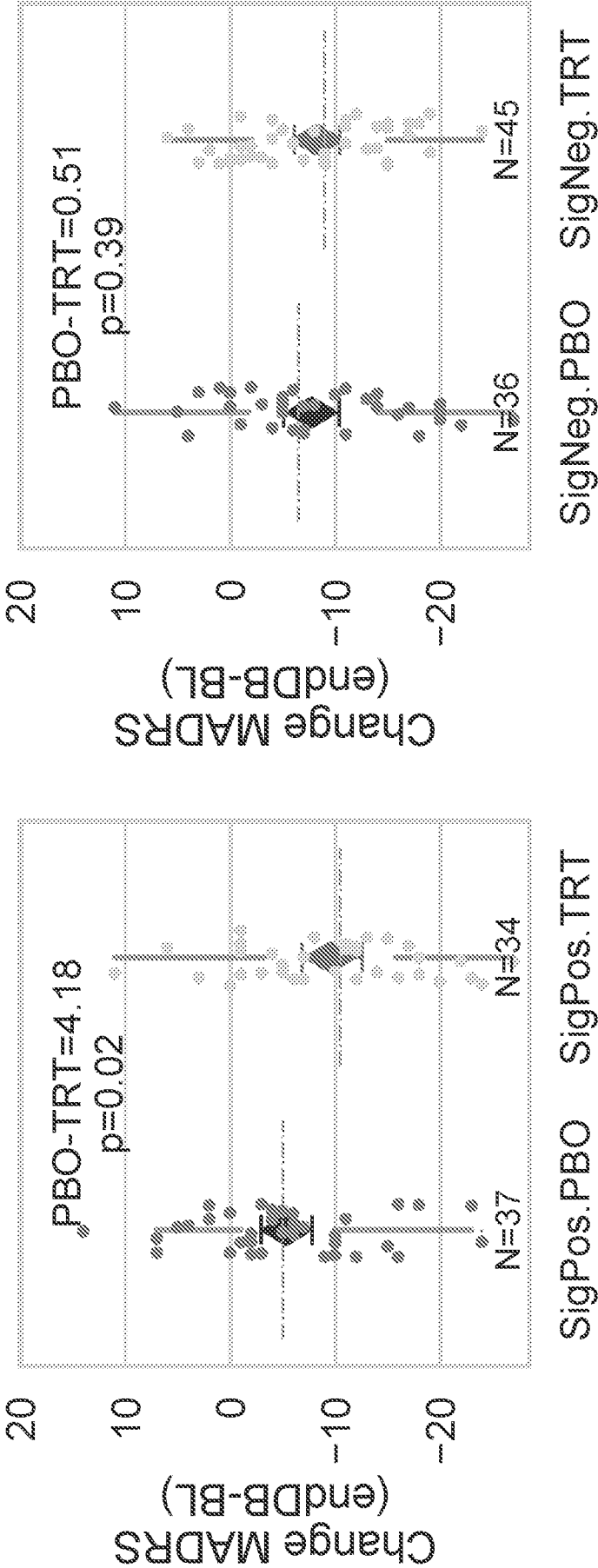


Fig. 28A

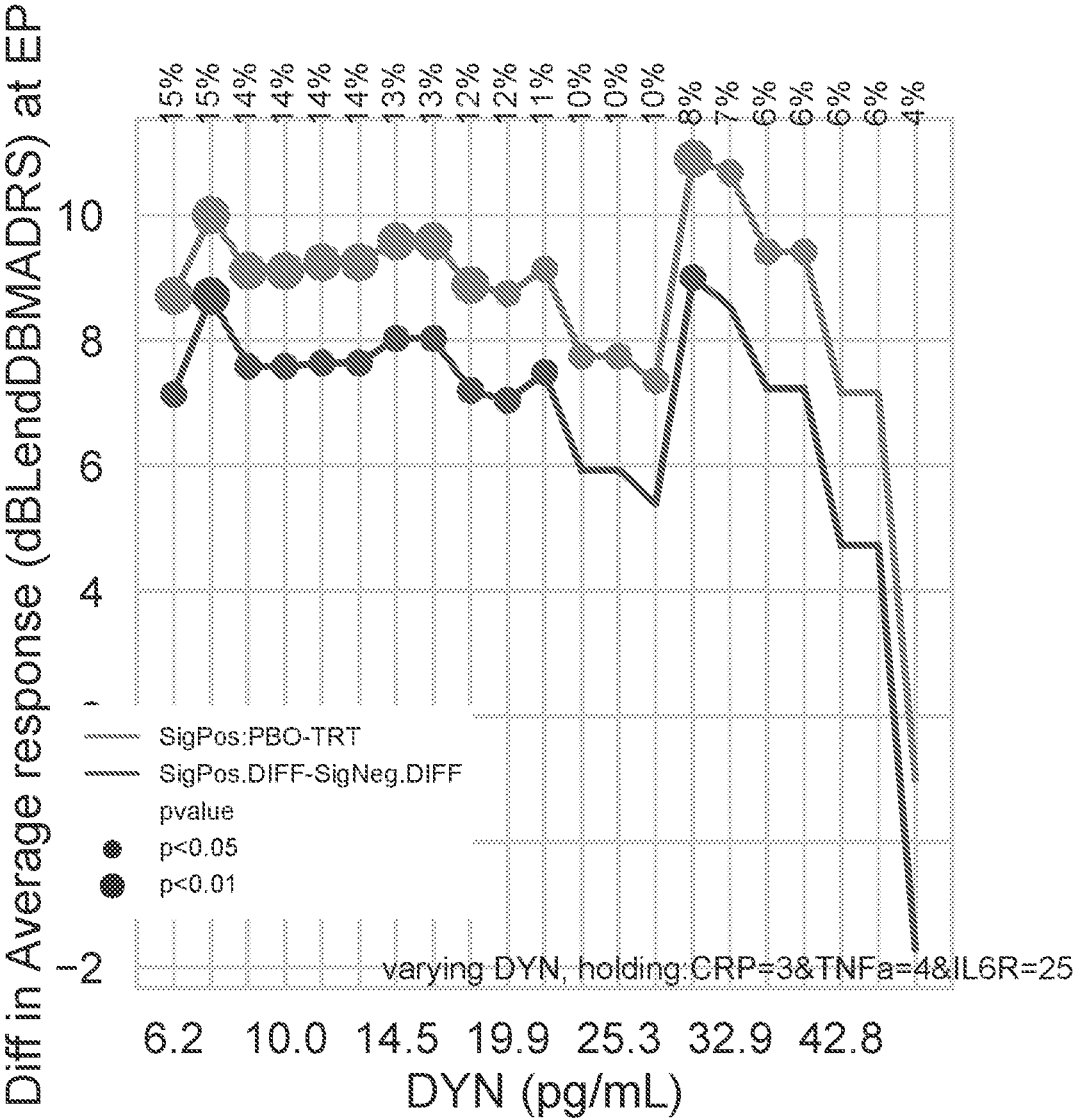


