ASCP
American Society of Clinical Psychopharmacology

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POSTER ABSTRACTS

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Friday, May 29, 2020

Poster Session I

F1. LONG-TERM EFFICACY AND SAFETY OF LEMBOREXANT IN ADULTS WITH INSOMNIA DISORDER: RESULTS ACROSS 12 MONTHS FROM SUNRISE-2

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Abstract: Introduction: Lemborexant (LEM) is a dual orexin receptor antagonist (DORA) recently approved in the US and Japan for treatment of insomnia (Rosenberg et al, 2019; Hoyer et al, 2018). SUNRISE-2 (NCT02952820; E2006-G000-303) was a Phase 3 study that demonstrated significant benefit of LEM versus placebo (PBO) on patient-reported (subjective) sleep onset and maintenance outcomes. Here we present the 12-month efficacy and safety data for LEM from SUNRISE-2.

Methods: This randomized, double-blind, placebo-controlled (first 6 months [Treatment Period 1]), 12-month global Phase 3 study enrolled adults aged ≥18y with insomnia disorder defined per DSM-5 criteria. During Treatment Period 1, subjects were randomized to PBO or LEM (5mg, [LEM5]; 10mg, [LEM10]). During Treatment Period 2 (second 6 months), PBO subjects were re-randomized to LEM5 or LEM10 (not reported here) and LEM subjects continued with their assigned dose. Changes from baseline in subjective sleep parameters (sleep onset latency [sSOL], sleep efficiency [sSE], wake after sleep onset [sWASO]) were calculated based on sleep diary data. P-values were based on mixed-effect repeated measurement analysis evaluating least squares mean treatment differences for placebo versus LEM at Month 6.

Results: The Full Analysis Set included 949 subjects (Period 1: Placebo, n=318; LEM5, n=316; LEM10, n=315). At the end of Treatment Period 1 (Month 6) 251 and 226 subjects continued LEM5 and LEM10, respectively. Median sSOL (min) was significantly decreased (improved) with LEM5 (−21.8) and LEM10 (−28.2) versus PBO (−11.4; both $P<0.0001$) at Month 6; improvements were sustained at Month 12 (LEM5, −25.9; LEM10, −33.6). Mean (SD) increases in sSE (%) were significantly greater (improved) with LEM5 (15.3 [14.6]) and LEM10 (15.6 [15.6]) versus PBO (10.4 [13.8]; both $P\leq0.0001$) at Month 6; increases were maintained at Month 12 (LEM5, 15.8 [14.4]; LEM10, 17.9 [16.1]). Mean (SD) decreases in sWASO (min) were significantly greater with LEM5 (−51.5 [67.3]) and LEM10 (−48.1 [68.6]) versus PBO (−32.1 [55.3]; $P<0.001$, $P<0.05$, respectively) at Month 6; decreases were maintained at Month 12 (LEM5, −53.1 [61.5]; LEM10, −58.0 [71.1]). The majority of treatment-emergent adverse events (TEAEs) were mild or moderate. The most common TEAEs across the year of treatment (occurring in >10% for either LEM group), with LEM5 and LEM10, respectively, were nasopharyngitis (13.7%, 13.4%), somnolence (9.6%, 14.3%), and headache (11.1%, 9.2%). No deaths were reported.

Conclusions: Improvements to subjective sleep outcomes observed with LEM at 6 months were sustained over 12 months; LEM was well tolerated. These data from SUNRISE-2 suggest that LEM is a potential long-term treatment option for patients with chronic insomnia.

SUPPORT: Eisai Inc.

F2. PUBLIC IMAGE AND SENTIMENT TOWARD THE PHARMACEUTICAL INDUSTRY: WHAT CAN WE DO TO REVERSE THE NEGATIVE TREND?

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Abstract: In late 2019 a Gallup poll reported that the pharmaceutical industry surpassed the oil industry, hitting "rock bottom," in terms of (public) trust. This fact has an undisputed negative impact on both clinical trial recruitment and enrollment; it may also adversely affect retention as well. There are numerous causes and widely publicized examples of behaviors and incidents perpetuating this public sentiment. Strangely, only recently have some excellent public relations efforts and public service announcements (e.g., PSAs) been conceptualized and implemented in an effort to improve the public awareness of, and respect for, our industry, especially as it relates to the clinical research process.

In 2014 the European Union (EU) Clinical Trial Regulation requiring Layperson/Plain Language Summaries (PLS) was passed and slated for implementation in 2018; however, due to patient portal-related "technical difficulties," mandatory implementation has been deferred until 2020. Here in the United States, many sponsors have evaluated the pros and cons, as well as the projected costs and perceived benefits, of a voluntary pro-active implementation of a PLS strategy. As of this date, while TransCelerate has published a document titled "Layperson Summaries of Clinical Trials: An Implementation Guide (with recommendations on how to do so in a non-promotional manner)," we remain far from a comprehensive and/or quasi-standardized strategy for the PLS creation and distribution processes. Moreover, voluntary, pro-active, compliance with and/or implementation of a PLS strategy is "low hanging fruit," when it comes to an industry-wide opportunity to help ameliorate the widely-embraced "distrust," as well as better inform and educate our trial participants.

This poster presentation will concisely provide publicly accessible resources to help guide smaller companies through the mine-fields of allegations regarding potential "pre-promotional" wrongdoing; it will also highlight how an effective creation and implementation of a PLS strategy will prove to be an exceedingly cost-effective long-term "voluntary" strategy. Furthermore, in the wake of such rampant public distrust, being fueled even further by politics throughout this election year, the timing of this opportunity to further educate and inform trial participants as well as enhance our public image, will also have a positive immediate- and long-term measurable impact on enrollment!

While delay is preferable to error(s) in implementation, the 2014 passage of the first applicable-to-PLS regulation has provided us with sufficient time --- and, now published guidelines --- to move forward without further delay. As sponsors, sites and CROs working together vis-a-vis a PLS dissemination process, we can not only utilize this as an opportunity to "Thank" patients, we can do so in a manner which also better educates them whilst bolstering their trust in us. Finally, it will also translate into a heightened willingness to possibly "volunteer again" and potentially "refer-a-friend"!!

F3. WHY ARE WE SWITCHING? A RETROSPECTIVE CHART REVIEW STUDY OF REASONS FOR ANTIPSYCHOTIC SWITCH AMONGST FIRST- AND SECOND-GENERATION ANTIPSYCHOTICS

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Abstract: Background and objectives: Antipsychotics are the cornerstone of successful acute treatment and relapse prevention in psychotic disorders. However, despite their efficacy, antipsychotics are prone to frequent switches (1).
Previous literature exploring the reasons leading physicians to switch antipsychotic treatments point towards the lack of tolerability/side effects (2). However, the relationship between antipsychotic generation (first- (FGA) vs. second-generation (SGA)) and reasons for medication switch have been less frequently studied.

Thus, we aimed to review and characterize antipsychotic medication switches and examine their potential relationship with antipsychotic generation (FGA vs. SGA).

Methods: We conducted a systematic retrospective chart review in order to extract data on antipsychotic medication switch for patients treated in the inpatient and outpatient units at the Zucker Hillside Hospital, New York between August 2017 and August 2018. Reasons for every switch were independently extracted by two investigators and categorized to: side effects, lack of efficacy, insurance problems, symptom remission, patient preference, poor adherence, and other. Comparisons between FGA vs. SGA were analyzed using chi-square tests ($\chi 2$) with a significance level of 0.05. Statistical analyses were carried out using IBM SPSS Statistics version 12.0.

Results: 400 charts were reviewed. 167 antipsychotic switches were detected, of which 159 reported reasons for the switch. A total of 65/159 switches (40.9%) were detected in males and 94/159 (59.1%) in females. 89/159 (56.0%) were reported in white subjects, 46/159 (28.9%) in African American, 16/159 (10.1%) in Asians, 4/159 (2.5%) in subjects of mixed race and race was not provided in 2/159 (1.3%).

Regarding the type of antipsychotic, 16/159 (10.1%) were FGA switches, whereas 143/159 (89.9%) were SGA switches. Our analysis showed no significant differences in reasons for switch based on antipsychotic generation (X2= 2.1, p= 0.909). The most common reason for switching overall was found to be side effects, n= 75 (47.2%), followed by a lack of efficacy, n= 34 (21.4%). Patient preference accounted for 23 (14.5%) of the switches, and poor adherence accounted for 12 (7.5%). Additionally, insurance problems accounted for 6 (3.8 %). Symptom remission was listed in 1 (0.6%) case and the remaining 8 (5.0%) were for other reasons.

Conclusion: In our sample, the majority of antipsychotic switches were related to side effects. Lack of efficacy and patient preference were listed as additional reasons for antipsychotic switching. Our analysis showed no significant differences between FGA and SGA in terms of reasons for the antipsychotic switch, although the low number of switches detected in FGA may have limited our power to detect differences. Further studies should focus on studying why switches appear to be less frequent on FGA and detail specific patient-reported side effects.

F4. THE IMPACT OF GINKGO BILOBA ON MENTAL ILLNESS AND PSYCHOTROPIC MEDICATIONS

Alex Mull[*1], Nikolas Cirillo[1], Leah Spigelman[1]*

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Abstract: Ginkgo Biloba (GB) is an herbal supplement that is growing in popularity in the United States that is purported to enhance cognitive abilities (Laws, Sweetnam, & Kondel, 2012). In addition to enhanced cognition, other alleged uses for GB is to treat anxiety, depression, schizophrenia, and neurocognitive disorders (Varteresian, & Lavretsky, 2014; Brondino et al., 2015; Shenoy, Somayaji, & Bairy, 2001; Ernst, 2007). Most commonly found in the form of an extract, GB is typically administered orally or added to a beverage to be consumed one to two times daily.

Many efficacy and effectiveness trials have been conducted to further elucidate the effects of GB with mixed outcomes, resultant in controversy amongst researchers and clinicians in terms of efficacy, dosage, and mechanisms of action that are responsible for improved outcomes in different disorders.

The pharmacological effects of GB extract are a function of terpene trilactones (TTL) (ginkgolide A (GKA), B (GKB), C (GKC), J (GKJ), and bilobalide (Bb)) and flavonoids (quercetin, kaempferol, and isorhamnetin) (Ude, Schubert-Zsilavecz, & Wurglics, 2013). The half-life of GB ranges between 3-5 hours, 60% oral bioavailability, the main absorption site being in the stomach and small intestine, and elimination occurred via exhalation (38%), urine (22%), and feces (29%) (Ude et al., 2013; Monreau et al., 1986).

The pharmacodynamic profile of GB contains numerous mechanisms of action that theoretically explain the outcomes found in clinical literature. Shenoy and colleagues (2001) suggest that GB decreases dihydroalprenolol binding and isoproterenol-stimulated adenylate cyclase activity acting as a beta-adrenergic blocker. There is also evidence it acts as a monoamine oxidase inhibitor (MAOI) and catechol-o-methyltransferase (COMT) inhibitor which suggests for its impact on neurocognitive disorders. COMT inhibition is particularly important when paired with psychopharmacological agents to treat neurocognitive disorders such as dementia and Parkinson's Disease (Lamberti et al., 2004). COMT inhibition allows for longer lasting effects on agents, such as levodopa, for improving symptomology for longer periods of time, providing lasting relief for the patient. This same mechanism has shown to be useful in antidepressant therapies. Schubert, and Halama (1993) found that GB when combined with a tricyclic antidepressant was more effective than antidepressant monotherapy. Due to GB's effects when paired with psychopharmacological agents, it is important for clinicians to also understand its interactions. Yin, Tomlinson, Waye, Chow, and Chow (2004) found that GB interacts with CYP2C19 substrates and effectively reduces the clearance of these medications and may reduce their effect below their therapeutic window. A case study conducted by Kupiec and Raj (2005) suggested GB reduced the clearance of Dilantin and Depakote resulting in a breakthrough seizure resulting in the patient's death, which was hypothesized to be due to GB's inductive effect on the CYP2C19 pathway. This is contrary to the research conducted by Izzo and Ernst (2009) which suggests there is inconclusive data on any cytochrome P450 interactions. This poster will explore the positives and negatives of GB's pharmacokinetic and pharmacodynamic profile with relation to relevant medications cited in

the literature. Moreover, this poster emphasizes the impact of GB use on the health of patients suffering from a variety of mental illnesses. As such, further research on GB's interactions and clinical implications are warranted.

F5. UNDERSTANDING THE ADOPTION OF DIGITAL MEDICINES IN BEHAVIORAL HEALTH CLINIC SETTINGS: AN IMPLEMENTATION SCIENCE APPROACH

ABSTRACT NOT INCLUDED

F6. WEARABLE DEVICES FOR THE REAL-TIME CAPTURE OF GAIT AND ACTIGRAPHY MEASURES: PRELIMINARY FEASIBILITY AND VALIDITY DATA IN OLDER ADULTS WITH AND WITHOUT SUBJECTIVE COGNITIVE DECLINE

ABSTRACT NOT INCLUDED

F7. LANGUAGE AND COMMUNICATION IN PSYCHOSIS: DIGITAL TOOLS AS NOVEL OPPORTUNITIES FOR BIOMARKER AND INTERVENTION

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Abstract: Background/Purpose: Psychotic disorders (PD) produce impairments in interpersonal processing, including language, which have major negative impacts on functioning and outcomes. Funded by the 2018 ASCP Early Career Research Award, this study investigates the opportunity for digital tools to serve as platforms for novel interventions and biomarkers. Experiment 1 (Ex1) evaluates access and use of technology and social media in young adults with PD, clinical risk for psychosis (CR) and healthy control (HC) individuals without psychosis symptoms. Experiment 2 (Ex2) compares automated natural language processing (NLP) methods for detecting linguistic changes in PD with traditional clinical ratings.

Methods: Ex1 included 55 young adults aged 18-32 years (PD n=21, CR n=22, HC n=12) who were surveyed regarding their access to technology and use of social media. Mean age in Ex1 was 23.2 years and 44% of participants were female. Ex2 included 31 adults (PD n=20, HC n=11) with transcribed open-ended interviews. Mean age in Ex2 was 36.2 years and 51% were female. Ex2 PD were not enriched for thought disorder. Blinded ratings were made on the Scale for the Assessment of Thought Language and Communication (TLC). Three NLP measures were explored to discern the PD group effect: weighted log-odds for individual word frequencies, prevalence of various parts-of-speech and sentiments, and next-sentence predictability using Bidirectional Encoder Representations from Transformers (BERT).

Results: In Ex1, there was a high level of access to technology across the groups and there were no differences in access to mobile phones, smartphones, computers, or the internet. Young adults with PD accessed social media to a similar extent but were less likely to actively post compared to both CR and HC ($p=0.02$). This effect was specific to psychosis among psychiatric disorders (mood disorders $p=0.31$; anxiety disorders $p=0.73$; ADHD $p=1.00$). In Ex2, there was no group effect on TLC ratings ($p=0.23$). However, PD used significantly more first-person pronouns ($p<0.001$), fewer descriptors (adjectives $p=0.006$ and adverbs $p=0.02$) and spoke more incomplete words ($p<0.001$). Naïve Bayes classification based on word frequencies alone produced an AUC of 75%. However, BERT next-sentence predictability was not significantly different between the groups ($p=0.11$).

Conclusions/Significance: The results encourage further development of internet and social media-based interventions and treatment monitoring for young people with psychosis. Lower active engagement may reflect impairments in social cognition and functioning. NLP tools show promise for sensitive discernment of a linguistic biomarker in psychosis. Linguistic biomarkers can potentially be automatically and objectively extracted from both digital and non-digital sources to aid in diagnosis and monitoring treatment effect.

F8. PHASE 1 PHARMACOKINETIC STUDY OF A ONCE-DAILY FORMULATION OF TNX-601 CR (TIANEPTINE OXALATE CONTROLLED-RELEASE) TABLETS

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Abstract: Background: Tianeptine sodium 12.5 mg (Stablon®), taken three-times daily (TID), is an atypical antidepressant approved in Europe, Asia, and Latin America for major depressive disorder (MDD), but not in the U.S. The active ingredient of Stablon is amorphous tianeptine sodium, and, as an antidepressant, prominent anxiolytic effects have been described. These attributes and preliminary clinical studies suggest tianeptine has potential therapeutic value in posttraumatic stress disorder (PTSD) in addition to MDD. We identified a new oxalate crystalline salt of tianeptine with improved pharmaceutical properties. In the present Phase I study of tianeptine oxalate, we compared the pharmacokinetics (PK) and safety of immediate-release (IR) tianeptine oxalate 13.1 mg (TNX-601) to tianeptine sodium 12.5 mg (which both contain 11.9 mg of tianeptine), and to a controlled-release (CR) formulation of tianeptine oxalate 39.4 mg (TNX-601 CR) selected for once-daily dosing, in fed and fasted states.
Methods: In this single-center, open-label, multiple sequential period study, a single cohort of 12 male and female healthy volunteers were administered in successive periods: tianeptine sodium 12.5 mg (Stablon), tianeptine oxalate 13.1 mg (TNX-601), and tianeptine oxalate CR 39.4 mg (TNX-601 CR) in a fasted state; and TNX-601 CR was also administered in the fed state. PK of tianeptine and its main active metabolite, MC5, and safety assessments were made up to 48 hours post-dose.

Results: Stablon and TNX-601 demonstrated similar PK for plasma tianeptine and MC5. For plasma tianeptine, Tmax was 1.5 hour (h) for Stablon and 1.0 h for TNX-601. Cmax, AUC0-24, and t1/2 for Stablon were 239 ng/mL, 935 ng*h/mL, and 3.13 h, and for TNX-601 were 237 ng/mL, 942 ng*h/mL, and 3.56 h, respectively. TNX-601 CR in fasted state demonstrated a delayed Tmax of 3.5 h, and a t1/2 at 6.86 h. For TNX-601 CR, the AUC0-24 at 2040 ng*h/mL was 22% lower than that estimated for TID-administered 12.5 mg tianeptine sodium. Food

increased the Cmax of TNX-601 CR by ~40%. In contrast, food decreased the C24 by ~40%. Importantly, for TNX-601 CR, the AUC0-24 was similar in the fed and fasted states for both plasma tianeptine and MC5. Multi-dose steady state simulations of TNX-601 CR in both fasted and fed states support the concept that once-daily TNX-601 CR will have therapeutic similarly to amorphous tianeptine sodium IR administered TID. TNX-601 and TNX-601 CR were both well-tolerated, and adverse events were consistent with the known safety profile of Stablon.

Discussion: TNX-601 CR 39.4 mg demonstrated PK appropriate for once-daily dosing with minimal food effect. Once-daily dosing is believed to be an advantage over TID dosing for adherence to treatment. TNX-601 and TNX-601 CR were also well-tolerated, without unexpected side effects, and with profiles consistent with the ex-US-marketed sodium salt form of tianeptine. These findings support Phase 2 testing of TNX-601 CR, the once-daily formulation of tianeptine, in MDD and PTSD.

F9. PSYCHOMETRIC EVALUATION OF A COMPUTER-ADMINISTERED COGNITIVE TEST BATTERY IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: RESULTS FROM A RANDOMIZED, MULTICENTER, CROSSOVER STUDY

ABSTRACT NOT INCLUDED

F10. NEXT-STEP TREATMENT CONSIDERATIONS IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION THAT RESPONDS TO LOW-DOSE INTRAVENOUS KETAMINE

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Abstract: Numerous short-term randomized trials support the acute phase efficacy of low-dose intravenous (IV) ketamine for patients with treatment-resistant unipolar or bipolar depression (TRD). Ketamine's antidepressive effects generally have limited duration, highlighting the need for maintenance treatment following an acute-phase response. It is increasingly likely that psychiatrists will be called upon to manage the care of patients with TRD who have responded acutely to ketamine, and to recommend or initiate next-step treatments. However, there is a paucity of controlled evidence to guide best practices for managing patients with TRD who have had a positive initial response to ketamine. We review the available evidence supporting specific strategies for extending and maintaining acute antidepressive responses to low-dose IV ketamine in patients with TRD. We reviewed the evidence for the following approaches to treatment after IV ketamine: (a) Continued intravenous [IV] or intranasal ketamine (b) Intranasal esketamine (c) Oral ketamine (d) Other glutamatergic drugs (e) Electroconvulsive therapy (ECT) (f) Other neuromodulatory therapies (g) Switching conventional antidepressants or mood stabilizing medications and (h) Continuation of effective psychotherapy. In the absence of specific randomized clinical trials, open-label studies were considered, along with primary efficacy and safety data for the other approaches. Expert opinion formed the basis of identifying potential treatment recommendations, without sufficient evidence or opinion to provide hierarchical recommendations of what might be

considered first-line, second-line, or subsequent treatments. We highlight the most promising strategies to study, in order to clarify direction for future research.

F11. OPEN BOARD

F12. ESKETAMINE, IN CONJUNCTION WITH ANTIDEPRESSANT MONOTHERAPY OR AUGMENTATION THERAPY, REDUCES DEPRESSIVE SYMPTOMS IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER AND ACTIVE SUICIDAL IDEATION WITH INTENT

Karimah S. Bell Lynum[1], Abigail Nash[1], Carla Canuso[1], Dong Jing Fu[1], Dawn F. Ionescu[1], Jennifer Kern-Sliwa[1], Ibrahim Turkoz[1], Abigail Nash[1]*

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Abstract: Objective: In the phase 3 ASPIRE I/II studies (NCT03039192/NCT03097133), esketamine nasal spray (ESK), plus comprehensive standard of care (SoC), rapidly reduced depressive symptoms versus placebo nasal spray (PBO)+SoC in adult patients with major depressive disorder and active suicidal ideation with intent (MDSI) (Fu et al., 2019; Ionescu et al., 2019). This post hoc pooled analysis evaluated the efficacy and safety of ESK given in conjunction with either oral antidepressant monotherapy or antidepressant augmentation therapy.

Methods: Adults (aged 18-64 years) with MDSI were randomized to ESK (84 mg) or PBO twice weekly for 4 weeks in conjunction with SoC. SoC included initial hospitalization and newly initiated or optimized standard oral antidepressant therapy (monotherapy or augmentation therapy). The primary endpoint was change in Montgomery–Åsberg Depression Rating Scale (MADRS) total score from baseline to 24 hours postdose (treatment differences examined using analysis of covariance models).

Results: In the full analysis set (n=451), ESK or PBO was given in conjunction with antidepressant monotherapy in 212 patients (47.0%; mean age, 37.0 years; female, 55.7%) or antidepressant augmentation therapy in 239 patients (53.0%; mean age, 42.8 years; female, 65.3%). Mean baseline MADRS total scores were 40.7 (range, 29-58) and 40.1 (range, 29-54) in patients receiving antidepressant monotherapy and augmentation therapy, respectively. In patients receiving antidepressant monotherapy, mean (±SD) changes in MADRS total score from baseline to 24 hours were –16.2 (±11.9) with ESK+SoC versus –12.4 (±10.3) with PBO+SoC (least squares means [LSM] difference [95% confidence interval], –4.0 [–6.8,–1.3]; P=0.005). Changes from baseline to 24 hours postdose in patients receiving antidepressant augmentation therapy were –15.9 (±11.6) with ESK+SoC versus –12.7 (±10.8) with PBO+SoC (LSM difference, –3.9 [–6.6, –1.2]; P=0.005). The safety profile of ESK was similar in patients receiving antidepressant monotherapy and those receiving antidepressant augmentation therapy. The most common adverse events were dizziness, somnolence, headache, dissociation, nausea, and dysgeusia. Additional results will be reported on prior and concomitant antidepressant therapies.

Conclusion: Compared with PBO+SoC, ESK+SoC rapidly reduces depressive symptoms in adults with MDSI regardless of choice of concomitant oral antidepressant monotherapy or augmentation therapy. ESK had a similar safety profile when used with either oral antidepressant regimen.

Financial support: Study funding and medical writing support (Sarah Feeny [ApotheCom]) was provided by Janssen Scientific Affairs, LLC, USA.

F13. CHARACTERISTICS OF RESPONDERS/REMITTERS IN A PHASE 4 STUDY OF ADULTS WITH MAJOR DEPRESSIVE DISORDER TREATED WITH VORTIOXETINE 10 MG

ABSTRACT NOT INCLUDED

F14. EFFICACY AND SAFETY OF VORTIOXETINE (5, 10, AND 20 MG) IN RELAPSE PREVENTION: RESULTS OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 4 STUDY IN ADULTS WITH MAJOR DEPRESSIVE DISORDER (MDD)

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Abstract: Background: Treatment leading to full remission and maintenance of efficacy are key priorities in recurrent MDD management. A relapse prevention study previously demonstrated the long-term efficacy of vortioxetine (VOR) at 5 and 10 mg, but included neither US patients nor the highest recommended 20-mg dose, which accounts for 45% of US prescriptions. Also, the optimal dose for maintenance, after response and stabilization to acute treatment with VOR, has not been formally evaluated.

Methods: This randomized withdrawal design study (NCT02371980) enrolled over 1100 US patients with recurrent MDD with a currently relapsed major depressive episode (Montgomery-Åsberg Depression Rating Scale [MADRS total score] ≥26). All patients were initially treated with VOR 10 mg in the open-label phase (OLP) for 16 weeks (wk). Those who responded and were stabilized (≥50% reduction from baseline (BL) in MADRS total scores at wk 8, and then a score ≤12 at wks 14 and 16) were eligible to enter the 32-wk double-blind (DB) treatment period. Eligible patients were randomized to 1 of 3 fixed doses of VOR (5, 10, or 20 mg) or placebo (PBO). The primary endpoint was time from randomization to relapse (defined as MADRS ≥22 or lack of efficacy or other unsatisfactory treatment response) during the first 28 wks of the DB period (DBP). Secondary endpoints included change from DB BL in MADRS; Clinical Global Impressions Scale-Severity (CGI-S); CGI-Improvement (CGI-I); time from randomization to relapse during the entire 32-wk DBP; and safety assessments. A Cox proportional hazards model, with treatment as a factor and BL MADRS total score as a covariate, was used to analyze the primary endpoint.

Results: Of 1106 patients enrolled in the OLP, 580 were randomized to the DBP (PBO, n=151; VOR 5 mg, n=140; VOR 10 mg, n=145; and VOR 20 mg, n=144). Patients in all groups had similar demographics and disease severity at the start of the DB treatment phase. For each dose of VOR, the relapse rate at wk 28 was significantly lower than with PBO, with VOR 5, 10, and 20 mg at 19.3%, 17.9%, and 17.4% vs PBO at 32.5% (P values: 0.006, 0.002, and 0.003,

respectively). Cox regression analyses for the first 28 wks of the DBP demonstrated an overall risk reduction of 48%−52% and a longer time to relapse of MDD for all 3 doses of VOR vs PBO as follows: VOR 5 mg, hazard ratio (HR)=0.517 (95% CI: 0.323, 0.828); VOR 10 mg, HR=0.476 (95% CI: 0.296, 0.767); VOR 20 mg, HR=0.483 (95% CI: 0.298, 0.782). For the secondary endpoints of changes from DB BL in MADRS and CGI-S scores throughout the 32-wk DBP, all doses of VOR compared favorably to PBO, with statistical significance reached for most time points assessed. The Kaplan-Meier plot showed clear separation between the curves for the 3 VOR groups and PBO, indicating a longer time to relapse for each VOR dose ($P<0.05$ vs PBO) over the 32-wk DBP. Most AEs (across all 4 groups during the DBP) were of mild to moderate severity, and the most frequently reported AEs were upper respiratory infections (5.7%), nasopharyngitis (4.5%), nausea (4.1%), weight increase (4.0%), and back pain (2.1%). Of note, during the OLP, rate of nausea was 26.4%, whereas during the DBP, rates were considerably lower for each treatment arm: VOR 5 mg, 2.9%; VOR 10 mg, 3.4%; and VOR 20 mg, 9.0%.

Conclusions: VOR showed robust maintenance efficacy in the US study population across the entire approved dose range (5−20 mg) in patients who initially responded and were in remission on the 10-mg dose. VOR was well tolerated with a safety profile consistent with previously reported data.

F15. SWITCHING TO AN MAO-I IN THE SETTING OF TREATMENT-RESISTANT DEPRESSION (TRD)

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Abstract: Background: Over forty percent of patients treated for depression fail to respond to the empiric algorithm of treatment modalities. This failure of response is known as treatment-resistant depression (TRD). When managing a patient with TRD, a clinician is only left with so many options, and thus it is imperative that he or she not overlook any viable alternatives, namely MAO-Is. Unfortunately, the correlation between the dreaded serotonin syndrome and MAO-Is has been engrained in physicians. This case report will shed light upon the safety of switching to an MAO-I, in the setting of TRD.

Case Report: A 68-year-old female patient with a past psychiatric history of TRD presented involuntarily to the hospital following decompensation in the PHP setting. The patient had already completed a trial of fourteen sessions of ECT with minimal improvement. The patient had been compliant with home medications, which included Lexapro and Remeron. The treatment team discontinued the Lexapro and started the patient on Phenelzine, the following morning.

Results: The patient was observed for over two weeks. During that time, moderate improvements in mood were observed. Of note, no signs or symptoms of serotonergic hyperactivity were reported.

Discussion: Because of their feared serotonergic consequences, clinicians have become averse to the utilization of MAO-Is. Even when a clinician finally considers switching to an MAO-I in the setting of TRD, most guidelines still recommend waiting two to four weeks for a washout

period. This case report demonstrates that clinicians could consider turning to MAO-Is more commonly in the setting of TRD.

F16. REAL-WORLD USE OF ESKETAMINE NASAL SPRAY FOR TREATMENT-RESISTANT DEPRESSION: CHARACTERIZING EARLY HEALTHCARE SETTINGS, PRESCRIBERS, AND PATIENTS

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Abstract: Objective: To examine the characteristics of patients, providers, and healthcare settings related to esketamine nasal spray (ESK) use in the first 4 months following approval in the United States, using data from the Risk Evaluation and Mitigation Strategy (REMS) program.

Methods: ESK, a noncompetitive N-methyl D-aspartate (NMDA) receptor antagonist, in conjunction with an oral antidepressant, was approved for the treatment of adults with treatment-resistant depression (TRD) on March 5, 2019, with implementation of an FDA-required Risk Evaluation and Mitigation Strategy (REMS) program to mitigate the risks of serious outcomes resulting from sedation, dissociation, and misuse and abuse (US FDA, 2019; Janssen Pharmaceuticals, Inc., 2019). Data from the initial REMS reporting period (March 5-July 7, 2019) were reviewed. REMS certification and categorization of healthcare settings, pharmacies, and prescribers and demographics and adverse event (AE) reports of patients enrolled in the REMS were analyzed.

Results: During the initial reporting period, 1998 healthcare settings (HCS) were certified in the REMS. Of these, 40.3% of HCS self-identified as independent/private practice settings, 35.6% as outpatient clinics, and 25.7% as group practices (more than one type could be selected). The highest proportion of prescribers associated with the certified HCS specialized in psychiatry (93.4%) and were credentialed as medical doctors (MDs; 80.1%). Of the 1179 pharmacies certified during the reporting period, 37.8% self-identified as outpatient pharmacies; 37.4% as long-term care facilities; and 33.8% as mental health facilities (more than one type could be selected). In this reporting period, 594 patients had received at least one ESK treatment. Over half the patients who received treatment were females (57.9%), and the mean age was 47.5 years (±15.3 years). Of 3760 total treatment sessions during this period, there were 2148 (57.1%) sessions in which a patient experienced one or more AEs. Overall, 80.6% of patients experienced one or more REMS-specific events of interest (ie, sedation, dissociation, increase in blood pressure) associated with one or more treatment sessions. Based on responses to questions captured at each treatment session, sedation was experienced by 63.0% of patients, dissociation by 61.3%, and an increase in blood pressure by 7.7%. Serious AEs were reported in 29 patients (4.9%).

