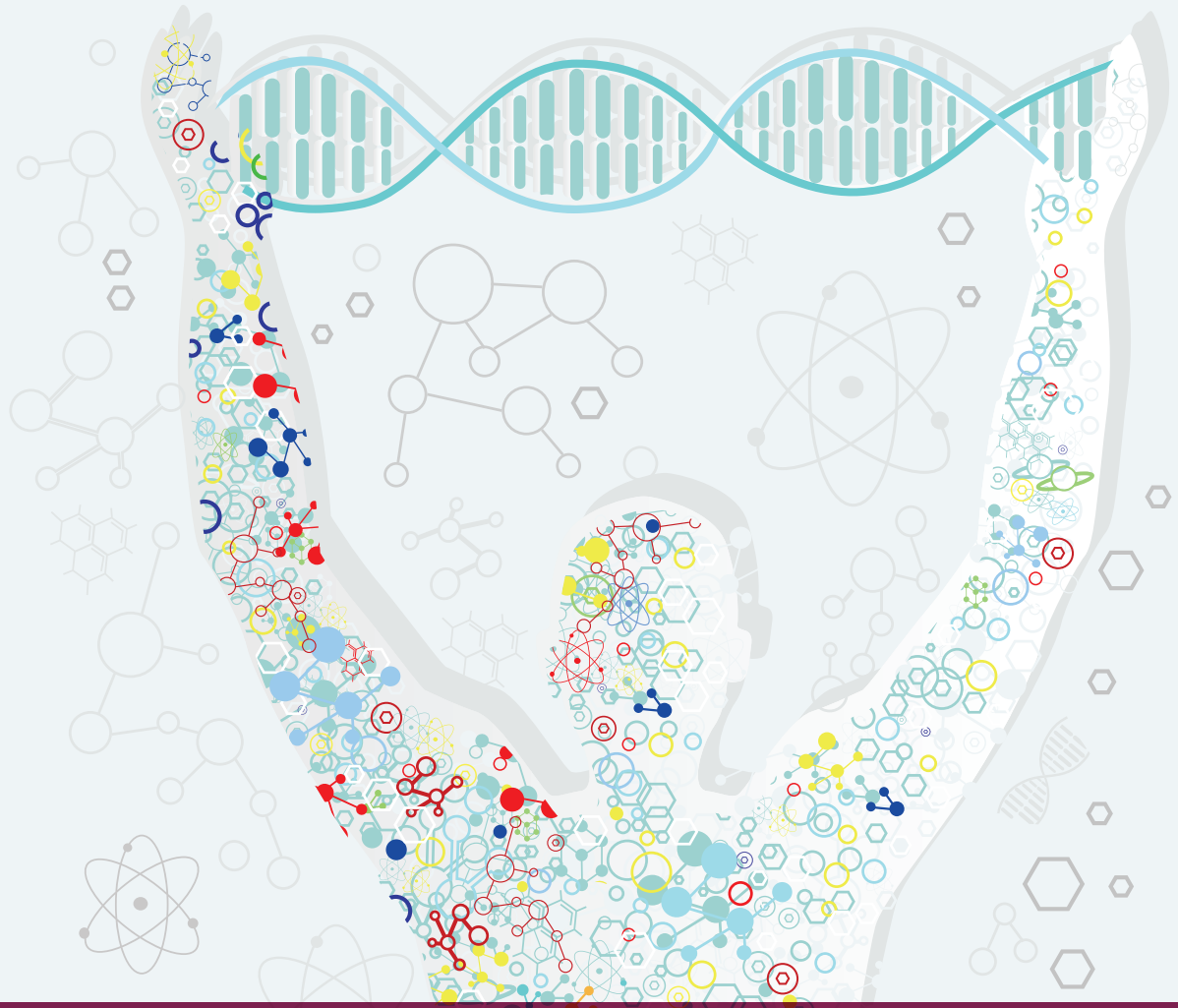
MAY 28-31, 2019 | FAIRMONT SCOTTSDALE PRINCESS



ASCP 2019 Annual Meeting

Innovations in Personalized Medicine: From Biomarkers to Patient-Centered Care

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POSTER ABSTRACT BOOK

Wednesday, May 29, 2019

Poster Session I with Lunch

W1. THE NATIONAL PREGNANCY REGISTRY FOR PSYCHIATRIC MEDICATIONS: EFFECTS OF FETAL EXPOSURE TO ARIPIPRAZOLE ON RISK FOR MAJOR MALFORMATIONS

*Marlene Freeman**[1], Adele Viguera[2], Lina Goez-Mogollon[1], Taylor Church[1], Sara McElheny[1], Amanda Young[1], David Chitayat[3], Sonia Hernández-Díaz[4], Lee Cohen[1]*

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Abstract: Background: Atypical antipsychotics are commonly prescribed to women of reproductive age for the treatment of a number of psychiatric disorders. To investigate the reproductive safety of this class of medications, the National Pregnancy Registry for Atypical Antipsychotics, now the National Pregnancy Registry for Psychiatric Medications (NPRPM) was established in 2008 at Massachusetts General Hospital. While preliminary data from the NPRPM have not demonstrated a significantly increased risk of major malformations following in utero exposure to atypical antipsychotics as a class, the reproductive safety of individual medications has yet to be systematically investigated from this initiative. Importantly, data are limited pertaining to the reproductive safety data of individual medications within this class. Aripiprazole has become one of the most widely used psychiatric medications for several indications that affect reproductive aged women. The goal of current analyses is to determine the risk of major malformations among infants exposed to aripiprazole during pregnancy compared to a group of infants whose mothers had histories of psychiatric morbidity but who did not use an atypical antipsychotic medication during pregnancy.
Website: www.womensmentalhealth.org/pregnancyregistry Toll-free number: 1-866-961-2388
Methods: Pregnant women ages 18-45 are prospectively followed during pregnancy and the postpartum period using 3 phone interviews, conducted at enrollment, 7 months gestation, and 3 months postpartum. Inclusion in the exposure group requires first-trimester use of aripiprazole during pregnancy. The comparison group is comprised of women who have not taken atypical antipsychotics during pregnancy. Maternal and pediatric medical records are reviewed for the occurrence of major malformations, and identified cases are adjudicated by a blinded dysmorphologist. A scientific advisory board, consisting of experts in the fields of teratology, pharmacoepidemiology, and psychiatry, governs the release of findings.
Results: As of January 8, 2019, total enrollment in the Registry was 1,491 women: 749 women were exposed to atypical antipsychotic medications, and 742 women were in the comparison group. A total of 1028 women had completed the study and were eligible for inclusion in the analysis. Medical records were obtained for 83.5% of study subjects. Among patients exposed in the first trimester to aripiprazole with evaluable data, 7 of 132 subjects' infants had a major malformation. Updated relative and absolute risks of major malformations in the exposed vs. comparison group are forthcoming in May 2019.

Discussion: This study represents the largest prospective analysis of major malformations in infants exposed to aripiprazole, providing needed data to clinicians who prescribe to reproductive age women and to women taking aripiprazole during pregnancy. Numbers remain relatively small and Results are not definitive, but to date there has been limited information to help women understand the risks and benefits of using aripiprazole during pregnancy. The importance of pregnancy registries is underscored by recent FDA guidance, (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ Development Resources/ Labeling/ucm093307.htm), and information about enrollment in the NPRPM can be found in the FDA label for aripiprazole as well as other psychiatric medications.

W2. THE NATIONAL PREGNANCY REGISTRY FOR PSYCHIATRIC MEDICATIONS: EFFECTS OF FETAL EXPOSURE TO ATYPICAL ANTIPSYCHOTICS ON RISK FOR MAJOR MALFORMATIONS

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Abstract: Background: The National Pregnancy Registry for Psychiatric Medications (NPRPM) is a systematic prospective pharmacovigilance program used to collect reproductive safety information in order to inform the care of reproductive aged women with psychiatric disorders. The Registry's scientific advisory board, consisting of experts in the fields of teratology, pharmacoepidemiology, and psychiatry governs the release of findings.

Methods: Data are prospectively collected from pregnant women, ages 18-45 years, with three phone interviews conducted at the time of enrollment, 7 months gestation, and 3 months postpartum. The exposed group is comprised of women who have taken one or more atypical antipsychotics during pregnancy; the comparison group is comprised of women with psychiatric disorders who have not taken this class of medication during pregnancy. Information regarding the presence of major malformations is abstracted from medical records and identified cases of major malformations are adjudicated by a dysmorphologist who is blinded to drug exposure and psychiatric diagnoses.

Results: As of January 8, 2019, 1491 women had enrolled, including 749 in the exposure group and 742 controls. Medical records were obtained for 83% of participants. A total of 1028 women completed the study and were eligible for inclusion in the analysis. Of 546 live births in the exposure group, 16 confirmed major malformations were reported. There were 9 major malformations (4 confirmed and 5 pending final adjudication) in the 482 live births of the control group. No consistent pattern of particular malformations was noted in either group. Updated relative and absolute risks of major malformations in the exposed vs comparison group are forthcoming in May 2019. At the time of previous analysis in 2018, the absolute risk of neonatal major malformations was 3.24% among infants exposed to an atypical antipsychotic during the first trimester and 1.51% among unexposed infants. The estimated risk ratio for major malformations was OR= 2.14 (n=494 exposed, n=464 unexposed, 95% CI: 0.89-5.16).

At the direction of our scientific advisory board and now that the sample size has grown, the absolute and relative risk of major malformations observed in the cohort are ready for an updated analysis.
Conclusion: Assessment of reproductive safety depends on magnitude of the effect as well as uncertainty around the estimate. With increasing enrollment, 2018 data suggest an OR of 2.14 with a narrower 95% CI from 0.89 to 5.16. New risk estimates will be forthcoming in May 2019. To provide context, according to CDC national data, the prevalence of major malformations is approximately 3% of all live births in the United States. In this analysis, the absolute risk of neonatal major malformations was higher (3.24%) in the exposed group and lower (1.51%) in the unexposed group compared to this external reference. This new estimate supports earlier preliminary data indicating that SGAs are unlikely to have a major teratogenic effect.

W3. IS DIMENSIONAL SCALE DATA MORE SENSITIVE THAN CATEGORICAL DATA IN DETECTING AN ANTI-SUICIDALITY EFFICACY SIGNAL?

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Abstract: Introduction: This case study reports the relative merits of using a categorical system and dimensional scale data to track the efficacy of an anti-suicidality treatment.
Methods: A 31-year-old female subject who experienced suicidality almost daily for over 20 years prospectively collected a self-report data series over 80 weeks using the computerized versions of the Sheehan - Suicidality Tracking Scale (S-STS), covering a timeframe before and during effective treatment for suicidality. The S-STS data was mapped into the FDA-CASA 2012 categories and compared to the corresponding seriousness scores, the event count, and the time spent in suicidality, all from the S-STS (a dimensional scale).
Results: The S-STS (dimensional) showed an efficacy signal as early as 2 to 6 weeks. The categorical data took between 14 and 21 weeks to show an efficacy signal. The "most time spent in suicidality per day" measure was more sensitive in showing the efficacy signal (or a loss of efficacy) than, in rank order: 1) the "usual time spent in suicidality per day", 2) the "least time spent in suicidality per day", 3) both the active and passive suicidal ideation event counts, and 4) the highest FDA-CASA 2012 category endorsed for the week. The use of the active and passive suicidal ideation counts of events in combination with the most, least, and the usual time spent in suicidality per day helps in distinguishing between efficacy signal and a signal of worsening.
Conclusion: For every category studied, there was a further delay of between 10 and 17 weeks in the ability of the categorical data to detect the anti-suicidality efficacy signal compared to the corresponding dimensional scale data. This has implications for the design of anti-suicidality treatment efficacy (and safety) outcome measures. The inclusion of a dimensional suicidality scale also increases the likelihood of serendipitously finding anti-suicidality efficacy while investigating candidate drug treatments for other CNS indications. Cerca trova.

W4. THE ALPINE STUDY: A RANDOMIZED, DOUBLE-BLIND, ACTIVE-CONTROLLED STUDY OF STARTING ARIPIPRAZOLE LAUROXIL WITH A 1-

DAY INITIATION REGIMEN IN ACUTELY ILL PATIENTS WITH SCHIZOPHRENIA

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Abstract: Background: Aripiprazole lauroxil (AL), a prodrug of aripiprazole, is a long-acting injectable (LAI) atypical antipsychotic that can be initiated using 21 days of oral aripiprazole supplementation or using ALNCD, coupled with a single 30 mg oral aripiprazole tablet in a 1-day regimen.(1,2) The 1064 mg dose strength of AL allows a dose interval of 2-months. The main objective of this study was to evaluate the efficacy and safety of the 1-day initiation regimen (ALNCD + oral aripiprazole 30 mg) followed by AL 1064 mg in patients hospitalized for an acute exacerbation of schizophrenia.
Methods: The phase 3 randomized, double-blind, double-dummy ALPINE study (NCT03345979) included hospitalized adult patients with schizophrenia experiencing acute symptoms. Patients were randomized 1:1 to receive either the ALNCD 1-day regimen on Day 1 followed by AL 1064 mg on Day 8 and every 8 weeks thereafter, or an active control agent (paliperidone palmitate [PP]), administered using the PP standard 1-week initiation regimen (PP 234 mg on Day 1 and PP 156 mg on Day 8) and then continued with 156 mg every 4 weeks. Patients were discharged after 2 weeks of hospitalization and followed every 4 weeks through Week 25. The primary endpoint was evaluation of within-group changes in PANSS total score from baseline to Week 4 using observed cases. Secondary analyses included within-group changes from baseline to Week 9 and Week 25. Additional secondary analyses were between-group comparisons at Weeks 4, 9, and 25 using MMRM models. Safety and tolerability were assessed by monitoring adverse events (AEs), physical exams, laboratory testing, and standard movement disorder scales.
Results: The entire study population included 200 participants (AL, n=99; PP, n=101) that, at baseline, were mostly male (74.5%) with a mean age of 43.4 years and a mean (SD) PANSS score of 94.5 (8.8). Most patients completed the 4-week acute treatment phase (AL, 79.8%; PP 74.3%). Completion rates at the end of the 25-week treatment period were 56.6% in the AL group and 42.6% in the PP group. Efficacy was assessed in all patients randomized who had ≥1 post-baseline PANSS assessment (AL, n=96; PP, n=99). Within-group changes in PANSS score from baseline to Week 4 were −17.4 in the AL group and −20.1 in the PP group ($P<0.001$ for both groups). PANSS scores continued to decline at Weeks 9 (AL, −19.8; PP, −22.5) and 25 (AL, −23.3; PP, −21.7). In a secondary analysis using MMRM, the confidence intervals for the estimates of mean change from baseline of each group overlapped at Weeks 4, 9, and 25. The three most common AEs in both groups were injection site pain (AL, 17.2%; PP, 24.8%), weight increased (AL, 9.1%; PP, 16.8%), and akathisia (AL, 9.1%; PP, 10.9%). The number of patients who experienced clinically significant weight gain as well as the results from the movement disorder scales and laboratory testing, including prolactin, will be presented.
Conclusions: AL and PP were both effective for the acute treatment of patients with schizophrenia, with significant reductions in PANSS at Week 4 ($P<0.001$). Within-group reductions in PANSS were also significant at Weeks 9 and 25. Both regimens were well tolerated, and there were no new safety concerns observed. We conclude that both treatment regimens can be effectively used to start patients in the hospital setting and continue treatment in the outpatient setting.

Funding Statement: This study was funded by Alkermes, Inc.

W5. OPEN-LABEL STUDY OF MAGNETIC SEIZURE THERAPY (MST) FOR SUICIDAL IDEATION IN TREATMENT-RESISTANT DEPRESSION

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Abstract: Background: There is a large, unmet clinical need for effective treatments for suicidal ideation (SI) in psychiatric disease. This is an investigation into the effects of magnetic seizure therapy (MST) on SI in patients with major depressive disorder (MDD). There is very limited data to date on MST as a potential treatment option for SI. Considering the known milder cognitive side effect profile of MST compared to electroconvulsive therapy (ECT), a highly effective treatment for SI, exploration into the treatment effects of MST on SI is warranted.
Methods: This open-label study included patients with MDD (N=86) that were treated with MST over the prefrontal cortex. The primary outcome for this analysis was remission from SI as measured by an endpoint zero score on the Beck Scale for Suicidal Ideation (SSI). Patients who completed the trial per-protocol (maximum of 24 treatment sessions) were included in this analysis. Treatments used 100% stimulator output, at low (25 Hz), medium (50/60 Hz) or high frequency (100 Hz). Cognitive measures were completed throughout the study. Binary logistic regression was used to determine the strength of association between treatment frequency received and remission from SI, in which baseline Hamilton Rating Scale for Depression (HRSD) and SSI scores, age, education level, cumulative Antidepressant Treatment History Form (ATHF) score, age at onset, and duration of the current depressive episode were accounted for.
Results: Remission from SI was clinically significant for patients receiving low frequency MST (55.2%) and moderate frequency MST (54.5%). Moderate frequency MST was significantly associated with remission from SI compared to high frequency MST (OR = 18.3, 95% CI = 1.2-272.7, p = .04). There was no significant difference between high frequency MST and low frequency MST for remission from SI (OR= .271, 95% CI = .07-1.042, p = .06).
Conclusion: MST appears to be a safe and effective treatment for SI in MDD at moderate and low treatment frequencies. Future studies should compare this treatment option for SI in a randomized fashion against traditional ECT. Treatment of SI across other DSM diagnostic categories with MST should also be explored.

W6. USING RESTING STATE INTRINSIC NETWORK CONNECTIVITY TO IDENTIFY SUICIDE RISK IN MOOD DISORDERS

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Abstract: Background: Little is known about the neural substrates of suicide risk in mood disorders. Improving the identification of biomarkers of suicide risk in mood disorders could lead to more targeted treatments to reduce risk. The aim of this study was to use resting-state intrinsic network connectivity to identify individuals at risk for suicide, as indicated by a history of suicide-related behavior (SB).
Method: A cross-sectional study was conducted at two urban communities with medical centers. Resting-state functional connectivity was examined within intrinsic networks, including the cognitive control network (CCN), a system involving frontoparietal and dorsal attention networks that is critical for problem-solving and executive functioning; the salience and emotional network (SEN), which is active in response to stimuli relevant to current goals, including emotional stimuli, and involves limbic and ventral attention networks; and the default mode network (DMN), which is active during self-focused thought and when not engaged with external stimuli. Two fMRI scans were conducted approximately two months apart to examine stability and reliability of group differences over time. Participants (Mage = 21.88, SD = 2.70; 67% female) were 112 individuals with a mood disorder with no history of suicide-related behavior (NSB), 18 young adults with a mood disorder who had a history of SB (as indicated by endorsing a past suicide attempt), and 82 healthy comparison participants (HC). Strength of resting-state connectivity of intrinsic networks was compared between SB, NSB, and HC groups.
Results: Several regions ($k > 57$, $p < .005$) were identified in the three networks in connectivity to fronto-parietal regions, including right middle and inferior frontal gyrus and inferior parietal lobule, that were significantly different in SB relative to NSB and HC groups for both within-network connectivity (in the CCN) and cross-network connectivity (DMN-CCN and DMN-SEN). Furthermore, deficits in connectivity (exhibited by the SB group) between the right middle frontal gyrus and the CCN were associated with poorer inhibitory control on a behavioral go/no-go task, and deficits in connectivity between the right middle frontal gyrus and DMN were associated with higher levels of self-reported rumination. Intrinsic network connectivity effects were stable over time and identified group membership with good accuracy, sensitivity, and specificity.
Conclusions: These results suggest that individuals with a history of SB may show distinct patterns of intrinsic network connectivity, even when compared to those with mood disorders and no history of SB. These deficits may underlie candidate behavioral risk factors for suicidal ideation and suicidal behavior, including rumination and inhibitory control deficits. Resting-state fMRI may serve as a promising tool for identifying subtypes of patients with mood disorders who are at risk for suicidal behavior.

W7. BREMELANOTIDE FOR HYPOACTIVE SEXUAL DESIRE DISORDER IN THE RECONNECT STUDIES: ANALYSIS OF BASELINE FREE TESTOSTERONE LEVEL QUARTILE SUBGROUPS

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Abstract: Objectives: Hypoactive sexual desire disorder (HSDD) is the most prevalent form of female sexual dysfunction in the United States and is characterized by a decrease or lack of sexual desire accompanied by distress. Bremelanotide, a melanocortin-4-receptor (MC4R) agonist and an analog of the endogenous neuropeptide α-melanocyte stimulating hormone, is an investigational drug that is currently being evaluated in premenopausal women with HSDD. The RECONNECT studies, which comprised two identically designed, phase 3 clinical trials, demonstrated that subcutaneous self-administration of bremelanotide significantly improved sexual desire and decreased personal distress in premenopausal women with HSDD. In this analysis, bremelanotide efficacy was assessed across baseline testosterone level quartile subgroups.
Materials and Methods: The RECONNECT studies comprised two identically designed studies with a 24-week, randomized, double-blind, placebo-controlled core study phase and an optional 52-week open-label safety extension phase. Participants self-administered bremelanotide 1.75 mg or placebo subcutaneously using an autoinjector, on demand, prior to sexual activity. A total of 1202 subjects were included in the integrated and subgroup analyses. Subjects were divided into subgroups according to free (bioavailable) testosterone level at screening. Free testosterone levels were calculated using baseline total testosterone, sex hormone-binding globulin (SHBG), and albumin levels. For the subgroup analysis, subjects with total testosterone levels >96 ng/dL or SHBG levels >170 nmol/L at screening were excluded, as those were above the normal physiological range. Efficacy was assessed using the co-primary endpoints of change from baseline to the end-of-study (EOS) for the Female Sexual Function Index-Desire domain (FSFI-D) and the Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO) Item 13 scores.
Results: In the total integrated population of RECONNECT (N=1202), differences in mean change in FSFI-D and FSDS-DAO Item 13 from baseline to EOS (bremelanotide-placebo) were 0.35 and -0.33, respectively ($P<0.0001$ for both endpoints). Differences in mean FSFI-D changes from baseline to EOS for each free testosterone level quartile were 0.34 (0.07-0.31 ng/dL; N=130-131), 0.29 (>0.31-0.47 ng/dL; N=134-137), 0.44 (>0.47-0.71 ng/dL; N=120-127), and 0.49 (>0.71-2.07 ng/dL; N=123-131). Differences in mean FSDS-DAO Item 13 changes for each free testosterone level quartile were 0.39 (0.07-0.31 ng/dL), -0.36 (>0.31-0.47 ng/dL), -0.33 (>0.47-0.71 ng/dL), and -0.30 (>0.71-2.07 ng/dL). Significantly greater improvements in FSFI-D ($P\leq0.0227$) and FSDS-DAO Item 13 ($P\leq0.0399$) were achieved with bremelanotide versus placebo in all free testosterone level quartiles.
Conclusions: In the RECONNECT studies, bremelanotide demonstrated consistent efficacy in premenopausal women with HSDD regardless of baseline bioavailable testosterone levels. Bremelanotide significantly increased sexual desire as measured by FSFI-D and decreased distress related to low sexual desire as measured by FSDS-DAO Item 13 across all baseline testosterone level quartile subgroups.

W8. EFFICACY AND SAFETY OF LURASIDONE IN CHILDREN AND ADOLESCENTS WITH BIPOLAR DEPRESSION: RESULTS FROM A 2-YEAR OPEN-LABEL EXTENSION STUDY

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Abstract: Background: Bipolar I disorder frequently has an early onset, with an estimated prevalence rate of 1.8% in pediatric populations. Early onset is associated with a high degree of chronicity; however, limited data are available on the long-term effectiveness of drug therapies in pediatric populations. The aim of the current study was to evaluate the long-term safety and efficacy of lurasidone in children and adolescents with bipolar depression.
Methods: Patients 10-17 years with bipolar I depression were randomized to 6 weeks of double-blind (DB) treatment with lurasidone or placebo. Patients who completed the study were eligible to enroll in a 2-year, open-label (OL) extension study in which patients were continued on flexibly-dosed lurasidone (20-80 mg/d; LUR-LUR) or switched from placebo to lurasidone (PBO-LUR). The primary efficacy measure was the Children's Depression Rating Scale, Revised (CDRS-R); response was defined as ≥50% reduction from DB baseline in the CDRS-R total score.
Results: A total of 306 patients completed the 6-week DB study and entered the extension study; 195 (63.7%) completed 52 weeks, and 168 (54.9%) completed 104 weeks of treatment. Mean CDRS-R total score at DB baseline was 59.4 in patients treated with lurasidone, and 58.7 in patients treated with placebo; and mean CDRS-R total score at OL baseline (after 6 weeks of DB treatment) was 36.6 in the LUR-LUR group and 41.9 in the PBO-LUR group. For the total sample of patients in the OL study, mean change (from OL baseline) in the CDRS-R score was -13.4 at week 52 and -16.4 at week 104. Responder rates were 51.0% at OL baseline (64.5% for LUR-LUR; 36.9% for PBO-LUR), 88.4% at week 52, and 91.1% at week 104. During OL treatment with lurasidone, 31 patients (10.1%) discontinued due to an adverse event. The most commonly reported events were headache (23.9%), nausea (16.4%), and somnolence (9.8%). OL treatment with lurasidone was associated with few effects on metabolic parameters or prolactin. Mean change from DB baseline in weight was +4.25 kg at week 52 (vs. an expected weight gain of 3.76 kg based on CDC normative data), and +6.75 kg at week 104 (vs. CDC expected weight gain of 6.67 kg).
Conclusions: In children and adolescents with bipolar depression, up to 2 years of treatment with lurasidone was generally well-tolerated, with relatively low rates of study discontinuation. Treatment with lurasidone was associated with few effects on weight, metabolic parameters or prolactin. Continued improvement in depressive symptoms was observed during long-term treatment with lurasidone.
Clinicaltrials.gov identifier: NCT01914393
Funded by Sunovion Pharmaceuticals Inc.

W9. LONG-TERM EFFICACY OF LURASIDONE IN ANTIPSYCHOTIC-NAïVE VS. ANTIPSYCHOTIC-EXPOSED ADOLESCENTS WITH SCHIZOPHRENIA: POST-HOC ANALYSIS OF A TWO YEAR, OPEN-LABEL STUDY

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Abstract: Background: Early-onset schizophrenia is characterized by greater severity and more functional impairment than adult-onset schizophrenia. Few studies have prospectively evaluated short- or long-term antipsychotic efficacy in treatment-naïve (vs. previously treated)

first-episode schizophrenia. The aim of this post-hoc analysis was to evaluate the long-term efficacy of lurasidone in antipsychotic-naïve, first-episode adolescents with schizophrenia.
Methods: Patients aged 13-17 years with schizophrenia, and a PANSS total score ≥70 and <120, were randomized to 6 weeks of double-blind (DB), fixed-dose treatment with lurasidone (40 or 80 mg/day) or placebo. Six-week completers were eligible to enroll in an open-label (OL), flexible dose 2-year lurasidone treatment study. Efficacy over 104 weeks of OL treatment with lurasidone was evaluated for 2 patient groups based on treatment status prior to entering the initial DB study (treatment-naïve [TN] vs. treated previously [TP]). Treatment-naïve was defined as never having received antipsychotic treatment prior to randomization. Efficacy measures included the PANSS total score and the Clinical Global Impressions-Severity (CGI-S) score. Treatment response was defined as ≥20% reduction from baseline in PANSS total score.
Results: A total of 50 TN and 221 TP patients completed the 6-week DB study and entered the extension study; and 30 (60.0%) TN and 126 (57.0%) TP patients completed 104 weeks. In the total ITT population, larger lurasidone treatment effects (vs. placebo) were noted at DB endpoint in the PANSS total score in the TN group (-25.0 vs. -14.4; P<0.02; effect size [ES]=0.75) compared to the TP group (-17.3 vs. -10.0; P<0.001; ES=0.45); and in the CGI-S score in the TN group (-1.07 vs. -0.28; P=0.002; ES=0.97) compared to the TP group (-0.91 vs. -0.55; P=0.005; ES=0.38). During OL treatment with lurasidone, the magnitude of improvement from DB baseline continued to be somewhat larger in the PANSS total score for TN patients (n=38) vs. TP patients (151) at week 52 (-32.6 vs. -28.1) and week 104 (-33.6 vs. -29.2); and in the CGI-S score for TN vs. TP patients at week 52 (-1.8 vs. -1.5) and week 104 (-1.8 and -1.5). Responder rates during treatment with lurasidone were 72.0% (TN group) and 61.1% (TP group) at OL baseline (number-needed-to-treat [NNT]=10), 100% and 90.1% at week 52 [NNT=11], and 100% and 88.9% at week 104 [NNT=11]. During OL treatment, the most common adverse events for TN vs. TP patients were headache (26.0% vs. 23.5%), nasopharyngitis (24.0% vs. 5.4%), and nausea (16.0% vs. 11.8%).
Discussion: In this post-hoc analysis of a 2-year OL extension study, antipsychotic-naïve adolescents with schizophrenia responded well to treatment with lurasidone at doses of 40 or 80 mg/d. TN patients achieved greater improvement than TP patients during acute treatment; and these greater treatment effects were largely maintained during 2 years of continued treatment with lurasidone.
Clinicaltrials.gov identifier: NCT01911429.
Funded by Sunovion Pharmaceuticals Inc.

W10. FUNCTIONAL RECOVERY AMONG PATIENTS WITH SCHIZOPHRENIA RECEIVING ARIPIPRAZOLE ONCE-MONTHLY IN A 52-WEEK, OPEN-LABEL, MAINTENANCE STUDY

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Abstract: Background: The primary goal in the treatment of schizophrenia has evolved from acute treatment toward relapse prevention and ultimately recovery. A consensus definition of recovery, however, has not yet been endorsed by the clinical community. The concept of

functional recovery in patients whose symptoms are controlled by medications is generally accepted as the ultimate treatment goal. Long-acting injectable atypical antipsychotics give patients with schizophrenia the best opportunity to achieve functional recovery, because they enhance adherence, provide sustained levels of therapeutic plasma drug concentrations, and a lower side effect profile than typical antipsychotic depots.

Aims: Here we attempt to operationalize functional recovery using secondary efficacy endpoint data on the personal and social performance (PSP) scale from a long-term (52-week), open-label extension study of aripiprazole once-monthly (AOM) (NCT00731549) [1]. Mean PSP scores and mean change in PSP scores are assessed to determine patients' functional status after up to 52 weeks of treatment with AOM.

Methods: Enrolled patients were 18 to 65 years of age with a current diagnosis of schizophrenia (DSM-IV-TR). Patients were naïve to AOM 400 treatment or previously randomized in one of two controlled trials assessing the efficacy and safety of AOM 400 (NCT00705783 [2], NCT00706654 [3]). Patients were stabilized on treatment during an oral stabilization phase; those meeting predefined stabilization criteria continued to 52 weeks of AOM 400 maintenance treatment. PSP scores were obtained at baseline and end of the oral stabilization period (baseline for 52-week maintenance period), and at Weeks 24 and 52 of the maintenance phase. PSP measures socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behaviors which are transformed to a 100-point scale. Scores from 71 to 100 represent mild to no functional difficulty, 30 to 70 represent manifest to marked difficulty, and 1 to 30 represent severe difficulty. Patients with scores >=71 may be considered "functionally recovered". Means and mean change in PSP scores for the observed case efficacy population are reported with standard deviation (SD).

Results: 1,144 patients entered the oral stabilization phase. 1,069 of these entered the AOM maintenance phase with a mean PSP score of 67 (SD=13ogether with 12 patients who entered the maintenance phase directly after completing one of the parent studies (1081 in total). Of the 1081 entering the maintenance phase, mean PSP scores were 68 (SD=12). At Week 24, patients had a mean change in PSP score of □□1 (n=870, SD=7.1with a mean PSP score of 69 (SD=12).At Week 52, patients had a mean change in PSP of 2.2 (n=664, SD=6.6) with a mean PSP score of 70 (SD=12). Of the 664 completers, 315 (47%) had PSP scores >70.

Conclusion: Results show maintenance of function after treatment with AOM for up to 52 weeks where the majority of patients completed 52 weeks of treatment. Nearly half of the completers had a PSP score indicating mild to no functional difficulty, adding to the evidence base for positive functional outcomes in patients treated with AOM [4].

W11. EFFICACY AND SAFETY OF SEP-363856, A NOVEL PSYCHOTROPIC AGENT WITH A NON-D2 MECHANISM OF ACTION, IN THE TREATMENT OF SCHIZOPHRENIA: A 4-WEEK, RANDOMIZED, PLACEBO-CONTROLLED TRIAL

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Abstract: Background: SEP-363856 is a novel psychotropic agent that has shown broad efficacy in animal models of schizophrenia and depression (data-on-file). Its antipsychotic effects appear to be mediated by agonist activity at both trace amine-associated receptor 1 (TAAR1) and 5-HT1A receptors. Notably, SEP-363856 does not bind to any dopaminergic, serotonergic (except 5-HT1A), glutamatergic, or other neuroreceptors thought to mediate the

effects of currently available antipsychotics. The aim of this Phase 2 study was to evaluate the efficacy and safety of SEP-363856 in acutely symptomatic patients with schizophrenia.
Methods: Hospitalized patients aged 18-40 years meeting DSM-5 criteria for schizophrenia (PANSS total score ≥80) were randomized, double-blind, to 4-weeks of flexible-dose SEP-363856 (50 or 75 mg/d) or placebo. Efficacy measures included the Positive and Negative Syndrome Scale (PANSS) total score (primary), PANSS subscale scores, and the Clinical Global Impressions-Severity (CGI-S) score. Change from baseline in primary and secondary measures were analyzed using a mixed model for repeated measures (MMRM) analysis.
Results: Study treatment groups were similar at baseline: SEP-363856 (N=120; male, 64.2%; mean age, 30.0 years; PANSS total score, 101.4) and placebo (N=125; male, 63.2%; mean age, 30.6 years; PANSS total score, 99.7). Least-squares (LS) mean reduction from baseline to week 4 was significantly greater for SEP-363856 vs. placebo on the PANSS total score (-17.2 vs. -9.7; P=0.001; effect size, 0.45), PANSS positive subscale score (-5.5 vs. -3.9; P=0.019; effect size, 0.32), PANSS negative subscale score (-3.1 vs. -1.6; P=0.008; effect size, 0.37), PANSS general psychopathology subscale score (-9.0 vs. -4.7; P<0.001; effect size, 0.51), and the CGI-Severity score (-1.0 vs. -0.5; P<0.001; effect size, 0.52). Discontinuation rates for SEP-363856 vs. placebo were similar overall (21.7% vs. 20.8%) and due to an adverse event (8.3% vs. 6.4%). Change in weight, lipids, glucose and prolactin was similar in SEP-363856 and placebo groups. Adverse events occurring with an incidence ≥2% on SEP363-856 or placebo (with SEP363-856 incidence higher than placebo) were: somnolence (6.7% vs. 4.8%), agitation (5.0% vs. 4.8%), nausea (5.0% vs. 3.2%), diarrhea (2.5% vs. 0.8%), and dyspepsia (2.5% vs. 0%). The proportion of patients who reported any extrapyramidal symptom was 3.3% on SEP-363856 and 3.2% on placebo.
Discussion: In this placebo-controlled study, treatment with SEP-363856, a novel psychotropic agent, was associated with statistically significant and clinically meaningful improvement in schizophrenia symptoms as demonstrated by endpoint change in PANSS total and subscale scores, and CGI-Severity scores. Safety and tolerability findings for SEP-363856 were in general similar to placebo. In particular, SEP-363856 was not associated with extrapyramidal symptoms, akathisia, or hyperprolactinemia, consistent with its non-D2 mechanism of action.
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W12. A COMBINATION OF OLANZAPINE AND SAMIDORPHAN FOR SCHIZOPHRENIA: EFFECTS ON WEIGHT GAIN AND METABOLIC PARAMETERS IN THE PHASE 3 ENLIGHTEN-2 STUDY AND SUBSEQUENT LONG-TERM, OPEN-LABEL SAFETY STUDY

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Abstract: Background: A combination of olanzapine and samidorphan (OLZ/SAM) is in development for schizophrenia. Samidorphan is an opioid receptor antagonist intended to mitigate weight gain and many of the long-term metabolic consequences from olanzapine,

while maintaining olanzapine's antipsychotic efficacy. In a prior 4-week study, OLZ/SAM significantly reduced schizophrenia symptoms vs placebo, similar to olanzapine alone. The phase 3 study, ENLIGHTEN-2, extended findings from previous phase 1 and 2 studies and evaluated weight gain with OLZ/SAM vs olanzapine alone over 24 weeks. Here, we report the effects of OLZ/SAM and olanzapine on weight and metabolic parameters from ENLIGHTEN-2. An interim analysis of weight and metabolic data will be presented from an ongoing, long-term, open-label safety extension study.

Methods: This was a phase 3, multicenter, randomized, double-blind study (ClinicalTrials.gov: NCT02694328) in adults 18–55 years of age with stable Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)-diagnosed schizophrenia suitable for outpatient treatment. Eligible patients were randomized 1:1 to once-daily matching OLZ/SAM (10/10 mg) or olanzapine (10 mg) oral tablets. Doses were titrated up to OLZ/SAM 20/10 mg or olanzapine 20 mg after 1 week (depending on tolerability, could be decreased back to initial dose), and were fixed for the study duration after week 4. Co-primary end points were percent change from baseline (BL) in body weight and proportion of patients with ≥10% weight gain at week 24. Weight, waist circumference, and fasting metabolic laboratory parameters (serum triglyceride [TG], low- and high-density lipoprotein [LDL, HDL], total cholesterol, glucose, and insulin) as well as hemoglobin (Hb) A1c were measured at screening, BL, and throughout the 24 weeks. Upon completion, patients could enroll into the open-label, 52-week safety extension study.

Results: A total of 561 patients were randomized (OLZ/SAM, n=280; olanzapine, n=281); 550 patients received ≥1 dose of study drug, 538 had at least 1 post-BL weight assessment, and 352 (62.7%) completed treatment. The most common reason for discontinuation was adverse events (AEs; 10.9%). BL characteristics were generally similar between groups (mean [SD] age, 40.2 [9.90] years; 73% male; 71% black). Mean (SD) weight at BL was 77.0 (13.7) kg in the OLZ/SAM group and 77.5 (13.5) kg in the olanzapine group. At week 24, least squares (LS) mean (SE) percent change from BL in weight was 4.21 (0.68)% vs 6.59 (0.67)% in the OLZ/SAM vs olanzapine groups, respectively (difference, −2.38 [0.76]%; P=.003). The proportion of patients in the OLZ/SAM and olanzapine groups with ≥10% weight gain was 17.8% vs 29.8% (P=.003; odds ratio [95% CI], 0.50 [0.31–0.80]), respectively. At week 24, LS mean (SE) change from BL in waist circumference was 2.36 cm (0.56) and 4.47 cm (0.55) in the OLZ/SAM and olanzapine groups, respectively (P<.001). No significant differences in metabolic laboratory parameter changes from BL to week 24 were noted between OLZ/SAM and olanzapine alone. Common AEs (≥10%) in the OLZ/SAM and olanzapine group were weight increased (24.8%, 36.2%), somnolence (21.2%, 18.1%), dry mouth (12.8%, 8.0%), and increased appetite (10.9%, 12.3%), respectively.

Discussion: In patients treated with OLZ/SAM, mean percent weight gain was significantly lower, and significantly fewer patients gained ≥10% weight in comparison with olanzapine alone. Metabolic laboratory parameter changes were similar over 24 weeks with OLZ/SAM and olanzapine alone.

W13. BODY AND BRAIN IMAGING CORRELATES OF ANTIPSYCHOTIC (AP)-INDUCED GLUCOSE DYSREGULATION IN AP-NAïVE SCHIZOPHRENIA PATIENTS

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Abstract: Background and Significance: Mortality rates in patients with schizophrenia are two- to three-fold higher than the general population with cardiovascular disease (CVD) identified as the main culprit. Increased authorized and off-label use of atypical antipsychotics (AAP) in children and adolescents necessitate a better understanding of the extent of their side effects in the pediatric population given their association with CVD and diabetes. Evidence supports the notion that regional distribution of body fat, rather than absolute weight, is the critical correlate of the metabolic abnormalities. However, the effect of AAP on these measures is not well understood in medication-naïve adolescents. Furthermore, the relationship between change in visceral adipose tissue and change in brain structure is unknown. This study proposes to obtain abdominal and brain magnetic resonance images (MRI) to quantify the accumulation of hepatic and visceral fat and structural changes in the brain following first-time use of antipsychotics in adolescents.

Methods: Eleven patients (4 female, 7 male) with an average age = 21.4 years participated in the study. Patients were recruited from the Emergency Department and/or inpatient unit for Early Psychosis. All antipsychotics were prescribed and titrated by their primary psychiatrist as required. Medications included risperidone (4), paliperidone (2), lurasidone (2) and aripiprazole (2). All medications were prescribed orally. At baseline and at 12 weeks, we completed a medical history and physical examination (including height, weight and waist circumference), lipid panel, fasting glucose, and an oral glucose tolerance test (OGTT). A 3T MRI was used to image the brain and abdomen with standard clinical protocols. Visceral and subcutaneous fat was measured using 3 axial abdominal MRI slices at the L4-L5 vertebrae level. A chemical-shift-based water-fat pulse sequence called Dixon based on a 3D spoiled gradient echo with multi-peak spectral modeling of fat and correction for T2* variations, was used to measure liver fat content. Subcortical structural volumes, adipose tissue volumes (subcutaneous and visceral components), and liver fat fraction averages are compared across time. Correlations between the imaging measures and anthropometric and biochemical measures were examined.

Results: We identified significant increases in weight (p=0.008), BMI (p=0.007), waist circumference (p=0.037), total cholesterol (p=0.032), and LDL (p=0.005) over 3 months. There was no significant difference in change in liver fat or overall visceral adipose tissue. Right striatum (p=0.025) and right globus pallidus (p=0.013) were found to increase in size after the antipsychotic trial.

Change in weight correlated significantly with the change in waist circumference (p=0.03), post-OGTT (120mins) glucose measurement (p=0.007), visceral adipose tissue (p=0.003) and liver fat (p=0.048). A strong correlation was observed between the change in post-OGTT (120mins) glucose measurement and the change in liver fat (p=0.004). Change in liver fat correlated with change in the volume of the right thalamus (p=0.03) and right amygdala (p=0.01) while change in waist circumference correlated with change in the volume of the left hippocampus (p=0.007) and right globus pallidus (p=0.016).

Conclusion: Our findings suggest that metabolic perturbations due to antipsychotic intake are multi-level and multi-systemic. The results also suggest a link between antipsychotic use, metabolic consequences, and brain structure and function that needs further exploration.

W14. A REAL-WORLD ANALYSIS OF OUTCOMES RELATED TO VETERANS WITH SCHIZOPHRENIA WHO TRANSITIONED TO ONCE-EVERY-3-MONTHS PALIPERIDONE PALMITATE VS. THOSE WHO REMAINED ON ONCE-MONTHLY PALIPERIDONE PALMITATE

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Abstract: Background: Compared to once-monthly paliperidone palmitate (PP1M), once-every-3-months paliperidone palmitate (PP3M) has been associated with longer time to relapse and more dosing flexibility. Prior studies have reported mixed findings on economic benefits of PP3M [1,2]. Hence, the current study aims to compare treatment patterns and economic outcomes among patients who transitioned to PP3M vs those who remained on PP1M.
Objective: Compare treatment patterns, healthcare resource utilization (HRU), and costs between veterans with schizophrenia who transitioned to PP3M vs those who remained on PP1M treatment.
Methods: Included were schizophrenia patients (aged ≥18) from the Veterans' Health Administration database who initiated PP1M during the identification period [IP] (01JAN2015-31MAR2018). The PP3M cohort consisted of PP1M patients who transitioned to PP3M during the IP (index date[ID]: first PP3M date). The PP1M cohort was identified by assigning a random index date (RID) to all PP1M initiators during the period from PP1M initiation through discontinuation (≥45-day gap between injections), drug supply end date, disenrollment, or study period end date, whichever occurred first. Patients who had PP3M use prior to the RID or ID were excluded. Eligible patients had continuous health plan eligibility for the 12-month baseline period; data were assessed until death, disenrollment, or study end. Patients were matched based on propensity score (PS) and duration defined as the time from PP1M initiation date to ID or RID with an allowable difference of ±30 days. Outcomes were compared using Chi-square and t-tests, as appropriate.
Results: The study included 2,973 PP1M and 257 PP3M patients (mean age: 53.7 and 53.1 years, respectively). PS matching yielded 111 matched pairs. During follow-up, adherence (proportion of days covered ≥80%) to any agent was higher among the PP3M cohort (78.4% vs 57.7%, p=0.0009). Relative to those initiating PP3M, patients continuing on PP1M experienced longer all-cause inpatient stays (0.7 vs 0.2 days, p=0.0354) and lower per patient per month (PPPM) all-cause pharmacy costs ($948 vs $1,332; p=0.0004). Compared to PP3M cohort, the PP1M cohort incurred higher inpatient costs but the difference was not statistically significant ($1,113 vs $460; p=0.0617). PP1M patients had more all-cause outpatient (4.1 vs 4.0; p=0.8335) and pharmacy visits (2.6 vs 2.3; p=0.2893) and incurred higher outpatient ($2,078 vs $1,974; p=0.6534), total medical ($3,191 vs $2,434; p=0.1010), and total costs PPPM ($4,140 vs $3,767; p=0.4433); however, the results were not statistically significant.

Conclusion: Compared to veterans who remained on PP1M treatment, those who transitioned to PP3M from PP1M may have experienced an improvement in clinical outcomes related to schizophrenia while remaining cost-neutral.

W15. EFFECT OF ARIPIPRAZOLE ONCE MONTHLY ON PERSONAL AND SOCIAL FUNCTIONING OF PATIENTS WITH SCHIZOPHRENIA: POST-HOC ANALYSES OF ACUTE AND LONG-TERM MAINTENANCE STUDIES

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Abstract: Aims: To evaluate the effect of Aripiprazole Once-Monthly 400 mg (AOM 400) on functioning in patients with schizophrenia, post-hoc analyses on personal and social functioning from the acute setting and open-label extension studies were conducted
Methods: Post-hoc analyses were conducted on data from Study 291 (NCT01663532), a 12-week, randomized, double-blind, placebo-controlled trial of AOM 400 in patients experiencing an acute psychotic episode, and Study 248 (NCT00731549), a 52-week open-label extension of two randomized, controlled trials of AOM 400 as maintenance therapy. Assessment of functioning was made using the Personal and Social Performance (PSP) scale. For Study 291, Results were also stratified by age (≤35 years or >35 years), and within-group difference in least squares mean (LSM) change from baseline for AOM 400 vs placebo was calculated in the efficacy sample to determine treatment effect using mixed-model repeated measures and analysis of covariance of observed case data. For Study 248, mean changes from baseline in PSP total score and across 4 domain subscales were tabulated by visit for the open-label AOM 400 maintenance phase and analyzed among observed cases in the efficacy sample.
Results: In Study 291, 340 patients were included in the analysis (AOM 400, n=168 [n=49 aged ≤5 years, n=119 aged >35 years]; placebo, n=172 [n=54 aged ≤35 years, n=118 aged >35 years]). LSM (SE) change from baseline in PSP total score was significantly greater with AOM 400 compared with placebo at week 12 (13.0 [1.2] vs 5.5 [1.2], respectively; P<0.001). Treatment effects in patients ≤35 years of age were larger (11.1 [95% CI, 4.8 to 17.5]; P=0.001) than those in patients >35 years of age (3.6 [95% CI, –0.6 to 7.9]; P=0.09). In Study 248, 1,081 patients entered the open-label maintenance phase and 858 completed the study. Mean (SD) PSP total score increased from 67.81 (11.79) at baseline to 68.62 (12.97) at the last study visit (week 52). Mean PSP domain scores at baseline were less than 2, indicating no greater than mild impairment. AOM 400 resulted in either small decreases or slight increases in scores for all PSP domain subscales, indicating maintenance of function over the course of the 52-week study.
Discussion: Results from two post-hoc analyses of data from studies in both the acute treatment and maintenance settings demonstrate the efficacy of AOM 400 in improving and maintaining personal and social functioning in patients with schizophrenia. In the acute setting, improvements in functioning were observed across age groups (≤35 years, >35 years). The magnitude of functional improvement was largest in patients aged ≤35 years on AOM 400 and smallest in patients aged ≤35 years on placebo, findings that suggest a greater sensitivity to improvements in social functioning in younger patients with schizophrenia treated with AOM 400. The results of the long-term study support the use of a long-acting injectable antipsychotic to preserve functioning in patients with schizophrenia.

W16. A PHASE 3, MULTICENTER STUDY TO ASSESS THE LONG-TERM SAFETY, TOLERABILITY AND EFFICACY OF ALKS 3831 IN SUBJECTS WITH SCHIZOPHRENIA

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Abstract: Background: ALKS 3831, currently under development for the treatment of schizophrenia, is composed of a flexible dose of olanzapine and a fixed dose of 10 mg of samidorphan (OLZ/SAM). Samidorphan is intended to mitigate weight gain associated with olanzapine treatment alone. Here, we report the safety, tolerability and efficacy of OLZ/SAM in subjects with schizophrenia that were enrolled in a phase 3, 52 week open-label extension study. Subjects had completed a phase 3, 4-week, double-blind, inpatient acute efficacy study of OLZ/SAM compared to olanzapine or placebo.
Methods: Subjects were switched from either OLZ/SAM, olanzapine or placebo from the previous study to receive treatment with OLZ/SAM 10/10 (10 mg olanzapine/10 mg samidorphan) as investigators were blinded to previous treatment. Subsequently, treatment could be increased to 15/10 or 20/10 at any time during the study at the discretion of the Investigator. Study assessments included adverse event monitoring, clinical laboratory testing, evaluation of extrapyramidal symptoms, PANSS and CGI-S rating scales (last observed on treatment visit), and weight (observed case). Sites were located in the United States, Ukraine, Serbia and Bulgaria.
Results: In total, 281 patients were enrolled in this extension study and 277 subjects received at least 1 dose of study drug with the majority of subjects being male (58.1%), a mean (SD) age of 41.4 (11.31) years, and white (78.7%). The baseline weight of all 277 subjects was 79.1 kg (SD=17.8 kg). A total of 183 (66.1%) subjects completed the treatment period. Overall, the most common reasons for early termination were withdrawal by subject (15.5%), lost to follow-up (6.9%) and adverse event (5.8%). 1.8% of subjects discontinued due to lack of efficacy. Adverse events (AEs) were reported in 136 (49.1%) subjects. Serious AEs were reported in 8 (2.9%) subjects and none were considered related to study drug. No deaths were reported. Most of the AEs were mild in severity. The common AEs (≥4%) were weight increase (13%), somnolence (8%), nasopharyngitis (4%), and headache (4%). The mean weight increase from baseline was 2.79%. There was a statistically significant improvement in PANSS and CGI-S scores with a 14.0 (SE=1.11; $p<0.001$) and 0.8 (SE=0.07; $p<0.001$) point improvement from baseline scores of 78.9 (SD=16.51), and 3.9 (SD=1.00), respectively.
Discussion: OLZ/SAM was generally well tolerated with a safety profile that supports long-term effective treatment. Over the course of this 52-week study, there was a significant improvement in schizophrenia symptoms.

