(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 July 2023 (13.07.2023)

WIPO | PCT

(10) International Publication Number
WO 2023/131920 A1

(51) International Patent Classification:
A61K 31/40 (2006.01) *A61P 25/24* (2006.01)

(21) International Application Number:
PCT/IB2023/050170

(22) International Filing Date:
09 January 2023 (09.01.2023)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/298,047 10 January 2022 (10.01.2022) US

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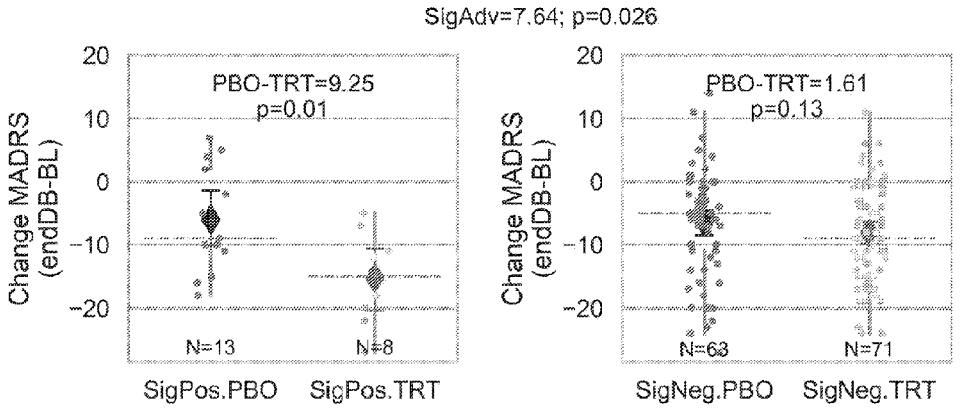
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH,

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

Fig. 28B



(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 aticaprant, or a pharmaceutically acceptable salt thereof. In some embodiments, the patient had an inadequate response to other antidepressant therapy prior to treatment with aticaprant. In other embodiments, the other antidepressant therapy comprised a selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), or a combination thereof.

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[Continued on next page]

TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *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))*

Published:

— *with international search report (Art. 21(3))*

— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

COMPOSITIONS AND METHODS FOR THE TREATMENT OF DEPRESSION

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application 63/298,047, 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 aticaprant wherein the patient has anhedonia and/or is identified as biomarker signature positive.

BACKGROUND

[0003] Kappa opioid receptors (KOR) and their native ligand dynorphin are localized in areas of the brain that effect reward and stress and may play a key role in mood, stress, and addictive disorders. Chronic stress, substance abuse, and acute withdrawal lead to increased dynorphin expression, activating KORs and subsequent downstream signaling pathways to inhibit mesolimbic dopamine surge, contributing to negative affective states. The behavioral pharmacology of KOR antagonism has been tested in animal models of anhedonia, depression, and anxiety and found to have meaningful effects that may translate to therapeutic benefit in humans. KOR antagonists may be effective for the treatment of patients with mood disorders, perhaps by modulating the negative affective state associated with stress response.

[0004] Anhedonia is one of the core symptoms of depression. At least mild symptoms of anhedonia are present in about 90% of patients suffering from major depressive disorder (MDD). Only about 50% of patients with MDD show a meaningful response (>50% improvement to a first line antidepressant treatment), leaving many patients with substantial persistent impairment. Therapeutic strategies such as switching antidepressants and using adjuvant drug treatments can improve response, however almost 40% of patients remain symptomatic and fail to achieve full remission.

[0005] What is needed are improved treatments for patients having depression and anhedonia.

SUMMARY

[0006] In some aspects, the present disclosure is directed to methods 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 certain embodiments, 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.

[0007] In further aspects, the present disclosure is directed to method of 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 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.

[0008] 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).

[0009] In certain aspects, the disclosed methods further comprise adjunctive treatment with an effective amount of one or more antidepressants for example with a selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), or a combination thereof.

[0010] 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. In certain aspects, the patient is identified as biomarker 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 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 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 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 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 aspects, 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 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Fig. 1 is the trial design of Example 1.

[0012] Fig. 2 is a line graph showing the MADRS (Montgomery–Åsberg Depression Rating Scale) total score: least squares mean changes from baseline (±SE) during the treatment period for the enriched intent-to-treat (eITT) analysis set.

[0013] 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.

[0014] Fig. 4 is a line graph showing SHAPS (Snaith-Hamilton Pleasure Scale) total score: least squares mean changes from baseline (±SE) during the treatment period for the eITT analysis set.

[0015] 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

[0016] Fig. 6 is a line graph showing MADRS total score: mean values (±SE) over time for the eITT analysis set.

[0017] Fig. 7A is a line graph showing MADRS total score: mean values (±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.

[0018] 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.

[0019] 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.

[0020] Fig. 10 is a line graph showing MADRS total score: percentage of responders (≥30% improvement from baseline) during the treatment period for the eITT analysis set.

[0021] Fig. 11 is a line graph showing MADRS total score: percentage of responders (≥30% improvement from baseline) during the treatment period for the fITT analysis set.

[0022] Fig. 12 is a line graph showing MADRS total score: percentage of responders (≥50% improvement from baseline) during the treatment period for the eITT analysis set.

[0023] Fig. 13 is a line graph showing MADRS total score: percentage of responders (≥50% improvement from baseline) during the treatment period for the fITT analysis set.

[0024] Fig. 14 is a line graph showing SHAPS total score: mean values (±SE) over time for the eITT analysis set.

[0025] Fig. 15 is a line graph showing SHAPS total score: mean values (±SE) over time for the fITT analysis set.

[0026] Fig. 16 illustrates the MADRS change from baseline by anhedonia severity.

[0027] 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.

[0028] Fig. 18 is bar graph showing the comparison of MADRS in patients having low and high anhedonia.

[0029] Fig. 19 is a line graph showing the ASEX total score mean change from baseline.

[0030] Fig. 20 is a bar graph showing ASEX item level change total score mean change from baseline.

[0031] 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.

[0032] 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.

[0033] 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.

[0034] 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.

[0035] 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.

[0036] 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).

[0037] 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 Fig. 27C, SigPos= 3MM or DYN > 29.5, 61% of cohort. For Fig. 27D, SigPos= 3MM or DYN > 48.7, 48% of cohort.

[0038] 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).

[0039] Fig. 29A-29C are plots summarizing the outcome of patient subtyping using a biomarker signature using a combination of high dynorphin (δ1) or 3MM with moderate dynorphin (δ2) subtypes, specifically: DYN > δ1 pg/mL or (DYN>δ2 pg/mL and CRP > 3 mg/L *and* ($TNF\alpha > 4\ pg/mL$ *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.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0040] 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).

[0041] 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.

[0042] 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. 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

[0043] 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.

[0044] 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. 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.

[0045] 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.

[0046] 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.

[0047] 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.

[0048] 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. 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.

[0049] 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.

[0050] 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.

[0051] 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.

[0052] 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.

[0053] 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.

[0054] 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 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.

[0055] 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 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.

[0056] 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 toa bout 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.

[0057] 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.

[0058] 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.

[0059] 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.

[0060] 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.

[0061] 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.

[0062] 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.

[0063] As used herein, the term "depression" (also referred to as depressive disorder) includes major depressive disorder, persistent depressive disorder, seasonal 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.

[0064] 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
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

[0065] In some embodiments, to be diagnosed with MDD, the following criteria also are met:

1. Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
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

[0066] 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.

Table B: DSM-5 Criteria for MDD

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

[0067] 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.

[0068] 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 apparent sadness, reported sadness, inner tension, sleep appetite, concentration, lassitude, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts.

[0069] 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.

[0070] 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.

[0071] 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

Question 1: Since starting this study medication, overall would you say your depression is:
o Improved
o Got worse
o Not changed
If the subject selects answer 1 (Improved), following question is asked:
Question 2: How much did your depression improve?
o Slightly improved
o Much improved
o Very much improved
If the subject selects answer 3 (Got worse), following question is asked:
Question 3:How much did your depression worsen?
o Slightly worse
o Much worse
o Very much worse

[0072] 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.

[0073] 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 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.

[0074] 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.

[0075] 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

includes 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, 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, levomepromazin), 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, zotepine, ziprasidone, iloperidone, perospirone, blonanserin, sertindole, ORG-5222, sonepiprazole, 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, vortioxeine or desvenlafaxine. There are also non-pharmacologic treatments, such as psychotherapy and transcranial magnetic stimulation, that are also available and options for adjunctive therapy.

[0076] 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.

[0077] 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.

[0078] 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.

[0079] 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.

[0080] 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.

[0081] 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.

[0082] 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.

[0083] 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 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%.

[0084] This is contrary to many other antidepressants where weight gain, including clinically relevant weight gain, is a common, but unfortunate, side-effect.

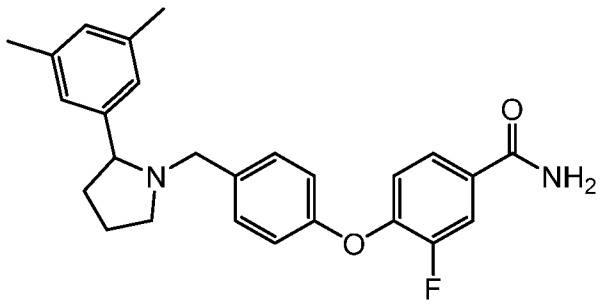
[0085] In certain embodiments, the administration of the aticaprant achieves a maximum plasma concentration (C_{max}) of aticaprant of about 20 to about 45 ng/mL. In further embodiments, the administration of the aticaprant achieves a maximum plasma concentration (C_{max}) of aticaprant of about 25 to 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.

[0086] 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.

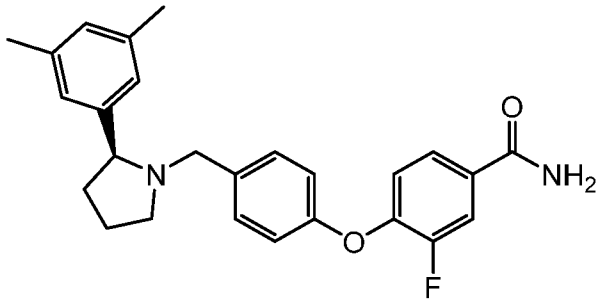
In further embodiments, the sexual functioning comprises vaginal lubrication satisfaction. In further embodiments, the sexual functioning comprises orgasm achievement. In yet other embodiments, the sexual functioning comprises orgasm satisfaction. Desirably, the patient's sexual functioning is assessed 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 and satisfaction. Scores range from 5 to 30, and two different versions of the scale are available (males and females).

[0087] 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.

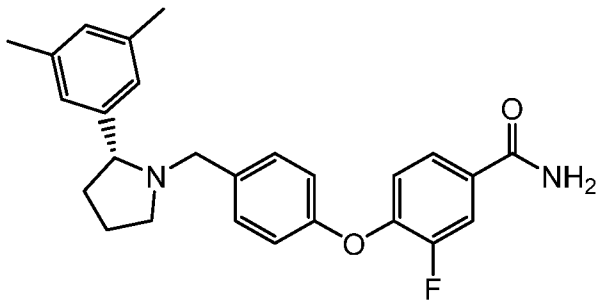
[0088] As used herein, unless otherwise noted, the term "aticaprant" refers to 3-fluoro-4-4-2-(3,5-dimethylphenyl)pyrrolidin-1-yl-methylphenoxybenzamide, *i.e.*, the following compound:



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:



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:



[0089] 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.

[0090] 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, 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.

[0091] 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, isobutyrates, 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.

[0092] 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.

[0093] 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 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.

[0094] 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. 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.

[0095] 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.

[0096] In certain embodiments, pharmaceutical composition for use herein, the composition further comprises one or more buffers, preservatives, penetration agents, wetting agents, surfactants, solubilizing agents, thickening agents, colorant agents, antioxidants, emulsifying agents, isotonizing agents, suspending agents, and/or viscosity increasing agents.

[0097] In some embodiments, the pharmaceutical compositions comprises one or more buffers and/or buffer systems (*i.e.* conjugate acid-base-pairs). 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. Suitable examples of buffers which may be used in the aqueous formulations described herein 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.

[0098] Optionally, the pharmaceutical compositions herein may contain a preservative. As used herein, unless otherwise noted, the terms "antimicrobial preservative" and "preservative" refer to any substance that is 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. 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. 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.

[0099] As used herein, the terms "penetration agent", "penetration enhancer", and "penetrant" refer to any substance that increases or facilitates absorption and / or bioavailability of aticaprant. Preferably, the penetration agent increases or facilitates absorption and / or bioavailability of aticaprant, following administration. Suitable examples include, but are not limited to tetradecyl maltoside, sodium glycocholate, tauroursodeoxycholic acid, lecithines, and the like; and chitosan (and salts), and surface active ingredients such as benzalkonium chloride, sodium dodecyl sulfate, sodium docusate, polysorbates, laureth-9, oxtoxynol, sodium deoxycholate, polyarginine, and the like. 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.

[00100] The pharmaceutical compositions for use herein may further contain one or more additional excipients for example, wetting agents, surfactant components, solubilizing agents, thickening agents, colorant agents, antioxidant components, and the like.

[00101] 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 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.

[00102] 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 the liquid carrier. Examples of a suitable emulsifying agent, if used, include, but are not limited to, for example, gelatin, cholesterol, acacia, tragacanth, pectin, methyl cellulose, carbomer, and mixtures thereof. Examples of suitable solubilizing agents include polyethylene glycol, glycerin, D-mannitol, trehalose, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, sodium salicylate, sodium acetate, and mixtures thereof. The solubilizing or emulsifying agent may be present in an amount sufficient to dissolve or disperse the active ingredient, *i.e.*, aticaprant, in the carrier.

[00103] A suitable isotonizing agent, if used, may include sodium chloride, glycerin, D-mannitol, D-sorbitol, glucose, and mixtures thereof.

[00104] Suspending agents or viscosity increasing agents may also be added to the pharmaceutical compositions. Suitable 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.

[00105] 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.

[00106] 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.

[00107] 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 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.

[00108] 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 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.

[00109] 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.

[00110] 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).

[00111] 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).

[00112] In certain embodiments, the patient is identified as biomarker signature positive.

[00113] 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 *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 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.

[00114] In certain embodiments, the biomarker signature is a dynorphin ("DYN") biomarker signature with positive status identified by: DYN > δ pg/mL. In the disclosed methods employing the dynorphin biomarker signature, the patient is identified as biomarker 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 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 am improvement in MADRS points at dynorphin levels greater than about 48 pg/mL.

[00115] 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 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 am improvement in MADRS points at dynorphin levels greater than about 48 pg/mL.

[00116] 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 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 am improvement in MADRS points at dynorphin levels greater than about 48 pg/mL.

[00117] 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.

[00118] 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 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 am improvement in MADRS points at dynorphin levels greater than about 48 pg/mL.

[00119] 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.

[00120] In any of the disclosed embodiments, the second reference dynorphin level is about 8 pg/mL.

[00121] 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.

[00122] 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.

[00123] As used herein, "CRP" refers to C-reactive protein. In certain embodiments, CRP has UniProtKB/Swiss-Prot number P02741.

[00124] As used herein, "TNF-alpha" refers to Tumor Necrosis Factor alpha. In certain embodiments, TNF-alpha as UniProtKB/Swiss-Prot number P01375.

[00125] 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.

[00126] As used herein, "DYN" refers to Dynorphin. In certain embodiments, CYN has UniProtKB/Swiss-Prot number P01213.

[00127] In any of the disclosed embodiments, the reference CRP level is about 3 mg/L.

[00128] In any of the disclosed embodiments, the reference TNF-alpha level is about 4 pg/mL.

[00129] In any of the disclosed embodiments, the reference sIL6R level is about 25 ng/mL.

[00130] 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.

[00131] 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
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 | HDRS-17	Hamilton Depression Rating Scale
HAM-A6	6 Item Subscale from HAM-A
HPA	Hypothalamus Pituitary Adrenal
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
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

[00132] 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

[00133] 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.

[00134] 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 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-A_6 subscale.

vi. To assess the plasma PK of aticaprant in subjects with MDD and explore its relationship with efficacy and safety parameters.

[00135] 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

[00136] 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.

[00137] 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.

[00138] 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.

[00139] 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.

[00140] Double-Blind Treatment Phase

[00141] 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.

Table 1: Time and Events Schedule (TES)

Phase	**Screening**	**[a]Double-blind treatment phase**									
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**[b]11 or EW**
Week (end of)	**-5 to 0**	**0**	**1**	**2**	**3**	**4**	**6**	**7**	**8**	**9**	**11**
Day	**-3 5 to -2**	**1**	**8**	**15**	**22**	**29**	**43**	**50**	**57**	**64**	**78**
Safety assessments											
Physical and neurological examination	X	X				X					X
ASEX		X			X	X	X			X	X
KSS		X			X	X	X			X	X
Suicidality by C-SSRS	X	X	X	X	X	X	X	X	X	X	X

Dosing											
Randomization		X	X	X	X						
Supply new medication		X	X	X	X	X	X	X	X	X	
Oral dose medication[d]		Day 2 until and including Day 78[e]									
Meal after dosing		X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]
Clinical Assessments											
Structured Interview Guide MADRS	X[j]	X	X	X	X	X	X	X	X	X	X
Structured Interview Guide SIGH-A		X	X	X	X	X	X	X	X	X	X
CGI-S		X	X	X	X	X	X	X	X	X	X
SMDDS		X			X	X	X			X	
CPFQ		X			X	X	X			X	
SHAPS	X	X	X	X	X	X	X	X	X	X	X
SATE[k]		once weekly while at home									
Ongoing subject review											
Assessment of subject engagement[k]	X	up to 3 occasion when at home									
Adverse events	continuous										
Concomitant medication	continuous										

EW = early withdrawal; a. Visits should be conducted ± 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.

[00142] *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.

[00143] *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.

[00144] *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

[00145] 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.

[00146] When Visit 11 was planned up to 3 days later, the subject continued medication until Visit 11.

[00147] 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.

[00148] The first dose was taken in fasting condition on Day 2 of the double-blind phase. The dose of the medication was:

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

[00149] 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.

[00150] 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

[00151] (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)

[00152] (ii) Anhedonia: Snaith-Hamilton Pleasure Scale (SHAPS)

[00153] (iii) Anxiety: Structured Interview Guide for the Hamilton Anxiety scale (SIGH-A) and HAM-A6

[00154] (iv) Effects on Cognition: The Cognitive and Physical Functioning Questionnaire (CPFQ)

[00155] (v) Safety assessments

[00156] 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.