Conclusion: Preliminary information from the ESK REMS program shows that most prescribers of ESK were psychiatrists. Early ESK REMS-certified treatment settings were distributed between private practices, outpatient clinics, and group practices. Pharmacies providing ESK were almost evenly split between outpatient, long-term care, and mental health facilities. More than half of patients receiving treatment were female. The most commonly

reported AEs were sedation and dissociation, both labelled and expected. Serious AEs and the overall safety profile were consistent with those observed in the phase 3 clinical studies.

Financial support: Study was funded by Janssen Pharmaceuticals, Inc., USA. Editorial support was provided by Sarah Feeny (ApotheCom).

F17. CHARACTERIZING PRIMARY CARE PATHWAYS FOR PATIENTS WITH A DEPRESSIVE DISORDER

ABSTRACT NOT INCLUDED

F18. EFFECT OF ADJUNCTIVE PIMAVANSERIN ON SUICIDALITY IN PATIENTS WITH MAJOR DEPRESSION: SECONDARY ANALYSIS FROM CLARITY

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Abstract: Background: Suicide is the third leading cause of mortality worldwide for ages 15–44 years, and about 1 million people die by suicide each year. Up to 15% of patients with major depressive disorder (MDD) attempt suicide and up to 12% succeed. Risk factors for increased suicidal ideation and behavior include depression severity, sleep disturbances, psychotic depression, and recurrence of depression or failure to achieve remission. Studies have shown that suicidal ideation and behavior often decline with improvement in depressive symptoms during antidepressant treatment, although some data have suggested that suicidal ideation may increase early in the treatment course of MDD. CLARITY was a phase 2 study of the efficacy and safety of pimavanserin as adjunctive therapy in patients with MDD. This secondary analysis of CLARITY describes the effects of pimavanserin on suicidal ideation and behavior. Even among patients without a recent history of suicidal ideation or behaviors, their emergence is not uncommon during the course of studies of MDD.

Methods: This was a secondary analysis from a multicenter, randomized, double-blind, placebo-controlled treatment study in patients with MDD and an inadequate response to a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI). Eligible patients were not actively suicidal and had not attempted suicide within 2 years. Using a 2-stage, sequential parallel-comparison design, patients were initially randomized in a 3:1 ratio to placebo or pimavanserin added to ongoing SSRI or SNRI therapy; at 5 weeks, placebo non-responders were re-randomized to placebo or pimavanserin for an additional 5 weeks. For this secondary analysis, endpoints were mean change from baseline for the Hamilton Depression (HAM-D) Rating Scale Item 3 (suicide). The incidence of suicidal ideation or behavior at baseline and with treatment was assessed from the Columbia-Suicide Severity Rating Scale (C-SSRS). Adverse events of suicidal ideation or behavior were recorded.

Results: In Stage 1, 155 patients were randomized to placebo and 52 to pimavanserin, while during Stage 2, 29 patients were re-randomized to placebo and pimavanserin groups. For the HAM-D Item 3, no significant difference was observed between placebo and pimavanserin at baseline or at Week 5 of either Stage 1 or Stage 2. At any post-baseline assessment during Stage 1, suicidal ideation on the C-SSRS was reported in 28 (18.1%) patients with placebo and 9 (17.3%) with pimavanserin. During Stage 2, suicidal ideation was reported in 7 (20.7%) with placebo and 4 (13.8%) with pimavanserin. One patient in the placebo group reported suicidal ideation on Study Day 2 that resolved by Day 12. During Stage 1, a shift to a worsening C-SSRS total score from baseline occurred in 15/152 (9.9%) with placebo and 4/51 (7.8%) with pimavanserin, and during Stage 2 in 5/29 (17.2%) with placebo and 1/29 (3.4%) with pimavanserin. No events of suicidal behavior were observed with either placebo or pimavanserin.

Conclusions: Even in studies of MDD that are not focused on patients who are suicidal at baseline, suicidal ideation and behaviors are key outcomes. No significant difference was observed between placebo and pimavanserin for the HAM-D Item 3 (suicide). Adjunctive pimavanserin was not associated with an increase in suicidal ideation compared with placebo.

F19. IMPLEMENTATION AND EVALUATION OF A CARE MANAGEMENT MODEL FOR PSYCHOPHARMACOLOGICAL TREATMENT IN PRIMARY CARE

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Abstract: Introduction: Depression and anxiety are two commonly diagnosed mental health disorders, and research has shown that a majority of individuals receive treatment for mental health concerns in a primary care setting.(1) Care management (CM) is a protocol-based, collaborative treatment approach to common mental health problems that present in primary care. One such example is for pharmacological treatment of depression and anxiety. CM programs have been shown to improve patient functioning, engagement, adherence, and all-cause mortality.(2) The purpose of this study was to evaluate the efficacy of a newly implemented facility-wide CM program for pharmacological management of depression and anxiety in primary care.

Methods: A retrospective review of an existing clinical database was conducted on all patients enrolled in the Tampa VA's Antidepressant Monitoring Program (ADM; a CM program providing consultation and management to individuals prescribed mental health medications through primary care clinics) over the first 12 months of implementation. An additional 6 month of data was obtained for analysis. Data collected included symptomatic assessments (PHQ-9 and GAD-7), mental health medications, and potential reason for program non-completion. Descriptive analyses were conducted on patient characteristics and outcomes measures of interest. Inferential analyses examined predictors of program completion.

Results: 529 patients were referred to the ADM program during the first 12 months of implementation. Patients still active in the program were excluded, leaving a total of 442 patients for analyses. Mean improvement in PHQ-9 and GAD-7 scores were 5.64 and 5.14 respectively. Patients who completed the program had greater improvements, with a mean decrease in PHQ-9 of 8.08 (SD = 5.54) and GAD-7 of 7.36 (SD = 5.28). Additionally, 118 (85.5%) of completers had a clinically significant improvement in anxiety (decrease of 5 or

more points in GAD-7) and 74.6% of patients achieved clinically significant improvements in depression (50% reduction in PHQ-9 scores.)

Of the 442 patients referred to the program 139 (31.4%) completed the entire program, 303 (68.6%) did not complete. Among non-completers, 23 (5.2%) of patients failed to respond to contact attempts and were never enrolled, 75 (25.5%) began treatment but were later referred to a specialty mental health clinic, 22 (7.5%) did not complete due to the emergence of adverse side effects without desire for alternative pharmacological trials, and 164 (55.7%) began the program but did not complete due to a failure to respond to follow up contacts and/or a request for disenrollment.

Potential predictors of program completion were analyzed. Binary logistic regression indicated that those patients who were early depression responders (defined as a 20% reduction in symptoms at three week follow up) were 4.43 times more likely to complete the program compared to patients who were not early responders. Similarly, early anxiety responders were 2.61 times more likely to complete the program. No other analyzed variables were associated with completion of the ADM program.

Conclusions: Overall, our results demonstrate successful implementation of a new care management program for pharmacological treatment in primary care, as evidenced by the large number of patients referred and the robust clinically significant improvements in depression and anxiety for individuals completing the program. Despite the demonstrated efficacy of the CM program, non-completion rates were high. Patients who are early responders were more likely to complete the program. More research is needed to identify other factors that may contribute to program completion.

F20. SUSTAINED REMISSION IN A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED PHASE 3 TRIAL OF ZURANOLONE (SAGE-217) IN POSTPARTUM DEPRESSION

ABSTRACT NOT INCLUDED

F21. USE OF CLINICAL GLOBAL IMPRESSIONS-SEVERITY (CGI-S) TO ASSESS RELAPSE DURING MAINTENANCE ANTIDEPRESSANT TREATMENT IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION

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Abstract: Objectives: The Montgomery-Åsberg Depression Rating Scale (MADRS), a 10-item questionnaire (each item scored on a 7-point scale [0-6]) is a validated, clinician-rated measure of depression severity, which is also used to determine clinical outcomes with antidepressant treatment. The MADRS is used widely in research and clinical trial settings. The Clinical Global Impressions-Severity (CGI-S) scale with one question assessing the patient's overall clinical status at the time of assessment, is scored on a 7-point response scale

and considered a more practical tool for clinicians in real-world practice.[1] The ability of CGI-S-based assessment to accurately capture relapse during maintenance antidepressant treatment among patients with treatment-resistant depression (TRD) was determined by a post hoc analysis evaluating agreement with the relapse defined using the MADRS-based assessment together with pre-specified qualifying clinical events.

Methods: Data from a phase-3 randomized, double-blind, relapse prevention study (NCT02493868, SUSTAIN 1)[2] of esketamine (or placebo) nasal spray in conjunction with a newly initiated oral antidepressant as maintenance treatment in adults with moderate-to-severe TRD were analyzed. Patients were considered as having a relapse if they met either of the following pre-specified criteria: two consecutive assessments (separated by 5 to 15 days) with MADRS ≥22 or hospitalization for worsened depression or other clinically relevant event determined per clinical judgment to be a relapse. Because of the unique safety profile of esketamine, in an effort to reduce bias due to potential unblinding on the primary efficacy measure in the main study, the MADRS was conducted prior to dosing by remote independent raters. The CGI-S was conducted pre-dose by the site investigator at the site. In this post hoc analysis, we assessed the relapse outcomes during the first six months in the maintenance phase among all the patients from both treatment arms as well as among patients from esketamine arm. Relapse for the CGI-S assessment was defined as occurrence of one of following events: two consecutive visits with CGI S ≥4 (and/or final visit with CGI-S ≥4), or a qualifying clinical event (e.g. hospitalization for worsened depression or clinically relevant event determined per clinical judgment to be a relapse). A relapse determined by the clinical event was counted in the same manner for both MADRS- and CGI-S-based relapse definitions. Cohen's kappa coefficient was calculated to assess agreement on the relapse rates between clinical trial defined outcome with MADRS and the CGI-S and clinical event-based assessment. Using the MADRS and clinical events definition as reference, the sensitivity and specificity of CGI-S and clinical event-determined relapse were estimated.

Results: Among all patients (n=297) entering the maintenance phase, relapse rate over six months based on the CGI-S and clinical event definition (34%) was similar to the MADRS and clinical events definition (35%). Substantial agreement between both methods was observed (Cohen’s kappa=0.79; sensitivity=85%; specificity= 94%). Similar relapse rates were observed in those patients randomized to continue esketamine: 35/152 [23%] (MADRS and clinical events definition) and 39/152 [26%] (CGI-S-based), with substantial agreement (Cohen’s kappa=0.75; sensitivity= 86%; specificity= 92%).

Conclusion: The CGI-S may be a practical tool with adequate sensitivity and specificity for clinicians to assess relapse during maintenance antidepressant treatment in patients with moderate-to-severe TRD in real-world practice.

F22. KNOWLEDGE, ATTITUDE AND PRACTICE OF MEDICAL STUDENTS/PHYSICIANS TOWARDS AMERICAN GERIATRIC SOCIETY UPDATED BEERS CRITERIA 2019 FOR POTENTIALLY INAPPROPRIATE MEDICATION USE IN OLDER ADULTS

ABSTRACT NOT INCLUDED

F23. HEPATITIS C SCREENING AND EDUCATION OF ACUTE PSYCHIATRIC INPATIENTS

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Abstract: Background: Hepatitis C Virus (HCV) infection is highly prevalent, with a large number of undiagnosed patients. These patients not only carry a high risk of progression to severe liver disease and related death, but also serve as a substrate for propagation of the infection to others. In 2015, HCV infection was the fourth most common reportable disease among Virginians, and the rate of reported cases continues to rise. The Virginia Department of Health (VDH) received over 8,000 new reports of chronic and acute HCV infection in 2015. CDC reports that the current primary risk factor for new HCV infection is intravenous drug use.

The US has faced an escalating IVDU epidemic in recent years and the Appalachian region has been identified as a hotspot with a shift toward young, non-Hispanic white individuals living in non-urban regions. The southwestern Appalachian region of Virginia has the highest incidence of newly reported chronic and acute HCV infection in the United States. Virginia was one of four states highlighted in a 2015 CDC report that illustrated the emerging triad of opioid abuse, IVDU, and HCV infection among persons aged 30 years or younger.

Methods: The psychiatry inpatient ward at Carilion Roanoke Memorial Hospital (CRMH) admits about 2,200 patients per year. Seventy-five percent of these patients have substance use disorders as the primary or secondary diagnosis. HCV antibody test screening orders, with reflex to confirmation viral load testing, was integrated as part of the admitting order set for all new admissions. Patients have the opportunity to opt out. All confirmed positive patients are educated and referred, as appropriate, for further evaluation as an outpatient. In addition, all psychiatric inpatients have exposure to weekly education groups concerning infectious disease spread.

Results: In the first 12 months of this process improvement grant, approximately 87% of acute psychiatry admissions were screened for HCV with a true positive rate of over 7%. Education groups about infectious disease and prevention have been well-liked by patients, staff and clinicians. Linkage to care in terms of outpatient follow up has been the largest barrier to patient care.

Conclusion: Routine Hepatitis C screening for high risk patients with mental illness, including substance use disorders, is a viable and cost-effective process to identify, educate and refer infected patients to care. Significant barriers remain to improve follow up and retention for those with both psychiatric and medical co-morbidities.

F24. PATHWAYS TO NONMEDICAL USE OF PRESCRIPTION STIMULANTS IN THE GENERAL POPULATION

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Abstract: Statement of the Problem: Nonmedical use (NMU) of prescription stimulants is increasing, presenting a growing public health concern nationwide, particularly in regard to polysubstance abuse. Most published studies have focused on prevalence, motivation, drug source, and risk factors associated with prescription stimulant NMU. The objective of this study was to explore the pathways to prescription stimulant NMU, an area not well understood.
Methods: Participants were recruited between July and September 2018 via email by YouGov, a survey panel company with an established participant registry and validated sampling methodology. The study used a self-administered internet survey drawn from the opt-in panelists using sample-matching methods to represent a target U.S. population 18-49 years of age. Of those who completed the survey, 12,000 who had the closest proximity score to the known sample of the U.S. population were included in the final analysis dataset.

For purposes of this study, NMU included ANY of the following: 1) Use for any reason, even once, without their own prescription, 2) Use in ways other than prescribed (such as taking more than prescribed, more often than prescribed, or for any other reason/way than prescribed), or 3) Use for the feeling or experience the medication caused (such as feeling of being high, enhancement of other drugs, prevention or treatment of withdrawal symptoms or other feelings).

Results: Of the 12,000 respondents, 1,284 (11%) reported lifetime use of prescription stimulant medication of which 762 (59%) reported prescription stimulant NMU. Those who reported prescription stimulant NMU were 44% female, 69% White, 13% of Hispanic origin, 50% single/never married, 37% married, 52% working full-time, and 28% currently enrolled in college. Only 38% had been diagnosed with ADHD. Approximately 2 out of 3 respondents reported diagnosis of depression or anxiety and 1 out of 4 reported diagnosis of bipolar disorder or substance use disorder (other than alcohol). Polysubstance abuse was common with concurrent use of marijuana reported in 39%, opioid NMU in 18%, cocaine in 14%, tranquilizers/sedatives in 12%, and methamphetamine in 10%.

Of those who reported prescription stimulant NMU (n=762), 78 (10%) reported prescription stimulant NMU only (no history of prescription opioid NMU or illicit drug use). Of the 684 that reported multiple drugs, the most common drug of initiation was an illicit drug (n=404; 59%) followed by prescription stimulant (n=139; 20%) and prescription opioid (n=69; 10%). The remaining 72 (11%) reported initiation of more than one drug at the same age.

Conclusions: Prescription stimulant NMU in the general population is often part of a multitude of broader substance use patterns, most commonly initiated with illicit drug abuse. Considering that only 38% of nonmedical users of prescription stimulants reported a diagnosis of ADHD, this study warrants increasing concern beyond the intended ADHD patient population.

This study was funded by Arbor Pharmaceuticals, LLC.

F25. PROJECT ROCKSTARR: FOSTERING CONNECTIONS TO ADVOCACY

ABSTRACT NOT INCLUDED

F26. IMPACT OF ECOA AND INDEPENDENT REVIEW OF RECORDED PANSS INTERVIEWS ON A MEASURE OF DATA QUALITY IN SCHIZOPHRENIA CLINICAL TRIALS

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Abstract: Introduction: Identical ratings of 30/30 PANSS items across consecutive visits is a marker of questionable data quality that raises concerns about the thoroughness of the interviews, data accuracy and independence of the ratings (Daniel and Kott 2014; Kott and Daniel 2015). Independently reviewed audio recordings of interviews conducted at the research site significantly reduces the presence of identical ratings (Kott and Daniel, 2015). In the current analysis we assessed the impact of electronic clinical outcome assessment (eCOA) coupled with audio/video recording on the prevalence of identical ratings of the PANSS compared to audio/video recordings alone.

Methods: The dataset consisted of PANSS assessments collected from 10,911 subjects across 26 schizophrenia clinical trials. For purposes of analysis the data were divided into paper collection (9,741 subjects) or eCOA collection (1,170 subjects). Audio/video recordings were available for 3,337 subjects. The data were queried for the presence of 30/30 PANSS identical ratings across consecutive visits. Logistic regression was used to explore the hypotheses.

Results: In the overall dataset a total of 2,649 identical ratings out of 72,240 were identified (3.7%). Overall, eCOA was associated with a significant reduction of identical ratings in the data (3.88% vs. 1.19%, OR = .30(.23 - .38), p <0.001) as did the presence of audio recordings (4.29% vs 2.05%, OR = .47(.42-.52). In an interaction model the odds ratio of identifying an identical rating in paper collected data coupled with audio/video recording compared to paper collection alone was .54(.49-.61), p<0.001. The odds ratio of identifying identical rating in eCOA collected data coupled with audio/video recording compared to paper collection alone was .27(.21-.34), p<0.001. The odds ratio of identifying an identical rating in audio/video recorded data with eCOA collection compared to audio recorded data with paper collection was .49(.38-.64).p<0.001.

Discussion: Our analyses indicate that eCOA coupled with audio/video recordings of interviews further improves the quality of data compared to audio/video recordings alone. Given the lack of data we could not test a direct head to head comparison between eCOA coupled with audio/video recordings against eCOA without the recording modality. However, the identified additive effect of eCOA coupled with audio/video recording in reducing the presence of identical ratings compared to audio/video recordings alone supports the trend in current schizophrenia trials to use the combined modality for data collection and quality assurance.

F27. NEUROPSYCHOLOGICAL ASSESSMENT DISCRIMINATES ADHD-I FROM SCT BY PARENT REPORT

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Abstract: Purpose: To utilize well-validated neuropsychological measures of attentional processes among youth with and without ADHD to identify measures that uniquely describe the Sluggish Cognitive Tempo (SCT) construct. SCT is a cluster of symptoms associated with severe impairment in multiple functional domains, and increased prevalence of somatic problems. When in context of ADHD, it is thought to be associated with reduced response to some medication treatments. Existing research on SCT indicates a moderate to high correlation (r = ~0.6) between SCT and the ADHD inattentive presentation (ADHD-I). However, half of youth with SCT do not have ADHD, and behavioral measures of SCT consistently separate (α=.64 -.91) from the symptoms that characterize ADHD-I. Currently, objective measures exist to map attentional processes, but there have been few if any attempts to extend and refine findings from behavioral studies differentiating SCT from ADHD-I to objective measures of specific components of the attention system in order to facilitate investigation and treatment.
Methodology: N=137 youth (107 with ADHD+30 healthy controls) who were screened for participation in two NIMH-funded ADHD treatment studies were administered a battery consisting of structured diagnostic interviews (K-SADS-PL; ADHD-RS (interview)), rating scales (including CBCL), neurocognitive and neuropsychological measures (WISC; CPT-II; Attention Network Test (ANT)) to examine neurobiological response of youth to stimulant and non-stimulant medications.

- K-SADS-PL guides diagnosis according to DSM-III, DSM-IV, and DSM-5 criteria.
- ADHD-RS provides dimensional measures of ADHD phenotype, with well-established thresholds for ADHD-I according to gender and age.
- The CBCL provides T-Score values for the SCT symptom cluster, with norms by gender and age.
- The WISC provides standardized scores for Perceptual and Verbal Reasoning, Processing Speed, and Working Memory.
- The CPT-II is commonly used in clinical practice and provides T-Scores for measures of attention, with norms by gender and age.
- The ANT is a well validated assessment often used in neuroimaging research to map attention networks; in this study it was used outside the scanner to provide information on different components of the attention system to be evaluated in relation to SCT. ANT raw scores met the expected threshold of Total Accuracy > 80% of trials, with Response Times between 200 to 1500ms. Alerting, Orienting, and Executive Control process ratios were calculated. Two-tailed Pearson correlation matrices of behavioral and objective measures were conducted, and Bonferoni corrected for multiple testing.

Results: CBCL ratings of SCT symptoms correlated moderately with ANT Alerting (r=-.291, p=.005, r2 = .085, Cohen's d= .8115), but not with Orienting and Executive Control domain scores. CPT measures did not correlate with SCT ratings. ADHD-I ratings correlated with CPT-II T-scores for missed cues (Omissions r=.254, p= .005 r2 = .065), ability to maintain attention over time (Variability r= .328, p= ,000, r2 = .10758), and consistently respond to stimuli (Hit Rate SE r=.272, p= .003, r2 = .074), but ANT measures did not. Ratings of ADHD-I and SCT were significantly correlated (r=.594, p=.000, r2 = .353).

Importance: This double dissociation finding is the first evidence that objective measures can capture and differentiate attentional processes linked to parental reports of ADHD and SCT behavioral descriptors. The modest degree of SCT behavior accounted for by measured

attentional deficits (~8%) suggests that additional research is needed to better characterize the construct.

F28. COGNITIVE PERFORMANCE AND PSYCHEDELIC EFFECTS FOLLOWING SINGLE AND MULTIPLE ASCENDING DOSES OF A NEW CANNABIS FORMULATION (PPP001) ADMINISTERED BY SMOKING/INHALATION IN MALE AND FEMALE VOLUNTEERS

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Abstract: Background: PPP001 is a dried cannabis product for smoked inhalation that is being developed for the treatment of chronic pain. Advantages of intrapulmonary administration of cannabinoids (e.g., by smoking) include high systemic bioavailability and fast onset of action. However, adverse events, including cognitive dysfunction, may be observed depending on exposure levels. The objectives of this study were to evaluate the safety, tolerability, and cognitive effects of PPP001 following its administration via smoked inhalation over 1 or 7 consecutive days in an escalating fashion.

Methods: This study was a randomized, double-blind, placebo-controlled, single (3 cohorts) and multiple (3 cohorts) staggered drug administration regimens (once [QD], twice [BID] or three times a day [TID]) design in 48 subjects (8 subjects/cohort;2 placebo:6 active). PPP001 (25 mg THC / 5.5 mg CBD) and placebo (0 mg THC / 0.8 mg CBD) were administered by smoking/inhalation with a titanium pipe at a dose of 9% (25 mg) THC / 2% (5.5 mg) CBD, QD (cohort A1), BID (cohort A2) or TID (cohort A3) daily, 4 hours apart, for 1 day (Part A) and following a 5-day titration and 2 days of full assigned regimens (Part B, cohorts B1 to B3). Pharmacodynamic (PD) assessments included the Bowdle Visual Analog Scales (VAS), assessing subjective drug effects, as well as Choice Reaction Time (RTI), Paired Associate Learning (PAL), Spatial Working Memory (SWM) and the Rapid Visual Information test (RVP) assessing cognition/psychomotor processing. PD assessments were performed at baseline and 0.5, 1 and 2.5 hours following each drug administration. Descriptive analysis was performed using summary statistics. Pharmacokinetic, safety assessments, and cardiac safety monitoring were performed during the study.

Results: A marked increase when compared to placebo (maximum peak effect ranging from 32.8 to 58.6 for the active arm and ranging from 0 to 15.2 for placebo arm) for the “feeling high” item in Part A. No cumulative effect was observed upon QD, BID or TID regimen (4 hours apart) administered on a single day. No clear difference with placebo was observed for “feeling drowsy” item. An increase when compared to placebo was detected for the composite scores “internal perception” (7 items) and external perception (6 items). Similar trend (marked change from baseline) was observed for the psychomotor testing (e.g. processing speed, episodic learning/memory, working memory, executive function, sustained attention and psychomotor speed). Similar results were obtained for Part B. Overall AE incidence was 92% (22 / 24) in subjects who received either cannabis or placebo. Majority of the AEs were mild in intensity (80%). For THC and CBD Tmax ranged from 0.05 - 0.17 h and 0.02 - 0.17 h, while AUC increased from 30 to 94 ng*h/mL and 7.8 to 21 ng*h/mL across cohorts, respectively. Both THC and CBD were eliminated in less than 1.6 hours (T1/2).

Discussion: Following controlled acute QD, BID or TID, 4 hours apart, administration(s) of cannabis by smoking/inhalation, psychedelic effects and cognitive performance measures were different compared to placebo (increase or decrease) while no accumulation of the cognitive effect was observed. PK results also showed no evidence of accumulation and treatments were generally well tolerated.

F29. AN EXAMINATION OF COMBINATORIAL PHARMACOGENETICS TESTING IN ADOLESCENT DEPRESSION: RESULTS FROM A DOUBLE-BLIND, RANDOMIZED, CONTROLLED EFFECTIVENESS TRIAL

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Abstract: Background: Pharmacogenetics testing has demonstrated potential promise for personalized medicine in psychiatry. However, there is a paucity of literature evaluating the use of combinatorial pharmacogenetics panels in youth diagnosed with depression. The objective of this study was to prospectively evaluate the clinical impact of combinatorial pharmacogenetics testing for the pharmacologic treatment of adolescents with depression.
Methods: Adolescents ages 13-18 (N=183) with a moderate to severe major depressive episode were randomized to treatment arm guided by testing in which pharmacogenetics testing results were available at the baseline visit (GENE arm, n=88) or a treatment as usual arm [(TAU) arm, n=95] in which testing results were not available until an 8 week visit. Participants were evaluated at baseline, 4 weeks, 8 weeks, and 6 months. Symptom improvement was measured by the Children's Depression Rating Scale-Revised (CDRS-R). Depressive symptoms, side effects and satisfaction were assessed throughout the study. Adolescents, parents, and raters were blinded to randomization and testing results until after ratings were completed at week 8.

Results: There were no differences between the GENE and TAU arms at 8 weeks or 6 months for symptom improvement or side effects. There was significant improvement in satisfaction regarding clinical care from baseline to week 8 for adolescents ($p=0.01$) and parents ($p<0.001$) in the GENE arm but not TAU arm.

Importance: Pharmacogenetics testing did not demonstrate improved outcomes compared to TAU regarding symptom improvement or side effect burden. There was significant improvement in adolescent and parent satisfaction scores in the GENE arm. Although pharmacogenetics testing has a great deal of promise as the gateway to personalized medicine, future studies should assess the clinical implementation and optimal use of these testing and related combinatorial decision support tools. Additional research with larger, prospective, randomized studies across more diverse ethnic groups is needed.

F30. ASSESSING THE BENEFIT-RISK RATIO OF APPROVED TREATMENTS FOR BIPOLAR DEPRESSION USING LIKELIHOOD TO BE HELPED OR HARMED (LHH) ANALYSES

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Abstract: Background: Four medications are FDA approved for acute bipolar depression: lurasidone (LUR), cariprazine (CAR), quetiapine IR & XR (QUE), and olanzapine-fluoxetine combination (OFC). Although no direct comparative data exist, indirect comparisons for efficacy using number needed to treat (NNT) and tolerability using number needed to harm (NNH) can be useful clinical benchmarks to aid treatment decisions. Both NNT and NNH can be considered when weighing the benefits and risk of individual treatments and this approach can be further refined by examining the likelihood to be helped or harmed (LHH). In this post-hoc analysis, we examined the benefit-risk ratio of the four treatments using LHH.

Methods: Individual and pooled monotherapy data from short-term clinical registration trials of patients with bipolar depression were assessed for LUR, CAR, pooled QUE (300 and 600 mg/d), and pooled OFC (considered as monotherapy for this study at fixed doses of 6/25, 6/50, 12/50 mg/d) data. NNT estimates were calculated using the proportions of MADRS responders (defined as ≥ 50% improvement at study endpoint) and MADRS remitters (defined as a score of ≤ 10 [for LUR and CAR] and ≤ 12 [for QUE and OFC]) at study endpoint. NNH data were calculated for the proportions of patients who discontinued due to an adverse event (AE) and for individual AEs commonly associated with each treatment. LHH was calculated as the ratio of NNH/NNT to determine the benefit-risk ratio.

Results: The NNT estimates for response vs placebo were: 5 for both LUR 20-60 mg/d and 80-120 mg/d; 10 for both CAR 1.5 mg/d and 3.0 mg/d; 6 for QUE; and 4 for OFC. The NNTs for remission vs placebo were: 7 for LUR 20-60 mg/d and 9 for LUR 80-120 mg; 10 for CAR 1.5 mg/d and 13 for CAR 3.0 mg/d; 6 for QUE; and 5 for OFC. The NNH estimates for discontinuations due to AEs were: 642 for LUR 20-60 mg/d and -181 for LUR 80-120 mg; 298 for CAR 1.5 mg/d and 31 for CAR 3.0 mg/d; 10 for QUE; and -37 OFC. When NNH is a negative number, LHH in uninterpretable and thus not reported. The LHHs for response vs discontinuation were: 128.4 for LUR 20-60 mg/d; 29.8 for CAR 1.5 mg/d and 3.1 for CAR 3.0 mg/d; and 1.7 for QUE. The LHHs for response vs akathisia were: 3.6 for LUR 20-60 mg/d and 2.4 for LUR 80-120 mg/d; 2.5 for CAR 1.5 mg/d and 1.3 for CAR 3.0 mg/d. The LHHs for response vs EPS were: 8 for LUR 20-60 mg/d and 3.2 for LUR 80-120 mg/d; 5 for CAR 1.5 mg/d and 2.5 for CAR 3.0 mg/d. The LHH for QUE for response vs somnolence is 0.5 and the LHH for OFC for response vs weight gain >=7% from baseline is 1.5.

Conclusions: Overall, lurasidone low and high doses were more likely to benefit patients in terms of response and remission of depressive symptoms than harm them due to poor tolerability.

While quetiapine and OFC demonstrated robust efficacy, their reduced tolerability resulted in a marginal benefit-risk ratio. The 1.5 mg/d dose of cariprazine evidenced a better benefit-risk profile than the 3.0 mg/d dose of cariprazine.

Supported by Funding from Sunovion Pharmaceuticals Inc.

F31. EFFECT OF LURASIDONE ON MANIC SYMPTOMS AND TREATMENT-EMERGENT MANIA IN ADULT AND PEDIATRIC POPULATIONS WITH BIPOLAR DEPRESSION

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Abstract: Background: Lurasidone is approved for the treatment of bipolar depression both as monotherapy and adjunctive therapy with lithium or valproate (Li/VPA). The aim of these analyses was to evaluate the risk of treatment-emergent mania, and worsening of mania symptom severity, in clinical trials of both adult and pediatric patients with bipolar depression treated with lurasidone.