Fig. 28B

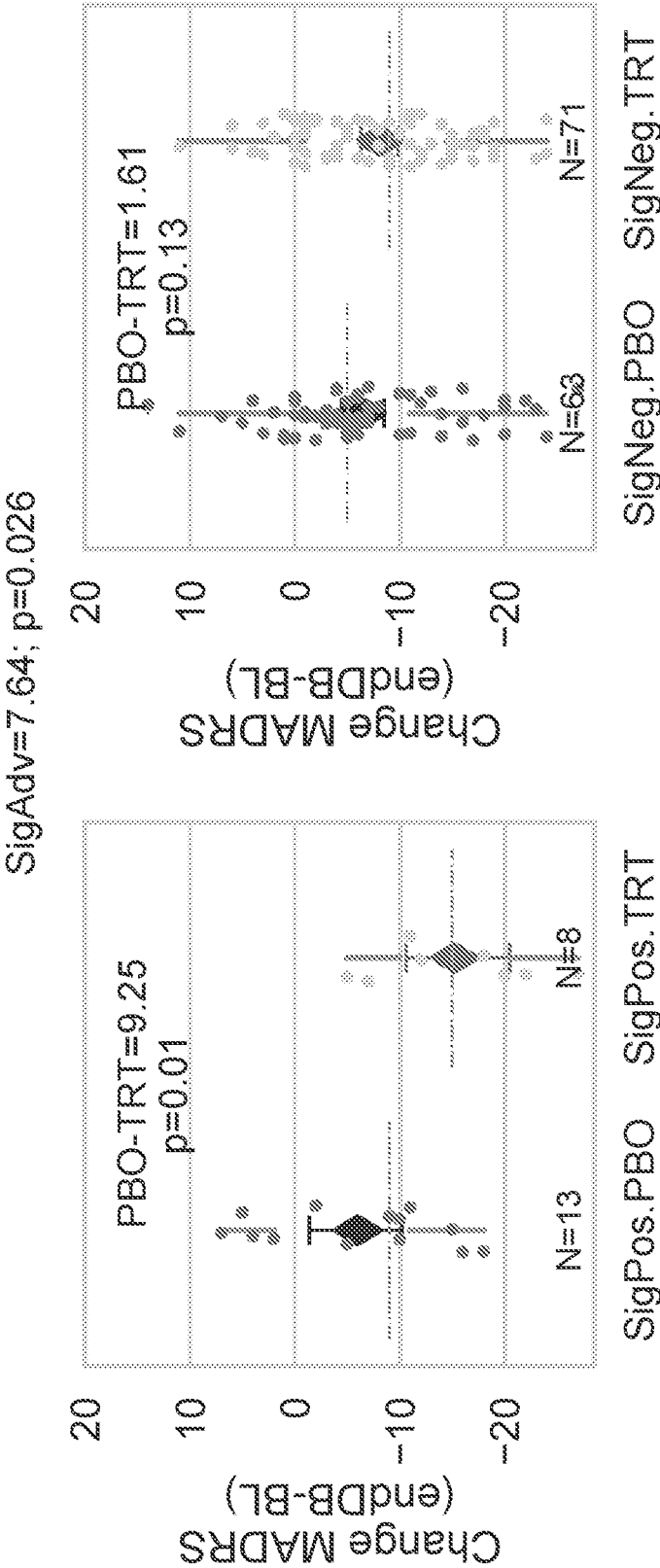