[00157] (vi) Suicidal ideation: C-SSRS

[00158] (vii) Exploratory: CPFQ

[00159] (viii) Central sedating effects: Karolinska Sleepiness Scale

[00160] (ix) Sexual dysfunction: ASEX

E. Patient Population

[00161] 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%)
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/m^2)			
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%)
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/m^2)			
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

[00162] 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-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: ≥30% reduction from baseline at the end of the lead-in period) and presence/absence of anhedonia (presence defined as SHAPS total score ≥ 20).

[00163] 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.

[00164] 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.

[00165] 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.

[00166] 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.

[00167] The efficacy endpoints were presented for both the eITT and the fITT.

[00168] 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.

F. Results

[00169] (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

[00170] 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 Visit Treatment	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
Treatment Week 6					
Placebo	59	-8.2 (8.53)			
aticaprant	59	-10.2 (8.44)	-2.0 (8.49)	[-4.6,0.6]	-0.23
Negative change from baseline indicates improvement. Negative change to Placebo indicates favorable aticaprant effect. Negative effect size favors aticaprant; positive effect size favors Placebo.					

Table 6: MADRS Total Score: MMRM Results - Estimated LS Means and Comparison versus Placebo; eITT Analysis Set

Analysis Visit Treatment	**N**	**Mean (SD)**	**Mean (SD)**	**LSMean (SE)**	**LSMean Difference (SE) \ Treatment Placebo**	**60% Confidence Interval on Difference**	**p-value[a]**
Treatment Week 1							
Placebo	61	26.9 (6.77)	-2.2 (3.73)	-2.0 (0.92)			
aticaprant	60	25.4 (5.93)	-3.3 (5.21)	-3.2 (0.93)	-1.2 (1.24)	[-2.28,-0.19]	0.1604
Treatment Week 3							
Placebo	59	24.8 (8.25)	-4.3 (5.99)	-4.2 (0.92)			
aticaprant	59	23.1 (6.58)	-5.7 (6.38)	-5.6 (0.93)	-1.5 (1.25)	[-2.55,-0.44]	0.1159
Treatment Week 4							
Placebo	60	22.7 (9.10)	-6.4 (6.66)	-6.2 (0.92)			
aticaprant	57	21.5 (7.49)	-7.3 (7.35)	-7.3 (0.93)	-1.1 (1.25)	[-2.19,-0.09]	0.1811
Treatment Week 5							
Placebo	60	21.7 (9.54)	-7.4 (7.15)	-7.2 (0.92)			
aticaprant	55	20.5 (7.44)	-8.4 (7.36)	-8.7 (0.94)	-1.5 (1.25)	[-2.60,-0.48]	0.1103
Treatment Week 6							
Placebo	59	20.9 (10.54)	-8.2 (8.53)	-8.0 (0.92)			
aticaprant	59	18.6 (8.14)	-10.2 (8.44)	-10.1 (0.93)	-2.1 (1.25)	[-3.20,-1.09]	0.0443
[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

[00171] 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

[00172] 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)

[00173] 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

Analysis Visit Treatment	N	Mean (SD)	Change from Baseline Mean (SD)	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 Visit Treatment	N	Mean Change to Placebo (SD pooled)	90% CI for Mean Change to Placebo	Effect Size
Treatment Week 1				
Placebo	83			
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

[00174] 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

[00175] 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

[00176] The percentage of subjects with ≥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

[00177] The percentage of subjects with ≥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

[00178] In eITT population, in a subgroup of subjects with high anhedonia level (baseline SHAPS total score ≥ 38), larger differences between aticaprant placebo at Treatment Week 6 were observed than in subjects with low anhedonia level (20 ≤ baseline SHAPS total score <38). The effect size was 0.38 and 0.11, respectively.

[00179] 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 Visit Treatment	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.

[00180] 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 Treatment	N	Mean (SD)	Mean (SD)	LSMean (SE)	LSMean Difference (SE) \ Treatment Placebo	60% Confidence Interval on Difference	p-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 **Treatment**	**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)			
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							

[00181] 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

[00182] 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 Treatment	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	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

[00183] 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 ≤ 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 Visit Treatment	N	Mean Change from Baseline (SD)	Mean Change to Placebo (SD pooled)	90% CI for Mean Change to Placebo	Effect size
Low anhedonia					
Treatment Week 1					
Placebo	34	-1.8 (3.43)			
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
High anhedonia					
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

[00184] 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 Visit Treatment	N	Mean Change from Baseline (SD)	Mean Change to Placebo (SD pooled)	90% CI for Mean Change to Placebo	Effect size
Low anhedonia					
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
High anhedonia					
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.					

[00185] 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.

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

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

[00186] 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

[00187] 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

[00188] 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

[00189] 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)
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.			

[00190] 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.			

[00191] 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.

[00192] 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. 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.			

[00193] 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.

[00194] No deaths were reported.

(iv) Anhedonia Analysis

[00195] 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 <20)	Anhedonia (SHAPS Total Score >=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			

[00196] 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.				

[00197] 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

[00198] 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

[00199] 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.

[00200] 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%)
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

[00201] 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.

[00202] 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.

[00203] 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%

[00204] 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.

[00205] 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

[00206] 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

[00207] 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.

[00208] 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.

[00209] 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.

[00210] 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.

[00211] Inclusion Criteria:

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 ≤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 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/m^2 (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).

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.

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.

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 (≤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 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.
- 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 ≥3×the ULN or total bilirubin >1.5×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.

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 ≤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).

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 FT_4 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 (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

[00212] 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.

[00213] 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.

[00214] 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.

[00215] 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 (≥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.

[00216] 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).
- 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.

[00217] 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.

[00218] 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

[00219] 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.

[00220] 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.
- 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, dexmethylphenidate), 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

[00221] 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.

[00222] 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.

[00223] 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.

[00224] Subjects who have completed the double-blind treatment phase may participate in an open-label long-term safety study.

[00225] 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.

[00226] 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.

[00227] 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.

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).

6. SHAPS total score of ≥ 38 at screening and baseline (Day 1 prior to randomization) corresponding to prominent (high level) of anhedonia.

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 ≤25% improvement to both, then the subject would not qualify based on exclusion criterion (first exclusion criterion).

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.

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).

10. BMI between 18 and 40 kg/m^2 (inclusive).

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)

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 (≤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

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 ≥3×the ULN or total bilirubin >1.5×the ULN in the screening phase. Repeat of screening 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.
    - Uncontrolled Type 1 or Type 2 diabetes mellitus. Subjects with Type 1 or Type 2 diabetes mellitus who are controlled (hemoglobin A1c ≤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).
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 FT_4 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, Barret'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 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

[00228] 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.

[00229] 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

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

[00230] 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.

[00231] 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 (≥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.

[00232] 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.
- Change from baseline to Day 43 in patient-reported sexual functioning using the ASEX.

[00233] 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

[00234] 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

[00235] 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.

Prohibited therapies:

[00236] 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. 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, dexmethylphenidate), 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 4: Biomarker Assay

[00237] 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 TNFα 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.

[00238] 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.

[00239] The following biomarker signatures were employed:

[00240] 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.

[00241] Sig^{Pos}: Patient meeting the criteria defined by signature of biomarkers and/or clinical scales.

[00242] 3MM: Inflammatory biomarker signature with positive status defined by CRP > 3 mg/L *and* ($TNF\alpha > 4$ pg/mL *or* $sIL6R > 25$ ng/mL).

[00243] 4MM: Inflammatory biomarker signature with positive status defined by 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* ($TNF\alpha > 4$ pg/mL *or* $sIL6R > 25$ 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.

[00244] 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.

[00245] TE Sig^{Neg}: Treatment Effect in Signature Negative group.

[00246] Sig Adv: Signature Advantage (interaction) Difference in TE between signature groups: Sig Adv = TE Sig^{Pos} - TE Sig^{Neg}.

[00247] 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.

[00248] Figs. 26A-26D demonstrate the outcome of patient subtyping using a biomarker signature composed only of dynorphin levels, namely: DYN $> \delta$ 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 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 δ=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.

[00249] 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.

[00250] 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 > δ 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 δ = 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.

[00251] Fig. 29A-29C summarize the outcome of patient subtyping using a biomarker signature using a combination of high dynorphin (δ1) or 3MM with moderate dynorphin (δ2) subtypes, specifically: DYN > δ1 pg/mL or (DYN>δ2 pg/mL and CRP > 3 mg/L and ($TNF\alpha > 4$ pg/mL or $sIL6R > 25$ ng/mL)). The effect of the biomarker signature is evaluated at a range of dynorphin cut-points (δ) for δ1, but the δ2 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.

What is Claimed Is:

1. A method of 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.

2. The method of claim 1, wherein the patient has an inadequate response to other antidepressant therapy prior to treatment with aticaprant or a pharmaceutically acceptable salt thereof.

3. The method of claim 2, wherein the other antidepressant therapy comprised one or more antidepressants.

4. The method of claim 3, wherein the one or more antidepressants comprised a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI) treatment, or a combination thereof.

5. The method of claim 1, wherein the patient has anhedonia.

6. The method of claim 5, wherein the patient has a total score of ≥ 32 on the Snaith Hamilton Pleasure Scale (SHAPS).

7. The method of any one of claims 1-6, further comprising adjunctive treatment with an effective amount of one or more antidepressants.

8. The method of claim 7, wherein the one or more antidepressants is a selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), or a combination thereof.

9. The method of any one of claims 1-8, wherein the aticaprant is S-aticaprant, or a pharmaceutically acceptable salt thereof.

10. The method of any one of claims 1-9, wherein the effective amount of aticaprant is about 2 to about 35 mg.

11. The method of claim 10, wherein the effective amount of aticaprant is about 10 mg.

12. The method of claim 10, wherein the effective amount of aticaprant is about 5 mg.

13. The method of any one of claims 1-12, wherein the aticaprant is administered orally.

14. The method of any one of claims 1-13, wherein the aticaprant is administered once daily.

15. The method of any one of claims 1-14, 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.

16. The method of any one of claims 1-14, wherein the patient is identified as biomarker 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.

17. The method of any one of claims 1-14, 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 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.

18. The method of any one of claims 1-14, 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 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.

19. The method of any one of claims 15 and 17-18, wherein the reference CRP level is about 3 mg/L.

20. The method of any one of claims 15 and 17-18, wherein the reference TNF-alpha level is about 4 pg/mL.

21. The method of any one of claims 15 and 17-18, wherein the reference sIL6R level is about 25 ng/mL.

22. The method of any one of claims 16-18, wherein the reference dynorphin level is about 20 pg/mL.

23. The method of any one of claims 16-18, wherein the reference dynorphin level is about 30 pg/mL.

24. The method of any one of claims 16-18, wherein the reference dynorphin level is about 11.4 pg/mL.

25. 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 dynorphin greater than a first reference dynorphin level; or
    b. both of (i) and (ii), wherein (i) is a level of CRP greater than a reference CRP level, and at 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.

26. The method of claim 25, wherein the first reference dynorphin level is about 50 pg/ml and the second reference dynorphin level is about 8 pg/ml.

27. The method of claim 25, wherein the first reference dynorphin level is about 24 pg/ml and the second reference dynorphin level is about 8 pg/ml.

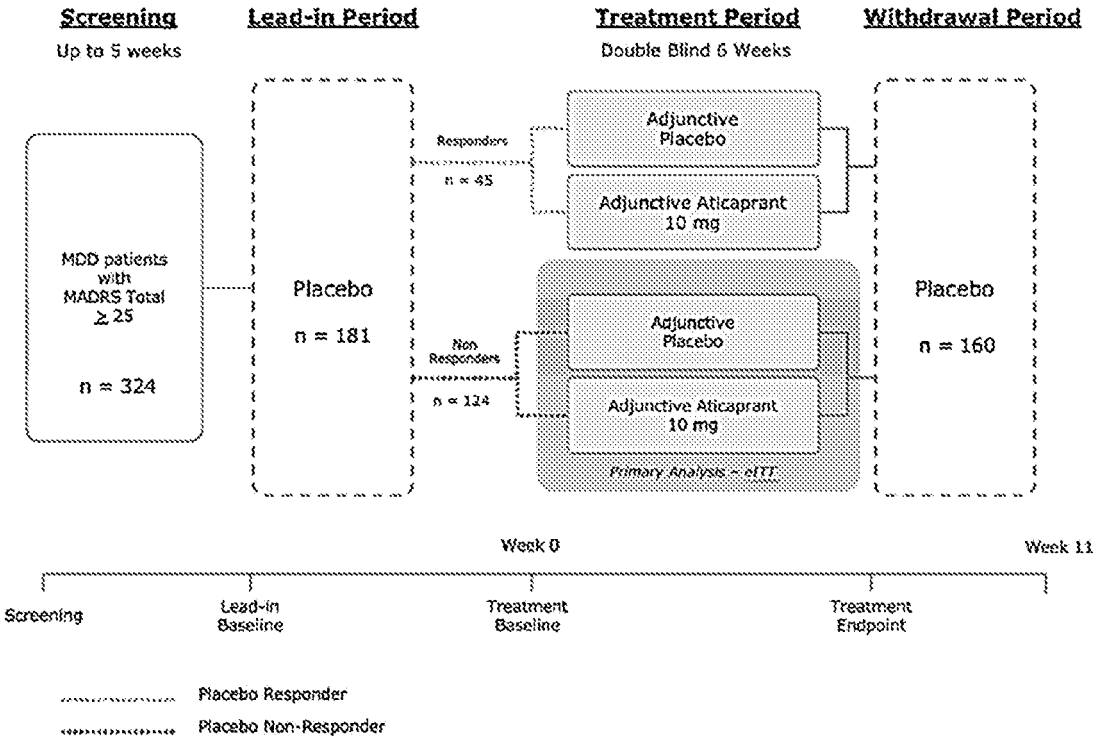

Screening
Up to 5 weeks
Lead-in Period
Treatment Period
Double Blind 6 Weeks
Withdrawal Period
MDD patients with MADRS Total ≥ 25
n = 324
Placebo
n = 181
Responders
n = 45
Non Responders
n = 124
Adjunctive Placebo
Adjunctive Aticaprant 10 mg
Adjunctive Placebo
Adjunctive Aticaprant 10 mg
Primary Analysis – eITT
Placebo
n = 160
Week 0
Week 11
Screening
Lead-in Baseline
Treatment Baseline
Treatment Endpoint
Placebo Responder
Placebo Non-Responder

Fig. 1

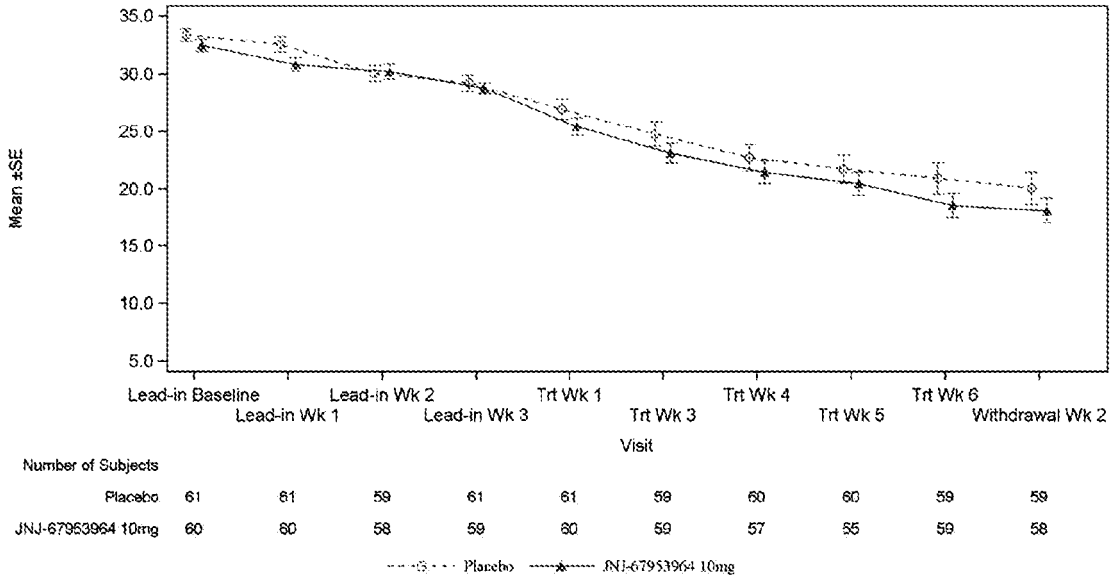

Mean ±SE
35.0
30.0
25.0
20.0
15.0
10.0
5.0
Lead-in Baseline
Lead-in Wk 1
Lead-in Wk 2
Lead-in Wk 3
Trt Wk 1
Trt Wk 3
Trt Wk 4
Trt Wk 5
Trt Wk 6
Withdrawal Wk 2
Visit
Number of Subjects
Placebo 61 61 59 61 61 59 60 60 59 59
JNJ-67953964 10mg 60 60 58 59 60 59 57 55 59 58
Placebo
JNJ-67953964 10mg

Fig. 2

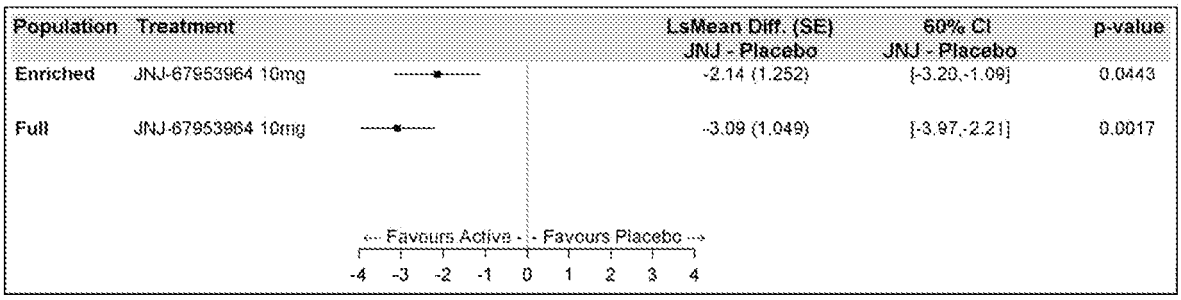

Population
Treatment
LsMean Diff. (SE)
JNJ - Placebo
60% CI
JNJ - Placebo
p-value
Enriched
JNJ-67953964 10mg
-2.14 (1.252)
[-3.28,-1.09]
0.0443
Full
JNJ-67953964 10mg
-3.09 (1.049)
[-3.97,-2.21]
0.0017
Favours Active
Favours Placebo
-4 -3 -2 -1 0 1 2 3 4