Methods: In these post-hoc analyses, risk for treatment-emergent mania and effect on manic symptom severity as measured by the Young Mania Rating Scale (YMRS) were evaluated in two double-blind, 6-week studies in adults of lurasidone monotherapy, 20-60 mg/d (n=161) and 80-120 mg/d (n=162) vs. placebo (n=162), and adjunctive therapy of lurasidone 20-120 mg/d + Li/VPA (n=179) vs. placebo + Li/VPA (n=161). Percent of patients experiencing treatment-emergent mania was also evaluated in a 6-month, open-label extension study of adult patients treated with lurasidone monotherapy (n=316) or adjunctive therapy (n=497). In pediatric patients (ages 10-17) risk for treatment-emergent mania and change in manic symptoms was evaluated in a double-blind, 6-week study of lurasidone monotherapy (n=173) vs. placebo (n=170) and in a 24-month open-label extension study. Treatment-emergent mania was defined as an adverse event of mania or hypomania and/or having a YMRS score ≥16 at 2 consecutive post-baseline weekly visits (or the final assessment) in short-term studies, or 1 post-baseline monthly visit in long-term studies.

Results: Adult studies: In short-term studies, treatment-emergent mania rates were comparable in patients treated with lurasidone monotherapy 20-60 mg/d (3.7%) and 80-120 mg/d (1.9%) vs. placebo (1.9%). Treatment-emergent mania rates were comparable in patients treated with lurasidone 20-120 mg/d (1.1%) adjunctive to Li/VPA vs. placebo + Li/VPA (1.2%). In the monotherapy study, significant reduction in YMRS score was observed at study endpoint for the 20-60 mg/d group compared to placebo (-1.9 vs. -1.3; $p<0.05$) but not significantly different in the 80-120 mg/d group. Change for YMRS score was comparable for lurasidone and placebo in the adjunctive study. In long-term studies, 1.3% of adult patients treated with lurasidone monotherapy (n=316) met criteria for mania, and 3.8% of patient on adjunctive lurasidone therapy (n=497) met treatment-emergent mania criteria. Pediatric studies: treatment-emergent mania rates were comparable in patients treated with lurasidone vs. placebo (1.7% vs. 2.3%). LS mean reduction in symptoms of mania from baseline to week 6 was significantly greater for lurasidone vs. placebo on YMRS score (-2.0 vs. -1.1; $p<0.05$). Pediatric long-term studies: After two years of open-label treatment with lurasidone, 5.2% of patients met treatment-emergent mania criteria. Mean change in YMRS total score from double-blind baseline to Month 24 continued to improve (-2.0).

Conclusion: Short-term and long-term treatment with lurasidone demonstrated significant improvement in manic symptoms and was not associated with an increased risk of treatment-emergent mania manic in either adult or pediatric patient populations compared to rates reported in clinical populations of patients.

Supported by Funding from Sunovion Pharmaceuticals Inc.

F32. AN ASSESSMENT OF QTC EFFECTS WITH SPN-812 (VILOXAZINE EXTENDED RELEASE) IN HEALTHY ADULTS

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Abstract: Background: SPN-812 (viloxazine extended release) is a structurally distinct, bicyclic, Serotonin Norepinephrine Modulating Agent (SNMA) under investigation as a treatment for attention-deficit/hyperactivity disorder (ADHD). One concern for any new drug is prolongation of the QT interval, which is associated with increased risk for a potentially very harmful ventricular cardiac arrhythmias such as torsades de pointes (TdP). The objective of this study was to assess the effects of SPN-812 at a supratherapeutic dose (1800 mg once daily [QD]) on cardiac repolarization (QTc) in healthy adults.

Methods: This study was a Phase 1, double-blind (except for the positive control moxifloxacin), randomized, 3-period, 6-sequence, crossover design in healthy adult male and female subjects evaluating the electrocardiographic effects of SPN-812. Subjects were randomized to receive a sequence of all 3 treatments—placebo, 400 mg moxifloxacin, and 1800 mg SPN-812 (supratherapeutic dose). Treatment was given for 2 consecutive days (separated by a washout of at least 3 days). The primary endpoint was based on concentration-QTc effect modeling, evaluating the relationship between plasma concentrations of viloxazine and its metabolite 5-hydroxyviloxazine glucuronide (5-HVLX-gluc) with the placebo-adjusted change from baseline (CFB) in QTcI, ΔΔQTcI (QT interval corrected for heart rate [HR] based on the individual-specific QT interval correction method). Secondary endpoints included time point CFB in QTcI, QTcF, HR, PR, and QRS; evaluation of the relationship between the plasma concentration of viloxazine and 5-HVLX-gluc and the placebo-adjusted CFB in HR, PR, QRS, and QTcF; evaluation of the relationship between the plasma concentration of moxifloxacin and ΔΔQTcI to demonstrate assay sensitivity; and changes in ECG morphology. Safety endpoints included assessment of adverse events and other parameters.

Results: The relationship between ΔΔQTcI and viloxazine plasma concentration demonstrated a negative slope (p=0.0012). Predicted mean ΔΔQTcI (2-sided 90% CI) for SPN-812 was -9.7 ms (-11.3, -8.1) at the mean Cmax of 12.4 µg/mL. The relationship of 5-HVLX-gluc plasma concentration and ΔΔQTcI similarly demonstrated a predicted negative slope (p=0.0007) with a predicted mean ΔΔQTcI (2-sided 90% CI) of -9.2 ms (-10.8, -7.8) at the mean Cmax of 10.0 µg/mL. Assay sensitivity was confirmed. Concentration-effect modeling demonstrated no relationship between plasma concentrations of viloxazine and 5-HVLX-gluc and other ECG parameters. The secondary time point analyses demonstrated no effect of SPN-812 on QTcI or other ECG intervals. SPN-812 produced no changes in ECG T wave or U wave morphology.

Conclusions: Data from this Phase 1, thorough QT study, demonstrate that a supratherapeutic dose of SPN-812 (1800 mg QD) has no effect on cardiac repolarization or other ECG parameters, and is thus not associated with a risk for cardiac arrhythmias such as TdP. SPN-812 is currently being evaluated by FDA for approval.

F33. TOWARD DEVELOPMENT OF AN ABBREVIATED PANSS FOR PEDIATRIC TRIALS: SECONDARY ANALYSES OF TEOSS AND OTHER PSYCHOPHARMACOLOGIC DATA SETS

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Abstract: Background: Global regulatory initiatives have resulted in an increasing number of psychopharmacology trials in the pediatric age range. Challenges in ensuring valid and reliable data in such trials are numerous, and include developmental limitations in symptom description, the need to integrate and weight information from varied sources including parents/caregivers and other informants, and the global shortage of child-trained clinical investigators (Busner, 2013; Farchione, 2013)). Adding to the challenges, for many indications there are few pediatric validated efficacy measures, and pediatric trials often use measures designed for and validated in adults; this is the case for pediatric schizophrenia trials, which with few exceptions, have used for primary efficacy assessment the (adult) Positive and Negative Syndrome Scale (PANSS) (Kay, et al, 1987), a complex and lengthy 30-item measure that has been extensively studied and shown to pose ratings challenges even used with the adult patients for whom it was designed. For adult populations there have been a variety of efforts to shorten the PANSS while retaining its clinical and research value (see Lindenmayer, 2017, for recent review). To our knowledge there have been no similar efforts for the pediatric population. The NIMH TEOSS study, of which RLF was an investigator, affords a unique opportunity to examine the psychometric properties of the PANSS in a pediatric clinical trials population.
Method: As part of an NIMH multisite study on schizophrenia (TEOSS study, completed and described previously; Sikich, et al, 2008), 116 8-10 year olds with schizophrenia/schizoaffective disorder were administered the PANSS at baseline and weekly throughout an 8 week randomized double blind study of molindone, risperidone, or olanzapine. Along with unblinded PANSS item and total scores, we have available for analysis unblinded CGI-S/I, and Brief Psychiatric Rating Scale for Children (BRPS-C) data. In addition we plan to include PANSS and CGI-S/I data from two additional ongoing placebo controlled trials once those data become available.
Results: Total, subscale, and individual item PANSS scores will be examined using item response theory, classical test theory reliability analyses, and factor analysis; the BPRS-C and CGI-S/I data allow for assessment of PANSS convergent and discriminant validity.
Conclusions: The work should inform the field and has the potential to result in an empirically derived shortened PANSS specific to children and adolescents.

F34. PALATABILITY ASSESSMENT OF A NEW AMPHETAMINE EXTENDED-RELEASE TABLET FORMULATION

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Abstract: Background: In 2016, the US FDA issued an industry guidance document "Quality Attribute Considerations for Chewable Tablets" which describes the critical quality attributes to be considered when developing chewable tablets. It includes recommendations on selection of acceptance criteria for measuring palatability (having a taste acceptable to the patient or has adequate masking). These data are now recommended as part of ANDA submissions. Palatability is a known positive contributing factor to drug adherence and persistence. We summarize here palatability data for a new amphetamine extended-release tablet (Dyanavel XR® Extended Release Tablet; AMPH ER TAB).
Methods: This was a 2-arm preplanned secondary analysis from a comparative bioavailability study: single-dose AMPH ER TAB 20 mg chewed under fasting (Treatment A) and fed

(Treatment B) conditions. Subjects rated the palatability of AMPH ER TAB (Treatments A+B) through a 5-question palatability questionnaire. The questions included in the palatability questionnaire were as follows:

1.Oral sensation/mouth feel of the drug product

2.Taste of the drug product

3.How strong is the taste?

4.Aftertaste of the product

5.How strong is the aftertaste?

Subjects completed the questionnaire within 10 minutes from the time of drug administration, which was evaluated and scored according to the rubric below:

Q1, Q2, Q4: palatability- Very unpleasant (score of 1), Unpleasant (2), No sensation or mouthfeel (3), Pleasant (4), and Very pleasant (5)

Q3, Q5 (Taste/aftertaste strength): Very strong (score of 1), Strong (2), Moderate (3), Mild (4), No aftertaste (5).

Scores of 1-2 for both categories were Negative; score of 3 was Neutral, and 4-5 were Positive.

Results: 35 subjects comprised the palatability dataset (completed one question on the questionnaire). In the palatability analysis, for treatments A and B, most of the subjects rated the oral sensation/mouth feel of AMPH ER TAB (Question 1) and the taste of AMPH ER TAB (Question 2) as positive (pleasant to very pleasant) (70.1% and 83.6%, respectively).

When evaluating taste strength (Question 3): 43.3% rated the strength as positive (mild/no taste) and 43.3% of subjects rated the strength as neutral (moderate taste). Also, 82.1% rated the aftertaste of AMPH ER TAB (Question 4) as positive (pleasant/very pleasant) and 52.2% rated the strength of the aftertaste as positive (mild/no taste).

Conclusion: Most subjects rated the oral sensation and taste as pleasant or very pleasant, whether chewed under fasted conditions or after a meal. With respect to the taste strength, most subjects rated it as moderate (chewed under fasted conditions) or mild/no taste (chewed after a meal). Aftertaste was rated as pleasant or very pleasant in most subjects, with the strength as moderate (chewed under fasted conditions) or mild/no aftertaste (chewed after a meal). AMPH ER Tablets provided an overall pleasant taste and mouthfeel experience for patients.

F35. THE CLINICAL IMPACT OF CBD ON PSYCHIATRIC DISORDERS

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Abstract: CBD (Cannabidiol) is a substance chemically derived from Cannabis sativa and discussed to be non-psychoactive. It is not regulated by the FDA but available at local convenience stores in the US and seen as a herbal supplement. According to the FDA all products from the hemp plant are included in the in 2017 newly created controlled substance code for marijuana extracts and classified as a schedule 1 substance. CBD is used for various medical and psychiatric conditions: Depression, Anxiety, PTSD, Alzheimers or other cognitive illnesses as well as pain. There is also a new trend to use CBD for the treatment of opioid use disorder. There is only one FDA approved CBD product on the market under the name

Epidiolex. This product is FDA approved for the treatment of childhood epilepsy forms Dravet and Lennox-Gastaut syndromes. The use of CBD bears challenges for the clinician and psychiatrist: How do I counsel my patient on the use of CBD? Is there clinical data available to support the use in the claimed conditions? What is really in a CBD product? What is the legal situation and regulations regarding CBD? How is it possible for the patient to have a positive UDS for THC even though they claim to have used only CBD? These questions will be addressed in the session. The over-the-counter CBD product are containing very inconsistent strength of CBD if they contain it at all and vary in percentage even from sample to sample. Frequently the so-called CBD product is contaminated or solely containing THC. This research session is based on a systematic review of literature reviewing the available clinical data on CBD in various medical and psychiatric conditions including a review of the pharmacology and toxicity. Resources used were ORVID, Pubmed, EMBASE with keywords CBD, Cannabidiol, hemp, cannabinoids.

F36. CO-OCCURRING CANNABIS USE IN FIRST-EPISODE PSYCHOSIS: RATIONALE FOR TREATMENT WITH NALTREXONE AND PROPOSED STUDY DESIGN

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Abstract: First-episode psychosis (FEP) usually occurs in late adolescence and early adulthood. Co-occurrence of cannabis use/cannabis use disorder is high and is associated with earlier onset, increased risk of hospitalization, lower adherence to treatment, and poorer long-term prognosis. Despite high prevalence and impact, there is no promising treatment for these patients. Cognitive-behavioral therapy and contingency management show modest effects in isolated cannabis use disorder, but have failed to demonstrate improvement in FEP patients with cannabis use.

Naltrexone, an opioid antagonist, is FDA approved for treatment of alcohol use disorder and has demonstrated efficacy in alcohol use comorbid with psychotic disorder. Naltrexone alters the kappa opioid receptor and endorphin system and some studies suggest a role in decreasing positive and negative symptoms of schizophrenia. Non-human studies suggest a role for opioid antagonists in cannabis use/cannabis use disorder because they indirectly alter the cannabinoid reward system thereby reducing the positive subjective effect. Clinical studies of naltrexone in cannabis use show reduction in frequency of use and positive subjective effects.

Naltrexone has not been studied in FEP patients with cannabis use. We hypothesize that adding naltrexone to an ongoing antipsychotic treatment regimen will reduce the frequency of cannabis use and decrease psychotic symptoms.

A double-blind, randomized, placebo-controlled trial to test its efficacy and safety could test this hypothesis. Sixty hospitalized FEP patients with reported cannabis use at least twice a week for four weeks before hospitalization and age 16 to 23 years old would be recruited. Sample size was estimated using four endpoints, alpha level of 0.05, power level of 0.8 and effect size of 0.3 and estimating attrition of 30% by study end. Diagnoses for inclusion are acute psychotic disorder, schizophreniform disorder, schizophrenia or schizoaffective disorder confirmed using the Structured Clinical Interview for DSM-5 (SCID-5). Cannabis use will be assessed by Timeline Followback for cannabis and verified by urine THC screening test. Participants will be randomly assigned to naltrexone or placebo and will receive either

naltrexone 50 mg or matching placebo daily for 12 weeks. Assessments will include the Positive and Negative Syndrome Scale, the Calgary Depression Scale for Schizophrenia, Clinical Global Impressions, Timeline Followback for cannabis and urine screen at baseline, week four, eight and 12. The primary outcome will be reduction in frequency of use during the last four weeks of study participation (weeks eight to 12) compared to the four weeks prior to hospitalization. The secondary outcome will be the improvement in positive and negative symptoms of psychosis.

Executing such a study has challenges. Enrollment may be difficult because patients who use cannabis may not be motivated to reduce use. Further, risk of treatment non-adherence in these patients is high. Nevertheless, this patient population is in substantial need of treatment. The lack of treatment with demonstrated efficacy warrants testing naltrexone for which there is both pre-clinical and clinical data that support the possibility of efficacy.

F37. ESKETAMINE NASAL SPRAY FOR RAPID REDUCTION OF DEPRESSIVE SYMPTOMS IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER WHO HAVE ACTIVE SUICIDAL IDEATION WITH INTENT: ASPIRE I AND II

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Abstract: Background: Two pivotal phase 3 studies evaluated efficacy and safety of esketamine nasal spray (ESK)+comprehensive standard of care (SOC) vs placebo nasal spray (PBO)+SOC in patients with major depressive disorder (MDD) and active suicidal ideation (SI) with intent.

Methods: ASPIRE I (NCT03039192) and ASPIRE II (NCT03097133) were double-blind (DB), randomized, PBO-controlled, identically-designed studies in patients (aged 18-64 yr) with MDD (DSM-5 criteria) and active SI and intent requiring psychiatric hospitalization. Patients were randomized (1:1) to ESK 84 mg or PBO twice weekly for 4 weeks + newly initiated or optimized SOC antidepressant(s). Endpoints: change from baseline at 24h postdose in Montgomery-Åsberg Depression Rating Scale (MADRS) total score (primary) and Clinical Global Impression–Severity of Suicidality–Revised (CGI-SS-r) (key secondary). Pooled analysis of the two studies was performed.

Results: 456 patients (ASPIRE I=226; ASPIRE II=230) were randomized (ESK+SOC=229, PBO+SOC=227); 379 (83%) completed DB treatment. Pooled efficacy analysis set: ESK+SOC=226; PBO+SOC=225. Baseline characteristics were comparable between treatment groups in both studies. Mean age: 40.1 yr; majority were women (61%). Mean (SD) baseline MADRS total score: 40.4 (5.82). Most patients (90%) were moderately to extremely suicidal (CGI-SS-r). Patients in ESK+SOC showed improvement in MADRS total score vs PBO+SOC at 24h post first dose (primary endpoint; least square means [LSM] difference: -3.8 [95%CI: -5.75; -1.89]). Treatment differences (LSM [95%CI]) based on Mixed Model for Repeated Measures (MMRM) for change in baseline MADRS total score at 4h postdose (-3.4 [-5.05; -1.71]) and day 25, 4h postdose (-3.4 [-5.36; -1.36]) numerically favored ESK+SOC. Treatment differences in MADRS total score at 24h post first dose were consistent with primary analysis in most prespecified subgroups, including patients with prior suicide attempt

(-4.81; 95%CI: -7.26; -2.36]). More patients achieved remission (MADRS score ≤12) in ESK+SOC vs PBO+SOC at day 25, 4h postdose (treatment difference: 13%; 95%CI: 4.03; 22.19). Although improvement in CGI-SS-r was observed in both groups, treatment difference was not statistically significant. Treatment difference in improvement in CGI-SS-r at 24h post first dose favored ESK+SOC in patients with prior suicide attempt (LSM: -0.31; 95%CI: -0.61; -0.01). Most common (≥20%) treatment-emergent adverse events (TEAEs) in ESK+SOC vs PBO+SOC during DB phase: dizziness (38 vs 14), dissociation (34 vs 6), nausea (27 vs 14), somnolence (21 vs 10) and headache (20 vs 20). Serious TEAEs: 9 (4%) patients in ESK+SOC vs 12 (5%) in PBO+SOC.

Conclusion: ESK+comprehensive SOC rapidly reduced depressive symptoms in this vulnerable and heretofore understudied population. Severity of suicidality improved in both treatment groups, though the treatment difference was not statistically significant. Safety data were consistent with established profile of ESK.

F38. CTP-692, A NOVEL DEUTERIUM-MODIFIED D-SERINE, PRODUCES HIGHER BRAIN EXPOSURE IN RATS COMPARED TO D-SERINE

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Abstract: Schizophrenia is associated with low levels of D-serine, the most important synaptic co-agonist of the N-methyl-D-aspartate (NMDA) type glutamate receptor in the brain. Currently-approved schizophrenia drugs predominantly modulate D2, or D2 and 5-HT2a receptors. Neurobiological and genetic findings link NMDA receptor hypofunction to the etiology of schizophrenia. 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. A potential limitation to the development of D-serine as a therapeutic is that it causes renal toxicity in rats at exposure levels similar to those reported to result in therapeutic effects in humans. In a direct comparative study, rats acutely dosed with D-serine exhibited increased serum creatinine and blood urea nitrogen, indicating renal toxicity, whereas CTP-692 did not cause changes in these blood markers. While the binding and functional activity of CTP-692 at the glycine site of the NMDA receptor are nearly identical to those of D-serine, deuterium modification resulted in greater plasma and brain exposure of CTP-692 vs D serine in rats. CTP-692 had linear exposure (AUC) for doses ranging from 150 mg/kg to 2000 mg/kg in rats and plasma steady state was achieved by Day 2. However, at Day 4, brain levels are still increasing as steady state had likely not yet been achieved. After 4 days of dosing, the exposure of CTP-692 in rat forebrains was ~1.7 times greater than D-serine. Because of the slow uptake and clearance of CTP-692 from rat brains, fluctuations in brain levels upon dosing CTP-692 are minimized. Based on IV and PO PK profiles in both rats and dogs, the oral bioavailability of CTP-692 was >80%. Additionally, CTP 692 is well-suited for adjunctive use as it is neither a CYP inhibitor nor a CYP substrate. In summary, based on these rat studies, CTP-692 is a potential first-in-class adjunctive treatment for schizophrenia that offers the pharmacological advantages of treatment with D-serine but with the potential for lower risk of renal toxicity, higher brain exposures and efficacy at lower doses.

F39. REDUCTION OF MOOD VARIABILITY VIA NUTRITIONAL INTERVENTION FOR BIPOLAR DISORDER: A FOCUS ON FATTY ACIDS

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Abstract: Importance: Interventions are needed to improve mood instability in bipolar disorder (BD) for individuals not optimally managed on existing treatments. Our goal was to determine if a high n-3 plus low n-6 (H3-L6) nutrition intervention improves mood stability when compared to a nutrition intervention with usual U.S. levels of n-6 and n-3 fatty acid intakes (control diet, CD).

Methods: This was a 2-arm, parallel-group, randomized, modified double-blind, controlled 48-week study of a 12-week intensive nutrition intervention in subjects with BD conducted at a single site. Primary outcome was change in day-to-day mood symptoms using an ecological momentary assessment (EMA) paradigm. Randomization to the H3-L6 intervention or CD was stratified on gender. A total of 128 participants in usual care were enrolled in the trial that met criteria for DSM-IV TR BD I or II, symptomatic with hypomanic or depressive symptoms. The analytical randomized sample included 82 participants. The nutritional intervention included provision of group-specific study foods and oils, intensive dietary counseling, access to a website with recipes and guidance for eating in restaurants. The a priori hypothesis was that the H3-L6 intervention will significantly reduce variability in daily mood symptoms, energy, and impulsivity compared to the CD, as measured by a twice-daily EMA paradigm on a Visual Analogue Scale during 12 weeks of intensive nutritional intervention. Statistical analysis using multilevel modeling of variability in the mood and pain scores during the intervention period was conducted, controlling for variability at baseline.

Results: Eight-two participants aged 20-75 years (mean 43.5 +/- 13.9 years), and 83% female were randomized. Mean levels of mood symptoms and pain were not significantly different pre and post intervention either within-groups or between groups. Multilevel analysis identified significant differences between group in within-subject variability across the time of the 12-week intervention. After controlling for baseline symptoms, significant reductions were seen in mood variability, energy, irritability and pain in the H3-L6 group ($p<0.001$). The only symptom that was significantly lowered in the CD group was impulsive thoughts ($p=0.004$).

Conclusions and Relevance: High n-3 plus low n-6 nutritional intervention adjunctive to usual care improved within-day variability in mood symptoms and pain in participants with BD. Future studies are needed to replicate and validate findings, optimize delivery of nutritional interventions and investigate mechanisms underlying clinical improvements.

F40. RISK OF NEUROLEPTIC MALIGNANT SYNDROME WITH VESICULAR MONOAMINE TRANSPORTER INHIBITORS

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Abstract: Objective: Recently developed novel and selective vesicular monoamine transporter-2 (VMAT2) inhibitors, valbenazine and deutetrabenazine, have proven to be effective for the treatment of tardive dyskinesia (TD). Although they appear to be better tolerated than the older VMAT2 inhibitor, tetrabenazine, there is a potential for the dopamine-depleting properties of all VMAT2 inhibitors to cause neuroleptic malignant syndrome (NMS). In view of the likelihood that the new VMAT2 inhibitors will be increasingly prescribed for more patients with TD, and the fact that the number of patients enrolled in clinical trials of VMAT2 inhibitors may have been too small to detect the rare occurrence of NMS, it is important to evaluate the accumulated evidence base of published case reports to substantiate or refute the risk of NMS that may occur during treatment with VMAT2 inhibitors.
Methods: Pubmed, Embase, Web of Science and PsycINFO databases were queried for all years using terms for "neuroleptic malignant syndrome", "hyperthermia" AND "vesicular monoamine transporter inhibitors", "reserpine", "tetrabenazine", "valbenazine" or "deutetrabenazine"

Results: Thirteen case reports were identified in which NMS-like episodes were described in patients who had been or were receiving VMAT2 inhibitors. Ages ranged from 7 to 81 years old among 4 women and 9 men. VMAT2 inhibitors were used for Huntington's disease (6), TD (4), idiopathic dystonia (1) or a psychotic disorder (2). Tetrabenazine (12.5−350 mg/day) was implicated in 10 cases, reserpine (1.25−4.5 mg/day) in 2 and valbenazine in 1. Duration of VMAT2 treatment ranged from 2 weeks to 10 years. Eight cases occurred in combination with antipsychotics. All but 1 case met International Expert Consensus Criteria for the diagnosis of NMS. The differential diagnosis included serotonin syndrome, baclofen withdrawal, systemic infection, malignant catatonia, and heatstroke. Three patients received tetrabenazine after recovery from NMS without recurrence of symptoms.

Conclusion: While rare cases of NMS meeting consensus criteria have been reported primarily with tetrabenazine, the risk with recently developed VMAT2 inhibitors may be even less. Evidence of causality of NMS with VMAT2 inhibitors was confounded by limited reporting of clinical data, variable temporal correlation with VMAT2 inhibitors, polypharmacy with antipsychotics, and uncertain differential diagnosis. Nevertheless, clinicians should remain vigilant for early signs of NMS in all patients treated with any drugs that affect brain dopamine activity, including VMAT2 inhibitors.

F41. THOSE WHO FAIL TO LEARN FROM HISTORY ARE CONDEMNED TO REPEAT (ENTERING BAD SUBJECTS)

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Abstract: Purpose: To make researchers aware that eliminating duplicate subjects may not be enough to protect their studies from professional subjects.
Abstract: Duplicate and professional subjects are a significant problem in CNS studies. Available subject registries have been increasingly used over the past decade to identify subjects who participate in other trials within an exclusionary timeframe. However, these registries do not always provide a complete picture of the behaviors of certain professional

subjects. These subjects may not be identified as meeting exclusion criteria (such as exclusionary condition or concurrent study participation) yet may still be extremely problematic for studies.

CTSdatabase, a subject registry with data on over 70,000 CNS and pain subjects, provides sponsors and investigators a complete history of previous study participation, not only current or recent duplication between studies. We have uncovered hundreds of examples of professional subjects who, even if they do not overtly violate study criteria, are likely to cause problems once entered into studies. They become part of the intent-to-treat (ITT) sample, but when the study was designed, they were not the type of subjects that were intended to be treated. They are a population of professional subjects, with or without the condition or the severity of the condition, with or without exclusionary conditions, with motivations certainly not reflective of the patient population.

We highlight two types of deception in professional subjects that may elude usual methods of detection. First, there are subjects who, without necessarily changing their presentation between sites, do not disclose that they have presented to multiple (six or more different) trial sites within the last two or three years. We present a case history of the Frequent Flier. Second, there are professional subjects that frequently change indications or diagnoses between sites, providing site personnel whatever responses they need to survive the screening process. We provide two case histories of these Chameleons. These subjects fell outside of typical I/E criteria specifying previous study participation or previous exposure to the compound. However, sponsors and investigators were provided with the historical information to inform a decision on whether to screen-fail these subjects based on a more general exclusion criterion such as "…considered likely to be non-compliant with the protocol or otherwise considered unsuitable by the investigator."

In making investigators and research sponsors aware of these atypical subjects and how to mitigate their effects, we hope to improve study data integrity and increase the chances for sponsors being able to more clearly ascertain study success or failure.

F42. OPEN BOARD

F43. THE PLACEBO-CONTROL REMINDER SCRIPT IN DEPRESSION AND PSYCHOSIS TRIALS: AN ANTIDOTE FOR THE PLACEBO AND NOCEBO RESPONSE

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Abstract: Introduction: Depression and psychosis clinical trials share a crucial commonality of perpetually and alarmingly high placebo and nocebo responses (Rutherford et al., 2014; Rief et al., 2009). At ASCP in May 2019, Cohen et al. (2019) presented data indicating that the

Placebo-Control Reminder Script (PCRS) significantly reduced the placebo effect among subjects in a major depressive episode (MDE). Since then, the same study design, including the dependent variable of depressive symptoms, was applied among subjects with a psychotic disorder. The current poster presents these data and the combined results from both populations with the goal of having a deeper understanding of the potential impact the PCRS has in mitigating these phenomena.
Methods: Across two US sites, schizophrenia / schizoaffective adult patients experiencing at least moderate depression as determine by the self-reported Beck Depression Inventory-II (BDI-II; Beck et al., 1996), were randomized into two groups. The Intervention Group (IG) was read the one-page, brief (2 minute) PCRS before administering the BDI-II. The Control Group (CG) was not read the PCRS. The script reviews key Placebo Response Factors known in the clinical trial industry to induce placebo and nocebo effects (e.g., participant and site expectations of benefit; Alphs et al., 2012). Depression, and not psychosis, was selected as the dependent variable due to a combination of scale psychometric limitations (e.g., the lack of targeted self-report psychosis measures) and administration duration. The BDI-II, Adverse Events (AEs), and subjective beliefs about treatment were collected at the baseline, one-week mid-point, and two-week end-point visits. All subjects were informed via the Informed Consent Form that there was a 50% chance of receiving placebo or active drug aimed to improve their depression, but all subjects received placebo. Given this deception, subjects received a Debriefing Form at the end of the study revealing the investigation's true intent and procedures.
Results: As hypothesized, data from the combined MDE and psychosis sample indicated that the IG (n=64) reported significantly smaller decreases in BDI scores than the CG (n=63) across study visits (visit-by-group interaction: $F[1,124]=9.81$, $p<.005$). The proportion of patients that reported AEs at Visit 2 was significantly smaller in the IG than the CG ($X2=5.04$, $p<.05$), though the groups did not differ at Visit 3 ($X2=1.52$, $p>0.05$). As expected, a significantly higher proportion in the IG perceived they had an overall improvement in depressive symptoms than the CG ($X2=6.76$, $p < .01$), but surprisingly, the groups did not differ in the proportions believing they were in the active medication versus placebo condition ($X2=1.39$, $p>.05$). The results were similar in the psychosis sample, except that the IG (n=23) and CG (n=23) subjects did not differ in reporting AEs at Visit 2, though the CG reported a trend toward higher AEs at Visit 3 ($p=.07$).
Conclusions: The combined data, along with the separate psychosis sample analysis, indicate that the PCRS is a powerful tool in managing the placebo effect within clinical trials. Given that the IG combined sample scored approximately 5.0 BDI-II points higher (i.e., less placebo response) than the CG at Visit 3, the PCRS has the potential to increase the effect size in placebo-controlled clinical trials in either indication. The PCRS has been positively implemented in such studies, which the poster will review. Current study limitations (e.g., 3 study visits as opposed to having more, which is typical for clinical trials) and future work (e.g., investigating the impact of the script on neurological indications, such as migraines) will also be described in the poster.