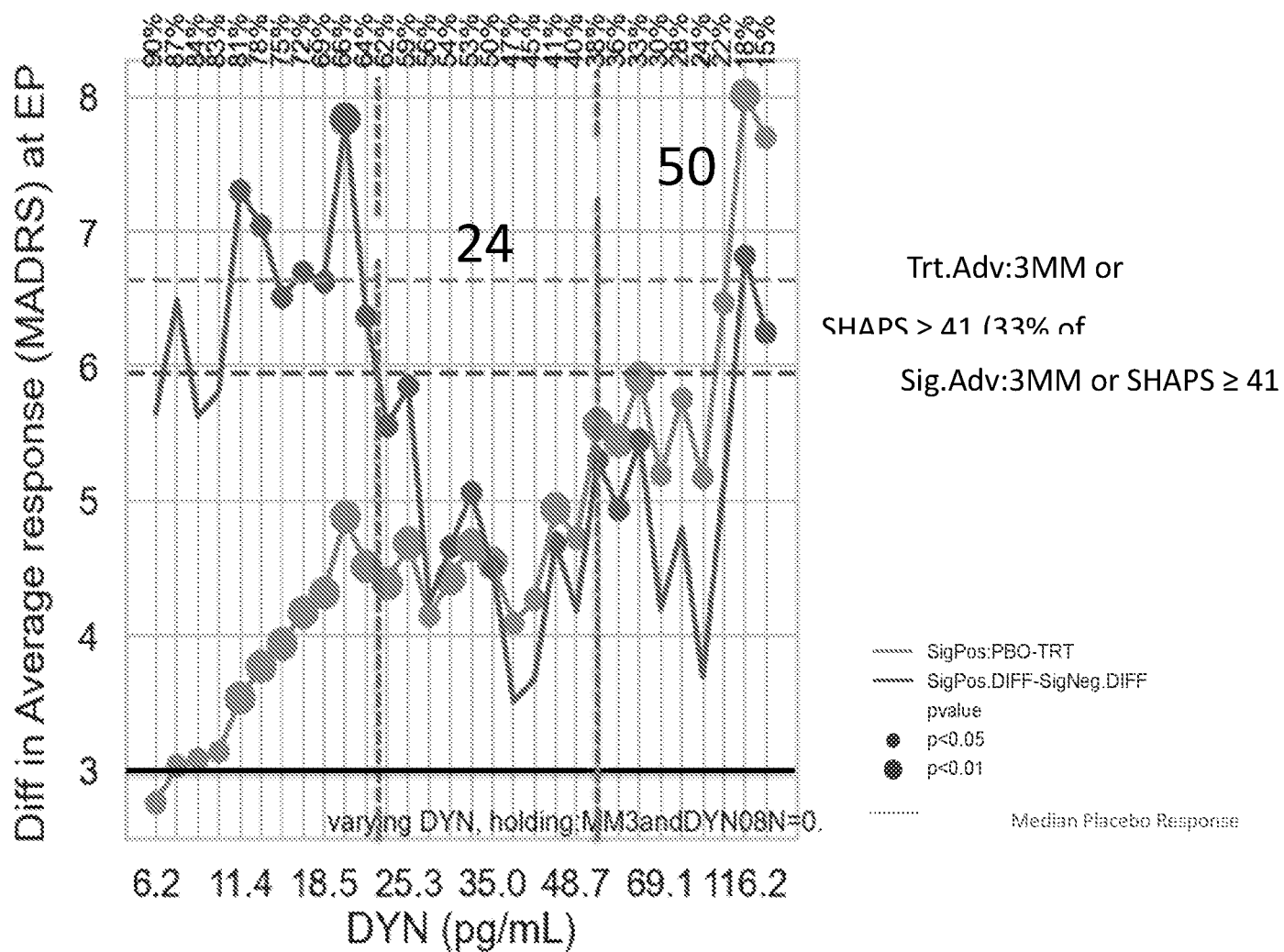
Fig. 29A

Fig. 29B