W17. POLYGENIC PREDICTION AND PROSPECTIVE STUDIES OF TREATMENT OUTCOMES IN SCHIZOPHRENIA

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Abstract: Background: Severe, heritable mental illnesses such as schizophrenia and bipolar disorder are leading causes of disability worldwide, representing a major source of public health expenditure. Despite recent progress in identification of genetic loci influencing risk, improving patients' health outcomes remains a major challenge, with comorbid conditions including cardiovascular disease and type II diabetes contributing greatly to morbidity and premature mortality associated with these disorders. In particular, treatment using so-called "second generation" (atypical) antipsychotics is known to cause significant weight gain, hypercholesterolemia, hyperglycemia, and other metabolic disturbances.
Study Participants: Veterans Affairs (VA) Cooperative Studies Program (CSP) #572 is a large, multisite, observational study focusing on the genetics of functional disability among veterans with either schizophrenia (N=4,000) or bipolar I disorder (N=5,000). Participants are "deeply" phenotyped, including assessments of functional capacity, neuropsychological performance, symptom severity, suicidality, and PTSD; and available complete electronic health records (EHR). Genotyping of common single nucleotide polymorphisms (SNPs) in cases (N=9,000) and screened controls (N=20,000) was performed using a customized Affymetrix Axiom Biobank array.
Approach: We present an analytic framework for prospective health studies integrating molecular genetic data and EHR-derived assessments of patient outcomes and consider the specific example of adverse metabolic side-effects of atypical antipsychotics. We query prescribed medications, height and weight, available lab values (e.g., total cholesterol, LDL, HDL, triglycerides, hemoglobin A1C), and inpatient/outpatient diagnoses (e.g., Type 2 Diabetes). Among patients treated with atypical antipsychotics, especially olanzapine, we identify and characterize those exhibiting extreme manifestations of antipsychotic-induced metabolic adverse side-effects. Using published Results from large genome-wide association studies (GWAS), we construct individual-level aggregate genetic risk scores, evaluating baseline effects by sex and genetic ancestry. We incorporate these polygenic scores into survival analyses to estimate their effects on selected outcomes after 6 and 12 months of continuous treatment. Towards identification of novel biomarkers, we perform exploratory, "case-only" GWAS of metabolic adverse side-effects.
Implications: Given the ability to retrospectively assess treatment outcomes based on EHR, CSP #572 presents an unprecedented opportunity to identify patients exhibiting extreme manifestations of antipsychotic-induced metabolic adverse side effects.

W18. THE IMPACT OF SECOND-GENERATION ANTIPSYCHOTIC SIDE-EFFECTS ON FUNCTIONING FROM A SCHIZOPHRENIA PATIENT PERSPECTIVE: A GLOBAL PATIENT CENTERED SURVEY

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Abstract: Background: Second-generation anti-psychotics (SGAs) used to treat patients with schizophrenia generally have lower risk of motor side effects than first generation anti-

psychotics, but are associated with other well-known side-effects (SE).1 The goal of the study was to understand how specific side effects of SGAs impact daily functioning, emotional well-being, and overall quality of life (QoL) of patients with schizophrenia from their own perspective.
Methods: This study was a cross-sectional, patient-reported web survey, conducted in the United States (N=180), Canada (N=99), Australia (N=28), and Europe (Italy; Spain; Denmark; Norway: N=128) in 2017-2018. The survey included patient socio-demographics, the Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF), and the Glasgow Antipsychotic Side-Effect Scale (GASS). In addition, specific questions about functional and emotional impacts were developed for SEs recognized as being bothersome to patients, such as activating SEs ('Feeling restless/unable to sit still,' 'Shaky hands or arms,' and 'Difficulty sleeping'), sedating SEs ('Feeling sleepy during the day' and 'Feeling drugged/like a zombie'), and metabolic or endocrine SEs ('Weight gain,' 'Problems enjoying sex')2. Patients noted on a visual analog scale (VAS) the degree of impact on functioning, 0 indicating 'no impact at all' and 100 indicating the 'largest degree of impact.' Patients with schizophrenia (≥18 years old), stable for at least one month, taking an SGA for 1-12 months, and self-reporting at least one SE were included (N=435).
Results: The majority of the patients were diagnosed within the last 5 years and nearly half were living with a spouse or partner. Employment rates in different countries ranged from 32.2% to 54.5%. The most prevalent SEs reported on the GASS were 'difficulty sleeping,' 'feeling sleepy during the day' and 'drugged like a zombie.' More than half of the participants stated they have experienced gaining weight. SEs perceived as bothersome by patients were reported to impact patient functioning and emotions. These SEs had at least a moderate to severe impact (defined by a VAS score ≥ 50) on all aspects of functioning (physical, psychological, social, and vocational). Activating, sedating, and other SEs investigated showed a low negative correlation with quality of life and satisfaction score indicating worse QOL in participants with higher frequency of SEs. The most common emotions reported by patients with SEs were feeling Frustrated, Ashamed/Embarrassed, and Impatient/Irritated/Angry.
Discussion: Findings confirm that stable patients taking SGAs still have many SEs including activating SEs and sedating SEs, sexual SEs, and weight gain. These SEs have considerable negative impact on patient's daily functioning and quality of life satisfaction, including on work, sexual drive and psychosocial effects.

W19. SYMPTOMATIC STABILITY IN SCHIZOPHRENIA WITH ARIPIPRAZOLE ONCE MONTHLY: POST-HOC EFFICACY ANALYSES FROM LONG-TERM MAINTENANCE STUDIES

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Abstract: Background: The treatment goal of schizophrenia in the acute setting is to achieve rapid control of positive symptoms. Once a patient is stabilized, the goal of maintenance treatment is to keep psychotic symptoms stabilized. Long-acting injectable (LAI) antipsychotics may play an important role in improving adherence to an antipsychotic treatment regimen because they remove the need for daily compliance with oral treatment regimens. Aripiprazole Once-Monthly 400 mg (AOM 400), an extended-release injectable

suspension of aripiprazole, has been shown to be effective both in the treatment of acute psychotic episodes and in the long-term maintenance of stability of symptoms and psychosocial functioning, including reducing the rates of impending relapse and hospitalization. Here we report results of post-hoc analyses evaluating the pattern of response in patients aged ≤35 years and in those aged >35 years on various symptom scales used in two pivotal maintenance studies of AOM 400 (NCT00705783] and NCT00706654); a 52-week open-label extension of these relapse-prevention studies (NCT00731549); and an open-label, mirror-image study (6 months pre- and post-initiation of AOM 400) in patients switching from oral antipsychotic therapy to AOM 400 (NCT01432444).
Methods: Post-hoc analyses of results from these 4 studies were conducted to assess symptom stability with AOM 400 using the Positive and Negative Syndrome Scale (PANSS), PANSS positive and negative subscales, the Clinical Global Impression of Severity Scale (CGI-S), and CGI-Improvement Scale (CGI-I). Adjusted mean change from baseline in patients stratified by age (≤35 years or >35 years) was derived from analysis of variance model with treatment as term for baseline and analysis of covariance model with treatment as term and baseline as covariate for change from baseline.
Results: In NCT007705783, AOM 400 demonstrated similar efficacy in patients aged ≤35 years and >35 years, with significantly greater improvements from baseline vs placebo in PANSS total score, positive and negative subscales, and CGI-S and CGI-I scores through 52 weeks. In NCT00706654, a noninferiority study, AOM 400 showed similar efficacy in patients aged ≤35 years and >35 years, resulting in numerically and, in some instances, statistically greater improvements from baseline across both age cohorts in PANSS total score, PANSS positive and negative subscale scores, and CGI-S and CGI-I scores vs oral aripiprazole 10–30 mg and a subtherapeutic dose of AOM (50/25 mg) through 38 weeks. In NCT007314549, AOM 400 resulted in long-term stability of the symptom improvements seen in its precursor studies, with numerically greater improvements from baseline to last visit seen in patients aged ≤35 years and >35 years across all measures. In NCT01432444, for the overall efficacy sample and among patients who received treatment for at least 3 months, AOM 400 resulted in significant improvements from baseline in PANSS total score, positive and negative subscale scores, and CGI-S score across both age cohorts (≤35 years and >35 years), with numerically larger treatment effects seen among patients aged >35 years across all measures.
Conclusion: Results from post-hoc data analyses from long-term studies of AOM 400 demonstrate its efficacy in long-term maintenance of symptom stability. The pattern of response in patients aged ≤35 years and >35 years was generally consistent in both age groups.

W20. SHOULD ANTIPSYCHOTIC MEDICATIONS FOR SCHIZOPHRENIA BE GIVEN FOR A LIFETIME? REPLICATION OF A NATURALISTIC, LONG-TERM, FOLLOW-UP STUDY OF ANTIPSYCHOTIC TREATMENT

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Abstract: Introduction: Since ethically and practically a randomized control trial (RCT) of antipsychotics will never be done, we recently conducted and reported a 8-50 year, naturalistic follow-up from an academic clinic of patients with chronic schizophrenia on antipsychotic medication. We found that better medication adherence was a statistically significant predictor

of better long-term global outcome and life satisfaction. Since these were important limitations on our findings, we now in this communication, using similar methodology, detail outcomes for a very different sample –inner city patients with chronic schizophrenia with a long past history of antipsychotic treatment, who were now enrolled in clinical trials for new medications for schizophrenia.

Materials and Methods: This is a retrospective, naturalistic, longitudinal 6-49 years of antipsychotic treatment (mean average 20) year follow-up of a consecutive series of patients volunteering for screening for studies with schizophrenia. Lifetime data was collected on 1) their medication adherence, 2) long-term global outcome and 3) life satisfaction. Outcomes were rated by two different clinicians, one with information on medication adherence (non-blind rater) and one without (blind-rater). We used linear regression models adjusted for age, family support, substance use disorder, race, marital status, and number of years in treatment to estimate the association between adherence and each outcome.

Results: A total of 34 patients were assessed. Medication adherence was positively associated with the blind clinician's rating of Global Outcome (p-value= 0.03) and the Global Assessment of Functioning (p-value = 0.05). On the non-blinded clinician rating, medication adherence was unrelated to Global Outcome (p-value=0.26) and with patient's report of life satisfaction (p-value =0.54).

Discussion: This replication-study, like our previous study, is not inconsistent with the recommendation for continuous, long-term treatment for chronic schizophrenia unless medically contra-indicated.

W21. NEW EDITION: A MODEL PSYCHOPHARMACOLOGY CURRICULUM FOR TEACHERS OF PSYCHIATRIC RESIDENTS

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Abstract: Started by the ACNP training committee in 1984, the ASCP Psychopharmacology Committee has developed unique and widely disseminated curricula for teaching clinical psychopharmacology to psychiatric residents, medical students and primary care physicians. It has increasingly had global penetration. We present here the 10th edition of the resident curriculum, and the joint 4th edition for medical students and for primary care. The ASCP Curriculum Committee composed of directors of both resident education as well as medical student education educators have developed materials related to the "what, why, and how" to teach and evaluate. In addition, for each curriculum, we included both a core series of lectures as well as optional lectures developed by experts in their fields. We have done follow-ups on all three curriculums within the last 2 years. We describe here the process of revising, updating, and moving to a web-based curriculum. We present the content for the three curriculums. Based on the follow up of all three curriculum, we have revised every lecture and updated the pedagogy. Depending on the size/resources of the program, teachers use the curriculum in its entirety or in parts. It works even in non-English speaking countries as committee members work with users to adapt/translate to local conditions and teaching strategies. It has been difficult to connect with primary care training programs. For residents, the curriculum is now in its 10th edition and has 88 lectures and over 4,000 slides. For teaching medical students and primary care physicians, there has never been a generally accepted curriculum or set of teaching

materials specifically designed for them. There is a great deal to teach in the four-year curriculum and medical students have widely divergent career paths. This curriculum has 22 lectures. Having the curriculum web-based has improved availability although some programs globally still need a hard copy version.

W22. PRECLINICAL AND EARLY CLINICAL PHARMACOLOGICAL PROFILE OF BASMISANIL, A GABA-A A5 RECEPTOR NEGATIVE ALLOSTERIC MODULATOR, CURRENTLY IN A PHASE 2 CLINICAL TRIAL FOR COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA

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Abstract: Background: Genetic and pharmacological studies demonstrate the importance of the GABA-A alpha5 subunit-containing receptors in cognitive processes. Located at distal dendrites of pyramidal cells, they control synaptic NMDA-receptor activation and synaptic plasticity. This indirect negative modulation of a key receptor involved in learning and memory provides a mechanistic explanation why GABAA α5 negative allosteric modulators (NAMs) improve LTP and cognitive functions in several animal models including those of NMDAR dysfunction. Treatment with GABAA α5 NAMs may therefore ameliorate cognitive impairment associated with schizophrenia (CIAS).
Basmisanil is a potent and highly selective negative allosteric modulator of GABA-A alpha5 receptors. Here we describe its preclinical and clinical pharmacological profile and provide an overview of a Phase 2 study in CIAS in which basmisanil is currently tested.
Methods: Binding and functional selectivity for the GABA-A alpha5 vs. alpha1/2/3 subunit-containing receptors were tested in vitro on GABA-A receptors expressed in HEK293 cells and Xenopus oocytes. Cognitive effects were assessed in rats and monkeys in tests of memory and executive function. In vivo receptor occupancy was determined using [□H]-RO0154513 in rats and [11C] RO0154513 in humans in a single-dose PET study. Functional target engagement was evaluated in an EEG study in human volunteers using with midazolam to demonstrate assay sensitivity.
A clinical study in patients with CIAS is currently underway. Patients are randomly assigned to six-month treatment with placebo, 240 mg or 80 mg BID. Key outcome measures include the MCCB and functional assessments.
Results: Basmisanil selectively binds to recombinant human GABA-A alpha5 receptors with 5 nM affinity and with more than 90-fold selectivity versus alpha1, alpha2, and alpha3 subunit-containing receptors. At saturating binding concentrations, basmisanil inhibited the GABA-induced current in cells expressing GABA-A alpha5 yet had little or no effect at the other receptor subtypes In vivo, basmisanil exhibited concentration-dependent occupancy of GABA-A alpha5 receptors in rats, baboons and human subjects. In addition, it reversed diazepam-induced impairment of spatial learning of rats in the Morris water maze and significantly improved performance in the object retrieval task in non-human primates. Basmisanil lacks anxiogenic and proconvulsive activity in rodent paradigms. In human, the PET study demonstrated a tight exposure-occupancy relationship of basmisanil, mainly in temporal and

frontal cortical regions, consistent with known expression patterns of this receptor. Basmisanil induced an increase in theta to alpha and decrease in beta frequency ranges in EEG spectral power – changes that were qualitatively opposite to those induced by of midazolam, a non-selective positive allosteric modulator of GABA-A receptors. In clinical studies in healthy volunteers and subjects with Down syndrome basmisanil was safe and well tolerated. No treatment-emergent epileptiform abnormalities were observed.
So far 166 patients have been randomized into a Phase 2 trial in CIAS patients. Key aspects of the study design and baseline data will be presented.
Discussion: These data suggest basmisanil is a promising candidate drug with a unique pharmacological and safety profile for further clinical testing in conditions associated with cognitive impairment such as schizophrenia.

W23. TAKING OUR CUE FROM PATIENTS: COLLABORATIVE DESIGN OF A MOBILE INTERVENTION FOR DEPRESSION AND ANXIETY

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Abstract: Background: Today, there is increasing interest in the development and testing of digital interventions to be used alone or in conjunction with medication. Under an NIMH-sponsored SBIR grant (R44MH113520), our mobile app startup is developing technology to address the needs of individuals with a variety of mental disorders. The primary focus of this grant is development and testing of a smartphone app that capitalizes on the sensors on commercial smartphones to 'passively' monitor behaviors relevant to mood and anxiety disorders, to provide psychoeducation about the role of sleep/wake, circadian and social rhythms in mood disorders and then use the sensed data to provide personalized suggestions for behavior change. To prepare for an RCT comparing sensing-only with an intervention app, we conducted a Beta test of the initial app prototype in which we engaged patients in a collaborative design process to refine the intervention to be deployed in the RCT. Unlike other common methods for co-design (e.g., focus groups), this process provides opportunities for long-term, ecologically-valid feedback from patients.
Methods: We approached 6 individuals with a depressive disorder from the research registry at the University of Utah Department of Psychiatry to participate in our collaborative design process. All 6 (100%) agreed to a protocol in which they would use a prototype of the sensing plus intervention app for four weeks. At the end of each week, either the first or third author conducted a 20 to 30-minute phone interview with the design collaborator. These interviews included both a 10-question semi-structured interview, as well as an unstructured discussion of the collaborator's reaction to the monitoring and intervention. Interviewers took careful notes during each call. These notes were then shared with the second author as part of a weekly conference about potential changes and improvements to the app.
Results: The design collaborators included 4 females and 2 males, ranging in age from 16 to 54. All 5 patient collaborators remained in the study for the full 4 weeks, provided >95% of the possible sensed data, and completed all 4 phone interviews. Several common themes emerged from the phone interviews. The majority wanted: 1) more psychoeducational modules 2) more in-depth information included in the psychoeducational modules; 3) the ability to interact with the app and the suggestion system 4) visualizations or other ways of knowing how

they were progressing. We were able to immediately add more psychoeducational modules and more in-depth material within them. These improvements were included in the 1.0 release of the app used by the first wave of RCT participants. The data analysis plan is structured to accommodate an updated release of the intervention app during the trial. We are about to release the 1.5 version of the intervention app which includes the capacity to interact with the app and visualizations of participant progress. This version will be used by the second wave of RCT participants, enabling us to assess any effects of these updates.
Comment: We found it easy and highly informative to engage patients in the collaborative design process. Their feedback led to several immediate changes to our prototype and set the stage for work on more technically demanding improvements. Our experience should encourage other groups developing technology for patient use to involve patients as design collaborators.

W24. DISCUSSION OF INNOVATIVE PSYCHOPHARMACOLOGY IN TREATMENT-REFRACTORY PATIENT POPULATION IN PSYCHIATRY

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Abstract: There is growing number of treatment-refractory patients in psychiatric practice. Although evidence-based treatments may be generally effective in most patients, they may be relatively ineffective in the treatment refractory population, especially patients in state hospital settings or community mental health centers. Over a relatively short period of time several molecules with extremely novel and exciting mechanisms of action have been approved by the FDA for indications that we never used to think would be possible, such as tardive dyskinesia, pseudobulbar affect, Parkinson's disease psychosis and female hypoactive sexual desire disorder. Development of these novel agents was facilitated by a failure to develop better "me too" drugs by the pharmaceutical industry, which has enabled their efforts to develop psychotropic medications at a subsyndromal level beyond DSM 5 diagnoses. These newly approved neuro-psychopharmacological molecules have quite interesting mechanisms of action and although they should not be used routinely for any indications not approved by the FDA, it is at least theoretically plausible to consider these novel agents in treatment-refractory patient population, when no other medications have made a difference. However, it is extremely important to provide neurobiological explanation to use these novel agents based on their putative mechanism(s) of action. For example, using an agent with glutamate-modulation may be a reasonable approach in patients with treatment refractory schizophrenia, if other antipsychotic medications, including clozapine, are not helpful. The main objective of this presentation is to initiate a discussion on novel uses of new and some relatively older psychotropic medications for indications above and beyond those approved by the FDA with neurobiological explanations. Recently published case reports/series and reviews by our group will be used to provide background information to initiate our discussion about innovative psychopharmacology, which will be facilitated by an electronic setup to capture audience responses in response to relevant questions to initiate discussion. More importantly, audience will be repeatedly cautioned to use these agents for novel indications only in treatment-refractory patients, who have failed all evidence-based treatments either due to lack of efficacy and/or adverse effects.

W25. EXPLORING THE UTILITY OF DATA ANALYTICS FOR IDENTIFICATION AND MANAGEMENT OF DATA QUALITY CONCERNS IN EPRO DATA

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Abstract: Introduction: Data analytics have proven highly effective in identification and management of data concerns in clinician rated outcomes in CNS clinical trials. It is important to address such data concerns because they can be associated with increased placebo response and decreased drug signal. (1, 2) In the past patient reported outcomes were not routinely addressed in analytical data quality programs , in part, because of the delay in obtaining the data and because of lack of clear path of action in the event data concerns were identified. With the industry wide adoption of ePROs as well as advances in cloud computing and analytical tools, PRO data can now be analyzed and meaningful interventions can be implemented in timely manner.
In the current retrospective analysis of data collected through an ePRO sleep diary we discuss some of the concerning data findings and discuss possible remedial paths to improve the quality of the collected data.
Methods: All data collected using the ePRO sleep diary were used for the analysis. We focused on the following data quality concerns – implausible values; repetitive responses; unexpected variability in responses, and unexpected duration of diary completion. Using chi2 test of association we explored the association of individual data findings among themselves.
Results: Our dataset consisted of 2,783 diaries collected from 169 subjects. Data findings were relatively frequent, 889 (31.9%) of diaries had at least 1 data quality concern identified: Diary was completed before indicated time of final awakening in 5.3% of cases, outlying number of repeated responses across multiple days affected 5.5% of collected data, extreme variability in final awakening time with an amplitude in several cases of almost 12 hours was seen in 8.6% of cases and extremely short durations of diary completion with durations below 1 minute were seen in 4.8% of cases. Numerous significant associations between various data concerns were identified, for example a high number of repetitions in subjects' responses were seen in those cases where diary was completed before final awakening time.
Discussion: Our findings indicate that the same data analytical approaches used in the case of ClinRO data can be utilized in identification of data concerns in ePRO data. While we have identified a number of data quality concerns in the dataset, almost 70% of diaries did not suffer from any. The identified data quality concerns can have various sources, such as random responses, data fabrication, etc., we speculate that the single most frequent cause are data entry errors. Current advances in cloud computing and analytical tools offer the opportunity to identify and address these data concerns in real time. Notifications and alerts can be pushed into the subjects' devices with requests to check the responses and make corrections as appropriate. In case of repeated offenders site staff can be alerted and subject can be retrained before completing the next ePRO. This would greatly reduce the number of potentially questionable data and thus substantially improve the quality of the collected datasets. We plan investigations addressing similar issues in other therapeutic areas and with a variety of ePRO instruments. In addition, in the future we will explore the relationship of ePRO data errors to placebo response and placebo-drug separation.

W26. THE EFFECTS OF VALBENAZINE ON ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS) ITEMS 8, 9, AND 10: RESULTS FROM THE KINECT 4 STUDY

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Abstract: Background: In contemporary clinical trials of tardive dyskinesia (TD), efficacy was primarily defined by the change from baseline in the Abnormal Involuntary Movement Scale (AIMS) total score. This score is derived from the sum of AIMS items 1 to 7, which rate the severity of abnormal movements in different body regions. However, the AIMS also includes questions about the overall severity of abnormal movements (item 8), incapacitation due to abnormal movements (item 9), and patient's awareness of abnormal movements and distress level (item 10). Data for AIMS items 8, 9, and 10 were collected in KINECT 4 (NCT02405091), a long-term study of once-daily valbenazine that showed sustained TD improvements based on the AIMS total score. AIMS items 8, 9, and 10 were analyzed to provide more context for understanding the effects of valbenazine in patients with TD.
Methods: KINECT 4 included 48 weeks of treatment followed by 4 weeks of washout. Key eligibility criteria included: ages 18 to 85 years; DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or mood disorder; neuroleptic-induced TD for ≥3 months; stable psychiatric status; no high risk of active suicidal ideation or behavior. Stable dosages of concomitant medications to treat psychiatric and medical disorders were allowed. Valbenazine was initiated at 40 mg, with escalation to 80 mg at Week 4 based on clinical assessment of TD response and tolerability; a reduction back to 40 mg was allowed if 80 mg was not tolerated (80/40 mg group). For AIMS items 8, 9, and 10, mean changes from baseline to Weeks 48 and 52 were analyzed descriptively. For AIMS items 8 and 9, which have the same scale for scoring (0=none to 4=severe), the percentages of participants who shifted from a baseline score ≥3 (moderate or severe) to score ≤2 (none to mild) were analyzed at Week 48 and Week 52. A shift analysis was not conducted for Item 10 because the scoring represents 2 different patient types: unaware (score=0) and aware with increasing levels of distress (score=1 to 4).
Results: At Week 48 (end of treatment: 40 mg, n=20; 80 mg, n=74; 80/40 mg, n=9), mean improvements from baseline were found for AIMS item 8 (40 mg, -1.9; 80 mg, -2.1; 80/40 mg, -1.2), item 9 (40 mg, -1.9; 80 mg, -2.0; 80/40 mg, -1.0), and item 10 (40 mg, -1.9; 80 mg, -2.0; 80/40 mg, -0.9). At Week 52 (end of 4-week washout: 40 mg, n=20; 80 mg, n=74; 80/40 mg, n=9), mean changes from baseline were smaller but indicated some maintenance of valbenazine effect: item 8 (40 mg, -0.7; 80 mg, -0.8; 80/40 mg, -0.7); item 9 (40 mg, -1.3; 80 mg, -1.0; 80/40 mg, -0.9; item 10 (40 mg, -1.2; 80 mg, -0.8; 80/40 mg, -0.7). Among participants at the Week 48 visit who had a score ≥3 at baseline for items 8 and 9, most shifted to a score ≤2 after treatment, suggesting clinically meaningful improvements with long-term valbenazine: item 8 (40 mg, 94.4% [17/18]; 80 mg, 97.3% [71/73]; 80/40 mg, 85.7% [6/7]); item 9 (40 mg, 100% [10/10]; 80 mg, 97.8% [45/46]; 80/40 mg, 100% [3/3]. Among those at Week 52 who had a score ≥3 at baseline for items 8 and 9, >40% maintained this clinically meaningful

improvement after washout: item 8 (40 mg, 44.4% [8/18]; 80 mg, 46.6% [34/73]; 80/40 mg, 57.1% [4/7]); item 9 (40 mg, 60.0% [6/10]; 80 mg, 58.7% [27/46]; 80/40 mg, 66.7% [2/3]).
Conclusion: Analysis of AIMS items 8, 9, and 10 indicated that long-term treatment with once-daily valbenazine (40 or 80 mg) improved overall severity of abnormal movements, incapacitation due to abnormal movements, and patient awareness/distress.

W27. UNEXPECTED FINDINGS: LOW CORRELATION BETWEEN CLINICIAN-ADMINISTERED MADRS RATINGS AND PATIENT-REPORTED HAM-D SCORES IN A CLINICAL TRIAL FOR MAJOR DEPRESSIVE DISORDER

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Abstract: Background: The Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Depression rating scale (HAM-D) are the most widely used assessments in clinical trials for depression. These scales are well-validated and studies indicate moderate (r= 0.62) to strong (r= 0.92) correlations when these scales are administered to the patient by the same rater (e.g., Jiang 2009, Ann Gen Psychiat. 8:1-6). Strong correlation (r=0.96) between patient and clinician ratings has also been reported for the HAMD (Kobak 2000, Drug Inf J. 34:145-156). Whether these instruments remain correlated when one is administered by a clinician and the other is completed by a patient, however, has not been established. This result has implications for alternative study design considerations which may be implemented to improve signal detection in depression trials.
Methods: Patients with an unsatisfactory response to an adequate trial of antidepressant medication were entered into a 6-week treatment augmentation study. At each visit, patients completed the 17-item version of the HAMD via Interactive Voice Response (IVR) and trained clinicians administered the MADRS. Eligibility was determined based on the HAM-D score at visits 1 and 2, and sites were blinded to the threshold required for study entry. Data from 575 individual patient visits were analyzed using SAS 9.3 and Spearman's correlations obtained between MADRS and HAM-D scores across visits. Individual item scores were compared to determine if closely-related symptom domains were being scored consistently across scales.
Results: MADRS and HAMD total scores by visit were moderately correlated at screening (r=0.454, p<.0001), with weak correlations at visit 2 (randomization visit; r=0.383, p<.0001), and moderate to strong correlations at weeks4, 5 and 6 (scales were not performed at week 3). Individual item correlations were weak and not significant between MADRS "Reported Sadness" and HAMD "Depressed Mood" at the baseline visit (r=0.055, p=0.590). The two items were more closely correlated by visit 4 (r=0.518, p<.0001). MADRS "Inner Tension" and HAMD "Psychic Anxiety" had similarly weak correlations at screening and visit 2, though the items across scales assessing both sleep and appetite had moderate to strong correlations across all visits.
Conclusions: We found the two most commonly-used depression scales, the MADRS and the HAM-D, did not agree strongly when administered by a clinician and completed as patient self-report, respectively. Individual items designed to measure similar constructs across scales also had very weak or no correlation with the exception of somatic symptoms. Although the correlations improved as the trial continued, this may have been an effect of reduced symptoms

in response to treatment and reaching the 'floor' of each scale. These results have implications for future trial design, particularly as the industry moves towards more 'at-home' or remote assessment methodologies.

W28. DASOTRALINE FOR TREATMENT OF ADULTS WITH BINGE-EATING DISORDER: EFFECT ON BINGE-RELATED OBSESSIONS AND COMPULSIONS

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Abstract: Background: Binge-eating disorder (BED), the most common eating disorder in the US (lifetime prevalence, 1.3-3.5% in women and 0.4-2.0% in men), is associated with impairment in quality of life and functioning. Dasotraline, a long-acting dopamine/norepinephrine reuptake inhibitor, has a PK profile characterized by slow absorption and an elimination half-life of 47-77 hours, permitting once-daily dosing. In a recent study, dasotraline demonstrated efficacy in patients with BED. We now report an analysis from this study of the effect of dasotraline on binge-related obsessions and compulsions.
Method: Patients with moderate-to-severe BED, based on DSM-5 criteria, were randomized to 12 weeks of double-blind, placebo controlled, flexibly-dosed treatment with flexible doses of dasotraline (4, 6, and 8 mg/d). The primary efficacy measure was number of binge-eating days/week; secondary measures included the Binge Eating Clinical Global Impression of Severity (BE-CGI-S) score and the Yale-Brown Obsessive-Compulsive Scale Modified for Binge-Eating (Y-BOCS-BE), a validated, 10-item interviewer-administered measure designed to assess the severity of obsessional thoughts and compulsive behaviors related to binge eating. Change from baseline in efficacy measures in the Intent-to-treat (ITT) population were analyzed using a mixed model for repeated measures (MMRM) analysis.
Results: The ITT population consisted of 317 patients (female, 84%; mean age, 38.2 years). LS mean reduction from baseline in number of Binge Eating (BE) days per week was significantly greater for dasotraline vs. placebo at week 12 (-3.74 vs. -2.75; $P<0.0001$; effect size [ES] = 0.74; primary endpoint); week 12 change was significantly greater for dasotraline vs. placebo on the Y-BOCS-BE total score (-17.05 vs. -9.88; $P<0.0001$; ES, 0.96), the obsession subscale score (-8.32 vs. -4.58; $P<0.0001$; ES, 0.95), and the compulsion subscale score (-8.69 vs. -5.35; $P<0.0001$; ES, 0.87). All 10 YBOCS-BE items were significantly improved on dasotraline vs. placebo at week 12 ($P<0.001$ for all comparisons; with effect sizes ranging from 0.54 to 0.90). At Week 12 (LOCF), for dasotraline and placebo, 52.3% and 18.4% of patients, respectively, had a BE-CGI-S score of 1 ("normal; not at all ill"; NNT=3). At endpoint, for patients with a global illness severity score of 1, the corresponding mean Y-BOCS-BE total scores were 0.5 and 0.7 for dasotraline and placebo, respectively, indicating a marked reduction in BED-related thoughts and behaviors.
Conclusion: In this placebo-controlled, 12-week study of patients with moderate-to-severe binge eating disorder, treatment with dasotraline (4-8 mg/d) was associated with significant and clinically meaningful reduction in binge-related obsessional thoughts and compulsive behaviors.
Clinicaltrials.gov number: NCT02564588
Funded by Sunovion Pharmaceuticals Inc.

W29. STEADY-STATE PHARMACOKINETIC PROPERTIES OF A SUBLINGUAL FORMULATION OF CYCLOBENZAPRINE (CBP) HCL (TNX-102 SL): COMPARISON TO SIMULATIONS OF ORAL IMMEDIATE RELEASE CBP

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Abstract: Objective: TNX-102 SL (TNX) is a sublingual (SL) formulation of CBP designed for bedtime dosing that is being developed for PTSD, fibromyalgia (FM) and agitation in Alzheimer's Disease (AAD). Previous Phase 1 pharmacokinetic (PK) studies comparing TNX with immediate release (IR) oral CBP show TNX provides transmucosal absorption, rapid systemic exposure, avoidance of first-pass metabolism, and lower exposure to long-lived active major metabolite, norcyclobenzaprine (nCBP)(unpublished). This study compared the PK and safety of TNX 5.6 mg with AMRIX (CBP extended-release capsules) 30 mg at steady-state (SS). The PK profile of TNX is contrasted with the predicted profile of oral IR CBP.
Design: Sixty healthy subjects were randomized to TNX (n=30; ages 18-75) or AMRIX (n=30; ages 18-65) for 20 days of dosing. Plasma samples were used to compare PK parameters. Safety was assessed by adverse events (AEs), C-SSRS, physical exam, vital signs, ECGs, and laboratory parameters.
Results: On Day 20, mean Cmax and AUC at SS for CBP was 11.2 ng/mL and 175 h*ng/mL, respectively for TNX, with a Tmax of 5 hours (h), compared to 40 ng/mL and 670 h*ng/mL, respectively for AMRIX, with a Tmax of 7 h. For nCBP, mean Cmax and AUC was 10 ng/mL and 205 h*ng/mL, respectively for TNX, with a Tmax of 8h, compared to 40 ng/mL and 813 h*ng/mL, respectively for AMRIX, with a Tmax of 8h. No unexpected AEs were observed with TNX or AMRIX. Most of the AEs reported were mild in severity and majority of AEs resolved without treatment. The most frequent AEs reported in TNX group were mild and transient oral administration site reactions, e.g. tongue or oral numbness. A simulation of oral IR CBP was created using data from a prior Phase 1 PK study. Comparison of these simulations with the TNX PK profiles in this study suggests that 10 mg once daily oral IR CBP results in only a 40% higher AUC for CBP, but a 128% higher AUC for nCBP compared to daily TNX 5.6 mg. This implies a higher ratio of CBP to nCBP exposure when CBP is administered by the SL rather than the oral route.
Conclusion: At SS concentration, exposure levels of CBP and its long-lasting major metabolite, nCBP, from TNX were less than AMRIX. Overall, daily administration of TNX 5.6 mg or AMRIX 30 mg for 20 days was well tolerated in healthy subjects. For the intended therapeutic daily bedtime administration, these data show that during typical hours of sleep (0-8 hours post-dose), CBP SS levels and AUC are higher than nCBP post TNX administration, which optimizes the effects of CBP on the sleeping brain. In contrast, a simulation of oral IR CBP predicts nCBP SS levels and AUC higher than CBP during sleep. It is reasonable to expect during waking hours (8-24 hours post-dose), TNX provides CBP levels lower than nCBP. The dynamic changes in CBP over 24 hours are believed to optimize the effects on the brain, and these changes are magnified in predicted occupancy of relevant receptors, since CBP has higher affinities for 5HT2A, α1, H1 and M1 receptors. In contrast, nCBP has a higher affinity for the norepinephrine (NE) transporter, which would be expected to impair sleep due to higher synaptic NE availability during period in which optimal sleep quality is associated with lower

NE activity. Together these data support the use of TNX as a potential chronic bedtime treatment for PTSD, FM and AAD.
Disclosures: TNX-102 SL is an investigational new drug and has not been approved for any indication. This study was funded in whole by Tonix. Presenter Gregory Sullivan is an employee of and owns stock in Tonix.

W30. A PHASE 1 STUDY OF THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SINGLE AND MULTIPLE DOSES OF DNS-7801, A HIGHLY SELECTIVE PHOSPHODIESTERASE-1 INHIBITOR

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Abstract: Introduction: Parkinson's disease (PD) is characterized by a progressive loss of dopaminergic neurons in the striatum leading to classical motor symptoms such as tremor and bradykinesia. In addition, patients with PD also exhibit cognitive impairment, particularly with executive function. PDE1 is expressed in brain areas regulating cognitive and motor function as well as habitual behavior. PDE1 modulates D1 signaling, and D1 agonists have shown pro-cognitive effects in humans and animal models. PDE1 inhibitors have demonstrated pro-cognitive effects in a variety of animal models, and they reduce catalepsy in animals induced by antipsychotic medications. DNS-7801 is a highly selective inhibitor for PDE1 (IC50 < 50 nM) that may represent a novel treatment for Parkinson's Disease and cognitive impairment.
Objectives: The primary objective is to assess the safety and tolerability of single and multiple ascending oral doses of DNS-7801 in healthy non-elderly and elderly volunteers. Additional objectives were to assess the food effect on the bioavailability of a single dose of DNS-7801 in healthy volunteers and to characterize the pharmacokinetic (PK) profile of single and multiple doses of DNS-7801 in healthy volunteers.
Methods: DNS-7801 was evaluated in two randomized, double-blind, placebo-controlled Phase 1 studies, a single ascending dose (SAD), DNS-7801-101, and a multiple ascending dose (MAD), DNS-7801-102, in healthy non-elderly (18-50 y.o.) and elderly (60-80 y.o.) male and female subjects. In the SAD study, subjects were randomized into planned escalating dose cohorts to receive either a single dose of DNS-7801 or matching placebo (6 active treatment/2 placebo). The MAD study was a 3-part study, where in Part A (healthy non-elderly) and in Part B (healthy elderly), subjects were randomized to either multiple oral doses of DNS-7801 or matching placebo (9 active treatment/3 placebo) for 21 days. In Part C, multiple doses DNS-7801 or matching placebo was administered for 14 days to healthy non-elderly subjects undergoing a cerebrospinal fluid collection to assess levels of DNS-7801.
Results: In the SAD study, 88 subjects were randomized to treatment. Dose levels of 0.33, 1, 2.5, 5, 10, 20, 30, and 45 mg doses were administered to healthy non-elderly and dose levels of 5, 20, and 30 mg were administered in healthy elderly subjects. DNS-7801 exposure increased proportionally to dose throughout the 0.33 to 45 mg dose range in non-elderly subjects and throughout the 5 to 30 mg dose range in elderly subjects. There were no clinically important treatment-related trends in the AE, clinical laboratory or vital sign assessments. The most common AE was headache. In the MAD study, 76 subjects were randomized to treatment. Multiple oral doses up to 20 mg of DNS-7801 were generally safe and well tolerated in healthy

non-elderly and elderly subjects, and no safety concerns were observed. No treatment-related trends were noted in clinical laboratory evaluations or vital signs measurements. Multiple doses of DNS-7801 were well-absorbed, exhibited linear exposure with a mean half-life of 56 hours. Concentrations of DNS-7801 were present in CSF after dosing with 1 and 10 mg/day for 14 days. Mean CSF concentrations of cAMP, cGMP and BDNF did not appear to be influenced after multiple dose administration.
Conclusion: DNS-7801 was safe and well tolerated in single doses up to 45 mg in healthy non-elderly and up to 30 mg in healthy elderly and as multiple doses up to 20 mg in healthy non-elderly and elderly subjects. DNS-7801 demonstrated a PK profile supporting once-daily dosing. The results from the Phase 1 studies support continued evaluation of the clinical development of DNS-7801 in larger studies.

W31. AN INDIRECT TREATMENT COMPARISON OF VALBENAZINE AND DEUTETRABENAZINE IN ADULTS WITH TARDIVE DYSKINESIA: COMPARISON OF RANDOMIZED, PLACEBO-CONTROLLED TRIALS

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Abstract: Background: The efficacy of valbenazine and deutetrabenazine in tardive dyskinesia (TD) has been demonstrated in randomized, placebo-controlled clinical trials. However, no head-to-head studies have been conducted to explore the potential differences in the effect of these medications on TD. The relative efficacy of valbenazine and deutetrabenazine was assessed using an indirect treatment comparison (ITC) of pooled data.
Methods: Four studies, identified systematically, were included in the analysis: two 6-week valbenazine trials (KINECT 2 [NCT01733121; 25-75 mg]; KINECT 3 [NCT02274558; 40 or 80 mg]) and two 12-week deutetrabenazine trials (ARM-TD [NCT02195700; 12-48 mg]; AIM-TD [NCT02291861; 12, 24, or 36 mg]). For KINECT 3 and AIM-TD, doses were pooled using the inverse-variance method. Trials were pooled (KINECT 2 + KINECT 3; ARM-TD + AIM-TD) using Cochrane's Revman 5.3. Analyses included: mean change from baseline (CFB) in the Abnormal Involuntary Movement Scale (AIMS) total score (sum of items 1-7); an AIMS response threshold (≥50% total score improvement from baseline); and a Clinical Global Impression of Change (CGI-C) response threshold ("very much improved" or "much improved"). For AIMS CFB, the Bucher ITC method was used to compare pooled valbenazine (25-80 mg, 6 weeks) to pooled deutetrabenazine (12-48 mg, 6/8 weeks). The pooled deutetrabenazine data for the 6/8-week timepoint were extracted from publications using a plot digitizer in order to compare the AIMS CFB over similar timeframes. Since the lowest deutetrabenazine dose (12 mg) did not demonstrate efficacy in AIM-TD, a more conservative analysis of AIMS CFB was conducted which excluded 12 mg from the pooled deutetrabenazine dataset. For AIMS and CGI-C response, an ITC of pooled valbenazine (25-80 mg, 6 weeks) was compared to pooled deutetrabenazine (12-48 mg, 12 weeks [data for earlier 6/8-week timepoint not publicly available]).
Results: At the AIMS CFB analysis timepoint (valbenazine, 6 weeks; deutetrabenazine, 6/8 weeks), the ITC statistically favored pooled valbenazine (25-80 mg, n=178; placebo, n=89) versus pooled deutetrabenazine (12-48 mg, n=222; placebo, n=117) (mean difference [95% CI], -1.39 [-2.39, -0.39]; P<0.01). Valbenazine was also statistically favored when removing

the deutetrabenazine 12 mg dose group (mean difference [95% CI], -1.17 [-2.19, -0.15]; P<0.05). At the AIMS and CGI-C response timepoint (valbenazine, 6 weeks; deutetrabenazine, 12 weeks), the ITC favored pooled valbenazine versus pooled deutetrabenazine, with odds ratios (95% CI) of 2.30 (0.91, 5.81) for AIMS response threshold and 2.34 (0.45, 12.12) for the CGI-C response threshold.
Conclusion: Results of this ITC suggest that valbenazine had stronger efficacy in treating TD than deutetrabenazine using AIMS and CGI-C. Additional analysis could help determine the influence of inclusion criteria, concomitant drugs, and TD severity on the results.

W32. EFFECTS OF PHARMACOLOGICAL TREATMENT ON WHITE MATTER IN TREATMENT NAIVE VS. TREATED OCD PATIENTS: A SYSTEMATIC REVIEW OF DTI STUDIES

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Abstract: Background: Obsessive Compulsive Disorder (OCD) is a common and difficult disorder to treat. Several studies have shown associations of white matter pathology in OCD, as well as various psychiatric illnesses, using Diffuse Tensor Imaging (DTI) on magnetic resonance scanners. We conducted a Systematic Review of controlled studies on treatment naive OCD patients vs. pharmacologically treated OCD patients to examine whether pharmacotherapy exerts changes on white matter in OCD.
Methods: A search through PubMed, Google Scholar, and Scopus was conducted to identify controlled trials published from January 2010 to July 2018. All studies used DTI to assess for white matter volume, allowing researchers to calculate several white matter integrity parameters, including Fractional anisotropy (FA), Axial Diffusivity (AD), Radial Diffusivity (RD), and Mean Diffusivity (MD). All studies assessed white matter volume in treatment naïve OCD patients, pharmacologically treated OCD patients, and healthy controls.
Results: 3 studies met the criteria for inclusion. The findings in one study suggest that pharmacotherapy of OCD, which is mainly SSRI medications, do exert some changes on white matter parameters, some of which appear to reverse abnormalities noted in the fronto-striato-thalamo-cortical pathways. In one study, high FA in the splenium correlated with a great severity of the OCD, as measured on the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS). In another study, no differences in white matter parameters were found between drug-naïve patients vs healthy controls.
Conclusion: Our Systematic Review suggests mixed results whether naïve patients with OCD have a difference in white matter in comparison to pharmacologically treated patients with OCD and whether patients with OCD have a difference in white matter in comparison to healthy controls. Due to the limited number of controlled studies of DTI in OCD before and after pharmacotherapy, additional investigations are needed to validate the findings of this systematic review, in both children and adults with OCD.

W33. PATTERNS OF RESTING STATE FUNCTIONAL CONNECTIVITY DIFFERENTIALLY PREDICT TREATMENT OUTCOMES TO SERTRALINE

VERSUS PLACEBO IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: RESULTS FROM THE EMBARC STUDY

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Abstract: Objective: Major depressive disorder (MDD) is associated with aberrant resting state functional connectivity across multiple brain networks that are involved in emotion processing, executive function, and reward processing. The purpose of this report is to determine if patterns of resting state connectivity predict differential outcomes to antidepressant medication (sertraline) versus placebo.

Method: Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) study participants who completed structural and resting state functional magnetic resonance imaging (rsfMRI) at baseline and were randomized to either sertraline or placebo for 8 weeks were included (n=279). A region of interest-based approach (using the Schaefer 100 cortical parcellation and 21 subcortical regions) was utilized to compute functional connectivity between brain regions (total of n=AAA connectivity pairs). Linear mixed model intent-to-treat analyses were used to identify brain regions that differentially predicted outcomes (change in depression severity from baseline to week 8) between sertraline and placebo with connectivity pair-by-treatment arm-by-time as the key independent variable of interest.

Results: Prediction of sertraline-specific response involved several connectivity patterns. In general, higher connectivity within sensory and higher-order cortical networks (e.g., dorsal attention, default mode, somatomotor, and executive control networks) predicted better outcomes for sertraline, as did greater between-network connectivity of the salience and dorsal attention networks. In contrast, both placebo and sertraline outcome were predicted (in opposite directions) by between-network hippocampal connectivity.

Conclusion: This first of its kind study used data-driven methods to identify specific functional network-based moderators of treatment outcome involving brain networks known to be impacted by MDD. Specifically, functional connectivity patterns of brain regions between and within networks play an important role in identifying a favorable response for an antidepressant treatment.

W34. CLINICAL AND COGNITIVE IMPACT OF INSULIN RESISTANCE IN A POPULATION-BASED COHORT OF PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract: The basis for clinical heterogeneity in Major Depressive Disorder remains a huge gap in knowledge and is vital for implementing more effective interventions to reduce the morbidity and mortality of this devastating disease. The presence or absence of insulin resistance may play a role in some of the heterogeneity found in depression. Cognitive symptoms of depression in particularly may be important given that some are independently associated with insulin resistance. In this study, we analyzed insulin resistance, performance on cognitive tasks from the NIH toolbox and assessed clinical psychiatric symptoms in a real-world cohort of depressed patients called Dallas 2K. In the total sample or in the insulin sensitive subgroup, we found QIDS did not predict flanker task performance (n=108, r =-0.09, p =0.3348 and n=89, r=0.13, p=0.2421 respectively). In the subgroup of participants with insulin resistance however, we found QIDS strongly predicted cognitive control (n=29, r =-0.67, p<0.001). These findings appear to be unique to this cognitive domain and were not observed in measures of memory and language. These results may explain some of the heterogeneity seen in cognitive performance among depressed patients and suggest insulin resistance may be a useful method of stratifying patients for cognitive interventions.

W35. PLACEBO RESPONSE PREDICTION IN ANTI-PSYCHOTIC PLACEBO-CONTROLLED CLINICAL TRIALS IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract: Introduction: Placebo effects have been well documented and observed in various studies involving psychiatric disorders such as Major Depressive disorders (MDD), Bipolar disorder and Schizophrenia [1,2,3]. Though various factors, both physiological and behavioral, have been explored as potential cause for placebo effect in psychiatric patients, there is no clear evidence to identify the causality [1,3]. In this work, we apply machine learning methods to predict response at the end of the prospective treatment phase in MDD patients enrolled in randomized, double-blind, placebo-controlled clinical trials. These trials are designed to assess efficacy of antipsychotics as adjunctive therapy to an assigned open-label marketed anti-depressant therapy (ADT) in depressed patients who have demonstrated an incomplete response to a prospective trial of the same ADT. Data from MDD clinical trials: NCT00095823, NCT00095758, NCT00105196, NCT01360632, NCT01360645.
Methods: Subjects enrolled in five different placebo-controlled MDD clinical trials (N = 3570 patients) were analyzed for response prediction. These trials typically consisted of a pre-treatment screening phase, a prospective treatment phase and a randomization phase. Subjects screened based on inclusion/exclusion criteria receive single-blind placebo plus an assigned open-label anti-depressant therapy during the prospective treatment phase and upon meeting criteria for incomplete response, these patients are then randomized into a double-blind randomization phase in a 1:1 ratio to either continue on placebo + ADT or an anti-psychotic + ADT. Subjects who satisfied HAMD-17 and CGI response criteria defined for the trial at the end of the prospective treatment phase are excluded from the trial. The non-responders

continue through the randomization phase of the trial. We apply the Gradient Boosting prediction algorithm on various clinical (Medical history, Assessments, Lab reports, Vital signs) and non-clinical data (Demography, Site characteristics) available at the screening phase to classify patients into responder or non-responder during the prospective treatment phase.
Results: The algorithm was trained on data from 2499 patients (70%) and tested on 1071 patients (30%) with k-fold cross validation. The classification algorithm achieved a prediction accuracy, precision and recall of 81%, 84% and 81% respectively. The area under the ROC curve was determined to be 0.8 which showed that the classifier significantly differentiated between a responder and a non-responder with data from the screening phase.
Conclusion: In conclusion, this classifier can be an effective tool in predicting potential responders at the initial phases of a clinical trial and thereby reduce operational costs and trial duration significantly.

W36. EFFICACY AND TOLERABILITY OF A SWITCH TO LEVOMILNACIPRAN EXTENDED RELEASE VERSUS ADJUNCTIVE QUETIAPINE EXTENDED RELEASE IN MAJOR DEPRESSIVE DISORDER

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Abstract: Background: Major depressive disorder (MDD) is the leading cause of disability in the world. Many pharmacological approaches for MDD are generically available including not only the antidepressants but also other psychotropic medications such as antipsychotics often used as adjuncts. In the STAR-D trial, only 36.8% of patients achieved remission in the first step treatment with citalopram and 27.0% after switching to bupropion, cognitive therapy, sertraline or venlafaxine. In clinical situations, clinicians frequently try to switch to other antidepressants use to adjunctive psychotropic medications. This trial compared the efficacy and tolerability of switching to levomilnacipran extended release (ER) versus adjunctive therapy with quetiapine extended release (XR) to the patients existing generic SSRI treatment in MDD patients.
Methods: This trial was an 8-week, randomized rater blinded parallel group, two-arm trial. The subjects were recruited at two sites by self-referral via ads or introducing by health providers. The subjects had taken SSRIs for MDD and had inadequate response to SSRIs. The subjects with a current or previous use of antipsychotics were excluded. The dose of levomilnacipran ER and quetiapine XR were flexibly adjusted by clinicians. The blinded rater performed specified ratings only and didn't address or ask any other clinical issues. The subjects were evaluated at 0, 1, 2, 3, 4, 6, 8 weeks.
Results: This study compared 29 subjects switching to levomilnacipran ER and 31 subjects with adjunctive quetiapine XR. Both groups showed improvement in MADRS scores and there were no significant difference between two groups (p=0.530). Anxiety symptoms also improved similarly in both groups (p=0.254). The subjects were evaluated on verbal memory and visual memory, with both groups showing improvement without significant difference between groups. The rate of adverse effects was not statistically different between two groups except drowsiness (p=0.004). The two groups showed some difference in distribution of sexual dysfunction but the change during the trial was not different. The subjects in levomilnacipran

ER switching group had a tendency to improve quality of life more in work (p=0.08) and social life (p=0.05) than the quetiapine XR adjunctive group.
Conclusion: Switching to levomilnacipran ER and adding quetiapine XR showed similar efficacy in patients who have shown inadequate relief with SSRIs in MDD. Although the subjects who had adjunctive therapy with quetiapine XR experienced more drowsiness than the subjects switch to levomilnacipran ER, they showed similar tolerability overall. Switching to levomilnacipran ER and adjunctive use of quetiapine XR with SSRIs may have similar potential in MDD patients who do not respond to SSRI monotherapy. Further studies with more subjects will be needed. This study was supported by Allergan plc.