F44. THE EFFICACY AND SAFETY OF ARIPIPRAZOLE ONCE-MONTHLY 400MG (AOM 400) IN AFRICAN AMERICAN/BLACK PATIENTS COMPARED TO NON-AFRICAN AMERICAN/BLACK PATIENTS

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Abstract: Background: Recent analyses have indicated that medical treatment for schizophrenia varies among racial groups.
Methods: Post-hoc analysis from a 12-week, randomized, double-blind, placebo-controlled trial was conducted in patients with schizophrenia who were experiencing an acute psychotic episode (NCT01663532). Patients were randomized to AOM 400 or placebo (PLB). This analysis examined mean differences from baseline on Positive and Negative Syndrome Scale (PANSS) and Personal and Social Performance scale (PSP) in African American/Black (AA/B) patients compared to non-AA/B (Caucasian, Asian, native Hawaiian, or other Pacific Islander) patients. Additionally, changes in weight and other metabolic parameters were also examined.

Results: There was a similar pattern of efficacy demonstrated in the AA/B group (n=223) compared to the non-AA/B (n=117) on both the PANSS and PSP from baseline to week 10. The difference in effect in the AA/B group compared to PLB, however, was less than the non-AA/B group. The safety results demonstrated that the AA/B patients had a significant mean weight change from baseline on AOM compared to the B/AA patients on PLB (+4.9 and +0.7, respectively; $p<0.0001$). This change was not seen in the non-AA/B patients on AOM compared to the non-AA/B patients on PLB (+1.4 and +1.3, respectively, $p=0.7942$).

Conclusion: There was no difference in efficacy between African American/Black patients and non-African American/Black patients. A difference in weight wasn't seen in the non-African American/Black group, however more weight gain was seen in the African American/Black group on AOM 400 compared to the PLB patients.

F45. EXAMINING DEPRESSIVE SYMPTOMS ACROSS DSM INDICATIONS: TREATMENT EFFECTS OF BREXPIPRAZOLE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER AND SCHIZOPHRENIA

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Abstract: Background: The National Institutes of Mental Health Research Domain Criteria (RDoC) framework is an example of the increased interest in understanding domains of human functioning. The RDoC framework is a matrix designed to incorporate all data, e.g., cells, circuits, self-report. Thus, the RDoC framework could be used to recategorize symptoms across the established Diagnostic and Statistical Manual (DSM) criteria for neuropsychiatric disorder indications. However, little work has been done to apply this concept to available clinical data sets. Within the spirit of these initiatives, this post-hoc analysis examined depressive symptoms across DSM indications for major depressive disorder (MDD) and for schizophrenia (SCZ). The analysis utilizes combined data from the Montgomery–Åsberg Depression Rating Scale (MADRS) Total score and the Positive and Negative Syndrome Scale (PANSS) depressive symptom factor (one of five PANSS factors established using factor analysis), for which a high correlation has been previously reported.
Methods: Data were obtained from short-term (6-week) clinical studies of brexpiprazole adjunctive use in MDD (Pyxis [NCT01360645], Polaris [NCT01360632], Sirius [NCT02196506]), and in SCZ (Vector [NCT01396421], Beacon [NCT01393613]). The studies used fixed doses of brexpiprazole (MDD 1–3 mg/day; SCZ 0.25–4 mg/day; 0.25 mg not included here) compared to placebo. MADRS Total scores were used for MDD studies. For

SCZ studies, scores on the PANSS depressive symptom factor items were used – Anxiety (G2), Guilt feelings (G3) and Depression (G6). To enable the data to be combined across indications, the data for the PANSS depressive symptom factor items were normalized so that the range was equivalent to the MADRS items, and then all data were expressed as percentage change from baseline at each treatment week. Brexpiprazole data were pooled, as were placebo data, so that brexpiprazole 1–3 mg was compared with placebo for MDD studies, 1–4 mg for SCZ studies, and 1–4 mg for the combined MDD and SCZ studies. Differences between treatment groups were compared using an MMRM analysis.

Results: With data expressed as percentage change from baseline, brexpiprazole 1–3 mg improved depressive symptoms, compared with placebo, at all timepoints in the combined MDD studies (Week 6: brexpiprazole [n=742] 32.1% vs. placebo [n=555] 25.1%; $p<0.001$), and at doses of 1–4 mg for the combined SCZ studies (Week 6: brexpiprazole [n=568] 48.8% vs. placebo [n=221] 41.0%; $p<0.05$). This agrees with previous brexpiprazole results reported for change from baseline to Week 6 in MADRS Total scores and PANSS Total scores, for the MDD and SCZ studies, respectively, suggesting that the conversion of scores to percentage change from baseline was appropriate. When the data were collapsed across indications in the five studies combined across MDD and SCZ indications, brexpiprazole 1–4 mg continued to demonstrate a beneficial treatment effect, compared with placebo, on change from baseline in depressive symptoms at all weeks of treatment (Week 6: brexpiprazole [n=1,310] 37.6% vs. placebo [n=776] 29.7%; $p<0.001$).

Conclusions: These data suggest that combining existing clinical data sets to understand treatment effects for common symptomatology across DSM indications is feasible. This type of analysis opens the opportunity to further explore symptoms that are reflective of human behavior across symptom domains, rather than being restricted to discretely defined indications.

F46. 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 effective in most patients, there is a significant number of psychiatric patients, who may not have an adequate response to currently available psychotropic medications, especially in treatment-refractory patient populations in a state hospital setting 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 some novel indications, such as tardive dyskinesia, pseudobulbar affect, Parkinson's disease psychosis and female hypoactive sexual desire disorder. These newly approved neuro-psychopharmacological molecules have novel mechanisms of action and although they should not be used routinely for indications not approved by the FDA, it may be useful to consider these new molecules in treatment-refractory patient population, when no other medications have made a difference. However, it remains extremely important to provide clinical and neurobiological rationale to use these 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 or even treatment refractory depression, if currently approved agents are not helpful. The main objective of this presentation is to have an interactive discussion on novel uses of new and some relatively older psychotropic medications for indications above and beyond those approved by the FDA. Recent case reports/series1-6 and reviews by our group will be used to provide some background information to initiate an interactive discussion on proposed "Innovative Psychopharmacology," facilitated by an electronic setup to capture audience responses in response to relevant questions.

F47. LONG-TERM SAFETY OF OLANZAPINE AND SAMIDORPHAN COMBINATION IN PATIENTS WITH SCHIZOPHRENIA: POOLED ANALYSES FROM PHASE 2 AND 3 STUDIES

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Abstract: Background: Antipsychotic medications are commonly used in maintenance therapy regimens for a variety of psychiatric conditions. As a result, patients may require chronic treatment; therefore, it is critical to evaluate safety and tolerability of new antipsychotic treatments over extended durations. A combination of olanzapine and the opioid antagonist samidorphan (OLZ/SAM) is being developed for the treatment of schizophrenia and bipolar I disorder. OLZ/SAM provides the efficacy of olanzapine while mitigating olanzapine-associated weight gain. Here, the long-term safety and tolerability of OLZ/SAM (up to 3 years) are reported from a pooled analysis of patients with schizophrenia from 6 clinical studies.

Methods: Data for patients exposed to OLZ/SAM in 1 of 3 blinded controlled studies and/or in 3 associated open-label safety extension studies were pooled and integrated to evaluate the long-term safety profile of OLZ/SAM. Baseline refers to pre-treatment status before initiating treatment with OLZ/SAM. Safety assessments reported here include adverse events (AEs), vital signs, and laboratory evaluations.

Results: Safety data from 831 patients (mean age, 41.4 years) were included. The median (range) OLZ/SAM exposure was 324.0 (1–1126) days. A total of 541 patients (65%) received OLZ/SAM for ≥6 months; 386 patients (46.5%) received OLZ/SAM for ≥52 weeks. The overall exposure to OLZ/SAM from baseline up to the data cutoff date of April 1, 2019 was 814.5 patient-years. AEs occurred in 67.7% of patients; those reported by ≥5% of patients included weight increased (18.9%), somnolence (12.8%), dry mouth (7.3%), headache (6.5%), and extra dose administered (5.1%; these extra doses were accidentally taken by patients and reported as AEs). In the majority of patients, AEs were mild or moderate in severity (35.5% and 27.8%, respectively). The onset of most AEs occurred between 4 and 24 weeks from OLZ/SAM initiation. Severe AEs were reported by 4.5% of subjects. AEs leading to treatment discontinuation occurred in 10.0% of patients; those occurring in ≥1% of patients included worsening/exacerbation of schizophrenia (1.6%) and glycosylated hemoglobin (HbA1c) increased (1.3%; HbA1c ≥6.5% was a discontinuation criterion). Serious AEs (SAEs) were reported in 37 (4.5%) patients, most commonly exacerbation of schizophrenia (1.4%). Evaluation of AEs of special interest, based on the known risks of olanzapine and effects associated with opioid antagonists, did not suggest any increased risks associated with OLZ/SAM compared with the known risks of olanzapine. Weight increased over the first 4 to

6 weeks of treatment and then stabilized, with limited subsequent weight gain (mean change was 1.73 kg at week 6, 2.20 kg at week 52, and 3.13 kg at week 104). Changes in metabolic laboratory parameters were generally small and stabilized with long-term treatment.

Conclusion: OLZ/SAM was well tolerated in adults with schizophrenia for up to 3 years of treatment.

F48. CARDIOMETABOLIC SAFETY OF LUMATEPERONE (ITI-007): POST HOC ANALYSES OF SHORT-TERM RANDOMIZED TRIALS AND AN OPEN-LABEL LONG-TERM STUDY

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Abstract: Background: Standard of care (SOC) treatment for schizophrenia is often associated with increased rates of metabolic syndrome (MetSy). MetSy is defined as meeting 3 of the following 5 criteria: waist circumference >40 in (men) or >35 in (women), triglycerides ≥150 mg/dL, high density lipoprotein cholesterol (HDL) <40 mg/dL (men) or <50 mg/dL (women), systolic blood pressure (BP) ≥130 mmHg or diastolic BP ≥85 mmHg, fasting glucose ≥100 mg/dL.

Patients with MetSy have an elevated risk of developing type II diabetes and increased mortality due to cardiovascular disease. Lumateperone (lumateperone tosylate, ITI-007), a mechanistically novel antipsychotic that simultaneously modulates serotonin, dopamine, and glutamate neurotransmission, is FDA-approved for the treatment of schizophrenia. This distinct pharmacological profile has been associated with favorable tolerability and a low risk of adverse metabolic effects in clinical trials.

This post hoc analysis of 2 randomized, double-blind, placebo-controlled studies of patients with an acute exacerbation of schizophrenia compared rates of MetSy with lumateperone and risperidone. Data from an open-label long-term trial of lumateperone were also evaluated.

Methods: The incidence and shift in MetSy were analyzed in data pooled from 2 short-term (4 or 6 week) placebo- and active-controlled (risperidone 4 mg) studies of lumateperone 42 mg (Studies 005 and 302). For these analyses, the pooled lumateperone data were compared with data for risperidone. Data from an open-label 1-year trial (Study 303) evaluated MetSy in patients with stable schizophrenia that were switched from SOC treatment to lumateperone 42 mg.

Results: The short-term pooled population comprised 511 patients (lumateperone 42 mg, 256; risperidone 4 mg, 255). The long-term population comprised 602 patients (lumateperone 42 mg).

In the acute studies, rates of MetSy were similar between groups at baseline (16% lumateperone and 19% risperidone). At the end of treatment (EOT), MetSy was less common with lumateperone than with risperidone (13% vs 25%). More lumateperone patients (46%) compared with risperidone (25%) patients improved from having MetSy at baseline to no longer meeting MetSy criteria at EOT. Conversely, more patients on risperidone than on lumateperone developed MetSy during treatment (13% vs 5%). Differences in MetSy conversion rates appeared to be driven by greater mean reductions with lumateperone

compared with risperidone in total cholesterol (−2.8 vs 4.8 mg/dL) and triglycerides (−0.7 vs 20.4 mg/dL) and greater increases in glucose for risperidone (7.7 mg/dL) versus lumateperone (0.9 mg/dL).

In the long-term study, 33% of patients had MetSy at SOC baseline. Thirty-six percent of patients (36%) with MetSy at SOC baseline improved to no longer meeting criteria at EOT. Fewer than half that percentage shifted from not meeting MetSy criteria to having MetSy (15%).

Conclusion: In this post hoc analysis, lumateperone 42 mg patients had reduced rates of MetSy compared with risperidone patients. In the long-term study, patients with MetSy on SOC treatment switched to lumateperone 42 mg had a reduction in the risk of MetSy. These results suggest that lumateperone 42 mg is a promising new treatment for schizophrenia with a favorable metabolic profile.

F49. LESS IS MORE: DEPRESCRIBING ANTICHOLINERIGCS IN PATIENTS WITH SEVERE MENTAL ILLNESS

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Abstract: Background: Long term prescribing of anticholinergic medications (ACM) for the treatment of antipsychotic associated extra pyramidal symptoms (EPS) is not recommend yet widely prevalent. Side effects of ACM include memory impairment, dry mouth, constipation, blurred vision, urinary retention and tachycardia, all of which can seriously impact quality of life. We thus implemented two sequential quality improvement projects in a large outpatient clinic specializing in the care of individuals with serious mental illness (SMI) focused on deprescribing ACMs.

Methods: Patients diagnosed with schizophrenia, schizoaffective, or bipolar disorder and receiving care through Western Psychiatric Hospital's Comprehensive Recovery Services' Clinic receiving benztropine for 6 months or longer duration by pharmacy record were identified for potential deprescription. In the expansion project, pharmacy database reports were used to identify additional patients prescribed one or more antipsychotic medications along with benztropine or trihexyphenidyl for at least six months. The pilot centered on a patient focused, clinical pharmacist championed deprescription intervention via physician referral of patients identified as described above; physicians could also refer additional patients they determined might benefit. In the expansion project, continuing medical education on anticholinergic deprescribing utilizing a small group educational format (i.e. problem-based learning) was provided to both referring attending psychiatrists and resident physicians (n=14). We also offered pharmacy patient consultation and support referrals as per our previous project. In both projects, pharmacy consultations consisted of comprehensive medication reviews to identify all possible ACM and to assess, through scales, anticholinergic side effects, including memory impairment, and their impact on the patients' quality of life. These scales included the Anticholinergic Cognitive Burden (ACB) Scale, the Pittsburgh Anticholinergic Scale Score (PASS), and the Memory Impairment Scale (MIS). Where clinically appropriate, ACM were tapered and/or discontinued by the psychiatrists over a period of 1 to 6 months with follow up

assessments with the clinical pharmacists in the interim. Patients who had a medication change were monitored for re-emergent EPS.

Results: In our pilot, 61 SMI patients receiving care at our WPH-based SMI clinic were selected for project inclusion; in our second study, 51 additional such patients were included. In the second study, forty-six patients (90%) were receiving benztropine; the remaining five (10%) were prescribed trihexyphenidyl. Most patients were prescribed one, second generation antipsychotic medication. Over 75 percent of targeted patients successfully tapered or discontinued ACM. 24% of patients identified for inclusion in the expansion project were able to work with their psychiatrists to taper or discontinue the ACM without the need for referral to the clinical pharmacist. Both studies showed similar decreases in Anti Cholinergic Burden Scale scores of around 30%. Successful taper coincided with significant improvements in anticholinergic side effects, memory impairment, and quality of life. Age, sex, or race of the patients did not have a significant impact on ACM medication changes. Ten percent of patients were restarted on ACM for reemergent EPS.

Conclusions: For the majority of clinically stable patients with SMI without EPS receiving ACM for extended periods, gradual deprescription of ACM is clinically appropriate, well tolerated, and improves anticholinergic associated side effects as well as overall patient quality of life.

F50. EFFECTS OF BREXPIPRAZOLE ON PATIENT ENGAGEMENT AND FUNCTIONING IN SCHIZOPHRENIA

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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/α2C receptors, all with subnanomolar affinity. The aim of this post hoc analysis was to explore whether treatment with brexpiprazole has the potential to improve patient 'engagement' in adults with schizophrenia, and whether any such improvement is linked to improvement in patient functioning, based on data from three short-term studies.

Methods: The studies (Vector: NCT01396421, Beacon: NCT01393613, and Lighthouse: NCT01810380) enrolled patients aged 18–65 years experiencing an acute exacerbation of schizophrenia, and who would benefit from hospitalization or continued hospitalization. Eligible patients were randomized to 6 weeks of double-blind treatment with brexpiprazole (0.25 to 4 mg/day, depending on the study) or placebo. As the three studies had similar designs, data were pooled for patients receiving brexpiprazole 2–4 mg/day, and for those who received placebo. An eleven-item version of the Positive and Negative Syndrome Scale (PANSS-Engagement) has previously been explored to measure patient engagement, with possible scores ranging from 11 (best) to 77 (worst). The present analysis determined the proportion of patients with a ≥8-point decrease (improvement) in PANSS-Engagement score over 6 weeks. Additionally, for the subgroups with and without a ≥8-point decrease, the mean change from baseline in Personal and Social Performance scale (PSP) score and its item scores were calculated.

Results: Mean baseline score on PANSS-Engagement was 35.6 in the brexpiprazole 2–4 mg group (n=868). At Week 6, 44.0% of patients who received brexpiprazole 2–4 mg achieved a ≥8-point improvement in PANSS-Engagement score, compared with 31.1% of those who received placebo. Among patients receiving brexpiprazole 2–4 mg with a ≥8-point improvement in PANSS-Engagement score, PSP score improved by least squares mean (standard error) of 17.82 (0.63) points. In comparison, among patients receiving brexpiprazole 2–4 mg with a <8-point improvement in PANSS-Engagement score, PSP score improved by 9.53 (0.60) points. Scores on individual PSP items improved with brexpiprazole treatment.

Conclusion: Brexpiprazole has the potential to improve patient engagement in schizophrenia. Improvements in patient engagement appear to be accompanied by improvements in patient functioning.

F51. EFFECT OF TREATMENT WITH SEP-363856 ON MEASURES OF COGNITION AND SOCIAL FUNCTIONING IN PATIENTS WITH SCHIZOPHRENIA

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Abstract: Background: SEP-363856 is a novel trace amine associated receptor-1 (TAAR1)/5-HT1A agonist with no dopamine-D2/5-HT2A antagonist activity. In a previous randomized clinical trial, SEP-363856 showed significant antipsychotic efficacy in patients with schizophrenia, and a safety and tolerability profile similar to placebo and consistent with a non-D2 mechanism of action. Here, we examined measures of cognition and social functioning in schizophrenia patients receiving SEP-363856 during a 26-week extension study.

Methods: Patients aged 18-40 years with an acute exacerbation of schizophrenia were randomized, double-blind (DB), to 4-weeks of flexible-dose treatment with once daily SEP-363856 (N=120; 50 or 75 mg) or placebo (N=125). Patients (N=156) entering a subsequent 26-week open-label (OL) extension study were evaluated utilizing the Cogstate Brief Battery, administered at DB baseline and week 4 (OL baseline), and at weeks 12 and 26. Standardized z-scores were calculated for the Cogstate composite and subscale tasks (Detection task, Identification task, One Card Learning task, One Back task). The University of California San Diego Performance Based Skills Assessment (UPSA-B) scale was assessed at the same time-points, as were the following psychiatric scales: Positive and Negative Syndrome Scale (PANSS), the Brief Negative Symptom Scale (BNSS), the Montgomery–Åsberg Depression Rating Scale (MADRS), the Clinical Global Impression Scale, severity scale (CGI-S), and the Pittsburgh Sleep Quality Index global score (PSQI-global). Pearson correlation analyses were performed between change in Cogstate composite and subscale scores and change in efficacy measures (DB baseline to week 26).

Results: Small improvements, from DB baseline to Week 26, were observed in standardized scores on the Cogstate composite (+0.29), Identification task (+0.19), Detection task (+0.28); One Card learning task (+0.33); and One Back task (+0.33). Improvement from OL baseline at Week 26 was also observed on the mean [SD] UPSA-B total score (+6.2 [11.6]). Week 26 improvement in the following Cogstate composite and subscale tasks were correlated with Week 26 improvement in the following efficacy measures: Cogstate composite score (PANSS

total, r=-0.26; BNSS total, r=-0.31; CGI-S, r=-0.30; MADRS total, r=-0.23; PSQI-global, r=-0.23); Identification task (PANSS total, r=-0.30; BNSS total, r=-0.30), Detection task (BNSS total, r=-0.30; CGI-S, r=-0.28; PSQI-global, r=-0.23); One Card learning task (MADRS total, r=-0.29); and One Back task (PANSS total, r=-0.26).

Discussion: During 6-months of open-label extension treatment with SEP-363856, improvement in overall functioning was observed on the UPSA-B scale; and small but consistent improvement in cognition was noted in the Cogstate composite and subscale task scores. Endpoint reduction in the severity of schizophrenia-related symptomatology (eg, on the PANSS, BNSS, MADRS, insomnia) was modestly correlated with improvement in cognitive performance as measured by the Cogstate battery, in the range of 0.2 to 0.3.

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F52. LONG-TERM WEIGHT AND METABOLIC EFFECTS OF OLANZAPINE AND SAMIDORPHAN COMBINATION IN PATIENTS WITH SCHIZOPHRENIA: POOLED ANALYSES FROM PHASE 3 STUDIES

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Abstract: Background: In schizophrenia, efficacious agents may be avoided to circumvent safety issues; for olanzapine, this includes weight gain liability. A combination of olanzapine and samidorphan (OLZ/SAM) is in development for schizophrenia and bipolar I disorder to provide the efficacy of olanzapine while mitigating olanzapine-associated weight gain. We report long-term weight and metabolic effects of OLZ/SAM in multiple phase 3 studies in patients with schizophrenia.

Methods: Results from 2 pivotal studies and their respective extension studies were integrated longitudinally into 2 groups. Group 1 included patients from ENLIGHTEN-1 (NCT02634346), a 4-week, randomized, double-blind study evaluating antipsychotic efficacy of OLZ/SAM, olanzapine and placebo in patients with an acute exacerbation of schizophrenia, who could enroll in a 52-week, single-arm, open-label safety extension (NCT02669758) and a 48-month follow-on study (NCT03201757, ongoing). Group 2 included patients from ENLIGHTEN-2 (NCT02694328), a 24-week, randomized, double-blind study evaluating mitigation of olanzapine-associated weight gain with OLZ/SAM in adult outpatients with schizophrenia, who could enroll in a 52-week, single-arm, open-label OLZ/SAM extension (NCT02873208, ongoing) and a 48-month follow-on study (NCT03201757, ongoing; this study also includes patients from group 1). Analyses included all patients exposed to OLZ/SAM with ≥1 postbaseline body weight and PANSS assessment. Changes from baseline (ie, relative to start of OLZ/SAM exposure) in body weight, waist circumference, metabolic parameters, and proportion of patients with ≥7% weight gain were summarized descriptively using observed data.

Results: Groups 1 and 2 included 281 and 381 patients, respectively. As of April 2019, mean OLZ/SAM exposure was 479.1 days in group 1; 64.1% received ≥52 weeks of OLZ/SAM. In group 2, mean OLZ/SAM exposure was 348.1 days; 42% were treated for ≥52 weeks. Baseline

mean (SD) weight was 77.28 (16.56) kg in group 1 and 78.82 (14.38) kg in group 2. At week 6, mean (SD) respective absolute and percent weight increase was 2.01 (3.07) kg and 2.63 (3.93)% in group 1 and 1.81 (3.12) kg and 2.42 (4.20)% in group 2. At week 76, mean (SD) absolute and percent weight increase was 2.83 (6.45) kg and 4.43 (9.14)% in group 1. In group 2, week 76 mean (SD) absolute and percent weight increase was 1.76 (7.90) kg and 2.71 (10.35)%. 34.6% (46/133) and 26.7% (28/105) of patients in groups 1 and 2 had ≥7% weight gain at week 76. Absolute mean (SD) increase in waist circumference was 2.22 (6.93) cm in group 1 and 0.93 (8.20) cm in group 2 at week 76. On average, changes in fasting lipid and glycemic parameters were not clinically significant.

Conclusion: After an initial 4 to 6 weeks of weight gain, weight stabilized with long-term OLZ/SAM treatment in patients with schizophrenia. Waist circumference and metabolic parameters exhibited long-term stability over 76 weeks in patients continuing treatment.

F53. AN EXPLORATORY ANALYSIS OF BNSS AND PANSS NEGATIVE SYMPTOM FACTOR ITEM CORRELATIONS

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Abstract: Introduction: Negative symptoms represent a significant unmet medical need. New instruments to assess the severity of negative symptoms, such as the Brief Negative Symptom Scale are being implemented into schizophrenia clinical trials We have previously examined the relationship between the BNSS and the PANSS scales [Kott, Daniel, 2018] and in the change from baseline in these scales [Kott, Daniel, 2019]. In the current exploratory analysis, we examine the relationship between the individual BNSS items and individual PANSS items in the negative factor.

Methods: Our dataset consisted of 838 subject data collected across 6 clinical trials in schizophrenia. Change from baseline for both the BNSS and PANSS items could be calculated for a total of 649 subjects. Polychoric correlations were estimated for each pair of items between the PANSS negative factor and the BNSS items (a total of 91 correlations). Similarly, we estimated the polychoric correlations for each item change from baseline.

Results: The rho coefficients ranged from 0.019 (G16[Active social avoidance] vs. BNSS4[Lack of normal distress]) to 0.751 (N1[Blunted affect] vs. BNSS9[Facial expression]). Of the PANSS items, the item with the lowest median correlations was item G16[Active social avoidance], the item with the highest median correlation was item N2[Emotional withdrawal]. Of the BNSS items, item BNSS 4[Lack of normal distress] showed the lowest median correlation while item BNSS 9[Facial expression] showed the strongest one. Correlation coefficients were substantially lower in the change from baseline data and ranged from 0.046(G7[Motor retardation] vs. BNSS4[Lack of normal distress]) to 0.471(N1[Blunted affect] vs. BNSS9[Facial expression]). The weakest median correlation in the change from baseline data was observed for PANSS item G7[Motor retardation] and BNSS item 4, while the strongest was observed for item N2[Emotional withdrawal] and item BNSS7[Avolition: Behavior].

Discussion: Our analyses indicate that unlike the strong correlations observed on the total score levels, on the item level the correlations between BNSS and PANSS negative factor items are

substantially lower. This is not unexpected as the BNSS unlike the PANSS negative factor addresses all five currently recognized domains of negative symptoms including anhedonia and attempts to differentiate anticipatory from consummatory states, areas that the PANSS negative factor neglects. Replication of our findings on different datasets is necessary.

F54. LONG-TERM ANTIPSYCHOTIC EFFICACY OF OLANZAPINE AND SAMIDORPHAN COMBINATION IN PATIENTS WITH SCHIZOPHRENIA: POOLED ANALYSES FROM PHASE 3 STUDIES

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Abstract: Background: The combination of olanzapine and samidorphan (OLZ/SAM) is in development for treatment of schizophrenia and bipolar I disorder. In 2 respective phase 3 studies, OLZ/SAM treatment resulted in similar antipsychotic efficacy to olanzapine and mitigated olanzapine-associated weight gain. This analysis describes the long-term (up to 76 weeks) antipsychotic effect of OLZ/SAM integrated from these 2 phase 3 studies and their extensions in patients with schizophrenia.

Methods: Results from 2 pivotal studies and their respective extension studies were integrated longitudinally into 2 groups. Group 1 included patients from ENLIGHTEN-1 (NCT02634346), a 4-week, randomized, double-blind study evaluating antipsychotic efficacy of OLZ/SAM, placebo, and olanzapine in patients with an acute exacerbation of schizophrenia, who could enroll in a 52-week, single-arm, open-label safety extension (NCT02669758) and a 48-month follow-on study (NCT03201757, ongoing). Group 2 included patients from ENLIGHTEN-2 (NCT02694328), a 24-week, randomized, double-blind study evaluating mitigation of olanzapine-associated weight gain by OLZ/SAM in adult outpatients with schizophrenia, who could enroll in a 52-week, single-arm, open-label OLZ/SAM extension (NCT02873208, ongoing) and 48 month follow-on study (NCT03201757, ongoing; this study also includes patients from group 1). Long-term efficacy was assessed descriptively via Positive and Negative Syndrome Scale (PANSS) total and Clinical Global Impression-Severity (CGI-S) scores using observed data without imputation for missing values. The analysis included all patients exposed to OLZ/SAM with ≥1 postbaseline PANSS and body weight assessment. Baseline was relative to the start of OLZ/SAM exposure.

Results: Groups 1 and 2 included 281 and 381 patients, respectively. As of April 2019, mean OLZ/SAM exposure was 479.1 days in group 1; 64.1% of patients received ≥52 weeks of OLZ/SAM. In group 2, mean OLZ/SAM exposure was 348.1 days; 42% were treated for ≥52 weeks. In group 1 (acute), mean (SD) PANSS total score was 89.4 (18.63) at baseline (n=281) and 61.3 (11.99) at week 52 (n=183); mean (SD) change from baseline was −25.3 (20.49) points. In group 2 (stable), mean (SD) PANSS total score was 65.2 (11.03) at baseline (n=381) and 57.9 (12.12) at week 52 (n=174); mean (SD) change from baseline was −6.0 (11.50) points. In group 1 at baseline, 144/281 (51.2%) patients were markedly to extremely ill (CGI-S score ≥5). At week 76, only 1/133 (0.8%) met this criterion. In group 2, 206/381 (54.1%) were normal to mildly ill (CGI-S score of ≤3) at baseline. After 76 weeks, 87/105 (82.9%) met this criterion. The mean (SD) change from baseline to week 76 in CGI-S score was −1.46 (1.22) for group 1 and −0.45 (0.65) for group 2.

Conclusion: Integrated data from multiple studies provided evidence of enduring antipsychotic effectiveness in patients with schizophrenia who continued long-term OLZ/SAM treatment.

F55. PHASE 3 SAFETY AND TOLERABILITY RESULTS OF THE COMBINATION OLANZAPINE AND SAMIDORPHAN IN PATIENTS WITH SCHIZOPHRENIA: THE 1 YEAR ENLIGHTEN-2-EXTENSION

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Abstract: Background: Combination olanzapine and samidorphan (OLZ/SAM) is in development for treatment of schizophrenia and bipolar I disorder and is intended to provide the antipsychotic efficacy of olanzapine while mitigating olanzapine-associated weight gain. This 52-week open-label extension study (NCT02873208; ENLIGHTEN-2-EXT) in schizophrenia assessed the safety and tolerability of OLZ/SAM.

Methods: Patients completing the 24-week, randomized, double-blind, phase 3 ENLIGHTEN-2 study comparing weight gain with OLZ/SAM vs olanzapine were eligible for ENLIGHTEN-2-EXT enrollment. Initial OLZ/SAM doses were based on olanzapine dose (10 or 20 mg) received at the conclusion of ENLIGHTEN-2; subsequent olanzapine dose adjustments were allowed. The samidorphan dose (10 mg) remained fixed throughout. Assessments included adverse events (AEs), weight, waist circumference, metabolic laboratory parameters, and Positive and Negative Syndrome Scale (PANSS) scores. Analyses were based on observed results using descriptive statistics. Baseline was relative to the first OLZ/SAM dose in the extension study.

Results: 265 patients received OLZ/SAM; 167 (63.0%) completed the extension study. Common AEs (≥5%) were weight decreased (n=23; 8.7%), extra dose administered (n=21; 7.9%), headache (n=18; 6.8%), and weight increased (n=16; 6.0%). At week 52, mean (SD) change from baseline for weight and waist circumference was −0.03 (6.216) kg and −0.35 (6.115) cm, respectively. Changes in fasting lipid and glycemic parameters were generally small and remained stable over 52 weeks. PANSS total scores remained stable during the extension.

Conclusions: OLZ/SAM was generally well tolerated over 52 weeks. Weight, waist circumference, metabolic laboratory parameters, and schizophrenia symptoms remained stable throughout the study.