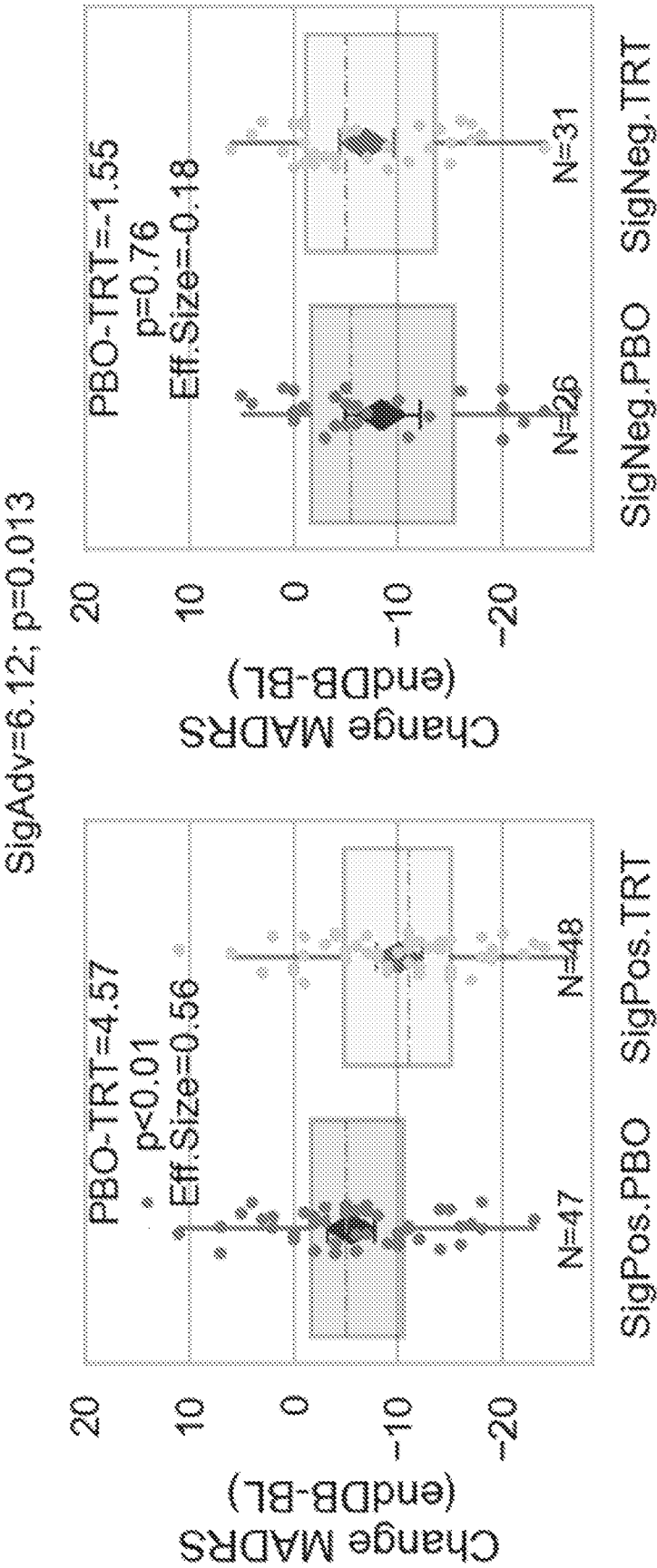
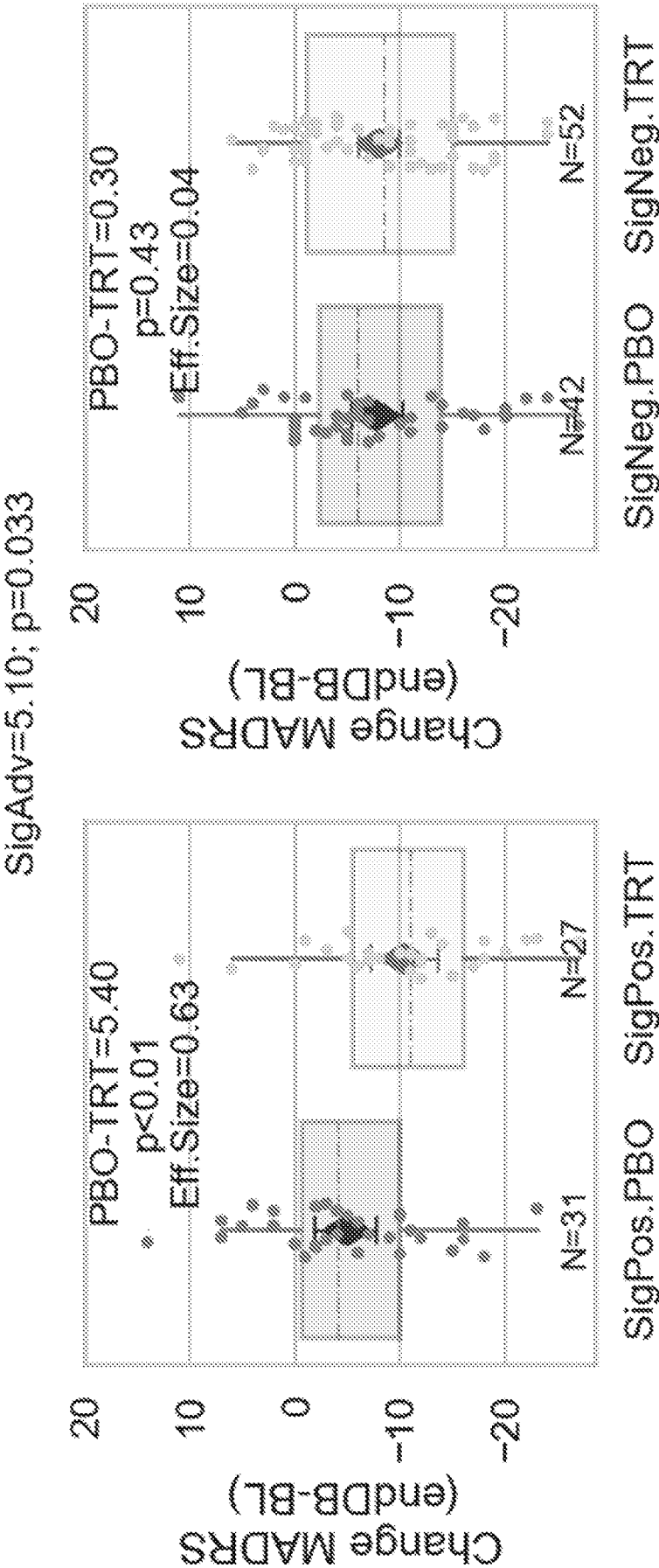