Fig. 3

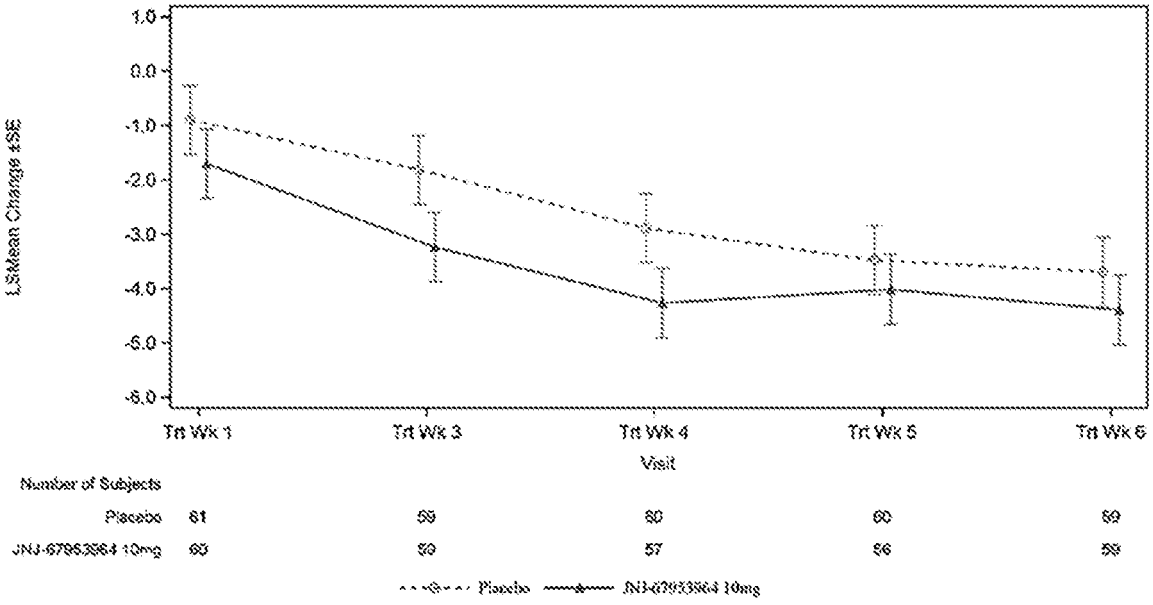

LSMean Change ±SE
1.0
0.0
-1.0
-2.0
-3.0
-4.0
-5.0
-6.0
Trt Wk 1
Trt Wk 3
Trt Wk 4
Trt Wk 5
Trt Wk 6
Visit
Number of Subjects
Placebo 61 59 60 60 59
JNJ-67953964 10mg 60 59 57 56 59
Placebo
JNJ-67953964 10mg

Fig. 4

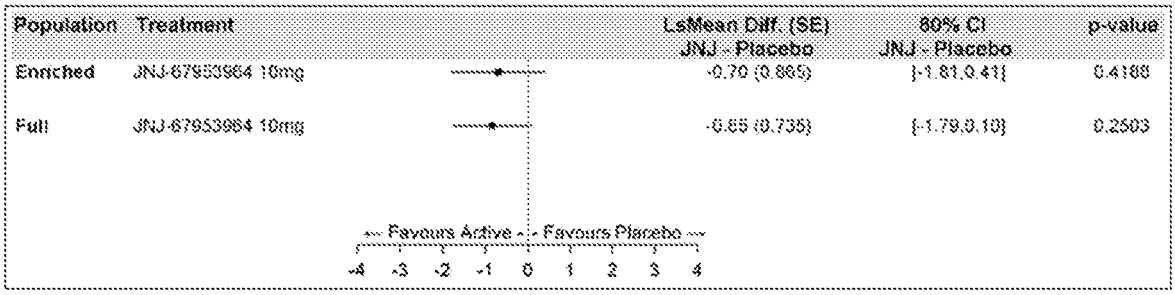

Population
Treatment
LsMean Diff. (SE) JNJ - Placebo
80% CI JNJ - Placebo
p-value
Enriched
JNJ-67953964 10mg
-0.70 (0.385)
[-1.81,0.41]
0.4188
Full
JNJ-67953964 10mg
-0.65 (0.735)
[-1.79,0.10]
0.2503
Favours Active
Favours Placebo
-4 -3 -2 -1 0 1 2 3 4

Fig. 5

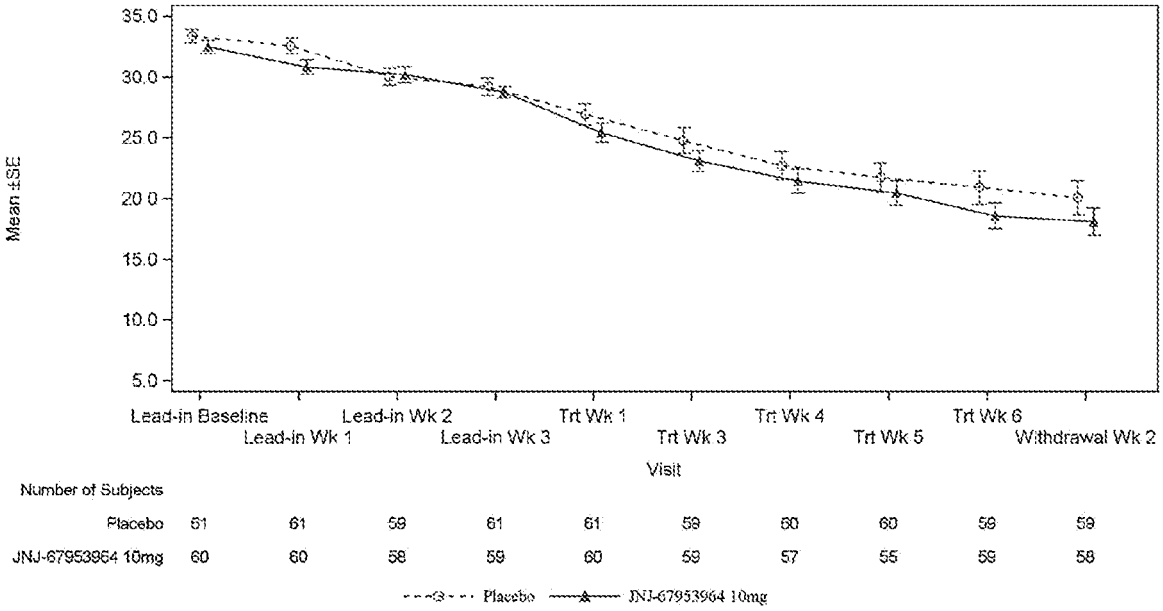

Mean ±SE
35.0
30.0
25.0
20.0
15.0
10.0
5.0
Lead-in Baseline
Lead-in Wk 1
Lead-in Wk 2
Lead-in Wk 3
Trt Wk 1
Trt Wk 3
Trt Wk 4
Trt Wk 5
Trt Wk 6
Withdrawal Wk 2
Visit
Number of Subjects
Placebo 61 61 59 61 61 59 60 60 59 59
JNJ-67953964 10mg 60 60 58 59 60 59 57 55 59 58
Placebo
JNJ-67953964 10mg

Fig. 6

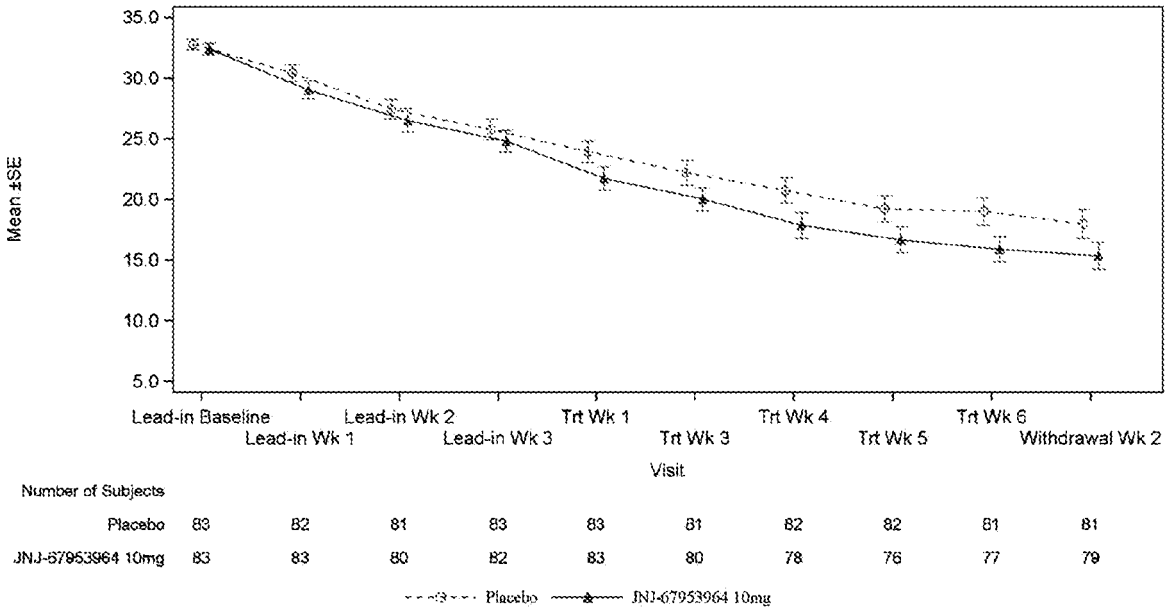

Mean ±SE
35.0
30.0
25.0
20.0
15.0
10.0
5.0
Lead-in Baseline
Lead-in Wk 1
Lead-in Wk 2
Lead-in Wk 3
Trt Wk 1
Trt Wk 3
Trt Wk 4
Trt Wk 5
Trt Wk 6
Withdrawal Wk 2
Visit
Number of Subjects
Placebo 83 82 81 83 83 81 82 82 81 81
JNJ-67953964 10mg 83 83 80 82 83 80 78 76 77 79
Placebo
JNJ-67953964 10mg

Fig. 7A

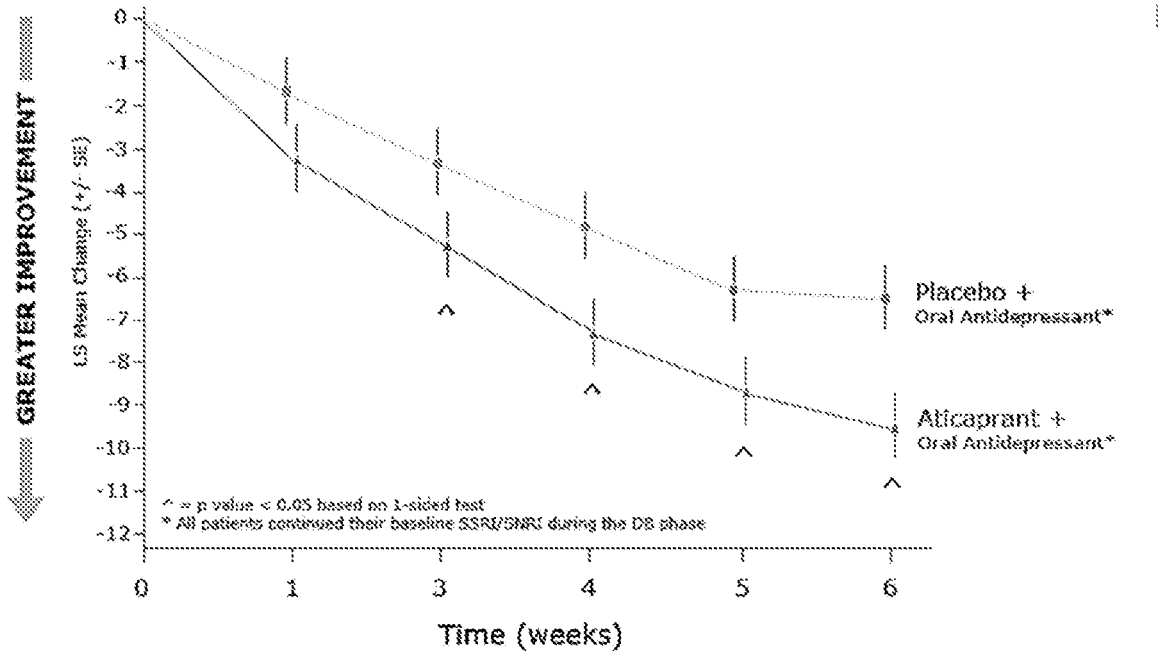
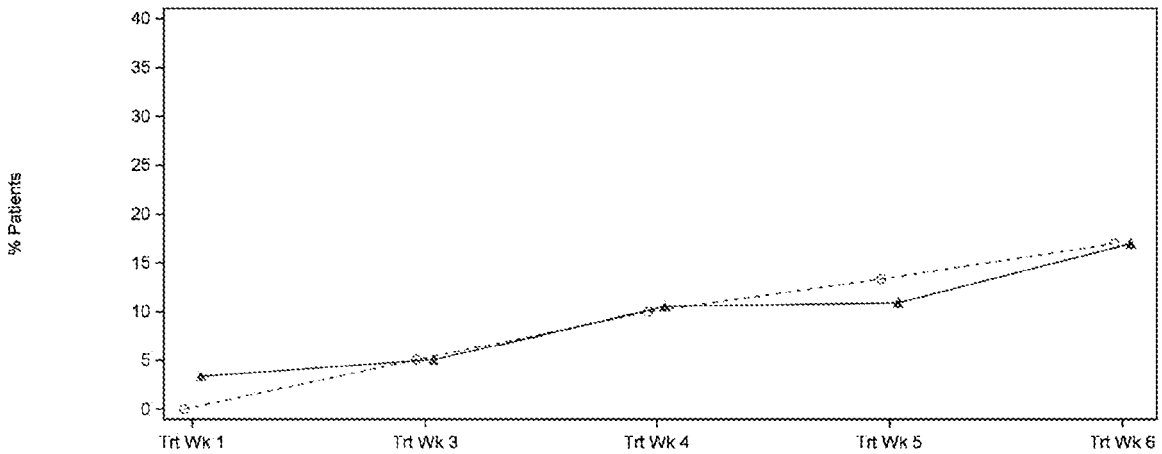

GREATER IMPROVEMENT
LS Mean Change (+/- SE)
0
-1
-2
-3
-4
-5
-6
-7
-8
-9
-10
-11
-12
^ = p value < 0.05 based on 1-sided test
* All patients continued their baseline SSRI/SNRI during the DB phase
Placebo +
Oral Antidepressant*
Aticaprant +
Oral Antidepressant*
0
1
3
4
5
6
Time (weeks)