F56. THE NATIONAL PREGNANCY REGISTRY FOR PSYCHIATRIC MEDICATIONS: EFFECTS OF FETAL EXPOSURE TO ATYPICAL ANTIPSYCHOTICS ON RISK FOR MAJOR MALFORMATIONS

ABSTRACT NOT INCLUDED

F57. EFFICACY AND SAFETY OF LUMATEPERONE (ITI-007) IN THE TREATMENT OF DEPRESSIVE EPISODES ASSOCIATED WITH BIPOLAR I AND II DISORDERS

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Abstract: Background: Approved treatments for bipolar depression are limited and are associated with a spectrum of undesirable side effects. Treatment options for depressive episodes associated with bipolar II disorder are even more limited. Lumateperone (lumateperone tosylate, ITI-007), a mechanistically novel antipsychotic that simultaneously modulates serotonin, dopamine, and glutamate neurotransmission, is FDA-approved for the treatment of schizophrenia. In trials in patients with schizophrenia, lumateperone was efficacious with a favorable safety profile and improved depression symptoms in patients with moderate-to-severe depression symptoms at baseline. Lumateperone is currently being investigated for the treatment of bipolar depression (major depressive episodes associated with bipolar I and bipolar II disorder).

This phase 3 randomized, double-blind, parallel-group, placebo-controlled multinational study (NCT03249376) investigated the efficacy and safety of lumateperone in patients with bipolar I or bipolar II disorder experiencing a major depressive episode.

Methods: Patients aged 18─75 years with a clinical diagnosis of bipolar I or II disorder who were experiencing a major depressive episode (Montgomery-Åsberg Depression Rating Scale [MADRS] Total score ≥20 and a Clinical Global Impression Scale-Bipolar Version-Severity [CGI-BP-S] score ≥4 at screening and baseline) were randomized to lumateperone 42 mg or placebo and treated for 6 weeks. The primary efficacy endpoint was change from baseline to Day 43 in MADRS Total score. Safety assessments included treatment emergent adverse events (TEAEs), laboratory parameters, vital signs, extrapyramidal symptoms (EPS), and suicidality.

Results: In this study, 377 patients were randomized (placebo, 189; lumateperone 42 mg, 188) and 333 completed treatment. Patients in the lumateperone 42-mg group had significantly greater mean improvement on MADRS Total score compared with placebo (least squares mean difference [LSMD]=−4.6; 95% confidence interval [CI]=−6.34, −2.83; effect size vs placebo [ES]=−0.56; P<.001). Lumateperone treatment significantly improved MADRS scores in patients with bipolar I (LSMD=−4.0; 95% CI=−5.92, −1.99; ES=−0.49; P<.0001) and bipolar II (LSMD=−7.0; 95% CI=−10.92, −3.16; ES=−0.81; P=.0004) disorder. Only 3 TEAEs occurred in ≥5% of patients receiving lumateperone and at rates greater than placebo: headache (17.6% vs 10.1%), somnolence (8.5% vs 1.1%), and nausea (6.4% vs 2.1%). Lumateperone treatment was well tolerated, with minimal risk of metabolic, EPS, and prolactin side effects.

Conclusion: Lumateperone 42 mg significantly improved depression symptoms in patients with bipolar I and bipolar II depression. Lumateperone was generally well tolerated. These results suggest that lumateperone 42 mg may be a promising new treatment for bipolar depression associated with bipolar I or bipolar II disorder.

F58. NEUROBEHAVIORAL PROFILE OF A HUMAN NMDA RECEPTOR NULL ALLELE

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Abstract: Background: N-methyl-D-aspartate (NMDA) receptors that incorporate the 3B subunit (NR3B) are endowed with distinct functional and pharmacological properties. Genetic knockout of NR3B in mice produces an anxious phenotype, altered sociality, and low body weight. Interestingly, ~8% of humans lack a functional NR3B subunit due to a common null allele, but the neurobehavioral and pharmacogenetic impacts of this polymorphism are not well described.

Methods: We genotyped the NR3B null allele (GRIN3B, rs10666583) in 319 human participants, including 211 healthy young adults and 108 patients with treatment-resistant depression. Personality traits were measured with the NEO-PI-R. Behavior, skin conductance responses, and fMRI activation (n=44) were quantified during performance of a monetary incentive task. Clinical response to electroconvulsive therapy was assessed prospectively. Statistical models controlled for sex, age, and ancestry.

Results: Compared to subjects carrying at least one functional NR3B allele, the personality profile of healthy homozygous-null subjects was distinct (p=0.007) and characterized by high neuroticism, high anxiety, and low trust. Body mass index of homozygous-null subjects trended higher (p=0.097). During task performance, homozygous-null participants reported less subjective arousal, skin conductance responses were decreased, and nucleus accumbens responses were diminished (p<0.01). The likelihood of clinical response to electroconvulsive therapy was lower among homozygous-null patients with depression (33% versus 72%, p=0.04).

Conclusions: Healthy humans lacking the NR3B subunit of the NMDA receptor have anxious-suspicious personality traits and atypical neurobehavioral responses during motivated behavior. Furthermore, depressed individuals lacking NR3B appear more likely to be highly treatment resistant. Clinical response to therapeutics that work through the NMDA receptor could be influenced by NR3B deletion. Pharmacogenetic investigations of NMDA receptor-targeted drugs should consider this common null allele.

F59. OPEN BOARD

F60. DIFFERENTIAL EFFECTS OF CHILDHOOD VS. ADULTHOOD TRAUMA IN CANNABINOID RECEPTOR TYPE 1 (CB1R) AVAILABILITY IN POST-TRAUMATIC STRESS DISORDER (PTSD): A REVIEW OF LITERATURE AND PILOT POSITRON EMISSION TOMOGRAPHY (PET) STUDY

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Abstract: Background: Trauma-induced alterations in the endocannabinoid (eCB) system have been consistently reported in animal models but only few human studies of post-traumatic stress disorder (PTSD) are available. Nevertheless, there is no consensus on the direction of these changes both in animal and human studies. Given the high rates of recreational and

medicinal cannabis use in individuals with PTSD, and promising preliminary studies to target eCB system in PTSD treatment, it is critical to understand the nature of the eCB system alterations in individuals with history of trauma and PTSD. The availability of a new high specific ligand for cannabinoid receptor type 1 (CB1R) makes it possible now to study the CB1R in vivo. Using [11C]OMAR an analog of rimonabant, and the high resolution tomograph (HRRT) scanner, we aimed at investigating the eCB in PTSD in humans.

Methods: To understand the current evidence, we made a comprehensive literature review of all available animal and human studies on the effects of trauma and PTSD on the eCB system. We attempted to clarify the contradictory results based on the potential confounding factors and tested our hypothesis in a pilot study of CB1R availability, using PET imaging and [11C]OMAR receptor antagonist radiotracer, in individuals with PTSD compared to healthy controls (sample size=18). The volume of distribution (VT) of [11C]OMAR was measured in different brain areas, which is linearly related to CB1R availability. Following our proposed theory, we compared the effects of childhood with adulthood trauma on the CB1R availability in individuals with PTSD. PTSD was evaluated using PTSD CheckList (PCL) and trauma was measured by Childhood Trauma Questionnaire (CTQ) and The Early Trauma Inventory Self Report-Short Form (ETISRSF).

Results: We proposed that the current contradictory results of eCB system alterations in PTSD in animal and human studies are partly explained by differential effects of childhood vs. adulthood trauma on eCB system. Based on the current evidence, childhood trauma results in decreased and adulthood trauma results in increased presentations of cannabinoid receptor type 1 (CB1R), consistently in animal and human studies. Similarly, the results of our pilot study showed that CB1R availability is lower in PTSD with childhood trauma and higher in PTSD with adulthood trauma, compared to healthy controls, in all brain regions. The mean composite VT value was 1.27 (SD 0.17) in individuals with PSTD and childhood trauma, 1.63 (SD 0.14) in PTSD with adulthood trauma and 1.40 (SD 0.17) in healthy controls.

Conclusions: Our pilot study, consistent with available animal and human studies, suggests that among individuals with PTSD, childhood trauma associates with decreased availability of CB1R, whereas adulthood trauma associates with increased availability of CB1R. To the best of our knowledge, this is the first study reporting this, which has important clinical implications in recreational and medicinal cannabis use in PTSD, and in potential therapeutic uses of cannabinoids in PTSD treatment. Decreased presentations of CB1R in PTSD with history of childhood trauma, vs. its increased presentations in PTSD with adulthood trauma may result in opposing effects of cannabinoids in these two groups, which needs further investigations, both for recreational and medicinal marijuana use and for novel pharmacological options for PTSD such as cannabidiol (CBD) and other cannabinoid modulators.

F61. ADOLESCENT DEPRESSION SYMPTOM CLUSTERING: UNSUPERVISED MACHINE LEARNING APPROACHES

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Abstract: Background: Although there has been consensus about the heterogeneity of major depression, models of depression subtypes have not converged for adolescent depression. As with precision medicine, understanding subtypes of depression may help identify groups with

differential treatment responses. While machine learning approaches such as hierarchical clustering has been used to study adult depression subtypes, it has not yet been applied to the pediatric population. Given the differences in symptoms of depression between adults and adolescents, we investigated symptom clusters of adolescent major depressive disorder using a variety of unsupervised machine learning techniques.

Methods: Patient and family reported data from the Treatment for Adolescents with Depression Study (TADS) (n=439), one of the largest randomized control trials for treating moderate-to-severe adolescent depression, were used. Clusters of baseline symptoms in the Children's Depression Rating Scale, Revised (CDRS), a primary endpoint in the TADS trail, were identified with agglomerative hierarchical clustering, a data-driven machine learning technique that does not require assumptions about the number of clusters in the data. To examine internal validity, these results were compared against hierarchical clusters over two subsequent checkpoints and with varying hyperparameters, clusters established by other unsupervised learning techniques (k-means clustering and HDBSCAN [hierarchical density based spatial clustering of applications with noise]), visualization with manifold learning techniques, and hierarchical clusters of secondary outcomes, the Beck Depression Inventory (BDI) and Reynold's Adolescent Depression Scale (RADS).

Results: The optimal number of clusters was determined by the silhouette score (bounded between -1 for incorrect clustering to +1 for dense clustering; scores around 0 indicate overlapping clusters). The optimal 3 cluster solution has a silhouette score of 0.252, bootstrapped 95% CI (0.226, 0.270).

Hierarchical clustering of baseline CDRS symptom scores revealed clusters that were largely consistent with that derived from that of the other algorithms. These also appeared to be robust across hyperparameter changes; while immediate groupings of symptoms tended to cluster together over subsequent time points, the larger groupings of symptoms changed. The three major clusters were: 1. Depressed feelings, difficulty having fun, low self-esteem, irritability, excessive fatigue, impaired schoolwork, social withdrawal, appetite disturbance, and sleep disturbance; 2. Suicidal ideation, morbid ideation, excessive guilt, excessive weeping, and physical complaints; 3. Hypoactivity, listless speech, and depressed facial affect. Compared to the other symptoms, appetite disturbance and sleep disturbance are in their own clusters in the K-means and HDBSCAN cluster solutions.

Conclusion: Using data from the TADS trial, hierarchical clustering may reveal subtypes of depression. While some of the clusters were more robust than others across clustering hyperparameters and over time, the variability in clusters may be related to the relatively small sample size in this adolescent study (as compared to that of adult studies). Although there are similarities with clusters of adult symptoms of depression, comparisons with adult studies is in part limited by the questionnaire items. Internal validation revealed some similarity in clusters, but further external validation via comparisons to external datasets would be required to draw further conclusions.

F62. BRUGADA SYNDROME AND RELATED CARDIAC CONDUCTION DISORDERS: A STRATEGY TO UNDERSTAND THE ETIOLOGY OF SUDDEN CARDIAC DEATH AMONG PATIENTS WITH SCHIZOPHRENIA AND PSYCHOTIC BIPOLAR DISORDER

ABSTRACT NOT INCLUDED

F63. ARE PATIENTS WITH SCHIZOPHRENIA BETTER OFF WITH LIFETIME ANTIPSYCHOTIC MEDICATION?: REPLICATION OF A NATURALISTIC, LONG-TERM, FOLLOW-UP STUDY OF ANTIPSYCHOTIC TREATMENT

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Abstract: Purpose/Background: The question of whether people with schizophrenia should be treated with antipsychotics for life has been debated for decades. We recently reported results of two retrospective long-term naturalistic studies examining the association of medication adherence and global outcomes in different demographic samples. In both, we found that patients with a history of better adherence to antipsychotic medication had better quality of life outcomes. Using similar methodology, here we present such associations for a very different sample – patients with chronic schizophrenia with a long past history of antipsychotic treatment that had been treated for 19 to 53 years in a Veterans Affairs Clinic.

Methods: This is a retrospective, naturalistic, longitudinal 19-53 year (mean average 33.5 years) lifetime follow-up of a consecutive series of patients with schizophrenia, who had at least eight years of antipsychotic treatment. 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). Linear regression models, adjusted for age, family support, substance use disorder, race, marital status, and number of years in treatment, were used to estimate the association between adherence and each outcome.

Results: A total of 20 patients were assessed. Medication adherence was positively associated with the blind clinician's rating of Global Outcome (p-value= 0.049) and the Global Assessment of Functioning (p-value = 0.021). In the non-blinded clinician's rating, medication adherence was positively related to Global Outcome (p-value=0.001) and to the patient's report of life satisfaction (p-value =0.028).

Implications/Conclusions: This replication study, together with our previous two studies, is consistent with the recommendation for continuous, long-term treatment for chronic schizophrenia over many years of a patient's lifetime unless medically contra-indicated.

F64. IMPACT OF LEMBOREXANT TREATMENT ON PATIENT-REPORTED DISTRESS WITH SLEEP AND INTERFERENCE WITH DAILY FUNCTIONING OVER 6 MONTHS: RESULTS FROM SUNRISE-2

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Abstract: *Introduction*: The insomnia severity index (ISI) is a 7-item self-report questionnaire that evaluates perception of insomnia severity (Bastien et al., 2001). Lemborexant (LEM) is a dual orexin receptor antagonist (Rosenberg et al, 2019) approved in the US and Japan for insomnia. In phase 3 SUNRISE-2, LEM showed greater reduction from baseline (BL) in ISI total score vs placebo (PBO) at 6 months. Here we examine the impact of LEM vs PBO on two important patient-reported outcomes, the ISI items related to worry/distress about subjects' sleep problems and impact of their insomnia on daily function.

Methods: SUNRISE-2 was a 12-month, randomized, double-blind, PBO-controlled (first 6 months [Period 1]), global phase 3 study. During Period 1, subjects were randomized to PBO or LEM (5mg, [LEM5]; 10mg, [LEM10]). During Period 2 (second 6 months), PBO subjects were rerandomized to LEM5 or LEM10; LEM subjects continued their assigned dose. Subjects completed the ISI at specified time points. Each item was rated on a 5-point Likert scale from 0 (no problem) to 4 (very severe problem). Changes from BL (CFB) in ISI scores for 2 questions (worried/distressed about sleep, interference with daily functioning), were analyzed at months 1 (M1), 3 (M3), and 6 (M6), for LEM5 and LEM10 vs PBO. Least squares mean (LSM) treatment differences were calculated based on an MMRM model adjusted for relevant factors.

Results: For the ISI item "worried/distressed with sleep," BL mean (SD) scores were similar for PBO (2.9 [0.7]; n=312), LEM5 (3.0 [0.7]; n=312), and LEM10 (2.9 [0.8]; n=311). Mean (SD) scores at M1 (PBO, 2.0 [1.1]; LEM5, 1.8 [1.2]; LEM10, 1.7 [1.1]) decreased (improved) from BL across all groups. The LSM (SE) difference in CFB was significantly greater for LEM10 vs PBO (−0.3 [0.1], P<0.01), but not LEM5 vs PBO (−0.2 [0.1], P=0.07). Mean (SD) scores at M3 (PBO, 1.8 [1.1]); LEM5, 1.5 [1.1]; LEM10, 1.5 [1.1]) further decreased from BL across all groups. The LSM (SE) difference in CFB was significantly greater for both LEM5 (−0.3 [0.1], P<0.001) and LEM10 (−0.4 [0.1], P<0.0001) vs PBO. Mean (SD) scores at M6 (PBO, 1.6 [1.0]; LEM5, 1.3 [1.1]; LEM10, 1.3 [1.0]) demonstrated continued decreases across all groups. The LSM (SE) difference in CFB was significantly greater for both LEM5 (−0.3 [0.1], P=0.001) and LEM10 vs PBO (−0.3 [0.1], P<0.01).

For the ISI item "interference with daily functioning," mean (SD) scores at BL were similar for PBO (2.6 [0.8]; n=312), LEM5 (2.7 [0.7]; n=312), and LEM10 (2.6 [0.8]; n=311). Mean (SD) scores at M1 (PBO, 1.8 [1.0]; LEM5, 1.7 [1.1]; LEM10, 1.6 [1.0]) decreased (improved) from BL across all groups. The LSM (SE) difference in CFB for LEM5 and LEM10 vs PBO was not significant (−0.1 [0.1], P=0.3; −0.1 [0.1], P=0.1, respectively). Mean (SD) scores at M3 (PBO, 1.6 [1.0]; LEM5, 1.4 [1.1]; LEM10, 1.3 [1.0]) further decreased from BL across all groups. The LSM (SE) difference in CFB was significantly greater for both LEM5 (−0.2 [0.1], P<0.05) and LEM10 (−0.3 [0.1], P<0.01) vs PBO. Mean (SD) scores at M6 (PBO, 1.5 [1.0]; LEM5, 1.2 [1.0]; LEM10, 1.2 [1.0]) demonstrated continued decreases from BL. The LSM (SE) difference in CFB was significantly greater for both LEM5 (−0.4 [0.1], P<0.0001) and LEM10 (−0.3 [0.1]), P<0.001) vs PBO.

Conclusions: These results suggest that LEM5 or LEM10 may reduce both worry/distress about a patient's insomnia condition and interference with daily function from insomnia, both of which findings may take longer than one month of treatment to achieve.

SUPPORT: Eisai Inc.

F65. PIMAVANSERIN FOR THE TREATMENT OF COMORBID DEPRESSION IN PATIENTS WITH PARKINSON'S DISEASE

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Abstract: *Background:* Depression occurs in ~50% of Parkinson's disease (PD) patients, increases in severity as the disease progresses, and is associated with increased morbidity.

Methods: This 8-week, open-label, single-arm study evaluated the safety and efficacy of pimavanserin (PIM) as an adjunct to selective serotonin reuptake inhibitor (SSRI) or serotonin/norepinephrine reuptake inhibitor (SNRI) treatment or as monotherapy in adults with PD and depressive symptoms (baseline Hamilton Depression Scale 17-item version [HAMD-17] total score ≥15). The primary endpoint was change from baseline to Week 8 in the HAMD-17. Secondary measures included scores on Clinical Global Impression (CGI) scales (improvement [I] and severity [S}) and Scales of Outcomes in PD-Sleep Scale (SCOPA)–global sleep (GS) quality, nighttime sleep (NS) quality, and daytime sleepiness (DS)). Safety measures included assessment of adverse events and electrocardiogram (ECG) and the Unified Parkinson's Disease Rating Scale (UPDRS) Part III.

Results: Of the 47 patients in the safety population, 51.1% were male and average age was 69.3 years. Twenty-six patients received PIM adjunct to an SSRI or SNRI and 21 patients received PIM monotherapy. Patients in the efficacy population (N=45) had a baseline mean (SD) HAMD-17 of 19.2 (3.1). Change from baseline to Week 8 (least squares mean [SE]) in HAMD-17 score was –10.8 (0.6) (95% CI, –12.0,–9.5; P<0.0001), with significant improvement seen by Week 2 (–7.3 [0.9]; P<0.0001). HAMD-17 changes from baseline to Week 8 were similar for adjunctive treatment and monotherapy: –10.2 (0.8) and –11.2 (1.0), respectively. Treatment responses (≥50% improvement in HAMD-17 score) were seen in 60.0% of PIM-treated patients at Week 8, and 44.4% reached remission (HAMD-17 score ≤7). There was also significant improvement seen in CGI-I status, CGI-S, SCOPA-GS, SCOPA-NS, and SCOPA-DS at Week 8. Forty patients (85.1%) completed the study, and 7 (14.9%) terminated early (due to an adverse event, n=3; protocol violation, n=2; lost to follow-up/other, n=1 each). Twenty-one patients (44.7%) reported adverse events, the most common being falls (n = 4, 8.5%), nausea (n = 3, 6.4%), diarrhea (n = 2, 4.3%), edema (n = 2, 4.3%), skin abrasion (n = 2, 4.3%), and urinary tract infection (n = 2, 4.3%). There were no negative changes on the UPDRS Part III and no clinically significant changes in the QTcF interval detected with ECG.

Conclusions: These data suggest that PIM treatment, as monotherapy or as an adjunct to an SSRI/SNRI, in patients with PD and depression was associated with early and sustained improvement of depressive symptoms as measured by HAMD-17 score and was well tolerated. Additional data from placebo-controlled studies are needed to determine the efficacy of PIM in patients with comorbid PD and depression.

F66. ARIPIPRAZOLE LAUROXIL 2-MONTH FORMULATION WITH 1-DAY INITIATION FOR ACUTE SCHIZOPHRENIA: ALPINE STUDY EXPLORATORY EFFICACY AND PATIENT-REPORTED OUTCOMES

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Abstract: *Background:* The randomized, controlled, phase 3b ALPINE (Aripiprazole Lauroxil and Paliperidone palmitate: INitiation Effectiveness) study evaluated efficacy and safety of a 2-month formulation of the long-acting injectable atypical antipsychotic aripiprazole lauroxil (AL) started with a 1-day initiation regimen during hospitalization for an acute exacerbation of schizophrenia. Primary and secondary efficacy outcomes have been reported previously; Positive and Negative Syndrome Scale (PANSS) total scores improved in patients treated with AL or the active control (paliperidone palmitate [PP]). Here we report exploratory efficacy endpoints and patient-reported outcomes (PROs) from ALPINE.

Methods: ALPINE participants were enrolled as inpatients, randomized to a long-acting injectable treatment, and discharged after 2 weeks if clinically stable. Patients were then followed as outpatients through week 25. Adult patients (aged 18–65 years) were randomly assigned to 1 of 2 blinded regimens: AL 1064 mg every 8 weeks or PP 156 mg every 4 weeks. Exploratory efficacy endpoints included PANSS subscales (Positive, Negative, and General) and illness severity (Clinical Global Impression−Severity [CGI-S]). Caregiver burden was assessed with the Burden Assessment Scale (BAS; completed by non-professional caregivers [eg, family members, friends]). Exploratory PROs (Quality of Life Enjoyment and Satisfaction Questionnaire Short Form [Q-LES-Q-SF] and Medication Satisfaction Questionnaire [MSQ]) were assessed during the outpatient portion of the trial. Within-group changes in PANSS subscales and CGI-S scores from baseline through week 25 were analyzed for AL and PP using mixed models with repeated measures. PROs were summarized based on observed data.

Results: A total of 200 patients were randomized (AL, n=99; PP, n=101), and 99 patients (AL, n=56; PP, n=43) completed the 25-week treatment period. PANSS Positive, Negative, and General subscale scores improved with AL treatment from baseline throughout the study (Positive: mean baseline score, 25.5 and least squares [LS] mean [SE] change from baseline at week 25, −7.0 [0.53]; Negative: 22.6 and −3.7 [0.48]; General: 45.9 and −11.1 [0.81]). CGI-S scores also improved with AL treatment (mean baseline score, 4.8 and LS mean [SE] change at week 25, –1.2 [0.10]). Caregiver burden decreased throughout the study, with the largest decline noted within the first 9 weeks (mean changes from baseline, −8.4 at week 9 and −8.9 at week 25) for caregivers of AL patients. Most AL patients were satisfied with treatment (range over weeks 5, 9, and 17, 70.8%−74.7% somewhat or very satisfied), and mean Q-LES-Q-SF total scores were stable. In the PP arm, PANSS subscale and CGI-S scores improved from baseline to study end (Positive: mean baseline score, 26.1 and LS mean [SE] change from baseline at week 25, –7.1 [0.57]; Negative: 22.6 and –3.5 [0.53]; General: 45.9 and −10.4 [0.88]; CGI-S: 4.9 and –1.2 [0.11]). Mean caregiver burden decreased (−8.8

at week 9 and −9.2 at week 25). Most PP patients were satisfied with treatment (range over weeks 5, 9, and 17, 64.7%−69.3% somewhat or very satisfied) and mean Q-LES-Q-SF total scores were stable.

Conclusions: In the ALPINE study, patients who initiated AL or PP in the hospital and continued treatment during outpatient care experienced improvement in schizophrenia symptoms, sustained patient satisfaction with medication, decreased caregiver burden, and stable quality of life.

F67. THE INTEGRATION OF A COMPUTER-BASED FUNCTIONAL SKILLS TRAINING PROGRAM IN INPATIENTS WITH CHRONIC SCHIZOPHRENIA

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Abstract: *Background:* Cognitive impairment is a fundamental feature of schizophrenia. The cognitive deficits observed in individuals with schizophrenia limit their ability to function in the community (Green, 2006). While it is widely documented that the cognitive deficits observed in schizophrenia impair individuals' functional skills, there are few treatments targeting impairment in functioning. While cognitive remediation therapy is effective in producing robust improvements in neurocognition, its ability to significantly improve functional capacity remains questionable (Bowie & Harvey., 2006). Thus, it may be necessary to specifically target functional skills to observe functional gains in this population. Novel treatments, such as functional skills training using computerized programs, may assist in restoring or improving the capacity of individuals with schizophrenia to do everyday tasks and may enhance the quality of life. Such programs include i-Function™ and BrainHQ™ which have been shown to be effective in functional skills training and cognitive remediation, respectively, as approaches to improve real-world functioning.

Aims: The primary aims are 1) to assess whether -i-Function™ training improves functional capacity in individuals with schizophrenia 2) to determine if combined cognitive training using BrainHQ™ and i-Function™ will show greater improvements of neurocognition than i-Function™ alone.

Methods: Inpatients with a DSM-V diagnosis of schizophrenia or schizoaffective disorder were enrolled in a randomized, double-blind 6-week trial (total of 18 sessions). Participants received either 3 sessions of i-Function or 3 sessions of i-Function + cognitive training with BrainHQ per week. The i-Function is a novel computer-based training program that aims to assess and incrementally improve ecologically valid everyday living skills (i.e., using an ATM, taking medications, and refilling prescriptions). BrainHQ™ includes both auditory and visual-based cognitive activities. The Brief Assessment of Cognition in Schizophrenia (BACS), and The Specific Levels of Functioning (SLOF) scale will be assessed using repeated measures analysis.

Projected Results: The planned sample size is n = 40. As of January 2020, 5 participants are enrolled. The total score on the SLOF is 108.8 (SD = 9.47) indicating low levels of functioning. PANSS total score is 74.4 (SD = 9.15) with PANSS Negative subscale score of 21.8 (SD = 1.30) and PANSS Positive subscale score17.0 (SD = 3.81) indicating currently enrolled subjects have significant negative symptom deficits. The mean BACS composite T score is 13.76 (SD = 21.47) indicating that individuals in patient population are 3.5 standard deviations below the mean for overall cognitive functioning. Individual patient's composite score ranged from -6.07 to 37.71 indicating a lower level of cognitive functioning within this population. The study team is expected to enroll an additional 15 subjects by May 2020 at which time we will update the results to include additional data on change in functioning and resend the abstract to the ASCP poster committee.

Discussion: This study can provide further insight into how functional skills training may improve cognitive functioning in inpatients with chronic schizophrenia that may better prepare them for community functioning upon discharge. Studies have suggested that combined cognitive remediation and functional skills training approaches are required to improve real-world functioning. Thus, this study can further elucidate the mechanism by which functional skills training mediates the relationship between cognitive functioning and functional outcomes.

Saturday, May 30, 2020

Poster Session II

S1. TRANSLATION AND CULTURAL ADAPTATION OF THE VIRTUAL REALITY FUNCTIONAL CAPACITY ASSESSMENT TOOL (VRFCAT) FOR ASSESSMENT OF FUNCTIONING IN GLOBAL CLINICAL TRIALS IN GERMAN, ITALIAN, RUSSIAN, POLISH AND SPANISH FOR THE U.S.

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Abstract: The Virtual Reality Functional Capacity Assessment Tool (VRFCAT) is a unique performance-based assessment of functional capacity. Using a simulated environment presented on a tablet device, the VRFCAT assesses a subject's ability to complete instrumental activities associated with a shopping trip, including creating a shopping list based on items available in the virtual kitchen, navigating and paying for public transportation to the grocery store, and shopping for and purchasing required items in the correct quantity. The VRFCAT has demonstrated high test-retest reliability and strong correlations with cognitive performance in schizophrenia and subjective cognitive decline (Keefe et al., 2016, Atkins et al., 2019). It is currently used in industry trials across diverse CNS indications including major depression and Parkinson's disease, and is presently being validated for use in MCI/mild AD and multiple sclerosis.

Originally developed in English for the US, the VRFCAT has been previously adapted for use in the UK (English for UK), Canada (English and French for Canada), and France (French for France). In order to meet a growing need for culturally appropriate performance-based assessments of functioning in global clinical trials, we recently completed translation and cultural adaptation of the VRFCAT for use in Italian, Polish, Russian, German and Spanish for the U.S.

Methods: Translation and cultural adaptation was completed in accordance with recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR; Wild, 2005, 2009). Linguistic and cultural adaptation of all text, test imagery, recipes and pricing were completed independently by two certified linguists in each language/region using concept sheets, screenshots and additional task materials. Discrepancies were reconciled through discussion and ultimate consensus amongst reviewers and content experts. In-country pilot testing and cognitive debriefing was completed at investigational sites in Italy, Poland, Russia, Austria (high German), and the U.S. (Spanish for U.S.). Pilot testing was completed in a total sample of 51 heathy adult participants (34 females) aged 21-70 (mean: 38, SD=11.6), including 10 participants each in German, Polish, Italian, Spanish for U.S., and 11 participants in Russian.

Results: Culturally adapted test versions comprise culturally specific graphic and linguistic content, including adapted virtual environments, objects and icons, and professionally recorded of

voiceovers for within assessment instructions and messaging. Customization of grocery items and recipes were required to account for cultural differences in item frequency and familiarity. Data from pilot testing was analyzed to assess regional differences in task performance in comparison to U.S. based norms. Differences in raw scores for VRFCAT completion time and errors by language were not significant ($p>.6$). Standard T scores (mean = 50, SD=10) were generated for each summary VRFCAT endpoint including VRFCAT completion time and total errors. Mean T scores for VRFCAT completion time were 46.43 (SD=6.9) for German, 52.2 (SD=8.9) for Italian, 53.4 (SD=9.6) for Polish, 54.8 (SD=6.8) for Russian, and 51.12 (SD=51.6, SD=8.8) for US Spanish, and did not significantly differ from the U.S. based norms. Similarly, T-scores for VRFCAT errors ranged from 47.6 to 50.3, and did not significantly differ from U.S. normative values.

S2. SEROQUEL MIGHT NEED A NEW BLACK BOX WARNING

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Abstract: In 1973, antidepressant or antipsychotic medication was reported beneficial in the treatment of anxiety and depression in sober alcoholics and more beneficial than benzodiazepines (Overall JE et al: Arch Gen Psychiatry 1973; 29, 218-21). Antagonism of alpha 1 adrenergic receptors as the mechanism of priapism secondary to psychotropic medication was announced in a later issue (Segraves RT: Arch Gen Psychiatry 1989;46, 275-84).