W37. EARLY TOLERABILITY PREDICTS LATER TOLERABILITY AFTER DOSING OF ESKETAMINE NASAL SPRAY FOR TREATMENT-RESISTANT DEPRESSION

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Abstract: Objective: To assess whether the occurrence or non-occurrence of select adverse events (AEs) during post-dose monitoring periods (PDMP) in the first month of treatment with esketamine nasal spray (ESK) can be used as a reliable prognostic indicator for the recurrence or non-recurrence of the same AEs during future PDMPs. We examined whether week 1 or week 4 incidence of AEs predicted AE incidence or absence in weeks 2-4, weeks 5-8, months 3-6, and months 6-12. We also sought to determine whether these results were impacted by ESK dose (56 mg or 84 mg).
Methods: Combined data were derived from 2 previously described flexible dose trials: (1) a double-blind, active-controlled trial (NCT02493868) comparing the efficacy of ESK + a newly initiated oral antidepressant (AD) with a newly initiated oral AD + placebo nasal spray (PBO) in delaying relapse of depressive symptoms in participants with treatment-resistant depression (TRD) who are in stable remission after an induction and optimization course of ESK + an oral AD,1 and (2) an open-label, multicenter study (NCT02497287) to assess the long-term safety and efficacy of ESK + an oral AD in participants with TRD.2 This post hoc analysis was limited to treatment sessions in which participants received ESK + an oral AD (week 1: n=949, weeks 5-8: n=918, month 3-6: n=595, months 6-12: n=595); the treatment sessions after month 4, in which some participants received PBO, were not counted. Patients were dosed with ESK twice per week for the first 4 weeks, weekly during weeks 5-8, and either weekly or every other week thereafter. Patients were monitored for ≥90 minutes after each ESK dose. AEs examined were those reported most frequently (incidence ≥10% and greater than with oral AD + PBO) by patients from one phase 2 and five phase 3 trials (n=1709).
Results: With one exception, if a given AE was not reported during either PDMP during week 1, fewer than 10% of participants experienced that AE in any PDMP for the duration of the trial thereafter (exception was dizziness at 3-6 months [11.6%]), and the incidence rates for the group without a given AE in the first week were always lower than the overall incidence or non-occurrence observed during a given time frame. Week 1 frequency was a useful predictor of AE recurrence or non-occurrence for all AEs except headache and was most predictive of

AE rates for the remainder of the induction period. Week 4 frequency added predictive utility to understanding later recurrence of all AEs except vomiting, which tended to occur earlier in the trial. Mode dose effects were evident for some AEs but were much smaller than dosing frequency effects. If no AEs occurred during week 1, mode dose had minimal impact on future recurrence.
Conclusion: Incidence or non-occurrence of specific AEs in the PDMP in the first and fourth week of treatment with ESK nasal spray + oral AD may be useful in predicting select AE recurrence or non-occurrence for most common AEs during subsequent PDMPs. Some AEs occur more frequently in the 84-mg mode dose group, but this observation is minimized when AEs are absent during first-week PDMP. This approach appears to be most predictive early during the course of treatment, when AEs are reported more frequently.

W38. PERSONALIZED GOAL ATTAINMENT AFTER A SWITCH TO VORTIOXETINE IN A PHASE 4 OPEN-LABEL TRIAL IN ADULTS WITH MAJOR DEPRESSIVE DISORDER (MDD): HEALTH OUTCOMES AND PROGRESS TOWARD FUNCTIONAL RECOVERY

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Abstract: Traditional measures of MDD treatment response may miss meaningful changes for individual patients (1). A novel approach using a Goal Attainment Scale (GAS) (2) Adapted for Depression (GAS-D) provides a framework to measure progress toward personalized treatment goals. This Phase 4 open-label trial evaluated real-world effectiveness of the antidepressant vortioxetine on patients' ability to achieve preidentified treatment goals. The functional impact to patients and health outcomes results are also presented.
Patients with MDD who required a switch in antidepressant treatment were given flexible-dose vortioxetine (10-20 mg) for 12 weeks. Successful attainment of preidentified goals (primary outcome) was demonstrated by a GAS-D score of ≥50 at week 12. Assessments of quality of life/life satisfaction (Q-LES-Q), well-being (WHO-5), workplace functioning (LEAPS), and healthcare resource utilization were completed.
Approximately 86% of patients (106/123) completed treatment (82.8% women, 69.2% white, mean age 45 years). For the primary endpoint, 57.8% of patients achieved a GAS-D score of ≥50 at week 12. Significant improvements ($p<0.001$) from baseline were noted at weeks 6 and 12 for WHO-5 and at week 12 for LEAPS (mean decrease, 5.7 points), Q-LES-Q total (mean increase, 1.13 points), and Q-LES-Q subscale scores that assessed physical health/activity, feelings, work, household duties, leisure activities, social relations, and general activities. No significant increases in number of healthcare provider visits, hospitalizations, or sick days were observed.
A substantial proportion of vortioxetine-treated patients achieved their personalized treatment goals at week 12. Functional recovery indicators showed significant improvement without an increase in resource utilization.
Clinical outcomes are presented in a separate abstract.

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W39. PERSONALIZED GOAL ATTAINMENT AFTER A SWITCH TO VORTIOXETINE IN ADULTS WITH MAJOR DEPRESSIVE DISORDER (MDD): RESULTS OF A PHASE 4 OPEN-LABEL CLINICAL TRIAL

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Abstract: This Phase 4 open-label trial evaluated real-world effectiveness of the antidepressant vortioxetine on the ability of patients with major depressive disorder (MDD) to achieve preidentified treatment goals. A novel approach using a Goal Attainment Scale (GAS) adapted for depression (GAS-D) was used to assess progress toward goal attainment. The GAS has been used in clinical care and program assessment for many years, in medical and nonmedical indications (1). Because the GAS incorporates an individualized goal development approach, it may be more apt to capture meaningful changes specific to each patient's condition than traditional validated clinician- and patient-reported outcome measures (2).

Patients with MDD who required a switch in antidepressant treatment for inadequate response or tolerability issues were given flexible-dose vortioxetine (10-20 mg) for 12 weeks. Achievement of preidentified treatment goals (primary outcome) was indicated by a GAS-D score of ≥50 at week 12. Total GAS-D scores, patient- and clinician-reported outcome measures, response/remission rates, and safety were also assessed.

Approximately 86% of enrolled patients (106/123) completed treatment (mean age 45 years, 82.8% women, and 69.2% white). A GAS-D score of ≥50 at week 12 was achieved by 57.8% of patients, with significant changes from baseline in total score ($p<0.001$). Significant improvements ($p<0.001$) were observed in depression severity (PHQ-9), cognitive functioning and performance (PDQ-D, DSST), well-being (WHO-5), and clinical global impression of severity (CGI-S). Numerical improvement was observed on assessments of functional capacity (VRFCAT) and clinical impression of improvement (CGI-I). Treatment response (≥50% total score reduction on PHQ-9) was reported by 64.2% of patients and remission (PHQ-9 ≤4) by 38.7%. Most adverse events were mild to moderately severe, consistent with product labeling.

A majority of patients treated with vortioxetine achieved their personalized treatment goals at week 12. Patients who switched to vortioxetine also experienced significant improvements in traditional patient- and clinician-reported outcome assessments.

Clinical outcomes are presented here; the functional impact to patients and health outcomes results are presented in a separate abstract.

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W40. HOW SHOULD SAMPLES BE SELECTED WHEN EVALUATING THE EFFECTIVENESS OF TREATMENTS FOR DEPRESSION IN ROUTINE CLINICAL PRACTICE?

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Abstract: Introduction: How should samples be selected when evaluating the effectiveness of treatments for depression in clinical practice? Should a study be of patients who meet formal diagnostic criteria for a disorder, whether it be a narrowly defined group such as major depressive disorder or a more broadly defined group including different mood disorders? Or, rather than a categorical diagnostic approach, should a dimensional perspective be taken which is aligned with recent empirically and theoretically derived models? Another important question in evaluating the effectiveness of treatment in clinical practice is whether to require a minimum score on an outcome measure at treatment initiation. In the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project we examined the influence of sample selection on the effectiveness of an intensive treatment program in treating depression.
Methods: One thousand five hundred and ninety-six patients were evaluated at admission and discharge from the Rhode Island Hospital partial hospital program. The patients completed a daily version of the Clinically Useful Depression Outcome Scale (CUDOS-D).
Results: The effect size in all diagnostic and symptom severity groups was large. The use of a minimum severity score had minimal impact on the percentage of patients who responded to treatment. However, requiring a minimum severity score resulted in lower remission rates and higher effect sizes.
Conclusion: Consensus recommendations should be adopted for reporting the results of effectiveness studies to enhance comparability across studies and to reduce the likelihood of bias due to sample selection decisions.

W41. PROPOFOL AS AN ANTIDEPRESSANT: EVIDENCE FOR MODULATION OF EXCITATION-INHIBITION BALANCE

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Abstract: Background: General anesthetics can trigger long-lasting changes in brain function and behavior. Propofol is a general anesthetic that engages gamma-aminobutyric acid (GABA) receptors and N-methyl-D-aspartate (NMDA) glutamate receptors. We recently completed a pilot study which provided the first evidence that high-dose propofol may have rapid and durable antidepressant effects (Int J Neuropsychopharmacol 21:1079). Here we describe preliminary data evaluating the hypothesis that propofol triggers therapeutic neuroplasticity by altering brain excitation-inhibition balance.
Methods: We studied 30 subjects (age 18-45, 50% female) with medication-resistant depression. Ten participants each received a series of 10 open-label propofol infusions, and 20 matched subjects received a series of 10 electroconvulsive therapy treatments. Depressive symptoms were measured with the Hamilton Depression Rating Scale (HDRS-24) and the Quick Inventory of Depressive Symptomatology (QIDS-SR). Transcriptome-wide sequencing

(RNA-Seq) was used to measure gene expression from peripheral blood before and after the series of propofol treatments. Candidate genes in the glutamate-GABA metabolic pathway (GAD1, GAD2, ABAT, and ALDH5A1) were examined. Proton magnetic resonance spectroscopy was used to serially quantify levels of GABA and glutamate in the medial prefrontal cortex in four subjects.
Results: Six of 10 propofol subjects were classified as treatment responders (HDRS-24 decrease >50%). QIDS-SR scores improved similarly in the propofol and electroconvulsive therapy groups ($p>0.20$). Expression of neither GAD1 nor GAD2 was detectable in blood. ABAT expression increased similarly in propofol responders and non-responders (mean increase 47%, $p=0.095$). In contrast, expression of ALDH5A1 changed differentially by response group ($p=0.0048$) with a 17% decrease observed among propofol responders. Prefrontal cortical GABA and glutamate levels correlated with each other ($p=0.0033$), consistent with the tight link between GABA and glutamate metabolism. The ratio of glutamate to GABA changed differentially by response group ($p=0.017$), decreasing in propofol responders and increasing in non-responders.
Conclusions: Propofol triggered antidepressant effects comparable to electroconvulsive therapy. Brain and blood biomarkers of excitation-inhibition balance tracked with propofol-induced symptom improvement. Disruption of ALDH5A1 is known to increase GABA levels, so the differential decrease in ALDH5A1 expression we observed among responders is consistent with the differential decrease in glutamate-GABA ratio among responders. Successful propofol treatment may require a shift from glutamate-predominant excitation toward GABA-predominant inhibition via changes in neurotransmitter metabolism. Controlled studies of propofol that integrate biomarkers of excitation-inhibition balance are warranted.

W42. EFFICACY OF ESKETAMINE AUGMENTATION IN MAJOR DEPRESSIVE DISORDER

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Abstract: Objective: Esketamine, the s-enantiomer of ketamine, a glutamatergic modulator and a potent NMDA receptor antagonist, is currently under development as a rapid-acting intranasal therapy for treatment resistant depression. The authors sought to determine through meta-analysis the efficacy of adjunctive intranasal esketamine in major depressive disorder (MDD).
Method: A systematic search of Pubmed/Medline was conducted without language or year of publication restrictions, in addition to abstracts of major psychiatric meeting held since 2010, of randomized, double-blind clinical trials comparing adjunctive intranasal esketamine/ketamine to adjunctive placebo for MDD. Where necessary, authors and/or study sponsors were contacted in order to obtain a copy of the presentation as well as any pertinent study details. Montgomery Asberg Depression Scale (MADRS) was used as the primary outcome measure. A random-effects model was used to calculate the standardized mean difference (SMD) between esketamine and placebo in the MADRS score change from baseline

to endpoint, serving as the primary outcome of the study. Secondary outcomes included risk ratios (RR) of response and remission rates. Forest plots and heterogeneity analyses were also performed.
Results: Six trials with 793 patients were pooled. Adjunctive esketamine was significantly more effective than placebo for MADRS score change, response, and remission (N=774, SMD = 0.36, 95% CI = 0.24 - 0.49, p < .0001; response: RR = 1.40, 95% CI: 1.22 - 1.61, p < .0001; remission: RR = 1.45, 95% CI: 1.20 - 1.75, p < .0001). Results remained statistically significant regardless of differences in the study sample, fixed vs. new/optimized baseline antidepressants, or duration of the study.
Conclusions: Adjunctive intranasal esketamine for patients with MDD who are either treatment-resistant or acutely suicidal is an effective and clinically useful treatment strategy.

W43. EFFICACY AND SAFETY OF AXS-05, AN ORAL NMDA RECEPTOR ANTAGONIST WITH MULTIMODAL ACTIVITY, IN MAJOR DEPRESSIVE DISORDER: RESULTS OF A PHASE 2, DOUBLE-BLIND, ACTIVE-CONTROLLED TRIAL

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Abstract: Background: Major Depressive Disorder (MDD) is a debilitating condition. According to the NIMH, over 16 million U.S. adults experience at least one major depressive episode in a given year. Nearly two-thirds of treated patients with MDD do not experience an adequate response with first-line therapy, and most of these also fail second-line treatment. Time to clinically meaningful response with currently available antidepressants (6-8 weeks) is also suboptimal. There is an urgent need for new, more effective, mechanistically novel MDD treatments.
AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity, consisting of dextromethorphan (DM) and bupropion. The DM component of AXS-05 is an NMDA receptor antagonist, sigma-1 receptor agonist and inhibitor of norepinephrine and serotonin reuptake. The bupropion component of AXS-05 increases plasma concentrations of DM by inhibiting its metabolism and is a norepinephrine and dopamine reuptake inhibitor. Both DM and bupropion are nicotinic acetylcholine receptor antagonists. The multimodal mechanisms of action of AXS-05 may be complementary and synergistic for MDD.
Objective: To evaluate the efficacy and safety of AXS-05 versus bupropion in MDD.
Methods: The study was a Phase 2, randomized, double-blind, active-controlled, multi-center, U.S. trial, in which 80 adult subjects with a diagnosis of moderate to severe MDD, confirmed by an independent clinical assessor, were treated either with AXS-05 (45 mg DM/105 mg bupropion) (n=43), or the active comparator bupropion (105 mg) (n=37), twice daily for 6 weeks. The primary endpoint was the change from baseline in the MADRS total score, calculated at each study timepoint and averaged (overall treatment effect).
Results: On the primary endpoint, AXS-05 demonstrated a statistically significant mean reduction from baseline in the MADRS total score over the 6-week treatment period of 13.7 points versus 8.8 for bupropion (p<0.001). At Week 6, AXS-05 demonstrated a 17.2-point reduction in the MADRS total score compared to a 12.1-point reduction for bupropion (p=0.013). AXS-05 rapidly reduced depressive symptoms, demonstrating a statistically

significant improvement over bupropion on the CGI-I scale at Week 1 (p=0.045). Starting at Week 1, AXS-05 achieved superiority over bupropion on the MADRS total score, with statistical significance achieved at Week 2 and maintained at all time points thereafter. At Week 6, 47% of AXS-05 patients achieved remission (MADRS total score of ≤ 10), compared with 16% of bupropion patients (p=0.004). There were no serious adverse events (AEs) and the most commonly reported AEs in the AXS-05 arm were nausea, dizziness, dry mouth, decreased appetite, and anxiety. Treatment with AXS-05 was not associated with psychotomimetic effects, weight gain, or increased sexual dysfunction.
Conclusion: Treatment with AXS-05 resulted in a substantial, rapid, and statistically significant reduction in depressive symptoms, as compared to the active comparator bupropion. AXS-05 was safe and well tolerated in the trial with no reported serious AEs. Based on the rapid and substantial antidepressant effects of AXS-05 as compared to bupropion, its novel NMDA and multimodal mechanisms of action, oral administration, and favorable safety profile, AXS-05 has the potential to address the urgent medical need for new, more effective and mechanistically different antidepressants.

W44. INTEGRATED ANALYSIS OF EFFICACY AND SAFETY OF BREXANOLONE INJECTION IN WOMEN WITH POSTPARTUM DEPRESSION FROM THREE PIVOTAL TRIALS

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Abstract: Background: Postpartum depression (PPD) is the most common medical complication of childbirth, impacting an estimated 10-20% of women giving birth each year globally. Brexanolone injection (BRX), an investigational proprietary intravenous formulation of allopregnanolone, is a positive allosteric modulator of γ-aminobutyric acid A (GABA-A) receptors. Three double-blind, randomized, placebo (PBO)-controlled studies examined the efficacy and safety of BRX in women with moderate to severe PPD.
Methods: An umbrella protocol for the 3 studies allowed integrated dataset analysis. Women aged 18-45 years, ≤ 6 months postpartum, diagnosed with PPD (i.e. the onset of a major depressive episode no earlier than third trimester and no later than 4 weeks post-delivery) and a qualifying 17-item Hamilton Rating Score for Depression total score (HAM-Dts ≥ 26 in Studies A and B; 20-25 in Study C) were enrolled. Randomized subjects received a single, continuous 60-hour infusion of PBO, BRX 60 μg/kg/hour (BRX60, in Study B only), or 90 μg/kg/hour (BRX90) after which they were followed through Day 30. Least squares mean (LSM) change from baseline during infusion (60 hours) and follow-up (30 days) were analyzed with a mixed effects model for repeated measures for BRX90 and PBO. HAM-Dts (Hour 60 primary endpoint in each study) and HAM-D subscales (Anxiety, Core, Bech-6, and Meier) were evaluated. LSM change from baseline for Montgomery-Åsberg Depression Rating Scale total score (MADRSts) was also assessed. Safety and tolerability were assessed by adverse event (AE) reporting and monitoring clinical laboratory results for all patients regardless of

treatment group. Efficacy was assessed in the integrated data set of BRX90 and PBO patients across studies.
Results: There were statistically significant greater LSM reductions at Hour 60 for BRX90 (N=102) versus PBO (N=107) for both scales (HAM-Dts: BRX90 -17.0 vs PBO -12.8; $p<0.0001$ and MADRSts: BRX90 -23.5 vs PBO -17.7; $p<0.0001$). The significant difference between BRX and PBO was maintained through Day 30 for HAM-Dts (BRX90 -16.9, PBO -14.3; $p=0.0213$) and Day 7 for MADRSts (BRX90 -21.1 vs PBO -17.1; $p=0.0119$). At Day 30 the LSM reduction of BRX90 vs PBO for MADRSts was numerically greater. The improvements in HAM-D subscales were also all statistically significant for BRX90 vs PBO at Hour 60 ($p<0.001$). The most common AEs ($\geq$ 10%) reported in all BRX subjects were headache, dizziness, and somnolence.
Conclusions: In this integrated analysis, brexanolone demonstrated a meaningful and statistically significant greater reduction of depressive symptoms, as measured by HAM-D and MADRS in women with PPD compared to placebo, and it was generally well tolerated.

W45. ADVERSE SIDE EFFECTS ASSOCIATED WITH SUBANESTHETIC INTRAVENOUS DOSE OF KETAMINE

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Abstract: Objective: Ketamine, a well-defined prototypic glutamatergic modulator, has been extensively used initially as an anesthetic agent, and more recently in studies examining its antidepressant effects at subanesthetic doses[1]. One of the concerns about using ketamine for the treatment of depression is the occurrence of psychotomimetic effects, which include dissociation, depersonalization, altered perceptions and hallucinations. Research has mostly focused on assessing these side effects with standardized tools like the Clinician-Administered Dissociative States Scale (CADSS) and the Brief Psychiatric Rating Scale (BPRS) and by passive monitoring[3]. In this study we aim to report adverse side effects associated with a single subanesthetic intravenous dose of ketamine that were collected at several time points before and after infusion via active solicitation by trained clinicians.
Methods: Data was pooled from three double-blind, placebo-controlled crossover ketamine studies and one open label study. The sample included 163 patients with treatment-resistant depression (either MDD or bipolar disorder I/II) who were currently experiencing a major depressive episode. The sample also included 23 healthy controls. Patients between the ages of 18 and 65 were included in the study. All participants were assessed to be in good medical health, as determined by medical history, physical examination and routine blood and urine tests. Adverse side effects were solicited by a clinician and collected in a standardized fashion, before and after infusion each infusion, and followed for up to 28 days afterwards. In this study, we will analyze those instances in which symptoms reported increased in severity by 2 points from baseline, meaning that they were moderate or severe. The time of onset and resolution of symptoms was also recorded.
Results: Preliminary results demonstrate that the rates of the most commonly occurring acute side effects of ketamine intravenous administration include feeling strange, weird or bizarre (79%), spacey (74%), woozy/loopy (72%), dissociation (62%), floating (55%), visual distortions (54%), difficulty speaking (51%), numbness (50%), confusion (44%), and

dizziness/faintness (37%). These side effects tend to resolve within four hours of ketamine administration.
Conclusion: Subanesthetic intravenous dose of ketamine is associated with transient high rates of adverse side effects as collected by active solicitation by trained clinicians.

W46. COMBINATORIAL PHARMACOGENOMIC TESTING PREDICTS IMPROVED OUTCOMES FOR DEPRESSION PATIENTS WHO SWITCHED FROM TEST-INCONGRUENT TO TEST-CONGRUENT MEDICATIONS: SUB-ANALYSIS OF THE GUIDED RANDOMIZED CONTROLLED TRIAL

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Abstract: Background: The Genomics Used to Improve Depression Decisions (GUIDED) prospective, large-scale, blinded and randomized controlled trial evaluated the clinical utility of a combinatorial pharmacogenomic (PGx) test for medication selection. The most comprehensive such trial to date, GUIDED included patients diagnosed with major depressive disorder (MDD) who previously had experienced inadequate response to psychotropic medication. A goal of the trial was to determine how well the PGx test predicted improved outcomes among patients who switched from medications projected to have significant gene-drug interactions. A previously published analysis showed improved outcomes among patients who entered the trial on at least one medication projected to have significant gene-drug interactions and switched to medications with fewer projected interactions by week 8. However, this previous analysis included patients who were taking medication with no predicted gene-drug interactions along with the medication predicted to have significant gene-drug interaction. Because the test's greatest utility is with patients taking medications that are impacted by genetic variation, the current sub-analysis excluded patients who did not fall into that category.
Methods: In the GUIDED trial, patients enrolled in both the PGx guided-care and Treatment as Usual (TAU) study arms received combinatorial PGx testing. The PGx test used a weighted algorithm to evaluate each medication based on an individual's combined phenotype. Medications were designated as 'use as directed' (no predicted gene-drug interactions), 'use with caution' (moderate gene-drug interactions), or 'use with increased caution and with more frequent monitoring' (severe gene-drug interactions). Medications were considered congruent with test results if they fell into the 'use as directed' or 'use with caution' groups, and incongruent if they were designated as 'use with increased caution and with more frequent monitoring'. This post-hoc analysis included 174 patients across both arms who were taking test-incongruent medication, with or without 'use with caution' congruent medications. Patients taking any 'use as directed' congruent medications were excluded. Outcomes were

assessed at the week 8 time point using the Hamilton Depression Rating Scale (HAM-D17) and included symptom improvement (percent change in HAM-D17 from baseline), response (50% decrease in HAM-D17 from baseline) and remission (HAM-D17 ≤7).
Results: By week 8, 61 (35.1%) of 174 patients had switched from incongruent medications and were taking only congruent medications. Patients who switched to congruent medications experienced significantly more symptom improvement by week 8 than were patients who did not switch (37.4% versus 21.8%, p=0.0002). Patients who switched medications also were significantly more likely to achieve response (32.1% versus 17.1%, p=0.0214) and remission (23.4% versus 7.2%, p=0.0031) by week 8.
Conclusions: Among depressed patients who entered the GUIDED study on test-incongruent medications, with no 'use as directed' medications, those who switched to congruent medications showed significantly better symptom improvement, response, and remission outcomes. These data support the utility of the combinatorial PGx test in predicting depression clinical outcomes based on the patient's projected gene-drug interactions.

W47. A PIVOTAL STUDY OF THE ORAL GABA-A RECEPTOR POSITIVE ALLOSTERIC MODULATOR SAGE-217 IN MAJOR DEPRESSIVE DISORDER: ANALYSIS OF HAM-D TOTAL SCORE, SUBSCALES, AND INDIVIDUAL ITEMS

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Abstract: Background: Major depressive disorder (MDD) is a disabling and potentially life-threatening condition affecting an estimated 300 million people globally. Dysfunctional GABA signaling has been implicated in MDD etiology, and this concept has supported the investigation of GABAA receptor positive allosteric modulators (PAMs) as potential therapeutics for MDD. A pivotal trial of SAGE-217, an investigational, orally-bioavailable GABAA receptor PAM evaluated the efficacy and safety of SAGE-217 in subjects with MDD.
Methods: Seven US centers enrolled 89 subjects (55 female, 34 male), ages 18-65, with MDD classified as moderate to severe by a 17-item Hamilton Rating Scale for Depression (HAM-D) total score ≥22. Subjects were randomized 1:1 to SAGE-217 Capsule 30 mg or placebo, administered in the evening for 14 days, with a follow-up period of 4 weeks. The HAM-D total score change from baseline for SAGE-217 versus placebo at Day 15 was the primary endpoint. Secondary endpoints included HAM-D total score at other time points and analysis of HAM-D individual items and subscales, including the Bech-6, Maier, Core, and Anxiety scales. Adverse events and standard clinical assessments were captured to assess safety and tolerability.
Results: A statistically significant reduction from baseline in least-squares mean HAM-D total score was observed in the SAGE-217 group compared to the placebo group (-17.4 vs. -10.3; p<0.0001) at the Day 15 primary endpoint. Significant differences favoring SAGE-217 were observed as early as Day 2 (p=0.0223) and were sustained through Day 28 (p=0.0243). At Day 15, SAGE-217 showed significant improvements versus placebo across unidimensional subscales of the HAM-D measuring depression (Bech-6, p=0.0005; Maier, p=0.0001; Core, p=0.0012) and anxiety (Anxiety, p=0.0010). Across the 17 HAM-D individual items, at Day 15, the SAGE-217 group showed significant improvements in 11 of 17 items versus the placebo

group ($p<0.05$ for all). There were no deaths, serious or severe AEs. In the SAGE-217 group, the most common (≥ 5%) treatment emergent AEs were headache, nausea, dizziness, and somnolence.
Conclusions: This first pivotal trial of SAGE-217 in MDD achieved the primary endpoint and demonstrated statistically significant, rapid (starting on Day 2) and sustained (over the study period) reductions in depressive symptoms. SAGE-217 administration resulted in a broad antidepressant response across the HAM-D individual items, in addition to demonstrating significant improvement in unidimensional measures of depression and anxiety. SAGE-217 was generally well tolerated. These results support the further exploration of positive allosteric modulation of GABAA receptors for potential MDD treatments and the further development of SAGE-217 for this indication.

W48. KETAMINE'S PROPHYLACTIC EFFECTS ON ATTENUATING LEARNED FEAR ARE PARTIALLY MEDIATED BY LONG-TERM CHANGES IN VENTRAL HIPPOCAMPAL EXCITATORY NEURAL ACTIVITY PATTERNS

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Abstract: Stress can lead to a wide variety of psychiatric illnesses such as major depressive disorder (MDD) and post-traumatic stress disorder (PTSD). However, some individuals are more susceptible to developing psychopathology in response to stress, while others exhibit stress resilience, but the research into the underlying neurobiology of this phenomenon is still in its infancy. We have previously shown that ketamine can act as a prophylactic against stress-induced depressive-like behavior when administered 1 week prior to various stress models and can buffer fear expression. We have also demonstrated that this prophylaxis is partially mediated by activity in ventral CA3 (vCA3) region of the hippocampus, which has been previously implicated in mood and anxiety disorders. Furthermore, dysregulated neural activity, specifically in regions such as the hippocampus that are known to mediate the stress response, are hallmarks of MDD and PTSD pathology. Yet, how exactly activity is changed, particularly in vCA3, during prophylactic ketamine treatment, stress, or expression of depressive-like or fear behaviors is unknown. Here, we used Inscopix nVoke's in vivo calcium imaging system in freely-moving animals to determine the neural dynamics underlying prophylactic ketamine efficacy in vCA3. A GCaMP6f virus was injected into vCA3 of 129S6/SvEv mice at 5 weeks of age, and subsequently a GRIN lens implanted over the injection site. Four to 6 weeks later, a baseplate was installed to visualize calcium transients, and 1 week later, calcium activity was recorded during and immediately following saline or ketamine (30 mg/kg) administration. One week following drug administration, calcium activity was recorded during contextual fear conditioning, as well as anxiety- and depressive-like behavioral assays. Results were analyzed using the enhanced constrained non-negative matrix factorization (CNMF-E) package for microendoscopic data. We demonstrate here that activity in vCA3 is increased immediately after ketamine administration, but that activity is blunted during fear memory expression. These data suggest that ketamine's resilience-enhancing effects may depend on differential activity changes in vCA3 throughout treatment and behavioral expression. These results also propose a potential node in the brain to target in order to increase stress resilience in susceptible populations.

W49. A RANDOMIZED, PLACEBO CONTROLLED, REPEAT DOSE PHASE 1B STUDY OF COR388 IN OLDER HEALTHY VOLUNTEERS AND PATIENTS WITH ALZHEIMER'S DISEASE WITH EXPLORATORY EFFICACY MEASURES

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Abstract: Background: COR388 is a novel bacterial virulence factors inhibitor being developed for the treatment of Alzheimer's disease (AD). The mechanism of action is based on the discovery of Porphyromonas gingivalis (Pg) in the brain and cerebral spinal fluid of AD patients. Toxic virulence factors from the bacterium, called gingipains, were also identified in the brain of AD patients and levels correlated with tau and ubiquitin pathology. Oral infection of mice with Pg resulted in brain colonization, increased production of Aβ1-42, and exerted detrimental effects on tau and loss of hippocampal neurons. Cortexyme designed and synthesized small-molecule gingipain inhibitors to block this neurotoxicity and COR388 was selected to progress to human trials. In a first-in-human single ascending dose study, COR388 was safe and well tolerated from 5 to 250 mg.

Methods: Cohorts 1-3 enrolled 24 healthy volunteers 55-80 years of age, housed in a phase 1 unit, who received 25, 50, and 100 mg (respectively) of COR388 or placebo q12h for 10 days. Cohort 4 enrolled AD subjects 55-85 with baseline MMSE between 14 and 25, screening MRI compatible with AD, and no other cause of dementia, who were allowed to stay on symptomatic treatments for AD. They received 50 mg of COR388 or placebo q12h for 28 days as outpatients. A lumbar puncture was performed on Days 1 and 28.

Results: In cohorts 1-3, 18 subjects received COR388 and 6 received placebo. In cohort 4, 6 received COR388 and 3 received placebo. COR388 was safe and well tolerated in this study. Adverse events were infrequent, transient, and mild-moderate in severity. No SAEs were reported and no patients withdrew from the study due to AEs. No clinically significant trends were seen in laboratory values or ECGs.

COR388 was absorbed rapidly (Tmax = 0.5-1.5 hours) and therapeutic levels in animal models were achieved. COR388 cleared rapidly with a half-life of 4.5-5 hours at steady state. COR388 was detected in human CSF at ratios consistent with that in other species indicating therapeutic CNS levels.

P. gingivalis DNA fragments were detected in the CSF of 9 out of 9 AD subjects analyzed by PCR. MMSE scores on Day 15 and 28 showed a numerical trend of improvement for COR388 compared to placebo. CANTAB measures also showed a numerical trend of improvement for COR388 compared to placebo, on measures of episodic memory, memory composite and psychomotor speed. Winterlight's speech and cognitive battery revealed statistically significant improvements in the COR388 group vs. placebo in total content units (the total number of details present the image), total number of objects (chair, blanket, etc.), and use of prepositions and subordinating conjunctions (to, on, although, because, etc.).

Conclusions: COR388 is a promising drug for the treatment of AD with a novel mechanism of action. COR388 is readily bioavailable after oral administration with a favorable PK profile. COR388 was safe and well tolerated by older subjects and patients with AD when given at

doses ranging from 25 to 100 mg BID for up to 28 days. There was a trend of improvement in some of the cognitive tests of the AD patients treated with COR388 HCl in this study, and significant improvement in language tests, however, these results should be interpreted with caution due to the small sample size. Based on these data, Cortexyme is planning to initiate a large phase 2/3 study of COR388 in mild to moderate AD in 2019.

W50. USE OF PSYCHOTROPIC MEDICATIONS AND FRAILTY IN LONG-STAY NURSING HOME RESIDENTS

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Abstract: Background: Frailty in older adults is characterized by the decline of physical function and physiologic reserve and may effectively predict adverse health outcomes. The prevalence of frailty is especially high in older adults residing in long-term care facilities, ranging from 30-89% under various scales. For older long-stay nursing home (NH) residents, there is limited research on the prevalence of frailty over time. Further, psychotropic medications are extensively used in older adults and have been associated with a higher risk of falls, hospitalization, and mortality. It is therefore imperative to be cautious when prescribing these medications, especially for older adults who are frail or at risk for frailty, but the use of psychotropic medications is unclear among older NH residents with frailty. This study aimed to examine the prevalence of frailty and the use of psychotropic medications by frailty status over time in long-stay NH residents in the U.S.
Method: The Minimum Data Set (MDS) 3.0 is mandated for all Medicare-/Medicaid-certified NH. MDS 3.0 was used to identify newly-admitted, long-stay older NH residents in 2015. We used the admission assessment and the assessment closest to 90 days after NH entry. Frailty status was measured by FRAIL-NH, a scale developed for long-term care settings with the MDS 3.0 items on fatigue, resistance, ambulation, incontinence, loss of weight, nutrition approach and help with dressing. The FRAIL-NH score (range: 0-14) was categorized as non-frail (0-5), pre-frail (6-7) and frail (>=8). Frailty status was determined both at admission and 90-day stay. Use of psychotropic medication in the past 7 days was measured as the receipt of antipsychotic, antianxiety, antidepressant and hypnotic medications. The final study sample included 432,640 newly-admitted, long-stay older residents.
Results: At admission, 34% of the sample were aged 75 to 84 years, 45% were 85 or older, and 67% were women. About 63% of all residents had moderate and 20% had severe impairments in activities of daily living. Mild to severe cognitive impairment was seen in 69% of residents. About 37% had a diagnosis of depression. At admission, 28% of the sample were pre-frail and 60% frail. After 90 days, 25% were pre-frail and 57% were frail. Use of antipsychotic, antianxiety, and hypnotic medication at admission was observed in 20%, 19% and 4% of all residents, respectively. This did not vary substantially across frailty levels and did not change after 90 days. Use of antidepressants in all residents increased from 45% at admission to 53% by 90 days. The percentage of increase in antidepressant use was highest in residents who were frail, from 45% to 55%. Among residents with frailty, 60% were on at least one psychotropic medication at admission, which increased to 67% after 90 days.
Conclusion: In NH, frailty is common. Psychotropic medication use is high at admission, regardless of frailty status, but appears to increase in residents with frailty in the first 90-day

stay. Additional research is needed to assess whether or not psychotropic medication use in NH is appropriate and the extent to which the presence of frailty places residents at higher risk for adverse health outcomes associated with psychotropic medications.

W51. IS THERE A VALUE IN SCREENING FOR DEPRESSION AND ANXIETY IN INDIVIDUALS WHO SMOKE?

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Abstract: Background: Nicotine use and dependence are major public health concerns. The direct and indirect cost of nicotine use to the society in United States is more than $300 billion per year. It is also responsible for more than 480,000 deaths per year. Quitting smoking is very difficult and complex. Data suggests that smokers who have psychiatric syndromes consume more cigarettes than general population. Some studies also suggest that this group of individuals also find it difficult to quit cigarette/nicotine use and have a high nicotine relapse rate. In our cohort, we had asked adult individuals who were smoking cigarettes to contact us either by phone or online to assess their basic eligibility for participation in several concurrent clinical trials. After initial screening we wanted to see the prevalence of depression and anxiety in our cohort of smokers.
Method: We had inquired adults (age 18+) cigarette smokers to see if they were interested in participating in research studies at Penn State Milton S Hershey Medical Center. They were invited to complete a survey either over the phone or online to assess basic eligibility criteria for consideration to participate in several concurrent clinical trials. We received a total of 4688 inquiries through our screening center. Out of these inquiries, 3826 individuals consented to participate in our trials. The cigarette smokers who consented, were asked additional questions which included their date of birth, gender, ability to understand English, educational level and the number of cigarettes they smoked daily. They were also asked if they ever had depression or anxiety. Once we had this information, we used a simple statistical analysis to see the prevalence of depression and anxiety in our cohort of smokers.
Results: Participants included in this analysis (n=3826) had a mean age of 41.1 (SD: 12.6), 59.6% were female, and 50.5% reported having at least some college education. They smoked an average of 18.3 (SD: 9.0) cigarettes per day. Nearly two-thirds (64.2%, n=2458) of the participants reported having suffered from problems with or being treated for depression or anxiety, a significantly greater proportion than those (35.8%, n=1368) who reported never having depression or anxiety($p < 0.0001$).Discussion: Smoking and nicotine use is a major public health concern. Smoking places a significant medical, emotional, psychological and financial burden on the individual and the society. The total cost of smoking in United States is more than $300 billion a year. In addition, more than 480,000 individuals die yearly secondary to smoking related illness. Due to the dependence potential of nicotine, it is difficult to stop smoking/using nicotine. In addition, individuals who suffer from mental health disorders have a higher rate of smoking and nicotine use compared to the general population. For these individuals, quitting smoking or nicotine use is especially difficult. We wanted to see the prevalence of depression and anxiety in our cohort of smokers who had agreed to participate in our ongoing clinical trials. We found that a significantly large percentage (64.2%, n= 2458)

versus (35.8%, n=1368), acknowledged as having either suffered from or being treated for depression and anxiety. As there is a strong correlation between smoking, mental health syndromes and quit rates, we suggest that smokers with depression and anxiety symptoms should be treated aggressively for their psychiatric syndromes so that decreasing and quitting smoking becomes less stressful. We further suggest that additional studies are needed to assess the relationship of other psychiatric syndromes with individuals who smoke.

W52. THE SELECTIVE OREXIN-1 RECEPTOR INHIBITOR JNJ-61393215 DECREASES SUBJECTIVE ANXIETY EVOKED BY 35% CARBON DIOXIDE INHALATION IN HEALTHY SUBJECTS

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Abstract: Background: JNJ-61393215 is a novel, selective, high affinity/potent orexin-1 receptor (OX1R) antagonist and is a potential first in class therapy for the treatment of panic, anxiety, PTSD, mood disorders and substance abuse. OX1R inhibitors show anxiolytic effects in several preclinical behavioral paradigms, including fear conditioning, fear potentiated startle, lactate infusion, hypercapnia, and yohimbine challenge. Activation of the OX1R is a critical component of CO2-mediated anxiety. JNJ-61393215 blocked CO2-induced anxiety behavior in the social interaction test at 10 and 30 mg/kg (p.o.) in a rat model of CO2-induced panic. Inhalation of CO2 induces anxiety symptoms and panic attacks in subjects with anxiety disorders as well as healthy subjects, and benzodiazepines attenuate those symptoms. In the current study, the anxiolytic effects of JNJ-61393215 were investigated in humans using an experimental medicine model of CO2 inhalation.
Methods: To investigate the potential anxiolytic effects of JNJ-61393215 in humans, 39 healthy male subjects sensitive to the anxiogenic effects of 35% CO2 inhalation at screening were randomized to receive JNJ-61393215 25mg QD (extrapolated peak receptor occupancy: 93%), JNJ-61393215 90mg QD (extrapolated peak receptor occupancy: 98.5%), alprazolam 1mg bid or placebo for 7 days. The study used an incomplete cross-over design and each subject was randomized to receive either placebo or one of the three active treatments. Subjects underwent a 35% CO2 inhalation challenge after 6 days of dosing with the study drug in each cross-over period and anxiety symptoms induced by the CO2 challenge were measured using the Panic Symptom List (PSL-IV). The CO2 challenge was performed 2.5 hours after the administration of the study drug (Tmax median: 1.5h; range: 1-3h); alprazolam was used as active comparator to establish assay sensitivity, to compare the magnitude of changes in the PSL-IV induced by JNJ 61393215 or alprazolam versus placebo.
Results: JNJ-61393215 90mg induced a statistically significant reduction of anxiety symptoms induced by inhalation of 35% CO2 in healthy volunteers according to the primary outcome measure PSL-IV (difference of LS Means vs. placebo: -2.3; $p<0.02$); a significant anxiolytic effect was also demonstrated for a therapeutic dose of alprazolam (difference of LS Means vs placebo: -3.4; $p<0.03$). The anxiolytic effect of JNJ-61393215 was present in most subjects and was driven by a reduction in severity of 9/13 items of the PSL-IV, suggesting a broad anxiolytic effect. The low dose of JNJ-61393215 caused a numerical, statistically non-significant decrease in anxiety symptoms.

Conclusions: JNJ-61393215 90mg showed a statistically significant effect on the PSL-IV total score compared to placebo; a significant anxiolytic effect was also demonstrated for alprazolam at a therapeutic dose. This study demonstrates for the first time in humans the anxiolytic effects of a selective orexin-1 receptor antagonist and provides supporting rationale to test the efficacy of JNJ-61393215 in a patient population.

W53. TRANSLATIONAL RESEARCH WITH DEXMEDETOMIDINE (DM) FOR THE TREATMENT OF AGITATION FROM HEALTHY VOLUNTEERS TO TWO PATIENT GROUPS: THOSE WITH SCHIZOPHRENIA OR WITH PROBABLE SENILE DEMENTIA OF THE ALZHEIMER'S TYPE (SDAT)

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Abstract: Background: DM is a highly selective alpha-2 adrenergic agonist currently marketed for intravenous (IV) administration to sedate/anesthetize patients prior to and/or during surgical and other procedures and to sedate intubated and mechanically ventilated patients. Given the role of the central adrenergic system in arousal, DM may be useful for the treatment of agitation in patients with various neuropsychiatric disorders including senile dementia of the Alzheimer's Type (SDAT) and schizophrenia.
Methods: Three identically designed, double-blind, placebo-controlled, randomized studies were conducted with the IV formulation of DM in (a) middle-aged to elderly healthy volunteers (HV), (b) agitated patients with schizophrenia, and (c) agitated patients with SDAT. The DM was administered IV with a starting dose of 0.1 mcg/kg/hour and the dose was increased by 0.1 mcg/kg/hour every 30 minutes up to a maximum dose of 0.6 mcg/kg/hour or until predetermined endpoints were met either for efficacy or safety specifically blood pressure (BP) and heart rate (HR). In the HV, mild sedation was taken as the surrogate for efficacy and measured using the Richmond Agitation Sedation Scale (RASS). The RASS was also used in the studies of agitated patients with either SDAT or schizophrenia. In addition, the PANSS excitatory component (PEC) scale was in the study of agitated patients with schizophrenia. The numbers of participant in each study had 12 – 14 and 4 -6 subjects treated with DM and placebo, respectively. Continuous assessment was made of level of arousal, BP and HR. Plasma samples were collected before dosing and then every 15 minutes for the determination of DM concentration. Statistics were descriptive and correlational in terms of pharmacodynamic and pharmacokinetic relationships.
Results: Similar results were found in all three studies. DM was capable of producing a light sedation in all subjects (RASS = -1) which was preceded by a calming effect (RASS = 0) in the agitated subjects as well as a reduction in PEC in agitated patients with schizophrenia. These beneficial effects occurred to a greater degree on DM than placebo and before causing clinically meaningful effects on BP or HR. There was an approximately 4-fold variability in the dose and plasma concentration needed to produce these effects in all three groups. The effective dose range was the same across all three groups. The effect occurred within 30 minutes of starting the dose which produced the desired effect. The calming and the drowsy effect persisted for 1.5-2 hours after the cessation of the infusion which was judged to be a

clinically relevant duration. Plasma drug concentration correlated with dosing rate and with drug effect both within and between subjects. Gender affected drug responsiveness with males requiring twice the dose of DM compared to females. Additional factors that may account for the difference in dose needed amongst HV and patients include genetic variations in the gene for the alpha-2 adrenergic receptor and sympathetic tome as measured by changes in blood pressure between lying and standing.
Conclusions: This study demonstrated the efficiency of an adaptive, translational design to early phase CNS drug development and is directly relevant to three topics of interest to the Society: Translational Research into Clinical Practice, Patient-focused Drug Development, and Genomics. Using this information, a sublingual film formulation has been developed for further studies.

W54. UNDERSTANDING SUBJECT BEHAVIORS AND TRAVEL HABITS IN PREVENTABLE INCLUSION AND EXCLUSION PROTOCOL VIOLATIONS IN CNS CLINICAL TRIALS BY USING VERIFIED CLINICAL TRIALS' RESEARCH SUBJECT DATABASE REGISTRY

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Abstract: CNS IEPV data was collected from a global research subject database registry utilized at approximately 2,000 sites in the US (Verified Clinical Trials). Subject partial identifiers were entered into the database after execution of the site-associated IRB approved consent form. IEPVs at research site locations were identified after entries were authenticated and compared with the subject's research history via proprietary algorithm. Participants with IEPVs were prevented from screening. Subject behaviors in attempting inappropriate re-enrollment or IEPVs ravel distances were evaluated
Results: Among the 495 potential IEPVs identified, 22.7% were due to exclusionary research history, 17.4% to washout period truncations, 11.3% to re-screening/re-enrollment attempts, 21.4% to dual enrollment attempts and 10.5% due to dual screening attempts. Average travel distance for all verifications for CNS studies was 76.4 miles and the median travel distance was 14.0. Average travel distance for IEPVs prevented by VCT was 108.5 miles and the median was 13.0. After filtering IEPV's, the mean travel distance of the rest verifications was 60.4 miles. This indicates the mean travel distance of IEPV's was approximately 1.8 times higher than the rest non-IEPV verifications.
Conclusion: Prospective identification of IEPVs is an important way to understand the scope of and prevent certain protocol violations in CNS trials. Without a research subject database registry these 495 IEPVs would not have been identified and prevented. We argue that all sponsors should use such a registry at their CNS research sites to better understand subject behaviors, protect clinical trial subject safety and improve data integrity.

W55. SNAP 101: RANDOMIZED, CROSSOVER, ACTIVE AND PLACEBO-CONTROLLED, SAFETY, PHARMACOKINETIC, AND PHARMACODYNAMIC STUDY OF THREE ASCENDING DOSES OF INP105 - NOVEL PRECISION OLFACTORY DELIVERY (POD) OF A NASAL FORMULATION OF OLANZAPINE

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Abstract: Objectives: 1) Establish safety and tolerability of three doses of INP105 (POD-olanzapine) 2) Compare PK data for olanzapine (OLZ) from 3 INP105 doses to OLZ IM (5 mg and 10 mg) and orally disintegrating tablets (OLZ-ODT, 10 mg) 3) Compare PD effects of INP105 to OLZ IM, OLZ-ODT and placebo.
Background: An estimated 1.7 million acute agitation events occur annually in US emergency room settings often from serious underlying psychiatric conditions such as bipolar I disorder or schizophrenia; OLZ IM is a preferred option due to a shorter Tmax than oral. However, IM administration, predominantly administered in a hospital setting, can be painful, traumatic, invasive, and requires cooperation or restraint which reduces trust and increases healthcare worker injuries. Further, heavily medicated patients may require "boarding" until sedative effects have resolved. Oral administration of OLZ is preferred but has a slower onset of effect and typically requires isolation and observation of the patient. INP105 is a drug-device combination product in development which delivers a novel powder formulation of OLZ by the Precision Olfactory Delivery (POD®) device to the vascular rich upper nasal space. It is being developed for rapid control of agitation either by self or caregiver administration to provide rapid onset of relief without a needle. INP105 may also be suitable for early use by patients who have insight into their condition and recognize early symptoms of agitation in the home setting. This may avoid escalating agitation leading to more intensive management, violence, and injury to the patient, their caregivers and/or healthcare workers.
Methods: Randomized, double-blind, active and placebo-controlled, single ascending-dose, 2-way, 2 period, crossover Phase 1 trial to compare the safety, tolerability, PK and PD of 3 doses of INP105 (5 mg, 10 mg and 15 mg) or POD-placebo with either OLZ IM (5 mg or 10 mg) or OLZ-ODT (10 mg) in NHVs. Period 1 was open label (the OLZ 10 mg IM dose was discontinued after dosing 2 NHVs); followed by a 14-day washout period and then a double-blind period with INP105 or POD-placebo. Dose escalation was staggered to allow safety monitoring committee assessment of tolerability of INP105 between dose levels. PK draws and PD assessments (VAS, ACES and DSST), were obtained at multiple timepoints. All subjects were observed as in-patients for at least 72 hours post-dosing with follow-up occurring 4, 5 and 14 days after dosing in both periods.
Results: 40 subjects were randomized; 37 dosed in Period 2 (Placebo=10, INP105 5 mg =10, 10 mg=9, 15 mg=8). INP105 was well tolerated with TEAEs reported in 100% IM OLZ 10 mg, 90% IM OLZ 5 mg, 83.3% OLZ ODT 10 mg, and 70% INP105 5 mg, 60% INP105 10 mg, and 55.6% INP105 15 mg. INP105 was rapidly absorbed with median Tmax of ~10 min, compared to 20 min for IM (both 5 mg and 10 mg doses) and ~120 min for OLZ ODT. Dose-related, statistically significant PD effects with VAS, ACES and DSST were observed for all three INP105 dose levels compared to placebo.
Conclusions: This study demonstrated that Tmax for nasally administered INP105 was twice as fast as IM and 12 times faster than OLZ ODT with a comparable Cmax and AUC to the corresponding IM dose of OLZ. INP105, OLZ delivered by the POD device to the upper nasal cavity, is a needle-free, rapidly available investigational product with potential application in the management of acute agitation

W56. TREATMENT OF DEPRESSION AND SUICIDAL IDEATION IN BIPOLAR DISORDER WITH MAGNETIC SEIZURE THERAPY

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Abstract: Introduction: Electroconvulsive therapy (ECT) is effective in treatment resistant bipolar depression (BD), however there is a risk for cognitive adverse effects. Magnetic seizure therapy (MST) is a novel convulsive therapy that is effective in treatment of depression and suicidality but with a more benign cognitive adverse effect profile. However, effectiveness in these symptoms for bipolar depression (BD) have not been previously characterized.

Method: Patients with treatment-resistant BD were treated openly with MST in either the frontal or vertex position for up to 24 treatments or until remission. The primary outcome measure was the 24-item Hamilton Depression Rating Scale (HDRS-24). Suicidality was assessed with both the Scale for Suicidal Ideation (SSI) and item 3 of the HDRS-24 which reports on suicidal intent. Assessments were completed at baseline, after every 3 treatments, and at the end of the treatment course. Remission of depression was defined as a post HDRS ≤ 10 and ≥ 60% decrease in scores from baseline on two consecutive ratings, and response was defined as ≥ 50% reduction in the HDRS on two consecutive ratings. Remission of suicidal ideation was defined as a final score of 0 on the SSI or HDRS-24 item 3. Only patients with baseline suicidal ideation (i.e., > 0) were included in this analysis.

Results: Of 31 patients who initiated a course of MST, 26 completed an adequate trial of ≥ 8 treatments (20 frontal, 6 vertex), and 20 completed a full treatment course per protocol (14 frontal, 6 vertex). After MST, patients on average showed a significant reduction in HAMD-24 scores. In adequate trial completers, depression remission rate was 23.1% and response rate 38.5%. Of this group, 30% remitted from frontal MST and 0 from vertex MST, and response rates were 45% and 16.7%, respectively. In per protocol completers, depression remission was 30% and response 50%. Mean number of treatments to reach response criteria was 17.4 ± 5.80 treatments, and for those who reached remission criteria it took a mean number of 17.5 ± 6.95. For suicidality, SSI remission was seen in 47.4% of adequate trial completers and 57.14% of per protocol completers. Mean number of treatments to reach SSI remission was 11.33 ± 8.71 for both groups. Remission on item 3 of the HDRS-24 was 47.4% of adequate trial completers and 69.23% of per protocol completers. Average time to remission was 16.33 ± 7.81 treatments. No patients receiving less than 8 treatments of MST had response or remission in their depression or suicidality.