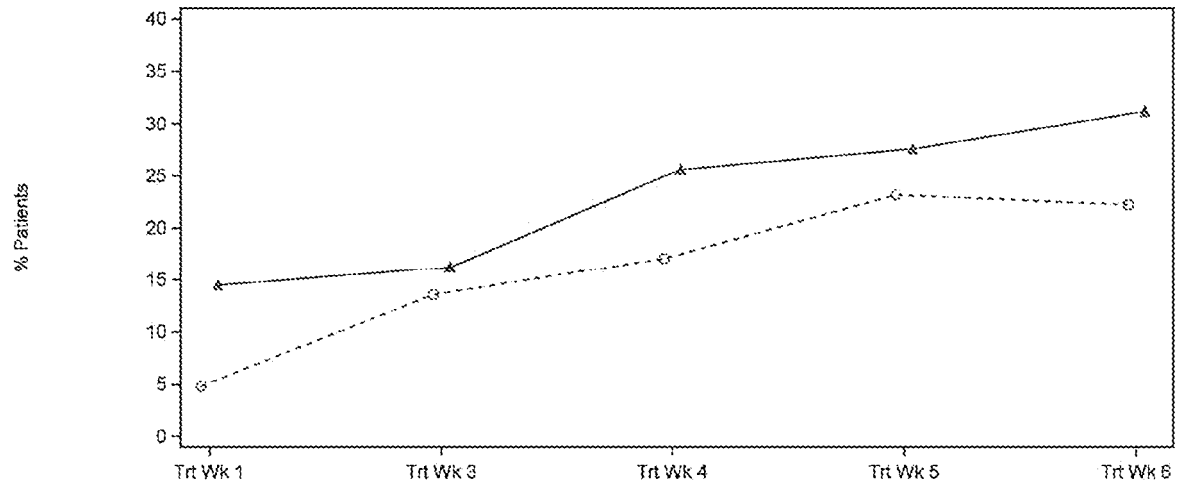
Fig. 7B



Number of Subjects					
Placebo	61	59	60	60	59
JNJ-67953964 10mg	60	59	57	55	59

Placebo JNJ-67953964 10mg

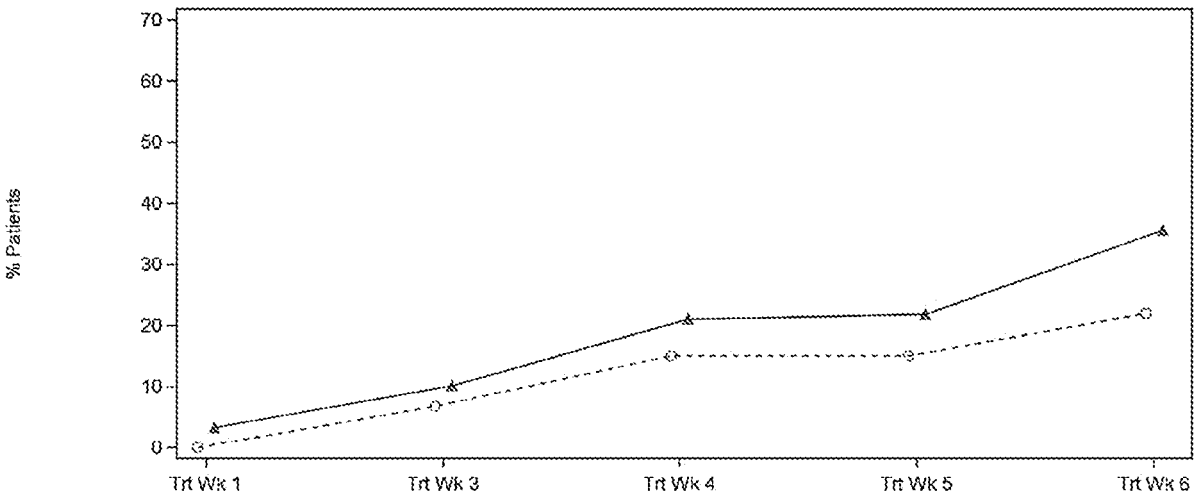
Fig. 8



Number of Subjects					
Placebo	83	81	82	82	81
JNJ-67953964 10mg	83	80	78	78	77

Placebo JNJ-67953964 10mg

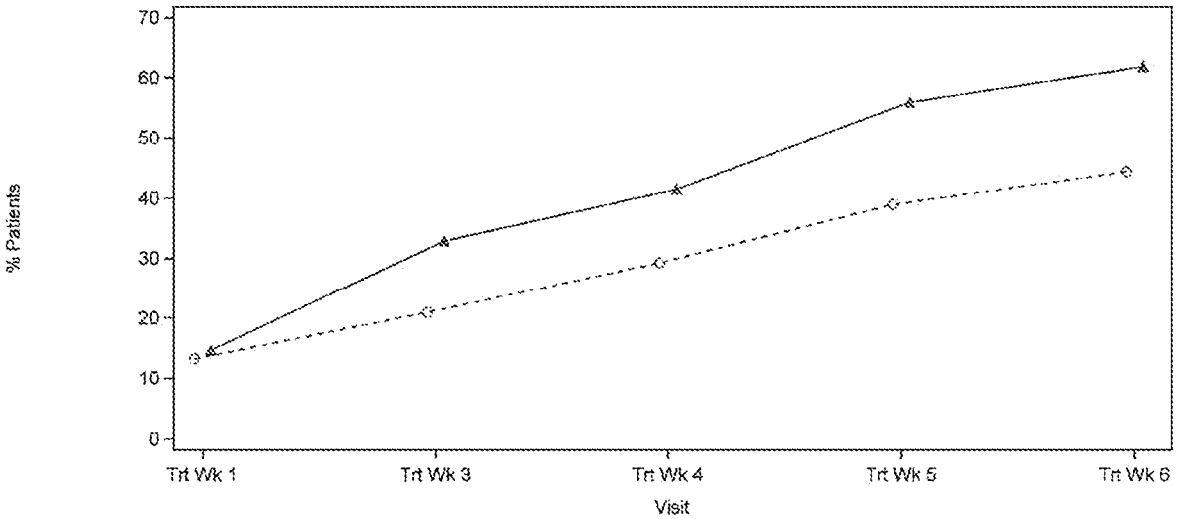
Fig. 9



Number of Subjects					
Placebo	61	59	60	60	59
JNJ-67953964 10mg	60	59	57	55	59

Placebo JNJ-67953964 10mg

Fig. 10



Number of Subjects					
Placebo	83	81	82	82	81
JNJ-67953964 10mg	82	79	77	75	76

Placebo JNJ-67953964 10mg

Fig. 11

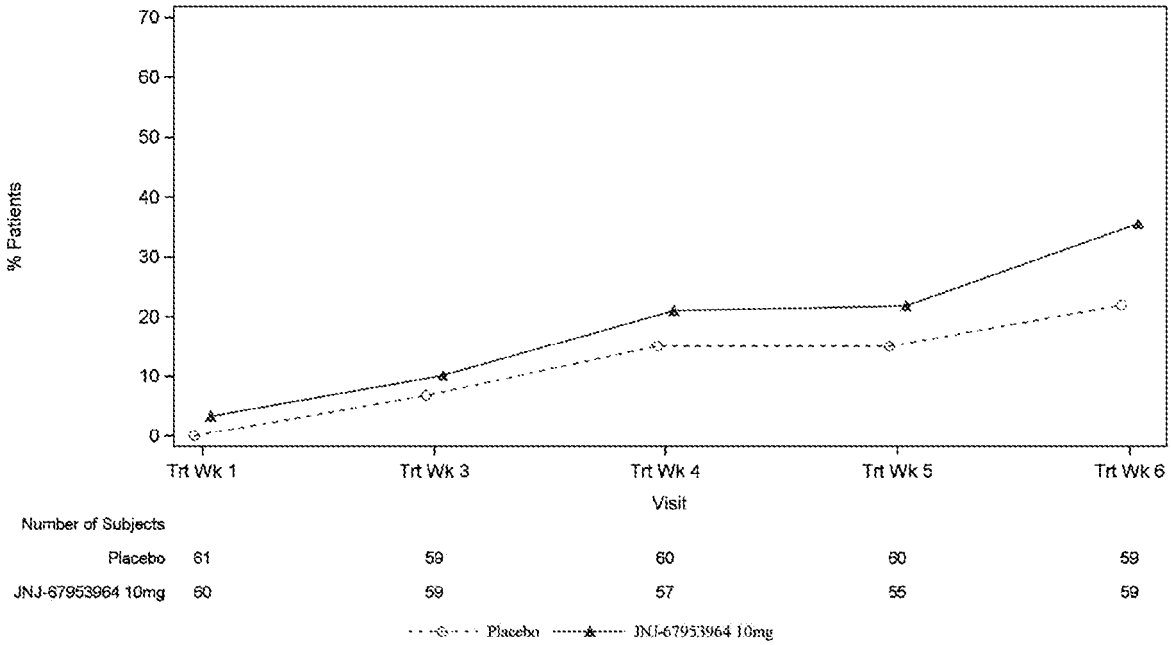

70
60
50
40
30
20
10
0
% Patients
Trt Wk 1
Trt Wk 3
Trt Wk 4
Trt Wk 5
Trt Wk 6
Visit
Number of Subjects
Placebo 61 59 60 60 59
JNJ-67953964 10mg 60 59 57 55 59
Placebo
JNJ-67953964 10mg

Fig. 12

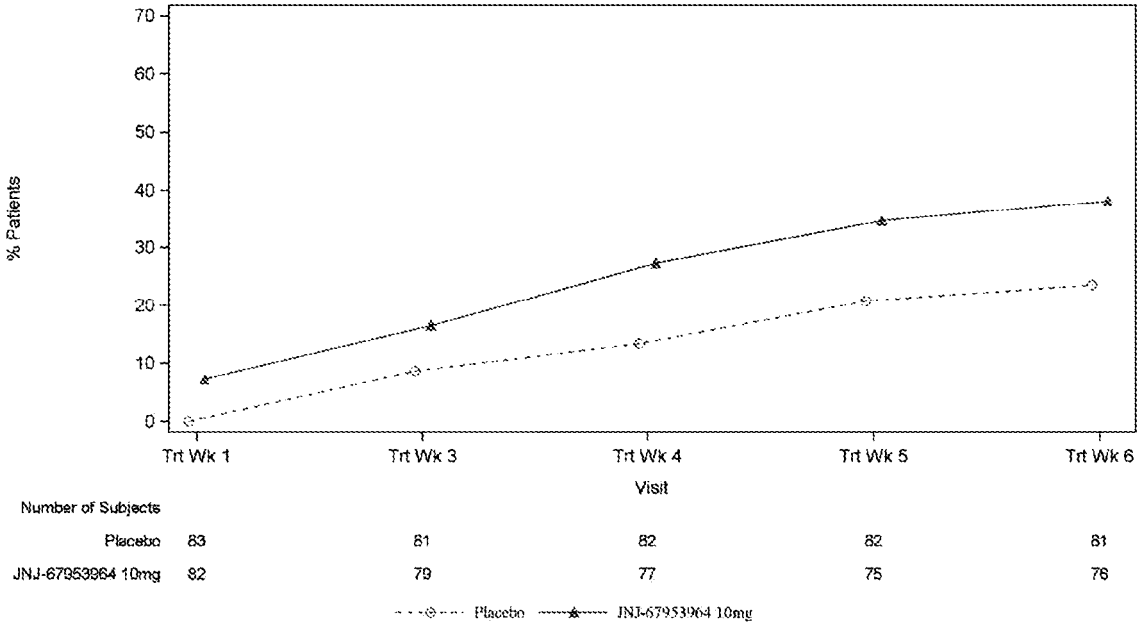

70
60
50
40
30
20
10
0
% Patients
Trt Wk 1
Trt Wk 3
Trt Wk 4
Trt Wk 5
Trt Wk 6
Visit
Number of Subjects
Placebo 83 81 82 82 81
JNJ-67953964 10mg 82 79 77 75 76
Placebo
JNJ-67953964 10mg

Fig. 13

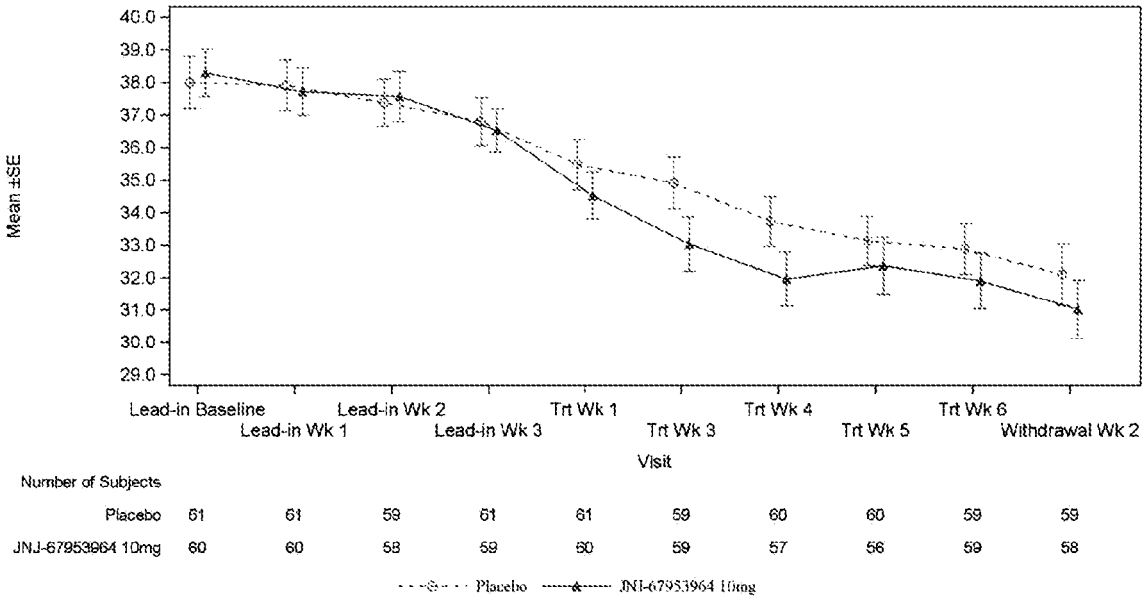

Mean ±SE
40.0
39.0
38.0
37.0
36.0
35.0
34.0
33.0
32.0
31.0
30.0
29.0
Lead-in Baseline
Lead-in Wk 1
Lead-in Wk 2
Lead-in Wk 3
Trt Wk 1
Trt Wk 3
Trt Wk 4
Trt Wk 5
Trt Wk 6
Withdrawal Wk 2
Visit
Number of Subjects
Placebo 61 61 59 61 61 59 60 60 59 59
JNJ-67953964 10mg 60 60 58 59 60 59 57 56 59 58
Placebo
JNJ-67953964 10mg

Fig. 14

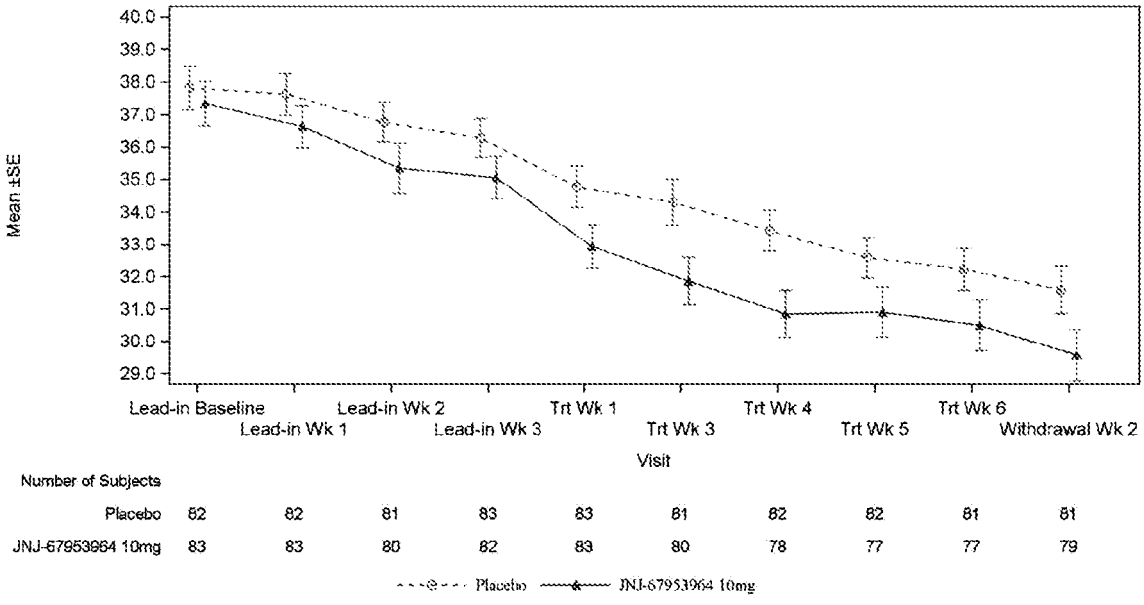

Mean ±SE
40.0
39.0
38.0
37.0
36.0
35.0
34.0
33.0
32.0
31.0
30.0
29.0
Lead-in Baseline
Lead-in Wk 1
Lead-in Wk 2
Lead-in Wk 3
Trt Wk 1
Trt Wk 3
Trt Wk 4
Trt Wk 5
Trt Wk 6
Withdrawal Wk 2
Visit
Number of Subjects
Placebo 82 82 81 83 83 81 82 82 81 81
JNJ-67953964 10mg 83 83 80 82 83 80 78 77 77 79
Placebo
JNJ-67953964 10mg