Fig. 29C



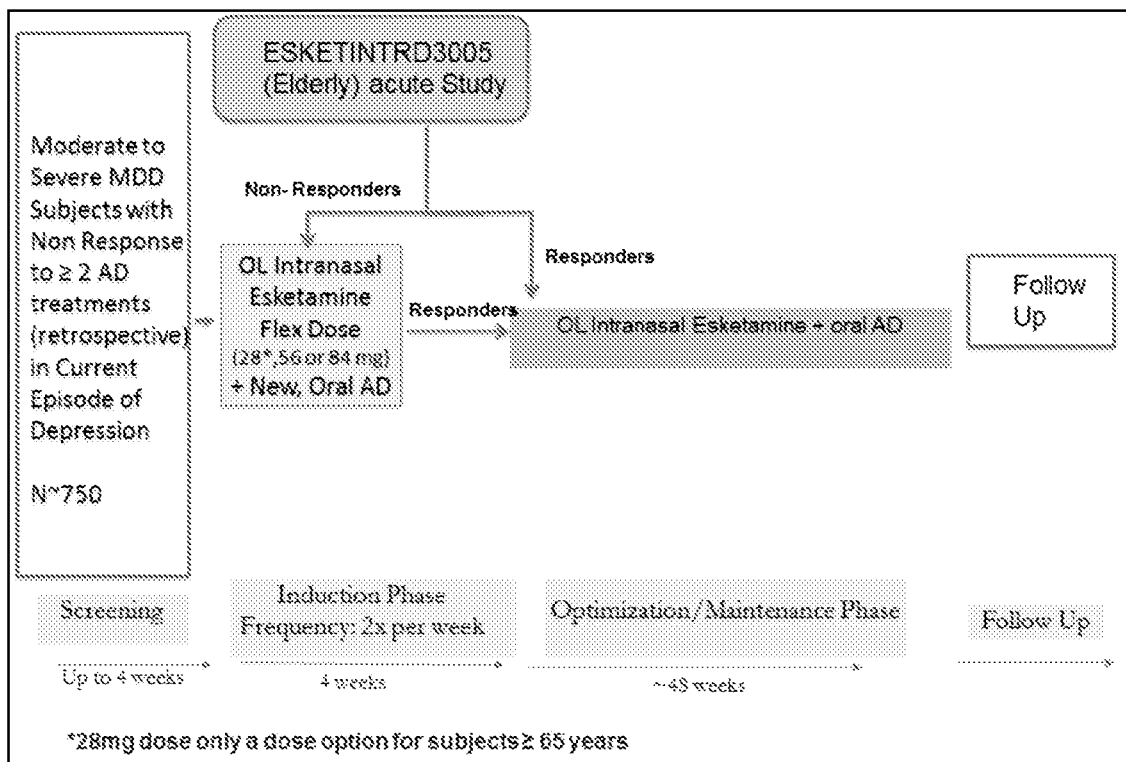
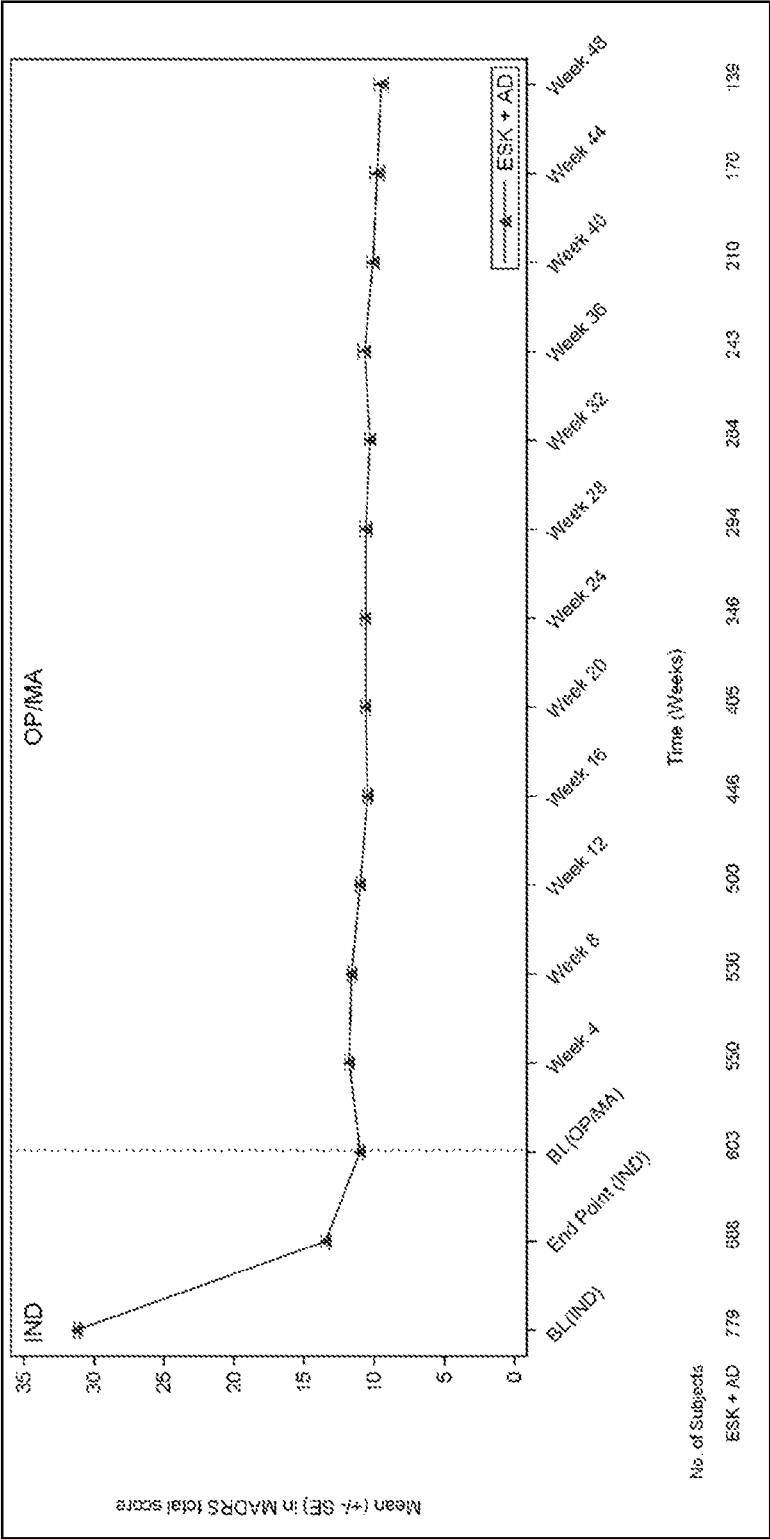
**FIG. 30**