Conclusions: MST was effective in treatment of depression and suicidal ideation in treatment resistant BD. Response and remission rates were higher and achieved earlier for suicidality relative to depression. These results are promising and warrant further investigation with larger clinical trials comparing MST to ECT.

W57. PERIPHERAL BLOOD LEVELS OF BRAIN-DERIVED NEUROTROPHIC FACTOR IN FIRST EPISODE PSYCHOSIS AS A MEASURABLE DIAGNOSTIC AND PROGNOSTIC TOOL: A META-ANALYSIS

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Abstract: Background: Schizophrenia is a brain disorder that usually requires long-term treatment. However, there is no reliable biomarker that can be used for diagnosis or tracking treatment response. Brain Derived Neurotrophic Factor (BDNF) promotes growth, differentiation and survival of neuronal cells. Previous research showed that BDNF expression decreased in various regions of the brain of schizophrenia patients compared to healthy controls, and therefore, potentially playing a role in the development of schizophrenia. Given the difficulty of accessing brain tissue in living patients, peripheral blood levels of BDNF may be a viable biomarker that can differentiate patients from controls. This meta-analysis aimed to examine whether there is a significant difference in peripheral BDNF blood levels in first episode psychotic patients prior to treatment versus healthy controls. Moreover, it was also investigated whether BDNF blood levels can track treatment response.
Methods: A systematic literature search was conducted via PubMed and Google Scholars. Studies that included patients with first-episode psychosis (FEP) and reported baseline BDNF blood levels in comparison with sex and age matched health controls (HC) or change in BDNF blood levels in response to antipsychotic drug treatment were included in this analysis. Studies that examined chronic patients or did not report data on BDNF blood levels were excluded. Primary analysis was group difference between FEP and HC with Hedge's g as the effect size measure. Secondary analysis was change of BDNF from baseline to a follow-up time point (mostly 1-2 months) after antipsychotic treatment. A random-effect model was used to run the meta-analysis. Heterogeneity was assessed with Q test and I-square. Publication bias was assessed with the "Trim and Fill" method. Meta-regression and subgroup analysis were conducted to examine moderator effects of age, sex, sample size, % drug-naïve, and symptom severity at baseline.
Results: The initial search found a total of 1434 articles, of which 24 studies met the inclusion criteria (total N = 2,296). Twenty-three studies included HC at baseline, and 7 studies reported data on change in BDNF after treatment. The mean age of sample was 26.96 years. The average percentage of male in the samples was 53.5%. Ten studies were conducted in Asian countries, 12 in Europe, and 2 in the United States. Fourteen studies included antipsychotic drug naïve patients only at the baseline assessment. The meta-analysis revealed that at baseline, FEP group had significantly lower BDNF blood levels than HC group in 23 studies, pooled effect size = 0.68, n=2,160, p<.001. There was substantial heterogeneity across studies, Q=208, df=22, p<.001, I2= 89%. Publication bias was also significant, although the bias appeared to favor HC group. After adjusting missing studies with the "Trim and Fill" method, the pooled ES became 1.06, indicating larger difference between FEP and HC groups. Moderator analysis showed that studies with younger patients, more drug-naïve patients, and higher symptom severity tended to have larger effect sizes. Meta-analysis of change of BDNF from baseline to 1-2-month follow-up after treatment showed that the change was not statistically significant across 7 studies (total n = 227).
Conclusion: At baseline, peripheral BDNF blood levels were significantly lower in patients with FEP than in HC, suggesting a potential role of BDNF in differentiating psychosis cases

from controls. In contrast, BDNF did not change significantly after treatment. It is proposed that more well-designed larger studies need to be conducted to further explore the role of BDNF as a biomarker in the diagnosis and treatment response of schizophrenia.

W58. ENDOGENOUS CANNABINOIDS AND THE TRYPTOPHAN/KYNURENINE PATHWAY IN MOOD DISORDERS

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Abstract: Preclinical studies have demonstrated the involvement of the endocannabinoid system (eCBs) in depression and its correlation with serotonin (5-HT) metabolism (Gobbi et al., 2005, PNAS) and inflammation (Klein et al., 2007, Nat Review Immun). However, the interaction between 5-HT, the main endocannabinoids (anandamide [AEA] and 2-arachidonyl glycerol [2-AG]) and their structurally related fatty acid compounds (2-oleoylglycerol [2-OG], oleoylethanolamide [OEA] and palmitoylethanolamide [PEA]) remain considerably unexplored in clinical settings and in patients with depression. Inflammation plays an important pathophysiological role in depression through the KYN pathway. Indeed, inflammatory mediators (i.e. cytokines such as tumor necrosis factor [TNF]) induce the expression of indoleamine 2,3-dioxygenase (IDO), leading to the degradation of Trp, the precursor of 5-HT, into KYN and its downstream metabolites. This in turn decreases the availability of Trp for the synthesis of 5-HT in the brain thus causing depressive symptoms. Therefore, we examined peripheral biomarkers of depression related to tryptophan (Trp) via 5-HT and kynurenine (KYN) pathways, and to eCBs. We enrolled 35 patients with unipolar depression, 20 patients with bipolar depression and 34 age- and sex-matched controls in which we assessed depression severity by using the Montgomery and Asberg Depression Rating Scale (MADRS), and serum levels of soluble TNF receptor type 1 (sTNFR1), Trp, Kyn, endocannabinoids (AEA, 2-AG) and their structurally related compounds 2-OG, OEA and PEA. Adjusting for the possible confounding factors age and sex, MADRS score was positively correlated with serum levels of PEA (r=0.239, p=0.027), AEA (r=0.224, p=0.038), but not 2-AG (r=0.145, p=0.184), as well as with the ratio KYN/Trp (r=0.236, p=0.031) that is an index of IDO activity. MADRS was negatively correlated with serum levels of Trp (r=-0.274, p=0.012). AEA levels were also positively correlated with the KYN/Trp ratio (r=0.326, p=0.002). Both AEA and the KYN/Trp ratio were positively correlated with sTNFR1 (r=0.284, p=0.024 and r=0.288, p=0.022; respectively). Finally, we conducted a multivariate linear regression analysis to examine which of these biomarkers were independently associated with elevated MADRS score. Accounting for possible confounders, PEA levels were significantly associated with MADRS scores (Unstandardized B=2.078 with 95% confidence interval=0.706-3.450, p=0.004), with the model significantly explaining 30% of the variability in the MADRS scale (p=0.005). These data indicate that the severity of depression is significantly correlated with the reduction of peripheral Trp due to the activation of the KYN pathway, as well as with eCBs activation (higher AEA and PEA levels). Inflammation (inferred in this case from sTNFR1 levels) is a potential mechanism underlying these effects. We can thus hypothesize that the activation of

the eCBs is a defensive mechanism that buffers the detrimental effects of inflammation, including the activated KYN pathway. Further studies are warranted to investigate whether PEA that has prominent anti-inflammatory properties may become a biomarker of depression, and whether the administration of exogenous PEA could be used for the psychopharmacological treatment of depression.

W59. EFFECT OF AMYGDALA ABLATION ON PTSD SYMPTOMS AND BIOMARKERS

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Abstract: Background: Posttraumatic stress disorder (PTSD) is a severe psychiatric response to a traumatic event with a prevalence of 5-10% in the general population. About 30-50% of patients are refractory to the recommended trauma-focused therapy and novel treatment options are warranted. Neuroimaging research has consistently indicated increased reactivity of the amygdala in PTSD. Moreover, amygdala hyper-reactivity predicts development and maintenance of PTSD symptoms and treatment non-response, suggesting that the amygdala could be a target for therapy. Notably, brain injury inclusive of the amygdala is protective against developing PTSD (1), and a case report suggests improved PTSD symptoms after unilateral temporal lobectomy for epilepsy (2). Patients with medial temporal lobe epilepsy (MTLE), a subset of whom may have comorbid PTSD, routinely require surgical ablation of the amygdala, providing a unique window into the role of the amygdala in PTSD. This case series reports on two such patients, and we completed multimodal assessments as a unique opportunity to prospectively investigate the effect of amygdala ablation upon PTSD without otherwise altering clinical care.
Methods: Patients with MTLE with comorbid PTSD were recruited from the Emory epilepsy surgery program. Preoperative and postoperative assessments included 1) PTSD symptoms by a licensed clinical psychologist using the clinician-administered PTSD scale (CAPS-5); 2) fear-potentiated startle during a fear conditioning and extinction paradigm; 3) emotional memory encoding; and 4) structural and functional MRI data (3T Siemens Trio) during viewing of fearful and neutral faces.
Results: A male MTLE patient with 30-year chronic combat-related PTSD clinically reported profound abatement of PTSD symptoms following ablation of the non-dominant amygdala. A subsequent female MTLE patient with 19-year chronic civilian PTSD was studied prospectively. She endorsed a high preoperative PTSD clinical symptom burden (CAPS-5 = 33), which improved (-31% at 6 m and -68% by 1 y) following surgery; the greatest reduction was found in the symptom domain of hyperarousal (-90%) when measured 1 year following surgery. On the fear-potentiated startle task, she showed improved discrimination between danger and safety cues from -23% pre-ablation to 72% post-ablation. Her emotional memory showed an increase in remembered items from 25% pre-ablation to 36% post-ablation. Region of interest functional MRI analyses showed an increase in activation in the rostral and dorsal anterior cingulate cortex of 21% and 14%, respectively, from pre- to post-ablation during the presentation of fearful versus neutral faces.

Discussion: The current study describes a series of patients in whom surgical removal of the right amygdala was associated with improvement of clinical and biological markers of PTSD. These findings provide insight into the causal role of the amygdala in PTSD and suggest a potential novel minimally-invasive surgical approach to treatment-refractory cases. It is possible that the significant enhancement to the patients' quality of life rendered by becoming seizure-free could have explained some aspects of the changes in the patients' PTSD symptoms. Yet, the other measures indicate improvement in objectively collected biological markers. The current study reports on two patients, and careful further replication is necessary to provide insights into ideal patient selection, lateralization, the role of postoperative CBT, and long-term effectiveness of amygdala ablation as a novel neurosurgical therapy for chronic medically-refractory PTSD.

W60. INNOVATIONS IN PERSONALIZED MEDICINE: A PILOT STUDY LOOKING AT THE POTENTIAL VS. THE PROMISE IN MAJOR DEPRESSIVE DISORDER

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Abstract: Background: Personalized medicine has been defined as "medicine that uses information about a person's genes, proteins and/or environment to prevent, diagnose or treat disease." Google defines the term as "the promise is that low-cost gene sequencing will lead to a new era of personalized medicine." There are numerous prior publications looking at genes which include ABCB1, CYP2B6, CYP2D6, CYP2C19, CYP3A4, CYP1A2, HTR2A, SLC6A4 and 5HTTLPR, individually and collectively, as biomarkers in Major Depressive Disorder (MDD). We are reporting on a pilot study looking at the impact of genotyping as it relates to response to treatment in outpatients suffering from MDD and having had an inadequate response to at least one antidepressant (ADT) during their current episode.
Methodology: This was a two-part study wherein during the part-one twelve-week phase 100% of the patients and efficacy rating clinicians were blinded to the genotyping results, while treating clinicians were blinded to 50% of the patients' genotyping results. In the subsequent twelve-week part-two segment, patients, clinicians and the treating psychiatrists were un-blinded. All of the patients met DSM-IV-TR diagnostic criteria for MDD, with a total 16-item Quick Inventory of Depression Symptomatology (QIDS-C16) score of 11 or greater, and an inadequate response within the current episode to one or more antidepressants. For efficacy-related measures, we compared Baseline, Week 12 and Week 24 scores on the QIDS-C16, 9-Item Patient Health Questionnaire (PHQ-9) and Clinical Global Impression Scale-Severity of Illness (CGI-S).
Results: Based on the genotyping results, antidepressants were categorized as #1 = best risk-benefit probability; #2 = mid-range risk-benefit probability; or #3 = least beneficial risk-benefit probability. The Baseline to Week 12 analyses compared the un-blinded to the treating psychiatrist "DNA-driven" treatment results to the blinded "standard of care" treatment results. The Baseline to Week 12 comparisons and Week 12 versus Week 24 analyses, were also grouped by comparing "DNA-driven" versus "standard of care" mean score changes on each scale. Our results indicated better efficacy vis-à-vis genotyping on all three efficacy measures

at Week 12: the PHQ-9 data were 46% improved when the reports were used vs. 32% when not used. Similarly, for the QIDS-C16 it was 39% vs. 24% and for the CGI-S it was 30% vs. 25%, also at Week 12. For patients switched from category #2 to category #1 ADT at the end of Week 12, their reduction in symptoms was less than that of the patients who received 24 total weeks of category #1 treatment: PHQ-9 - 62% vs. 54%, QIDS-C16 - 65% vs. 45% and CGI-S - 56% vs. 41%.
Conclusions: While our small sample size [n = 18] prohibits any definitive conclusions, the results do indicate that a DNA-results driven treatment assignment, when both the patients and clinicians were blinded, had value. To wit, when compared to standard of care in the absence of genotyping, the efficacy results were measurably better on all three outcome measures.
Additionally, when both patients and clinicians were fully informed about the genotyping results and ADTs were then prescribed accordingly, our results indicated that once patients were switched to a category #1 ADT their reductions in symptomatology were not as robust as those assigned to a category #1 ADT at the outset.
In harmony with the aforementioned quantified results and noting we are a full-time clinical research center, patient attitudes toward and acceptance of "personalized medicine" vis-à-vis this type of genotyping was 100% enthusiastically embraced by our depressed patient population, i.e., not a single person declined the opportunity to participate!

W61. GENOME-WIDE ASSOCIATION STUDY OF AGGRESSION AND VIOLENCE IN SCHIZOPHRENIA

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Abstract: Background: Patients with schizophrenia tend to have higher rates of aggressive or violent behavior, though these tendencies are only present in a minority of individuals. While it is generally known that these behaviors can be attributed to both genetic and environmental factors, the role of genetics remains largely unclear. In this study, we aim to assess verbal and physical aggression as well as aggression against property in schizophrenia patients and perform a genome-wide association study (GWAS) to identify single-nucleotide polymorphisms (SNPs) associated with aggression and violence.
Methods: A total of 176 patients (141 males, 35 females) diagnosed with schizophrenia spectrum disorder were included in this study, of which 72 had histories of lifetime physical violence, 72 had histories of verbal aggression, and 49 had histories of aggression against property. The diagnosis of schizophrenia was ascertained using the Structured Clinical Interview (SCID). We reviewed participants' electronic medical records and applied the physical aggression sub-criteria of the Modified Overt Aggression Scale (MOAS) to determine aggression and violence status. Blood samples were collected from each patient at the time of interview. Genomic DNA was extracted from white blood cells using a high-salt protocol. Genotyping was completed using Illumina Omni 2.5. Logistic regression analyses were performed, coding the genotype for an additive effect.
Results: From this preliminary analysis, we found that approximately 41% of the participants with schizophrenia exhibited lifetime aggression or violent behavior. We did not find any genome-wide significant associations for physical aggression, verbal aggression, and

aggression against property when conducting the GWAS. However, the top SNPs we found for physical aggression, verbal aggression, and aggression against property were rs7026497 (located on chromosome 9, p-value = 1.26E-05), rs58527176 (located on chromosome 5, p-value = 9.67E-06), and rs10798302 (located on chromosome 1, p-value = 1.10E-05).
Discussion: Future studies should attempt to utilize larger sample sizes, as well as incorporate assessment scales that revolve primarily on physical and verbal aggression and also the aggression against property during a patient's lifetime.

W62. INFLAMMATION AND THE DIMENSIONS OF DEPRESSION: A REVIEW

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Abstract: Background: Depression is a heterogeneous disorder in both its symptomatology and pathophysiology. It has been suggested that parsing depression into specific symptoms or dimensions may provide insight into its underlying neurobiology. Although inflammation in depressive disorders has been an extensive area of research in recent years, little attention has been given to the dimensions of depression. Hence, the primary aims of this review are to investigate whether cognitive and neurovegetative dimensions of depression differentially associate with inflammation, and if so, to what degree.
Methods: A literature search of the PubMed, Web of Science, and PsychINFO electronic databases was performed of peer-reviewed journals published through October 2018. Studies were retained if they: 1) were conducted in community samples and/or patients with depressive disorders (e.g., major depressive disorder [MDD]), 2) employed a validated instrument to measure depressive symptoms or diagnose MDD, 3) assessed distinct dimensions of depression (neurovegetative symptoms, cognitive symptoms, or both), and 4) assessed at least one measure of systemic inflammation (e.g., CRP) shown to be reliably associated with depression. Twenty-one studies were included in this review: 14 cross-sectional and 7 longitudinal studies.
Results: Among the fourteen cross-sectional studies, five found a positive association between mood/cognitive symptoms and CRP. In three of these studies, this association was no longer significant once neurovegetative symptoms were added to the analysis (as a covariate). The other two studies found a positive association between cognitive symptoms and CRP, independent of covariates (neurovegetative symptoms were not included). The majority of studies that examined mood/cognitive symptoms in relation to IL-6 and TNF-α reported null results. Among the twelve studies relating neurovegetative symptoms to CRP, six found positive associations; moreover, three found that neurovegetative symptoms related to higher CRP levels independent of cognitive symptoms. Among the seven longitudinal studies, three studies found that higher baseline neurovegetative symptoms predicted increases in inflammation over time. Conversely, numerous studies found that inflammation predicted future depressive symptoms. Specifically, over time, higher baseline IL-6 predicted neurovegetative symptoms, higher baseline CRP predicted increases in depressed mood, and both higher baseline CRP and IL-6 predicted cognitive symptoms. One study reported null results.
Conclusion: There is evidence that an association exists between neurovegetative symptoms and inflammation, independent of cognitive symptoms. The same cannot be said of cognitive

symptoms and inflammation. This may simply be due to a more robust association between neurovegetative symptoms and inflammation. Alternatively, neurovegetative symptoms (e.g., sleep, fatigue) and associated inflammation may act as mediators of cognitive dysfunction in depression. These findings need to be interpreted in light of the many inconsistencies that exist across studies. Suggestions for future research design and considerations are discussed.

W63. UTILITY OF AN ELECTRONIC, AUDIOTAPED VERSION OF THE VINELAND ADAPTIVE BEHAVIOR SCALE (VINELAND-II) IN RATER QUALITY MONITORING FOR STUDIES OF AUTISM SPECTRUM DISORDER (ASD)

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Abstract: Background: ASD is a heterogeneous and complex disorder with many potential pharmacologic targets. Increasing emphasis on disease modification as well as functional outcomes has led to an interest in the Vineland-II as an efficacy measure for clinical trials. We developed and validated an electronic version of the Vineland-II for use as a clinical outcome assessment (eCOA) measure in international ASD trials. The eCOA scale incorporates automated score conversions using published norms, administration tips such as per-item guidance from the printed manual, carry-forward of age across visits, and built-in audiocapture and uploading capability to facilitate external expert review and rater remediation. The scale is currently in use as a primary efficacy measure in ongoing international child and adult ASD trials. To begin to evaluate the feasibility of the scale as well as its utility in rater quality monitoring in this ongoing trial, we report here the results to date of the US pediatric component.
Method: As part of an IRB-approved clinical trial, the parents/caregivers of children aged 5-17 years with ASD were administered the electronic Vineland-II at multiple clinic visits by qualified raters who had undergone thorough training. The interviews were audio recorded and uploaded for quality review/remediation by an independent vendor using a priori developed quality indicators. Raw scores were converted into standard domain scores using age norms and examined using a risk-based blinded data analytics program to detect site or rater statistical outliers, with targeted clinical assessment and remediation as indicated. We report here the results of all administrations as of 12/26/18.
Results: A total of 631 administrations were collected and audio-evaluated from study partners of 382 subjects, at 42 clinical trial sites. Of the 631, 63 (10%) required contact/retraining with the site rater for quality concerns including administration proficiency (e.g., basal, ceiling rules), adherence to scale scoring guidance, and adherence to trained placebo response minimization guidance. When Vineland-II standard scores were evaluated in the blinded monitoring program, 5 sites hit predetermined criteria triggering deeper dive reviews and additional remediation/guidance.
Conclusions: This is the first examination of the clinical utility of the eCOA Vineland-II in an ASD clinical trial. The results suggest that such an approach is feasible, with standard score conversion, central review, and remediation occurring in close proximity to data collection. Audiocapture and blinded score analyses allow for independent assessment of interview skill and unusual data patterns, respectively. For pediatric ASD, as has been shown with other pediatric indications, the ability to monitor quality of efficacy data can be improved by electronic capture, external review, and ongoing blinded data analytics. Evaluation of the

utility of the eCOA Vineland-II in adults with ASD and in countries outside of the US will be useful for the scientific community and are currently underway.

W64. CLINICAL LABORATORY DATA SUGGESTING THAT MORE NALOXONE IS NOT NEEDED TO INDUCE WITHDRAWAL AMONG HEROIN USERS WHO ALSO USE FENTANYL

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Abstract: Background: Overdose deaths involving synthetic opioids, like fentanyl are estimated to have increased 47% from 2016 to 2017. Expanded availability and use of the opioid receptor antagonist, naloxone (NLX), has become the foremost opioid overdose harm reduction intervention. However, anecdotal reports suggest that more NLX is needed to reverse an opioid overdose event in which fentanyl is a contributing drug. The current pilot study sought to determine if more NLX is needed to precipitate withdrawal among opioid-dependent individuals who regularly use heroin with fentanyl, as opposed to those who do not.
Methods: This retrospective analysis utilized data from non-treatment-seeking heroin users screening for clinical research at Columbia University Medical Center. Over the course of 3-4 screening visits, opioid users completed various self-report and clinician-administered assessments of drug use, medical, and psychiatric history. Urine drug tests were also performed at each visit. The final screening procedure was a naloxone challenge test used to verify opioid physical dependence. During the challenge, an intramuscular dose of NLX (0.2mg - 0.4mg) was administered and the severity of withdrawal (e.g., runny nose, vomiting, sweating, etc.) was quantified (using a rating system developed by Wang et al., 1974) by an experienced nurse in 10-minute intervals, for 50 minutes (total score: 0-150). Naloxone challenge tests from the past two years were compared between individuals whose screening urine toxicology regularly tested positive for the presence of fentanyl (or tested positive for fentanyl the day of the challenge) and those who did not.
Results: Data were analyzed from 14 individuals who tested positive for fentanyl and 16 from those who were only positive for other opioids. Those who tested positive for methadone or buprenorphine on the day of the challenge were not included in the current analysis. No significant differences were found in demographic or drug use outcomes (e.g., duration, current route, or daily quantity of opioid use) between the Fentanyl Positive (mean: age 41.1 years, 14/14 male, 9.1 bags heroin/day) and Fentanyl Negative (42.0 years, 14/16 male, 10.0 bags heroin/day) groups. Intramuscular NLX precipitated robust withdrawal in both samples ($p< 0.01$). However, no significant difference ($p = 0.8$) was observed in the severity of withdrawal (total score) between the Fentanyl Positive (94.6 ± 10.4) and Fentanyl Negative (82.7 ± 9.0) groups, or at any individual timepoint. There was also no group difference in naloxone-induced changes in pupil diameter.
Discussion: The current pilot data suggest that a standard NLX dose can be equally effective at precipitating withdrawal in individuals using fentanyl compared to heroin. However, none of the current individuals reported being primarily fentanyl users, or regularly seeking heroin with fentanyl. Therefore, this interpretation is limited in generalizability to only heroin users whose heroin is being "cut" with fentanyl by their dealers. These data must be interpreted with

caution given the lack of controls inherent to its retrospective design. A prospective clinical laboratory study with the proper opioid maintenance controls is needed to provide a more definitive answer concerning the efficacy of NLX to precipitate withdrawal in individuals using fentanyl.

W65. INCREASED CANNABIS USE IN PSYCHOTIC INDIVIDUALS WITH HISTORY OF PHYSICAL AND SEXUAL TRAUMA

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Abstract: Background: Individuals with history of childhood trauma are at increased risk of developing cannabis use disorder. In a nationally representative sample, lifetime trauma was associated with greater risk of cannabis use [1]. On the other hand, there is a well-known high rate of cannabis use in individuals with psychosis [2]. But there is limited evidence on the long-lasting effects of trauma on cannabis use in individuals with psychosis. In this study, in a sample of individuals with psychosis, we investigated lifetime years of cannabis use in relation to lifetime history of physical and sexual trauma.
Methods: This is a cross-sectional study of individuals with psychosis admitted to a dual diagnosis unit at Mount Sinai Beth Israel hospital, New York. Positive history of sexual and physical abuse was extracted from the Life Event Checklist (LEC) and Drug History Questionnaire was used for life time history of cannabis use. Severity of psychosis was measured using Positive and Negative Syndrome Scale (PANSS).
Results: A total number of 118 subjects were enrolled in the study. Mean age was 35.98 (SD 12.06) and 69.8% of subjects were male. History of childhood sexual or physical trauma was positive in 34.2% of subjects. There was no significant difference in age, gender, or severity of acute psychosis between individuals with positive and negative history of trauma. Subjects with positive history of trauma significantly had longer lifetime history of cannabis use, compared to controls (13.07, SD 12.50, vs. 7.78, SD 8.73, respectively). This difference remained significant after controlling for age and gender (B 4.40, CI 95% .236-8.575).
Conclusion: History of sexual or physical abuse associates with longer periods of cannabis use later in life in individuals with psychosis. The results suggest that history of trauma may partly explain the high rate of cannabis use in individuals with psychosis.

W66. PATIENT SATISFACTION WITH INJECTABLE WEEKLY AND MONTHLY BUPRENORPHINE AND BUPRENORPHINE TREATMENT EXPERIENCE

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Abstract: Interventions addressing opioid use disorder (OUD) are often evaluated by objective measures including treatment retention, illicit opioid use, and morbidity/mortality. These criteria, though important, do not necessarily reflect patient priorities. Patient satisfaction is viewed as an important healthcare outcome and has been used as a measure of quality of care. The relationship between patient satisfaction and healthcare outcomes is not straightforward,

however, evidence suggests that patient satisfaction is a signal for positive outcomes in OUD treatment.

Long-term safety, tolerability and efficacy of a weekly and monthly extended-release injectable buprenorphine (CAM2038) was evaluated in a 48-week, open-label, multi-center, multi-national study in adults with moderate-to-severe OUD. New entrants to treatment were initiated with CAM2038 weekly and after stabilization, could be transitioned to CAM2038 monthly. Individuals receiving sublingual buprenorphine +/- naloxone (SL BPN) at baseline were converted to a corresponding dose of CAM2038 weekly or monthly, and then were maintained on CAM2038 weekly or monthly. Dose adjustments and transitions between CAM2038 weekly and monthly were individualized in accordance with clinical needs. At months 6 and 12, participants in both groups completed a non-validated survey to evaluate patient satisfaction with CAM2038 and experience regarding BPN treatment for OUD. To evaluate satisfaction with CAM2038 at month 12, participants who converted from SL BPN were asked to evaluate their overall experience with CAM2038 as compared to their pre-study SL BPN on a 5-unit scale from "much worse" to "much better". To evaluate BPN treatment experience, participants in both groups were asked to rate the importance of 7 characteristics regarding BPN treatment for OUD, in general, on a scale of 1-7, where 1 was "not important" and 7 was "extremely important". Items addressed were ease of travel, daily compliance, privacy, need for daily medication and trips to the pharmacy, accidental pediatric exposure, and access for others to medications.

167 participants completed the treatment period; 29 (17%) in the new to treatment (NTT) group and 138 (83%) in the conversion from SL BPN group. 110 surveys were completed month 6, 34 by the NTT group and 76 by the conversion group. 162 surveys were completed month 12, 29 by the NTT group and 133 by the conversion group. For patient satisfaction at month 12, of the 133 responding participants who converted from SL BPN to CAM2038, 91 (68.4%) answered that treatment with CAM2038 was "much better" than their previous BPN treatment, 20 (15%) answered that it was "slightly better", 9 (6.8%) responded that CAM2038 was "slightly worse" and 4 (3.0%) responded that CAM2038 was "much worse". 1 of the 4 participants who responded treatment with CAM2038 was "much worse" experienced an adverse event (AE) of moderate or greater severity. This AE was a migraine headache of moderate severity assessed by the principal investigator to be "possibly" related to investigational product. For BPN treatment experience, at 6 and 12 months, the median score (in both groups) across the outlined characteristics of their BPN treatment was 7.0 (extremely important) for all items except for a median score of 6.5 for "prevents others access to my medication" at month 6 for the NTT group.

Participants reported high levels of satisfaction with treatment provided by weekly/monthly CAM2038. Participants found ease of travel, supported daily adherence, improved privacy, lack of need for daily medication or regular trips to pharmacy, prevention of accidental pediatric exposure and access by others to medications as important characteristics of BPN treatment.

W67. EARLY-ONSET EFFICACY AND SAFETY PILOT STUDY OF AMPHETAMINE EXTENDED-RELEASE ORAL SUSPENSION (AMPH EROS) IN THE TREATMENT OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

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Abstract: Objective: To determine whether amphetamine extended-release oral suspension (AMPH EROS) has an onset of effect at 30 minutes postdose in children with ADHD.
Methods: This randomized, double-blind, 2-treatment, 2-sequence, placebo-controlled crossover pilot study enrolled subjects aged 6 to 12 years with attention-deficit/hyperactivity disorder (ADHD) and ADHD-Rating Scale-5 scores of ≥90th percentile for sex and age. A dose of 5 to 20 mg/day of AMPH EROS was determined during a 1-week open-label phase based on medication history, symptom control, and tolerability. Subjects completed a practice laboratory classroom then received one day of double-blind active drug or placebo each in random sequence during 2 double-blind laboratory classroom days. Subjects completed the first double-blind laboratory classroom session, returned to open label drug for 5 days then crossed over on day 6 during a second double-blind laboratory classroom session. DB dose was fixed at AMPH EROS 15, 17.5, or 20 mg. The primary endpoint was change from predose in the Swanson, Kotkin, Agler, M-Flynn, Pelham rating scale-combined score (SKAMP-C) at 30 minutes postdose on two DB days. The key secondary endpoint was change from predose in the SKAMP-C score at 3 hours postdose for AMPH EROS compared with placebo. Safety assessments included vital signs and adverse events.
Results: Eighteen subjects were enrolled in the study (14 males and 4 females) with a mean age of 9 years. At both 30 minutes and 3 hours postdose, changes from baseline in SKAMP-C for AMPH EROS vs. placebo were statistically significant ($p<0.01$ and $p=0.0002$, respectively) with corresponding effect sizes of 0.96 and 1.57. Adverse events (>10%) during the open-label phase included upper respiratory tract infection, fatigue, upper abdominal pain, headache, decreased appetite, and affect lability.
Conclusions: AMPH EROS was effective in reducing ADHD symptoms at 30 minutes postdose. AEs were mild or moderate and consistent with those of other extended-release amphetamines.

W68. EVALUATION OF THE EFFECT OF SPN-812 EXTENDED-RELEASE VILOXAZINE ON THE PHARMACOKINETICS OF VYVANSE® IN HEALTHY ADULTS

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Abstract: Introduction: Viloxazine is currently being developed by Supernus Pharmaceuticals as a non-stimulant extended-release formulation for the treatment of attention-deficit/hyperactivity disorder (ADHD) (SPN-812). Co-administration of FDA-approved stimulant and non-stimulant medications for the treatment of ADHD is a common practice among healthcare practitioners in the U.S. who commonly diagnose and treat the condition. Therefore, co-administration of SPN-812 with Vyvanse® (lisdexamfetamine dimesylate), one of the most frequently prescribed stimulant medications for the treatment of ADHD in children and adults, is possible.

Methods: Thirty-six subjects were enrolled in an open-label, randomized, 3-treatment, 3-period, 6-sequence, 3-way, crossover study, and received a single oral dose of SPN-812 (700 mg), Vyvanse (50 mg), or both under fasted conditions. The doses were separated by a washout period of at least 4 days. Blood samples for PK evaluations were collected up to 96 hours following the administration of the study drug. PK parameters were estimated using non-compartmental methods, PK evaluations were conducted for d-amphetamine (resulting from administration of Vyvanse) for maximum plasma concentration (Cmax), area under the concentration–time curve from 0 to the last measurable time (AUC0-t), and 0 to infinity (AUCinf). The drug–drug interaction of viloxazine on d-amphetamine was evaluated using analysis of variance on log-transformed PK parameters: AUC0-t, AUCinf, and Cmax. The least squares (LS) mean for each treatment group, the difference in the LS means, and the 2-sided 90% confidence interval for the difference were calculated. Safety and tolerability were evaluated throughout the study.
Results: PK parameters for d-amphetamine with and without co-administration of SPN-812 will be presented. Adverse events by treatment will also be presented.
Conclusion: The pharmacokinetics, safety, and tolerability of d-amphetamine alone and co-administered with SPN-812 will be discussed.

W69. MORNING POSTURAL STABILITY IN OLDER ADULTS TREATED WITH LEMBOREXANT VERSUS PLACEBO AND ZOLPIDEM TARTRATE EXTENDED RELEASE

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Abstract: Introduction: Impaired postural stability and an increased risk of falls are undesirable attributes with some medications used to treat insomnia, including non-benzodiazepine hypnotics (e.g., zolpidem tartrate extended release [ZOL]) (Otmani, 2012; Allain, 2005). Lemborexant (LEM) is a dual-orexin-receptor antagonist in development for the treatment of insomnia. In the Phase 3 SUNRISE-1 study (NCT02783729), both objective sleep onset and maintenance parameters were significantly improved by LEM compared with placebo (PBO) and ZOL in subjects with insomnia. The LEM clinical program included extensive safety assessments, including analyses of postural stability upon morning awakening. Results of two studies that examined the effects of LEM vs PBO and LEM vs ZOL on postural stability at morning awakening following bedtime dosing are reported here.
Methods: Both studies enrolled male and female subjects aged ≥55 years. Study E2006-A001-108 (Study 108; n=63) was a 4-period, randomized, double-blind, double-dummy, crossover study consisting of four 1-day treatment periods separated by 14-day washouts between periods in healthy subjects without insomnia. SUNRISE-1 (E2006-G000-304; n=1006) was a 1-mo, double-blind, randomized, parallel group, PBO- and active-controlled study in subjects with insomnia. In both studies, subjects were randomized to PBO, ZOL (6.25mg), LEM 5mg (LEM5) or LEM 10mg (LEM10). Postural stability was evaluated within 5 min of morning awakening at approximately 8h postdose. An ataxiameter was used to assess body sway after each single dose treatment in Study 108 and after the first 2 and last 2 doses in SUNRISE-1.

While standing on a firm surface with feet comfortably apart, study participants were instructed to stand still with eyes closed for 1 min. The amount of body sway in 1 min in 1/3° angle of arc (units; higher values = greater body sway, i.e. less postural stability) was evaluated using crossover model for Study 108 and mixed model with repeated measures (MMRM) for SUNRISE-1.
Results: After a single dose in Study 108, study completers (n=56), the least squares mean (LSM) changes from baseline in body sway approximately 8h postdose for PBO, ZOL, LEM5, and LEM10 were –1.1, 5.9, 1.3, and 0.7 units, respectively. In the SUNRISE-1 full analysis set (n=1006), LSM changes from baseline in body sway approximately 8h postdose were −6.5, 7.0, −2.7, and −3.8 units, respectively after the first 2 doses, and −3.5, 4.6, −2.9, −4.4 units, respectively after last 2 doses. Comparisons of PBO vs LEM5 and LEM10 were not statistically significant (all P>0.05) in either study. However, for ZOL, body sway was statistically significantly higher vs PBO (Study 108: P=0.01 after single doses; SUNRISE-1: P<0.01 after the first 2 doses), vs both LEM5 and LEM10 after the first 2 doses (SUNRISE-1: both P<0.02), and vs LEM10 after the last 2 doses (SUNRISE-1: P=0.03).
Conclusions: In 2 clinical studies, LEM did not impair postural stability upon typical morning awakening vs PBO when administered at bedtime, 8 hours earlier, while ZOL produced larger changes in body sway than PBO, both after single doses and at the end of a month of continuous treatment.
Support: Eisai Inc. and Purdue

W70. ARTISTS: AN OPEN-LABEL, LONG-TERM SAFETY STUDY OF DEUTETRABENAZINE FOR THE TREATMENT OF TOURETTE SYNDROME IN CHILDREN AND ADOLESCENTS

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Abstract: Background: Tourette syndrome (TS), a tic disorder with involuntary movements and vocalizations, is frequently accompanied by a variety of behavioral and psychiatric comorbidities1. Antipsychotics, such as haloperidol, pimozide and aripiprazole, are approved for the treatment of TS in the US; however, there are no European Medicines Agency–approved medicinal products throughout the EU, although haloperidol and tiapride are approved in some EU countries. Antipsychotics have been associated with serious adverse effects, including tardive dyskinesia (TD).
Deutetrabenazine is a generally well-tolerated vesicular monoamine transporter type 2 inhibitor (VMAT2) recently approved by the US Food and Drug Administration for the treatment of chorea associated with Huntington's disease (April 2017) and TD (August 2017). It is currently under investigation for the treatment of tics in pediatric and adolescent patients with TS2. This controlled study evaluates the safety and tolerability of long-term therapy with deutetrabenazine and persistence of effect with a randomized withdrawal period for patients with TS who have previously completed participation in study SD-809-C-17, study TV50717-CNS-30046, or study TV50717-CNS-30060.

Methods: ARTISTS (Alternatives for Reducing Tics in TS) is a 56-week, open-label, single-arm, long-term safety study in approximately 210 children and adolescents with TS after they have successfully completed a parent study (SD-809-C-17, TV50717-CNS-30046, or TV50717-CNS-30060). All patients will undergo a randomized drug withdrawal period followed by a deutetrabenazine re-titration and maintenance period. The primary outcome is assessment of safety via assessing incidence of adverse events, clinical laboratory parameters, 12 lead ECG and safety scales during the study. Secondary outcomes are change from Day 1 to each visit the scale is administered in: Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS), TS-Clinical Global Impression (TS-CGI) score, TS-Patient Global Impression of Impact (TS-PGII) score, and child and adolescent Giles de la TS-Quality of Life (C&A-GTS-QoL) activities of daily living (ADL) subscale score.
Results: Not available yet.
Conclusion: TS is a chronic condition impairing major life activities, such as occupational, social, and educational activities, during childhood and adolescence. TS presents an area of significant unmet medical need in the pediatric population for effective and well-tolerated treatment options. ARTISTS is an open-label Phase 3 study to further evaluate the long-term safety and the persistence of effect of deutetrabenazine in patients with tics associated with TS. The study is sponsored by Teva Pharmaceuticals and operationalized by Teva's development partner Nuvelution TS Pharma Inc.

W71. BOTULINUM TOXIN THERAPY OF SOCIAL ANXIETY DISORDER: A CASE SERIES

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Abstract: We and others have recently found that botulinum toxin injected into the brow muscles has significant antidepressant properties as compared to placebo in randomized controlled trials in patients with major depressive disorder. However, data for the treatment of social anxiety disorder with botulinum toxin is lacking. We report here on six patients with moderate to severe social anxiety disorder whom we treated with botulinum toxin, given their persistent symptoms and adverse side effects from medications. Three of six patients with social anxiety disorder experienced a sustained remission following treatment with botulinum toxin. In addition, the three patients who did not go into remission experienced a reduction of social anxiety symptoms. When the effect of botulinum toxin on the frown muscles began to wear off, social anxiety symptoms began to return and retreatment with botulinum toxin provided relief of social anxiety symptoms again, further suggesting a role for botulinum toxin in patient improvement.

W72. BOTULINUM TOXIN THERAPY OF BIPOLAR DEPRESSION: A CASE SERIES

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Abstract: We and others have recently found that botulinum toxin injected into the brow muscles has significant antidepressant properties as compared to placebo in randomized controlled trials in patients with major depressive disorder. However, data for the treatment of bipolar depression with botulinum toxin is lacking. We report here the case histories of six patients with bipolar disorder experiencing moderate to severe depressive episodes who were treated on a compassionate basis with botulinum toxin given their persistent depressive symptoms and adverse side effects from medications. Four of six patients with bipolar depression experienced a sustained remission following treatment with botulinum toxin. In addition, the two patients who did not go into remission experienced a reduction of depressive symptoms. When the effect of botulinum toxin on the frown muscles began to wear off, depressive symptoms returned in some patients. Retreatment with botulinum toxin provided successful relief of depressive symptoms again, suggesting a role for botulinum toxin in patient improvement.

W73. EFFICACY OF ADJUNCTIVE ARMODAFINIL IN BIPOLAR DEPRESSION: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Abstract: Background: Patients with bipolar disorder spend a significant amount of time in depressive episodes contributing to impaired functioning and disability (1). In contrast to major depression, mania, and schizophrenia, drug development for bipolar depression is limited to three FDA approved medications; furthermore, inadequate remission rates are frequently observed (2). Modafinil and its R enantiomer-armodafinil are wakefulness promoting agents approved by FDA for daytime somnolence, narcolepsy, and fatigue, associated with shift work disorder. They mechanistically function in part, as dopamine reuptake inhibitors, a potential target for bipolar depressive symptoms. Given the paucity of evidence-based guidelines and low remission rates for bipolar depression with current augmentation treatments, these compounds may offer potential benefit.
Methods: A comprehensive search of major electronic databases was conducted to identify relevant randomized controlled trials (RCT). Only studies that included patients with a DSM-IV criteria for bipolar disorder type I (BD-I) and bipolar disorder type II (BD-II) prescribed ar/modafinil as augmentation were included. Data for response/remission and all cause discontinuation were analyzed. Effect size was summarized by relative risk (RR) using the Random effects model.

Results: Of 58 studies, only 5 RCT studies (N=795, N=792 placebo) met the inclusion criteria. 4 armodafinil studies included only patients with a BD-I disorder and 1 modafinil study included both bipolar subtypes. Patients were receiving concurrent treatment with second generation antipsychotics and mood stabilizers either in monotherapy or in combination. Augmentation with ar /modafinil exhibited a significant greater response and remission rates compared to placebo (RR, 1.18; 95% CI, 1.01-1.37; P=0.03; RR, 1.38; 95% CI, 1.10–1.73; P=0.005, respectively) with no significant heterogeneity (I2 = 34%, P = 0.19; I2 = 18%, P = 0.30). All cause discontinuation was not significant (RR, 1.08; 95% CI, 0.89-1.30, P=0.45) with no evidence of increased risk of mood switches or suicide events associated with the treatment (RR, 0.99; 95% CI, 0.39-2.5, P=0.98; RR, 1.02; 95% CI, 0.37-2.85, P=0.97).
Conclusion: This meta-analysis underscores the efficacy of ar/modafinil as augmentation options for bipolar depression without increasing the rate/risk of switching and suicide. Further studies delineating the efficacy of ar/modafinil augmentation in BD-I vs BD-II depression are required.

W74. CARDIAC SAFETY OF ESKETAMINE NASAL SPRAY IN TREATMENT-RESISTANT DEPRESSION: RESULTS FROM THE CLINICAL DEVELOPMENT PROGRAM

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Abstract: Background: Esketamine, the S-enantiomer of racemic ketamine, is being developed for treatment-resistant depression (TRD). Transient sympathomimetic effects have been reported with ketamine, beginning shortly after dosing.
Methods: Cardiovascular (CV) effects of esketamine nasal spray (28-84 mg twice weekly, once weekly, or every other week), in combination with an oral antidepressant (AD), were evaluated in 1,708 esketamine-treated adults with TRD enrolled in 5 double-blind (DB), placebo-controlled and 1 open-label trials (1 Ph 2; 5 Ph 3). Patients with uncontrolled hypertension or clinically significant ECG abnormalities were excluded. Risk mitigation for high blood pressure (BP) was implemented in Ph 3 (i.e., no dosing if SBP ≥140 mmHg [≥150 for age >65] or DBP ≥90 mmHg). Assessments: seriousness, outcomes, and severity of CV adverse events (AEs) including frequency and odds ratio (OR) [95% CI] for esketamine+AD vs. AD+placebo; changes in vital signs; and ECG.
Results: AEs of increased BP occurred in 12.8% of all esketamine-treated patients, with a ~3-fold higher rate in esketamine+AD vs. AD+placebo groups (11.6% vs. 3.9%; OR 3.2 [1.9, 5.8]). AEs related to abnormal heart rate (e.g. palpitations, tachycardia) were reported in 3.0% of all esketamine-treated patients (in DB trials: 1.6% vs. 0.8%; OR 1.9 [0.5, 8.6]), of which 96% of CV events were mild or moderate and 88% of the events resolved. In the all-clinical trials population, 3 AEs were reported as serious (SAE) and severe: BP increase, hypertensive crisis, sinus tachycardia; 3 severe (not SAE): palpitations (1), BP increase (2); in addition, 1 fatal unrelated SAE: acute cardiac failure.

BP increases reached maximum within 40 minutes of esketamine dosing (consistent with peak plasma levels) and typically returned to predose range by 1.5 hours postdose. In 2 studies (4-week; age 18-64 years), the largest mean maximum SBP/DBP increases across all intranasal dosing days were 13.3/8.7 mmHg for esketamine+AD and 6.1/4.9 mmHg for AD+placebo; in elderly study (age ≥65) were 16.0/9.5 mmHg and 11.1/6.8 mmHg, respectively. The percentage of patients (age 18-64) with markedly abnormal BP elevation (SBP ≥180 and/or DBP ≥110) ranged from 2.0–4.9% in esketamine+AD vs. 0¬–0.9% in AD+placebo treatment groups across studies/phases and was higher in patients with (5.5–7.6%) vs. without (2.9–4.3%) histories of hypertension; in elderly, BP elevations were higher (11.1% in esketamine+AD vs. 6.2% in AD+placebo). No clinically relevant effect on ECG parameters was observed in the esketamine clinical program.
Conclusions: In TRD patients, the CV safety of intranasal esketamine administration was acceptable. BP elevations following dosing of esketamine are generally transient, asymptomatic, self-limiting without rescue medications, and not associated with serious CV safety sequalae. Further monitoring for long-term CV outcomes of these transient BP changes is needed.

W75. IMPACT OF MIDAZOLAM VS. SALINE ON EFFECT SIZE ESTIMATES IN CONTROLLED TRIALS OF KETAMINE AS A RAPID-ACTING ANTIDEPRESSANT

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Abstract: The goal of this study was to infer the effectiveness of midazolam as a comparator in preserving the blind in ketamine studies for mood disorders through patient-level analyses of efficacy trial outcomes. In this integrative data analysis (k=9, N=367 patients with mood disorders), clinical outcomes were compared across four groups: ketamine (midazolam-controlled), ketamine (saline-controlled), midazolam, and saline. Ketamine doses ranged from 0.5–0.54mg/kg and midazolam doses ranged from 0.02–0.045mg/kg. The baseline-to-Day 1 effect size was d=0.7 (95% CI: 0.4–0.9) for ketamine (midazolam) versus midazolam and d = 1.8 (95% CI: 1.4–2.2) for ketamine (saline) versus saline. The effect of ketamine relative to control was larger in saline-controlled studies than in midazolam-controlled studies ($t(276) = 2.32$, $p = .02$). This was driven by a comparatively larger effect under midazolam than saline ($t(111)=5.40$, $p<.0001$), whereas there was no difference between ketamine (midazolam) versus ketamine (saline) ($t(177)=0.65$, $p=.51$). Model-estimated rates of response (with 95% CI) yielded similar results: ketamine (midazolam), 45% (34-56%); ketamine (saline), 46% (34-58%); midazolam, 18% (6-30%); saline, 1% (0-11%). The response rate for ketamine was higher than the control condition for both saline ($t(353) = 7.41$, $p < .0001$) and midazolam ($t(353) = 4.59$, $p < .0001$). Studies that used midazolam as a comparator yielded smaller effects of ketamine than those which used saline, which was accounted for by greater improvement following midazolam compared to saline.

W76. DIFFERENTIAL INFLUENCE OF SEROTONIN TRANSPORTER-LINKED POLYMORPHIC REGION 5-HTTLPR GENOTYPE BY RACE ON SUICIDAL BEHAVIORS AMONG PATIENTS DIAGNOSED WITH BIPOLAR DISORDER

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Abstract: Bipolar Disorder (BD) confers a heightened vulnerability of suicidal behavior, particularly on populations already at risk, such as African Americans. This study examines the interactive effect of 5-HTTLPR genotype ("s" and "l" alleles) X race on suicide behaviors among patients diagnosed with BD. A total of 119 low-income BD patients (n = 88 African Americans and n = 31 non-African Americans) enrolled in the study. Accounting for covariates (gender and employment), the interaction between race (African Americans vs. non-African Americans) X genotype (S/S and S/L vs. L/L) was significant in predicting suicide risk. This interaction effect was particularly significant when predicting the frequency of suicide risk in the past year. Findings suggest that the s allele of the 5-HTTLPR genotype as a genetic influence on suicidal behavior had a differing effect based on racial background among patients diagnosed with BD: the short allele functioned as a protective factor for African Americans; whereas, it was a risk factor for non-African Americans.

W77. A RANDOMIZED CONTROLLED TRIAL OF KETAMINE FOR ADOLESCENT TREATMENT-RESISTANT DEPRESSION

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Abstract: Nearly one in four adolescents will experience major depressive disorder (MDD), and suicide is the 2nd leading cause of death in this age group. 40% of adolescents with MDD fail to respond to initial treatment with selective serotonin reuptake inhibitors (SSRIs). Better treatments for adolescent depression are urgently needed. Ketamine has rapid antidepressant and anti-suicidal effects in adults with treatment resistant-depression (TRD), but there have been no prospective controlled trials in adolescents. The adolescent brain is a unique pharmacologic substrate and the proposed sites of ketamine's action (e.g. prefrontal cortex and hippocampus) are actively maturing during this time. Thus, it is important to carefully and directly test ketamine's antidepressant effects in adolescents with TRD. We have conducted a midazolam-controlled crossover trial to evaluate the effects of ketamine in treatment-refractory adolescent MDD over four weeks. Adolescents (13-17 years old) must have failed at least one adequate trial of a standard antidepressant to enroll. On day 1 and day 14 adolescent receive either ketamine (0.5mg/kg over 40 minutes) or midazolam (0.045mg/kg over 40 minutes). Subjects stayed on their psychiatric mediations, with stable dosing for the four weeks prior to the trial and the duration of the trial. For the primary outcome, paired t-tests compare MADRS score at 1 day following infusion between midazolam and ketamine. Scores of the other rating scales and timecourse are assessed as secondary measures. A subset of subjects (n=5) also underwent MRI neuroimaging at baseline, one day following ketamine, and one day following

midazolam. Seventeen adolescents completed the trial (average age 15.4 years old, range 13-17; 72% female). The average number of prior failed medication trials was 4.7 trials (+/- 3.3). On Day 1 ketamine significantly improved MADRS scores compared to midazolam. Adolescent TRD is a significant public health problem that is associated with significant morbidity and mortality. The brain undergoes substantial maturation during childhood and adolescence, and novel therapeutics must be carefully tested with attention to developmental context. Here we report the results of the first randomized controlled clinical trial of ketamine in adolescents with treatment-resistant depression. While encouraging, additional studies are needed to carefully evaluate the safety and efficacy of repeated ketamine dosing in this vulnerable population.