Fig. 15

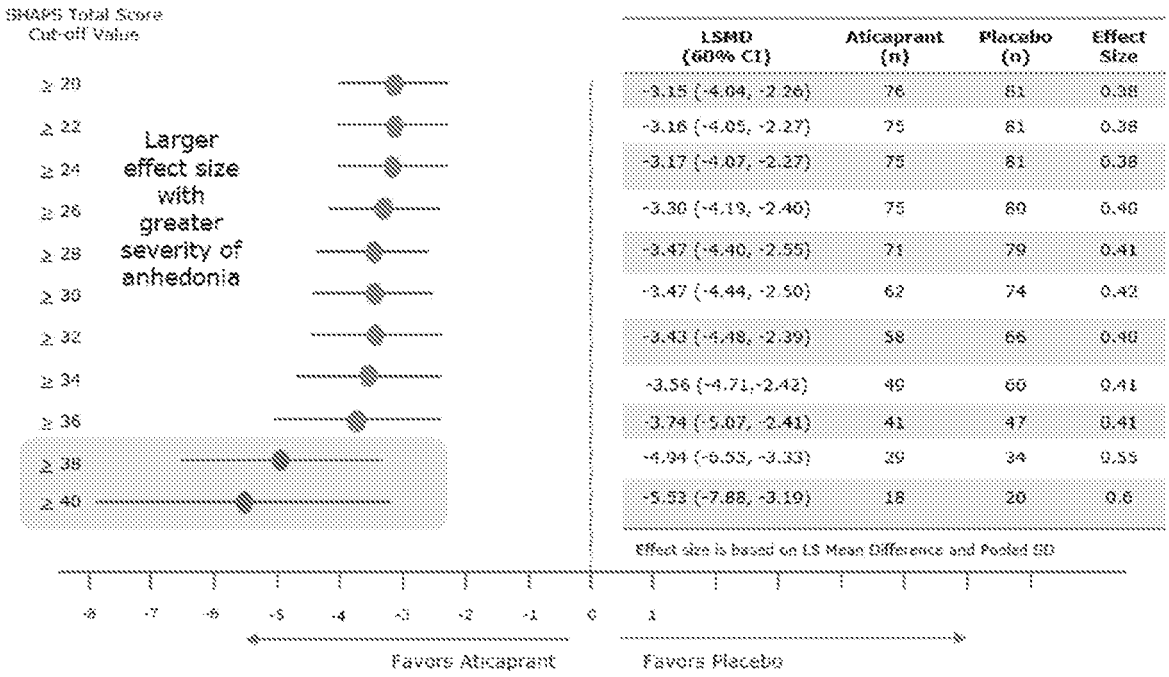


Fig. 16

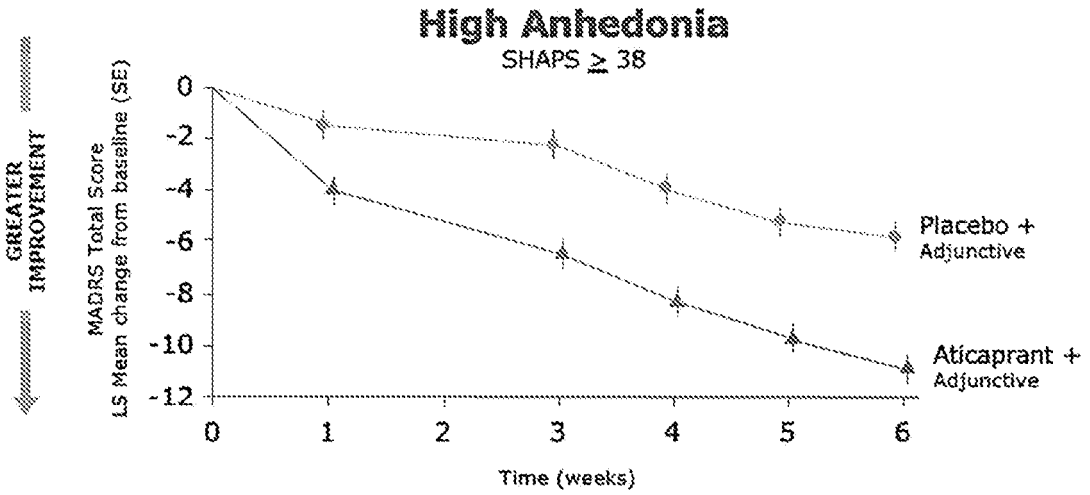


Fig. 17A

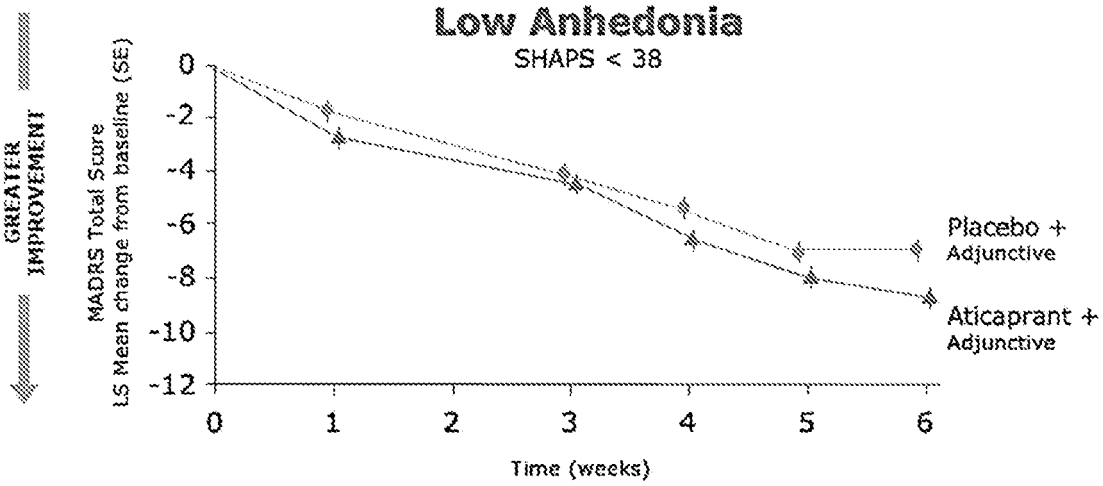


Fig. 17B

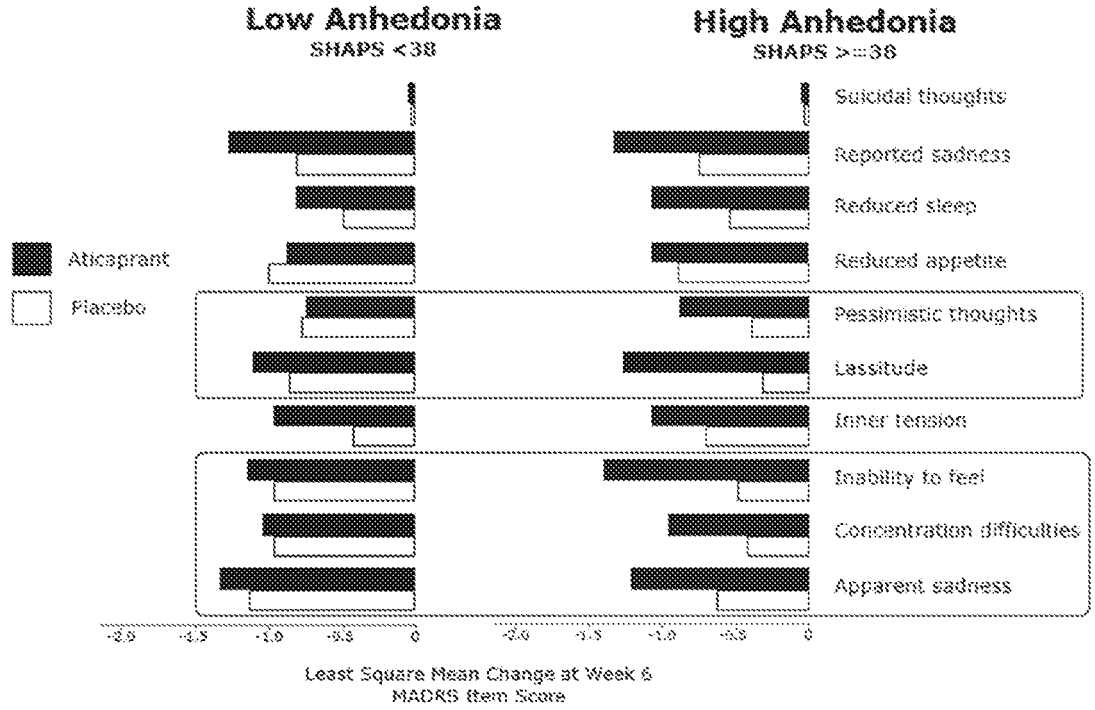


Fig. 18

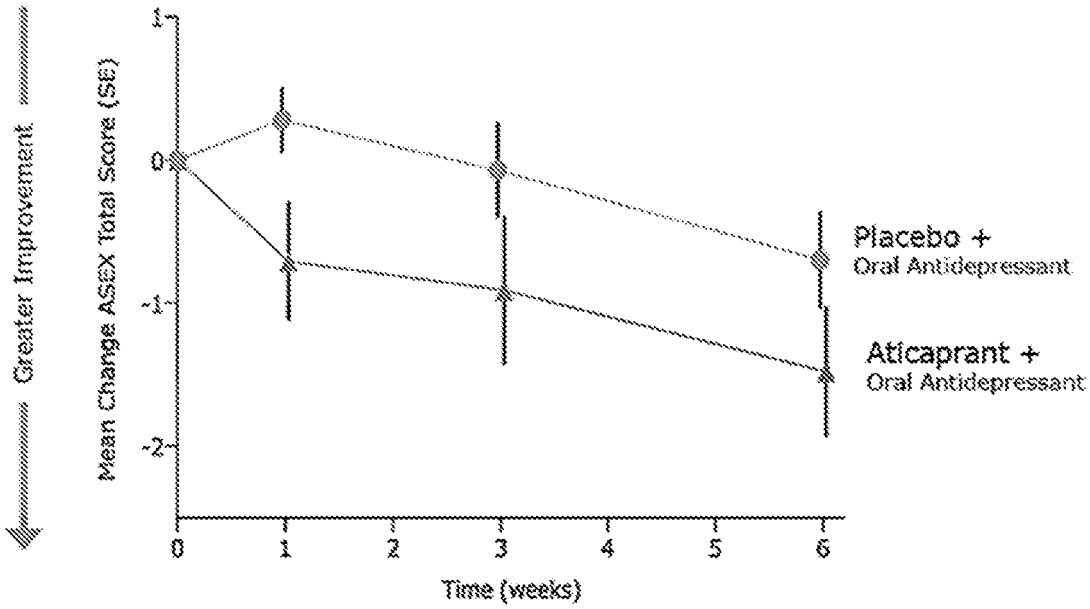

Greater Improvement
Mean Change ASEX Total Score (SE)
1
0
-1
-2
0
1
2
3
4
5
6
Time (weeks)
Placebo +
Oral Antidepressant
Aticaprant +
Oral Antidepressant

Fig. 19

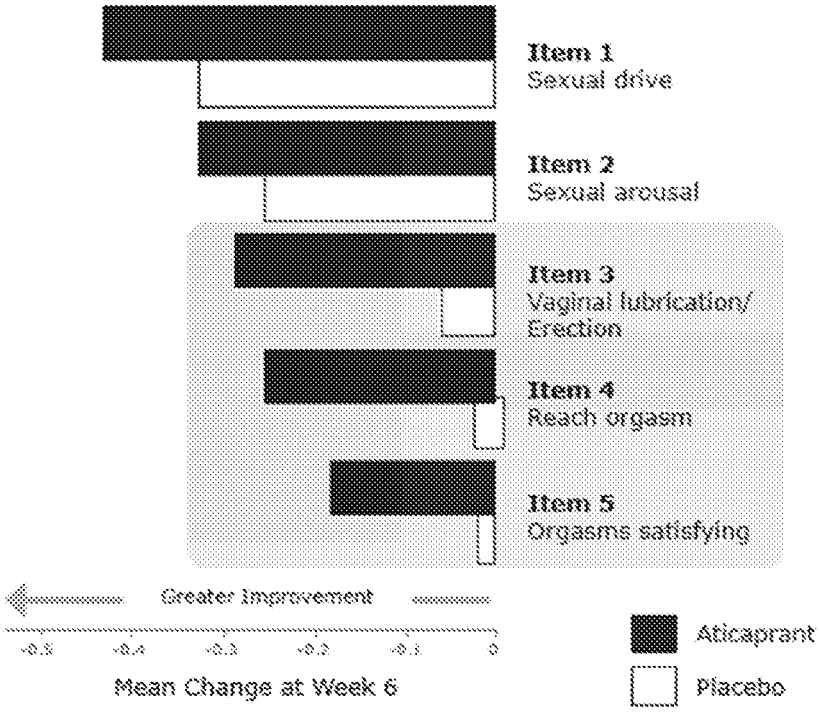

Item 1
Sexual drive
Item 2
Sexual arousal
Item 3
Vaginal lubrication/
Erection
Item 4
Reach orgasm
Item 5
Orgasms satisfying
Greater Improvement
-0.5
-0.4
-0.3
-0.2
-0.1
0
Mean Change at Week 6
Aticaprant
Placebo

Fig. 20

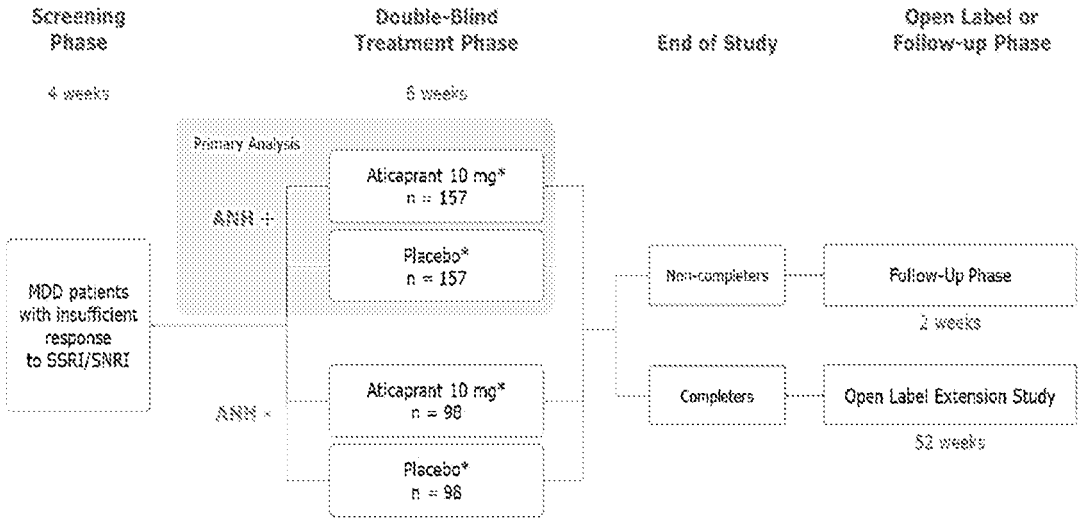

Screening Phase
4 weeks
Double-Blind Treatment Phase
8 weeks
End of Study
Open Label or Follow-up Phase
Primary Analysis
ANN +
Aticaprant 10 mg*
n = 157
Placebo*
n = 157
MDD patients with insufficient response to SSRI/SNRI
ANN -
Aticaprant 10 mg*
n = 98
Placebo*
n = 98
Non-completers
Follow-Up Phase
2 weeks
Completers
Open Label Extension Study
52 weeks

Fig. 21

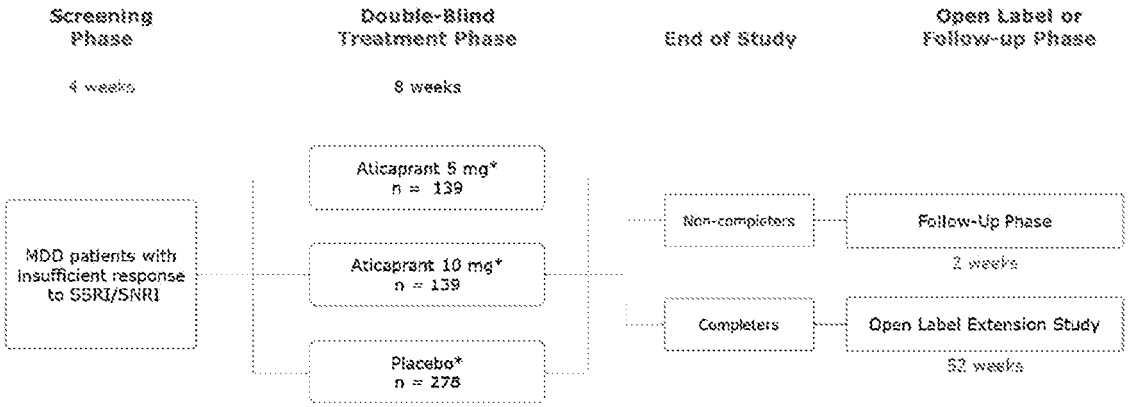

Screening Phase
4 weeks
Double-Blind Treatment Phase
8 weeks
End of Study
Open Label or Follow-up Phase
Aticaprant 5 mg*
n = 139
MDD patients with insufficient response to SSRI/SNRI
Aticaprant 10 mg*
n = 139
Placebo*
n = 278
Non-completers
Follow-Up Phase
2 weeks
Completers
Open Label Extension Study
52 weeks

Fig. 22

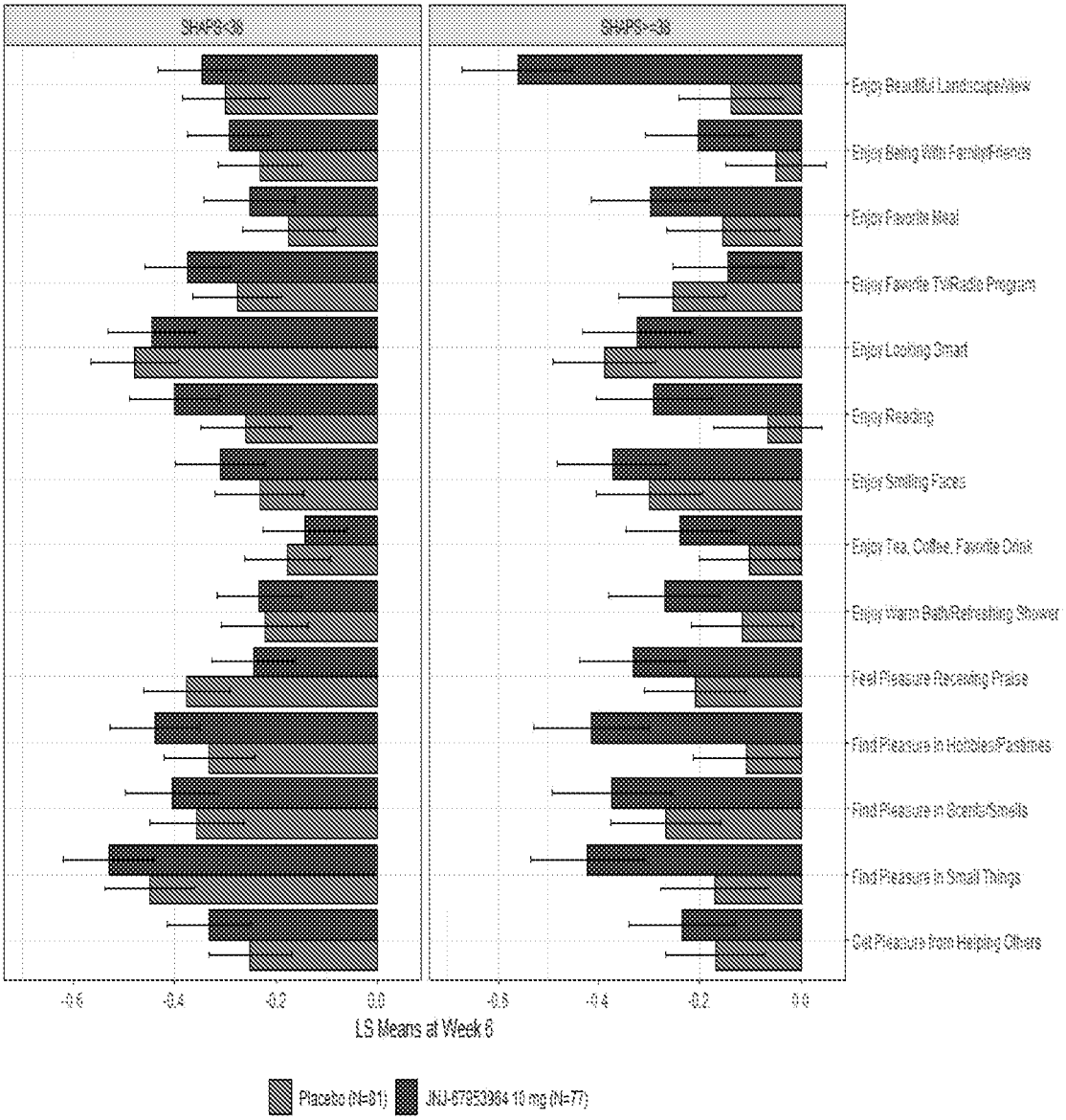

SHAPS<=3
SHAPS>=3
Enjoy Beautiful Landscape/View
Enjoy Being With Family/Friends
Enjoy Favorite Meal
Enjoy Favorite TV/Radio Program
Enjoy Looking Smart
Enjoy Reading
Enjoy Smiling Faces
Enjoy Tea, Coffee, Favorite Drink
Enjoy Warm Bath/Refreshing Shower
Feel Pleasure Receiving Praise
Find Pleasure in Hobbies/Pastimes
Find Pleasure in Scents/Smells
Find Pleasure in Small Things
Get Pleasure from Helping Others
-0.6
-0.4
-0.2
0.0
LS Means at Week 6
Placebo (N=81)
JNJ-67953964 10 mg (N=77)