FIG. 31



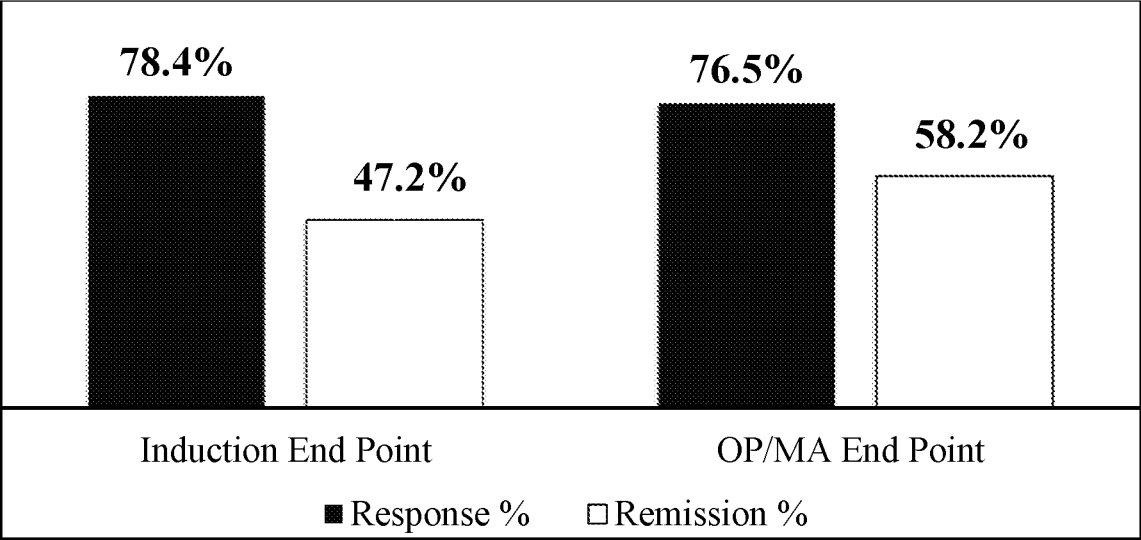


FIG. 32

FIG. 33

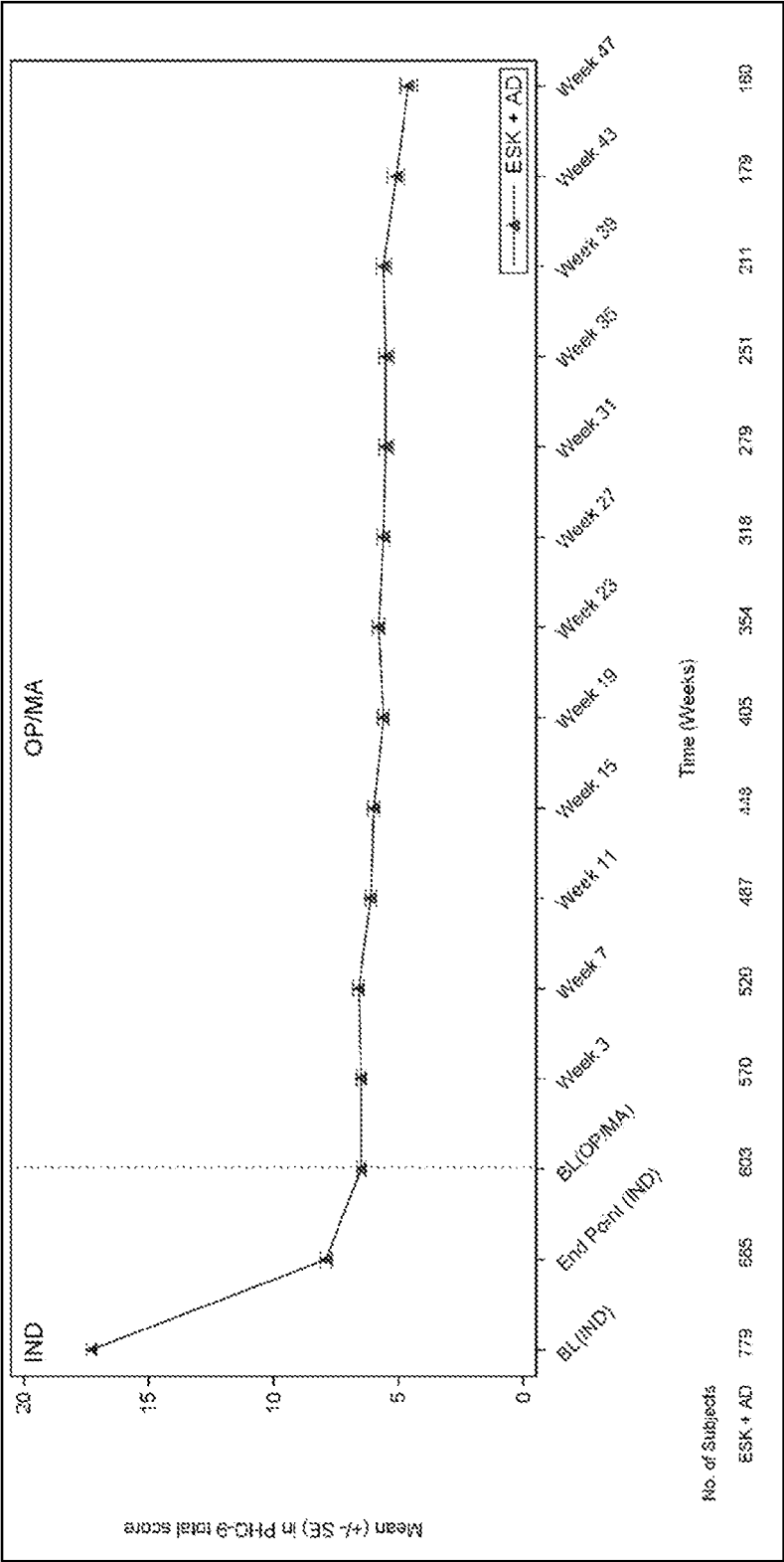