W78. INSURANCE COVERAGE OF PHARMACOGENOMIC TESTING AMONG PATIENTS WITH DEPRESSION

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Abstract: Purpose: Pharmacogenomics (PGx), a component of personalized and precision medicine, focuses on how genetic variation contributes to inter-individual variability in drug disposition, response, and adverse effects. Up to 42% of variance in antidepressant (AD) response is thought to be associated with genetic variation. The use of PGx-guided treatment in depression has been associated with increased treatment efficacy, decreased adverse drug events, and increased adherence rates. The most commonly prescribed classes of ADs are selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI). Actionable drug-gene pairs relevant to depression treatment include CYP2D6 genotyping for paroxetine (SSRI) and venlafaxine (SNRI), and CYP2C19 genotyping for citalopram, escitalopram, and sertraline (SSRIs). While clinical use of PGx testing is growing, little is known about how many patients receive PGx testing related to depression treatment through their insurance.
Methodology: We used an existing insurance claims dataset populated with medical and pharmacy claims for over 89 million patients from over 75 commercial health plans in the US. We identified a retrospective cohort of adult patients (age 18+) with at least one depression episode from January 1, 2013 to June 30, 2018 using the following criteria: (1) a diagnosis code indicating major depressive disorder (single or recurrent episode), neurotic depression, or depression not otherwise specified; (2) no depression related diagnoses during the 120 days prior to the depression episode; and (3) no AD fills during the 90 days prior to the depression episode. We identified covered claims for CYP2D6 and CYP2C19 PGx tests using procedure codes. Patients who paid for 100% of the costs of these PGx tests out-of-pocket were not represented in this data source. We estimated the incidence of CYP2D6 and CYP2C19 tests and described the demographic characteristics and antidepressant fills of patients that received such tests.
Results: 921,842 adult patients had at least one depression episode. Only 1274 (<1%) received a PGx test for CYP2D6 and 1394 (<1%) received a PGx test for CYP2C19 within 30 days of their earliest depression episode. Incidence of PGx testing for CYP2D6 and CYP2C19 increased over time, from 0.03% and 0.05%, respectively, in 2013, to 0.23% and 0.23%, respectively, in 2018. Of the patients who received a CYP2D6 or CYP2C19 PGx test (n=1441),

62% were female and 57% had some form of government insurance (i.e., Medicare or Medicaid); the average age was 41 years. Patients who received one of these tests were younger, less likely to be female, and more likely to have government insurance compared to patients who did not receive such a test. Of those who received a CYP2D6 or CYP2C19 test, 26% filled an AD within 30 days of their depression episode; 14% filled an SSRI and 6% filled an SNRI. Of those who filled an SSRI, 34% received the PGx test prior to filling the SSRI. Of those who filled an SNRI, 60% received the PGx test first.
Importance: Insurance coverage of PGx testing that can be used to guide depression treatment was low (<1% of the depressed cohort) but increased by 667% from 2013 to 2018. While PGx test results were not available for this cohort, many patients prescribed an SSRI or SNRI filled the prescription after the PGx test, indicating the results may have been used to guide their depression treatment. This study emphasizes the need to better understand utilization patterns and insurance coverage for PGx tests in patients with depression and other mental health conditions treated with ADs.

W79. MANAGING ESKETAMINE TREATMENT FREQUENCY TOWARD SUCCESSFUL OUTCOMES: ANALYSIS OF PHASE 3 DATA

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Abstract: Background: Esketamine nasal spray, a first-in-class glutamate modulator, is currently being developed for treatment-resistant depression (TRD). The aim of the current analysis was to evaluate the impact of symptom-based dosing frequency changes during esketamine treatment on clinical outcomes.
Methods: An open-label, long-term (up to 1 year), multicenter, phase 3 study of esketamine nasal spray enrolled 802 adults with TRD (NCT02497287, SUSTAIN-2 trial). During the initial 4-week induction period, eligible patients self-administered esketamine nasal spray twice weekly (28 [elderly only], 56, or 84 mg) and started a new oral antidepressant daily. In responders, esketamine dosing frequency was decreased to weekly (QW) for the next 4 weeks and then adjusted to the lowest frequency dosing interval (QW or every other week [EOW]) needed to maintain remission (as assessed by Montgomery-Åsberg Depression Rating Scale [MADRS] ≤12) in the Optimization/Maintenance (OP/MA) phase, with re-evaluation every 4 weeks. Symptom response was evaluated using Clinical Global Impression–Severity (CGI-S) score and MADRS total score.
In post hoc analyses, the relationship between assigned dosing frequency of esketamine and treatment response was evaluated. For CGI-S, treatment response (from the time of dosing frequency change to 4 weeks later) was defined as improved (Δ−1 to −4), stable (Δ 0), or worsened (Δ 1 to 4). The proportion of visits with remission were summarized by the following subgroups of patients by dosing frequency: required QW dosing throughout, switched to EOW once, and dosing frequency alternated back-and-forth (ALT) in the OP/MA phase.
Results: Of 778 patients treated with esketamine in the induction phase, 580 proceeded to the OP/MA phase. After 4 weeks of induction and based on the change in CGI-S, patients who responded had a 54% likelihood of maintaining the clinical benefit achieved and 26% likelihood of continued improvement despite a reduction in dosing frequency to QW for the

first 4 weeks. Thereafter, when dosing frequency could be further reduced from QW to EOW, 19% further improved, 50% maintained the benefit, and 31% worsened. For the patients no longer in remission after dosing frequency was reduced, an increase from EOW back to QW was correlated with positive outcomes: Based on 4 week change in CGI-S, 48% improved, 42% maintained benefit, and 10% did not improve 4 weeks after increasing the dosing frequency to QW.
Conclusions: Symptom-based lowering of the esketamine dosing frequency to QW after induction was successful in 80% of patients; 69% of regimen changes to EOW resulted in improvement/maintained clinical benefit. For patients who needed a temporary increase in dosing frequency, 90% of regimen changes back to QW resulted in improvement/maintained benefit. These data support individualization of esketamine nasal spray dosing frequency to optimize treatment response.

Thursday, May 30, 2019

Poster Session II

T1. ESTABLISHMENT OF THE MASSACHUSETTS GENERAL HOSPITAL POSTPARTUM PSYCHOSIS PROJECT (MGHP3)

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Abstract: Background: Postpartum psychosis (PP) is a severe and relatively rare disorder, occurring in 1-2 per 1000 women after delivery according to recent estimates (1). While previous research has consistently demonstrated a strong link between PP and bipolar disorder, about half of women who present with PP have no prior psychiatric history, obstructing identification of women at greatest risk (2). There have been significant discrepancies among studies attempting to identify risk factors for PP, a fact that may reflect differences in methodology and underlying heterogeneity in this population. The aims of MGHP3 are 1) to describe the phenomenology of PP regarding timing of onset, symptomology, and comorbidities, and 2) to identify clinical and genomic predictors of PP.
Methods: DNA is collected from women ages 18 and older who have experienced a psychotic episode within 6 months of a live birth, stillbirth, or intrauterine fetal demise occurring within the past 10 years. Participants are mailed saliva collection kits and are rigorously phenotyped by phone using a structured questionnaire and the DSM-5 Mini International Neuropsychiatric Interview for Psychotic Disorder Studies to gather demographics, medical and psychiatric history, and psychiatric symptoms before the postpartum period, during the episode of PP, and since the postpartum episode. Women who are identified as having pre-existing diagnoses for psychotic disorders such as schizophrenia or schizoaffective disorder before postpartum are excluded, as are women who endorse substance abuse aside from alcohol and marijuana within

the postpartum timeframe. DNA samples are processed for genome-wide analysis and genotype quality control. Clinical information is abstracted from subject interviews.
Results: Since the start-date of October 16, 2018 (https://womensmentalhealth.org/posts/mghp3-announcement/), participants have been enrolled with increasing recruitment pace, and a system of DNA sample procurement has been established. A multitude of recruitment avenues are utilized to reach eligible women, including the Massachusetts General Hospital Center for Women's Mental Health (CWMH) clinic, previous research participants at the CWMH, flyers, and provider referrals. In addition to these avenues, novel platforms including digital partnerships with advocacy groups and parenthood resource centers, provider networks, mental health forums, targeted social media outreach, and a CWMH registry of patients interested in research are leveraged to accession a diverse population of women who have experienced PP. The goal is establishment of a global PP consortium which will use consistent methods of phenotyping and genetic testing.
Conclusion: Modeled after existing psychiatric genetics initiatives, MGHP3 represents the first American initiative in reproductive neuroscience with this level of rigor and specificity. While previous studies have revealed inconsistent findings in part due to study population heterogeneity, the broad range of MGHP3 recruitment platforms allows accession of a diverse population of participants racially and geographically, permitting delineation of phenotypes in understudied populations using established, validated tools. Through the expansion of participant population and the pairing of genomic and clinical data collection, we will determine the degree to which PP risk reflects higher polygenic loading for schizophrenia or bipolar disorder versus a novel genetic signature. MGHP3 will examine genetic underpinning for this serious disorder and address critical questions about clinical presentation, attendant morbidity, and potential mortality of PP, which have eluded researchers.

T2. PREMENSTRUAL SUICIDAL IDEATION AS A DIMENSION OF PREMENSTRUAL SYNDROME: A CROSS-SECTIONAL STUDY OF A CLINICAL SAMPLE

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Abstract: Background/Significance: Premenstrual dysphoric disorder (PMDD) is a constellation of physical, cognitive, and affective symptoms causing clinically significant distress or interference occurring in the seven days prior to the onset of menses, after which they are minimal or absent (1). The DSM-5 reports a 1.8-5.8% 12-month prevalence of PMDD among menstruating women (1). While the definitive pathophysiology is not established, several lines of evidence support the theory that psychoactive metabolites of the ovarian steroid hormone progesterone, which rises steeply in the late luteal phase, exert an effect on GABAA receptors in the brain to produce the negative mood symptoms of PMDD in susceptible women (2, 3). Suicidal ideation is not included in the DSM-5 diagnostic criteria for PMDD, but the disorder is associated with increased suicidal ideation, plans, and attempts in epidemiological studies (4-6). Additionally, studies report increased prevalence of PMDD among female suicide attempters with rates from 15-54% (7-10).

Objectives: The aims of the present study are to assess the prevalence of passive or active suicidal ideation as a specific dimension of premenstrual syndrome as well as to use descriptive statistics to characterize the sample of women who experience premenstrual passive or active suicidal ideation.
Methods: The Women's Mood Disorder Task group of the National Network of Depression Centers developed a survey assessing women's mood across the lifespan that is being distributed in up to14 academic sites nationally. The survey encompasses demographics, current anxiety and depressive symptomatology (GAD-7 and PHQ-9), current and past psychiatric diagnoses and treatments, menstrual mood, perinatal mood, perimenopausal mood, and stressors including the Adverse Childhood Experiences (ACE) Questionnaire. Two questions assessing passive and active suicidal ideation (SI) in the premenstrual period were added to the menstrual mood section. Data collection is ongoing across the Zucker Hillside Hospital (ZHH) and Long Island Jewish Medical Center (LIJMC) campuses, including in ambulatory psychiatry and obstetrics-gynecology clinics, inpatient psychiatric units, and the partial hospitalization program. Women 18 and older utilizing these clinical services are approached by research or clinical staff and offered a one-time, anonymous, IRB-exempt survey.
Interim Results: During July-November 2018, 256 total surveys were collected. 54% had a positive screen for premenstrual symptoms with 11% concurrent passive SI and 9% concurrent active SI. For subjects psychiatrically hospitalized at ZHH: 53 total surveys collected with 70% positive premenstrual symptoms screen and 32% concurrent passive SI and 23% concurrent active SI. For subjects in outpatient psychiatry clinics: 75 total surveys collected with 52% positive premenstrual symptoms screen and 13% concurrent passive SI and 13% concurrent active SI. For subjects in outpatient obstetrics-gynecology clinics: 114 total surveys collected with 50% positive premenstrual symptoms screen and <1% concurrent passive and active SI. Further data analysis is planned following completion of the study database using REDCap survey and data management software (https://www.project-redcap.org/).
Conclusion: A subset of women with premenstrual syndrome may also experience concurrent SI, further highlighting the urgency of diagnosing and adequately treating this often-overlooked disorder.

T3. BREMELANOTIDE FOR HYPOACTIVE SEXUAL DESIRE DISORDER: CONTRACEPTIVE SUBGROUPS EFFICACY ANALYSIS

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Abstract: Objectives: Hypoactive sexual desire disorder (HSDD) is the most prevalent form of female sexual dysfunction in the United States and is characterized by a decrease or lack of sexual desire accompanied by distress. Bremelanotide, a melanocortin-4-receptor (MC4R) agonist and an analog of the endogenous neuropeptide α-melanocyte stimulating hormone, is an investigational drug that is currently being evaluated in premenopausal women with HSDD. The RECONNECT studies demonstrated that subcutaneous self-administration of

bremelanotide significantly improved sexual desire and decreased personal distress in premenopausal women with HSDD. The estimated prevalence of hormonal contraceptive use is approximately 17% among US women aged 15-44 years. In this analysis, bremelanotide efficacy was investigated across hormonal contraceptive subgroups.
Materials and Methods: The RECONNECT studies comprised two identically designed, phase 3, double-blind, randomized, placebo-controlled, IRB-approved studies. Subjects self-administered bremelanotide 1.75 mg or placebo subcutaneously for 24 weeks, using an autoinjector pen, on demand, prior to sexual activity. Subjects were evaluated ("yes" and "no" subgroups) based on concurrent use of hormonal contraceptives (including oral contraceptives and other estrogen-containing products). Efficacy was assessed using RECONNECT co-primary endpoints: change from baseline to end-of-study (EOS) for Female Sexual Function Index-desire domain (FSFI-D) and Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO) Item 13 scores.
Results: In the integrated population (N=1202), difference in mean change in FSFI-D and FSDS-DAO Item 13 from baseline to EOS (bremelanotide-placebo) was 0.35 and -0.33, respectively (P<0.0001 for both endpoints). In the study, 18.4% (N=221) concurrently used hormonal contraceptives ("yes" subgroup). Subjects in "no" subgroup who were treated with bremelanotide (N=484) showed a statistically significant increase in FSFI-D relative to placebo (N=497; 0.39, P<0.0001). Those in "yes" subgroup showed a numerical difference in favor of bremelanotide (N=112) versus placebo (N=109; 0.19, P=0.1557). Change from baseline to EOS in FSDS-DAO Item 13 was statistically significant in favor of bremelanotide relative to placebo in both subgroups (-0.30 and -0.34; P=0.0471 and P<0.0001, respectively).
Conclusions: In the RECONNECT studies, bremelanotide demonstrated consistent efficacy in premenopausal women with HSDD regardless of the type of contraceptive used. Bremelanotide restored sexual desire and improved related distress in premenopausal women with HSDD independent of concurrent use of hormonal contraceptives.

T4. TREATMENT UTILIZATION AMONG MEDICAID PATIENTS WITH NEWLY DIAGNOSED SCHIZOPHRENIA

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Abstract: Background: Schizophrenia is commonly treated with antipsychotics available in oral (OAP) and long-acting injectable (LAI) formulations. LAIs require less frequent administration and show better adherence than OAPs yet seem to be underutilized. This study described the use of LAI-aripiprazole (AP) and LAI-paliperidone (PP) among Medicaid patients with newly diagnosed schizophrenia in a real-world setting.
Methods: This was a retrospective study using the IBM® MarketScan® Medicaid Multi-State Database. Adults (≥18 years) with ≥1 medical claim for schizophrenia (ICD-9-CM diagnosis code 295 excluding 295.7, or ICD-10-CM code F20) and ≥1 pharmacy claim for an OAP between 1/1/2014 and 12/31/2015 were selected. The date of first schizophrenia diagnosis was the index date; the date of first observed OAP claim after index date was the OAP date. Patients were required to have at least 12 months' continuous enrollment before and after the index date. Patients with a claim for schizophrenia or any type of LAI during the 12-month pre-index

period, or those with dual eligibility for Medicaid and Medicare were excluded. The percentage of LAI-AP/PP use after diagnosis, percentage and type of OAP used before LAI-AP/PP initiation, and elapsed time between OAP and initiation of LAI-AP/PP were described. Patients were further categorized into those with or without pre-index OAP use based on whether an OAP was observed in the 12-month pre-index period.

Results: A total of 12,748 schizophrenia patients were included; mean (±SD) age was 42 (±14) years and 53.8% were female. The most frequently observed mental health–related comorbidities were depression (48.2%), substance abuse (47.2%), and bipolar disorder (38.6%). In the 12-month post-index period, 92.8% showed OAP use. 480 (4.1%) patients showed subsequent LAI-AP or LAI-PP use; of these, 74.0% used LAI-PP. Of LAI-AP users, 72.0% preceded use of LAI-AP with a second-generation (SG) OAP, with an average of 143 (±108) days from index date and 112 (±102) days from the OAP date to the LAI-AP initiation. 74.6% of patients with LAI-PP used SG OAP right before the first LAI-PP, and average time to LAI-PP was 151 (±110) days from the index date and 125 (±106) days from the OAP date. Among patients with pre-index OAP use (n=10,042), average time(±SD) to LAI-AP/PP was about 149 (±110)/156 (±113) days from the index date and 125 (±103)/134 (±109) days from OAP date. For patients without pre-index OAP use (n=2,706), average time (±SD) to LAI-AP/PP was about 129 (±116)/141 (±103) days from the index date and 79 (±91)/103 (±93) days from the OAP date.

Conclusions: Findings suggest that more patients with schizophrenia used LAI-PP than LAI-AP, although the overall rate of LAI utilization was low. Regardless of LAI-AP or LAI-PP, time to the LAI use was shorter for patients without pre-index OAP use compared with those with pre-index OAP use.

T5. INSULIN SENSITIVITY AND GLUCOSE METABOLISM OF OLANZAPINE AND A COMBINATION OF OLANZAPINE AND SAMIDORPHAN: PHASE 1 STUDY IN HEALTHY VOLUNTEERS

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Abstract: Background: ALKS 3831, a combination of the atypical antipsychotic olanzapine and the opioid receptor antagonist samidorphan (OLZ/SAM), is in development for the treatment of schizophrenia to provide the antipsychotic efficacy of olanzapine while mitigating olanzapine-associated weight gain. This phase 1 exploratory study compared short-term effects of OLZ/SAM, olanzapine, and placebo on measures of glucose, insulin, energy metabolism, and food intake over 3 weeks of treatment in healthy volunteers.

Methods: Healthy adults aged 18–40 years (BMI: 18.0 to <25.0 kg/m2) were randomized 2:2:1 to receive OLZ/SAM (10 mg olanzapine/10 mg samidorphan), olanzapine (10 mg), or placebo once daily for 21 days. Oral glucose tolerance tests (OGTT) were conducted under fasted conditions. Insulin sensitivity was assessed via hyperinsulinemic-euglycemic glucose clamp. Safety assessments included adverse events (AEs). Analysis of covariance was used to assess

treatment effects on insulin and metabolic end points. Due to the exploratory nature and small sample size, statistical significance was set at 0.10.
Results: Sixty subjects were randomized (OLZ/SAM, n=24; olanzapine, n=24; placebo, n=12) and received ≥1 dose of study drug. Overall, 19 (79.2%) in the OLZ/SAM, 22 (91.7%) in the olanzapine, and 11 (91.7%) in the placebo groups completed the study. In the OGTT, olanzapine led to significant hyperinsulinemia at day 19 vs baseline (geometric least squares mean [GLSM] ratio [90% CI], 1.408 [1.2304, 1.6108]; P<0.0001) that was not observed for OLZ/SAM (0.960 [0.8508, 1.0836]; P=0.5762) or placebo (1.062 [0.8986, 1.2559]; P=0.5476). Olanzapine significantly reduced insulin sensitivity on the 2-hour Matsuda index at day 19 vs baseline (GLSM ratio [90% CI], 0.766 [0.6732, 0.8726]; P=0.0012), a reduction not observed with OLZ/SAM (0.979 [0.8714, 1.1001]; P=0.7624) or placebo (1.114 [0.9495, 1.3068]; P=0.2631). In a post hoc analysis, significant increases in the hepatic insulin resistance index were observed on day 21 with olanzapine (Least squares mean [LSM] change from baseline [90% CI], 4.886 [2.3036, 7.4685]; P=0.0026) but not with OLZ/SAM (−0.518 [−2.7878, 1.7522]; P=0.7037) or placebo (−0.829 [−3.8285, 2.1707]; P=0.6451). No significant between-group differences were observed for change from baseline in the clamp-derived insulin sensitivity index at day 21. LSM change from baseline in weight, adjusted for race, was similar with OLZ/SAM (3.16 kg) and olanzapine (2.87 kg); these LSM changes were significantly higher than placebo (0.57 kg; both P<0.01). Caloric intake significantly decreased from baseline to day 22 with OLZ/SAM (−297.6 kcal; P=0.015); nonsignificant increases in caloric intake occurred with olanzapine (201.6 kcal) and placebo (92.6 kcal). Forty-nine subjects (81.7%) experienced ≥1 AE (OLZ/SAM, n=21/24 [87.5%]; olanzapine, n=19/24 [79.2%]; placebo, n=9/12 [75.0%]). Most AEs were mild or moderate.
Conclusions: In this short-term, exploratory study, 3 weeks of olanzapine treatment led to hyperinsulinemia and decreased insulin sensitivity with the OGTT and an increase in hepatic insulin resistance. These changes were not observed following treatment with OLZ/SAM or placebo. There was no difference between OLZ/SAM and olanzapine on the clamp-derived insulin sensitivity index or weight gain in these non-obese healthy subjects during the 3-week study. Treatment with OLZ/SAM was generally well tolerated.
Funding Statement: This study was funded by Alkermes, Inc.

T6. EXTRAPOLATING EVIDENCE OF ANTIPSYCHOTIC EFFICACY FROM ADULTS TO ADOLESCENTS: A QUANTITATIVE APPROACH TO INFLUENCE REGULATORY POLICY

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Abstract: Objective: Pediatric drug development is challenged by disease heterogeneity, patient recruitment, high attrition, and ethical concerns regarding specific trial designs. The enactment of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) provided pathways to obtain information regarding the safety and effectiveness of certain products in pediatric patients. In order to expedite future drug development, extrapolation-based methods have been proposed by the U.S. Food and Drug

Administration (FDA) to gather prior knowledge from previous studies to inform the need for additional information in the pediatric population. Evidence of a similar disease course and drug effect (exposure-response) could support the extrapolation of drug effectiveness. Although schizophrenia in adolescents is known to be continuous with that in adulthood, quantitative relationships between antipsychotic exposure and clinical response are relatively unexplored in adolescents. This analysis will provide an insight to FDA's justification on extrapolating efficacy from adults to adolescents with schizophrenia.
Methods: An adult and pediatric schizophrenia database was constructed using sponsor submitted applications to FDA and consisted of nine adult (N=17,778) and six adolescent (N=2,122) second-generation antipsychotic programs. A non-linear mixed effect and parametric time to event modeling approach was utilized to develop a disease-drug-trial model that examines the underlying placebo response, exposure-response relationship, and dropout patterns to predict longitudinal changes in the total Positive and Negative Symptom Scale (PANSS) scores. Similarities in placebo and antipsychotic-specific exposure-response relationships were evaluated by comparing model parameter estimate and longitudinally simulating adolescent total PANSS scores using an adult model. Clinical trial simulations were also explored to identify potential reasons for negative findings in two adolescent programs. Differences in major adverse effects were analyzed using FDA authored reviews and approved products labels.
Results: Placebo response was found to be similar between adults and adolescents at the week 6 trial endpoint. A non-linear model adequately described the relationship between average concentrations and the proportional change in total PANSS scores relative to baseline. Parameter estimates and simulations suggested similar exposure-response relationships between both populations. Inappropriate trial design and lack of statistical power were major reasons that led to negative findings in two adolescent programs. No new adverse events were reported in adolescent trials and minor differences in sedation, metabolic changes, and extrapyramidal symptoms were found between adults and adolescents.
Conclusions: This analysis demonstrates that extrapolation is possible to approve second-generation antipsychotics that have already been approved for adult use without the need for a dedicated adolescent efficacy trial. For drugs that have novel mechanisms of action, the FDA is considering including adolescent patients into adult pivotal trials. Pharmacokinetic and safety data in adolescents is still required to provide accurate dosing information on drug labels.

T7. THE EFFICACY OF LUMATEPERONE 42 MG IN THE TREATMENT OF SCHIZOPHRENIA: A POOLED ANALYSIS OF PHASE 2 AND 3 RANDOMIZED CONTROLLED TRIALS

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Abstract: Introduction: Lumateperone (ITI-007) is in late-phase clinical development for schizophrenia and other disorders. Lumateperone has a unique mechanism of action that modulates serotonin, dopamine, and glutamate neurotransmission. Lumateperone was evaluated in 3 randomized, double-blind, placebo-controlled studies in patients with acute exacerbation of schizophrenia. In 2 of the studies, lumateperone 42 mg (ITI-007 [lumateperone

tosylate] 60 mg) met the primary endpoint, significant reduction vs placebo in the Positive and Negative Syndrome Scale (PANSS) Total score. In 1 study, no significant difference between lumateperone 42 mg vs placebo was seen; however, the magnitude of improvement in PANSS Total score was similar to that seen in the positive studies. In all 3 studies, lumateperone was well tolerated. This pooled analysis of the 2 positive studies evaluated the efficacy of lumateperone 42 mg in the treatment of schizophrenia.
Methods: Data were pooled from the 2 positive studies for analysis. The primary efficacy endpoint in the pooled analysis was change from baseline to Day 28 in PANSS Total score. Secondary assessments included change from baseline in PANSS subscale scores (Positive Subscale [PS], Negative Subscale [NS], General Psychopathology Subscale [GPS], derived Prosocial Factor [PF]), and Clinical Global Impressions–Severity (CGI-S) score. Additional secondary endpoints were percent of patients meeting various PANSS response criteria (20%, 30%, and 40% PANSS improvement). Analysis of PANSS Total and subscale scores, and CGI-S score was conducted via a mixed model for repeated measures; PANSS response rates were analyzed using Fisher's exact test.
Results: The intent-to-treat population comprised 520 patients (n=221, placebo; n=224, lumateperone 42 mg; n=75, risperidone 4 mg). Lumateperone 42 mg significantly reduced PANSS Total score compared with placebo (least squares mean difference versus placebo [LSMD]= −4.76, P<.001) with efficacy similar to risperidone 4 mg (LSMD= −4.97, P=.014). Lumateperone 42 mg also showed significant efficacy vs placebo across 3 of the 4 PANSS subscales analyzed: PS, LSMD= −1.71, P<.001; NS, LSMD= −0.76, P=.098; GPS, −2.04, P=.009; PF, LSMD= −1.47, P<.001) and on the CGI-S (LSMD= −0.29, P<.001). Lumateperone 42 mg was associated with significantly higher PANSS response rates than placebo for each criterion level (20% improvement, 37% vs 50%, P=.010; 30% improvement, 24% vs 38%, P=.002; 40% improvement, 15% vs 25%, P=.010). Negative results from the third study did not impact the ability of lumateperone 42 mg to significantly separate from placebo when the 3 studies were pooled.
Conclusions: In this pooled analysis in patients with acute exacerbation of schizophrenia, lumateperone 42 mg significantly improved the symptoms of schizophrenia. Improvement on various PANSS subscales and greater rates of PANSS response suggest that lumateperone 42 mg has broad efficacy across schizophrenia symptoms and is associated with clinically meaningful improvement.

T8. RESULTS FROM A 12-MONTH OPEN-LABEL SAFETY STUDY OF LUMATEPERONE (ITI-007) IN PATIENTS WITH STABLE SYMPTOMS OF SCHIZOPHRENIA

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Abstract: Introduction: Lumateperone (ITI-007) is an investigational drug for the treatment of schizophrenia, bipolar depression, and other neuropsychiatric disorders. With a unique mechanism of action, lumateperone modulates serotonin, dopamine and glutamate neurotransmission. More specifically, lumateperone is a potent serotonin 5-HT2A receptor

antagonist, a dopamine D2 receptor pre-synaptic partial agonist and post-synaptic antagonist, a dopamine D1 receptor-dependent modulator of glutamate, and a serotonin reuptake inhibitor. In 2 previous placebo-controlled trials, lumateperone demonstrated statistically significant improvements over placebo on change from baseline on the Positive and Negative Syndrome Scale (PANSS) total score in patients with acute schizophrenia. In this population, lumateperone was found to be well tolerated with a safety profile similar to placebo. Moreover, the first part of an open-label safety study demonstrated a favorable safety profile, with improvement in metabolic parameters, when patients with stable schizophrenia were switched from standard-of-care (SOC) to lumateperone for 6 weeks of treatment. These safety benefits were lost when patients were switched back to SOC. The purpose of the present study, the second part of the open-label safety study, was to evaluate the safety and tolerability of lumateperone with treatment for up to 1 year.

Methods: The study population comprised 603 patients with schizophrenia who were treated for up to 1 year with lumateperone 42 mg (ITI-007 [lumateperone tosylate] 60 mg) QPM, with no dose titration. The primary objective was to determine the safety of lumateperone as assessed by adverse events, body weight, 12-lead electrocardiograms, vital signs, clinical laboratory tests, motor assessments, and the Columbia-Suicide Severity Rating Scale. The secondary objectives were to determine the effectiveness of lumateperone to maintain or improve psychopathology as measured by the PANSS and the Clinical Global Impressions–Severity (CGI-S).

Results: Lumateperone was well tolerated with a favorable safety profile. No new or worsening safety signals were reported with long-term treatment compared with short-term treatment. There were no clinically relevant changes in extrapyramidal adverse effect assessments. Mean body weight decreased from SOC antipsychotic baseline with long-term lumateperone treatment. Lumateperone also demonstrated a favorable cardiometabolic and endocrine safety profile. Symptoms of schizophrenia generally remained stable or improved as measured by PANSS and CGI-S scores.

Conclusion: Lumateperone represents a novel approach to the treatment of schizophrenia with a favorable safety profile in clinical trials. The lack of metabolic, motor, and cardiovascular safety issues presents a safety profile differentiated from SOC antipsychotic therapy. These data, taken together, are consistent with and extend data previously reported in placebo-controlled studies of lumateperone in patients with acute schizophrenia and in short-term studies of lumateperone's safety.

T9. THE SAFETY AND TOLERABILITY OF LUMATEPERONE 42 MG FOR THE TREATMENT OF SCHIZOPHRENIA: A POOLED ANALYSIS OF 3 RANDOMIZED PLACEBO-CONTROLLED TRIALS

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Abstract: Introduction: Lumateperone (ITI-007) is in late-phase clinical development for schizophrenia and other disorders. Lumateperone has a unique mechanism of action that modulates serotonin, dopamine, and glutamate neurotransmission. Lumateperone was evaluated in 3 randomized, double-blind, placebo-controlled studies in patients with an acute

exacerbation of schizophrenia. A pooled analysis of these studies was conducted to evaluate the safety and tolerability of lumateperone 42 mg (ITI-007 [lumateperone tosylate] 60 mg).
Methods: Data were pooled from the 3 phase 2 or 3 studies of lumateperone 42 mg in patients with schizophrenia. The safety population was defined as all patients who received at least one dose of placebo, lumateperone 42 mg, or risperidone 4 mg. Safety assessments included treatment-emergent adverse events (TEAEs), changes in laboratory parameters, and vital signs. Additional assessments included changes on the Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS), and Simpson-Angus Scale (SAS).
Results: The safety population comprised 1,073 patients (n=412, placebo; n=406, lumateperone 42 mg; n=255, risperidone). The only TEAEs that occurred in the lumateperone 42 mg group at a rate of ≥5% and twice placebo were somnolence/sedation (24.1% vs 10.0%) and dry mouth (5.9% vs 2.2%); rates for these TEAEs in the risperidone group were 23.9% and 4.7%, respectively. Rates of discontinuation due to TEAEs with lumateperone 42 mg (0.5%) were similar to PBO (0.5%) and lower than risperidone (4.7%). Mean change in weight was smaller for lumateperone 42 mg and placebo patients (1.6 kg and 1.3 kg, respectively) than risperidone patients (2.6 kg). Similarly, the percent of patients with clinically meaningful weight increase (≥7%) was similar for the lumateperone 42 mg and placebo groups (9.1% and 9.2%, respectively) and greater in the risperidone group (22.0%). Mean change from baseline in metabolic parameters were similar or smaller for lumateperone 42 mg vs placebo. Mean changes were notably higher in risperidone patients vs lumateperone 42 mg and placebo patients for glucose (7.7 mg/dL vs 0.7 mg/dL and 2.1 mg/dL), cholesterol (4.8 mg/dL vs −3.0 mg/dL and −1.6 mg/dL), and triglycerides (20.4 mg/dL vs −1.7 mg/dL and 4.6 mg/dL). Risperidone but not lumateperone 42 mg or placebo increased mean prolactin levels (34.9 ng/mL vs −1.3 ng/mL and −0.2 ng/mL). Changes in ECG parameters were low across treatment groups. Lumateperone 42 mg showed similar rates of EPS-related TEAEs using both narrow and broad standard MedDRA terms (3.0% and 6.7%) vs placebo (3.2% and 6.3%) and lower than risperidone (6.3% and 10.6%). Mean changes from baseline for BARS, AIMS, and SAS scores were similar across groups.
Conclusion: In this pooled analysis of 3 randomized, placebo- and active-controlled studies in patients with acute exacerbation of schizophrenia, lumateperone 42 mg showed good tolerability with potential benefits over risperidone for metabolic, prolactin, and EPS risks. These results suggest that lumateperone 42 mg may be a promising new treatment for schizophrenia.

T10. FOLLOW-UP ON THE DEVELOPMENT OF KARXT: RESULTS OF KAR-003, A MULTIPLE ASCENDING DOSE (MAD) STUDY OF A COMBINATION PRODUCT

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Abstract: Background: KarXT is a novel therapeutic consisting of xanomeline plus trospium. A previous Phase I clinical trial demonstrated that the addition of trospium, a peripheral cholinergic receptor antagonist that does not cross the blood brain barrier, to xanomeline substantially improved its tolerability by reducing peripheral cholinergic side effects. We now report the results of a Phase 1, multi-dose safety study aimed at optimizing the KarXT combination of xanomeline with trospium using a new BID co-formulation.

Methods: 69 healthy volunteers participated in the phase 1 multiple ascending dose (MAD) study of KarXT focusing on peripheral cholinergic side effects (nausea, vomiting, diarrhea, excess sweating and salivation), safety and tolerability. The study design was comprised of a 2-day titration period of either placebo or a KarXT dose of 50 mg xanomeline + 20 mg trospium followed by a 5-day treatment period. The doses (all BID) assessed were: xanomeline 100 mg, 125 mg and 150 mg in combination with trospium 20 mg or 40 mg.
Results: The 2-day titration of 50/20 was well tolerated in all cohorts. Cohorts dosing 100 and 125 BID of xanomeline were also well tolerated when paired with 20 mg and 40 mg BID of trospium, respectively. Doses of 150 mg were not well tolerated. Across the cohorts, cholinergic adverse events (ChAEs) were correlated with xanomeline dose. Increasing trospium dose to 40 mg BID ameliorated ChAEs, and lead to the observance of some anticholinergic adverse events (i.e., dry mouth). Saliva volumes collected corroborated with these findings. The saliva volume of the most affected cohort (125/40) decreased by 1.42 ml relative to baseline, contrasted with placebo which showed a 1.31 ml increase. Most AEs occurred within the first few days of starting or increasing the study drug. The majority of these AEs at 100 mg and 125 mg xanomeline-dose levels were mild and transient in nature. None of the cohorts showed meaningful changes in orthostatic HR or obvious differences in BP between placebo and KarXT compared to placebo. All cohorts receiving KarXT showed placebo-adjusted increases in mean resting HR consistent with past studies with xanomeline where short-term increases in resting HR were observed that normalized to baseline over time. Both trospium and xanomeline exposures (AUCs) and variability were comparable to KAR-001 where the compounds were given using separate formulations.
Conclusions: The new KarXT co-formulation of xanomeline and trospium performed well in healthy controls and is currently being tested in schizophrenia patients with acute psychosis at 100/20 and 125/30 doses. Longer term studies will provide further data around the safety and tolerability of KarXT, as well as the possible attenuation of AEs over time. No new safety signals were reported in the present study. The timing and duration of AEs were related to peak drug levels (Cmax) and suggest that there is a potential for increased tolerability over time. Importantly, the tolerability observed in this healthy volunteer study may not be representative of schizophrenic patients, who tolerate currently marketed antipsychotic medicines better than healthy volunteers.

T11. ANALYSIS OF SEXUAL FUNCTION IN A STUDY WITH ARIPIPRAZOLE ONCE-MONTHLY VERSUS PALIPERIDONE PALMITATE ONCE-MONTHLY

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Abstract: Introduction: People with schizophrenia may need life-long treatment with antipsychotic medication. In addition to providing good efficacy, the side-effect profile of a specific medication has influence on the patient's daily life and on the ability to adhere to treatment. Sexual dysfunction is a common side-effect of antipsychotic treatment and may contribute to non-adherence.
In the Qualify study (NCT01795547) the effectiveness of aripiprazole once-monthly 400 mg (AOM 400) was compared to paliperidone palmitate once-monthly intra-muscular injection

(PP1M) in a 28-week, open-label, rater-blinded for the primary outcome, setting in patients with schizophrenia aged 18-60 years. As previous treatment, a prescription of oral antipsychotic medication for at least 3 months was required.
AOM 400 showed superior improvements relative to PP1M on quality of life and functioning measured by the Heinrichs–Carpenter Quality-of-Life Scale (QLS) and had a favorable tolerability profile (1). AOM 400 treatment also resulted in significant improvements relative to PP1M in CGI-S.
A smaller proportion of patients in the study reported sexual dysfunction with AOM 400 versus PP1M at week 28, and a greater proportion of patients shifted from having sexual dysfunction at baseline to not having sexual dysfunction at week 28 with AOM 400 versus PP1M (2). Here, the results for sexual function are analyzed further.
Methods: Sexual function was evaluated as a secondary objective using the Arizona Sexual Experiences Scale (ASEX) at weeks 4, 8, 16, and 28. The ASEX is a patient-reported five-item scale with which patients rate their sexual experiences over the last week. Each item is rated from 1 to 6, for a possible total score of 5-30, with higher scores indicating greater sexual dysfunction. The ASEX items were analyzed descriptively in the two treatment groups and in younger (adults <35 years) and older patients (>35 years) and results are presented as mean values.
Results: Younger patients (adults <35 years) in the AOM 400 group showed numerical improvements at weeks 4, 8, 16, and 28 on all ASEX items, except for lubrication (women). At week 28, improvements shown as changes from baseline ranged from 0.5 to 0.8, whereas lubrication (women) worsened by 0.7. In the PP1M group, the effect was less consistent during the 28 weeks across ASEX items. At week 28 there was improvement in sex drive, erection (men), lubrication (women), orgasm, and satisfaction with changes from baseline ranging from 0.1 to 0.7.
In older patients (>35 years), AOM showed similar, yet less robust numerically improvement during the 28 weeks of treatment; Improvements at week 28 in all items except lubrication (women) with changes from baseline ranging from 0.1 to 0.6. In the PP1M group, there was no improvement in any items at week 4, 8, and 16. At week 28, there was a numerically improved sex drive, arousal, erection (men), and orgasm with changes from baseline ranging from 0.1 to 0.3.
The post-hoc results presented here represent small groups of patients, which may account for the variations in the results. A larger-scale study or a study specifically designed to measure sexual function would give more robust information about the effects of AOM 400 on ASEX items. It shows, however, how details of a side-effect can be presented to support the discussion with the individual patient about their specific medication concerns.

T12. ASENAPINE TRANSDERMAL PATCH (ASENAPINE TRANSDERMAL SYSTEM, HP-3070) IN THE TREATMENT OF ADULTS WITH SCHIZOPHRENIA: EFFICACY AND SAFETY IN A PHASE 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 6-WEEK, INPATIENT STUDY

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Abstract: Background: Asenapine is a 2nd-generation antipsychotic currently marketed in the US in sublingual (SL) form for the treatment of schizophrenia. HP-3070, asenapine transdermal system, is a once-daily patch for the treatment of schizophrenia in adults. Low- and high-dose HP-3070 were designed to be therapeutically equivalent to SL asenapine 5 mg BID and 10 mg BID, respectively.
Methods: In this international Phase 3, randomized, double-blind, placebo (PBO)-controlled, 6-week inpatient study, adults with an acute exacerbation of schizophrenia, Positive and Negative Syndrome Scale (PANSS) total score ≥80, and Clinical Global Impression–Severity of Illness Scale (CGI-S) score ≥4 were randomized 1:1:1 to HP-3070 high-dose, HP-3070 low-dose, or PBO. The primary objective was to evaluate efficacy of HP-3070 vs PBO by change from baseline (CFB) in PANSS total score to Week 6. The key secondary objective was CFB in CGI-S score at Week 6 vs PBO. Safety assessments included treatment-emergent adverse events (TEAEs), laboratory results, vital signs, dermal safety, and extrapyramidal symptoms (EPS) assessments (Barnes Akathisia Rating Scale, Abnormal Involuntary Movement Scale, and Simpson-Angus Scale).
Results: A total of 616 patients were randomized and 486 patients completed the study. Discontinuation rates were 23.3%, 18.6%, and 21.4% for HP-3070 high-dose, HP-3070 low-dose, and PBO, respectively; withdrawal of consent and AEs were the most common reasons for discontinuation across groups. Demographics and baseline characteristics were generally well-balanced among treatment groups. The majority of patients were male (60.6%), white (76.0%), and <55 years old (83.0%). For PANSS total score, least squares mean (LSM) estimates (standard error [SE]) of the treatment comparison (HP-3070 vs PBO) for CFB at Week 6 were -4.8 (1.634; 95% CI: -8.06, -1.64; p=0.003) and -6.6 (1.630; 95% CI: 9.81, 3.40; p<0.001) for HP-3070 high- and low-dose, respectively. For CGI-S CFB at Week 6, LSM (SE) for the treatment comparison were 0.4 (0.100; 95% CI: 0.55, 0.16; p<0.001) for HP-3070 high-dose and 0.4 (0.099; 95% CI: 0.64, 0.25; p<0.001) for HP-3070 low-dose. There were no deaths and no serious AEs related to study treatment. Most TEAEs were mild or moderate in severity and consistent with SL asenapine. The most frequently reported group of TEAEs in HP-3070-treated patients was nervous system disorders (24.0% and 21.6%, for high- and low-dose, respectively vs 12.6% for PBO), with headache and extrapyramidal disorder being most common. PBO patients had higher rates of psychiatric disorders (24.3% vs 15.7% and 17.6% for HP-3070 high- and low-dose, respectively), with insomnia and anxiety being most common. Application site TEAEs were higher with HP-3070 (14.2% and 15.2% for high- and low-dose, respectively) compared with PBO (4.4%). Rates of TEAEs leading to discontinuation of study treatment were 7.8%, 4.9%, and 6.8% for HP-3070 high-dose, HP-3070 low-dose, and PBO, respectively. Discontinuations due to application site reactions or skin disorders were low (≤0.5%) across treatment groups. There was no marked mean CFB for vital signs or ECG parameters, nor treatment differences observed on EPS assessments.
Conclusion: In this study, HP-3070 was efficacious, safe, and well-tolerated for treating schizophrenia in adults; both doses met primary and key secondary endpoints. As the first transdermal antipsychotic in the US, HP-3070 will provide patients with a novel treatment option.

T13. PHASE 1 HEALTHY VOLUNTEER PHARMACOKINETIC AND SAFETY PROFILE OF D-SERINE COMPARED TO CTP-692, A NOVEL DEUTERIUM-MODIFIED D-SERINE FOR ADJUNCTIVE TREATMENT OF SCHIZOPHRENIA

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Abstract: Currently approved schizophrenia drugs act predominantly by modulation of dopamine, or dopamine and serotonin receptors. However, genetic and neurobiological findings link N-methyl-D-aspartate (NMDA) receptor hypofunction to the etiology of schizophrenia. Moreover, treatment of patients with schizophrenia with the NMDA receptor co-agonist, D-serine, has been reported to result in improvement in positive and negative symptoms and cognitive dysfunction. CTP-692, a deuterated analog of D-serine, has the potential to be an effective, new adjunctive treatment for schizophrenia. The in vitro pharmacological properties of CTP-692 have been shown to be nearly identical to those of D-serine in terms of binding and functional activity at the glycine site of the NMDA receptor. A potential limitation to the development of D serine as a therapeutic is that it has been shown to cause nephrotoxicity in rats. In preclinical studies conducted by Concert, D-serine-induced nephrotoxicity in rats, reflected by significant increases in blood urea nitrogen (BUN) and serum creatinine, was found across a dose range consistent with that reported in the literature. However, rats treated with CTP-692 over the same dose range had BUN and serum creatinine levels in the normal range, suggesting a potentially improved renal toxicity profile. In preclinical pharmacokinetic (PK) studies, CTP-692 was found to have an increase in plasma and brain exposure and half-life compared to D-serine. The first-in-human, Phase 1 clinical trial evaluated the safety, tolerability, and PK of CTP 692 versus D-serine. Thirteen healthy volunteers between the ages of 18 to 55 were enrolled in the study. Eleven subjects completed the study and received a single oral dose of CTP-692 and a single oral dose of D-serine in a crossover design, separated by a 4-day washout period. The subjects were confined to the clinic until all safety and PK assessments were completed. CTP-692 blood samples for PK analysis were obtained at several time points after dose administration. Safety assessments included monitoring of adverse events, vital signs, 12-lead ECGs, physical examination and clinical laboratory testing including monitoring of kidney function. Consistent with the preclinical studies, CTP-692 was found to have increased plasma exposure compared to D-serine. In addition, CTP-692 was found to be generally well tolerated in healthy volunteers and no serious adverse events were reported. The results from this study will be presented.

T14. CLOZAPINE PRESCRIBING AND PATIENT CHARACTERISTICS AMONG OEF/OIF VETERANS TREATED AT THE DEPARTMENT OF VETERANS AFFAIRS: A DESCRIPTIVE REPORT

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Abstract: Introduction: Clozapine has demonstrated superior efficacy over other antipsychotics in treatment resistant schizophrenia, including reducing the risks of recurrent suicidal behaviors in this population (1). Still, clozapine prescribing rates remain low. While the suggested prescribing rate of clozapine to persons with schizophrenia is 20%, in the United States this rate is under 5% (2). In the VA, clozapine utilization rates vary significantly. (2)

The current study examined clozapine utilization and patient characteristics in Operation Enduring Freedom (OEF)/Operation Iraqi Freedom (OIF) Veterans treated in VA settings.
Methods: A longitudinal retrospective cohort analysis was conducted. Data was obtained from the VA Corporate Data Warehouse (CDW) and the national VA Informatics and Computing Infrastructure (VINCI). The initial cohort consisted of all OEF/OIF Veterans treated at the VA from 2006-2016 (N=1,316,531). Current analyses were performed on an identified sub-cohort consisting of all Veterans with VA-filled clozapine prescriptions during this period. We also extracted demographic characteristics, psychiatric hospitalizations, and all-cause mortality. Descriptive analyses included prescribing patterns among clozapine users. Inferential analyses examined predictors of clozapine use and associations between clozapine use with all-cause mortality and psychiatric hospitalizations.
Results: A total of 22,454 clozapine orders were filled by 90 VA facilities. Only 238 Veterans filled clozapine prescriptions through the VA during our study period. Excluding individuals with only inpatient fills, our analyses focused on the 203 Veterans with outpatient prescriptions. Veteran age ranged from 22 to 50 (M=31.29 +/- 5.96 years). Only 18 clozapine recipients were female (8.87%). Racial composition was: 147 white (72.41%), 29 black (14.29%), and 27 other races or declined to identify race (13.30%). The median number of days on outpatient clozapine was 288. Fifteen Veterans in our sub-cohort died during the study period. The median number of psychiatric hospitalizations was 4. Spearman correlations revealed no association between age and number of psychiatric hospitalizations or total days on clozapine. Mann-Whitney U tests indicated that females had a significantly higher number of hospitalizations than males. No race differences in hospitalizations were observed. Further analyses were performed on quartile groups based on Veterans' total outpatient days on clozapine: 1) <70; 2) 70-287; 3) 288-689; 4) >689 days. Binary logistic regression analysis indicated that neither age, race, gender, nor clozapine group were associated with mortality rate. Multinomial logistic regression indicated that the likelihood of being non-white to white was 2.04 times lower in the second compared to the fourth quartile. Conversely, the likelihood of being non-white to white was 35% higher in the third compared to the fourth quartile. Neither age nor gender effected the odds of being in any particular quartile.
Conclusions: Clozapine utilization amongst OEF/OIF Veterans treated at the VA appears very low, with only 203 of the 1,316,531 individuals in our sample filling outpatient prescriptions of clozapine through the VA over our study period. Race was the only demographic characteristic associated with differences in number of outpatient days on clozapine. No differences were observed between outpatient days on clozapine and either psychiatric hospitalizations or all-cause mortality, findings that may partially be explained by our limited sample size and the low mortality base rate in our sample.

T15. A PHASE 1 STUDY OF THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SINGLE AND MULTIPLE DOSES OF DNS-6288, A HIGHLY SELECTIVE PHOSPHODIESTERASE-2 INHIBITOR

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Abstract: Introduction: Schizophrenia is a serious mental disorder characterized by three domains that include positive symptoms, negative symptoms and cognitive impairment. Cognitive impairment associated with schizophrenia (CIAS) which appears early in the course of the illness has been correlated with poor functional outcome and adherence to treatment. Currently antipsychotic therapy is effective in managing positive symptoms but has demonstrated limited benefit in improving negative symptoms and cognitive impairment. Phosphodiesterase's (PDEs) are a superfamily consisting of 11 different families responsible for the metabolic degradation of the cyclic nucleotides (cAMP and cGMP) substrates. Phosphodiesterase 2A (PDE2A) is a dual-substrate enzyme and is allosterically activated by increased cGMP concentrations. Pharmacologic inhibition of PDE2A in rodent models of cognition have been shown to improve performance in object recognition and reverse drug-induced deficits in working memory and attentional set shift task. DNS-6288 is a highly selective inhibitor of PDE2A and may represent a novel treatment for CIAS.
Objectives: The primary objective is to assess the safety and tolerability of single and multiple ascending oral doses of DNS-6288 in healthy non-elderly and elderly volunteers. Additional objectives were to assess the food effect on the bioavailability of a single dose of DNS-6288 and to characterize the pharmacokinetic (PK) profile of single and multiple doses of DNS-6288.
Methods: DNS-6288 was evaluated in two randomized, double-blind, placebo-controlled Phase 1 studies, a single ascending dose (SAD), DNS-6288-101, and a multiple ascending dose (MAD), DNS-6288-102, in healthy non-elderly (18-55 y.o.) and elderly (65-80 y.o.) male and female subjects. In the SAD study, cohorts were administered single doses of DNS-6288 or matching placebo (6 active treatment/2 placebo). The effect of food on DNS-6288 was evaluated in the SAD study. In the MAD study, each cohort was administered DNS-6288 or matching placebo (7 active treatment/2 placebo) once daily for 14 days. Safety assessments and PK measurements were obtained up to discharge.
Results: Overall, DNS-6288 was well-tolerated when administered as single doses up to 125 mg in healthy non-elderly and up to 75 mg in elderly subjects. DNS-6288 was well-tolerated when administered once daily for 14 consecutive days in doses up to 75 mg to both healthy non-elderly adults and elderly adults. The most common reported adverse events in the SAD study were orthostatic hypotension and headache and in the MAD study, orthostatic tachycardia and constipation. No clinically significant abnormalities in other safety assessments were observed in healthy non-elderly and elderly subjects. DNS-6288 exposure increased proportionally with an increase in single and multiple doses administered to healthy non-elderly subjects. PK exposure increased proportionally with single doses of DNS-6288 but was slightly greater than proportionally in elderly subjects. DNS-6288 exposure was approximately 77%-110% higher for elderly subjects compared to non-elderly subjects
Conclusion: DNS-6288 was safe and well tolerated in single doses up to 125 mg and in multiple doses up to 75 mg in healthy non-elderly and elderly subjects, and demonstrated a pharmacokinetic profile supporting once-daily dosing. The results from the Phase 1 studies support continued evaluation of the clinical safety and efficacy of DNS-6288 in future studies.