Fig. 23

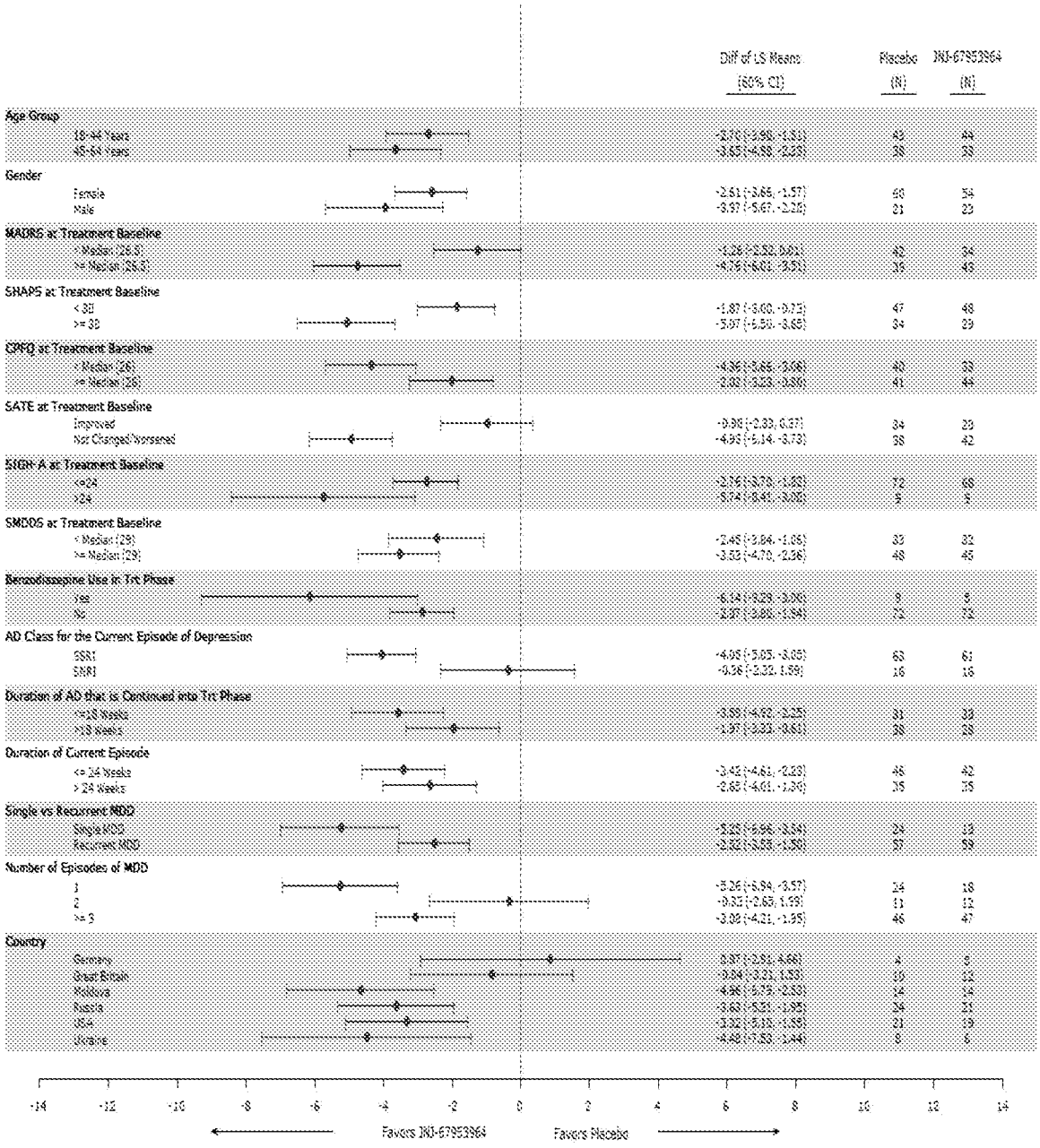

Diff of LS Means (80% CI)
Placebo (N)
JNJ-67953964 (N)
Age Group
18-44 Years
45-64 Years
Gender
Female
Male
MADRS at Treatment Baseline
< Median (28.5)
>= Median (28.5)
SNAPS at Treatment Baseline
< 38
>= 38
CPFQ at Treatment Baseline
< Median (26)
>= Median (26)
SATE at Treatment Baseline
Improved
Not Changed/Worsened
SIGH-A at Treatment Baseline
<=24
>24
SMDDS at Treatment Baseline
< Median (29)
>= Median (29)
Benzodiazepine Use in Trt Phase
Yes
No
AD Class for the Current Episode of Depression
SSRI
SNRI
Duration of AD that is Continued into Trt Phase
<=18 Weeks
>18 Weeks
Duration of Current Episode
<= 24 Weeks
> 24 Weeks
Single vs Recurrent MDD
Single MDD
Recurrent MDD
Number of Episodes of MDD
1
2
>= 3
Country
Germany
Great Britain
Moldova
Russia
USA
Ukraine
-14
-12
-10
-8
-6
-4
-2
0
2
4
6
8
10
12
14
Favors JNJ-67953964
Favors Placebo

Fig. 24

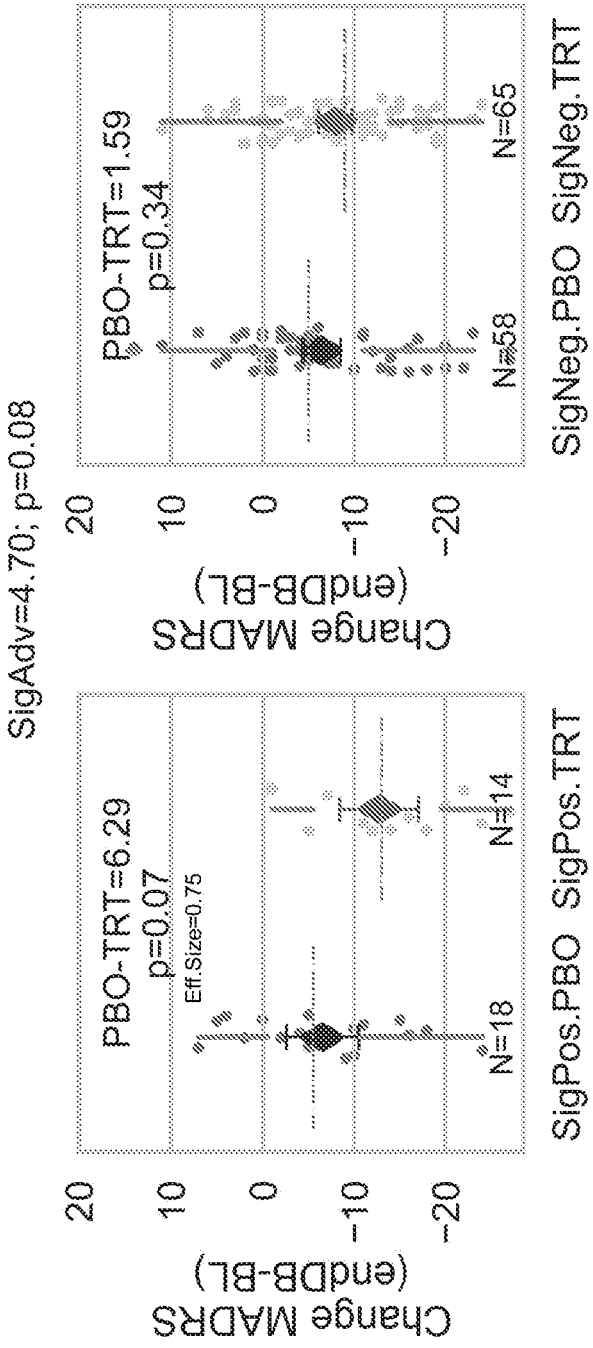

SigAdv=4.70; p=0.08
Change MADRS (endDB-BL)
20
10
0
−10
−20
PBO-TRT=6.29
p=0.07
Eff.Size=0.75
N=18
N=14
SigPos.PBO
SigPos.TRT
PBO-TRT=1.59
p=0.34
N=58
N=65
SigNeg.PBO
SigNeg.TRT

Fig. 25

Fig. 26A

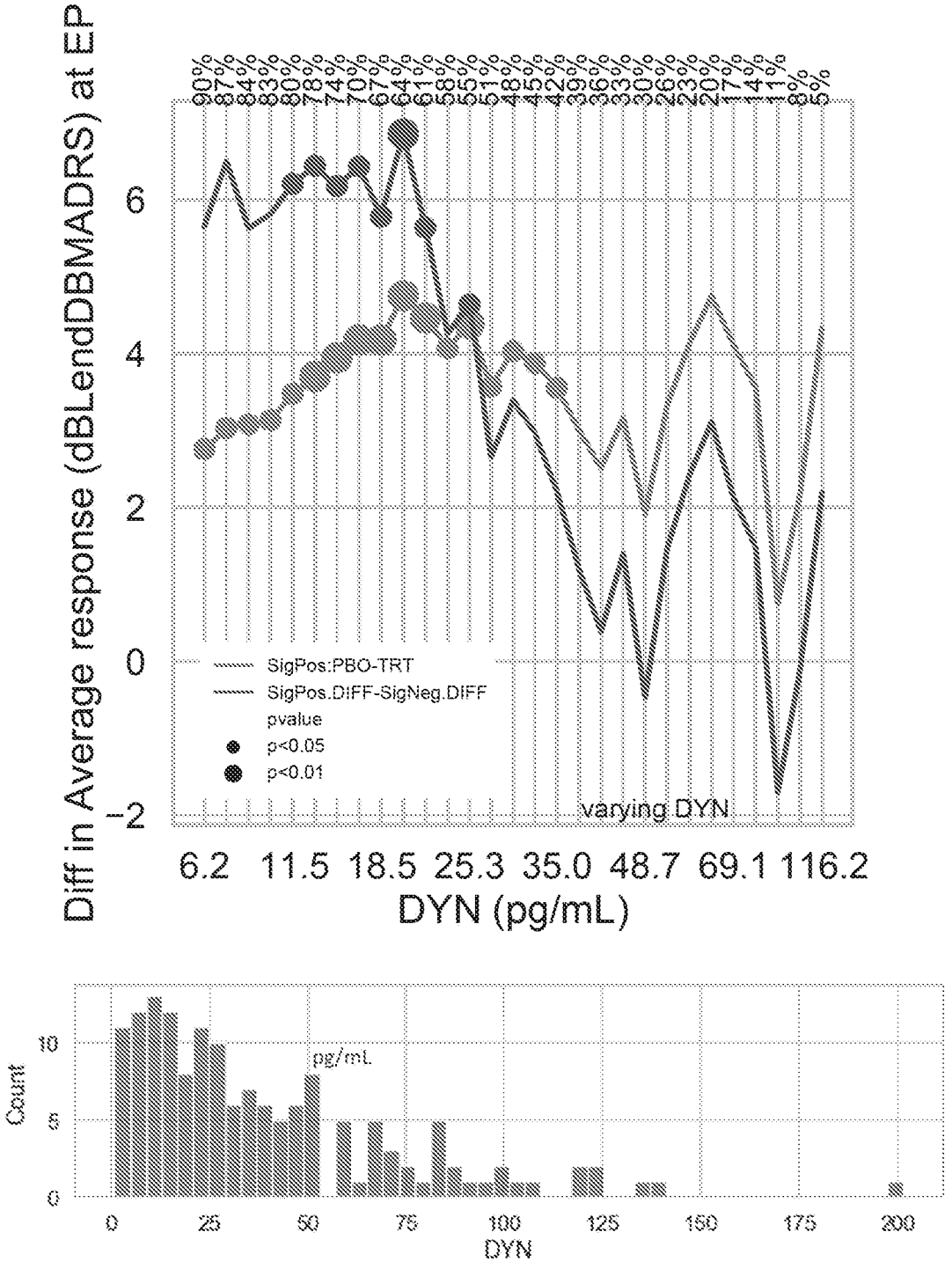

90%
87%
84%
83%
80%
78%
74%
70%
67%
64%
61%
58%
55%
51%
48%
45%
42%
39%
36%
33%
30%
26%
23%
20%
17%
14%
11%
8%
5%
Diff in Average response (dBLendDBMADRS) at EP
6
4
2
0
−2
SigPos:PBO-TRT
SigPos.DIFF-SigNeg.DIFF
pvalue
p<0.05
p<0.01
varying DYN
6.2 11.5 18.5 25.3 35.0 48.7 69.1 116.2
DYN (pg/mL)
Count
10
5
0
pg/mL
0 25 50 75 100 125 150 175 200
DYN

Fig. 26B

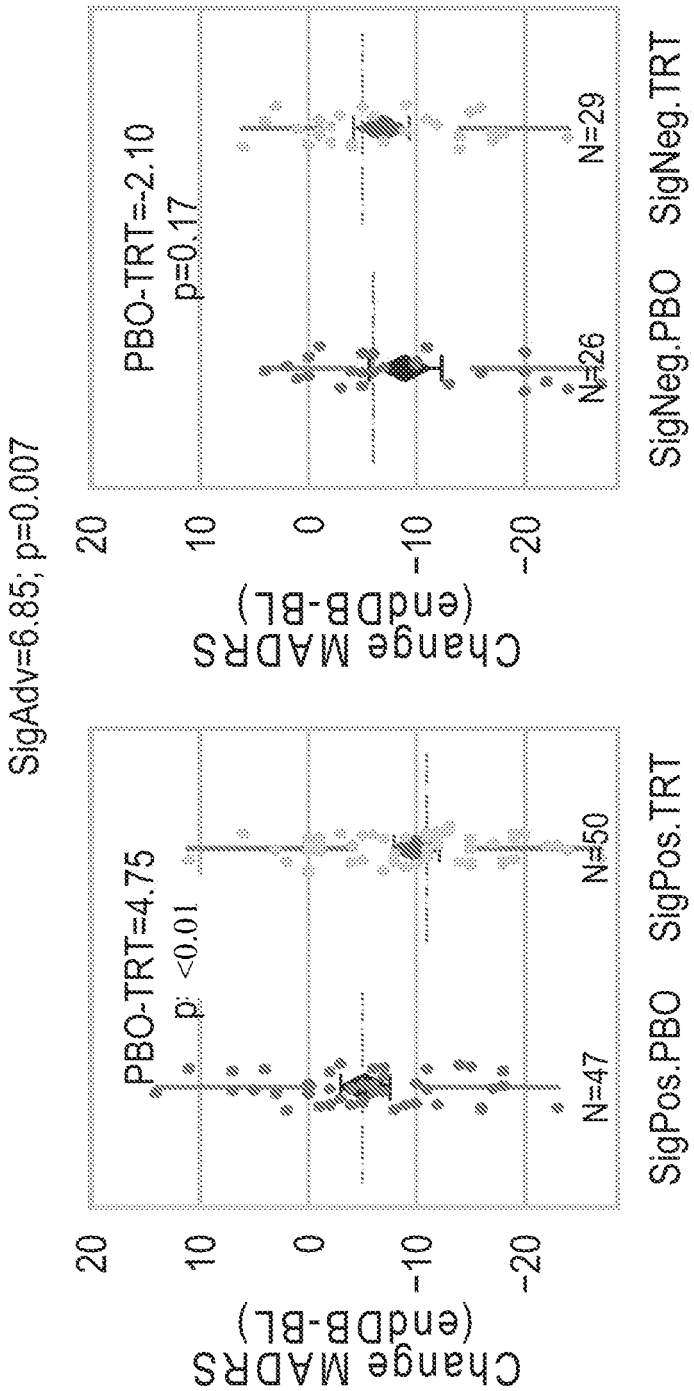

SigAdv=6.85; p=0.007
Change MADRS (endDB-BL)
20
10
0
-10
-20
PBO-TRT=4.75
p: <0.01
N=47
N=50
SigPos.PBO
SigPos.TRT
PBO-TRT=-2.10
p=0.17
N=26
N=29
SigNeg.PBO
SigNeg.TRT

Fig. 26C

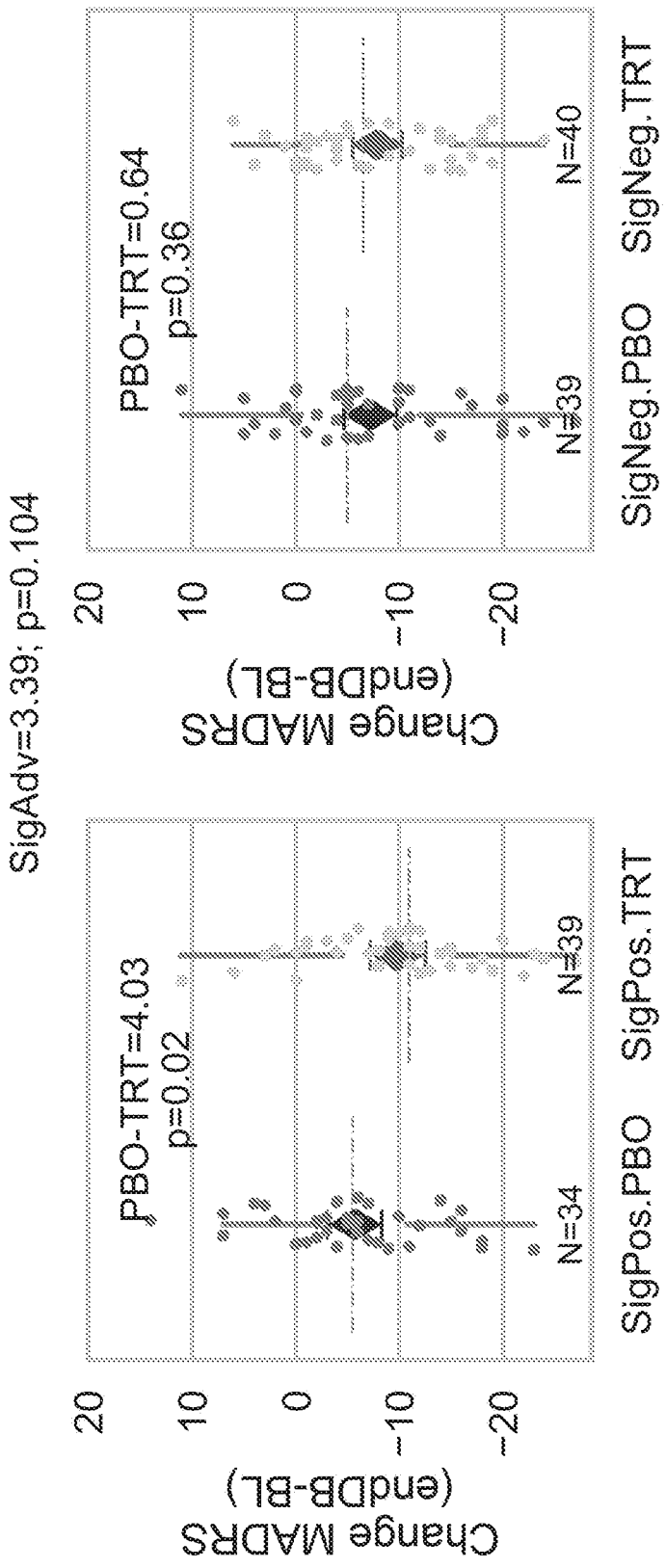

SigAdv=3.39; p=0.104
Change MADRS (endDB-BL)
20
10
0
−10
−20
PBO-TRT=4.03
p=0.02
N=34
N=39
SigPos.PBO
SigPos.TRT
PBO-TRT=0.64
p=0.36
N=39
N=40
SigNeg.PBO
SigNeg.TRT