In 2004, quetiapine, an antipsychotic and antidepressant, was reported useful in the treatment of anxiety and depression in patients with substance dependence and substance-induced anxiety disorder who had minimal improvement on SSRIs or other non-benzodiazepine medications used for anxiety (Sattar SP, et al; J Psychiatry Neurosci 2004; 29, 452-57). PubMed reports that the manuscript has been cited by 17 other indexed articles. The cogency of their method might be illustrated by the fact that quetiapine was ordered for a man in a Turkish prison because he "had drug abuse." Dr. Torun reported that the prisoner who had no other medical illness suffered priapism after the first dose, 200 mg (Torun F et al: Turk Psikiyatri Derg 2011; 22, 195-9).

In a review article on priapism and antipsychotics, Andersohn and colleagues reiterated (J Clin Psychopharmacology 2010; 30, 68-71) that antagonism of alpha 1 adrenergic receptors is responsible for the side effect of priapism. The quetiapine moiety is midrange in its affinity for the alpha 1 adrenergic receptor but had the highest number of case reports associated with its administration. This points to the possibility that it is a metabolite(s) of quetiapine that contributes to the side effect of priapism.

Quetiapine is metabolized by both CYP3A4 and CYP3A5 enzymes1. CYP3A5 is expressed in '10-30% of whites and 60 % of African Americans' 1. "CYP3A5 is of minor importance for the overall metabolism of quetiapine in vivo," but the formation of O-desalkylquetiapine is 1.5 to 2.5 fold higher 1. The binding of O-desalkylquetiapine to the alpha 1 adrenergic receptor has not been characterized. N-desalkylquetiapine (norquetiapine) is the main active metabolite, important in quetiapine's antidepressant effect. CYP3A4 and CYP2D6 metabolize norquetiapine, and "in

human liver one might expect the relative importance of these two enzymes is fairly the same" per Bakken GV and colleagues (Drug Metab Dispos 2012; 40, 1778-84). The inhibitory constant (Ki) for the alpha 1 binding of norquetiapine is 325 nanomoles (nM) and for quetiapine 975 nM by inspection of Figure 1 in the article by Lopez-Munoz and Alamo 2. Thus, the binding of norquetiapine to the alpha 1 adrenergic receptor is 3 times that of the parent compound quetiapine, and CYP2D6 "poor metabolizer" status is present in 7-19% of Africans (Mpye and Dzobo: Glob Health Epidemiol Genom 2017; 2). This would imply a likelihood of higher alpha 1 adrenergic receptor binding in this population due to increased concentrations of norquetiapine.

Thus, the report that the administration of quetiapine may be disproportionately associated with priapism could be explained by alteration in the concentrations of metabolites, particularly in those of African heritage. Our analysis of the possibilities would call for characterization of the binding of O-desalkylquetiapine to the alpha 1 adrenergic receptor and a possible change in the black box warning of quetiapine (Seroquel).

S3. A PHASE 1 STUDY TO DETERMINE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND COGNITIVE EFFECTS OF SAGE-718

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Abstract: Objective: To assess the safety, tolerability, pharmacokinetic (PK) profile, and cognitive effects of SAGE-718 in healthy volunteers (phase 1 double-blind multiple-ascending dose study) and patients with Huntington's Disease (HD; open label) (NCT03787758).

Background: SAGE-718 is an oral investigational positive allosteric modulator of the NMDA receptor (NMDAR). Altered NMDAR functionality has been implicated in a variety of neurodegenerative diseases, including HD. Enhancement of NMDAR-related neurotransmission via positive allosteric modulation may represent a novel treatment opportunity for HD and related conditions.

Design/Methods: Participants of both sexes, ages 18-65, were enrolled. Cohorts 1 and 2 enrolled healthy volunteers (N=12 each), and Cohort 3 enrolled HD patients (N=6) positive for mutant HTT gene (CAG repeats ≥40 units), with qualifying cognitive and motor assessments ≤6 months of screening. Healthy volunteers were randomized 3:1 to SAGE-718: placebo in Cohorts 1 (0.5 mg) and 2 (1.0 mg). Cohort 3 received open-label SAGE-718 1.0 mg. Study drug was administered once daily for 14 days, with follow up through Day 21. Assessment of safety and tolerability by adverse event (AE) reporting was the primary endpoint. Other endpoints included assessment of PK parameters and performance on a cognitive battery.

Results: SAGE-718 was generally well-tolerated, with no serious AEs or discontinuations due to AEs. SAGE-718 plasma levels increased in a dose-proportional manner; exposure was similar across cohorts. Compared to baseline, HD patients exhibited statistically significant improvement on the Two Back Test (Days 8-14, $p<0.05$) and numerical improvement on the Groton Maze Test

(Days 6-14). Significant changes from baseline were not observed on assessments of psychomotor speed, simple working memory, or response inhibition.

Conclusions: SAGE-718 was generally well-tolerated, exhibited PK parameters suitable for once daily oral dosing, and was associated with improved performance on cognitive testing in patients with HD, supporting further investigation of SAGE-718 in disease states characterized by NMDA hypofunction.

S4. CARE PATHWAYS PRECEDING SUICIDAL IDEATION OR PROBABLE SUICIDE ATTEMPT IN ADULT PATIENTS WITH MAJOR DEPRESSIVE DISORDER

Maryia Zhdanava[1], Jennifer Voelker[2], Dominic Pilon[1], Laura Morrison[1], Maude Vermette-Laforme[1], Patrick Lefebvre[1], Abigail Nash[2], Cheryl Neslusan[2]*

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Abstract: Background: Little is known about care pathways of patients with major depressive disorder (MDD) who have suicidal ideation (SI) or make a suicide attempt (SA). This study described demographics and interactions with healthcare systems of patients with MDD+SI/SA before and during the suicide-related event.

Methods: Adults (≥18 years) with an MDD diagnosis ≤6 months prior to an insurance claim for SI or probable SA were identified in the IBM MarketScan Research Databases (10/01/2014-04/30/2019) on or after 10/01/2015. The date of the first claim with SI or probable SA defined the index event. Patient demographics and healthcare encounters were described during the 12-month period before the index date or at the index event. Patients were considered predominantly involved in mental health care for MDD if ≥50% of outpatient claims with an MDD diagnosis had a code identifying mental health specialists; those with <50% of such claims related to mental health specialists were considered predominantly involved in primary care for MDD. Adherence to antidepressant therapy was defined as a proportion of days covered (PDC) by antidepressants ≥80%.

Results: Among 38,876 patients with MDD+SI/SA (mean age 34.7 years, 46.2% aged 18-25 years, 57.4% female), 81.2% were identified with SI and 19.8% with probable SA at the index event. During the index event, 58.9% were cared for in an inpatient setting, 30.9% in an emergency department, and 10.2% in an outpatient setting. The first diagnosis of MDD was observed at the index event in 46.0% of patients, and within 30 days before or at the index event in 52.4% of patients. During the 12-month pre-period, 60.6% had ≥1 claim with a diagnosis for a co-occurring mental health condition; the most prevalent conditions were anxiety disorder (44.2%) and substance-related disorder (20.4%). Of the 38.6% with ≥1 claim with a diagnosis for a comorbid physical condition, the most prevalent conditions were metabolic disease (23.2%) and hypertension (19.0%).

A total of 58.5% of patients had ≥1 antidepressant claim during the 12-month pre-period; among those, 71.4% were on antidepressant monotherapy and 28.6% on an antidepressant and augmentation therapy. A total of 25.7% of patients with ≥1 antidepressant claim during the 12-month pre-period were adherent to antidepressant therapy. Among 44.3% of patients with MDD-

related outpatient visits in the 12-month pre-period, 73.9% received MDD care predominantly in a primary care setting while 26.1% predominantly from a mental health specialist. In the 12-month pre-period, 31.7% and 25.9% had ≥1 claim for psychotherapy and a psychiatric diagnostic evaluation, respectively, and 19.6% for a psychiatrist visit.

Conclusions: Patients with MDD+SI/SA are young and often have co-occurring health conditions. Approximately half do not appear to receive an MDD diagnosis until shortly before the suicide-related event, and many have no prior claims for an antidepressant. Thus, an opportunity exists to improve screening for MDD and optimize pharmacologic treatment. Since those who received prior outpatient care for MDD were predominantly cared for in a primary care setting, collaboration by referral to a mental health specialist or increasing awareness and training for MDD management in the primary care setting might be of value. Future research on health outcomes associated with the heterogeneity in care pathways of patients with MDD+SI/SA is warranted.

S5. INCREASING SHOW RATES FOR MDD CLINICAL TRIAL SCREENING VISITS: THE IMPACT OF SCHEDULING SPEED ON SCREENING VISIT ATTENDANCE

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Abstract: Background: Recruitment for major depressive disorder (MDD) trials is particularly challenging given the nature of depression symptoms (e.g., fatigue, low motivation, anxiety). High no-show rates for screening visits can impede the recruitment process and delay study enrollment. Thus, identifying strategies to increase show rates for screening visits has the potential to speed up enrollment in clinical trials. In this study, we examined the impact of scheduling speed on show rates for MDD trial prescreening visits.

Methods: Our sample includes prospective MDD trial participants recruited in 2019 by advertising with Facebook, Instagram, and Google. After submitting contact information online, a recruiter called subjects for a phone interview. Potentially eligible subjects were then scheduled for an in-person prescreening visit with a clinician to assess their eligibility for an MDD clinical trial. These in-person visits were scheduled in timeframes ranging anywhere from the same day as the phone screen up to a month later. This analysis examined the impact of scheduling speed (number of days between phone screen and date of scheduled prescreening visit) on prescreening visit attendance.

Results: In 2019, 12,870 individuals applied to participate in MDD trials at our site through social media and web advertisements. Of those, 40% (5,093) completed a phone screen interview and of those interviewed, 25% (1,287) were scheduled for an in-person prescreening visit. Scheduling speed ranged from 0 days to 36 days (M=5.2, SD=4). The overall attendance rate was 55%. Scheduling speed was found to be a significant predictor of prescreening visit attendance, with subjects who were scheduled sooner (i.e., fewer days between their phone screen and scheduled prescreening visit) being more likely to attend their visit (β=-.114, $p<.001$). Scheduling speed remained a significant predictor of prescreening visit attendance even when controlling for subjects' distance from the site.

Conclusions: Scheduling prescreening visits sooner could be a relatively easy and effective way to speed up enrollment and reduce recruitment costs. To our knowledge, this is the first study to examine the impact of scheduling speed on visit attendance for MDD trials. Future directions will be discussed, including a randomized experiment to compare attendance rates for visits scheduled within different time frames.

S6. EFFECT OF ADJUNCTIVE PIMAVANSERIN ON INSOMNIA AND FUNCTION IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: SECONDARY ANALYSIS FROM CLARITY

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Abstract: Background: Up to 90% of patients with major depressive disorder (MDD) experience sleep disturbances, which in turn are associated with increased rates of relapse. CLARITY was a phase 2 study of the efficacy and safety of adjunctive pimavanserin, a 5-hydroxytryptamine2A receptor antagonist/inverse agonist in patients with MDD and an inadequate antidepressant response. This exploratory analysis describes the effects of pimavanserin on insomnia.

Methods: This was a double-blind, placebo-controlled study in patients with MDD and an inadequate response to a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI). Using a 2-stage, sequential parallel-comparison design, 207 patients were initially randomized in a 3:1 ratio to placebo or pimavanserin added to ongoing SSRI or SNRI therapy; at 5 weeks, placebo non-responders were re-randomized to placebo or pimavanserin for an additional 5 weeks. For this secondary analysis, key endpoints were mean change from baseline for the Hamilton Depression (HAM-D) Rating Scale sleep disturbance factor score (Items 4, 5, and 6) among patients with a baseline sleep disturbance score ≥3 and the Karolinska Sleepiness Scale (KSS). The correlation between the HAM-D sleep disturbance score and KSS was also assessed. For the Sheehan Disability Scale (SDS) overall score and Unproductive Days subscore, mean change from baseline was examined in patients with a baseline KSS ≥6 (some signs of sleepiness).

Results: At baseline, HAM-D sleep disturbance score ≥3 occurred in 76% with placebo and 85% with pimavanserin. In Stage 1, a significant ($P<0.05$) improvement for pimavanserin vs placebo was observed for the sleep disturbance score at Weeks 2, 3, and 4. For KSS, a significant ($P\leq0.05$) reduction from baseline was observed with pimavanserin vs placebo from Week 1 through Week 5 with a Cohen's d effect size of 0.627 at Week 5. Among those with a KSS ≥6 (sleepiness) at baseline (n=120 placebo and n=42 pimavanserin), a significant ($P<0.05$) improvement from baseline was observed from Week 1 to 5 for the SDS overall score and Unproductive Days

subscore. Effect sizes for pimavanserin vs placebo were 0.363 or greater for the overall score and 0.446 or greater for the Unproductive Days subscore. Concomitant sedative/hypnotic medications were taken by <10% of patients during the study.

Conclusions: During Stage 1 and Stage 2, adjunctive pimavanserin significantly improved insomnia and sleepiness during treatment of MDD, which was associated with greater improvements in function. Pimavanserin may represent an option for adjunctive treatment of MDD, especially in the presence of insomnia.

S7. IMPACT ANALYSIS OF VORTIOXETINE DOSE CHANGE AMONG REMITTERS IN A RANDOMIZED WITHDRAWAL DESIGN STUDY

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Abstract: Background: 30% to 50% of adult patients with major depression fail to respond to their initial dose of antidepressant. One of the most common solutions to a minimal or partial antidepressant response is dose escalation and/or up-titration of the initial dose. However, dose adjustments of antidepressants are usually mitigated by changes to either the efficacy or tolerability.

Methods: The RESET study was a randomized withdrawal study in US patients with recurrent major depressive disorder with a history of ≥2 current acute major depressive episodes (Montgomery-Åsberg Depression Rating Scale [MADRS] total score ≥26). All patients who passed screening (planned N=1100) were treated with vortioxetine 10 mg dose daily in the open-label phase for 16 weeks. Those who remitted and were stabilized (MADRS total score ≤12 at weeks 14 and 16) were eligible for entry into the 32-week double-blind (DB) treatment period. In the DB period, patients (planned N=600) were randomized equally to 1 of 3 fixed doses of vortioxetine (5, 10, or 20 mg) or placebo. Here we evaluate the impact of dose decrease (10 mg to 5 mg) and dose increase (10 mg to 20 mg) on safety and efficacy among stabilized remitted patients.

Results: Of the 580 study participants randomized to the DB period, 140, 144, and 151 participants were randomized to dose decrease, dose increase, and placebo groups, respectively. All groups had similar baseline demographic characteristics and disease severity measures. The effect on delaying the relapse relative to placebo during 28 weeks of the DB period was comparable in dose decrease (19.3%) and dose increase (17.4%) groups (hazard ratio, 0.517 and 0.483, respectively). Over the first 2 weeks of the DB period, both dose decrease and dose increase groups did not show differential change from DB-period baseline in MADRS total scores (dose decrease: least squared [LS] mean, placebo-adjusted: -0.48 [standard error, SE=0.59]; dose increase: LS mean, placebo-adjusted: -0.41 [SE=0.59]). Secondary endpoints, including Clinical Global Impression-Severity (CGI-S), Clinical Global Impression-Improvement (CGI-I), and Columbia-Suicide Severity Rating Scale (C-SSRS), were similar in those with a dose decrease and those with a dose increase.

Assessment of treatment-emergent adverse events during the DB period revealed that frequency and severity were similar in the dose decrease and dose increase groups. Only nausea was reported at a higher frequency in the dose increase group (9.0%) than in the dose decrease (2.9%) and placebo (1.3%) groups.

Conclusion: Contrary to conventional clinical practice guidelines, decreasing the dose of vortioxetine during the maintenance phase after stabilization on the 10-mg dose did not compromise the effect on delaying time to relapses, while escalating the dose of vortioxetine did not increase tolerability issues and did not provide increased efficacy benefit in patients stabilized on 10 mg. These findings offer additional clarity for prescribers of vortioxetine during the maintenance phase of treatment.

S8. EXCESSIVE DAYTIME SLEEPINESS AMONG POTENTIAL CLINICAL TRIAL PARTICIPANTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract: Introduction: Excessive daytime sleepiness (EDS) affects 10-20% of the United States population, and can result in reduced occupational function, critical decision-making errors, and traffic fatalities. EDS is most often thought to be the result of inadequate sleep at night, but may also be higher in individuals with psychiatric conditions. Rates of EDS in those with major depressive disorder (MDD) are reported to be 2-6x the general population rate and may be linked to greater depression severity. EDS is rarely considered in clinical trial designs, despite the fact that it may impact study results. In the current study we examined a population of MDD trial participants for rates of EDS, associations between EDS and depressive symptoms, and the impact of EDS on trial participation.

Methods: In 2019, a total of 122 individuals interested in participating in an MDD clinical trial completed a site-sponsored prospective lead-in trial, the TRAIT study. Details regarding TRAIT have been published elsewhere, but briefly, participants who meet criteria for MDD receive standard of care antidepressant treatment over the course of 4-12 weeks. Those who fail to respond to treatment, as assessed using the Structured Interview Guide for the Montgomery-Asberg (SIGMA), are then offered an opportunity to participate in an industry-sponsored clinical trial. TRAIT was amended in July 2019 to include the Epworth Sleepiness Scale at baseline and study completion, so a portion of the full 122 completers of 2019 (N=51) completed the Epworth Sleepiness Scale (ESS) at baseline. Based on the literature, a series of Pearson correlations were performed to examine the relationship between scores on the ESS, BMI, Age, and SIGMA scores at baseline, as well as change in SIGMA scores over the course of 6-weeks of treatment. In addition, we assessed the frequency of EDS, as defined as an ESS score > 10, and conducted a one-way ANOVA to examine whether baseline ESS scores were associated with eventual trial participation.

Results: At screening, the average ESS score was 9.7 (SD=4.4), with 22 of 51 individuals (43%) meeting criteria for EDS. There was no significant relationship between ESS and BMI, Age, or Gender. However, there was a trend relationship (r = .26, p = .08) between ESS and SIGMA score at screening, with higher ESS scores associated with higher SIGMA scores. There was not a significant association between ESS and score on item 4 of the SIGMA, insomnia (r = .17, n.s.). There was no association between ESS score and response to antidepressant treatment (r = -.10, n.s.), although individuals who eventually screened for a clinical trial showed a trend toward higher ESS scores at baseline, F(1,44) = 3.4, p = .07.

Conclusion: Among individuals with MDD seeking a clinical trial, EDS is common, occurring in just over 40% in our sample. Consistent with previous studies, we found that symptoms of EDS are associated with greater depression severity, and that this relationship is not due to depression-related insomnia. Although this is a small sample, our results suggest EDS should be carefully considered in future clinical trial designs.

S9. EFFECTS OF ADJUNCTIVE BREXPIPRAZOLE ON PATIENT ENGAGEMENT AND FUNCTIONING IN MAJOR DEPRESSIVE DISORDER

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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/α2C receptors, all with subnanomolar affinity. The aim of this post hoc analysis was to explore whether treatment with adjunctive brexpiprazole has the potential to improve patient 'engagement' in adults with major depressive disorder (MDD), and whether any such improvement is linked to improvement in patient functioning, based on data from three short-term studies.

Methods: The studies (Pyxis: NCT01360645, Polaris: NCT01360632, and Sirius: NCT02196506) enrolled patients aged 18–65 years with MDD and inadequate response to 1–3 prior antidepressant treatments (ADTs). Eligible patients received open-label ADT for 8 weeks. Patients with inadequate response after this prospective phase were randomized to 6 weeks of ADT + brexpiprazole (1 to 3 mg/day, depending on the study) or ADT + placebo. As the three studies had similar designs, data were pooled for patients receiving ADT + brexpiprazole 2–3 mg/day, and for ADT + placebo. A ten-item version of the Inventory of Depressive Symptomatology Self-Report (IDS-SR-Engagement) has previously been explored to measure patient engagement, with possible scores ranging from 0 (best) to 30 (worst). The present analysis determined the proportion of patients with a ≥5-point decrease (improvement) in IDS-SR-Engagement score over 6 weeks. Additionally, for the subgroups with and without a 5-point decrease, the mean changes from baseline in Sheehan Disability Scale (SDS) Mean and domain scores were calculated.

Results: Mean (standard deviation) baseline scores on IDS-SR-Engagement were 15.5 (5.3) in the ADT + brexpiprazole 2–3 mg group (n=579) and 15.3 (5.2) in the ADT + placebo group (n=583). At Week 6, the proportion of patients with a ≥5-point improvement in IDS-SR-Engagement score

was 37.7% for ADT + brexpiprazole 2–3 mg and 26.2% for ADT + placebo (risk ratio 1.43, p<0.001). Among patients receiving ADT + brexpiprazole 2–3 mg with a ≥5-point improvement in IDS-SR-Engagement score, SDS Mean score improved by a mean (standard error) of 2.73 (0.16) points. In comparison, among patients receiving ADT + brexpiprazole 2–3 mg with a <5-point improvement in IDS-SR-Engagement score, SDS Mean score improved by 0.50 (0.11) points. Changes on the SDS domain scores followed a similar pattern.

Conclusion: Adjunctive brexpiprazole has the potential to improve patient engagement in MDD. Improved patient engagement was accompanied by improved functioning, as assessed by SDS.

S10. EFFICACY AND SAFETY OF AXS-05, AN ORAL NMDA RECEPTOR ANTAGONIST WITH MULTIMODAL ACTIVITY, IN MAJOR DEPRESSIVE DISORDER: RESULTS FROM THE GEMINI PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Abstract: Background: Major depressive disorder (MDD) is a debilitating and prevalent condition with over 17 million U.S. adults experiencing at least one major depressive episode in a given year. Nearly two-thirds of treated patients with MDD do not experience an adequate response to first-line therapy, and most of these inadequate responders also fail second-line treatment. Time to clinically meaningful response with currently available antidepressants (up to 6-8 weeks) is also suboptimal. There is an urgent need for new, more effective, mechanistically novel, and faster-acting MDD treatments.
AXS-05 (dextromethorphan/bupropion modulated delivery tablet) is a novel, oral, investigational NMDA receptor antagonist with multimodal activity, including sigma-1 receptor agonism. AXS-05 is being developed for the treatment of MDD.

Objective: To evaluate the efficacy and safety of AXS-05 versus placebo in MDD.

Methods: The GEMINI study was a Phase 3, randomized, double-blind, placebo-controlled, multi-center, U.S. trial, in which 327 adult subjects with a diagnosis of moderate to severe MDD were randomized to treatment with either with AXS-05 (45 mg DM/105 mg bupropion) (n=163), or placebo (n=164), twice daily for 6 weeks.

Results: On the primary endpoint, AXS-05 demonstrated a statistically significant mean reduction from baseline in the MADRS total score of 16.6 points versus 11.9 for placebo (p=0.002) after 6 weeks of treatment. AXS-05 rapidly, robustly and durably reduced depressive symptoms, demonstrating a statistically significant improvement compared to placebo on the key secondary endpoint of change from baseline in the MADRS total score at Week 1, the earliest time point measured (p=0.007), and at all timepoints thereafter. Rates of response (≥ 50% MADRS improvement) were statistically significantly greater for AXS-05 compared to placebo at Week 1 (p=0.035) and at every time point thereafter, being achieved by 54% of AXS-05 patients versus 34% of placebo patients at Week 6 (p<0.001). Rates of remission (MADRS ≤10) were statistically significantly greater for AXS-05 compared to placebo at Week 2 (p=0.013) and at every time point

thereafter, being achieved by 40% of AXS-05 patients versus 17% of placebo patients at Week 6 ($p<0.001$).

The observed rapid and durable antidepressant effects translated into early and statistically significant improvements in daily functioning as measured by the Sheehan Disability Scale, and in quality of life as measured by the Quality of Life Enjoyment and Satisfaction Questionnaire.

AXS-05 was safe and well tolerated with the most commonly reported adverse events being dizziness, nausea, headache, diarrhea, somnolence and dry mouth. Treatment with AXS-05 was not associated with psychotomimetic effects. Rates of discontinuation due to adverse events in the trial were low (6.2% for AXS-05 and 0.6% for placebo).

Conclusion: Treatment with AXS-05 resulted in rapid, substantial, durable and statistically significant improvements in depressive symptomatology across multiple efficacy endpoints as compared to placebo in patients with MDD. Symptomatic benefits translated into statistically significant improvements on validated measures of daily functioning and quality of life. AXS-05 was safe and well tolerated in this trial and was not associated with psychotomimetic effects.

S11. RAPID ONSET OF ANTIDEPRESSANT EFFICACY IN POSTPARTUM DEPRESSION RCTS BY MULTIPLE MEASURES IN AN INTEGRATED ANALYSIS OF BREXANOLONE INJECTION WITH A DURABLE BENEFIT OBSERVED AT 30 DAYS FOLLOW-UP VERSUS PLACEBO

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Abstract: Background: Postpartum depression (PPD) is one of the most common medical complications during and after pregnancy. In the United States (US), an average of 11.5% of new mothers experience symptoms of postpartum depression (PPD). Brexanolone injection (BRX) is an intravenous formulation of allopregnanolone, a positive allosteric modulator of synaptic and extrasynaptic γ-aminobutyric acid A (GABA-A) receptors that is pharmacologically distinct from benzodiazepines, which target only synaptic GABA-A receptors. Following three double-blind, randomized, placebo-controlled trials (NCT02614547; NCT02942004; NCT02942017), BRX was approved by the US Food and Drug Administration for treatment of adults with PPD. Here, we present both predefined and post hoc efficacy assessments from an integrated BRX clinical trial dataset.

Methods: BRX trials used an umbrella protocol to facilitate integrated analysis of these multi-center randomized, placebo-controlled trials. 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. Placebo (PBO), BRX 60 μg/kg/hour (BRX60, in Study B only), or 90 μg/kg/hour (BRX90) was

administered to randomized subjects as a single, continuous 60-hour infusion in which the BRX60 and BRX90 dose titrations were the same through Hour 24. Change from baseline in least-squares mean (LSM) HAM-Dts over time (Hour 60 primary endpoint), HAM-Dts response (reduction ≥50%), and HAM-Dts remission rates (score ≤7) were assessed through Day 30. A predefined HAM-Dts minimal important difference (MID) of 2.1 was applied to assess clinical significance. Secondary endpoints were not adjusted for multiplicity. Safety and tolerability were assessed by the frequency and severity of adverse events (AEs).

Results: In a pooled 24-hour analyses of BRX60 and BRX90 patients, the BRX group (N=140) showed numerically greater improvements in LSM HAM-Dts versus PBO (N=107) at all post-baseline time points through Hour 24 and statistically significant improvements at Hour 8 (-1.49, p=0.0402) and Hour 24 (-3.41, p<0.0001) that exceeded the MID versus PBO at Hour 24. At Hour 60 (primary endpoint), there were statistically and clinically significant improvements in LSM HAM-Dts favoring BRX90 (N=102; -17.0, p<0.0001) over PBO (N=107; -12.8) that were sustained through Day 30 (BRX90 -16.9, PBO -14.3; p=0.0213). The BRX90 group showed statistically significant increases in HAM-Dts response and remission rates versus the PBO group at Hour 60 (Response: 74.5% vs. 55.7%, p=0.0003; Remission: 50.0% vs. 26.4%, p<0.0001). Post hoc Kaplan-Meier analysis showed a statistically significant decrease in median time to response for BRX90 versus PBO (24 hours vs. 36 hours; p=0.0265). BRX was generally well tolerated. Adverse events occurring in all BRX groups (BRX90 and BRX60) in ≥5% of BRX and two or more times the rate of placebo were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush.

Conclusions: In these clinical trials, BRX showed statistically and clinically significant reductions in depressive symptoms compared with placebo.

S12. PLACEBO RESPONSE ASSESSED BY PET-MR NEUROIMAGING IN MAJOR DEPRESSIVE DISORDER - A RANDOMIZED, DOUBLE-BLIND, SEQUENTIAL PARALLEL COMPARISON DESIGN CLINICAL TRIAL

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Abstract: Background: Progressively increasing placebo response rate in Major Depressive Disorder (MDD) clinical trials is a major obstacle in developing new interventions. The neurobiological mechanisms implicated in the placebo response remain poorly understood. We designed a double-blind, placebo-controlled randomized clinical trial (RCT) to generate a large cohort of placebo responders and investigate with combined PET (using the radiotracer 11C-raclopride for imaging availability of dopamine D2 receptors) and fMRI whether neuroimaging biomarkers and clinical measures of anhedonia predict clinical improvement in patients diagnosed

with MDD treated with placebo. The study is ongoing, and assignment of subjects is still under blind to the investigators.

Methods: We recruited adult subjects with MDD (n = 64). In accordance with the sequential parallel comparison design (SPCD), the 8-week, double-blind RCT was divided into 2 phases. During Phase 1, the subjects were randomized to active drug (bupropion 300mg/day; oral administration) or placebo, with imbalanced placebo: drug ratio of 7:1 (i.e. 87.5% assigned to the placebo condition). During Phase 2, placebo responders and non-responders were randomized in the inverse proportion (i.e. 87.5% assigned to the active drug condition). The primary outcome was response (≥ 50% reduction of HAM-D) at the end of Phase 1. The nucleus accumbens, caudate and putamen were identified as a priori regions of interest (ROIs). Imaging sessions were spaced at baseline and after Phase 1. Subjects performed the Monetary Incentive Delay (MID) task in the PET-MR scanner. Self-report measures of anhedonia were obtained using the Temporal Experience of Pleasure Scale (TEPS) and Snaith-Hamilton Pleasure Scale (SHPS).

Results: Preliminary analysis indicated an overall response rate of 45%. PET analyses revealed a significant increase in 11C-raclopride binding potential in the caudate nucleus, putamen, and executive striatum between baseline and follow-up ($p = 0.01$). Displacement of 11C-raclopride binding, indicative of task-induced dopamine release, was detected during the MID in several striatal ROIs during baseline and follow-up. No statistically significant changes in displacement magnitude were observed between baseline and follow-up. Hierarchical regression analyses demonstrated that fMRI activation and anhedonia at baseline did not significantly predict clinical improvement, characterized by ≥ 50% reduction in total HAM-D-32 scores between baseline and follow-up.

Conclusions: The preliminary results of blinded data implicate a potential role for mesolimbic dopamine (DA) mechanisms in mediating the placebo response in MDD. Neural activation and anhedonia at baseline do not appear to be significant predictors of clinical improvement with regards to depressive symptom severity. Analyses of unblinded data will help to further understand the role of the dopaminergic system in the neurobiological basis of placebo response in MDD patients.

S13. EFFECT OF ADJUNCTIVE BREXPIPRAZOLE ON SEXUAL FUNCTIONING IN MDD ACCORDING TO CONCOMITANT ANTIDEPRESSANT: POST HOC ANALYSIS OF FOUR SHORT-TERM STUDIES

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Abstract: Background: Brexpiprazole is a serotonin–dopamine activity modulator that has shown efficacy and safety as adjunctive therapy to antidepressant treatment (ADT) in four short-term studies in adults with major depressive disorder (MDD) and inadequate response to ADTs. This analysis aimed to determine the effects of adjunctive brexpiprazole on sexual functioning in adults with MDD, according to ADT.