T16. EXTERNAL MONITORING AND PANSS DATA QUALITY: FOCUS ON IDENTICAL RATINGS ACROSS VISITS

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Abstract: Introduction: In clinical trials identical scoring of all 30 PANSS items across visits is considered a marker of questionable data quality and raises questions about the thoroughness of the current interview and bias from scoring recollection of the previous visit. (Daniel and Kott, 2014) Independent review of recorded clinical trials interviews has been shown to detect poor interview and rating quality. (Daniel and Kott, 2014) In the current post-hoc analyses we examined the whether the presence of identical scoring of all 30 PANSS items from one visit to another was reflected in assessments of interview quality and whether external expert review was associated with a lower incidence of identical ratings.
Methods: Data from 8 multicenter double-blind randomized placebo-controlled schizophrenia studies were pooled for the analysis. Recordings of PANSS interviews were blindly assessed for interview and scoring quality by trained, calibrated independent reviewers. The reviewers were not aware of the presence or absence of identical scoring prior to evaluating interview quality in the current visit. For the purposes of the analysis interviews were dichotomized into interviews of adequate quality and deficient interviews. Association of interview quality with the presence of 30/30 PANSS items rated exactly the same across consecutive visits was examined using chi2 test of association.
Results: Our dataset consisted of 43,068 PANSS interviews, out of which 2,854 (6.6%) interviews were independently reviewed. In the overall dataset 5.15% of PANSS assessment were 100% identical in all 30/30 items compared to the prior visit. In the reviewed dataset the percentage of identical ratings was significantly reduced to 2.3% ($p<0.001$). In the reviewed assessments, identical ratings were more than twice as likely to be associated with interviews of deficient quality than with good quality interviews (3.7% vs. 1.7%, $p = 0.021$).
Discussion: External reviewers who were unaware of the presence of identically scored PANSS across visits judged the interview quality of identically scored visits to be deficient compared to other visits. This is consistent with the notion that identical ratings across visits are sometimes a product of being biased by the ratings of the previous visit instead of conducting a full, thorough interview in the present. Moreover, the presence of recording and external review was associated with a reduced prevalence of identical ratings compared to study visits where there was no recorded surveillance. The latter finding may be explained by both the effect of feedback and remediation from the external reviewers as well as the Hawthorne effect.

T17. IDENTIFYING YOUNG CANNABIS USERS AT RISK OF DEVELOPING PSYCHOSIS

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Abstract: Introduction: More than 50% of US youth have used cannabis (1) and it is currently unclear which cannabis users are at risk of developing persistent psychosis. Previous studies, based on self-reports, suggested that those who are exposed to cannabis in adolescence are at a particularly high risk of developing psychosis in adulthood (2). The first objective of this study was to use toxicology results from urine drug screens (UDS) to test the hypothesis that adolescent cannabis use is associated with developing psychosis in young adulthood. Secondly, previous self-report studies suggest that teenagers who use more cannabis are at a higher risk

of developing psychosis (2). The second aim of our investigation was to use urine tetrahydrocannabinol (THC) concentrations to test this association. Thirdly, only a fraction of cannabis users will develop a psychotic illness and it is currently unclear which users are most susceptible to developing psychosis. Our third aim was to identify a phenotype of cannabis users at highest risk of developing psychosis.
Methods: These studies were done in collaboration with the Rochester Epidemiology Project. We performed a retrospective analysis of all 13-18 years old residents of the Olmsted County (MN) who received a completed UDS test between 1998 and 2012. Our final cohort consisted of 2,772 subjects. We first compared UDS negative teenagers to THC positive teenagers. The main outcome measure was the rate of new-onset non-substance induced psychosis in young adulthood (19-24 years of age). We then compared the maximal THC/creatinine concentration detected between ages 13-24 in patients with and without non-substance induced psychosis. Thirdly, we gathered data on postnatal complications (e.g. preterm birth, hyperbilirubinemia) to test the interaction between postnatal events and adolescent cannabis use in increasing the risk of psychosis.
Results: Male THC positive teenagers have a higher risk of developing psychosis in young adulthood (OR= 1.8 (1.1-2.9), p=0.009), this effect was not found in females. THC positive youth had a higher risk of continued illicit substance abuse in young adulthood (OR=3.1 (2.6-3.8), p<0.0001). Our post-hoc analysis to control for the effects of substance use in young adulthood showed that using illicit substances between 19-24 years of age is more strongly associated with developing psychosis in young adults (OR=8.5 (5.1-14.0), p<0.0001) compared to THC results in adolescence. Secondly, we found significantly higher THC/creatinine concentrations in patients who develop a non-substance induced psychotic disorder (p=0.02). Our preliminary results show that THC positive youth with a history of postnatal complications have significantly higher risk of developing non-substance induced psychosis compared to THC positive peers without postnatal complications (p=0.02).
Conclusions: Our results support the role of cannabis use in developing non-substance induced psychosis. However, we found no evidence in support of an incubation period between using cannabis in adolescence and developing psychosis in young adulthood. Instead, our results suggest that adolescent cannabis users have a higher risk of continued substance use in young adulthood, which in turn increases the risk of developing psychosis. Our results also support a "double hit" hypothesis of perinatal complications interacting with cannabis use to increase the risk of developing psychosis in youth.

T18. QUALITY OF REST AND TREATMENT ADHERENCE IN SERIOUSLY MENTALLY ILL PATIENTS RECEIVING TREATMENT WITH A DIGITAL MEDICINE SYSTEM

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Abstract: Objective: The aim of this study was to define a cluster-based methodology for quantifying 'rest quality' patterns in seriously mentally ill patients using accelerometer data and to subsequently examine potential relationships between quality of rest patterns and medication ingestion behaviour.

Methods: A total of 102 patients from two clinical studies [1, 2] with digital medication ingestions were used. Body posture and step-rate were used to differentiate rest and non-rest records within the accelerometer data, which was partitioned into 15-minute non-overlapping time intervals (windows): These windows were categorized as rest, non-rest or missing based on the predominant state of the window. This classification was used to identify the longest period of rest (LPR) within each day. For all data in LPR, K-means clustering (K=2) was used to identify the patient's rest-reference (RR) and deviation-from-reference (DFR) cluster leveraging 4 actimetry-based features. The Euclidean distance between the RR's center and each point in DFR was calculated. The total rest quality (RQ) score for each window in LPR was defined by summation of all DFR distances within that interval. LPR duration, start time, and total RQ were normalized to their respective Z-scores across all days. Rest Z-score was calculated as a summation of these three Z-scores for each treatment day. Ingestion time deviations were also normalized to Z-scores and compared with daily rest Z-score to explore possible association between ingestion time pattern and RQ metric for each patient. The Data manipulation and analysis was completed using Python.
Results: Patients in this dataset were largely adherent to medication, making it challenging to characterize naturalistic behavior for patients with low-adherence (only 6% of population had less than 40% ingestion coverage). 12 out of 26 patients with relatively lower rest quality (lower 25th percentile), had more than 70% ingestion coverage and 4 out of 7 patients with low ingestion coverage (less than 40%), had relatively low rest quality. The distribution of rest score for days with and without ingestion were compared and no specific difference were observed; However, 31 out of 68 patients with at least one day of increased ingestion time deviation, had a subsequent elevated rest Z-score within a one-day period. The Z-score threshold was calculated based on the 95th percentile of ingestion time and rest score. There was also no correlation with number of occurrences and magnitude of deviation.
Conclusions: This work aimed to identify and investigate the longest period of rest and quantify the quality, consistency and stability of rest within each patient. It was shown that rest quality was not a strong indicator of ingestion behavior in this population and it begs the question of how informative rest patterns are in the absence of ingestion data. Patients in this dataset were largely adherent to the medication, so there was not enough data representing non-adherent or low adherent patients. Future work to apply this frame work to larger sample size that has enough patients to represent different adherence level.

T19. FROM SCIENCE TO PRACTICE: STRATEGIES FOR PHARMACOTHERAPISTS MANAGING COMPLICATED GRIEF

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Abstract: Purpose: Describe how pharmacotherapy results of a recently reported 4-site randomized controlled treatment study of complicated grief (CG) can inform clinical practice.
Content: Bereavement is a severe life stressor. Some bereaved individuals struggle to adapt to the death of a loved and experience prolonged, intense affects, behaviors and life situations that interfere with adaptation. The resulting condition, Complicated Grief (CG), is an especially

severe, protracted and disabling form of grief. Providing effective treatment for individuals with CG is of great consequence because CG elevates risk for medical and psychiatric morbidity and mortality, including increased suicide risk. CG can be diagnosed with a clinical interview, ideally aided by readily available screening instruments and questionnaires. Yet in clinical practice CG often is missed entirely and/or misdiagnosed as Major Depressive Disorder (MDD). Although sorrow is often prominent, CG's core symptoms of persistent and pervasive yearning and/or preoccupying thoughts of the deceased are different from the depressed mood, anhedonia, worthlessness, psychomotor and neuro-vegetative symptoms that are the hallmarks of MDD. When accurately diagnosed and properly managed, CG can carry a good prognosis. We completed a multicenter study that confirmed efficacy of short-term complicated grief therapy (CGT) aimed at facilitating adaptation to loss. We did not confirm efficacy of antidepressant medication for CG, either with or without CGT. However, we found evidence that administering a pill plus a 20-minute clinical management session was helpful to many patients. This form of clinical management was based on the principles used in CGT. We believe these can be easily learned and provided by pharmacotherapists and would greatly improve the care of suffering patients. The purpose of this poster is to outline principles, strategies and procedures for managing patients with CG that can be integrated into a general psychiatric practice.
Methodology: Our 4-site study enrolled 395 bereaved adults who met criteria for CG and were randomized to: citalopram alone (n=101), placebo alone (n=99), citalopram + CGT (n=99) or placebo + CGT (n=96). Two-thirds also met criteria for current MDD. Pharmacotherapists monitored grief symptoms and provided CGT-informed clinical management that included helping patients understand grief and adaptation to loss. Pharmacotherapists also provided support for resuming normal life activities and monitored depressive symptoms, suicidal thinking, medication adherence, and adverse effects.
Results: Overall CG response rates were: citalopram without CGT - 69%, placebo without CGT- 55%, citalopram + CGT- 84%, placebo + CGT- 83%. While we confirmed the efficacy of CGT, we were unable to document a medication effect on CG symptoms. However, of particular interest to clinical practitioners, we found a moderate response to pill (whether citalopram or placebo) plus clinical management on CG symptoms and a significant citalopram effect on depressive symptoms among those who received citalopram + CGT.
Conclusions and Importance: Our findings suggest that a simple, efficient version of CGT that can be readily integrated into clinical practice may be very helpful for bereaved patients. We believe that pharmacotherapists can improve the care of bereaved patients considerably if they learn to recognize and monitor grief symptoms, understand what is needed to adapt to loss, and learn to provide a simple supportive grief-focused management strategy in conjunction with clinical judgment regarding the use of adjunctive medication.

T20. RARE OPHTHALMOLOGIC SIDE EFFECTS OF ARIPIPRAZOLE

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Abstract: Background: Aripiprazole is a commonly used atypical antipsychotic medication, with rarely reported ophthalmologic side effects. To date, only 8 cases of aripiprazole-induced

myopia have been described in the literature. We report two additional more cases of aripiprazole-induced ophthalmologic side effects.
Methods: We review extensive literature and present two cases of aripiprazole-induced ophthalmologic side effects.
CASE 1: A 28-year-old woman of mixed ethnicity presented to an outpatient clinic for irritability, having recently been discharged from an inpatient psychiatric unit, where duloxetine 30 mg and aripiprazole 2 mg were initiated. Thereafter, she experienced new-onset jerky eye movements. As the combination was started concurrently, it was unclear which medication was responsible for these effects. She described her eye movements as uncontrolled crossing, lasting approximately one second, and occurring roughly twice a day, associated with neither any particular activity nor specific time of the day. She denied associated eye pain and said these did not affect her ability to read or drive. These symptoms were neither exacerbated nor improved when aripiprazole was increased to 5 mg to target her psychiatric symptoms, but neither did the increased dose improve those symptoms. In light of possible side effects and inefficacy, aripiprazole was tapered to discontinuation. Her side effects abated only after the aripiprazole was stopped.
CASE 2: A 48-year-old Caucasian man presented to an outpatient clinic for severe obsessive-compulsive disorder (OCD), having failed several psychotropic trials. Aripiprazole 2 mg was initiated and tolerated well for 2 weeks with partial OCD symptom improvement. A week after the dose was doubled, he reported new onset episodic blurry vision. His vision changes were not associated with any other symptoms but were more pronounced when using his computer. A dose decrease back to 2 mg improved but did not abolish these episodes over the next two weeks, so aripiprazole was discontinued, resulting in worsening OCD symptoms but complete resolution of the blurry vision.
Conclusion: Psychiatrists need to be vigilant for ophthalmologic side effects from aripiprazole. Most reported cases involve myopia, but one of our cases experienced uncontrolled eye movements, the mechanism of which is unclear. Expanding the case literature to include such incidents adds to our collective understanding of potential ophthalmologic side effects of this commonly prescribed medication.

T21. EFFICACY AND SAFETY OF DASOTRALINE IN ADULTS WITH BINGE-EATING DISORDER: A RANDOMIZED, DOUBLE-BLIND, FIXED-DOSE TRIAL

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Abstract: Background: Dasotraline is a long-acting dopamine/norepinephrine reuptake inhibitor with a PK profile characterized by slow absorption and a t½ of 47-77 hours, permitting once-daily dosing. In a previous flexible dose study, dasotraline demonstrated significant efficacy in the treatment of binge-eating disorder (BED). The aim of this fixed-dose confirmatory study was to evaluate efficacy and safety of dasotraline in the treatment of patients with BED.
Methods: Patients meeting DSM-5 criteria for BED were randomized to 12 weeks of double-blind treatment with dasotraline (4 mg/d and 6 mg/d), or placebo. The primary efficacy

endpoint was change in number of binge-eating days per week at week 12. Secondary efficacy endpoints included Week 12 change on the Binge Eating Clinical Global Impression of Severity Scale (BE-CGI-S), the Yale-Brown Obsessive-Compulsive Scale Modified for Binge Eating (Y-BOCS-BE), and the proportion of patients with 4-week cessation of binge-eating episodes at Week 12-endpoint. Efficacy was assessed using an MMRM analysis with a pre-specified sequential testing procedure used to control overall type I error rate.
Results: The modified ITT population consisted of 485 patients. At week 12, treatment with dasotraline was associated with significant reduction in number of binge-eating days per week in the 6 mg/d group vs. placebo (-3.47 vs. -2.92; P=0.0045), and non-significant improvement in the 4 mg/d group vs. placebo (-3.21; P=0.12). Improvement in secondary efficacy measures and nominal p-values (not adjusted for multiplicity) generally favored dasotraline. Changes on the BE-CGI-S for the 6 mg/d and 4 mg/d groups vs. placebo were -2.27 vs. 1.77 (P<0.01), and -2.13 vs. 1.77 (P<0.05), respectively. On the YBOCS-BE scores for the 6 mg/d and 4 mg/d groups the changes were -15.2 vs. -11.8 (P<0.01) and -14.1 vs. -11.8 (P<0.05), respectively. The proportion of patients who achieved 4-week cessation of binge-eating episodes was 34.0%, 33.5% and 30.2% for the dasotraline 6mg/d (p=0.64), dasotraline 4mg/d (p=0.80), and placebo groups, respectively. The most common adverse events on dasotraline 6 mg/d and 4 mg/d were combined insomnia (early, middle, late), dry mouth, headache, decreased appetite, nausea, and anxiety. Changes in systolic and diastolic blood pressure were minimal. Mean baseline to endpoint changes in supine pulse rate on dasotraline 6 mg/d and 4 mg/d vs. placebo was +6.2 bpm and +4.8 vs. +0.2 bpm.
Conclusions: In this 12-week, placebo-controlled, fixed-dose study, treatment with dasotraline 6 mg/d was associated with a significant reduction in frequency of binge-eating days per week; efficacy was not demonstrated for the 4 mg dose. Treatment with both doses of dasotraline resulted in improvement in binge-eating related obsessional thoughts and compulsive behaviors on the Y-BOCS-BE, and in global improvement on the BE-CGI-S. Dasotraline was safe and generally well-tolerated at both doses; most common adverse events were insomnia, dry mouth and headache.
Clinicaltrials.gov number: NCT03107026

T22. EFFECT OF DASOTRALINE ON BODY WEIGHT IN PATIENTS WITH BINGE-EATING DISORDER

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Abstract: Background: Binge-eating disorder (BED) is associated with obesity (BMI ≥30) in ~40-45% of patients, with approximately 20% of the obese subgroup meeting class III criteria (BMI≥40). Dasotraline is a long-acting dopamine/norepinephrine reuptake inhibitor with a PK profile characterized by slow absorption and an elimination half-life of 47-77 hours, permitting once-daily dosing. In a recent placebo-controlled, flexible-dose study, dasotraline demonstrated significant efficacy in patients with BED. We now report an analysis from this study of the effect of dasotraline on body weight.
Method: Patients with moderate-to-severe BED, based on DSM-5 criteria, were randomized into a 12-week, double-blind, placebo controlled, flexible-dose trial of dasotraline (4-8 mg/d).

The primary efficacy measure was number of binge-eating days/week. Mean change in body weight at Week 12 was analyzed by baseline body mass index (BMI, kg/m2) category, and by mean modal dose of dasotraline (4, 6, or 8 mg/d). Inferential statistics were not performed.
Results: The safety population consisted of 317 patients (female, 84%; mean age, 38.2 years; mean weight, 97.3 kg). At baseline, the proportions of patients in each BMI category were as follows: normal (<25 kg/m2: 5.7%), overweight (25 to <30: 18.1%), obesity class I (30 to <35: 25.1%), class II (35 to <40: 29.2%), and class III (≥40: 21.9%). For the overall patient sample, treatment with dasotraline significantly reduced the number of binge-eating days per week vs. placebo (-3.74 vs. -2.75; P<0.0001; effect size = 0.74). Mean LOCF-endpoint changes in weight (kg) for dasotraline vs. placebo, by baseline BMI category, were as follows: normal weight (-3.40 vs. -0.13), overweight (-4.98 vs. +1.29), obesity class I (-4.17 vs. +0.17), class II (-3.47 vs. +0.26), class III (-7.52 vs. +0.35); and obesity classes I-III combined (-4.81 vs. +0.26). For the dasotraline group, the proportion of patients at LOCF-endpoint with ≥5% or ≥10% reduction in weight, respectively, were as follows: normal weight (57.1% and 28.6%), overweight (64.5% and 22.6%), obesity class I (44.7% and 15.8%), class II (36.2% and 6.4%), and class III (59.4% and 21.9%). No patients on placebo had ≥5% reduction in weight during the study. No dose-related effect of dasotraline on change in weight was observed across the baseline BMI categories. For the dasotraline group, the Spearman correlation between LOCF-endpoint change in binge-eating days per week and change in weight was 0.34 (P<0.001).
Conclusion: In this placebo-controlled 12-week study of dasotraline in patients with moderate-to-severe binge-eating disorder, treatment with dasotraline (4-8 mg/d) was associated with significant reduction in binge-eating days per week. Among patients completing 12 weeks of treatment with dasotraline, weight reduction ≥5% was observed in approximately 40% of obese patients with a BMI ≥30. There was a significant correlation between endpoint reduction in binge-eating and reduction in weight.
Clinicaltrials.gov number: NCT02564588

T23. A MODIFIED-RELEASE DRUG DELIVERY TECHNOLOGY CONTAINING AMPHETAMINE-ION EXCHANGE COMPLEXES

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Abstract: The proprietary, immediate and extended drug delivery technology LiquiXR® utilizes an ion-exchange resin that complexes with amphetamine or any other active moiety that can be protonated and is water-soluble. The active ingredient of the drug product forms a complex with an ion exchange polymer of the resin resulting in very fine, micron-sized particles. A portion of these particles is then coated with an aqueous, pH-independent polymer designed to provide sustained release of drug product. The polymer coating applied to the ion-exchange resin particles is of varying thickness, allowing for extended release of active drug product while uncoated particles provide for immediate release of active drug product.
The micron-sized particles lend themselves to being formulated into an appropriate dosage form (solid or chewable tablet, liquid suspension, orally disintegrating tablet, film, or capsules). Active ingredient of drug product is subsequently released from the dosage form in millions of particles, with the release driven by a combination of ion exchange and diffusion. After drug release, the ion-exchange resin particles are excreted in the feces.

The release characteristics of LiquiXR® allow for customized, sustained release of active drug for up to 24 hours post-dose. Mechanistically, drug particles enter the gastrointestinal (GI) tract. As positively-charged ions from GI fluids diffuse across the coating, it displaces drug ions from product and they diffuse through the coating and into the GI fluids for absorption. As the coating is of variable thickness, some drug product takes longer to diffuse and absorb, providing for the delayed drug release characteristics.
The LiquiXR™ drug delivery technology has already been successfully utilized in the development of treatment options (liquid suspension and chewable tablet) that offer rapid absorption and sustained plasma levels after once-daily dosing. LiquiXR is utilized in Dyanavel® XR (amphetamine extended-release oral suspension; AMPH EROS), which is indicated for the treatment of attention-deficit hyperactivity disorder. It comprises 2.5 mg/mL amphetamine base and uses LiquiXR technology to provide an immediate release component followed by an extended-release profile.
The efficacy of AMPH EROS was established in children ages 6 to 12 years in a Phase 3, placebo-controlled laboratory classroom study. In that study, ADHD symptoms in children on an individually optimized dose of amphetamine (range 10-20 mg/day) were statistically significantly improved compared with symptoms in children treated with placebo. For children treated with AMPH EROS, onset of effect was demonstrated at 1 hour after dosing, and efficacy was observed through 13 hours post-dose. The effect size was comparable to effect sizes demonstrated for other psychostimulants tested in studies using a similar design. The efficacy data reported for AMPH EROS provides an excellent example of the potential utility and clinical application for other active drug products requiring an immediate release and extended release profile.

T24. CUMULATIVE BURDEN OF ILLNESS IN VETERANS WITH TARDIVE DYSKINESIA AND SERIOUS MENTAL ILLNESS

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Abstract: Objectives: Data on the impact of tardive dyskinesia (TD) affecting health, financial status, and quality of life remain scarce. To inform cost-benefit treatment decisions, the prevalence of TD and patient characteristics, comorbidities and outcomes by TD status were assessed in Veterans with serious mental illness (SMI) in a retrospective cross-sectional study.
Methods: Veterans with schizophrenia/schizoaffective, bipolar and major depressive disorders receiving antipsychotics for ≥ 30 days in VISN 4 facilities during 10/1/2014─9/30/2015 were identified. Prevalence of TD was determined by ICD-9-CM codes and compared with Abnormal Involuntary Movement Scale (AIMS) scores via Student's t-tests. Risk factors and correlates of TD were examined using Chi-square or t-tests. Odds ratios (OR) and beta parameters with 95% confidence intervals (CI) for categorical and continuous outcomes associated with TD were derived from a multivariate logistic and linear regression respectively, adjusting for risk factors associated with TD.
Results: Among 7985 Veterans with SMI on antipsychotics, 332 (4.2%) were diagnosed with TD. Veterans with TD were more likely to be older (mean ± SD; 59.9 ± 10.8 vs. 54.5 ± 12.8,

p<0.0001). There were no significant differences between Veterans with and without TD in gender or race (both p>0.05). Those with TD were more likely to have schizophrenia/schizoaffective disorder (50.3% vs. 39.7%, p<0.001) and less likely to have bipolar disorder (29.2% vs. 35.4%, p=0.02) but there were no significant differences in major depressive or post-traumatic stress disorder diagnoses (both p>0.08). There were no differences in receiving antidepressants, mood stabilizers, or the type or number of antipsychotics (all p>0.07). There were no differences in marital status, homelessness, or financial status (all p>0.3). Veterans with TD had a higher mean ± SD Charlson Comorbidity Index (1.6 ± 1.8 vs.1.0 ± 1.6, p=0.0007) and a higher rate of medical hospitalizations (16.9% vs.11.0%, p=0.017) but did not differ in mortality rate (1.2% vs. 1.5%, p=0.378). Veterans with TD compared to those without TD were not significantly different in rates of emergency visits (0.3% vs.0.4%) and hospitalizations for substance use (5.4% vs. 6.1%) or psychiatric disorders (16.0% vs. 13.6%) (all p>0.09). Mean ± SD total AIMS awareness/incapacitation scores (0.7 ± 1.2 vs. 0.1 ± 0.6, p<0.0001) were significantly higher for patients with TD. Updated results from regression analyses adjusted for risk factors of TD (age, diagnosis) will be presented at the meeting.
Conclusions: TD was recorded as a diagnosis in 4.2% of Veterans receiving antipsychotics and was strongly associated with age, schizophrenia/schizoaffective disorder, medical comorbidity and medical hospitalization. TD may be a marker for a cluster of variables predictive of serious adverse health outcomes and impairments in quality of life. But TD remains underreported and undocumented due to lack of consensus on diagnosis and coding. More assertive screening, monitoring and treatment of patients at risk of TD is needed.

T25. COMPREHENSIVE MODEL OF INFORMATION SEEKING FOR UNDERSTANDING THE PROBABILITY OF REQUESTING PHARMACOGENOMIC TESTING FOR PSYCHOTROPIC MEDICATIONS

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Abstract: Background: Research has identified potential benefits and risks of psychopharmacogenomic testing (PPGT). More research is needed to understand the actual effects of PPGT on patient outcomes. One potential unexplored facet in this domain is understanding what influences patients' decisions to elect PPGT. Patients' decisions to choose PPGT when offered may be influenced by multiple factors, which are currently unknown. Understanding patients' decisions regarding PPGT may allow for optimization of PPGT integration into clinical practice, which may enhance clinical outcomes.
Objective: Determine relationships between probability of requesting PPGT and: (1) potential risks and benefits of PPGT; (2) thoughts, emotions, behaviors, and psychosocial factors; (3) predicted responses to genetic testing.
Methods: Ninety consecutive adult patients naïve to genetic and pharmacogenomic testing were enrolled in a prospective study after providing informed consent when presenting for first-time appointments in an outpatient psychiatry department over a period of 10 months. All participants completed a three-part experiment: 1. Participants were presented with a

hypothetical genotype-positive genetic testing result, and rated their expected emotional response, expected risk of developing a psychiatric disorder, and probability of changing their behavior in response to disease risk; 2. Participants were exposed to potential benefits of PPGT, and rated the probability (0-100%) of electing PPGT; 3. Participants were subsequently exposed to potential risks of PPGT simultaneously with benefits and re-rated the probability of electing PPGT. To control for potential confounders participants also completed measures of symptom severity (Symptom Checklist-90-R), disability severity (Sheehan Disability Scale), locus of control (Multidimensional Health Locus of Control Scales), health history and family health history.
Results: A series of linear regression analyses were performed. Results indicate that probability of PPGT was significantly predicted by the effect of psychiatric symptoms on family/home life responsibilities (β=.248; p=.019), and predicted behavior change in response to positive genetic testing results (β=.391; p<.001). The only significant predictor of change in probability of PPGT from baseline was effect of psychiatric symptoms on family/home life responsibilities on risk that best medications would not be usable due to medical problems (β=.247; p=.019).
Conclusion: The pilot data from this experimental study demonstrate that patients' interest in PPGT is dynamic. Patients' valuation of PPGT varies based on psychosocial factors, health status, and disease severity. Although most PPGT research to date has emphasized the effects on physicians' clinical decisions, our data point toward the importance of examining patients' perspectives. Future lines of research must seek to replicate these results to identify their robustness and extend them to understanding how the factors identified in our study interact with physician decision-making. Understanding the patient-physician interaction in the use of PPGT will allow for a more accurate estimate of the actual effect of PPGT as part of patient care.

T26. "LIVING WITH TARDIVE DYSKINESIA": A PATIENT EDUCATION INITIATIVE

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Abstract: The purpose of the proposed poster is to share with physicians the "Living With Tardive Dyskinesia" patient education initiative that the CME Institute of Physicians Postgraduate Press (PPP) created in collaboration with the Depression and Bipolar Support Alliance, Mental Health America, and Schizophrenia and Related Disorders Alliance of America. The objectives of the initiative are to help patients and caregivers understand the risk for tardive dyskinesia (TD), recognize early signs of TD, and understand the importance of talking with their physicians about TD treatment. Part of the initiative includes a series of 6 brief educational videos for which Joseph P. McEvoy, MD, Department of Psychiatry and Health Behavior, Medical College of Georgia, Augusta University, interviewed several of his current patients and their caregivers about their experiences living with TD. The videos explore patient stories ranging from diagnosis to treatment, including illness burden, insights into challenges they face and how they cope, and resources they turn to. The initiative also features a downloadable/printable brochure about TD and 6 'Share Your Story' online commentaries, which are brief text stories from actual patients living with TD. To measure educational outcomes, the CME Institute of PPP is conducting a survey asking patients and doctors if the

patient education initiative was helpful, what else they would like to know, and/or if patients would be more likely as a result to contact their physician if they noticed TD signs. Some of the qualitative feedback received to date, which has been favorable, includes the following from patients/caregivers: "It's disturbing that so many doctors do not tell people what is going on…"; "Why are these young people so affected?"; and "What medical information should I give to my psychiatrist?" Clinician feedback includes comments such as "How does TD present in adolescents or children—if at all?"; "I'd like to know more about management of side effects of psychotropic medication." and "What is the suicide risk related to TD?" The importance of the proposed talk is to generate awareness among physicians that patients and their family members need to receive information that is specific to their needs. Because of the serious and potentially irreversible nature of TD, early recognition, accurate diagnosis, and effective treatment are crucial.

T27. CANNABINOID AUGMENTATION OF EXPOSURE-BASED COGNITIVE BEHAVIORAL THERAPY FOR OCD: A PILOT STUDY

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Abstract: Introduction: Treatments for obsessive compulsive disorder (OCD) include medications (e.g. serotonin reuptake inhibitors) and psychotherapy (e.g. exposure therapy with response prevention or ERP). However, some patients do not respond to either, highlighting a need for new treatment approaches. Fear extinction learning is thought to occur during ERP, and emerging data suggest that modulators of the endocannabinoid (eCB) system could enhance fear extinction learning and/or recall. An implication of these findings is that medications such as nabilone (a THC analogue and cannabinoid 1 receptor agonist) could theoretically be used to enhance fear extinction learning during ERP, thereby improving outcomes. However, this potential application has not been tested clinically. Here, we describe a pilot study in 11 adult patients with OCD which explored the effects of nabilone with ERP in adults (21 and older) with OCD.
Method: Patients were randomized to treatment with nabilone 1mg BID either alone (n=6) or in combination with ERP (n=5) over 4 weeks. Patients met with the same study therapist, psychiatrist, and an independent evaluator who assessed symptoms of OCD using the Yale-Brown Obsessive Compulsive Scale (YBOCS) and depression using the 17-item Hamilton Depression Rating Scale (HDRS-17). Patients met weekly with the study psychiatrist to assess for side effects and physiological effects (e.g. change in blood pressure and heart rate). Outcomes were compared with those from a separate group of 21 patients, enrolled in a parallel study, who received 4 weeks of ERP alone.
Results: Both groups were similar demographically and in baseline YBOCS (nabilone only = 26.5, nabilone+ERP = 26.0, ERP only = 25.1) and HDRS-17 scores (nabilone only = 6.5, nabilone+ERP = 6.0, ERP only = 6.2). YBOCS at week 4 was significantly lower in the nabilone+ERP group (14.2) compared to nabilone alone (24.0), and 4-week change in YBOCS was significantly greater for nabilone+ERP (11.2) than in the other 2 groups (nabilone only = 2.5, ERP only = 6.1). Nabilone treatment did not produce significant changes in HDRS-17 or physiological measures. All subjects who completed the protocol tolerated nabilone without

significant adverse events. Anxiety, dry mouth, and increased appetite were the most commonly-reported side effects.
Conclusion: The nabilone+ERP group improved at nearly twice the rate of the control group, supporting our hypothesis that nabilone may enhance fear extinction learning in patients with OCD to improve responsiveness to ERP. These pilot data suggest an alternative approach to OCD treatment in which medications and psychotherapy could be delivered synergistically and in a time-limited fashion to increase overall treatment efficacy. Future studies of nabilone-assisted ERP are warranted and should include larger samples as well as measures of target engagement.

T28. A STUDY TO ASSESS DIGITALLY ENABLED ENGAGEMENT IN MAJOR DEPRESSIVE DISORDER

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Abstract: Background: Enhanced patient-provider engagement can improve patient health outcomes for multiple chronic conditions, including major depressive disorder (MDD) (1). However, time constraints and the need to frequently manage multiple conditions during a single visit in a primary care setting may make it difficult to fully engage with patients in their MDD treatment (2). Mobile health applications (apps) may expand health interventions beyond traditional face-to-face contacts but need to be integrated into the clinical care pathway and easy to use for both patient and provider. Apps that connect the patient and provider may provide an opportunity to enhance engagement and patient outcomes.
Objective: This study aims to assess an app-enabled care pathway designed to improve patient-provider engagement using a patient interface to track data and early quantitative assessment of treatment progress for patients with MDD.
Methods: This ongoing study enrolled and randomized 40 patients (n=20 usual care with app, n=20 usual care) diagnosed with MDD starting a new antidepressant monotherapy (newly diagnosed or medication switch). Eighty percent of the patients randomized were females, with mean age of 36.3± 11.2 years, and a baseline mean PHQ-9 score of 14.7 ± 5.0. Patients in the app arm are instructed to engage with the app daily, and a report is generated at 6-week intervals. The app records mood and cognitive symptoms, emotional well-being, medication adherence, and side effects. The data are communicated at regular intervals to the healthcare provider to help facilitate shared patient-provider treatment decision-making discussions. The primary endpoint is change from baseline in the Patient Activation Measure (PAM-13) and Patient Provider Engagement Scale (PPES-7) at week 18. Secondary outcomes include depression severity (PHQ-9), cognitive dysfunction (PDQ-D5), medication switches and adherence, quality of life (WHO-5), employment productivity (LEAPS), resource utilization (RUQ-D), patient and provider satisfaction with the level of provider engagement (week 18), and measure of healthcare utilization at 1 year.
Discussion: Study results expected in early 2019 will help determine whether the use of this app-enabled clinical care pathway is beneficial for measurement-based care and can enhance patient-provider engagement. It is anticipated that study results will highlight the advantages of integrating this app-enabled care pathway to monitor patient progress and enhance patient-

provider communication. Clinical implications for improving outcomes and minimizing resource utilization for patients with MDD will also be discussed.

Disclosure and Acknowledgments: We thank Jennifer Schuster for her contribution to this study. MM, SS, and ER are employees of Takeda Pharmaceuticals. BF and FC are employees of Cognition Kit. CB, CK, and DK are employees of Advocate Health Care. DK participates on the Speaker Bureau for Takeda, Lundbeck, and Teva. AE is an employee of Lundbeck LLC.

T29. VALIDATION OF GOAL ATTAINMENT SCALING FOR DEPRESSION: INITIAL FINDINGS FROM AN OPEN-LABEL STUDY IN PATIENTS SWITCHING TO VORTIOXETINE

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Abstract: The Goal Attainment Scale (GAS) has been used in clinical care and program assessment for medical and nonmedical indications (1). However, the validity, responsiveness and reliability of GAS assessments have not been studied extensively in clinical trials of pharmacological agents (2).

A goal attainment approach for evaluating individualized patient treatment goals and progress was adapted for major depressive disorder (GAS-D) in an open-label study in patients switching to vortioxetine (n=122). Subjects established 3 goals at baseline (1 self-defined and 2 "domain-defined"), with evaluation over 12 weeks. Importance/achievability rankings of goals were collected with other endpoints.

Convergent and divergent validity of GAS-D and correlations with measures of depressive symptoms (PHQ-9), illness severity and improvement (CGI-S, CGI-I), quality of life (QOL)/functioning (Q-LES-Q), cognitive performance (DSST), and cognitive symptoms (PDQ-D) were evaluated. A latent factor analysis/structural equation model was developed to evaluate relationships between GAS-D, depressive symptoms, cognitive performance, and functional improvement.

At weeks 6 and 12, all 3 goal scores correlated significantly with measures of depressive symptoms (PHQ-9) and illness severity and improvement (CGI-S, CGI-I) ($p<0.05$). QOL measures demonstrated strong relationships to GAS-D, particularly Work domain and self-defined goal ($r=0.382$, $p<0.001$). Cognitive symptoms evaluated by PDQ-D and PDQ-D5 subset were significant at weeks 6 ($r=–0.225$, $p<0.001$ and $r=–0.201$, $p<0.05$, respectively) and 12 ($r=–0.249$, $p<0.05$ and $r=–0.251$, $p<0.05$, respectively). Cognitive performance evaluated by DSST was related to self-defined goals at week 12 ($r=0.332$, $p<0.01$) and demonstrated statistically significant correlations with DSST change over time ($r=0.201$, $p<0.05$). Using latent factor analysis and structural equation model, GAS-D, specifically the self-defined goal, was persistently related to functionality, regardless of level of improvement in depressive symptoms.

GAS-D differs from most traditional depression, QOL, and psychosocial functioning rating scales in that the goals developed are individualized and based on the patient's personal

preferences and priorities. The correlation of GAS-D scores with depressive symptoms, QOL, and cognitive performance ratings as measured by traditional scales is encouraging.
GAS-D demonstrates many features of a valid, sensitive assessment tool. Using a variable-construct approach, GAS-D scores may be an indicator of functional recovery in depression. Even further, benefits related to patients' engagement in their treatment and development of individualized goals may prove this goal-setting approach to be a driver of research and clinical practice in the direction of personalized medicine.
Disclosure and Acknowledgments: The study was funded by Takeda Pharmaceuticals U.S.A., Inc., and Lundbeck LLC. Medical writing assistance, provided by Syneos Health, was supported by Takeda Pharmaceuticals U.S.A., Inc., and Lundbeck LLC.

T30. DEVELOPMENT OF A REAL-WORLD KETAMINE DATABASE REGISTRY: CENTERS OF PSYCHIATRIC EXCELLENCE (COPE)

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Abstract: Background: Subanesthetic doses of intravenous ketamine exert rapid benefits in patients with depressive disorders, anxiety disorders, posttraumatic stress disorder, obsessive compulsive disorder and chronic pain. Nearly all studies reflect treatment resistant patients receiving limited infusions to ketamine monotherapy in government and academic research settings. A deficit of research knowledge exists in real-world patients receiving multiple infusions of adjunctive ketamine to treatment as usual. The Centers of Psychiatric Excellence (COPE) created a research infrastructure to obtain registry data that tethers patient characteristics to treatment outcomes in efforts to personalize ketamine treatment based on real-world data.
Methods: An on-line database registry was created by COPE to obtain real-world data in patients receiving adjunctive ketamine. Board-certified psychiatrists at six community treatment centers provided patients with ketamine infusions (Atlanta, Charlotte, Houston, New York, Philadelphia, St Louis). Prospective patients completed screening scales and a telemedicine or in-person psychiatric assessment conducted by a psychiatrist determined eligibility for ketamine treatment. Once a patient was deemed medically and psychiatrically appropriate, pretreatment and posttreatment scales to each infusion were completed during acute, sustained, and maintenance phase treatments.
Results: Patient and provider data from two of six COPE clinics were primarily used in this analysis. Out of 979 inquires, 84 patients were considered appropriate, signed informed consent, and received ketamine treatments. Fifty-eight patients were captured in our database registry. Validated patient and provider rating scales on symptoms severity, treatment efficacy, and side-effects were obtained. As an example, mean scores on the Montgomery-Asberg Depression Rating Scale (MADRS) in patients at baseline was 36 (n=58; SD=8) and reduced to 12 by infusion 6 (n=41; SD=10). This represents a 67% reduction in depressive symptoms by infusion 6 and a 30% reduction by infusion 2. Depression scores at infusion 5 (MADRS=13,

n=44) were no different than at infusion 6 (MADRS 12, n=41). Only 2 of 58 patients had a MADRS score that was higher at their last treatment than at baseline. Approximately 70% of patients received all six acute phase treatments.
Conclusion: This real-world data set in patients receiving six adjunctive infusions of ketamine over two-weeks demonstrated robust decreases in depression scores during the acute phase treatment (30% at infusion 2 and 67% at infusion 6). Development of treatment algorithms based on patient characteristics using objective measures while monitoring for comorbid symptoms and abuse liability will help direct appropriateness of ketamine in the real-world setting. These data are also poised to inform on ketamine dosing, time course to characterize treatment response, and maintenance schedules to sustain treatment benefit.

T31. RESPONSE ANALYSIS OF BREXANOLONE INJECTION BY HAMILTON RATING SCALE FOR DEPRESSION TOTAL SCORE, INDIVIDUAL ITEMS, AND SUBSCALES IN THREE PIVOTAL STUDIES IN WOMEN WITH POSTPARTUM DEPRESSION

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Abstract: Background: Postpartum depression is the most common complication of childbirth. Each year an estimated 11.5% of new mothers in the United States experience PPD symptoms. PPD etiology is multifactorial, and reduced GABA signaling has been implicated. Three pivotal trials examined brexanolone injection (BRX), an investigational, intravenous formulation of the GABAA receptor positive allosteric modulator allopregnanolone in women with PPD. BRX showed a significant reduction in depressive symptoms by Hour 60 (assessed by the 17-item Hamilton Rating Scale for Depression; HAM-D) in each trial. The trials used an umbrella protocol, supporting pre-planned analyses of data from an integrated dataset.
Methods: Women ages 18-45, ≤6 months postpartum, with a diagnosis of PPD and a qualifying HAM-D total score were enrolled (Study A: NCT02614547, HAM-D ≥26; B: NCT02942004, HAM-D ≥26; C: NCT02942017, HAM-D 20-25). Subjects were randomized 1:1:1 (Study B) to receive a 60-hour continuous infusion of placebo (PBO), brexanolone injection 90 μg/kg/h (BRX90), or brexanolone injection 60 μg/kg/h (BRX60) or 1:1 (Studies A and C) to receive PBO or BRX90, with follow-up through Day 30. An integrated BRX90 dataset was used for efficacy analyses. The primary endpoint was the HAM-D total score change from baseline at Hour 60, and secondary efficacy endpoints included HAM-D total score at other time points, HAM-D individual items, and unidimensional HAM-D subscales measuring depression (Core, Bech-6, and Maier) and anxiety. Categorical response (reduction in score ≥50% from baseline) was assessed for HAM-D total, individual item, and subscale scores. Safety and tolerability were assessed for all subjects receiving any BRX dose by adverse event (AE) reports and standard clinical measures.
Results: Across studies, 107 subjects received PBO, and 140 subjects received BRX (102 BRX90 and 38 BRX60). The primary endpoint of a significant reduction in HAM-D total score

versus PBO at Hour 60 was achieved in the integrated BRX90 dataset (17.0 vs. 12.8, p<0.0001), with significant improvement in depressive symptoms sustained through Day 30 (p=0.0213). At Hour 60, the HAM-D total score response rate for BRX90 subjects was significantly greater versus PBO subjects (75% vs. 56%, p=0.0003). In addition to the depressed mood item, 8 HAM-D individual items showed response rates favoring BRX90 versus PBO (all p≤0.01). All three unidimensional depression subscales showed significantly greater response favoring BRX90 (p<0.005 for all), as did the anxiety subscale (p<0.05). In all subjects receiving any BRX dose, the most common AEs (≥10%) were headache, dizziness, and somnolence.
Conclusions: BRX administration was generally well tolerated and demonstrated statistically significant, rapid (by Hour 60) and sustained (through Day 30) reductions in depressive symptoms as measured by categorical assessment of response using HAM-D total score, individual item scores, and subscale scores.

T32. ASSESSMENT OF WITHDRAWAL SYMPTOMS: LONG-TERM, OPEN-LABEL STUDY OF ESKETAMINE NASAL SPRAY AND AN ORAL ANTIDEPRESSANT IN TREATMENT-RESISTANT DEPRESSION

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Abstract: Background: SUSTAIN-2 (NCT02782104) was an open-label, phase III trial evaluating the safety of intranasal esketamine (ESK) plus a newly initiated oral antidepressant (AD) for up to 1 year in adults with treatment-resistant depression (TRD). ESK, a schedule III drug, acts via glutamate receptor modulation. ESK is rapidly cleared from the plasma, and with intermittent dosing there is no accumulation. Thus, no withdrawal syndrome is expected. This analysis assessed potential withdrawal symptoms upon discontinuing ESK after long-term use. In the absence of a glutamatergic-specific withdrawal scale, the Physicians Withdrawal Checklist (PWC-20) was used. The PWC-20 was designed to assess new or worsening benzodiazepine-like discontinuation symptoms after stopping non-SSRI anxiolytics.
Methods: ESK nasal spray was administered 2x/week during a 4-week induction phase (IND). Responders entered the optimization/maintenance phase (O/M) where ESK was dosed either weekly or every two weeks (up to 48 weeks); Patients entered a 4-week follow up period (F/U) after discontinuation from either phase, during which continuation of the AD was recommended. PWC-20 assessments were conducted at the last ESK dosing (endpoint of IND or O/M) and at weeks 1, 2 and 4 of F/U. Symptoms were rated using a 0-3-point scale (Not present = 0, Mild = 1, Moderate = 2, Severe = 3). To account for worsening of underlying depression, subset calculations were performed for depressive symptoms (PWC-DS: loss of appetite; anxiety/nervousness; irritability; dysphoric mood-depression; insomnia; fatigue, lethargy- lack of energy; restlessness-agitation; headaches; muscle aches-stiffness; weakness; difficulty concentrating-remembering; depersonalization-derealization) and withdrawal symptoms (PWC-WS: nausea-vomiting; diarrhea; poor coordination; diaphoresis;

tremor/tremulousness; dizziness-light-headedness; increased acuity-sound, smell, touch; paresthesia).

Results: Data on 357 patients entering F/U were included in the analysis (91 completed treatment during the IND phase and 141 were treated during O/M). The mean (SD) PWC-20 total scores (range 0-60) at the last ESK dosing, Week 1, 2 and 4 were 7.7 (7.3), 7.9 (6.91), 8.0 (7.42) and 7.7 (7.07), respectively. At these same assessments, mean PWC-WS scores (range 0-24) were 1.0 (1.95), 1.01 (1.69), 1.0 (1.81), and 0.9 (1.75). Mean PWC-DS scores (range 0-36) were 6.7 (5.91), 6.9 (5.69), 7.0 (6.13), and 6.8 (5.86), respectively. The mean maximum PCW-20 total score and subset scores occurred 2 weeks after discontinuation of ESK. In comparison, peak PWC-20 total scores for successful and unsuccessful taper off benzodiazepines were 17.2 (11.6) and 24.6 (12.6) respectively. (J Clin Psychopharmacol.2008;28(4):447-5.) Complete analysis of data from the entire SUSTAIN-2 dataset will be presented.

Conclusions: No indication of drug-specific withdrawal symptoms was seen after stopping up to 1-year of intermittent ESK dosing.

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T33. THE ANTIDEPRESSANT AV-101 IS A SUBSTRATE FOR LAT1 (SLC7A5) AT THE BLOOD-BRAIN BARRIER

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Abstract: Major depressive disorder represents a common mood disorder that is the leading cause of disability worldwide. The prodrug of 7-chlorokynurenic acid (7-Cl-KYNA), AV-101 (4-chlorokynurenine) is currently in phase II clinical trials as an adjunct antidepressant therapy and has received fast track designation by the FDA. The movement of compounds across the blood-brain barrier (BBB) represents a bottleneck in the delivery of neurotherapeutics. To this end, the large neutral amino acid transporter (LAT1) has been increasingly recognised as a conduit for the passage of neurotherapeutics across the BBB. Thus, we sought to determine whether AV-101 is a substrate of LAT1 and characterise the movement of AV-101 through the transporter. Using [14C]-AV-101, we followed the uptake of the compound in HEK 293 cells stably overexpressing LAT1 or matched control cells, with the inhibitor JPH203 used to test for specificity. We found AV-101 (10 μM) uptake to be 689.7 ± 69.5 pmoles/million cells in LAT1 expressing cells compared to 76.5 ± 9.8 pmoles/million cells ($n=3$, $p<0.05$) in control cells. Addition of the LAT1 inhibitor, JPH203, (10 μM) reduced this uptake to 21.8 ± 2.4 pmoles/million cells ($n=3$, $p<0.05$) and 14.3 ± 1.4 pmoles/million cells ($n=3$, $p<0.05$) in LAT1 expressing and control cells, respectively, indicating AV-101 was indeed being transported via LAT1. We also characterised the uptake kinetics of AV-101; the Vmax was 4522 ± 1016 pmoles/million cells/min and the Km was 1799 ± 372.5 μM. In comparison, the model LAT1

substrate, phenylalanine (10 μM), showed an uptake of 754.2 ± 103.8 pmoles/million cells in LAT1 expressing cells compared to 319.8 ± 34.25 pmoles/million cells (n=3, $p<0.05$) in control cells. Overall, AV-101 showed a LAT1-mediated uptake of 613.1 ± 77.8 pmoles/million cells whilst phenylalanine had an uptake of 434.4 ± 121.1 pmoles/million cells. Together with the uptake data, these similarities in LAT1-mediated uptake suggested that AV-101 showed a greater selectivity for LAT1 in comparison to phenylalanine. In contrast, 7-Cl-KYNA (10 μM) showed no LAT1-mediated uptake (2.7 ± 0.5 pmoles/million cells in LAT1 expressing cells compared to 3.6 ± 2.2 pmoles/million cells in control cells), validating the use of the prodrug as an approach for delivery of the active drug. Additionally, we found that when human brain endothelial cells (HBEC-5i) were exposed to the approximate plasma concentration (250 μM) of AV-101, these cells showed an uptake of 1216 ± 87.4 pmoles/million cells. This uptake was reduced to 649.9 ± 117.7 pmoles/million cells (n=3, $p<0.05$) with the addition of JPH203, indicating that AV-101 is a substrate for LAT1 in the cells that compose the BBB. Future experiments will determine whether AV-101 is a substrate of other transporters, in an attempt to further characterise the movement of the drug across the BBB. Additionally, we will perform a genotype to phenotype approach to assess if genetic variants in the LAT1 transporter (SLC7A5) and additional candidate genes correlate with AV-101 efficacy as an adjunct antidepressant therapy in patients with major depressive disorder (ELEVATE).
Clinicaltrials.gov identifier: NCT03078322

T34. USING MACHINE LEARNING ALGORITHMS AND AVAILABLE DATA TO TAKE THE "TRIAL AND ERROR" OUT OF PRESCRIBING

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Abstract: Patient response to antidepressant treatment is frequently defined at the end of treatment, as an improvement of 50% or greater from the initial depression score. However, this definition does not take into account the 'time to response', therefore not allowing for any differentiation between response rates. Of course, time to response can be an important factor when trying to determine features influencing the efficacy to antidepressant treatments as the genetic backgrounds of 'fast' and 'slow' responders may be different. Additionally, many genetic and environmental differences may impact the efficacy to antidepressants, and analysis of combinations of these factors is needed to define novel predictors of response to antidepressant treatments. We have developed a pipe-line of algorithms and procedures which allows the use of machine learning on genetic data combined with environmental (including clinical and demographic) information. Based on this method we have designed a comprehensive ensemble prediction model of efficacy to antidepressant medications.
Using the raw data of the Sequence Treatment Alternatives to Relieve Depression (STAR*D) clinical trial, we have designed two response models for the antidepressant treatment group: 1. 50% depression score reduction approach - a percentage of depression score reduction using the first and last scores. 2. exponential approach - an exponential formula, taking into account all depression scores for each patient, plotted against their number of days in treatment. We have applied our pipe-line of algorithms and procedures to develop a prediction model.

We have tested the antidepressant response of STAR*D patients. The 50% depression score reduction approach found that for the various anti-depressants, on average, 44% patients were responders and 56% patients were non-responders. The exponential approach however, labeled 50% patients as responders and 50% patients as non-responders. We then randomly split the patients into train and validation groups. Next, we applied our pipeline of algorithms and procedure, after which an ensemble of machine learning algorithms were applied. A prediction model based on combinations of novel genetic and environmental features was achieved for the exponential response model groups, but not for the 50% depression score reduction approach. The prediction model yielded the following results on the validation group, as averaged over the various medications: Area Under the Curve (AUC) of 0.7, accuracy of 69%, sensitivity of 67.3%, specificity of 70.1%, positive predictive value of 68.4% and negative predictive value of 69.7%. Examination of the "between-medications" ranking element of our prediction model showed that it predicts the recommended anti-depressant for patients with a success rate of 71.6%.
A model taking into consideration both changes in depression score and time of response, revealed novel combinations of genetic and environmental features which predict the response to antidepressant treatments. These features could not be found using the commonly used one-dimensional 50% depression score reduction model, emphasizing the strengths of using a two-dimensional approach. Furthermore, by using machine learning algorithms we have managed to design a highly accurate prediction model of response to antidepressant, based on the combinatorial approach between genetics and environment. Applying new models and new algorithmic methods on currently available large datasets can lead to novel findings which will advance our understanding of psychiatric disorders and advance the design of accurate prediction models for psychiatric medications.