Fig. 26D

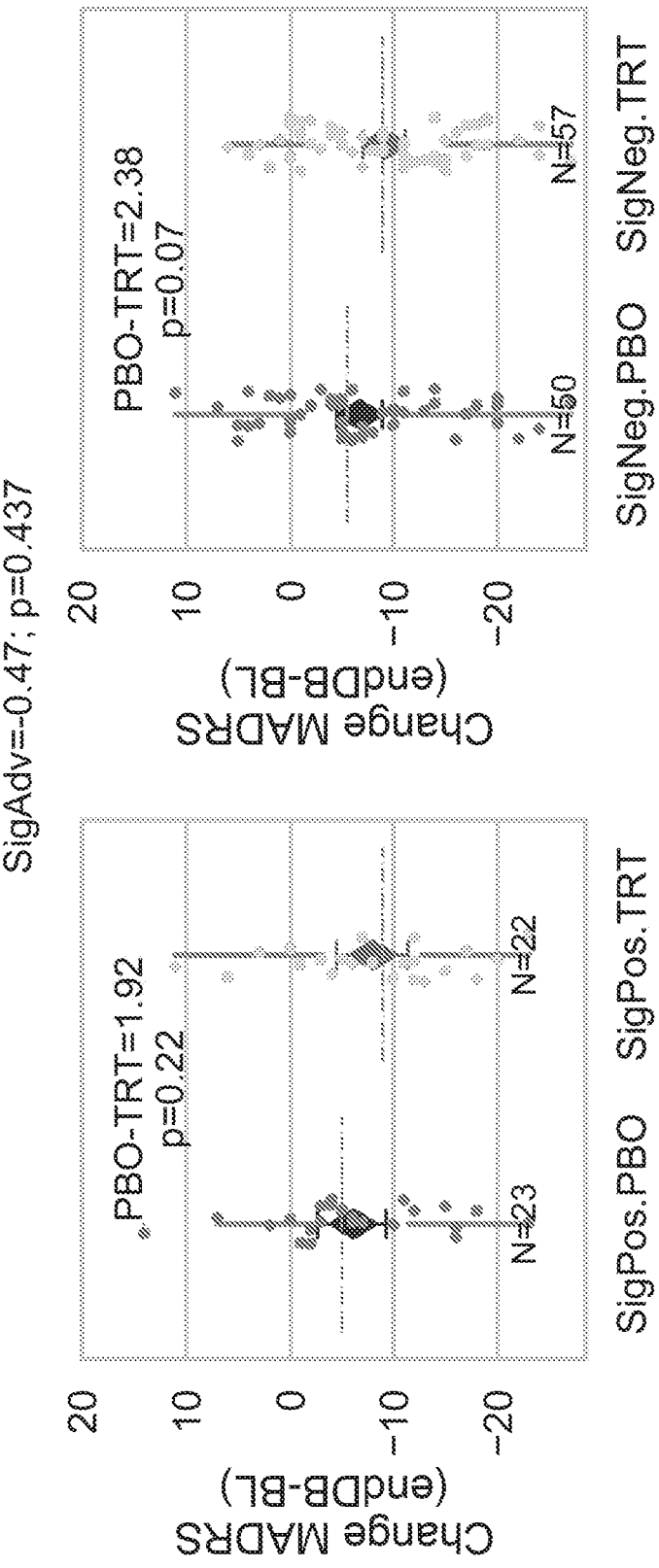

SigAdv=-0.47; p=0.437
Change MADRS (endDB-BL)
20
10
0
−10
−20
PBO-TRT=1.92
p=0.22
N=23
N=22
SigPos.PBO
SigPos.TRT
PBO-TRT=2.38
p=0.07
N=50
N=57
SigNeg.PBO
SigNeg.TRT

Fig. 27A

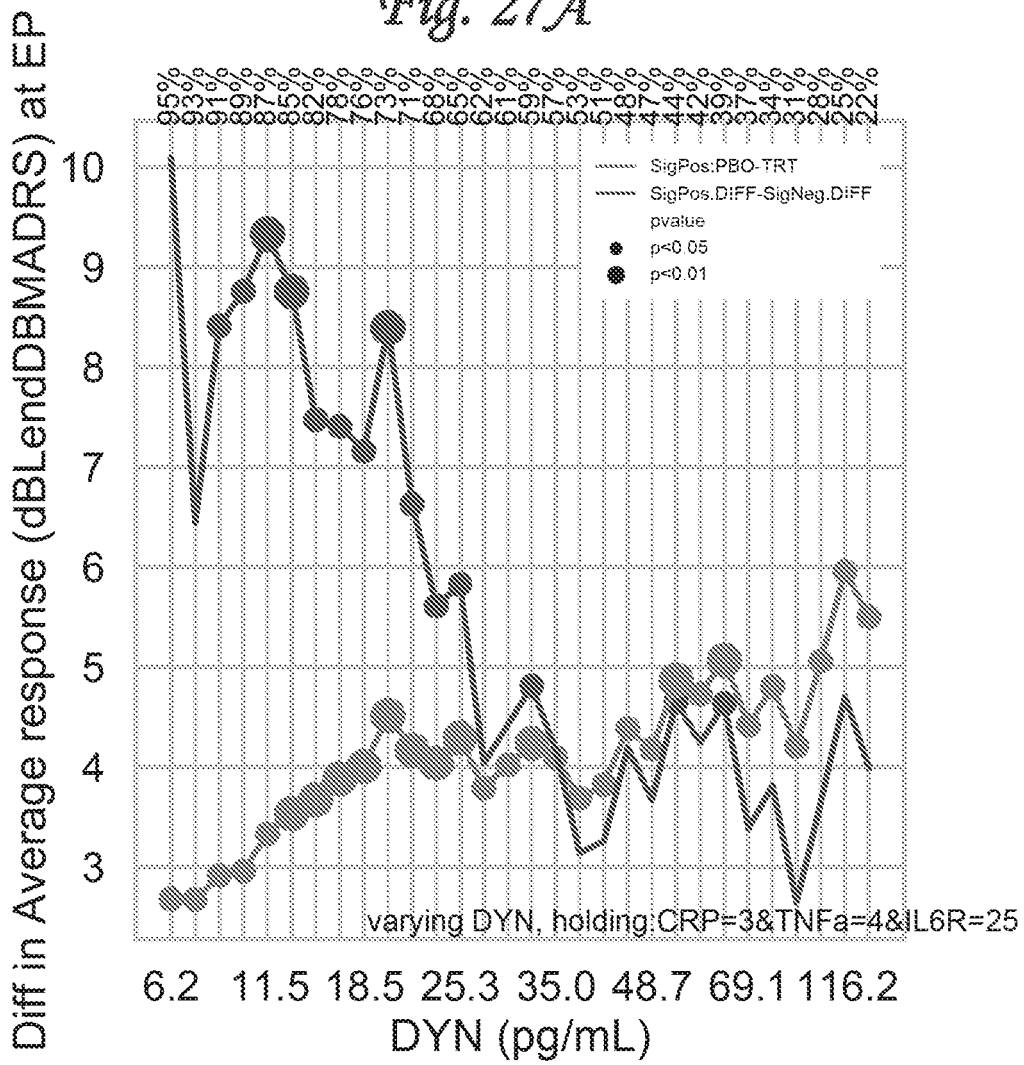

95%
93%
91%
89%
87%
85%
82%
78%
76%
73%
71%
68%
65%
62%
61%
59%
57%
53%
51%
48%
47%
44%
42%
39%
37%
34%
31%
28%
25%
22%
SigPos:PBO-TRT
SigPos.DIFF-SigNeg.DIFF
pvalue
p<0.05
p<0.01
Diff in Average response (dBLendDBMADRS) at EP
10
9
8
7
6
5
4
3
varying DYN, holding CRP=3&TNFa=4&IL6R=25
6.2 11.5 18.5 25.3 35.0 48.7 69.1 116.2
DYN (pg/mL)

Fig. 27B

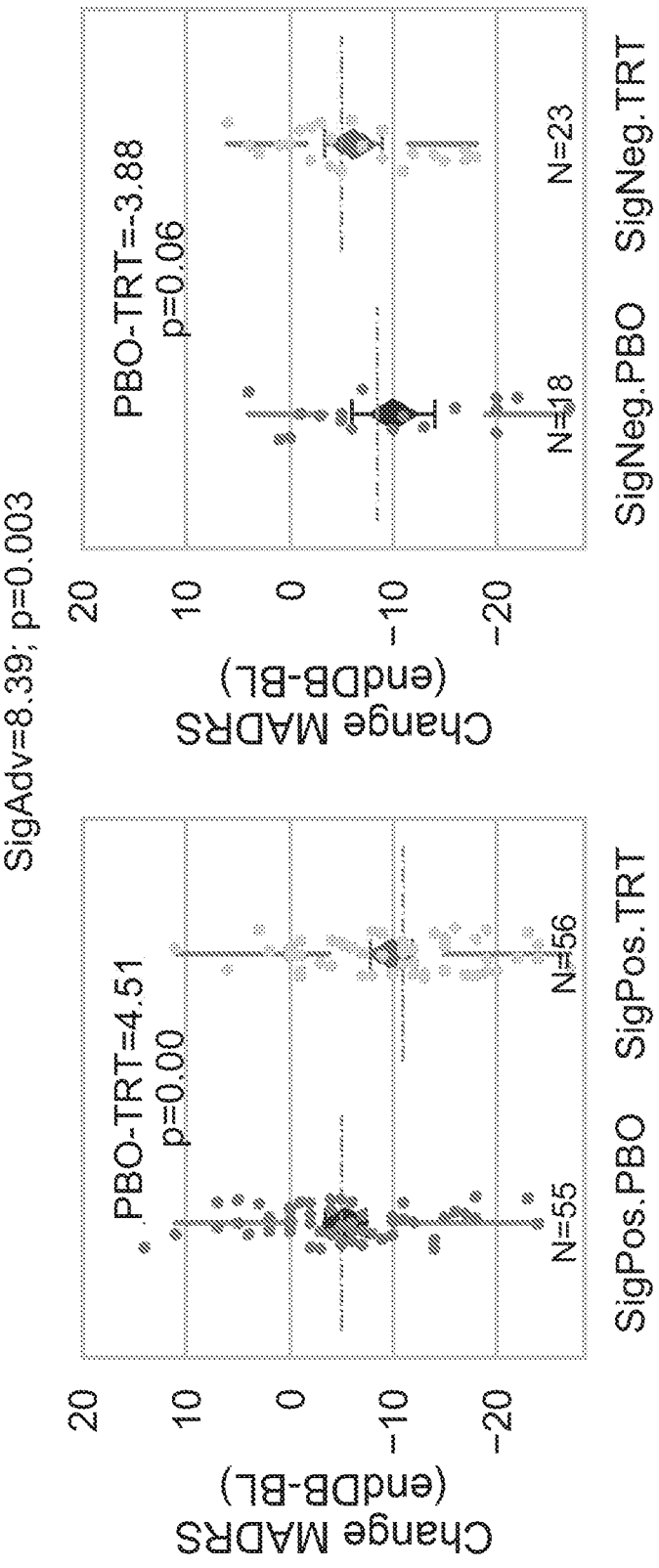

SigAdv=8.39; p=0.003
Change MADRS (endDB-BL)
20
10
0
−10
−20
PBO-TRT=4.51
p=0.00
N=55
N=56
SigPos.PBO
SigPos.TRT
PBO-TRT=-3.88
p=0.06
N=18
N=23
SigNeg.PBO
SigNeg.TRT

Fig. 27C

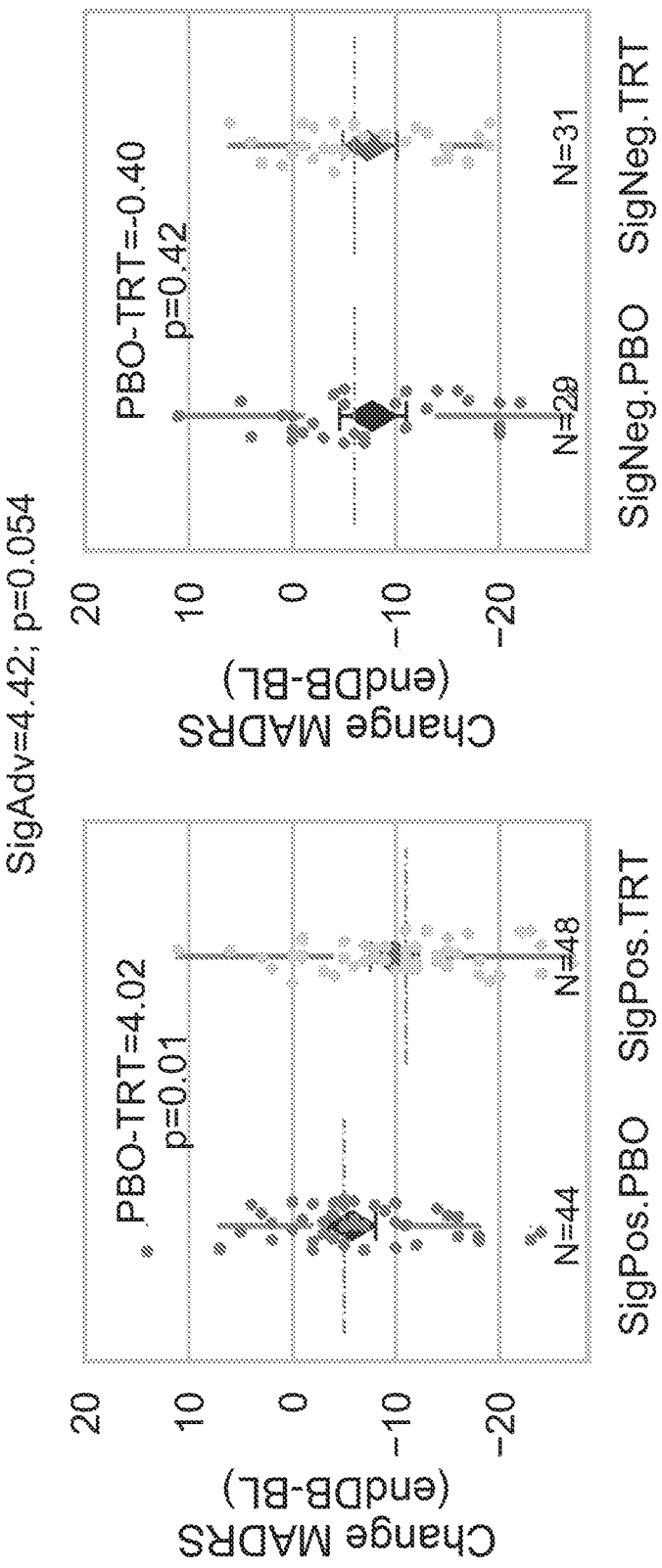

SigAdv=4.42; p=0.054
Change MADRS (endDB-BL)
20
10
0
−10
−20
PBO-TRT=4.02
p=0.01
N=44
N=48
SigPos.PBO
SigPos.TRT
PBO-TRT=-0.40
p=0.42
N=29
N=31
SigNeg.PBO
SigNeg.TRT

Fig. 27D

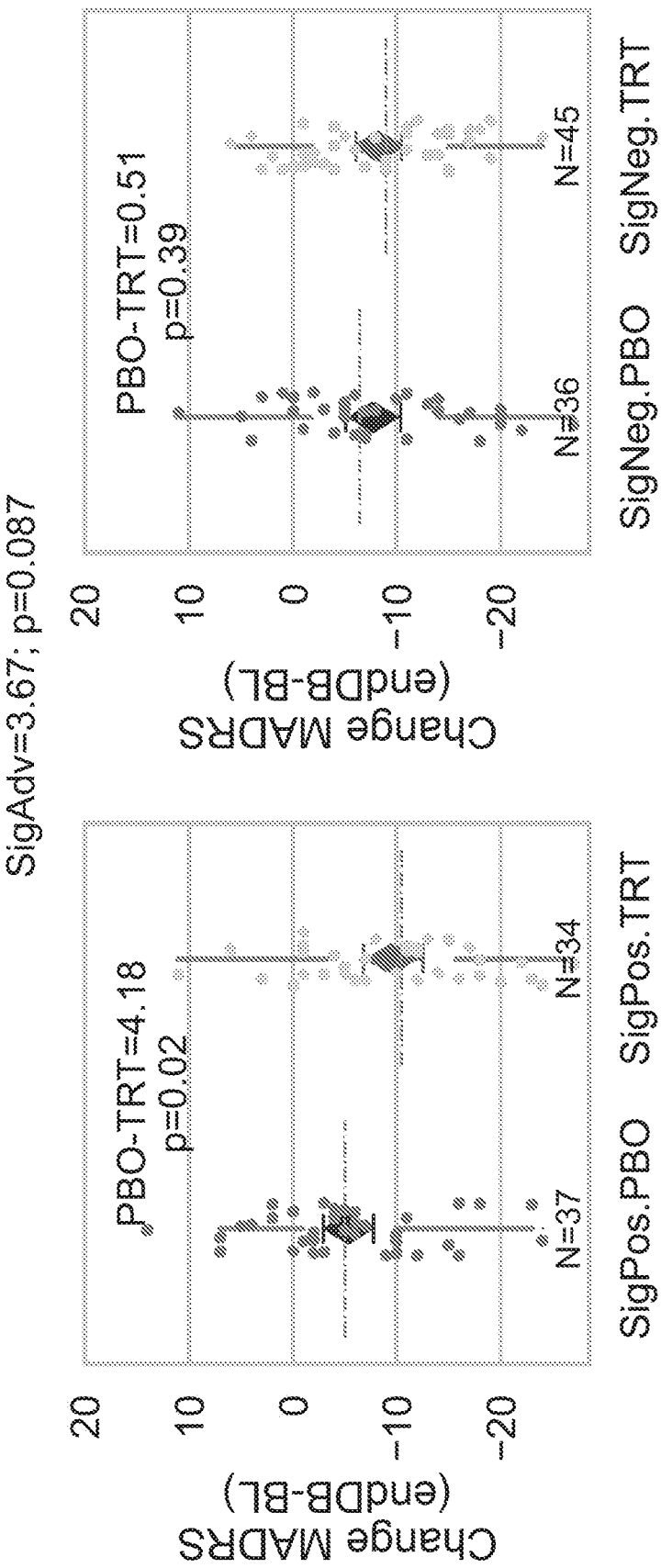

SigAdv=3.67; p=0.087
Change MADRS (endDB-BL)
20
10
0
−10
−20
PBO-TRT=4.18
p=0.02
N=37
N=34
SigPos.PBO
SigPos.TRT
PBO-TRT=0.51
p=0.39
N=36
N=45
SigNeg.PBO
SigNeg.TRT