FIG. 35

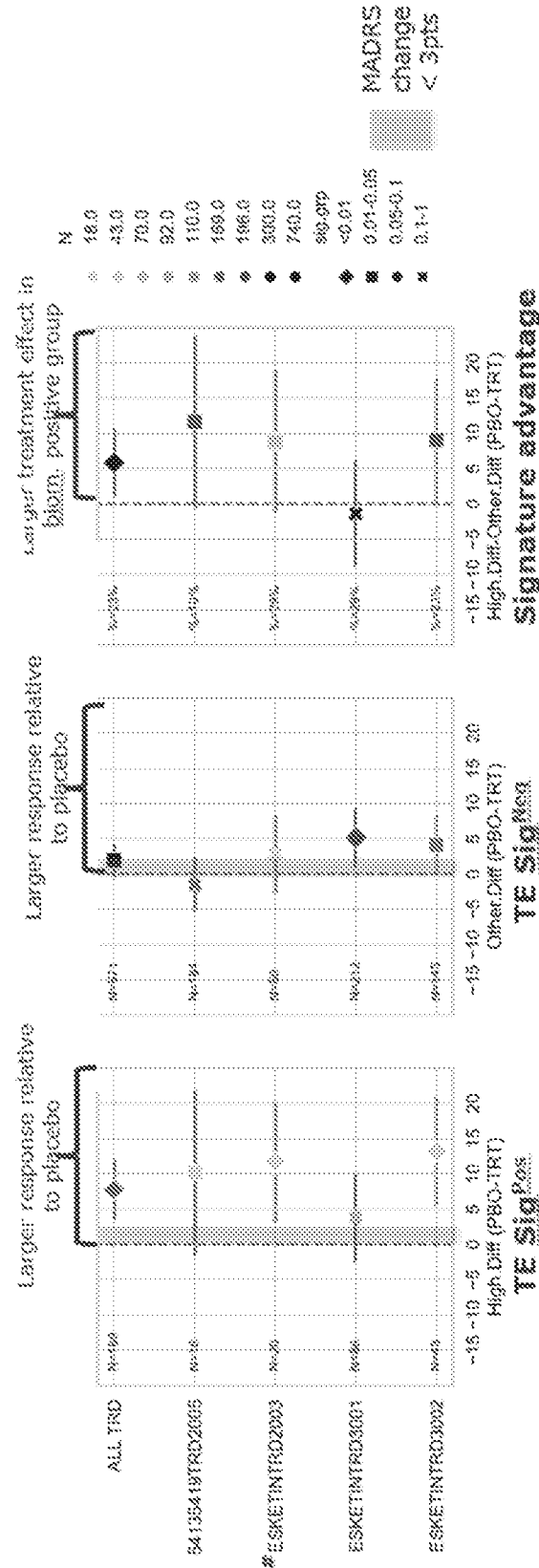
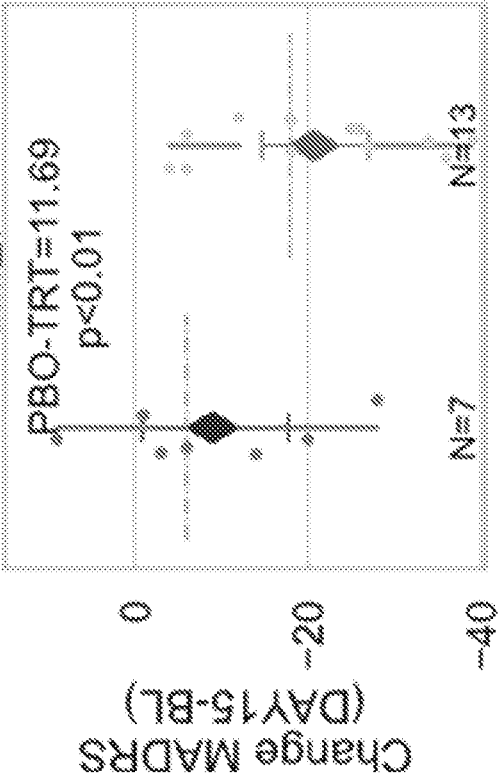