T35. AN INTEGRATIVE NETWORK ANALYSIS IDENTIFIES NOVEL PATHWAYS IN TREATMENT RESPONSE TO ANTIDEPRESSANTS

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Abstract: Background: Patient response to antidepressant varies greatly, likely contributed by multiple factors, including genomic, signaling and metabolic pathways. Previous studies have examined the role of individual genomic pathways (DNA, microRNA, RNA) in antidepressant treatment response. This project aimed to integrate DNA, microRNA and RNA data to discover molecular pathways associated with treatment response to antidepressants using an integrated network analysis approach.
Methods: Biological samples were obtained from three antidepressant clinical trials (11918A, 11984A, 13267A). The cohort included patients treated with duloxetine, and data comprised DNA samples from 186 subjects, microRNA and RNA samples from 124 subjects. The molecular data was integrated using mirDIP, IID and pathDIP, annotated resources for microRNA:gene predictions, protein:protein physical interactions, and comprehensive pathway enrichment analysis (http://ophid.utoronto.ca/mirDIP, …/iid, …/pathDIP). The highly represented pathways emerging from the integrative analysis were examined in the light of current knowledge of antidepressant response.

Results: Analysis of DNA and RNA data yielded no significant pathways and the microRNA data yielded 338 significant pathways; however, network-based analysis across microRNA, RNA and DNA samples identified 1,142 significantly enriched pathways. These significantly enriched pathways included several known (e.g. IL-7, VEGF, etc) and novel pathways (e.g. potassium signalling) in antidepressant response. Neuronal development, intracellular signalling cascades, and immune signaling pathways were highly represented among the enriched pathways, the top immune signaling pathways were then successfully demonstrated to have differential expression among predicted responders to duloxetine. The top 10 differentially expressed immune signaling pathways were examined using a logistic regression model and IL10 values at baseline emerged as a significant predictor of antidepressant response (p=0.008).
Conclusions: The integrative analysis confirmed currently implicated pathways and pointed towards novel pathways for further exploration and demonstrated the utility of integrating heterogeneous datatypes. Pathways implicated in neuronal development and inflammation appear to play a key role in antidepressant response. Among the inflammatory pathways, several previously known and novel pathways were identified as being involved in antidepressant treatment response. In particular, the inflammatory marker IL10 emerged as key player and predictor in antidepressant treatment response to duloxetine. Further, within the validated immune signaling pathways could exist proteins that serve as unique molecular targets to decipher the biology of antidepressant treatment response. The integrative network analysis approach demonstrates that variations of a small effect size at the molecular level can aggregate within pathways that could be meaningfully explored and targeted in antidepressant response.

T36. EMOTIONAL PROPRIOCEPTION: TREATMENT OF EMOTIONAL DISORDERS WITH AFFERENT FACIAL FEEDBACK

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Abstract: We develop the concept of emotional proprioception, whereby the muscles of facial expression play a central role in encoding and transmitting information to the brain's emotional circuitry, and describe its underlying neuroanatomy, involving the trigeminal nerve, locus ceruleus and amygdala, and prefrontal cortex. We explore the role of facial expression in both reflecting and influencing depressed mood. The circuitry involved in the latter effect is a logical target for treatment with botulinum toxin, and we review evidence in support of this strategy. Clinical trial data suggest that botulinum toxin is effective in treating depression. We discuss the clinical and theoretical implications of these data, including the broader use of this strategy to treat disorders of negative emotion and emotional regulation in general.

T37. EFFICACY OF ADJUNCT BUPRENORPHINE/SAMIDORPHAN IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER ACCORDING TO BASELINE DISEASE CHARACTERISTICS

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Abstract: Background: Buprenorphine/samidorphan combination (BUP/SAM), an investigational opioid system modulator for adjunctive treatment of major depressive order (MDD), has shown efficacy in placebo (PBO)-controlled trials. This post hoc analysis evaluated efficacy based on baseline disease characteristics. Safety data are reported elsewhere.
Methods: Data were pooled from FORWARD-4 (NCT02158533) and FORWARD-5 (NCT02218008), sequential parallel comparison design phase 3 studies of adjunct BUP/SAM 2 mg/2 mg and PBO in MDD patients receiving antidepressant therapy (ADT) despite inadequate response. Efficacy endpoints included least squares mean difference (LSMD) change from baseline (CFB) to end of treatment in the Montgomery–Åsberg Depression Rating Scale 10-item score (MADRS-10EOT) and average LSMD CFB to week 3 through EOT (MADRS-10AVG). Efficacy of BUP/SAM was assessed as LSMD from PBO, derived from mixed models for repeated measures predicting CFB by time point, within each of 2 stages and by subgroup, and then combined using equally weighted stages. Subgroups analyzed were baseline MADRS-10 scores <30 or ≥30, duration of current major depressive episode (MDE) ≤6 or >6 months, 1 or ≥2 inadequate responses to ADT, and ADT type (selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor [SNRI], or bupropion).
Results: Efficacy data were pooled from stages 1 (BUP/SAM, n=122; PBO, n=529) and 2 (BUP/SAM, n=117; PBO, n=114). For patients with baseline MADRS-10 scores of <30 and ≥30, differences from PBO for the MADRS-10AVG were –2.0 (95% CI, –4.1 to 0.1) and –1.7 (95% CI, –3.2 to –0.2), respectively. For patients with a duration of MDE ≤6 and >6 months, differences from PBO for the MADRS-10AVG were –1.4 (95% CI, –3.3 to 0.5) and –2.1 (95% CI, –3.6 to –0.5), respectively. For patients with 1 and ≥2 inadequate responses to ADT, differences from PBO were –1.5 (95% CI, –2.9 to –0.2) and –3.0 (95% CI, –6.0 to 0.1), respectively. For patients receiving concomitant SSRIs, SNRIs, and bupropion, differences from PBO for MADRS-10AVG scores were –1.5 (95% CI, –3.1 to 0.1), –1.9 (95% CI, –4.0 to 0.3), and –3.7 (95% CI, –7.6 to 0.2), respectively. Note that negative numbers indicate greater improvement than placebo. Similar results were observed with the MADRS-10EOT.
Conclusions: Changes from baseline in MADRS-10 efficacy measures across all baseline disease characteristics in this post hoc analysis demonstrated a trend in favor of adjunct BUP/SAM versus PBO. A significant limitation to this post hoc analysis is the small sample size in several subgroups.

T38. EFFECT OF ESKETAMINE NASAL SPRAY ON COGNITION IN PATIENTS WITH TREATMENT RESISTANT DEPRESSION: RESULTS FROM FIVE PHASE 3 STUDIES

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Abstract: Objective: To assess effect of esketamine nasal spray (ESK) on cognition in patients (pts) with treatment resistant depression (TRD) in five phase 3 studies: 3 acute randomized, double blind (DB1, DB2, DB4); 1 maintenance of effect (randomized withdrawal design, DB3); 1 open label (OL1).
Methods: Adult pts (18-64 yrs [DB4, ≥65 yrs; OL1, >18]) with TRD were enrolled. In DB1, 2, 4, pts were randomized to ESK (28 [DB4 only], 56 or 84 mg) or placebo (PBO), + newly-initiated oral antidepressant (AD). After 4 wk induction (IND), DB1 and DB2 responders entered DB3; DB4 pts entered OL1. DB3 phases: 4 wk OL IND (ESK 56 or 84 mg) + AD, 12 wk optimization (OP) to individualize treatment frequency (1/wk or 1/every other wk), and maintenance (MA) in which pts receiving ESK + AD were randomized to continue ESK + AD or switched to AD + PBO until relapse or study completion. Direct entry pts: OL IND (ESK 56 or 84 mg) + AD, 12 wk OP, and MA. OL1: 4 wk OL IND (28, 56, or 84 mg) + AD followed by up to 48 wk OP/MA. Follow-up (FU): DB1, DB2: 24 wks; DB3, DB4: 2 wks; OL1: 4 wks. Cognitive assessments included the Cogstate computerized test battery (Detection [DET]: simple reaction time ; Identification [IDN]: choice reaction time; One Card Learning [OCL]: visual memory; One Back Memory [ONB]: working memory; and Groton Maze Learning[GML]: executive function) and Hopkins Verbal Learning Test Revised (HVLT-R), administered at baseline, day 28, early withdrawal (EW), and FU (wk 2) in DB1, DB2, DB4, and at 12 wk intervals, from wk 16 (DB3) and 20 (OL1), EW and FU (DB3, 2 wks; OL1 4 wks). Cognitive assessments were also administered at baseline and day 28 for DB3 direct entry pts or OL1 pts (including DB4 non-responders) and at EW visits. Descriptive statistics were used to summarize scores and change from baseline at each timepoint.
Results: Mean performance in ESK + AD and AD + PBO groups on each cognitive test generally either improved from or remained similar to baseline at both the end of DB treatment (day 28) and during FU, in each acute study. A slight slowing of reaction time (RT) was observed in pts ≥65 yrs (DB4) at day 28; mean slowing (log10 ms) from baseline in the ESK + AD group = 0.0182; SD = 0.14018 (effect size, change from baseline, Cohen's d = 0.12, n = 56) and in AD + PBO = 0.0245; SD = 0.13437 (Cohen's d = 0.18, n = 58).
In long term studies (DB3, OL1), cognitive performance was generally either slightly improved from, or remained similar to baseline during OP, MA or OP/MA treatment, including those treated with either ESK + AD or AD + PBO in the DB MA phase of DB3 (n = 133 to 145/group at 'Last Observation Carried Forward' endpoint).
In OL1 pts ≥ 65 yrs, mean performance on simple and choice RT tests slowed moderately from baseline, from wk 20 (n = 72) and continuing through wk 52 endpoint (n = 24). However, RT performance was variable within pts over time, few subjects slowed consistently without a later improvement of RT performance. Performance of pts ≥65 yrs on all tests of higher cognition (visual memory, verbal memory, working memory, executive function) remained stable or showed slight improvements.
Conclusions: Cognition generally remained stable in adult and elderly pts (>65 yrs) with TRD during both acute and long-term treatment with either ESK + AD or AD + PBO. Performance of pts ≥ 65 yrs. in OL1 exhibited slowing of RT during OP/MA and appeared to be an isolated observation related to processing speed and not a broad attentional impairment. Overall in this study, ESK did not appear to have an impact on cognition in pts with TRD.

T39. IS THE DSM-5 ANXIOUS DISTRESS SPECIFIER SUFFICIENT FOR MEASURING ANXIETY IN DEPRESSED PATIENTS? IMPLICATIONS FOR MEASUREMENT-BASED CARE

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Abstract: Introduction: Anxiety is common in patients with depression. In recognition of the importance of considering anxiety in depressed patients, DSM-5 introduced the anxious distress specifier. The anxious distress specifier includes 5 symptoms drawn from the diagnostic criteria of panic disorder and generalized anxiety disorder (feeling keyed up or tense, feeling restless, difficulty concentrating because of worry, fear that something awful might happen, and feeling that one might lose control). Of note is absence of somatic features characteristic of anxiety such as gastrointestinal, autonomic, cardiac, or pulmonary symptoms. In the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project we tested the hypothesis that a 5-item self-report measure of the DSM-5 specifier (the Clinically Useful Depression Anxious Distress subscale (CUDOS-A) was as valid as a 20-item more comprehensive measure (Clinically Useful Anxiety Outcome Scale (CUXOS) as an anxiety severity measure in depressed patients.
Methods: Two hundred ninety-four psychiatric patients with MDD were interviewed by trained diagnostic raters who administered a semi-structured interview. The patients completed self-report measures of depression, anxiety, and irritability. Sensitivity to change was examined in a subset of patients.
Results: Both the CUDOS-A and CUXOS were more highly correlated with measures of anxiety than with measures of the other symptom domains. Patients with anxiety disorders scored significantly higher on both measures than did patients with no current anxiety disorder. Both measures were equally correlated with measures of coping, general well-being and functioning. A large effect size of treatment was found for both measures (CUDOS-A: d=1.2; CUXOS: d=1.3).
Conclusion: Both the CUDOS-A and CUXOS were valid self-report measures of anxiety symptom severity in depressed patients. Because anxiety is so common in depressed patients, the addition of a small number of items assessing the DSM-5 anxious distress criteria should be added to depression measures and used in measurement-based care efforts.

T40. UNDERSTANDING THE PATIENT EXPERIENCE THROUGH THE SELF-REPORTED REVIEW OF THE VALUE OF ESKETAMINE (STRIVE) STUDY IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION

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Abstract: Background: The use of direct patient interviews in clinical trial settings is increasing, with regulators expressing emerging interest in these data to support the meaningfulness of clinical trial results. The present analysis evaluated patient-reported early

health changes related to emotional health, daily functioning, and social functioning in adults with treatment-resistant depression (TRD) treated with esketamine nasal spray (ESK).
Objective: To understand the early patient experience with flexibly dosed ESK in the treatment of TRD through direct interviews with participants in an open-label, long-term extension safety study.
Methods: STRIVE was a prospective, noninterventional, qualitative study examining self-reported early health changes with ESK in the treatment of TRD. Select US-based patients from an open-label, long-term extension safety study of ESK (NCT02782104) were invited to participate. Eligible patients were within 30 months of starting initial ESK treatment and currently receiving ESK. Patients excluded were those previously enrolled in an efficacy and safety study of ESK in patients with TRD aged ≥65 years (NCT02422186), those with a partial response or nonresponse to ESK in a parent study with reinduction in the open-label extension study, and those who demonstrated response (i.e., ≥50% decrease in the Montgomery–Åsberg Depression Rating Scale total score) to an oral antidepressant + placebo nasal spray in 1 of 2 prior double-blind studies in adults aged 18-64 years (NCT02417064 and NCT02418585) before their first ESK dose. A single, 45-min telephone interview was conducted with each participant to understand early experiences with ESK and any changes related to emotional health, daily functioning, and social functioning. Open-ended questions with standardized probes and closed-ended questions, where participants selected responses from a predefined list, were used. Results were assessed using constant comparative analysis.
Results: Results from 23 patients (9 male, 14 female) with a mean (range) age of 46 (28-64) years were analyzed. A total of 191 health changes were reported: 89 emotional health, 47 daily functioning, 37 social functioning, and 18 other. Most changes were experienced early in treatment, with continued improvement over time. Participants rated 174 of these changes to be “much improved” or “improved” within the first week or month after starting ESK: 80 emotional health, 44 daily functioning, 33 social functioning, and 17 other. Participants identified 147 of the changes as “extremely important” or “very important”: 80 emotional health, 32 daily functioning, 24 social functioning, and 11 other. Among the 23 participants, the most frequently reported changes were: improved mood (n=16), increased energy (n=13), improved socialization (n=16), and improved concentration (n=9). Other changes such as improved motivation (n=9) improved sleep (n=7), and appetite (n=4) were noted. Overall, 87% of patients stated that ESK treatment made them feel “better” (n=15) or “a lot better” (n=5), with most patients reporting they were “satisfied” (n=12) or “very satisfied” (n=11) with their treatment. Adverse events were consistent with the safety profile reported for ESK in prior publications.
Conclusion: Direct participant feedback provides additional context and insights that may prepare clinicians and patients for the early clinical experience of ESK in the treatment of TRD and its use in real-world clinical practice.

T41. A PHASE-2, DOUBLE-BLIND, PLACEBO-CONTROLLED, SEQUENTIAL PARALLEL COMPARISON DESIGN STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ADJUNCTIVE PIMAVANSERIN IN MAJOR DEPRESSIVE DISORDER

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Abstract: Introduction: Depression is the leading cause of disability worldwide, with large unmet medical need: fewer than 50% of treated patients achieve full remission. Compounds acting as antagonists or inverse agonists at 5-HT2A receptors have demonstrated antidepressant activity. This study ("CLARITY," ACP-103-042: NCT03018340) examined the 5-HT2A inverse agonist pimavanserin (PIM) as a potential adjunctive treatment for major depressive disorder (MDD).

Methods: Adult female and male subjects with a DSM-5 primary diagnosis of a major depressive episode as part of MDD, inadequate response to ongoing selective serotonergic reuptake inhibitors (SSRIs) or serotonin–norepinephrine reuptake inhibitors (SNRIs) of adequate dose and duration as confirmed by the Massachusetts General Hospital Antidepressant Treatment History Questionnaire, and a Montgomery-Åsberg Depression Rating Scale (MADRS) total score >20 were randomized to PIM 34 mg/day or placebo (PBO) added to their SSRI/SNRI treatment. A sequential parallel comparison design was used, consisting of two 5-week stages. PBO nonresponders in Stage-1 who met prespecified criteria were re-randomized to PIM or PBO for the second period (Stage-2). The primary efficacy measure was the weighted average of Stage-1 and Stage-2 total scores of the HAMD-17.

Results: Of the 207 patients enrolled, 52 received PIM, and 155 received PBO in Stage 1. Mean age was 46.2 years, and 72.9% of patients were female. Baseline MADRS total (mean [SD]: 31.5 [0.4]) and HAMD-17 total scores (22.2 [0.3]) indicated a moderate overall severity of illness. PIM met the primary endpoint, reducing the weighted Stage-1/Stage-2 HAMD-17 total score relative to PBO (least-square means [LSM] difference, –1.7; standard error [SE], 0.9; P=0.04). Stage-1 PIM patients demonstrated highly significant 5-week improvement on the HAMD-17 (LSM difference=–4.0, SE=1.1; P<0.001; effect size, Cohen's d: 0.626), separating from placebo by the end of Week 1 (LSM difference=–1.7, SE=0.8; P=0.04). Stage-2 results showed no significant separation among Stage-1 placebo nonresponders (P=0.69). In Stage 2, a substantively smaller number of subjects (n=58) were rerandomized than planned, likely due to restrictive criteria for re-randomization. Greater overall improvement was seen with PIM relative to PBO on the key secondary endpoint, the Sheehan Disability Scale (LSM difference=–0.8, SE=0.3; P=0.004), and positive results were also seen on 7 of the 11 other secondary endpoints, including responder rate (≥50% reduction in HAMD-17 total; P=0.007), Massachusetts General Hospital Sexual Functioning Index (P<0.001), and Karolinska Sleepiness Scale for daytime sleepiness (P=0.02). Discontinuations due to adverse events were low (PIM 1.2%, PBO 3.2%). One serious adverse event was reported in each treatment group, deemed unrelated to treatment. No deaths were reported. Laboratory assessments, electrocardiography, and changes in vital signs were unremarkable, and no new safety signals were reported.

Conclusions: Study data provide evidence of the efficacy, safety, and tolerability of adjunctive PIM in treating MDD inadequately responsive to SSRI or SNRI therapy. ACADIA plans to confirm these results in a Phase 3 program to be initiated in the first half of 2019.

T42. A PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF SAGE-217 IN POSTPARTUM DEPRESSION: TOPLINE ASSESSMENT OF SECONDARY EFFICACY MEASURES OF ANXIETY AND DEPRESSION

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Abstract: Background: Postpartum depression (PPD), a major depressive episode during the perinatal period, may have substantial impacts on the mother and child. In addition to depressive symptomatology, anxiety is a common feature of PPD. GABA signaling dysregulation has been hypothesized to play a role in PPD development. SAGE-217 is an investigational GABAA receptor PAM with pharmacokinetics suitable for once-daily oral dosing. In a Phase 3 trial in major depressive disorder, SAGE-217 demonstrated rapid (by Day 2) and statistically significant improvements in depressive symptoms. This Phase 3 study (NCT02978326) is the first double-blind, randomized, placebo-controlled trial of SAGE-217 in women with PPD.

Methods: Enrolled subjects (n=151) were women, ages 18-45, ≤6 months postpartum, diagnosed with PPD, with onset in the 3rd trimester or ≤4 weeks postpartum, and a baseline Hamilton Rating Scale for Depression (HAM-D) total score ≥26. Subjects were randomized 1:1 to receive either SAGE-217 30 mg or placebo for 14 days, and follow-up was through Day 45. The primary endpoint was the change from baseline in HAM-D total score at Day 15. Secondary endpoints included the change from baseline in HAM-D total score for all other time points, change from baseline in the Hamilton Rating Scale for Anxiety (HAM-A), and Clinical Global Impression-Improvement response (score of "very much improved" or "much improved"). Safety and tolerability were assessed by adverse event (AE) reporting and standard clinical assessments.

Results: At Day 15 (primary endpoint), SAGE-217 showed a statistically significant decrease in least-squares (LS) mean HAM-D total score compared to placebo (-17.8 vs. -13.6, p=0.0028). Statistically significant separation between SAGE-217 and placebo occurred at Day 3 (-12.5 vs. -9.8, p=0.0252) and was sustained through Day 45 (-19.2 vs. -15.1, p=0.0027). Significant reductions from baseline anxiety for the SAGE-217 group versus the placebo group were observed by the HAM-A (LS mean -16.6 vs. -12.7, p=0.0063) at Day 15 and were sustained through Day 45 (LS mean -18.6 vs. -13.6, p=0.0002). The SAGE-217 group also showed significant improvements versus placebo in CGI-I response at Day 15 (72% vs. 52%, p=0.0276). Somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, and sedation were the most common (≥5%) AEs in the SAGE-217 group.

Conclusions: SAGE-217 achieved the primary endpoint of a reduction in depressive symptoms versus placebo as assessed by HAM-D total score change from baseline at Day 15. Reductions in anxiety were observed by HAM-A as a secondary endpoint. Improvements in depression and anxiety with SAGE-217 were reflected by CGI-I response rates, and SAGE-217 was generally well-tolerated, supporting further development of SAGE-217 for the treatment of PPD.

T43. EFFICACY AND SAFETY OF ANYU PEIBO IN CHINESE PATIENTS WITH MDD: A PHASE II RANDOMIZED, DOUBLE-BLIND, PLACEBO-PARALLELED, MULTI-CENTER CLINICAL TRIAL

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Abstract: Background: This study evaluated the efficacy and safety of Anyu Peibo Capsule compared to placebo for acute-phase treatment of Chinese patients with major depressive disorder (MDD).
Methods: This randomized (1:1), double-blind, placebo-control study conducted between June 2017 and October 2018 included patients with MDD (DSM-5) (N=172). The treatment phase had fixed dose levels, which included Anyu Peibo Capsule 1600 mg per day or Placebo, respectively. Primary outcome was mean change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 6.
Results: Overall, 163 patients (Anyu Peibo, n=82; placebo, n=81) received at least one dose of study medication, except for cases with major violation of protocol (n=8) and a case without drug use (n=1). The mean change from baseline in MADRS total score at Week 6 was -16.58 (6.79) in Anyu Peibo group and -14.80 (8.16) in placebo group (no significant difference, P=0.1512). The response rate was 65.28% versus 57.97%, remission rate was 42.31% versus 34.78%, respectively, for Anyu Peibo group versus placebo group. The mean change from baseline in HAMD-17 total score at Week 6 was -12.00 (6.12) in Anyu Peibo group and -9.87 (7.09) in placebo group (significant difference P=0.0464). Adverse events were reported by 82 patients (Anyu Peibo, n=43; placebo, n=39); the most common on-treatment adverse event in both groups were gastrointestinal symptoms (25.61% versus 12.35%, respectively).
Limitations: A short-term (6 weeks) study with small sample size.
Conclusion: Results from this study suggested that Anyu Peibo was potential advantages in efficacy and similar safety profile to that of placebo in Chinese patients with MDD.

T44. SHORT-TERM AND LONG-TERM EFFICACY OF ADJUNCTIVE BREXPIPRAZOLE IN ADULTS WITH MDD: EFFECT ON THE INVENTORY OF DEPRESSIVE SYMPTOMATOLOGY SELF-REPORT (IDS-SR) SCALE

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Abstract: Background: Brexpiprazole is a serotonin–dopamine activity modulator that acts as a partial agonist at serotonin 5-HT1A and dopamine D2 receptors, and as an antagonist at serotonin 5-HT2A and noradrenaline α1B/2C receptors, all with subnanomolar potency. The efficacy and safety of brexpiprazole as adjunctive therapy to ADT have been demonstrated in four short-term studies in adults with MDD and inadequate response to ADTs (Pyxis [NCT01360645], Polaris [NCT01360632], Sirius [NCT02196506], and Delphinus [NCT01727726]). Long-term effects of brexpiprazole, as adjunct to ADT in adult patients with MDD, were evaluated in Orion (NCT01360866).

The Inventory of Depressive Symptomatology self-report (IDS-SR) is a 30-item patient-rated scale that can be used to rate the severity and frequency of specific symptoms present over the 7 days prior to assessment.
Methods: In three similarly designed, short-term, fixed-dose studies (Pyxis, Polaris and Sirius), patients with MDD and inadequate response to 1–3 ADTs were enrolled and received single-blind ADT for 8 weeks. Patients with inadequate response after this prospective phase were randomized to ADT plus adjunctive brexpiprazole (2 mg/day in Pyxis; 1 mg/day or 3 mg/day in Polaris; 2 mg/day in Sirius), or ADT plus adjunctive placebo for 6 weeks. In Orion, patients rolled over from short-term studies into this 52-week (amended to 26 weeks) open-label study of flexible-dose ADT + brexpiprazole (0.5–3 mg/day).
In the present analysis, data from the short-term studies were pooled for patients allocated to brexpiprazole 2–3 mg/day, and to placebo. Mean changes from baseline in IDS-SR Total score and item scores were analyzed using a mixed model repeated measures approach. Long-term data are presented with descriptive statistics at Weeks 26 and 52.
Results: In the short-term studies, the IDS-SR scale was completed at baseline by a total of 1,162 patients, ADT + brexpiprazole 2–3 mg (n=579); ADT + placebo (n=583). Mean (SD) baseline IDS-SR Total scores were 36.12 (10.61) for ADT + brexpiprazole, and 35.46 (10.54) for ADT + placebo), indicating that patients were experiencing clinically relevant depressive symptoms. The IDS-SR Total score decreased (improved) by LS mean (SE) of 7.76 (0.43) from baseline to Week 6 in the ADT + brexpiprazole group and by 6.42 (0.43) in the ADT + placebo group, $p=0.03$. At Week 6, an improvement ($p<0.05$) was observed on approximately half of the IDS-SR items evaluated, with LS mean differences versus placebo in the range of -0.07 to -0.18. A further 8 IDS-SR items showed numerical improvement versus placebo in brexpiprazole-treated patients. In the long-term study, a total of 2,911 patients had an IDS-SR Total score evaluation at baseline – mean (SD), 23.93 (13.14). IDS-SR Total score decreased by 5.23 (9.97) at Week 26 and by 7.80 (10.97) at Week 52, indicating that symptoms of depression continued to improve over the course of this study. Improvements were seen in the majority of IDS-SR items.
Conclusion: Patients' self-assessment of their depressive symptoms, rated using the IDS-SR, indicated improvements with adjunctive brexpiprazole treatment across a range of symptoms, including items related to patients' view of themselves and their future. Patients' self-report, using the IDS-SR, indicated that depressive symptoms continued to improve during long term treatment with brexpiprazole.

T45. TIME TO RELAPSE AFTER A SINGLE ADMINISTRATION OF INTRAVENOUS KETAMINE AUGMENTATION IN UNIPOLAR TREATMENT-RESISTANT DEPRESSION

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Abstract: Objective: To examine the rate and time to relapse for remitters and responders to ketamine in treatment-resistant depression (TRD).
Methods: Subjects with TRD were randomized to a single infusion of one of several doses of intravenous ketamine, or midazolam. Using Kaplan-Meier survival function, the current report examines the rate and time to relapse, defined as MADRS ≥ 22, over a period of 30 days, in subjects who achieved remission (MARDS ≤ 10) or response (≥ 50% reduction in MADRS) on day three post-infusion of intravenous ketamine 0.1, 0.5, or 1.0 mg/kg.
Results: Of the 60 randomized participants who received a single ketamine (0.1, 0.5, or 1.0 mg/kg) infusion, 19 (34%) met criteria for remission and 27 (48%) for response, on day 3 post-infusion. A numerical dose-response relationship was observed, with remitters/responders on ketamine 1.0 mg/kg having the lowest relapse rate, followed by ketamine 0.5 mg/kg and 0.1 mg/kg, respectively (% of remitters who relapsed by day 14: 38% with 1.0 mg/kg, 50% with 0.5 mg/kg, 100% with 0.1 mg/kg; % of responders who relapsed by day 14: 30% with 1.0 mg/kg, 50% with 0.5 mg/kg, 80% with 0.1 mg/kg).
Conclusion: Time to relapse after successful treatment with a single infusion of ketamine appears to follow a dose-response relationship, where higher dosage leads to increased time to relapse.

T46. RAPASTINEL FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER: A PATIENT-CENTRIC CLINICAL DEVELOPMENT PROGRAM

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Abstract: Background: According to estimates from the World Health Organization, depression and major depressive disorder (MDD) are the leading causes of ill health and disability worldwide and affects approximately 300 million people globally. Approved antidepressants generally require several weeks of continued treatment before an acceptable response is achieved, and nearly half of all patients fail to respond adequately to treatment. Novel pharmacological approaches that modulate the central N-methyl-D-aspartate receptors (NMDARs) are in development as rapid-acting and long-lasting antidepressants. Rapastinel, a novel NMDAR modulator with a unique mechanism of action, promises rapid-acting and long-lasting antidepressant effects in patients with MDD through weekly intravenous injections; in addition, rapastinel has a good safety and tolerability profile compared with the current standard of care or investigational NMDAR antagonists and has a low propensity for abuse or dissociative/psychotomimetic side effects. Rapastinel received FDA Fast Track and Breakthrough Therapy designations based on Phase 2 clinical data. The late-stage development program for MDD has been designed to thoroughly evaluate rapastinel's acute and long-term efficacy, as well as its safety and tolerability.
Methods: Two separate Phase 3 programs are being conducted for rapastinel: as adjunctive treatment to standard antidepressants in patients with MDD (aMDD; US only, N=~1500) and as monotherapy (global; N=~2000), each with acute studies, maintenance study, and an opportunity for continued long-term treatment. Adult patients meeting the DSM-5 criteria for MDD with a current major depressive episode were eligible for enrollment into the rapastinel

clinical program. Intravenous doses used in the studies included 225 mg, 450 mg, or 900 mg of rapastinel or placebo on either a predetermined (weekly or biweekly) or clinically-driven schedule.
Results: For acute treatment, three 3-week studies are conducted in aMDD (MD 01, 02, and 03) and three 6-week studies evaluate rapastinel monotherapy (MD-30, -31, and -32). In the maintenance studies, patients are stabilized with weekly rapastinel injections for 8-16 weeks to determine stable responders, who are then randomized to double-blind injections of rapastinel or placebo. In the aMDD maintenance trial (MD-04), patients receive weekly rapastinel, biweekly rapastinel, or placebo for up to 2 years of individual treatment. In the monotherapy maintenance trial (MD-33), patients receive weekly rapastinel or placebo for up to 1 year; this study also includes an individualized treatment arm, in which patients are assigned placebo or rapastinel in a blinded manner depending on weekly clinical assessments. In the continued long-term study, completers or patients who relapsed from MD 04 can continue open-label treatment in MD 06 for up to 1 year. In addition, rapastinel is also being evaluated as a treatment in addition to standard of care for patients with MDD who are at imminent risk of suicide (MD-20; US only, N=~300).
Conclusion: First results from the acute aMDD trials are expected in the first half of 2019, with the option to present data at the ASCP 2019 Annual Meeting. First results from the monotherapy and suicidality trials are expected in 2021.

T47. IS THERE AN INCREASE IN THE PSYCHIATRIC ADVERSE EVENTS IN SMOKERS USING USUAL NICOTINE CONTENT CIGARETTES VERSES SMOKERS USING REDUCED NICOTINE CONTENT CIGARETTES?

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Abstract: Background: Nicotine use and dependence are major public health concerns. The data suggests that patients with complex psychiatric histories are often smoking more cigarettes compared to the general population. These psychiatric patients also find it very difficult to quit smoking. Some studies suggest that the more active the psychiatric symptoms are, the more difficult it is for patients to quit smoking.
In our study to review the quit rates amongst individual with depression and or anxiety, we did a secondary analysis looking at psychiatric Adverse Events (AE's) between our double blinded, parallel group of smokers on Usual Nicotine Content (UNC) versus Reduced Nicotine Content (RNC) cigarettes.
Method: Our current study is a double-blind, parallel-group, randomized controlled trial in which 188 adult smokers with depression and or anxiety disorders and with no intention to quit smoking in the next 6 months received either Usual Nicotine Content (UNC, 11.6 mg/cig) cigarettes (n=94) or progressively Reduced Nicotine Content (RNC, lowest dose of 0.2 mg/cig) cigarettes (n=94) over a period of 18 weeks. Basic demographics including age, gender, level of education and number of cigarettes smoked per day were collected at baseline. Throughout the 18-week intervention phase, Adverse Events (AEs) were assessed at each study contact and systematically coded by organ system, including psychiatric disorders, using the Medical Dictionary for Regulatory Activities (MedDRA). Chi-squared tests were used to assess

differences in the proportion of participants in each treatment group who reported at least one psychiatric AEs during the intervention phase.
Results: Of the total participants (n=188), 60.6% (n=114) were female, with a mean age of 43.2 years (SD: 12.5). On an average our cohort smoked 18.5 cigarettes per day (SD: 9.9). Of the n=188 randomized participants, 36.2% (n=68) reported at least one psychiatric AE during the intervention phase. We found no differences between the two groups (UNC vs RNC) in the proportion of participants who reported a psychiatric AE (30 [31.9%] in the UNC group vs. 38 [40.4%] in the RNC group, p = 0.29).
Discussion: Smoking and nicotine use is a major public health concern. Smoking causes a significant medical, emotional, psychological and financial burden on the individual and on society. The total direct and in direct cost of smoking related problems and United States is above $300 billion a year. Due to the dependence potential of nicotine, it is difficult to stop smoking. In addition, individuals who suffer from mental health disorders have a higher rate of smoking and nicotine use compared to the general population. For these individuals, quitting smoking is especially difficult. We wanted to explore the relationship between psychiatric Adverse Events (AE's) in our cohort of individuals, who had depression/anxiety and were either using Usual Nicotine Content (UNC) or Reduced Nicotine Content (RNC) cigarettes. Contrary to our hypothesis that there will be increase is psychiatric AE's as individual decrease their nicotine use. We, in our cohort did not find differences between individuals who were using Usual Nicotine Content (UNC) versus Reduced Nicotine Content (RNC) cigarettes.
We suggest that future studies on smoking cessation in individual with depression/anxiety should look at psychiatric AE's to see if our findings are replicated. If so, these findings can improve smoking cessation outcome in individuals with depression and or anxiety.

T48. A MANUALIZED EIGHT-WEEK VIDEOCONFERENCE-BASED VIRTUAL COGNITIVE BEHAVIORAL THERAPY (CBT) GROUP FOR CHRONIC LOW BACK PAIN (CLBP)

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Abstract: Background: Chronic low back pain has deleterious effects on mood, sleep, functioning, and quality of life. Long-term opioid analgesic use compounds these effects, introducing further psychiatric, cognitive, and social consequences. CBT has shown efficacy for CLBP symptoms, but many patients cannot readily access treatment.
Methods: For this ongoing, prospective, open-label pilot study, we adapted a validated pain CBT paradigm (Jamison 1996). Participants received a manualized 8-session CBT program via secure WebEx with an MD or PhD facilitator. Participants were 18-75 years old with diagnosed CLBP of mean daily intensity ≥4/10 at least half the time. Participants rated baseline (M0), month 2 (M2), and month 4 (M4) prescription opioid misuse (POM) risk (Current Opioid Misuse Measure [COMM]), pain catastrophizing (PCS), pain interference (Brief Pain Inventory [BPI]), CLBP-related disability (Oswestry Disability Inventory [ODI]), and sleep quality (Insomnia Severity Index [ISI]), as well as study-specific satisfaction.
Results: Currently the study has enrolled 41 participants (27 female). As of a November 2018 interim data review, mean (± standard deviation) participant age was 55.2±14.3 years. Mean scores decreased for COMM (M0: 11.1±9.7; M2: 7.7±5.6: M4: 3.6±2.3), PCS (M0: 21.0±13.3;

M2: 18.3±11.7; M4: 14.8±9.3), BPI severity (M0: 5.8±1.8; M2: 5.5±1.7; M4: 5.1±1.6), BPI interference (M0: 6.1±2.2; M2: 5.3±2.4; M4: 4.8±2.3), ODI (M0: 45.3±15.9; M2: 45.3±13.1; M4: 43.8±14.8), and ISI (M0: 14.6±6.7; M2: 13.1±6.7; M4: 11.0±7.6). Most participants were highly satisfied with the course (71.6±17.6%).
Conclusion: Our preliminary results suggest that virtual group CBT could be a low-cost way to extend care to CLBP patients with limited mobility or located in remote or under-resourced areas.

T49. FEASIBILITY OF A SPECIALIZED AVATAR SYSTEM AS A RATER TRAINING TOOL FOR CNS CLINICAL TRIALS

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Abstract: Background: We built a configurable avatar system to explore its feasibility as a tool for training interview skills, diagnostic assessment, and symptom severity measurement in clinical trials. In the current pilot study, the avatar prototype was coded to teach scoring and detection of intentionally embedded interview errors in the administration of a common depression efficacy scale (Montgomery Asberg Depression Rating Scale, MADRS). We also assessed the system for overall practicality and likeability impressions.
Method: In collaboration with an artificial intelligence academic group, a prototype avatar system was built that presented an avatar clinician interviewing an avatar depressed patient on 5 MADRS items. For this study, the prototype allowed for configurable appearance and interview proficiency of the interviewer. Subjects were 10 clinicians (8 masters or doctoral level; 1 psychiatric nurse, 1 bachelor's level) who had been exposed to standard high-quality live MADRS and interview skills training sessions. To assess interrater scoring agreement (using Cicchetti kappa accounting for agreement with gold standard scoring), subjects first viewed and independently provided MADRS ratings of the avatar patient as interviewed by the high-proficiency avatar interviewer. Subjects were then shown the same patient avatar interviewed by the low-proficiency avatar interviewer and asked to independently identify interviewer errors made. These two procedures approximated expert training exercises often conducted at live investigators' meetings. After scores were collected, subjects were shown 12 features of the prototype and asked to rate the value/feasibility of each feature from 1=none to 5=very much.
Results: Interrater agreement on scoring of symptom severity of the avatar on the MADRS was high (kappa=0.95). Subjects correctly identified 75% of embedded avatar interviewer errors (range=50% to 80% correct). The mean value/feasibility for the 12 features overall was 4.2 (range=3.0 to 4.9). The feature with the highest mean rating (4.9) was a feedback switch to display interviewer errors; the feature with the lowest mean rating (3.0) was interview setting configurability (office, hospital room, examination room).
Conclusions: Rater subjects in our study achieved high interrater agreement when scoring the avatar interview and were able to detect the majority of errors made by the avatar interviewer. This supports the potential utility of the system as a component in efficacy scale scoring and interview skills assessment. Subject raters provided generally high likeability/feasibility ratings, suggesting that this novel form of computer-generated rater training may engage and interest clinical trials raters in other training venues and with other efficacy and diagnostic

scales. As many sponsors move to full or partial online rater training environments, configurable avatar training tools may help enhance rater involvement and attention to trained messages provided. Advantages of the system include the ability to program different levels of symptom severity, various interview errors for detection, and artificial intelligence algorithms to customize the experience to a given rater's strengths and weaknesses.

T50. TRANSLATIONAL RESEARCH WITH DEXMEDETOMIDINE (DM) FOR THE TREATMENT OF AGITATION FROM HEALTHY VOLUNTEERS TO TWO PATIENT GROUPS: THOSE WITH SCHIZOPHRENIA OR WITH PROBABLE SENILE DEMENTIA OF THE ALZHEIMER'S TYPE (SDAT)

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Abstract: Background: DM is a highly selective alpha-2 adrenergic agonist currently marketed for intravenous (IV) administration to sedate/anesthetize patients prior to and/or during surgical and other procedures and to sedate intubated and mechanically ventilated patients. Given the role of the central adrenergic system in arousal, DM may be useful for the treatment of agitation in patients with various neuropsychiatric disorders including senile dementia of the Alzheimer's Type (SDAT) and schizophrenia.

Methods: Three identically designed, double-blind, placebo-controlled, randomized studies were conducted with the IV formulation of DM in (a) middle-aged to elderly healthy volunteers (HV), (b) agitated patients with schizophrenia, and (c) agitated patients with SDAT. The DM was administered IV with a starting dose of 0.1 mcg/kg/hour and the dose was increased by 0.1 mcg/kg/hour every 30 minutes up to a maximum dose of 0.6 mcg/kg/hour or until predetermined endpoints were met either for efficacy or safety specifically blood pressure (BP) and heart rate (HR). In the HV, mild sedation was taken as the surrogate for efficacy and measured using the Richmond Agitation Sedation Scale (RASS). The RASS was also used in the studies of agitated patients with either SDAT or schizophrenia. In addition, the PANSS excitatory component (PEC) scale was in the study of agitated patients with schizophrenia. The numbers of participant in each study had 12 – 14 and 4 -6 subjects treated with DM and placebo, respectively. Continuous assessment was made of level of arousal, BP and HR. Plasma samples were collected before dosing and then every 15 minutes for the determination of DM concentration. Statistics were descriptive and correlational in terms of pharmacodynamic and pharmacokinetic relationships.

Results: Similar results were found in all three studies. DM was capable of producing a light sedation in all subjects (RASS = -1) which was preceded by a calming effect (RASS = 0) in the agitated subjects as well as a reduction in PEC in agitated patients with schizophrenia. These beneficial effects occurred to a greater degree on DM than placebo and before causing clinically meaningful effects on BP or HR. There was an approximately 4-fold variability in the dose and plasma concentration needed to produce these effects in all three groups. The effective dose range was the same across all three groups. The effect occurred within 30 minutes of starting the dose which produced the desired effect. The calming and the drowsy effect persisted for 1.5-2 hours after the cessation of the infusion which was judged to be a

clinically relevant duration. Plasma drug concentration correlated with dosing rate and with drug effect both within and between subjects. Gender affected drug responsiveness with males requiring twice the dose of DM compared to females. Additional factors that may account for the difference in dose needed amongst HV and patients include genetic variations in the gene for the alpha-2 adrenergic receptor and sympathetic tome as measured by changes in blood pressure between lying and standing.
Conclusions: This study demonstrated the efficiency of an adaptive, translational design to early phase CNS drug development and is directly relevant to three topics of interest to the Society: Translational Research into Clinical Practice, Patient-focused Drug Development, and Genomics. Using this information, a sublingual film formulation has been developed for further studies.

T51. RETHINKING DRUG SIDE-EFFECT VERIFICATION

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Abstract: Over the last 20 years there have been a number of heavily debated safety signals for psychotropic drugs. The discovery of these phenomenon often come from case series, which when appropriate document challenge, dechallenge and rechallenge relationships. Investigators often try to corroborate these events in other research types such as observational studies and experimental trials. When the events are rare, or the methodology of the study is insufficient to detect them, the findings can be conflicting. If the phenomenon in questions is catastrophic, such as drug induced suicidal behavior and the disease it treats serious the debate can become quickly polarized. In these uncertain cases the medical consensus can have huge implications for drug makers through mandated labeling changes, liability lawsuits and loss of public confidence. On the other side, when a patient is injured by a genuine side effect professional acknowledgement is the first step towards effective treatment and further research into mitigating the side effect for the rest of the population. Given what is at stake arbiters are under immense pressure to make determinations on the validity of these phenomenon. Over the last 50 years many regulatory and legal decisions concerning drug safety issues appear to have hinged on whether randomized controlled trials or their meta-analyses were able to find statistically significant risk differences between medication and placebo. While deferring to the pinnacle of the evidence-based medicine hierarchy is a good rule of thumb what is often overlooked is that clinical trials, primarily powered to measure efficacy, are riddled with flaws when it comes to detecting complex or rare side effects and abstracting their occurrence to the general population. Even when designed specifically to investigate side effects the wide variation in researchers' assiduity and ability to detect and record the events of interest can lead to a discerning lack of confidence in their findings. When the findings from a randomized controlled trial doesn't ratify a suspected side effect it can be interpreted by the public and non-specialists in the medical community as not existing. This bureaucratic view of causal inference has led to drug induced problems being unduly dismissed as lacking sufficient empirical support. I will be discussing the case of antidepressant-induced suicidal behavior and how conflicting findings from case series and randomized controlled trials have led to unclear public safety messages. Further I will be discussing how a high-quality case reports are an absolutely

necessity when it comes to generating a clear and comprehensive understanding of how adverse drug events result in complex phenomenon like suicidal behavior.

T52. A SUBJECT-TARGETED PLACEBO-CONTROL REMINDER SCRIPT: AN IN-DEPTH EMPIRICAL EXPLORATION OF HOW SUBJECT CHARACTERISTICS MODERATE PLACEBO RESPONSE

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Abstract: Introduction: With an increasing rate of clinical trials failing due to large placebo responses, researchers have investigated how subject characteristics (e.g., age, gender, body mass index or BMI) have impacted this response, with noteworthy inconsistent findings (Fraguas et al., 2018). A thorough review of the literature revealed no empirical investigation exploring how a subject-targeted intervention may control placebo response and how the response may vary based on subject characteristics. As such, this study adds important data to further our understanding about the relationship between subject intrapersonal variables and the placebo effect.
Methods: In this US multicenter, single-blind, all placebo investigation, moderate to severe depressed patients (assessed by the self-reported Beck Depression Inventory-II / BDI-II; Beck et al., 1996) aged 18-65 were randomized to the Control Group (CG) or Intervention Group (IG). IG subjects were read the Placebo-Control Reminder Script (PCRS), educating them on the commonly cited key causes of the placebo effect, including participant expectations of benefit, lack of placebo understanding, misconception of expected interactions with research site staff, and subject role uncertainty (Rutherford & Roose, 2013). CG subjects were not read the PCRS. All subjects were informed of the 50% chance of being assigned placebo or active drug but received only placebo. Given this deception, subjects were provided a Debriefing Form at the end of the study revealing the investigation's true intent.
Results: As expected, the IG (n=41) and CG (n=40) subjects did not differ in Baseline characteristics, including depression (BDI-II: IG M=33.80, SD=9.08 vs. CG M=31.10, SD=7.28; p=.144). A significant (p=0.018) time-by-group interaction, as hypothesized, indicated IG subjects reported significantly less improvement in BDI-II scores than CG subjects (IG M=26.10, SD=1.56 vs. CG M=20.68, SD=7.58). Post hoc subgroup analyses examined whether rate of change in BDI-II was different depending on subject characteristics. These stratified analyses were not powered to detect time-by-group interactions, and as such, between-group (IG vs. CG) effect sizes were computed for each subgroup at the end of the study. Analyses revealed that the PCRS tended to be more effective for females (d=.73), subjects who are under the age of 40 (d=.77), African-American (d=.66), have a high school degree or less (d=.59), have never been in a clinical trial (d=.73), have a normal BMI (d=1.04), currently in psychotherapy (d=1.43), presently not on psychotropic medication (d=.81), and have BDI-II scores at Baseline in the severe range as opposed to moderate (d=.62).
Conclusions: The primary finding of the current study, that the PCRS helped manage the placebo effect among depressed subjects compared to those not read the PCRS, suggests that implementing this strategy within MDD RCT clinical trials may be crucial in managing this

effect. Post hoc data also indicated that the PCRS may be particularly important in reducing the placebo effect for certain subjects. For example, many clinical trials have BMI restrictions and the current study results lend support for this exclusion and coincide with similar empirical findings (Talley et al., 2006) but counter others (Han et al., 2018) from a placebo response perspective. Implications of the subgroup findings to clinical trial placebo response, as well as study limitations, will be thoroughly discussed in the poster.

T53. USING A COMPUTER SIMULATED RATER TO EVALUATE CLINICAL TRIAL OUTCOMES: CARBAMAZEPINE EXTENDED-RELEASE FOR THE TREATMENT OF BIPOLAR DEPRESSION

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Abstract: Objective: Clinical trials in psychiatry rely on subjective ratings scales administered by trained clinical raters, but the expense, burden, and fluctuating reliability of this process make it difficult to assess the utility of many potentially promising medications and other interventions. To explore the utility and feasibility of using a computer simulated rater to administer and score outcome assessments, we conducted a single blind study of the efficacy and safety of beaded extended-release capsule carbamazepine (ERC-CBZ) in the treatment of patients with bipolar disorder, depressed phase.
Methods: Forty-six consenting subjects with a diagnosis of bipolar disorder, type I or II currently experiencing a depressive episode were enrolled in a prospectively 8-week, open label, monotherapy trial of ERC-CBZ. The dose of ERC-CBZ was initiated at 200mg/d and increased as tolerated by 200mg/d every 3 days to 1200mg/d by week 2 (target dose) and up to1600mg/d as tolerated by week 8, if needed for a greater therapeutic response. The primary outcome was defined based on the scores obtained by the computer simulated rater administering the Montgomery-Asberg Depression Rating Scale (MADRS; primary outcome), and the Young Mania Rating Scale (YMRS) assessed biweekly.
The computer simulated rater (CSR) is an algorithm driven interview and scoring system that has been demonstrated excellent agreement with site-based rater scores on the MADRS and YMRS while used as a quality metric in global clinical trials (1,2). Subjects are given a Rater Station (laptop computer) a quiet room and receive on-screen instructions. Subjects respond to prompts by selecting the best answer from a list of multiple-choice options. For each scale item, an algorithm selects the next question based on the subject's prior response. When the enough information is gathered for the algorithm to generate a unique score for the item, the first question for the next item is presented. This process continued until all scale items are scored. The Hamilton Rating Scale for Anxiety (HAM-A), and Clinical Global Impression-Bipolar (CGI-BP) were clinician administered biweekly. Safety was assessed biweekly by self-reports of adverse events.
Results: Thirty-two evaluable subjects were considered in the efficacy analysis. Eighteen subjects completed the entire 8-week study. Paired t-tests were used to compare changes in scale scores from baseline to week 8 (using the last observation carried forward approach). The primary outcome measure was the MADRS and revealed statistically significant change from baseline to week 8 ($p < .001$; Cohen's $d=0.79$). All secondary outcome measures also showed

significant improvement. Ten subjects (31.3%) had a 50% or greater reduction in MADRS score from baseline to week 8. Four subjects (12.5%) were considered to be in full remission (MADRS < 8) after 8 weeks. The medication was well tolerated.
Conclusions: Our results based on assessments from a computer simulated rater suggest extended-release carbamazepine may be a well-tolerated treatment associated with significant improvement in depressive symptomatology for subjects with bipolar I or II depression.
Using a computer simulated rater gives these results the benefit of a single blinded rating system. This may improve the efficiency and reduce the bias of clinical trials conducted in the context of open treatment in order to identify promising interventions

T54. PSYCHOPHARMACOLOGICAL TREATMENT OF INATTENTION IN CHILDREN PRENATALLY EXPOSED TO TERATOGENIC SUBSTANCES: MORE IS MORE?