Fig. 28A

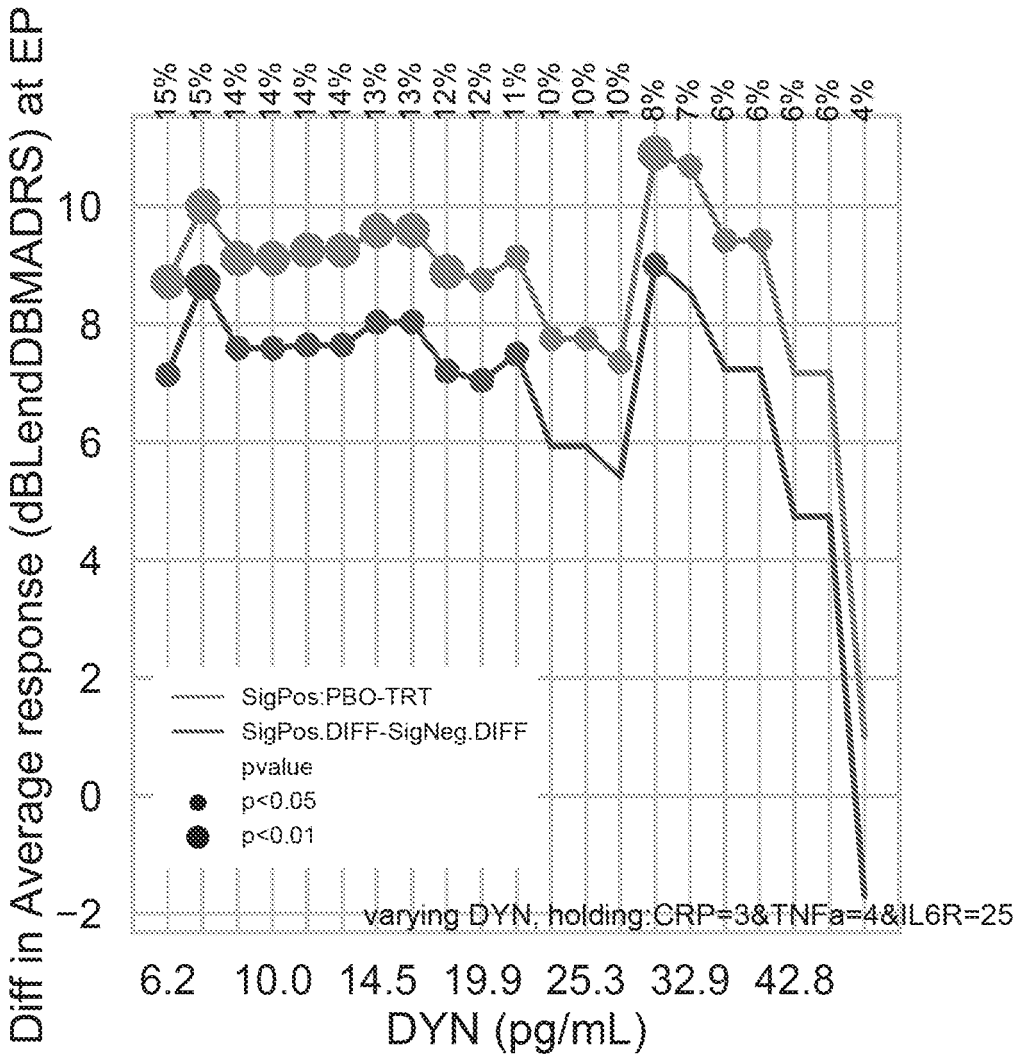

Diff in Average response (dBLendDBMADRS) at EP
15% 15% 14% 14% 14% 14% 13% 13% 12% 12% 11% 10% 10% 10% 8% 7% 6% 6% 6% 6% 4%
10
8
6
4
2
0
−2
SigPos:PBO-TRT
SigPos.DIFF-SigNeg.DIFF
pvalue
p<0.05
p<0.01
varying DYN, holding:CRP=3&TNFa=4&IL6R=25
6.2 10.0 14.5 19.9 25.3 32.9 42.8
DYN (pg/mL)

Fig. 28B

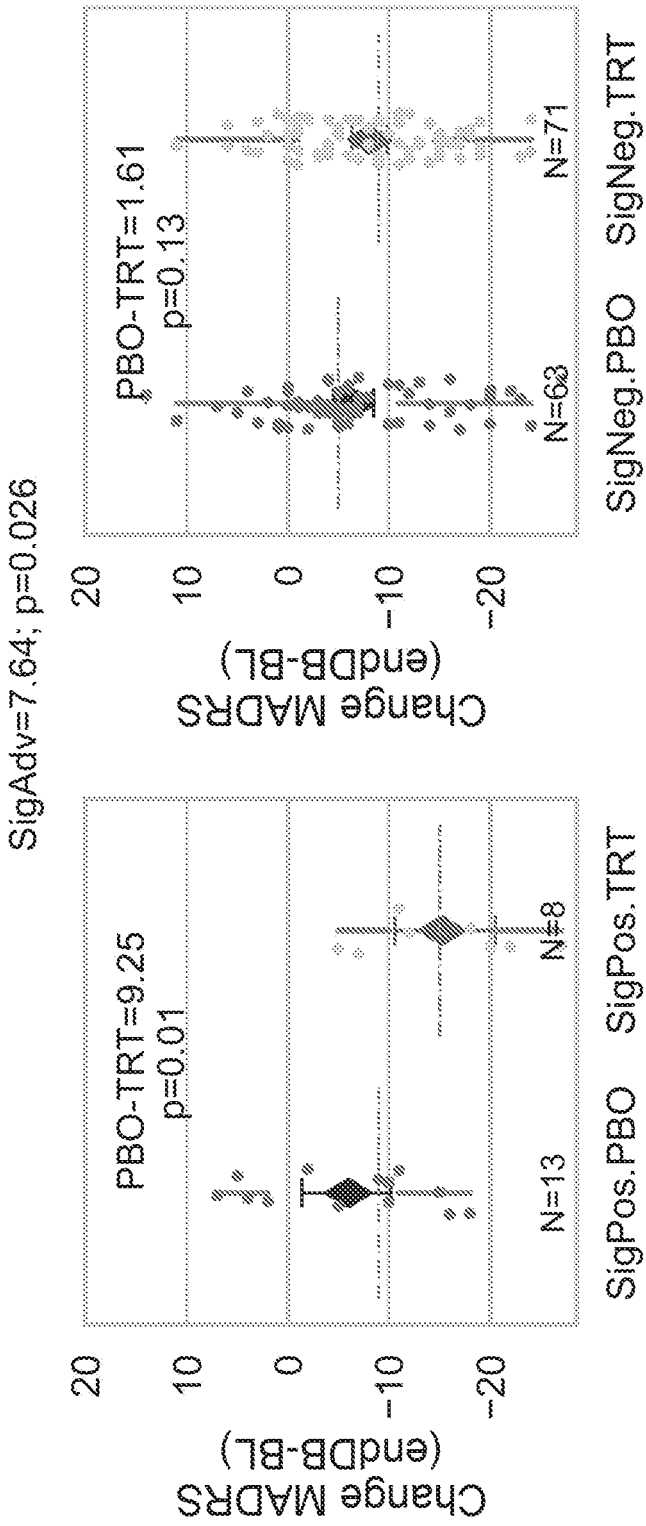

SigAdv=7.64; p=0.026
Change MADRS (endDB-BL)
20
10
0
−10
−20
PBO-TRT=9.25
p=0.01
N=13
N=8
SigPos.PBO
SigPos.TRT
PBO-TRT=1.61
p=0.13
N=63
N=71
SigNeg.PBO
SigNeg.TRT

Fig. 29A

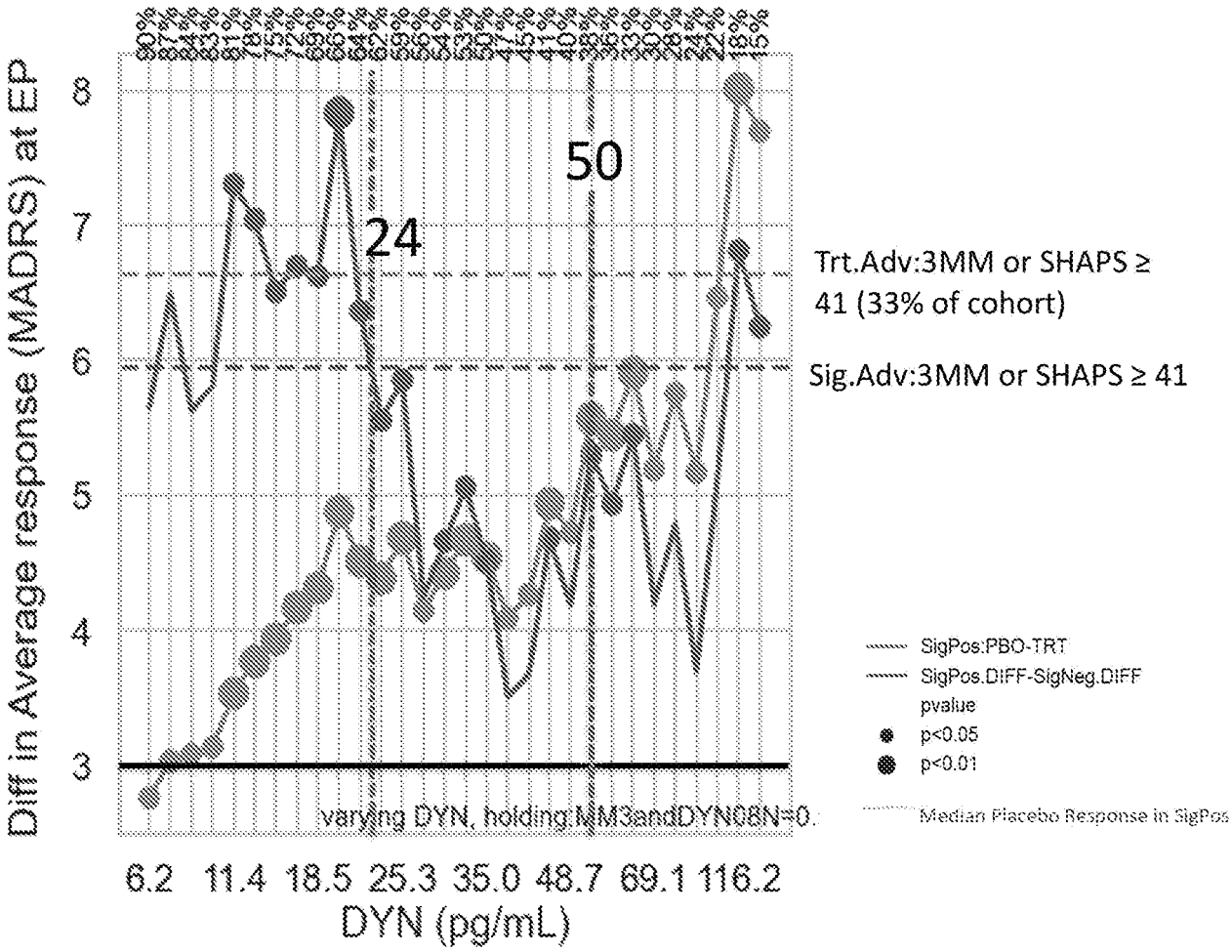

Diff in Average response (MADRS) at EP
3
4
5
6
7
8
24
50
varying DYN, holding MM3andDYN08N=0.
6.2 11.4 18.5 25.3 35.0 48.7 69.1 116.2
DYN (pg/mL)
Trt.Adv:3MM or SHAPS ≥ 41 (33% of cohort)
Sig.Adv:3MM or SHAPS ≥ 41
SigPos:PBO-TRT
SigPos.DIFF-SigNeg.DIFF
pvalue
p<0.05
p<0.01
Median Placebo Response in SigPos

Fig. 29B

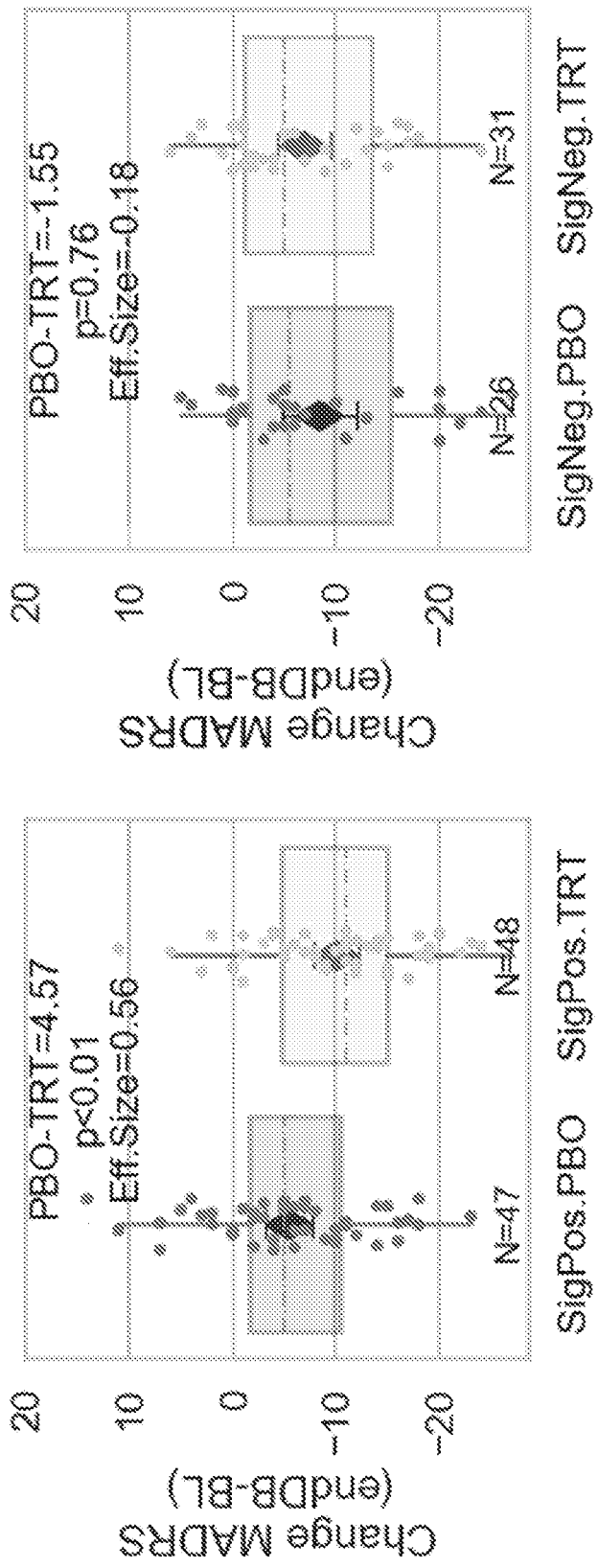
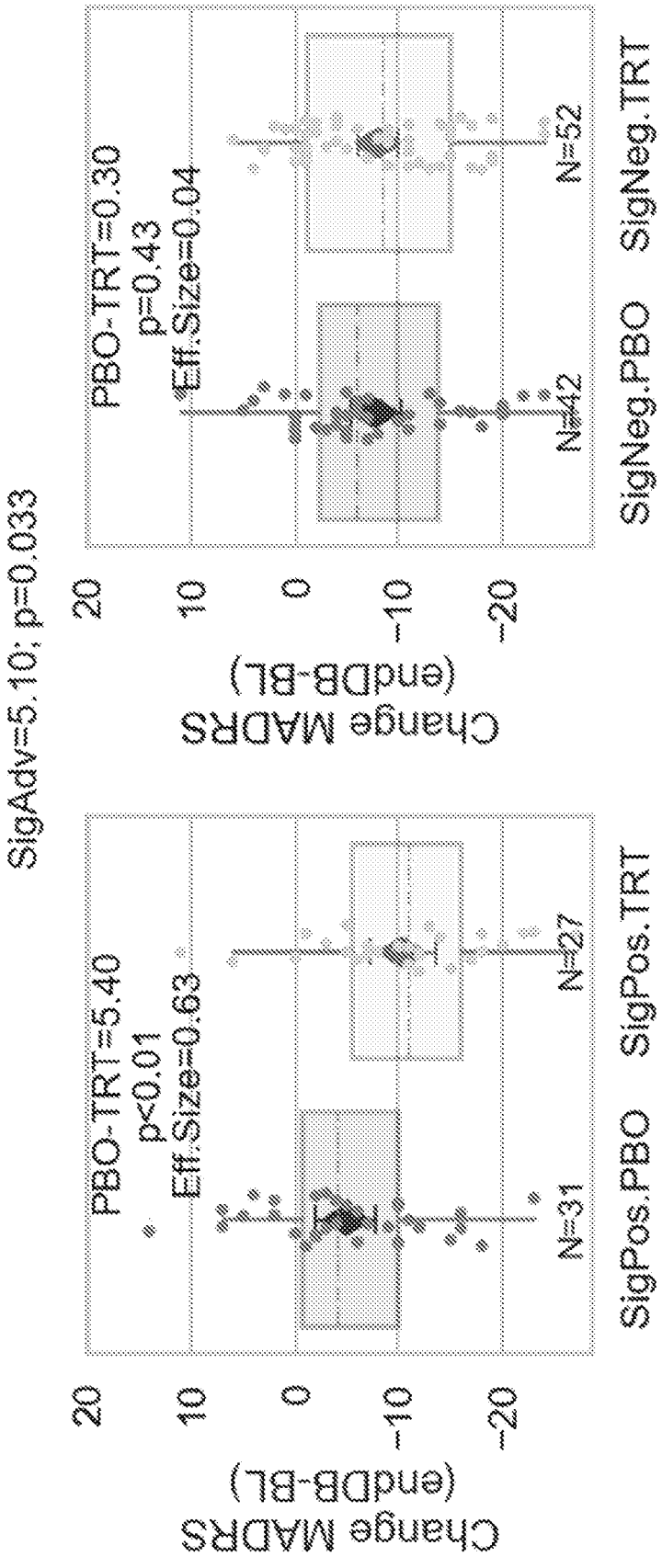

SigAdv=6.12; p=0.013
Change MADRS (endDB-BL)
20
10
0
−10
−20
PBO-TRT=4.57
p<0.01
Eff.Size=0.56
N=47
N=48
SigPos.PBO
SigPos.TRT
PBO-TRT=−1.55
p=0.76
Eff.Size=−0.18
N=26
N=31
SigNeg.PBO
SigNeg.TRT

Fig. 29C


SigAdv=5.10; p=0.033
Change MADRS (endDB-BL)
20
10
0
−10
−20
PBO-TRT=5.40
p<0.01
Eff.Size=0.63
N=31
N=27
SigPos.PBO
SigPos.TRT
PBO-TRT=0.30
p=0.43
Eff.Size=0.04
N=42
N=52
SigNeg.PBO
SigNeg.TRT