Methods: Pyxis (NCT01360645), Polaris (NCT01360632), Sirius (NCT02196506) and Delphinus (NCT01727726) were randomized, double-blind, placebo-controlled studies in outpatients with MDD (DSM-IV-TR criteria) and inadequate response to 1–3 prior ADTs. Patients received a prospective ADT with placebo for 8–10 weeks; patients with inadequate response continued on the same ADT and were randomized to 6 weeks of adjunctive brexpiprazole, quetiapine extended-release (XR) (one study, data not shown), or continued placebo. Change in Massachusetts General Hospital Sexual Functioning Questionnaire (MSFQ), and Montgomery–Åsberg Depression Rating Scale (MADRS) Total score were calculated post hoc for ADT+brexpiprazole 2–3 mg and ADT+placebo groups, and for subgroups according to concomitant ADT.

Results: 1,574 patients were randomized to ADT+brexpiprazole 2–3 mg (n=782) or ADT+placebo (n=792). Concomitant ADTs were: escitalopram, fluoxetine, paroxetine controlled-release (CR), sertraline, venlafaxine XR, and duloxetine. Baseline demographic and clinical characteristics were similar across ADT subgroups. Mean baseline MSFQ scores (ADT+brexpiprazole, ADT+placebo) were: overall sexual satisfaction 4.57, 4.70; interest in sex 4.41, 4.56; sexually aroused 4.33, 4.51; achieve orgasm 4.53, 4.65; maintain erection 3.74, 3.67. On the MSFQ, mean overall sexual satisfaction score changed (improved) by -0.37 from baseline to Week 6 for ADT+brexpiprazole and by -0.22 for ADT+placebo, p=0.014; range -0.67 (venlafaxine XR) to -0.09 (paroxetine CR). Similar mean changes (ADT+brexpiprazole vs ADT+placebo) were observed for interest in sex (-0.37 vs -0.16, p<0.01), sexually aroused (-0.35 vs -0.15, p<0.01), and achieve orgasm (-0.29 vs -0.20, p=0.13), with small differences between ADT subgroups. Although maintain erection changed by -0.18 overall in the ADT+brexpiprazole group and by -0.04 in the ADT+placebo group, p=0.18, subgroups varied from -0.57 (improvement) with venlafaxine XR to 0.20 (worsening) with paroxetine CR. MADRS Total score changed by a mean of -8.3 points from baseline to Week 6 in the ADT+brexpiprazole group compared with -6.2 points the ADT+placebo group (p<0.0001), with small differences between ADT subgroups.

Conclusion: In short-term MDD studies, adjunctive brexpiprazole did not adversely affect sexual functioning based on changes in MSFQ scores. ADT selection appeared to have little impact on sexual functioning, although patients receiving paroxetine CR appeared to fare worse than those receiving other concomitant ADTs.

S14. EVALUATION OF VIDEO-BASED ADMINISTRATION OF CLINICAL OUTCOME ASSESSMENTS AND MOBILE PATIENT REPORTED OUTCOMES FOR MAJOR DEPRESSIVE EPISODE IN A TELEMEDICINE RESEARCH MODEL

ABSTRACT NOT INCLUDED

S15. LONG-TERM EFFICACY OF LURASIDONE IN PEDIATRIC BIPOLAR DEPRESSION: RESPONSE, REMISSION AND RECOVERY

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Abstract: Background: Bipolar disorder frequently has an early onset, with an estimated 1.8% prevalence of bipolar I disorder in pediatric populations. Childhood onset of bipolar disorder is typically associated with a more chronic, severe, and disabling course of illness compared to onset in adulthood. Relatively few prospective studies are available that evaluate the long-term efficacy of atypical antipsychotics in achieving, and sustaining, response or remission over 2 years or longer in pediatric patients presenting with bipolar depression. Lurasidone has been approved by the FDA as monotherapy for bipolar depression in pediatric patients ages 10-17 years. The aim of the current post-hoc analysis was to evaluate the long-term efficacy of lurasidone in achieving response or remission in children and adolescents with bipolar depression.

Methods: Patients 10-17 years with bipolar I depression who completed a 6-week double-blind (DB) study of lurasidone vs. placebo 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) or switched from placebo to lurasidone. Efficacy measures included the Children's Depression Rating Scale, Revised (CDRS-R) and the Clinical Global Impression, Bipolar Depression Severity scale (CGI-BP-S). Functioning was evaluated utilizing the Clinician-rated Children's Global Assessment Scale (CGAS) score, with a score ≥70 indicating no clinically meaningful functional impairment. Responder criteria were met if a patient achieved criteria ≥50% reduction from DB baseline in the CDRS-R total score: remission criteria were met if a patient achieved a CDRS-R Total Score ≤28 and a YMRS total score ≤8 and CGI-BP-S depression score ≤3, and a patient was considered to have met recovery criteria if they achieved remission and had a CGAS score ≥70. In addition, a more stringent outcome, sustained remission, was also analyzed, which required a patient to meet remission criteria for ≥24 consecutive weeks.

Results: A total of 305 patients completed the 6-week DB study and entered the extension study; 195 and 93 completed 52 and 104 weeks of treatment, respectively. Responder rates at OL baseline, and weeks 52 and 104 were 51.0%, 88.4% and 91.1%, respectively; remission rates were 24.3%, 61.3%, and 75.6%, respectively; and recovery rates were 17.7%, 53.8%, and 73.8%. On a Pearson correlation analysis, there was a strong inverse relationship (r = -0.71) between CDRS-R total score, and global functioning as measured by the CGAS. Sustained remission was achieved at weeks 52 and 104 by 37.2% and 57% of patients.

Conclusions: In children and adolescents with bipolar depression, up to 2 years of treatment with lurasidone was associated with continued improvement in depressive symptoms, resulting in progressively higher rates of remission, recovery, and sustained remission.

Clinicaltrials.gov identifier: NCT01914393.

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S16. GUIDING ACCURATE AND TIMELY DIAGNOSIS OF BIPOLAR DEPRESSION: A NOVEL PRAGMATIC SCREENING TOOL FOR IDENTIFYING PATIENTS WITH BIPOLAR DISORDER

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Abstract: Background: Approximately 70% of patients with bipolar disorder (BPD) are initially misdiagnosed, resulting in significantly delayed diagnosis of BPD (7-10 years on average). Misdiagnosis and diagnostic delay adversely affect health outcomes and lead to the use of inappropriate treatments. As depressive episodes/symptoms are the predominant presentation of BPD, misdiagnosis as major depressive disorder (MDD) is common. Self-rated screening instruments for BPD exist but their length and underemphasis on BPD diagnostic validators are barriers to implementation, especially in primary care settings where many of these patients initially present. We developed a brief, pragmatic bipolar I disorder (BPD-I) screening tool that not only screens for manic symptoms but also includes risk factors for BPD-I (e.g., number of prior antidepressants, age of onset) to help clinicians reduce misdiagnosis of BPD-I as MDD.
Methods: Existing questionnaires and risk factors were identified through a targeted literature search; a diverse panel of experts was enlisted to select concepts thought to differentiate BPD-I from MDD. Individuals with self-reported BPD-I or MDD participated in iterative sets of cognitive debriefing interviews (N=12) to test and refine the item-wording. A multisite, cross-sectional, observational study was conducted to evaluate the screening tool's predictive validity. Participants with clinical interview-confirmed diagnoses of BPD-I or MDD completed a 10-item screening tool and other questionnaires. Data were analyzed to identify a subset of items and item-thresholds to optimize tool sensitivity and specificity, with the goal of providing strong psychometric properties with the fewest number of items.

Results: A total of 160 clinical interviews were conducted; 139 patients had clinical interview-confirmed BPD-I (n=67) or MDD (n=72). The screening tool was reduced from 10 to 6 items based on item-level analysis. When 4 items or more were endorsed ("yes"), the sensitivity of this tool for identifying patients with BPD-I was 0.92 and specificity was 0.78; positive and negative predictive values, based on the analysis sample, were 0.78 and 0.92, respectively. These properties represent an improvement over the Mood Disorder Questionnaire, while using >50% fewer items.

Conclusion: This new 6-item BPD-I screening tool serves to identify patients with depression who may instead have BPD-I. Use of this tool can provide real-world guidance to practitioners on whether more comprehensive assessment for BPD is warranted. Implementation of a brief and valid tool provides opportunity to improve diagnostic accuracy, appropriate treatment selection, and positive patient outcomes, especially for busy clinical practices.

S17. CLINICAL OUTCOMES OF LONG-TERM LITHIUM-THERAPY AND DEVELOPMENT OF THYROID DISEASE IN BIPOLAR DISORDER: A LONGITUDINAL STUDY

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Abstract: Background: Lithium (Li) is an effective medicine for the treatment of the acute and maintenance phase of bipolar disorder (BP). Long-term lithium-therapy (LTLT) has been associated with the development of goiter, hyper and hypothyroidism in patients with BP (1). There is concern regarding poor Li response among BP patients with thyroid disorders. There is limited data regarding the impact of thyroid disorders and clinical outcomes in BP patients on LTLT. In this study, we compared the clinical characteristics of BP patients who were on LTLT (≥1year) among patients with and without thyroid disorders and the impact of LTLT on thyroid functioning.

Methods: We included adult subjects with a diagnosis of BP-I or BP-II disorder who were on Li at the time of enrollment in the Mayo Clinic BP Biobank (2). Alda score was used to retrospectively assess the clinical response to Li treatment. We compared demographics, psychosocial factors, psychiatric comorbidities and treatment response (defined as Alda score-A ≥7) among patients with and without thyroid disorders on LTLT. We investigated the impact of LTLT on thyroid functioning, by measuring the change in Thyroid-stimulating hormone (TSH) levels from baseline and at one year of treatment.

Results: 146 BP patients were on LTLT; mean age 44 years, 60% were females and the majority had BP-I diagnosis (67%). 37% of patients on LTLT had hypothyroidism, 1% had hyperthyroidism, while 61% of patients remained euthyroid. There was no significant difference in Li response among patients with or without thyroid disorders (42 % vs 50%, p = 0.3). Baseline TSH was not associated with a significant change in Alda scores among BP patients on LTLT. Hypothyroidism was more prevalent in females as compared to males (76% vs 50%, p =0.002) and patients with a history of trauma had a higher prevalence of hypothyroidism (50 % vs 33%, p =0.04). There was no significant difference in age, psychosocial factors, and other psychiatric comorbidities including rapid cycling among patients with and without hypothyroidism.

Baseline TSH was similar among lithium responders and non-responders. There was a significant increase in mean TSH among BP patients on LTLT at 1 year, mean difference 0.79±SE 0.34 (p = 0.01) without a significant difference in lithium response. Our limitation has been the lack of data regarding thyroid hormone treatment. We will plan to extract this data and update the results.

Conclusion: Findings from this suggests that hypothyroidism does not increase the risk of non-response to lithium in bipolar disorder patients on long-term lithium therapy. This could be due to the adequate treatment of thyroid disorders. These finding needs to be further investigated in a larger sample size study.

S18. A RETROSPECTIVE STUDY OF THE ADJUNCT USE OF GABAPENTIN WITH BENZODIAZEPINES FOR THE TREATMENT OF BENZODIAZEPINE WITHDRAWAL

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Abstract: Background: Gabapentin, an anticonvulsant and neuropathic pain medication, is often used to treat anxiety. Anxiety is also a common symptom associated with benzodiazepine withdrawal. Treatment of the withdrawal symptoms traditionally has been with usage of short-term benzodiazepines. However, benzodiazepines come with risk of addiction and other unfavorable side effects. Therefore, finding alternative agents for the treatment of the benzodiazepine withdrawal is needed. Gabapentin is a much more favorable medication than benzodiazepines as the abuse potential is lower. In addition, gabapentin may reduce symptoms of alcohol withdrawal and alcohol cravings (1). Given that alcohol and benzodiazepines are commonly abused together, and both affect the GABAergic pathway, using gabapentin as an adjunct for the treatment of benzodiazepine withdrawal is plausible and promising. However, this proposal has never been formally evaluated.

Methods: In this retrospective study we investigated whether gabapentin as an adjunct treatment reduces the withdrawal symptoms and benzodiazepine dependence in patients treated with benzodiazepines withdrawal and concomitantly were given gabapentin for anxiety or neuropathic pain. We screened the patient records retrospectively from a large inpatient psychiatric hospital with annual admission numbers of 8000-9000 and identified 10 patients who met the inclusion criteria in a period of 4 weeks. Observational data of the acute withdrawal symptoms were measured by CIWAs score. Other patient demographics including gender, race, medications, medical problems, length of stay, and number of readmissions were recorded.

Results: Ten patients from December 2019 to January 2020 were found to meet criteria of being treated both with gabapentin and benzodiazepines for withdrawal (Table 1).

Table 1. Demographic and characteristics of subjects with benzodiazepine withdrawal:

- Age (Years): 25-57 (Mean +- SD /) 41.5)
- Gender (female/male) 3/7
- Patients with depression: 4
- Patients with unspecified psychosis: 2
- Patients with bipolar disorder: 3
- Patients with unspecified mood disorder: 1
- Patients with a history of withdrawal seizures from benzodiazepine abuse: 4
- Number of patients with co-substance use: 7 (substances include cannabis, alcohol, cocaine, prescribed medications, benzodiazepines, hallucinogens, amphetamines, heroin, KUSH, and crack)
- Number of patients with alcohol use disorder: 5
- Length of hospital stay: 4-27 days

A total of three patients were re-admitted, none of the re-admissions, however, were associated with withdrawals. Dosage of gabapentin given to patients ranged from 600-1800 mg total daily dose. Patients who were given gabapentin and benzodiazepines were off the CIWAs protocol within 3-5 days.

Discussion: Previous studies have shown using gabapentin at a total daily dose of 600-1800 mg reduces the withdrawal symptoms of alcohol (2). This is the first retrospective study to observe the conjunctive use of benzodiazepines and gabapentin in treating benzodiazepine withdrawal. We found the combination of gabapentin and benzodiazepines is safe as no complications were reported during this study. Total daily dose of gabapentin at a range of 600-1800 mg appears valuable in treating benzodiazepine withdrawal as there was a reduction of withdrawal symptoms. The shortcoming of this study is that there is no benzodiazepine or gabapentin only control group as this study was not designed as an interventional study. Therefore, further studies comparing combined use of benzodiazepine and gabapentin versus use of benzodiazepines alone is warranted to further clarify this observation.

S19. SINGLE-DOSE PHARMACOKINETICS OF AMPHETAMINE EXTENDED-RELEASE TABLET (AMPH ER TAB) COMPARED WITH AMPHETAMINE EXTENDED-RELEASE ORAL SUSPENSION (AMPH EROS)

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Abstract: Objectives: Evaluate the comparative bioavailability of a single-dose amphetamine extended-release tablet (AMPH ER TAB) 20 mg, swallowed whole and chewed, and amphetamine extended-release oral suspension (AMPH EROS) 2.5 mg/mL; and evaluate food effect on AMPH ER TAB (contains a 3.2:1 ratio of d- to l-amphetamine).

Methods: Healthy volunteers (18-55 yr) were randomized to AMPH ER TAB 20 mg swallowed (fasted), chewed (fed/fasted), or 20 mg AMPH EROS (fasted). A crossover design was used. Plasma samples were collected pre-dose and at time intervals to 60 h post-dose. D- and l-amphetamine measured, Cmax, AUCt, and AUC0∞ were calculated. Comparative bioavailability was determined when ratios were 80-125%. Safety was assessed by monitoring of adverse events.

Results: 32 subjects completed the study.

Ratios: AMPH ER TAB swallowed vs. AMPH EROS fasted: For d-amphetamine: AUC0-t: 100.68-108.08%, AUC0-∞:101.47-109.52%, Cmax: 98.10-103.17%. For l-amphetamine: AUC0-t: 100.31-108.57%, AUC0-∞:101.27-111.09%, Cmax: 98.2-103.37%.

AMPH ER TAB chewed vs. AMPH EROS fasted: For d-amphetamine: AUC0-t: 99.23-106.62%, AUC0-∞: 99.58-107.59%, Cmax: 99.91-105.14%. For l-amphetamine: AUC0-t: 98.16-106.35%, AUC0-∞: 98.44-108.11%, Cmax: 99.53-104.75%.

Food effect: AMPH ER TAB, chewed, fasted vs. fed: For d-amphetamine: AUC0-t: 92.57-99.49%, AUC0-∞: 91.12-98.48%, Cmax: 94.22-99.17%. For l-amphetamine: AUC0-t: 91.27-98.91%, AUC0-∞: 88.44-97.17%, Cmax: 94.52-99.50%.

No serious AEs were reported, and the AE profiles were similar to other amphetamine formulations used in ADHD.

Conclusions: The bioavailability of AMPH ER TAB for both d- and l-amphetamine was determined to be comparable, swallowed whole or chewed, to an equivalent 20 mg dose of the reference product AMPH EROS, 2.5 mg/mL fasted, and showed equivalent peak and overall exposure, without any apparent food effect. All AEs were mild in severity and the overall safety profile was similar to other amphetamine formulations used for ADHD.

S20. THE CLINICAL UTILITY OF COMBINATORIAL PHARMACOGENOMIC TESTING FOR PATIENTS WITH DEPRESSION: A META-ANALYSIS

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Abstract: Background: Pharmacogenomic testing has emerged as a possible data-driven approach to treatment decisions for patients with Major Depressive Disorder (MDD); however, there is mixed evidence available for the utility of pharmacogenomic testing depending on the test used and population being studied. Meta-analyses provide a high level of evidence and can be useful in evaluating the overall utility of a testing approach for clinical use. Given the meaningful differences between tests, it is not appropriate to evaluate pharmacogenomic tests as a class, and meta-analyses should be performed for each individual test. Here, we performed a meta-analysis of prospective, two-arm studies examining the clinical utility of using the combinatorial pharmacogenomic test, GeneSight Psychotropic®, to inform treatment decisions for patients with MDD who had at least one prior medication failure.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines were used for this meta-analysis. A systematic search was performed, and all identified reports were screened to identify two-arm, prospective studies evaluating the clinical utility of this specific test that included patients ≥18 years of age diagnosed with MDD who had at least one prior medication failure. All included studies assessed symptom improvement, response, and remission using the 17-item Hamilton Depression Rating Scale (HAM-D17). The pooled mean effect of symptom improvement and pooled relative risk ratio (RR) of response and remission were calculated using a random effect model.

Results: Overall, 1,556 patients were included from four studies (two open-label studies and two randomized controlled trials (RCT). Patient outcomes were significantly improved for patients with MDD whose care was guided by the specific combinatorial pharmacogenomic test results compared to unguided-care (symptom improvement Δ=10.08%, 95% CI=1.67-18.50, p=0.02; response RR=1.40, 95% CI=1.17-1.67, p<0.01; remission RR=1.49, 95% CI=1.17-1.89, p<0.01). Sub-analyses were performed according to study type. Symptom improvement, response, and remission were all significant within the RCTs and within the open-label trials.

Conclusions: In a meta-analysis of four independent, prospective clinical utility studies, GeneSight Psychotropic® guided-care improves outcomes among patients with MDD who have had at least one prior medication failure.

S21. 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 5th 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.

S22. DEVELOPMENT OF A CHILD AND ADOLESCENT ECOA GUIDED INTERVIEW FOR THE PANSS INTERVIEW FOR ASSESSING PSYCHOSIS IN CLINICAL TRIALS

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Abstract: Background: Global regulatory initiatives have resulted in an increasing number of psychopharmacology trials in the pediatric age range. Challenges in ensuring valid and reliable data in such trials are numerous, and include developmental limitations in symptom description,

the need to integrate and weight information from varied sources including parents/caregivers and other informants, and the global shortage of child-trained clinical investigators (Busner, 2013; Farchione, 2013). To add to the challenges, there are few validated efficacy measures, and many pediatric trials use measures designed for and validated in adults; this is the case for adolescent schizophrenia trials, which almost invariably use for primary efficacy assessment the (adult) Positive and Negative Syndrome Scale (PANSS), a complex, time-consuming, 30-item measure that has been extensively studied and shown to pose ratings challenges even used with the adult patients for whom it was designed. We have previously identified PANSS items with poorest interrater reliability amongst clinical trial investigators in adolescent trials (Busner, Daniel, Findling, 2013). We have developed training tools and conventions aimed at improving raters' ability to inquire about and score those and other PANSS items more consistently in the pediatric population. We have applied these training tools around the globe with hundreds of raters across multiple sponsors resulting in multiple drug approvals. To further the work, with the goals of streamlining administration, enhancing consistency, and improving data quality, we are developing, and describing herein, a new guided electronic clinician administered outcome assessment (eCOA) tool to assist trials raters when administering the PANSS to children and adolescents and their caregivers. Consistent with our trained conventions, the tool will provide suggested pediatric prompts and will include edit checks modified from those developed by our group for the adult PANSS (Daniel and Kott, 2019).
Method: We have collected item prompts for the child/adolescent and the parent/caregiver from expert-conducted videotaped PANSS interviews and scripted investigators' meeting training sessions. The eCOA scale will incorporate the prompts for potential use by raters in an item per item format, along with per-item trained reminders and conventions. Similar to our adult PANSS eCOA work, internal edit checks will notify raters when logic errors appear to have occurred (e.g., wholly contradictory information for same time period.) As with our adult PANSS eCOA work, edits are provided for assistance, but the rater will always retain the scoring choice. Child/adolescent and parent/caregiver interviews will occur serially at a visit, with the responses from the first interviewee shown to the rater during the second interview, per item, and a final "best estimate" score captured (as true with paper PANSS).
Results: We will pilot the scale for feasibility at identified child psychiatric research sites and will conduct standard eCOA vs paper equivalency analyses.
Conclusions: We believe our work represents an advance in the field as the first pediatric-specific eCOA interview for the PANSS. As has been shown repeatedly for other eCOA outcome measures, we expect the pediatric eCOA PANSS to result in more consistent and less error-prone data for clinical trials.

S23. THE VALUE OF ECONSENT ACROSS THERAPEUTIC INDICATIONS

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Abstract: Background: Despite its potential value to trial participants, eConsent, an electronic media to supplement or replace the traditional paper based informed consent process, is one

technology yet to be adopted by many in industry. eConsent helps inform and educate participants clinical trial requirements, risks, benefits and expectations by leveraging digital content such as videos and animation, word tagging, and knowledge checks. Further eConsent data enables objective measures of process effectiveness, evidence-based improvements and identifying differences across therapeutic indication. Current such data is very limited.

Methods: eConsent data from 20 closed studies, totaling over 4000 participants gathered from CNS, nephrology, and dermatology was analyzed. Indications include attention deficit hyperactivity disorder (ADHD), autosomal dominant polycystic kidney disease (ADPKD), post-traumatic stress disorder (PTSD), schizophrenia, bipolar disorder, major depression disorder (MDD), and eczema were analyzed. Read time, video watch time, and knowledge check scores were calculated across all studies and by indication. Analysis of trends relating time engaged in eConsent to study enrollment and completion were conducted.

Results: Across indications, 91% of participants consented. ADPKD had the lowest consent rate at 85%. Schizophrenia trials had the highest consent rate of 96%. Bipolar trial participant spent the least time on the informed consent form (ICF). Among schizophrenia and eczema participants, trends show higher participant time on the ICF was associated with increased likelihood of study completion.

In all, 9% of potential participants exited the process and did not consent. Of those, 36% exited while reading the informed consent form. MDD made up the largest segment of this group at 30%, and Eczema the smallest at 4%.

Knowledge check scores also varied among indications. Eczema had the lowest percentage (90%) of participants answer all questions correctly on the first attempt, and PTSD had the highest (99%).

All eConsents contained a 4-9 minutes animated video. Nearly all participants in the PTSD, eczema, and schizophrenia trials watched the complete video. For all indications except ADHD, those who spent more time on the video were more likely to complete the study. Contrarily, participants in the ADHD trials who spent less time on the video were more likely to complete the study.

Conclusion: A substantial value of eConsent in clinical trials is the inherent ability to track, measure and adjust the informed consent process. This could allow evidence based, meaningful improvements to patient understanding and participation.

This eConsent data show differences in consent process results among different therapeutic indications. Engagement with the eConsent process can be inferred from time spent in each part of the process, with differences between included indications. This suggests opportunities to tailor the delivery of information, such as videos or electronic print, to best effect for each patient cohort. For example, altering the video for participants with ADHD with patient advocacy group input may ensure it is helpful for participants in ADHD trials. An eConsent process tailored to indication could lead to a more informed and more likely participant and more satisfied sites and investigators. More analysis can contribute new insights on e-consent application design to ensure that stakeholder needs are met for future trials.

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S24. THE BENEFITS AND COSTS OF CHANGING TREATMENT TECHNIQUE IN ELECTROCONVULSIVE THERAPY DUE TO INSUFFICIENT IMPROVEMENT OF A MAJOR DEPRESSIVE EPISODE

ABSTRACT NOT INCLUDED

S25. KRATOM A NEW DRUG OF CONCERN

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Abstract: Kratom was first discovered by Dutch botanist Pieter Korthals in 1831 in Malaysia. It stems from the Nitragyna speciose korth a tropical forest tree found in Malaysia, Thailand and Myanmar. The leaves of this tree are containing psychoactive opioid compounds and have been consumed for thousands of years. Kratom contains alkaloids that bind to opioid receptors but it is an opioid drug per structure. Kratom is an increasingly popular substance in the US and easily available. The powdered form of kratom are sold in convenience stores, online or gas stations. The usual form of administration is usually threw chewing the leaves, tea, or nowadays in form of capsules or even gum. Kratom induces effects of euphoria, in lower doses it acts similar to a stimulant, increasing energy, alertness while in higher doses it induces sedative effects. Kratom is used for anxiety, depression, inflammation, libido and also for the treatment of opioid withdrawal. With long term use, Kratom can cause dependence and addiction. In the US increasing number of persons are seen with acute withdrawal symptoms similar to opioid withdrawal: diarrhea, hypertension, insomnia, irritability, arthralgias, myalgias, rhinorrhea as well as hot and cold sweats. The FDA banned the import of Kratom into the US in 2014 but it is otherwise not a FDA controlled substance, it is listed as “drug and chemical of concern” with the note that “there is no legitimate medical use for Kratom”. Some states banned Kratom completely, including Indiana, Tennessee, Wyoming. There are currently very limited clinical studies available that demonstrate safety and efficacy in humans. The available information is mostly based on reports from users or animal models. Also, Kratom is not detectable on urine drug screens which makes the diagnosis eventually more difficult and delay treatment. Since Kratom is becoming an increasing problem in the US, physician education about the substance needs to occur with treatment recommendations for Kratom withdrawal and addiction. Studies suggest that up to 50% of regular users will develop an addiction. This research presentation is based on a systematic review of literature on the current available data on Kratom guided for physician and clinician education.

S26. THE PHARMACOKINETIC AND SAFETY PROFILE OF CTP-692 (DEUTERATED D-SERINE) IN HEALTHY VOLUNTEERS: PHASE 1 PROGRAM RESULTS

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Abstract: Schizophrenia is associated with low levels of D-serine, the most important synaptic co-agonist of the N-methyl-D-aspartate (NMDA) type glutamate receptor in the brain. Genetic and neurobiological findings have linked NMDA receptor hypofunction to the etiology of schizophrenia. CTP-692 is a deuterated analog of D-serine with demonstrated advantages in safety and pharmacokinetics (PK) in nonclinical studies. Antipsychotic drugs that act by blocking D2 receptors or both the D2 and 5-HT2a receptors have been the mainstay of treatment for schizophrenia for many years. However, a substantial proportion of patients remain symptomatic due to lack of efficacy or poor tolerability. While treatment of patients with schizophrenia with D-serine has been reported to result in improvement of positive and negative symptoms and cognitive function, its development has been limited due to potential renal safety concerns. The in vitro binding and functional activity of CTP-692 are nearly identical to those of D-serine at the NMDA receptor. In rats, administration of high doses of CTP-692 did not cause increased serum creatinine and blood urea nitrogen levels, indicative of renal toxicity, as is observed with non-deuterated D-serine. The CTP-692 early clinical development program characterized the single-and multiple-dose plasma PK and safety profile to guide dose selection in subsequent efficacy studies in patients with schizophrenia. In the single ascending dose (SAD) study, healthy subjects were administered 0.5, 1, 2, 3, or 4 g of CTP-692 or placebo, once-daily, in a double-blind design. Following the completion of the SAD study, the multiple-ascending dose (MAD) study was conducted in which healthy subjects were administered 1, 2, or 4 g of CTP-692 or placebo, once-daily, in a double-blind design for 7 consecutive days. Blood samples for PK analysis were obtained at several time points after dose administration. Safety assessments in the SAD and MAD studies included monitoring of adverse events, ECGs, and clinical laboratory testing including monitoring of kidney function. CTP-692 was well-tolerated in both the studies. The most common treatment-emergent adverse event was headache, with no dose-related trends. All adverse events were mild to moderate in severity and recovered/resolved by the end of each study. Serum and urine kidney function parameters remained within the normal range in both studies and there were no clinically significant CTP-692-related effects on other clinical laboratory parameters. CTP-692 had a well-defined PK profile with low inter-individual variability. The CTP-692 dose-exposure relationship was linear following single and multiple doses (at Day 7). The terminal half-life of CTP-692 was approximately 19 hours which enables once-daily dose administration. Accumulation of CTP-692 was minimal to modest following 7 consecutive days of administration. Based on the results of the Phase 1 studies, once-daily CTP-692 doses of 1, 2, and 4 g are being evaluated in an ongoing double-blind, placebo-controlled Phase 2 study to evaluate the safety and efficacy of CTP-692 as an adjunctive treatment in adult patients with schizophrenia with a novel mechanism of action.

S27. ABUSE POTENTIAL CONSIDERATIONS FOR LEMBOREXANT, A DUAL OREXIN RECEPTOR ANTAGONIST FOR THE TREATMENT OF INSOMNIA

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Abstract: Introduction: GABAergic sleep-promoting drugs (benzodiazepines, non-benzodiazepine z-drugs) are associated with abuse liability (Atkin et al, 2018). As required for registration purposes for treating patients with insomnia, the dual orexin receptor antagonist, lemborexant (LEM) (Rosenberg et al, 2019), recently approved in the US and Japan for treating insomnia, was assessed for abuse potential per US FDA guidelines.

Methods: LEM abuse potential was evaluated via multiple components including assessments of binding affinity for brain receptors linked to abuse; ease of manipulation for non-approved consumption; nonclinical dependence and drug discrimination studies; adverse events (AEs) in the Phase 3 program indicative of abuse potential by others; evidence of abuse/diversion in the clinical studies; and abuse data from other drugs with the same mechanism of action. A Phase 1 human abuse potential study (NCT03158025; E2006-A001-103), which enrolled healthy, nondependent, recreational sedative users, was also conducted. Data from the Phase 3 clinical program assessing efficacy and safety of LEM 5mg (LEM5) and 10mg (LEM10) vs placebo (PBO) (SUNRISE-1 [NCT02783729; E2006-G000-304], SUNRISE-2 [NCT02952820; E2006-G000-303]), were pooled to assess abuse-related treatment emergent AEs (TEAEs).

Results: LEM binds selectively to orexin-1 and -2 receptors, with no off-target binding to GABAergic, opioid or DA receptors. Tablets were not readily manipulated for alternate administration methods (i.e. intravenous).

Nonclinical studies included physical-dependence and drug discrimination studies in SD rats and a self-administration study in rhesus monkeys. Plasma concentrations in animals in these studies were ≥2.7 fold the Cmax (61.6ng/mL) at the proposed highest dose for insomnia treatment (LEM10). Neither physical dependence nor reinforcement occurred, suggesting no abuse potential. LEM did not generalize to zolpidem (ZOL) in a discrimination study conducted in rats trained with ZOL.