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Abstract: Fetal alcohol spectrum disorder (FASD) affects an estimated 1-5 % of the population, with additional children affected by other teratogenic substance exposure. The toxic neurodevelopmental sequelae of prenatal alcohol exposure, combined with the high frequencies of psychosocial risk factors in exposed children including abuse, neglect and multiple home placements, puts these children at high risk for psychiatric symptoms and disorders. Common symptoms include inattention, hyperactivity, emotion dysregulation, sleep problems, disruptive behavior, and mood problems, often affecting academic and social functioning. Many require psychopharmacological interventions in addition to behavioral and educational interventions. However, no guidelines exist regarding optimal psychopharmacological treatments in this complex population. Stimulant use for treatment of comorbid ADHD is controversial in this population, and questions related to responsiveness to stimulants, necessity for additional nonstimulant medications and addressing polypharmacy remain unanswered. The Emory Neurodevelopmental and Exposure Clinic (ENEC), the only multidisciplinary center specialized in assessing and treating children prenatally exposed to teratogenic substances in the Southeast, has recently started to provide psychopharmacological consultation to this population. The current study provides descriptive data of the clinical cohort (n=38) in the ENEC psychopharmacology clinic, including demographics, psychopharmacological treatments and empirical outcomes. We focus specifically on the treatment responsiveness of stimulant and non-stimulant medications for inattention in this cohort, using parental verbal reports, parent questionnaires and computerized assessments of sustained attention. We evaluate determinants of treatment response and recommend areas for further study.

T55. OUTCOME PREDICTION FOR PATIENTS WITH BIPOLAR DISORDER USING PRODROMAL AND ONSET DATA

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Abstract: Background: Outcome prediction in serious mental illnesses, such as bipolar disorder (BD), remains very challenging. Objectives: Our study aimed to experiment an innovative method to predict adverse outcome of veterans with incident BD via deep neural network learning algorithm to the temporal images of clinical features of each individual patient.
Methods: A total of 20,000 veterans were randomly selected for the prodrome fingerprinting analysis. Clinical features included prior hospitalizations, diagnoses, procedures, medications, note types, vital signs, lab results and BD symptoms occurred within 1 year before and at onset of incident BD. A temporal graph of clinical features of each individual patient was created. A deep neural network learning algorithm to the temporal images was used to build prediction model.
Results: Using an image representation of clinical data during the prodromal and onset period and a deep neural network, we could achieve accuracies of 0.766-0.949 and AUC of 0.745-0.815.
Conclusion: Applying deep learning and temporal graphics is a promising approach to predict adverse health outcomes of BD patients.
Disclosures: This study is funded by Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ

T56. OPEN BOARD

T57. LURASIDONE AND METABOLIC SYNDROME: RESULTS FROM SHORT AND LONG-TERM CLINICAL STUDIES IN PATIENTS WITH BIPOLAR DEPRESSION

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Abstract: Background: Among patients with depressive disorders, the prevalence of metabolic syndrome (MetS) is estimated to range from 35-45% and has been associated with increased mortality rates. The aim of this analysis was to assess the effect of treatment with lurasidone on risk of MetS in patients with bipolar depression.
Method: Lurasidone data (20-120 mg/d) utilized in the current analyses consisted of 3 double-blind (DB), placebo-controlled, 6-week studies in adults with bipolar I depression (total N=1,193): one monotherapy and 2 adjunctive therapy trials with lithium or valproate. Patients who completed the short-term trials continued into a 6-month open-label (OL) extension study, with 6-month data available on 336 patients treated with lurasidone monotherapy, and 224 patients treated with lurasidone adjunctive therapy. Also analyzed was a recurrence prevention study in stabilized bipolar patients who completed up to 20 weeks of OL adjunctive treatment with lurasidone, and then were randomized to 28 weeks of DB adjunctive therapy with lurasidone or placebo (N=496). MetS was defined based on NCEP ATP III criteria (2005 revision).
Results: In the short-term monotherapy and adjunctive therapy studies, the proportion of patients at baseline meeting NCEP III criteria for MetS were 25.8% and 23.6%, respectively,

for lurasidone, and 22.5% and 25.1%, respectively, for placebo; and at week 6 (LOCF) the proportion with MetS was 24.4% and 26.6%, respectively, for lurasidone and 27.2% and 20.2%, respectively, for placebo. The proportion of patients who developed MetS at week 6 (LOCF) was comparable for lurasidone vs. placebo in the monotherapy study (9.9% vs. 11.6%; odds ratio [OR]=0.73; [95%-CI, 0.44-1.21]); and in the two adjunctive therapy studies (10.3% vs. 8.3%; OR=1.63; [95%-CI,1.07-2.50]). During the 6-month OL extension study, the proportion of patients treated with lurasidone monotherapy and adjunctive therapy who did not meet MetS criteria at OL baseline but developed new MetS at month 6 was 13.1% and 11.2%, respectively. Conversely, the proportion of patients who met MetS criteria at OL baseline, but no longer met criteria at month 6 was 7.4% and 9.8%, respectively. In the 20-week, OL phase of the recurrence prevention study, the proportion of patients treated with adjunctive lurasidone who met criteria for MetS at OL baseline and endpoint was 15.7% (OC). After up to 24 weeks of DB treatment, the proportion of patients who met criteria for MetS was 27.9% (OC) among patients who continued lurasidone treatment, and 31.3% (OC) among patients who were randomized to placebo (OR=0.83 [95%-CI, 0.46, 1.51]; n.s.; OC).
Conclusion: This post-hoc analysis found that short and long-term treatment with lurasidone was associated with a relatively low risk for the development of metabolic syndrome in patients with bipolar I disorder. These findings are consistent with similar analyses in patients with schizophrenia.

T58. DRUG/PLACEBO RESPONDERS VS. DRUG/PLACEBO PARTIAL RESPONDERS: WHICH GROUP IS MORE LIKELY TO CONTRIBUTE TO SIGNAL DETECTION IN CLINICAL TRIALS? RESULTS FROM A LURASIDONE STUDY IN PATIENTS WITH BIPOLAR DEPRESSION

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Abstract: Objective: To characterize differences in lurasidone/placebo response versus partial response, and the relative contribution of each group to signal detection, based on MADRS score change in a 6-week study in patients with bipolar depression.
Methods: Patients were randomized to receive monotherapy with lurasidone 20-60 mg/day (N=161), lurasidone 80-120 mg/day (N=162) or placebo (N=162). Primary and key secondary study endpoints were change from baseline to week 6 on MADRS and Clinical Global Impression Bipolar Version, Severity of Illness (CGI BP-S) score (depression), respectively. The CGI responder rate was defined as CGI (depression) at week 6/LOCF endpoint <= 2. Association between CGI response status (i.e. responder vs. partial responder at week 6) and changes in MADRS scores from baseline to week 6 with lurasidone vs placebo treatment was evaluated using mixed model repeated measure and ANCOVA models.
Results: Improvement in MADRS total score from baseline to week 6 endpoint was not different for responders to lurasidone (mean change = -22.5) vs. placebo responders (mean change = -22.3). Change from baseline in all 10 MADRS item scores was similar among lurasidone and placebo responders.

For patients who did not meet the "response" criterion (partial responders), improvement in MADRS total score from baseline to week 6 endpoint in the lurasidone group (-8.4) was significantly greater than the placebo group (-5.4) ($P<0.05$, effect size = 0.4). Among partial responders, there were significant differences in improvement in the following five MADRS items favoring lurasidone vs. placebo: apparent sadness (MADRS item 1), reported sadness (MADRS 2), reduced sleep (MADRS 4), lassitude (MADRS 7), and pessimistic thoughts (MADRS 9) (all $p<0.05$).
Conclusions: In this post hoc analysis, derived from a 6-week, placebo-controlled study in patients with bipolar depression, the magnitude of improvement in depressive symptoms (assessed by mean change in MADRS score) was comparable for patients classified as lurasidone and placebo responders. In contrast, significantly greater improvement was observed at study endpoint for patients classified as partial responders treated with lurasidone vs placebo. These findings suggest that signal detection is more likely to be robust among patients with bipolar depression who do not fully respond to either active drug or placebo treatment, and therefore have implications for patient selection in such trials.

T59. THE BROAD EFFICACY OF CARIPRAZINE ACROSS SYMPTOMS IN PATIENTS WITH BIPOLAR I DISORDER: POST HOC ANALYSIS OF RANDOMIZED, PLACEBO-CONTROLLED TRIALS

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Abstract: Background: Patients with bipolar disorder experience a wide range of depressive and manic symptoms. With only 1 drug FDA-approved to treat episodes of both mania and depression in patients with bipolar disorder, there is an unmet need for treatments with proven efficacy at opposite poles of the bipolar spectrum. Cariprazine, a dopamine D3-preferring D3/D2 receptor partial agonist and serotonin 5-HT1A receptor partial agonist, has previously demonstrated broad efficacy in patients with bipolar mania, with significantly greater improvement in favor of cariprazine vs placebo (PBO) across all individual symptom domains ($P<.001$) measured by the Young Mania Rating Scale (YMRS)(1). Additionally, cariprazine has demonstrated efficacy vs PBO in 3 phase II/III clinical studies in patients with depressive episodes associated with bipolar I disorder (NCT01396447(2), NCT02670538, NCT02670551). To further assess the broad efficacy of cariprazine in patients with bipolar I disorder, we performed post hoc analyses to evaluate the range of depressive symptoms comprising the individual items of the Montgomery-Åsberg Depression Rating Scale (MADRS) in patients from the bipolar depression studies.
Methods: Data from the 3 randomized, double-blind, PBO-controlled trials in patients with bipolar depression were pooled. Least squares (LS) mean change from baseline to week 6 in MADRS individual items was assessed in the pooled cariprazine 1.5 and 3 mg/d groups vs PBO using a mixed-effects model for repeated measures in the intent-to-treat (ITT) population.
Results: There were 1383 patients in the ITT population (placebo=460; cariprazine1.5-3 mg/d=923). At week 6, LS mean change from baseline was significantly greater for cariprazine

1.5-3 mg/d vs PBO on 9 of 10 individual MADRS items: Apparent Sadness (-2.0 vs -1.6, P<.0001); Reported Sadness (-2.0 vs -1.6, P<.0001); Reduced Sleep (-1.6 vs -1.4, P=.0357); Reduced Appetite (-1.2 vs -1.0, P=.0001); Concentration Difficulties (-1.5 vs -1.2, P=.0002); Lassitude (-1.7 vs -1.4, P=.0003); Inability To Feel (-1.7 vs -1.5, P=.0009); Pessimistic Thoughts (-1.4 vs -1.2, P=.0054) and Suicidal Thoughts (-0.3 vs -0.2, P=.0383); differences between cariprazine and PBO on the Inner Tension item were not significant.
Conclusions: Significant improvement in most MADRS single items suggests broad efficacy in depressive symptoms for cariprazine 1.5-3 mg/d vs PBO in patients with bipolar depression. Coupled with broad efficacy in manic symptoms as demonstrated by significant improvement in all YMRS individual items in patients with bipolar mania or mixed episodes, cariprazine appears be effective across the range of symptoms that affect patients with bipolar disorder. Cariprazine is approved for the treatment of manic and mixed episodes associated with bipolar I disorder; a regulatory submission for cariprazine for an indication to treat patients with bipolar depression is currently under review by the FDA.

T60. GREY AND WHITE MATTER STRUCTURE ASSOCIATES WITH THE ACTIVATION OF THE TRYPTOPHAN TO KYNURENINE PATHWAY IN BIPOLAR DISORDER

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Abstract: Bipolar disorder (BD) is a severe mental illness characterised by reduced grey matter (GM) volumes and cortical thickness and disrupted white matter (WM) microstructure. Activation of indoleamine 2,3-dioxygenase following a pro-inflammatory state could increase the amount of tryptophan (Trp) converted to kynurenine (Kyn) possibly leading to the production of detrimental catabolites of the Kyn pathway with neurotoxic effects. We tested the hypothesis that peripheral levels of Trp and Kyn and the breakdown of Trp into Kyn (Kyn/Trp ratio) are related to WM and GM integrity in BD. Peripheral levels of Trp and Kyn were analysed in 72 patients with BD and 33 controls. Patients showed higher Kyn levels and Kyn/Trp ratio compared to controls. MRI analyses performed in patients with BD showed a negative association between the Kyn/Trp ratio and the integrity of corpus callosum microstructure, the volume of the amygdala and cortical thickness in fronto-temporal regions. The activation of the Kyn pathway as suggested by the increased Kyn/Trp ratio may lead to an imbalance of the neurotoxic vs the neuroprotective arm of the biochemical pathway, resulting in significant changes in GM and WM regions of brain areas strongly implicated in the pathophysiology of BD, such as amygdala and corpus callosum.

T61. MDMA-ASSISTED PSYCHOTHERAPY FOR TREATMENT OF ANXIETY RELATED TO LIFE-THREATENING ILLNESSES

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Abstract: Background: Before MDMA (commonly known as "Ecstasy") was classified as a Schedule 1 controlled substance in 1985, there were published reports of its use as an adjunct to psychotherapy. However, no controlled research was done at that time. The nonprofit organization the Multidisciplinary Association for Psychedelic Studies (MAPS) sponsored six Phase 2 clinical trials from 2004-2017 using MDMA-assisted psychotherapy for treatment of PTSD. The significant efficacy results and favorable safety profile led the FDA to grant Breakthrough Therapy designation in 2017 for this promising treatment for PTSD. These studies have prompted interest in investigating other anxiety-related conditions that could possibly benefit from MDMA-assisted psychotherapy. Here we present results from a double-blind, randomized Phase 2 trial of MDMA-assisted psychotherapy for anxiety related to life-threatening illnesses (LTI).
Methods: Participants with anxiety from an LTI were randomized in a double-blind study to receive MDMA (125 mg, n=13) or placebo (n=5) during two 8-hour psychotherapy sessions. Non-drug therapy sessions were conducted prior to and after experimental sessions. The primary outcome was change from baseline in State-Trait Anxiety Inventory (STAI) Trait scores at one month post the second experimental session. After the blind was broken, participants in the MDMA group had an additional open-label MDMA session, and placebo participants crossed over to receive three open-label MDMA sessions. The treatment period lasted from 4-6 months with long-term follow-up assessments six and twelve months after the final MDMA session.
Outcomes: For the primary outcome, the MDMA group had the largest mean (SD) drop in STAI-Trait scores -23.5 (13.2) indicating less anxiety compared to placebo group -8.8 (14.7), with results trending towards significant group differences ($p=0.056$). Cohen's d between group effect size was 1.7 (CI: -0.30, 3.65), indicating a large treatment effect. At the six- and twelve-month follow-ups, most domains of psychological functioning were markedly improved compared to baseline, including anxiety (STAI State and Trait, $p<0.0001$), depression (BDI-II and MADRS, $p<0.0001$), sleep quality (PSQI, $p<0.001$), and global functioning ($p<0.001$). MDMA was well-tolerated in this population with a good safety profile in terms of adverse event rates and transient increases in vital signs after MDMA administration.
Conclusion: Few treatments available adequately address psychological symptoms that often accompany physical illnesses. Initial safety and efficacy data from this pilot study support the expansion of clinical trials of MDMA-assisted psychotherapy into a larger sample of individuals with anxiety associated with life-threatening illnesses.
Funding: Multidisciplinary Association for Psychedelic Studies (MAPS)
Trial Registration: clinicaltrials.gov Identifier: NCT02427568

T62. EFFECTS OF A NOVEL COMBINATION DRUG ON PSYCHOSTIMULANT CUE REACTIVITY AND NICOTINE WITHDRAWAL SYMPTOMS IN ABSTINENT PSYCHOSTIMULANT USE DISORDER PATIENTS

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Abstract: There are currently no approved pharmacologic agents which have shown convincing efficacy in the treatment of cocaine or methamphetamine use disorder (collectively termed "psychostimulant use disorder" or PUD). The majority of PUD patients also use tobacco products regardless whether they are diagnosed with tobacco use disorder (TUD) as a co-morbid disorder. The Shiffman-Jarvik Withdrawal Scale (SJWS) is one of psychological tests used to assess nicotine withdrawal symptoms (Shiffman and Jarvik, 1976). [MPh-IR + Ond-PR2] is a combination drug candidate, consisting of an immediate-release methylphenidate formulation and a novel formulation of the antiemetic ondansetron, that has been under development for the treatment of PUD and other substance use disorders. In a proof-of-concept Phase 2A, single-site, randomized, double-blind, placebo-controlled clinical trial (ClinicalTrials.gov identifier: NCT01290276), we determined the efficacy of [MPh-IR + Ond-PR2] in abstinent PUD patients in reducing psychostimulant cue-reactivity using standard cue-reactivity and resting-state neuroimaging paradigms. In addition, a short version of the SJWS was administered to study participants to assess the efficacy of [MPh-IR + Ond-PR2] in reducing nicotine withdrawal symptoms. Subjects were treated with either 20 mg MPh-IR + 8 mg Ond-PR2 ([MPh-IR + Ond-PR2]) or identical-appearing placebo (dextrose) for 2 weeks under a protocol approved by the Duke University Health System Institutional Review Board. The neuroimaging procedures were performed 1-7 days before and 2-7 days after the 2-week treatment. A total of 30 qualifying subjects were randomized into either [MPh-IR + Ond-PR2] or placebo treatment group. Twenty-eight subjects completed the 2-week drug treatment and pre- and post-treatment fMRI assessments. Compared to placebo, [MPh-IR + Ond-PR2] induced significant changes in the psychostimulant cue-induced activation in selected prefrontal, parietal and anterior cingulate cortical areas. Furthermore, "seed-to-voxel" analyses showed reduced resting-state connectivity between selected cortical and striatal/cerebellar areas following [MPh-IR + Ond-PR2] treatment. The combination treatment also significantly reduced scores on SJS craving and negative affect subscales in patients diagnosed with PUD. Follow-up clinical trials are being planned to confirm the preliminary results that [MPh-IR + Ond-PR2] might provide for an effective option for PUD treatment and/or TUD.

T63. FUNCTIONAL CONNECTIVITY BETWEEN THE ORBITOFRONTAL CORTEX AND DORSAL STRIATUM IN ADDICTION

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Abstract: Substance use disorder is a major health problem characterized by the persistence of intoxication, bingeing, craving and withdrawal. Because of the negative consequences of substance use, this results in a major question: why do some individuals become problem users after being exposed to the effects of a drug, while others don't? Recent preclinical work has shown that increased activity from neurons of orbitofrontal cortex (OFC) to the dorsal striatum was associated with the compulsive behavior despite of punishment (Pascoli et al., 2018). This study investigates the resting state functional connectivity (RSFC) between the OFC and other brain areas (including dorsal striatum, habenula and insula) in psychiatric patients with substance use problems. We hypothesized that patients with high risk of substance use would show increased RSFC in a circuit including the OFC, striatum and habenula.

Psychiatric patients (N = 154) were recruited from The Menninger Clinic in Houston, Texas as a part of the McNair Initiative for Neuroscience Discovery – Menninger/Baylor (MIND-MB) research study. Drug use was determined using the World Health Organization ASSIST questionnaire. Patients were divided into two groups (High and No risk) and the two groups were matched for demographic characteristics (age, sex, race) plus any psychiatric comorbidity (depression, anxiety, personality disorders, etc.) except for substance use-related diagnoses, using a Euclidean distance-matching algorithm. Participants were scanned in a 3T Siemens Trio MR scanner in the Center for Advanced MR Imaging at Baylor College of Medicine. A 4.5 min structural MPRAGE sequence (TR = 2.66 ms, TR = 1200 ms, flip angle = 12°, 256 x 256 matrix, 1mm isotropic voxels) was collected, followed by a 5 min resting state scan (TE = 40ms, TR = 2s, flip angle = 90°, 3.4x3.4x4 mm voxels). RSFC data were pre-processed using the CONN Functional Connectivity Toolbox. The preprocessing pipeline included realignment, slice-timing correction, structural normalization to the MNI template, functional normalization, ART-based outlier detection and smoothing with an 8mm full width at half maximum Gaussian smoothing kernel.

We studied OFC functional connectivity with related brain areas (e.g. striatum, habenula). We compared psychiatric patients with high risk of addiction (N = 77) to psychiatric patients with no risk (N = 77) to identify possible differences in the RSFC between those regions. Higher RSFC between the middle left OFC and dorsal striatum (p = .0008), OFC and the habenula (p = 0.016), and habenula and dorsal striatum (p = 0.006) were observed in the drug user group. Additionally, we found that functional connectivity between superior left OFC and anterior right insula (p = 0.00005) was increased in the substance use group, but not in patients with no risk.

Findings revealed that the substance use group showed higher functional connectivity between OFC and the dorsal striatum than the psychiatric control group. Moreover, the OFC connectivity with the habenula was also increased in the addiction group, which implies the habenula may be a part of the same circuit. Our data clearly shows that the medial OFC may be a promising brain target area for brain stimulation or psychopharmacological techniques for psychiatric patients with high risk of substance use disorder. Considering the modulation of reward-related brain connectivity in the high-risk group, we will examine reward and disappointment brain processing within OFC, striatum, habenula and insula using the same group of patients. Data has already been collected on a paradigm using small quirts of sweet juice to elicit reward (juice delivered) and disappointment (juice expected but not delivered).

T64. LOWEST EFFECTIVE DOSE OF BUPRENORPHINE IN OFFICE BASED OPIOID MAINTENANCE TREATMENT

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Abstract: In 2002, the Food and Drug Administration (FDA) approved Buprenorphine/Naloxone (Bup/NX) to be used for outpatient opioid maintenance therapy. Empirical studies in the last decade have demonstrated that Bup/NX treatment helps decrease opioid use, improves treatment adherence, and increases sobriety rates. There is limited research which explores the clinical outcomes of tapering in a stable opioid maintenance patient population. We approached 101 long term Bup/Nx maintenance patients in full remission

between 1.5 to 12 years regarding their interest in a very slow downward adjustment in Bup/Nx dose. The tapering was guided by the pharmacokinetics of buprenorphine including its extremely high relative potency (1 mg = 30 morphine equivalence) and long half-life of at least 36 hrs when provided over an extended period of time. Tapering was recommended in those who were interested in no more than 1 mg decrease of dosage every one to three months. For those patients whose Bup/Nx dose reached 2 mg or less, the tapering recommendations were 0.25 mg to 0.5mg every three months. Data was collected regarding the patient's age, sex, race, insurance status, employment, urine toxicology history, Bup/NX dosage history, outpatient program adherence, and withdrawal symptoms. On average, the daily Bup/NX dosage of patients prior to taper was 11 mg and overall ranged from 6 mg to 16 mg. Using the above taper method produced minimal to no withdrawal symptoms or opioid cravings. The average final Bup/NX dose for tapering patients was 5.4 mg with a range of 0 mg to 12 mg. Of the 45 patients who chose to taper, 5 patients reduced their dose to zero, and 4 patients were unable to tolerate the tapering and returned to their initial Bup/NX dosage. There was no relapse or abnormal urine drug screen in the patients tapering their dose. In conclusion, by using a slow voluntary taper that was guided by the Bup/Nx's pharmacokinetics, the majority of our patients were able to tolerate a lower effective dose with little to no withdrawal symptoms. We would like to take this pilot data and recruit other medication-assistant treatment clinics to offer a similar voluntary taper approach to their patients and evaluate it prospectively.

T65. FURTHER EVALUATION OF THE VALIDITY OF THE MADDERS SYSTEM FOR EVALUATING ABUSE POTENTIAL OF CNS-ACTIVE MEDICATIONS IN CLINICAL TRIALS

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Abstract: Aim: The MADDERS® system was developed to monitor safety and efficacy clinical trials of CNS-active medications for potentially abuse-related events to aid in the assessment of their abuse potential prior to approval. There are currently no other validated tools to assess a drug's abuse potential during phase II & III clinical trials, and traditional methods of assessing abuse potential in clinical trials are flawed and can cause misclassification of events. To date, the MADDERS system has been implemented in 17 phase II through IV clinical trials investigating opioid and cannabinoid medications. The purpose of this analysis is to describe the MADDERS process, evaluate the ability of the system to discriminate between compounds with higher and lower abuse potential, and evaluate the performance of the psychometric elements of the system.
Methods: MADDERS data from 7 completed clinical trials involving 3 different opioid and cannabinoid compounds (CBD, THC/CBD, and a new opioid) were analyzed for the overall incidence of MADDERS triggering events, types of triggering events and relative rates of abuse-related final classifications. Triggering events were classified as either Adverse Events (AEs) or Drug Accountability Discrepancy Events (DADEs) and were classified into one of 6 event categories by investigators at the site and an independent adjudication committee. Psychometric performance was assessed via inter-rater reliability (IRR) between site and adjudicator classifications by calculating percentage of agreement and Cohen's kappa

statistics. Data were pooled for all trials of each respective formulation to create separate treatment populations for comparison.
Results: The MADDERS system identified 15 subjects, 52 subjects and 79 subjects with potentially abuse-related events in the pooled treatment populations of CBD (n=221), THC/CBD (n=268), and opioid trials (n=1,186), respectively. The number of subjects with an event classified as Abuse, were 0 (0%), 0 (0%), and 5 (0.4%) in pooled studies of CBD, THC/CBD and an opioid, respectively; which aligned with previously published data on each compound's respective abuse potential. MADDERS also discriminated between compounds based on the type of triggering event; DADEs were more common in studies of compounds with lower expected abuse potential, and CNS-related AEs were more common in compounds with higher expected potential for abuse. The IRR between the MAC and site classifications showed moderate, but statistically significant agreement with a simple kappa coefficient of 0.57 (95% confidence interval [CI]:0.41-0.74, p-value <0.001) and adjudicator-site agreement in 74.5% of cases in the pooled opioid sample. Participants' responses were aligned with final classifications, indicating that they were considered to be truthful and taken into account by the adjudication committee.
Conclusion: Despite relatively few cases overall, the MADDERS system was shown to possess the ability to discriminate between compounds with varying levels of abuse potential. Results from the psychometric analysis indicate that the interview questions provided useful information to the adjudication committee and allowed for reliable classification of events. Our findings suggest that MADDERS is both a reliable and valid approach to the prospective identification of abuse-related events in clinical trials.

T66. EFFICACY AND SAFETY OF DR/ER-MPH, A DELAYED-RELEASE AND EXTENDED-RELEASE METHYLPHENIDATE, IN CHILDREN WITH ADHD: RESULTS FROM A PIVOTAL PHASE 3 CLASSROOM TRIAL

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Abstract: Background: Evening-dosed HLD200 is a once-daily delayed-release and extended-release formulation of methylphenidate (DR/ER-MPH) designed to delay initial drug release by 8–10 hours to provide an onset of treatment effect upon awakening and lasting into the evening. Herein, we present the efficacy and safety of DR/ER-MPH from a pivotal, multicenter, phase 3, placebo (PBO)-controlled laboratory classroom study that enrolled 125 children (6–12 years) with attention-deficit/hyperactivity disorder (ADHD) (NCT02493777).
Methods: During a 6-week open-label (OL) phase, once-daily DR/ER-MPH was titrated to an optimal dose (20, 40, 60, 80, or 100 mg/d) and dosing time (8 PM ± 1.5 h) based on improvements on ADHD Rating Scale IV, Before School Functioning Questionnaire, and Conners' Global Index – Parent. Participants were then randomized 1:1 to double-blind (DB) optimized DR/ER-MPH or PBO for 1 week. The primary endpoint was the model-adjusted average of post-dose Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale combined score (SKAMP CS) over a 12-h laboratory classroom day (8 AM to 8 PM). Key/other secondary measures included the Parent Rating of Evening and Morning Behavior-Revised,

Morning (PREMB-R AM) and Evening (PREMB-R PM) subscales, and Permanent Product Measure of Performance-Attempted (PERMP-A) and -Correct (PERMP-C). Safety endpoints included treatment-emergent adverse events (TEAEs), with direct questioning for sleep disturbances.

Results: After the OL phase, the mean optimized dose was 66.2 mg and the most common prescribed dosing time was 8 PM (64.1% of participants). Efficacy outcomes were analyzed in 117 participants (64 DR/ER-MPH; 53 PBO). After 1 week of DR/ER-MPH treatment, outcomes over a 12-h classroom day were significantly improved versus PBO: SKAMP CS (least squares [LS] mean ± standard error [SE]: 14.8 ± 1.17 vs. 20.7 ± 1.22; P<0.001), PERMP-A (LS mean ± SE: 125.8 ± 8.78 vs. 92.1 ± 9.16; P=0.006), and PERMP-C (LS mean ± SE: 121.2 ± 8.78 vs. 89.0 ± 9.15; P=0.009). DR/ER-MPH also significantly improved functional impairment versus PBO in the early morning (PREMB-R AM [LS mean ± SE]: 0.9 ± 0.27 vs. 2.7 ± 0.27; P<0.001) and late afternoon/evening (PREMB-R PM [LS mean ± SE]: 6.1 ± 0.78 vs. 9.3 ± 0.81; P=0.003). No serious TEAEs or TEAEs leading to discontinuation were reported during the DB period. The most common TEAEs (≥5% in any group) were increased diastolic blood pressure (DR/ER-MPH: 13.8%; PBO: 13.0%) and any type of insomnia (DR/ER-MPH: 7.7%; PBO: 9.3%); all TEAEs during the DB period were mild/moderate in severity.

Conclusions: DR/ER-MPH was well tolerated and demonstrated significant improvements in ADHD-related symptoms and functional impairment from the early morning and into the evening versus PBO in children with ADHD.

T67. EVALUATION OF THE EFFECT OF SPN-812 EXTENDED-RELEASE VILOXAZINE ON THE PHARMACOKINETICS OF CONCERTA® IN HEALTHY ADULTS

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Abstract: Introduction: Viloxazine is currently being developed by Supernus Pharmaceuticals as a non-stimulant extended-release formulation for the treatment of attention-deficit/hyperactivity disorder (ADHD) (SPN-812). Co-administration of FDA-approved stimulant and non-stimulant medications for the treatment of ADHD is a common practice among healthcare practitioners in the U.S. who commonly diagnose and treat the condition. Therefore, co-administration of SPN-812 with Concerta® (methylphenidate hydrochloride), one of the frequently prescribed stimulant medications for the treatment of ADHD in children and adults, is possible.

Methods: Thirty-six subjects were enrolled in an open-label, randomized, 3-treatment, 3-period, 6-sequence, 3-way, crossover study, and received a single oral dose of SPN-812 (700 mg), Concerta (36 mg), or both under fasted conditions. The doses were separated by a washout period of at least 4 days. Blood samples for PK evaluations were collected up to 96 hours following the administration of study drug. PK parameters were estimated using non-compartmental methods, PK evaluations were conducted for methylphenidate for maximum plasma concentration (Cmax), area under the concentration–time curve from 0 to the last measurable time (AUC0-t), and 0 to infinity (AUCinf). The drug–drug interaction of viloxazine on methylphenidate was evaluated using analysis of variance on log-transformed PK

parameters: AUC0-t, AUCinf, and Cmax. The least squares (LS) mean for each treatment group, the difference in the LS means, and the 2-sided 90% confidence interval for the difference were calculated. Safety and tolerability were evaluated throughout the study.
Results: PK parameters for methylphenidate with and without co-administration of SPN-812 will be presented. Adverse events by treatment will also be presented.
Conclusion: The pharmacokinetics, safety, and tolerability of methylphenidate alone and co-administered with SPN-812 will be discussed.

T68. ARTISTS2: A WELL-CONTROLLED, FIXED-DOSE STUDY OF DEUTETRABENAZINE FOR THE TREATMENT OF TICS ASSOCIATED WITH TOURETTE SYNDROME

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[1]Baylor College of Medicine, [2]University of Miami Miller School of Medicine, [3]Vanderbilt University Medical Center, [4]Teva Pharmaceuticals, [5]Nuvelution TS Pharma Inc.

Abstract: Background: Tourette syndrome (TS) is a neurodevelopmental disorder manifested by motor and phonic tics.1 Behavioral and psychiatric comorbidities often accompany TS. In the US, antipsychotics, including haloperidol, pimozide and aripiprazole, are approved for the treatment of TS. However, the EU currently lacks European Medicines Agency–approved medicinal products for the treatment of TS. Only haloperidol and tiapride are approved nationally in some EU countries. Antipsychotics have been associated with serious side effects, such as tardive dyskinesia (TD). Deutetrabenazine, a generally well-tolerated vesicular monoamine transporter type 2 (VMAT2) inhibitor, was recently approved by the US Food and Drug Administration for the treatment of chorea associated with Huntington's disease (April 2017) and TD (August 2017). It is currently under evaluation for the treatment of tics in pediatric and adolescent patients with TS.2 This controlled study evaluates the efficacy of fixed doses of deutetrabenazine in reducing motor and phonic tics associated with TS compared with placebo.
Methods: ARTISTS2 (Alternatives for Reducing Tics in TS) is a Phase 3 placebo-controlled study of 150 patients between 6 and 16 years of age with tics associated with TS. Patients will be randomized 1:1:1 to deutetrabenazine high dose, low dose, or placebo. Doses will be titrated for a period of 4 weeks followed by 4 weeks of maintenance at their randomized study dose. The primary outcome is change from baseline to Week 8 in the Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS) between high dose deutetrabenazine and placebo. Secondary outcomes are change from baseline to Week 8 in: TS Clinical Global Impression (TS-CGI) score (high dose vs placebo), TTS of the YGTSS score (low dose vs placebo), TS-CGI score (low dose vs placebo), TS-Patient Global Impression of Impact (TS-PGII) score (high dose vs placebo), TS-PGII score (low dose vs placebo), child and adolescent Giles de la TS-Quality of Life (C&A-GTS-QoL) activities of daily living (ADL) subscale (high dose vs placebo) score, and C&A-GTS-QOL ADL subscale (low dose vs placebo) score. Additionally, safety and tolerability will be evaluated. The primary analysis will use a mixed-model, repeated-measures model. A hierarchical (fixed-sequence) testing approach will be used for the analysis of the primary and key secondary endpoints to maintain the experiment-wise type I error rate of 5% (two-sided).

Results: Not available yet.
Conclusion: TS is a neurodevelopmental disorder that often impairs quality of life in young patients, impacting occupational, social, and educational activities. TS presents an important unmet medical need for effective and well-tolerated treatment options. ARTISTS2 is a Phase 3 study with fixed doses of deutetrabenazine in pediatric patients with TS.
The study is sponsored by Teva Pharmaceuticals and operationalized by Teva's development partner Nuvelution TS Pharma Inc.

T69. ARTISTS1: A STUDY OF DEUTETRABENAZINE FOR THE TREATMENT OF TOURETTE SYNDROME IN CHILDREN AND ADOLESCENTS

Joseph Jankovic[1], Barbara Coffey[2], Daniel Claassen[3], David Stamler[4], Barry Gertz[5], Elisabeth Garofalo[5], Maria Wieman[4], Juha-Matti Savola[4]*
[1]Baylor College of Medicine, [2]University of Miami Miller School of Medicine, [3]Vanderbilt University Medical Center, [4]Teva Pharmaceuticals, [5]Nuvelution TS Pharma Inc.

Abstract: Background: Tourette syndrome (TS) is a neurodevelopmental disorder manifested by motor and phonic tics and often accompanied by behavioral and psychiatric comorbidities. In the US, antipsychotics, including haloperidol, pimozide and aripiprazole, are approved for the treatment of TS. However, the EU currently lacks European Medicines Agency–approved medicinal products for the treatment of TS. Only haloperidol and tiapride are approved nationally in some EU countries. Antipsychotics have been associated with serious side effects, such as tardive dyskinesia (TD).
Deutetrabenazine, a generally well-tolerated vesicular monoamine transporter type 2 (VMAT2) inhibitor, was recently approved by the US Food and Drug Administration for the treatment of chorea associated with Huntington's disease (April 2017) and TD (August 2017). Deutetrabenazine is currently under evaluation for the treatment of tics in pediatric and adolescent patients with TS2. This controlled study evaluates efficacy of flexible doses of deutetrabenazine in reducing motor and phonic tics associated with TS compared with placebo.
Methods: ARTISTS1 (Alternatives for Reducing Tics in TS) is a Phase 2/3 placebo-controlled study of approximately 100 patients between 6 and 16 years of age with tics associated with TS. Patients will be randomized 1:1 to deutetrabenazine or placebo. The dose for each patient will be titrated over 7 weeks to an optimal level, followed by a 5-week maintenance period at that dose. The primary outcome is change from baseline to Week 12 in the Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS). Secondary outcomes are change from baseline to Week 12 in TS Clinical Global Impression (TS-CGI) score, TS-Patient Global Impression of Impact (TS-PGII) score, and child and adolescent Giles de la TS-Quality of Life (C&A-GTS-QoL) activities of daily living (ADL) subscale score. Additionally, safety and tolerability will be evaluated. The primary analysis will use a mixed-model, repeated-measures model. A hierarchical (fixed-sequence) testing approach will be used for the analysis of the primary and key secondary endpoints to maintain the experiment-wise type I error rate of 5% (two-sided).
Results: Not available yet.
Conclusion: TS is a neurodevelopmental disorder that often impairs quality of life in young patients, impacting occupational, social, and educational activities. TS presents an important unmet medical need for effective and well-tolerated treatment options. ARTISTS1 is a Phase

2/3 placebo-controlled study with personalized optimal dosing of deutetrabenazine, a VMAT2 inhibitor, for pediatric patients with TS.
The study is sponsored by Teva Pharmaceuticals and operationalized by Teva's development partner Nuvelution TS Pharma Inc.

T70. EFFECT OF POLYGENIC RISK SCORES ON VIOLENCE IN SCHIZOPHRENIA

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Abstract: Background: Research on genetics of violence in schizophrenia has been neglected, on the other hand there are studies primarily focused on candidate genes, although genetic effects are known to be polygenic.
Aims: To test whether the effect of polygenic risk scores on violence in schizophrenia.
Method: The study sample consisted of 136 participants with a DSM-5 diagnosis of schizophrenia. Episodes of violence lifetime were assessed from electronic medical records, evaluating verbal, property and physical violence using a scoring similar to the MOAS, rating the worst episode lifetime for the three different types of violence. The schizophrenia polygenic risk scores were based on genome-wide meta-analysis results from the Psychiatric Genomics Consortium. The analysis of the polygenic scores was performed using PRSice version 1.25.
Results: The polygenic risk scores did not affect verbal, physical or property violence for p-value threshold between 0.01 and 1.0, indicating that the effect of schizophrenia polygenic risk scores on violence are not associated with violence lifetime and eventually with the severity of illness. The best fitting threshold p-values were 0.6 for verbal violence, 0.01 for property destruction and 0.3 for physical violence 0.01. All subjects showed positive polygenic scores confirming that the calculation was performed using only the risk alleles.
Conclusions: The effect of polygenic risk does not affect the risk of violence in schizophrenia. However, the effect of the scores was not tested in interaction with early life adversities or the treatment received that seem to modulate the risk of violence in schizophrenia.

T71. THE APPLICATION OF PET NEUROIMAGING PROBES TARGETING EPIGENETICS

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Abstract: Molecular imaging, such as positron emission tomography (PET), has been widely used in medical research and drug discovery. We have developed new imaging tools and applied them in clinical research and drug discovery. In this presentation, I will discuss the development and application of molecular neuroimaging techniques for brain research. In the past few years, we have developed the first generation of epigenetic PET probes for HDACs an bromodomains. The first probe for class I HDAC imaging has successfully advanced to human imaging studies and shows promising results so far. With these tools, we know the epigenetic changes in patients for the first time, and we also developed a series of new epigenetic inhibitor. Our work is a unique example on the multidisciplinary research, including molecular imaging, medicinal chemistry, clinical research and drug discovery.

Accumulating evidence implicates epigenetic changes and transcriptional dysfunction in alcohol and opioid use disorder, which is an important area of research for the field of drug addiction. However, these findings are only limited to rodent preclinical research and single drug abuse. Further, a limitation of these reports lies in that it was only possible/feasible to investigate a fraction of the brain for changes in epigenetic expression, despite those dynamic changes may occur to drive dysregulation of key neural circuits. PET imaging with epigenetic probes will: (i) allow characterization of "normal" epigenetic status in vivo as a function of age and sex; (ii) provide an early diagnostic method by serving as a biomarker for SUD; (iii) provide a predictive tool for individual drug response to epigenetic drugs; and (iv) accelerate the development of new epigenetic inhibitors to be used as therapeutic drugs
In this abstract, we will report our progress on measuring HDAC density and distribution in the human brain using a unique brain-specific simultaneous magnetic resonance (MR) and PET scanner with [11C]Martinostat, which will deliver answers to fundamental questions about chromatin modifying enzymes in the human brain in a way that has not been possible until now.

T72. A PRECLINICAL STUDY OF RAPASTINEL VERSUS KETAMINE IN OPIOID USE DISORDER

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Abstract: Background: Research in animal models suggests that the NMDA receptor is involved in the maintenance of opioid dependence and that its blockade might reverse opioid-induced neuroadaptation that contributes to dependence. Ketamine, an NMDA antagonist, has potential as a treatment, but is restricted due to side effects. Rapastinel, a novel antidepressant, acts as a partial agonist of an allosteric site of the glycine site of the NMDA receptor complex. Rapastinel has not been shown to produce any negative side effects during treatment in animal models or in human clinical trials for depression. The purpose of this study was to determine if rapastinel could accelerate the loss of opioid withdrawal symptoms in adolescents and adults without sedating or dissociative side effects associated with ketamine treatment.
Methods: All experiments were approved by the Duke University IACUC and conducted in accordance with the NIH Guide for the Care and Use of Laboratory. Male and female adolescent and adult rats (PN 28-30 and PN 60-62) from Charles River Laboratories were treated with a 5-day, increasing dose morphine regimen. In Study 1, animals received a 25 mg/kg morphine dose on day 6 followed 1 hour later by a naloxone challenge (1 mg/kg) and withdrawal behaviors were quantified. A second naloxone challenge given 21 days later. In Study 2, male and female adolescent rats received the same morphine treatment, but on day 6 they received naloxone only (1 mg/kg) and withdrawal signs were assessed as in Study 1.Then animals received saline, ketamine (1 mg/kg) or rapastinel (5 mg/kg) twice daily for 2 days. On day 9, animals received a second naloxone challenge (1 mg/kg) without a previous morphine treatment. Aggregate scores from day 9 were subtracted from those on day 6 to produce a difference score reflecting the extent to which withdrawal signs had decreased. Study 3 compared the ability of rapastinel to accelerate the loss of opioid withdrawal signs in adult and

adolescent rats. Treatment results were analyzed by sequential 3-way and 1-way ANOVA followed by post-hoc Fishers LSD multiple comparison test.
Results: The results of Study 1 indicated that naloxone elicited a robust withdrawal response on Day 6 ($p < 0.0001$ for effect of treatment by ANOVA) but there was no effect of sex or age. The response to the second naloxone challenge on Day 27 was smaller but statistically significant ($p < 0.003$ for effect of treatment) with significant effect of sex ($p < 0.04$) and interaction of sex x age ($p < 0.0009$). Female adults exhibited slightly higher withdrawal scores than male adults, while male and female adolescents had comparable withdrawal scores. In Study 2, no sex differences were observed so results were collapsed by sex. Rapastinel but not ketamine caused an enhanced loss of opioid withdrawal signs between day 6 and day 9 in adolescent males and females. Finally, Study 3 showed rapastinel was effective ($p < 0.002$ for effect of treatment) but no age or sex differences were observed.
Discussion: These studies show that opioid withdrawal signs are comparable early during withdrawal in adolescent and adult males and females. Females showed comparable withdrawal times on Day 6 and Day 9 but slightly exaggerated signs on Day 27, suggesting that they may show slightly slower loss of opioid dependence, but these effects were modest. Rapastinel significantly enhanced recovery from opioid dependence in both adolescent and adult rats, while ketamine was only marginally effective. Future studies will investigate the ability of rapastinel to blunt relapse during prolonged withdrawal using morphine conditioned place preference.
Supported by Duke Institute for Brain Sciences, Department of Pharmacology and Cancer Biology funds

T73. THE PATIENT'S PERSPECTIVE IN BENEFIT-RISK: HOW A PREFERENCE STUDY SUPPORTED THE ESKETAMINE APPLICATION FOR REGULATORY APPROVAL IN TREATMENT-RESISTANT DEPRESSION

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Abstract: Background: Motivated by factors including PDUFA VI, 21st Century Cures and ICH's revised expectations for drug submissions, regulatory agencies, pharmaceutical companies, and patient groups are increasingly engaging patients in medical product decision-making. In alignment with these policies, we conducted a patient preference study in the development of esketamine for the treatment of treatment-resistant depression (TRD) to understand the patient perspective on the tradeoffs between the benefits of depression relief in exchange for the risks of side-effects.
Methods: A preference survey was administered to: (1) Esketamine-treated subjects enrolled in clinical trials SUSTAIN-2 and SUSTAIN-3 at English-speaking sites (n=159), and (2) TRD subjects from an online panel (n=297). Respondents were asked to choose between hypothetical antidepressant treatments defined by varying levels of benefit and risk attributes. The 5 attributes were (1) improved mood (aligned to the Montgomery–Åsberg Depression Rating Scale (MADRS)), (2) how quickly the medication works, (3) the compound attribute of unusual sensations, wait time after dosing, and help getting home, and side effects associated

with ketamine abuse, namely, (4) likelihood of permanent bladder problems starting at 1 year (0%-5%), and (5) likelihood of permanent memory and thinking problems starting at 1 year (0%-5%). The clinical trial and panel samples were analyzed separately using random-parameters logit models.
Results: Mood improvement and reduced chance of cognitive and memory problems were the most valued attributes. The short-term post-dose symptoms and logistical issues associated with treatment were of low importance and were regarded as less important among clinical trial patients. In exchange for an improvement in depression symptoms from a MADRS total score of 40 (severe) to 20 (moderate) (similar to the change observed with esketamine in the clinical trials), respondents, on average, were willing to accept a maximum risk (95% CI) of permanent and severe bladder/cystitis problems above the maximum 5% level presented in the survey (clinical trial) and of 4.7% (3.4 - >5.0) (panel). For the same benefit, on average, patients would accept a maximum risk of permanent cognitive impairment of 4.7% (3.5 - >5.0) (clinical trial) and 3.2% (2.4 - 4.1) (panel).
Conclusion: To our knowledge, this study is one of the first to collect preference data from clinical trial participants and to include both in-trial and external samples. Results were included in the Clinical Overview to support regulatory review. Patients in the clinical trial and the panel had similar risk preferences. Patients valued treatments that would provide efficacy, far more than they valued avoiding the short-term post-dose symptoms and logistical issues associated with dosing. Patients were willing to accept between 3% and 5% risk of long-term hypothesized bladder or cognitive-impairment, risks associated with ketamine abuse and not seen in the Esketamine clinical studies, in exchange for improvement in depression symptoms from severe to moderate.

T74. A PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF SAGE-217 IN POSTPARTUM DEPRESSION: ASSESSMENT OF DEPRESSIVE SYMPTOMS ACROSS MULTIPLE MEASURES

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Abstract: Background: An estimated 10-20% of new mothers globally experience postpartum depression (PPD) each year, making PPD the most common medical complication of childbirth. GABAergic dysfunction has been implicated in the etiology of both PPD and major depressive disorder (MDD). SAGE-217, an investigational oral GABAA receptor PAM demonstrated rapid (by Day 2) and statistically significant improvement of symptoms of depression in subjects with MDD in a double-blind, randomized, placebo-controlled trial. This Phase 3 study (NCT02978326) is the first double-blind, randomized, placebo-controlled trial of SAGE-217 in women with PPD.
Methods: Women (n=151), ages 18-45, ≤6 months postpartum, diagnosed with PPD (defined here as a major depressive episode with onset in the 3rd trimester or ≤4 weeks postpartum), and a Hamilton Rating Scale for Depression (HAM-D) total score ≥26 at baseline were enrolled. Randomization was 1:1 to receive either SAGE-217 30 mg or placebo capsules for 14 days, with follow-up through Day 45. The Day 15 change from baseline in HAM-D total

score was the primary endpoint. The change from baseline in HAM-D total score at all other time points, HAM-D response (total score reduction ≥50%), HAM-D remission (total score ≤7), and the change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) were secondary endpoints. Adverse event (AE) reports and standard clinical measures were used to assess safety and tolerability.
Results: SAGE-217 achieved the primary endpoint of a significant reduction in least-squares (LS) mean HAM-D total score versus placebo (-17.8 vs. -13.6, p=0.0028) at Day 15. Significant differences favoring SAGE-217 vs. placebo were observed at Day 3 (p=0.0252) and were sustained through Day 45 (p=0.0027). HAM-D response (72%% vs. 48%, p=0.0049) and remission rates (45% vs. 23%, p=0.0110) were significantly greater in the SAGE-217 group compared to the placebo group at Day 15, and these clinically and statistically significant improvements were maintained through Day 45 (response p=0.0216; remission p=0.0091). At Day 15, SAGE-217 was associated with a significant decrease from baseline in LS mean MADRS score (-22.0 vs. -17.7, p=0.0180). The most common (≥5%) AEs in the SAGE-217 group were somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, and sedation.
Conclusions: In this Phase 3, double-blind, randomized, placebo-controlled trial, SAGE-217 treatment resulted in rapid (by Day 3), statistically significant, and sustained (over the study period) reductions in depressive symptoms in women with PPD. SAGE-217 was generally well-tolerated supporting the further development of SAGE-217 as a potential treatment for PPD.

T75. DEVELOPMENT OF THE N-METHYL-D-ASPARTATE RECEPTOR (NMDAR) ANTAGONIST D-METHADONE FOR THE TREATMENT OF DEPRESSION AND OTHER CNS DISORDERS

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Abstract: NMDA receptor (NMDAR) antagonists are potential agents for the treatment of several central nervous system (CNS) disorders including major depressive disorder. Racemic methadone and its stereoisomers, l-methadone and d-methadone, bind NMDARs with an affinity similar to that of established NMDAR antagonists, while only l-methadone and racemic methadone bind to opioid receptors with high affinity. Therefore, d-methadone is expected to have no clinically significant opioid effects at therapeutic doses mediated by its NMDAR antagonism. Relmada Therapeutics is developing d-methadone as a potential new treatment for depression and other CNS conditions. We conducted several pre-clinical studies comparing the effect of d-methadone and ketamine in different behavioral animal models commonly used to assess antidepressant activity. These include the Forced Swim Test, the Female Urine Sniffing Test and the Novelty Suppressed Feeding Test. We also performed behavioral analysis of the effect of both d-methadone and ketamine on rats exposed to a Chronic Unpredictable Stress (CUS) protocol. In all of the aforementioned tests, d-methadone like ketamine produced significant improvements in drug treated vs. vehicle treated animals. In addition, we observed positive effects on the expression of synaptic proteins and receptors critically involved in

synaptic plasticity. These biochemical effects were also paralleled by favorable changes in electrophysiology. We then investigated the safety, tolerability and pharmacokinetic (PK) profile of d-methadone in healthy opioid-naïve volunteers in two Phase 1, double-blind, randomized, placebo-controlled, single and multiple ascending dose (SAD and MAD) studies. d-Methadone exhibited linear PK with dose proportionality for most single dose and multiple dose parameters. Single doses up to 150 mg and daily doses up to 75 mg for 10 days were well tolerated with mostly mild treatment emergent adverse events and no severe or serious adverse events. At the tested doses, d-methadone did not cause dissociative or psychotomimetic adverse events, no clinically relevant opioid effects and no signs or symptoms of withdrawal upon abrupt discontinuation. Brain derived neurotrophic factor (BDNF) plasma levels from the 25 mg cohort of the MAD study were tested before any treatment and 4 hours after administration of d-methadone 25 mg (six patients) or placebo (two patients) on days 2, 6 and 10. In the d-methadone treatment group, 6 of 6 subjects showed an increase in BDNF levels post d-methadone treatment compared to pre-treatment levels, with post-treatment day 10 BDNF plasma levels ranging from twice to 17 times the pre-treatment BDNF levels. By contrast, in the two placebo subjects, the BDNF plasma levels remained unchanged. Plasma BDNF levels measured at day 2 and day 10 were significantly correlated to the plasma levels of d-methadone when placebo subjects are included in the analysis. We are currently conducting a phase 2a, multicenter, randomized, double-blind, placebo controlled, 3-arm study to assess the safety, tolerability, PK profile, and antidepressant effect of 7-day dosing with d-methadone 25 mg QD and 50 mg QD as adjunctive therapy in the treatment of patients diagnosed with major depressive disorder, who have not responded to 1 to 3 courses of treatment with an antidepressant medication in the presenting episode. In summary, the evidence gathered so far supports the development of d-methadone in depression and other CNS conditions for which NMDAR antagonism could be an effective mechanism of action for a potential treatment.