FIG. 36A

SigAdv=8.86; p=0.04

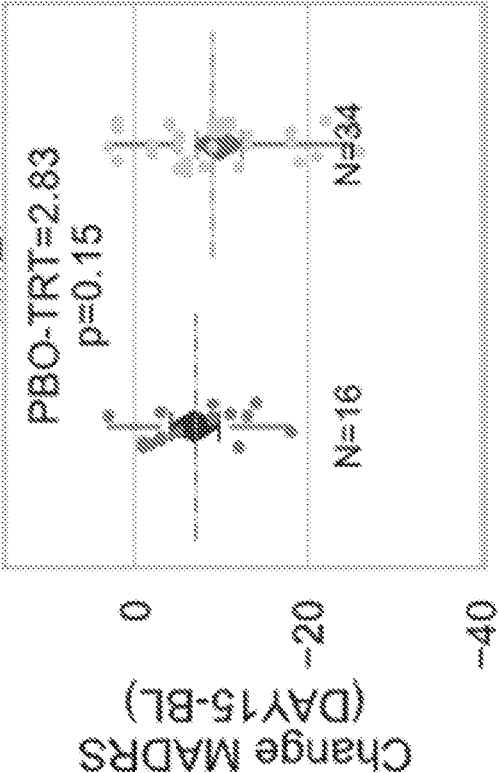
TE SigPos



High.PBO High.TRT
ESKETINTRD2003

FIG. 36B

TE SigNeg



Other.PBO Other.TRT
ESKETINTRD2003

FIG. 37A

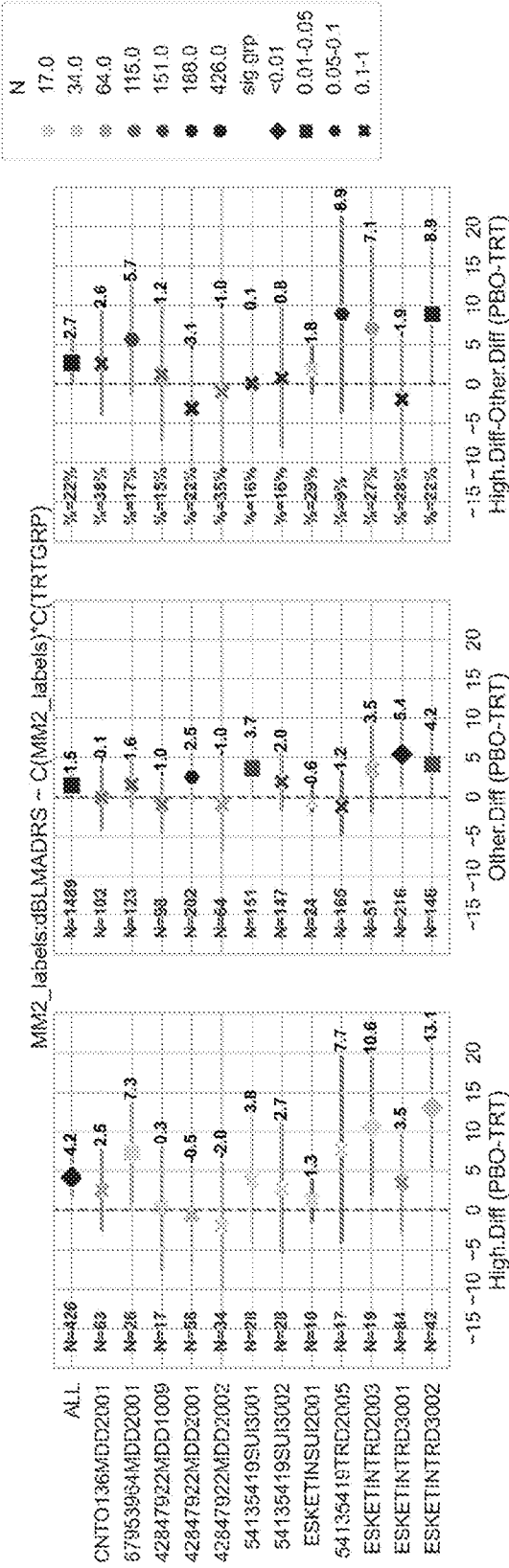


FIG. 37B

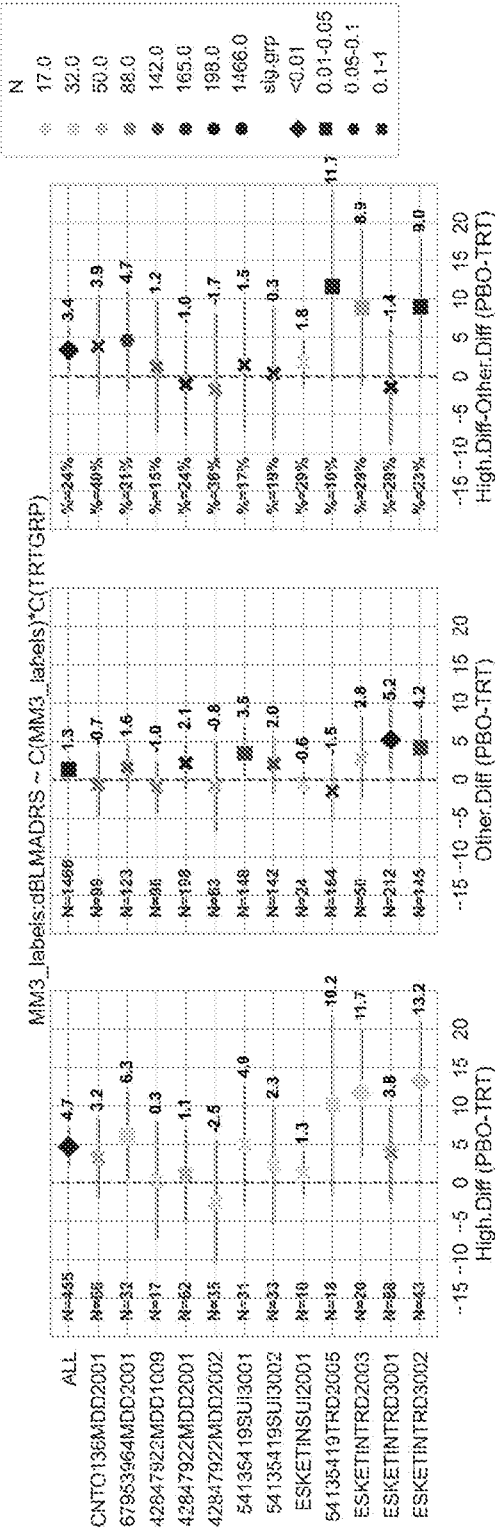


FIG. 38