Clinical studies did not show evidence for LEM abuse or diversion. The most common TEAEs (≥2% in LEM5 or LEM10) related to abuse potential were somnolence, fatigue, and dizziness; no euphoria was reported.

In the Phase 3 pool, somnolence drove the higher incidence of TEAEs related to abuse potential (LEM5, 15.3%; LEM10, 18.3%) vs PBO (7.2%). Excluding somnolence, TEAEs linked to abuse potential were similar for PBO and LEM groups (based on pooled analysis of all subjects with sleep disorders in the development program). Adjusted by duration of exposure, for PBO, LEM5 and LEM10, incidence (subjects/patient-y) of TEAEs related to abuse potential between groups was 0.2, 0.3, and 0.4; rates (events/patient-y) of TEAEs related to abuse potential were 0.3, 0.5, and 0.6.

The primary objective of the Phase 1 study was to assess abuse potential of LEM vs PBO and 2 active comparators (ZOL immediate release [30mg]; suvorexant [40mg; SUV40]), in nondependent, recreational sedative users able to differentiate and express sufficient drug liking for ZOL and SUV40 vs PBO during a qualification period. Administering LEM elicited higher "at this moment" positive subjective and global drug effects and higher hypothetical subjective street drug value vs PBO, but not vs ZOL or SUV. All LEM doses (LEM10, LEM20, LEM30) had similar abuse potential profiles.

Conclusion: These data support that LEM is unlikely to result in significant risk to public health from drug abuse.

SUPPORT: Eisai Inc.

S28. BENEFIT-RISK ASSESSMENT OF ESKETAMINE NASAL SPRAY VERSUS PLACEBO IN TREATMENT-RESISTANT DEPRESSION

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Abstract: Background: Effective treatment of major depressive disorder (MDD) remains a challenge despite the availability of numerous oral antidepressants (AD). Up to one-third of patients with MDD show an inadequate response to medications and are considered "treatment-resistant" (TRD). Esketamine, the S-enantiomer of ketamine, provides a novel mechanism of action and was approved by the U.S. Food & Drug Administration and European Medicines Agency for TRD in conjunction with an oral antidepressant. In phase 3 studies, esketamine treatment provided evidence of efficacy, safety and sustainability of effect.

Methods: A structured benefit-risk assessment of esketamine for TRD was conducted to quantitatively assess the treatment benefits versus risks of esketamine+AD compared to placebo nasal spray+AD, using double-blind data from three phase 3 short-term induction studies (TRANSFORM-1, TRANSFORM-2, and TRANSFORM-3) and one maintenance study (SUSTAIN-1).

To assess clinically meaningful improvements, benefits were proportion of remitters (MADRS total score <12) or responders (MADRS total score reduction >50%) at the end of the double-blind phase (4 weeks) in the induction studies and proportion of stable remitters or stable responders who remained relapse-free in the maintenance study. The assessed risks were death, suicidal ideation, and the most common adverse events (AEs), defined as ≥10% incidence and greater frequency for esketamine+AD than AD+placebo. These AEs included dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoesthesia, blood pressure increase, anxiety, and vomiting. Additionally, potential risks of long-term cognitive impairment and interstitial cystitis were assessed based on data from the ketamine abuse literature.

Results: Depression improvement was observed as early as 24 hours with esketamine+AD. Per 100 patients on esketamine+AD vs. AD+placebo, 14-17 additional patients would achieve response and 5-21 additional patients would achieve remission of depressive symptoms after 4 weeks of treatment. In maintenance therapy, 19-32 fewer relapses would occur with esketamine.

The overall rates of serious or severe common AEs and those leading to discontinuation were higher in the esketamine+AD group for TRANSFORM-1 and TRANSFORM-2. Per 100 patients, esketamine+AD treatment vs. AD+placebo resulted in 2.6 more discontinuations due to a common AE, and 8.4 (95% CI: 4.1, 12.6) more serious or severe common AEs. These events were mainly dissociation, vertigo and dizziness. Treatment differences per 100 patients for serious or severe common AEs that occurred and resolved on the day of dosing, typically within two hours of dosing,

while patients are under medical supervision, was 8.9 (95% CI: 5.3; 12.4), those that occurred on a day of dosing and resolved on a different day was 0.7, and those that occurred on a non-dosing day was -0.8. There were no cases of interstitial cystitis or differences in cognition between treatments.

Discussion: In patients with TRD, clinical studies of esketamine+AD, as induction and maintenance treatment, demonstrate the rapid, robust and sustained efficacy over oral AD+placebo. Self-limiting, transient adverse effects are likely to occur within 2 hours of dosing while patients are under medical supervision. Taken together, the evidence supports a positive benefit-risk balance for esketamine in combination with a newly initiated oral AD as a novel therapeutic option for this difficult to treat condition of TRD.

S29. EFFECTS OF SEP-363856 ON NEGATIVE SYMPTOMS IN SCHIZOPHRENIA: ANALYSIS OF AN ACUTE, PLACEBO-CONTROLLED TRIAL OF A NOVEL PSYCHOTROPIC AGENT WITHOUT DOPAMINE D2 RECEPTOR OCCUPANCY

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Abstract: Background: SEP-363856 is a novel psychotropic agent without dopamine D2 receptor occupancy that has demonstrated efficacy in animal models of psychosis. Although its mechanism of action has not been fully elucidated, preclinical data suggest that agonism at trace amine receptor 1 (TAAR1) and the serotonin 5-H1A receptor contributes to its efficacy. In a previous double-blind (DB), placebo-controlled study, SEP-363856 demonstrated significant efficacy in the treatment of patients with an acute exacerbation of schizophrenia. We now present results of a secondary analysis of this study that examines the effects of SEP-363856 on negative symptoms in schizophrenia, and a post-hoc analysis that examines the specificity of its effects in patients with prominent negative symptoms at pre-treatment baseline.

Methods: Patients with an acute exacerbation of schizophrenia were randomized, double-blind, to 4-weeks of flexible-dose treatment with SEP-363856 (n=120) given once daily (50 or 75 mg) or placebo (n=125). Prespecified efficacy measures included the PANSS total score, the Brief Negative Symptom Scale (BNSS) total score, and the Uncorrelated PANSS Score Matrix (UPSM) transformation of the PANSS scale comprising UPSM-PANSS negative-apathy/avolition (UPSM-NAA) and negative-deficit of expression (UPSM-DE) factors. The UPSM-PANSS transformation has been previously validated (Hopkins et al., Schizophr Bull. 2018;44:593-602), and has been shown to reduce the between-PANSS-factor correlations across a wide variety of clinical trials in schizophrenia. In addition, the effect of SEP-363856 was studied in the patient type defined by prominent severity of UPSM-PANSS negative symptom factors at baseline.

Results: The primary analysis showed significant week 4 improvement in LS mean PANSS total score for SEP-363856 vs. placebo at week 4 (-17.2 vs. -9.7; p=0.001; effect size [ES] = 0.45). Treatment with SEP-363856 (vs. placebo) showed week 4 improvement in negative symptoms as assessed by the BNSS total score (ES, 0.49), and BNSS subscale scores for blunted affect (ES, 0.51), avolition (ES, 0.42), anhedonia (ES, 0.39), asociality (ES, 0.47), alogia (ES, 0.32), and

distress (ES, 0.13); as well as for the UPSM-DE (ES, 0.32) and UPSM-AA (ES, 0.32). A higher correlation was noted between the UPSM-PANSS positive symptom factor score and the BNSS total score (0.319), while a lower correlation was noted between the UPSM-PANSS positive factor score and the UPSM-DE and UPSM-NAA factors (-0.050 and 0.143, respectively). This suggests that the BNSS total score is a less specific measure of negative symptoms than the UPSM-DE or UPSM-NAA. In an exploratory analysis of patients with UPSM-defined prominent negative symptoms at baseline (n=51), treatment with SEP-363856 was associated with greater improvement in negative symptom measures compared to the improvement observed for lurasidone in a pooled benchmark sample (n=1710) of 5 placebo-controlled trials.

Conclusion: SEP-363856 demonstrated improvements relative to placebo on PANSS total, BNSS total and UPSM-transformed negative symptom scores, and in patients with UPSM-prominent negative symptoms at baseline, consistent with the hypothesis that SEP-363856 has a specific effect on negative symptoms, uncorrelated with improvement in positive symptoms. The potential specific effects on negative symptoms of SEP-363856, a novel psychotropic agent without dopamine D2 receptor occupancy, will need to be confirmed in future controlled studies.

ClinicalTrials.gov Identifier: NCT01969382

Supported by funding from Sunovion Pharmaceuticals, Inc.

S30. THE VIRTUAL REALITY FUNCTIONAL CAPACITY ASSESSMENT TOOL (VRFCAT): A PROGRESS REPORT ON ITS DEVELOPMENT IN THE FDA CLINICAL OUTCOME ASSESSMENT QUALIFICATION PROGRAM

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Abstract: Introduction: In regulatory trials of cognitive enhancement in schizophrenia, the FDA requires drug developers to demonstrate the functional relevance of any improvements with a co-primary measure of functional capacity. The Virtual Reality Functional Capacity Assessment Tool (VRFCAT) is a computerized measure that requires subjects to complete tasks of daily living using a realistic, simulated environment. The FDA recently accepted the VRFCAT into its Clinical Outcome Assessment (COA) Qualification Program as a co-primary measure of functional capacity in schizophrenia. This program qualifies COAs that can be relied on to have a specific interpretation and application in any drug development program and regulatory review. This presentation describes data supporting the successful application for the VRFCAT to enter into the FDA COA Qualification Program, as well as progress towards producing a final qualification package.

Methods: The VRFCAT is a digital performance-based outcome measure that assesses the ability to prepare a meal, shop, use transportation, and handle money, four of the key functional outcome challenges in schizophrenia. Following a series of early method development studies, data were collected in a large (N=334) psychometric and validation study of the VRFCAT in primarily

chronically ill patients with schizophrenia and healthy controls that assessed cognition with the MATRICS battery (MCCB) and functional capacity with the UCSD Performance-based Skills Assessment (UPSA). More recently, complementary data were collected in a study of 55 patients with recent-onset psychosis and matched controls conducted at UCLA.
Results: In the large study of primarily chronically ill patients, the VRFCAT demonstrated high sensitivity to impairment in patients vs. healthy controls (d=1.2), high test-retest reliability (ICC=0.81), no practice effects (d=-0.04 compared to d = 0.35 for the UPSA), and large correlations with the UPSA (r=−0.56) and MCCB (r=−0.57). Similar results were found in early phase patients, including a large patient vs. control difference (d = .82) and large correlations with the UPSA (r = -0.66) and MCCB (r = .70), as well as strong correlations with real-world role (r = -.52) and social (r= -0.41) functioning. The VRFCAT was also found to have low burden from the perspectives of patients and testers.
Conclusion: The VRFCAT demonstrates a wide range of good psychometric characteristics, convergent validity, and practical strengths in early and late phases of schizophrenia that supported its acceptance into the FDA COA Qualification Program. The FDA requires additional data analyses and further data collection to support a full qualification package. Our current data analytic activities include evaluating the latent structure and treatment sensitivity of the VRFCAT. We also recently received an FDA grant to collect new qualitative evidence to confirm the content validity of the VRFCAT. We are now conducting semi-structured interviews with patients, family members, and peer support specialists to determine whether they view the VRFCAT as important and meaningful for independent functioning.

S31. EFFECT OF LEMBOREXANT TREATMENT ON INSOMNIA DISEASE SEVERITY AND FATIGUE ACROSS 12 MONTHS IN SUNRISE-2

ABSTRACT NOT INCLUDED

S32. CHART EXTRACTION/CLINICIAN SURVEY SHOWS SYMPTOM IMPACT AND FAVORABLE TREATMENT OUTCOMES WITH VMAT2 INHIBITORS IN PATIENTS WITH TARDIVE DYSKINESIA

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Abstract: Background: Tardive dyskinesia (TD) is a persistent and potentially disabling movement disorder associated with prolonged exposure to dopamine receptor blocking agents such as antipsychotics. Based on evidence from clinical trials, approved vesicular monoamine transporter 2 (VMAT2) inhibitors (e.g., valbenazine) are currently recommended as first-line therapies for TD. Data based on real-world experience with these drugs are now available.
Objective: To describe symptom impact and treatment outcomes in patients prescribed VMAT2 inhibitors for the treatment of TD.

Methods: From July 24 to August 30, 2019, clinicians who prescribed a VMAT2 inhibitor within the past 24 months were invited to complete a survey and provide 1-10 patient charts for data

extraction. The survey included questions regarding TD symptomatology and impact, psychiatric condition (primary and comorbid), and treatment outcomes. Data extracted from patients' charts included demographics, treatment with a VMAT2 inhibitor (valbenazine, deutetrabenazine, tetrabenazine), antipsychotic treatment, and any documented outcomes.

Results: Data for 601 adult TD patients were provided by 163 clinicians (113 psychiatrists; 46 neurologists; 4 primary care physicians). 50% of patients were male; mean age was 50.6 years. Although a majority of patients were taking an antipsychotic for schizophrenia (32%) or schizoaffective disorder (23%), many patients with bipolar disorder (29%) or major depressive disorder (11%) were also treated with an antipsychotic. Psychiatric comorbidities included anxiety (33%), depressive symptoms (28%), and substance abuse (18%). TD symptoms were most frequently found in the head/face/mouth region (82%), followed by upper extremities (42%), trunk (26%), and lower extremities (18%). Almost 50% of patients had TD symptoms in >1 body region: two (32%), three (11%), four (4%). More than 70% of patients reported negative functional impacts on socializing (33% "significantly impacted", 51% "somewhat impacted"), engagement with family/friends (25%, 52%), engagement in outside functions (26%, 47%), and speech/communication (23%, 48%). Valbenazine was the more commonly used (69%) VMAT2 inhibitor, and TD improvement with a VMAT2 inhibitor was reported in 540 (90%) patients; most of these patients also had functional improvements in ≥1 area. Among patients with TD improvement, 374 (69%) had "much" or "significant" improvement in their psychiatric condition.

Conclusions: In this real-world sample of patients, TD had negative impacts on >70% of survey respondents. VMAT2 inhibitors were effective in improving TD symptoms and these TD-related impacts, which additionally coincided with improved psychiatric conditions. Clinicians, payers, and professional organizations should consider the symptoms, functional impacts, and treatment outcomes when evaluating TD therapy access and continuation.

S33. PROJECT STARR 911: A MODEL FOR RESEARCHERS TO ENGAGE IN SUICIDE PREVENTION

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Abstract: Objective: A strong link exists between mental illness and suicide. Up to 20% of individuals with a diagnosis of mental illness die by suicide.1 Approximately 90% of those who complete suicide experience mental illness.2 People considering suicide usually seek help: approximately 64% of individuals who attempt suicide visit a doctor within a month before their attempt.3 Having a chronic condition increases the odds of suicide by 363%. Clinical research call centers field thousands of calls on a yearly basis. The purpose of project STARR 911 is to build collaboration between clinical research and suicide prevention. The first step is to identify current

practices. We surveyed clinical research sites to identify current practices for recognizing and taking action for callers who report suicidal ideation.

Results: Preliminary results indicated that some clinical research sites have scripts for their call centers and suicide hotline information readily available. It was generally agreed that national experts in suicide prevention are preferred referral sources over local resources that can be variable in accessibility and quality. Script suggestions included asking about intent to act and to determine how long the caller has felt suicidal, to determine the acuity. Creating a designated 'warm' line for call centers. In response to the limited process identified, Project 911 will identify intervention resources that could be provided to callers. A short script and best practices for recognition and de-escalation, and a brief training program that could be made widely available and implemented, will be developed. For example, a suicide prevention program can be disseminated at investigator meetings. A tracking system to record number of successful referrals or 'warm' hand-offs to suicide prevention specialists will be implemented, if possible.

Conclusions: Research can be a part of the solution to suicide prevention. Potential suicidal ideation or behavior can be identified through clinical research call centers and referred to national suicide prevention experts in a systematic way for broad-reaching impact.

S34. QUALITATIVE CLINICAL TRIAL EXIT INTERVIEWS EVALUATING TREATMENT BENEFIT, BURDEN, AND SATISFACTION IN PATIENTS WITH SCHIZOPHRENIA

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Abstract: Background: An open-label extension study (NCT02873208) evaluated the long-term tolerability, safety, and efficacy of combination olanzapine/samidorphan (OLZ/SAM) treatment in patients with schizophrenia. This qualitative substudy explored perceptions of benefit, burden, and satisfaction with previous medications and OLZ/SAM.

Methods: Semi-structured interviews (≈60 minutes; audio-recorded) were conducted. Interviewer sensitivity training, senior interviewer oversight, and a list of common medications to aid recall supported data collection. Interview transcripts were content coded and analyzed (NVivo v11.0).

Results: All 41 patients reported a lifetime burden with schizophrenia adversely impacting employment, relationships, emotional health, social activities, and daily tasks. Hospitalization for schizophrenia management was another reported aspect of disease burden. Although most (n=32) patients reported previous medication benefits, side effects affecting physical, emotional/behavioral, and cognitive functioning were reported by all (n=41). Following OLZ/SAM treatment, 39/41 patients (95%) reported improvements in symptoms including hallucinations, paranoia, depression, sleep, and concentration. Furthermore, patients described improvements in self-esteem, social activities, relationships, and daily activities. Twenty-three patients (56%) reported side effects attributed to OLZ/SAM; lack of energy (n=12 [29%]) and dry

mouth (n=5 [12%]) were most common. Twenty-four (59%) patients were "very satisfied" with OLZ/SAM; most (n=35 [85%]) preferred to continue OLZ/SAM vs switching to another medication. As most substudy patients (n=40; 98%) completed the extension study, satisfied patients may be overrepresented in this analysis.

Conclusion: This qualitative interview approach provided valuable insight into patients' experiences with previous medications and OLZ/SAM. Overall, most patients reported treatment satisfaction and improvements in symptoms, function, and health-related quality of life with OLZ/SAM.

S35. SAFETY AND EFFECTIVENESS OF SEP-363856 IN SCHIZOPHRENIA: RESULTS OF A 6-MONTH, OPEN-LABEL EXTENSION STUDY

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Abstract: Background: SEP-363856 is a novel psychotropic agent without dopamine D2 receptor occupancy that has demonstrated efficacy in animal models of psychosis. Although its mechanism of action has not been fully elucidated, preclinical data suggest that agonism at trace amine receptor 1 (TAAR1) and the serotonin 5-H1A receptor contributes to its efficacy. In a previous double-blind (DB), placebo-controlled study, SEP-363856 demonstrated significant efficacy in the treatment of an acute exacerbation of schizophrenia. We now present results of a 6-month extension of the acute study whose aim was to evaluate the safety and effectiveness of longer-term treatment with SEP-363856.

Methods: Patients with an acute exacerbation of schizophrenia who completed a 4-week, DB, placebo-controlled, flexible-dose (50 or 75 mg) study of SEP-363856 were given the option to enroll in an extension study in which they were treated, open-label (OL), with flexible doses (25/50/75 mg/d) of SEP-363856 for 26 weeks. The primary outcomes were safety measures; effectiveness outcomes were secondary and included the PANSS total score and the Brief Negative Symptom Scale (BNSS) total score.

Results: Altogether, 193 patients (78.8%) completed the 4-week DB study, and 156 (80.8%) entered the OL extension study and received at least one dose of SEP-363856 (safety population). The study completer rate was 67.3%; reasons for discontinuation consisted of adverse event (AE; 11.5%), withdrawal of consent (10.2%), lack of efficacy (5.1%), and other reasons (6.4%). Fifteen patients experienced a serious AE: schizophrenia (n=11), depression, psychotic disorder, uterine hemorrhage (n=1 each), and one patient had acute psychosis and suicidal ideation; there were no deaths in the study. Individual AEs with an incidence ≥2% were schizophrenia (12.2%), headache (11.5%), insomnia (8.3%), anxiety (5.1%), somnolence (4.5%), nasopharyngitis (4.5%), nausea (3.8%), irritability (3.2%), influenza (3.2%), weight decrease (3.2%), and prolactin increase (2.6%). On movement scales, minimal mean change from OL-baseline to Week 26 occurred on the Barnes total score (-0.1), Abnormal Involuntary Movement Scale total score (0.0) and Simpson-Angus Scale score (-0.01). Mean month 6 change from DB baseline in weight was -0.3

kg. No clinically meaningful median changes were observed at week 26 in metabolic laboratory parameters (total and low density lipoprotein-cholesterol, triglycerides, hemoglobin A1c) or in prolactin levels. During 6 months of OL treatment, one patient had an increase in QTcF ≥60 msec and none had a QTcF interval ≥480 msec. SEP-363856 treatment was associated with significant improvement from OL baseline to week 26 in the PANSS total score (-22.6) and BNSS total score (-11.3).

Conclusion: Treatment with SEP-363856 was associated with continued, clinically-relevant improvement from open-label baseline in the PANSS total and BNSS total scores. The most frequently reported AEs (≥5%) were schizophrenia, headache, insomnia and anxiety. SEP-363856 had minimal effects on weight, lipids, glycemic indices, prolactin, and was associated with minimal risk of akathisia and extrapyramidal symptoms.

ClinicalTrials.gov Identifier: NCT02970929

Supported by funding from Sunovion Pharmaceuticals, Inc.

S36. LURASIDONE IN ADOLESCENTS WITH SCHIZOPHRENIA: REMISSION AND RECOVERY DURING 2 YEARS OF OPEN-LABEL TREATMENT

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Abstract: Background: Onset of psychotic symptoms occurs in adolescence in more than 20% of individuals with a diagnosis of schizophrenia. Compared with adult onset, early-onset schizophrenia occurs more commonly in males and is characterized by greater illness severity, chronicity and functional impairment, and a less favorable prognosis. In a previously reported double-blind, placebo-controlled, fixed-dose, 6-week trial, lurasidone (40 and 80 mg/d) demonstrated significant efficacy in the treatment of adolescents with schizophrenia.

Objectives: The aim of the current post-hoc analysis was to evaluate the proportion of adolescent patients with schizophrenia who achieved sustained remission and recovery during 2 years of treatment with lurasidone.

Methods: Patients aged 13-17 years with a DSM-IV-TR diagnosis of schizophrenia, and a Positive and Negative Symptom Scale (PANSS) total score ≥70 and <120, were randomized to 6 weeks of double-blind (DB), fixed-dose treatment with lurasidone (40 or 80 mg/d) or placebo. Patients who completed 6 weeks of DB treatment were eligible to enroll in a 2-year, open-label (OL), flexible dose extension study of lurasidone (40-80 mg/d). Efficacy measures included the PANSS total score and the Children's Global Assessment Scale (CGAS). The criterion for response was ≥20% reduction from DB baseline in PANSS total score. Criteria for remission, and sustained remission, were the consensus criteria summarized by Andreasen et al. (Am J Psychiatry. 2005;162:441-9). Criteria for recovery consisted of meeting remission criteria plus having a CGAS score ≥70 with consensus 6-month criteria indicating no clinically significant functional impairment at that visit.

Results: A total of 271 patients completed the 6-week DB study and entered the extension study, and 186 (68.6%) and 156 (57.6%) completed 52 weeks and 104 weeks of treatment, respectively.

For patients who entered the OL extension phase, mean change from DB to OL baseline in PANSS total score was -17.5; and mean change from DB baseline in the PANSS total score in the OL phase at weeks 52 and 104 was -32.4 and -34.3, respectively. Responder rates (20% reduction from DB baseline) at OL baseline, weeks 52 and 104 were 63.1%, 92.1% and 91.0%, respectively. During OL treatment with lurasidone (n=271 patients), a total of 143 patients (52.8%) met sustained remission criteria, and the Kaplan-Meier estimate of the median time to earliest sustained remission was 64.1 weeks (95%-CI, (40.4, 76.1) weeks) in the OL treatment period; a total of 78 (28.8%) subjects met sustained recovery criteria, and the Kaplan-Meier estimate of the median time to earliest sustained recovery was 104.6 weeks.

Conclusions: For adolescents with schizophrenia, treatment with lurasidone was associated with continued improvement in psychotic symptoms, resulting in high rates of sustained remission and recovery over a two-year period.

Clinicaltrials.gov identifier: NCT01914393.

Supported by funding from Sunovion Pharmaceuticals, Inc.

S37. A POOLED ANALYSIS OF 4 PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDIES ASSESSING EFFICACY OF SPN-812 (VILOXAZINE EXTENDED RELEASE) IN CHILDREN AND ADOLESCENTS WITH ADHD

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Abstract: Background: SPN-812 (viloxazine extended release) is a structurally distinct, bicyclic, Serotonin Norepinephrine Modulating Agent (SNMA) in development as a treatment for attention-deficit/hyperactivity disorder (ADHD) in children and adolescents. This pooled analysis of 4 Phase 3 studies evaluated the efficacy of once-daily 200 and 400 mg SPN-812 compared to placebo in children and adolescents ages 6-17 with ADHD.

Methods: The results of 4 Phase 3 trials of SPN-812 (P301, P302, P303, P304; described elsewhere), which were designed to evaluate the safety and efficacy of SPN-812 at 100, 200, 400 and 600 mg/day, were pooled to assess the primary and secondary endpoints across studies and doses. The primary endpoint of these studies was change from baseline (CFB) at week 6 in ADHD Rating Scale-5 (ADHD RS-5) Total Score. The key secondary endpoint was CFB at week 6 in Clinical Global Impression-Improvement (CGI-I). Other secondary endpoints included the CFB at week 6 in the ADHD RS-5 Hyperactivity/Impulsivity and Inattention subscales. To ensure consistency of the analyses of the pooled data with those from the individual study, Analysis Data Model (ADaM) datasets for the individual studies were combined into integrated datasets. Two analysis pools were formed to compare placebo to either 200 mg SPN-812 (Pool 200; placebo: n= 356; 200 mg SPN-812: n=359) or 400 mg SPN-812 (Pool 400; placebo: n=297; 400 mg SPN-812:

n=299). The Mixed Models Repeated Measures (MMRM) and Analysis of Covariance (ANCOVA) were used to analyze these primary and secondary endpoints.

Results: Compared to placebo, a significantly greater improvement in ADHD-RS-5 Total Score was observed with 200 and 400 mg SPN-812 beginning at week 1 ($p=0.0004$ and $p=0.0023$, respectively), which was maintained through week 6 ($p<0.0001$ and $p<0.0001$, respectively). The CFB in both the ADHD RS-5 Hyperactivity/Impulsivity subscale scores was significantly improved with 200 and 400 mg SPN-812 at week 1 ($p<0.0001$ and $p=0.0017$, respectively) and at week 6 ($p<0.0001$ and $p=0.0001$, respectively). A similar improvement with 200 and 400 mg SPN-812 was found in the Inattention subscale at week 1 ($p<0.0189$ and $p=0.0151$, respectively) and at week 6 ($p<0.0001$ and $p=0.0001$, respectively). Significant improvement in CGI-I was also seen at week 6 for both 200 and 400 mg SPN-812 ($p<0.0001$ and $p<0.0001$, respectively) compared to placebo.

Conclusions: This pooled analysis evaluating the efficacy of SPN-812 at 200 and 400 mg confirms that this drug is effective in reducing ADHD symptoms with an onset of action that can be measured as early as week 1 of treatment. Improvement in the CGI-I score also indicates that the effects of SPN-812 in treating ADHD are clinically relevant. Together, these data suggest that SPN-812 is a viable candidate for the treatment of ADHD in children and adolescents. SPN-812 is currently being evaluated by FDA for approval.

S38. CLOZAPINE UTILIZATION AT THE VETERANS HEALTH ADMINISTRATION

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Abstract: Introduction: Clozapine has superior efficacy for treatment resistance schizophrenia and is the only pharmacological agent with an FDA indication for reducing suicidal behaviors, yet prescribing rates remain low. The suggested prescribing rate of clozapine to persons with schizophrenia is 20%, however, utilization in the United States has been reported to be between 2.5-5%. In the Veteran's Health Administration (VHA), clozapine utilization rates vary significantly amongst VHA facilities, and further information on clozapine prescribing at VHA is needed. The purpose of this study was twofold: first to identify the clozapine utilization rate in the VHA; and second, to identify patient characteristics and correlates of utilization to garner a better understanding of the VHA-treated clozapine population.

Methods: A longitudinal retrospective cohort analysis was conducted on a sample consisting of all OEF/OIF Veterans treated at VHA from 2006-2016. Data was obtained from the VA Informatics and Computing Infrastructure (VINCI) and VA Corporate Data Warehouse (CDW). A sub-cohort consisting of all individuals with VHA-filled clozapine prescriptions was used for analyses. Patient characteristics, prescribing patterns, and correlates of clozapine use were analyzed. Acute

use of clozapine vs. clozapine maintenance was examined in relation to hospitalizations and mortality. Descriptive and inferential analyses were conducted.

Results: The initial cohort identified 1,316,531 OEF/OIF Veterans who received treatment at VHA during our study period, of which 15,416 (1.17%) had diagnoses of schizophrenic illness. A total of 22,454 clozapine orders were filled by 87 VA facilities. 197 Veterans received outpatient clozapine prescriptions through VHA; a clozapine utilization rate of 1.28%. The mean age of the cohort was 31.54 years, and the majority of patients were white (72.41%) and male (91.37%). 174 (88.32%) of the individuals prescribed clozapine had a diagnosis of schizophrenia-spectrum disorder illness and the most common co-occurring mental health diagnoses were anxiety disorders (57.87%), substance use disorders (56.85%), and depressive disorders (75.63%). Median days on outpatient clozapine was 305. Median number of antipsychotic medication trials was 12, with a median rank of clozapine being the 8th antipsychotic trialed. The majority (59.90%) of individuals had at least one period of maintenance clozapine treatment (defined as >180 days of consecutive treatment). The median number of psychiatric hospitalizations was four, and clozapine rank was strongly associated with number of psychiatric hospitalizations. There were 14 deaths in the cohort. There were no associations between acute versus maintenance clozapine use and either hospitalizations or mortality.

Conclusions: The identified clozapine utilization rate of 1.28% is very low relative to suggested prescribing rates. Although clozapine rank was strongly associated with number of psychiatric hospitalizations, suggesting that earlier clozapine intervention may decrease hospitalizations, there were no associations observed between acute versus maintenance clozapine use and either psychiatric hospitalizations or all-cause mortality; findings which may be explained by our limited sample size and low number of mortalities. Further studies examining clozapine use at VHA, such as a study examining current versus former clozapine users and mortality, should be conducted.

S39. GENDER DIFFERENCES IN THE RECEIPT OF PSYCHOPHARMACOLOGICAL TREATMENT AMONG WORKING-AGE RESIDENTS WITH SCHIZOPHRENIA IN U.S. NURSING HOMES

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Abstract: Introduction: The past decade has seen increases in the prevalence of schizophrenia and in the proportion of working-age (22-64 years) in U.S. nursing homes (NHs).[1] NHs may be inappropriately substituted for community-based services or specialized psychiatric care. Moreover, gender differences have been observed in the onset of schizophrenia, presentations of psychotic symptoms, and the use of psychopharmacological treatment.[2] Information on the clinical characteristics of working-age NH residents with schizophrenia and the association between gender and receipt of psychotherapeutic treatment among these residents is scarce. This study aimed to 1) describe the sociodemographic and clinical characteristics of working-age NH residents with schizophrenia at NH admission and 2) examine the association between gender and receipt of psychopharmacological treatment for these residents.

Method: The Minimum Data Set (MDS) 3.0 is a comprehensive assessment of residents in all Medicaid/Medicare-certified NHs. We used MDS 3.0 from 2012-16 to identify working-age adults with schizophrenia at NH admission, which was defined as having an active diagnosis or an ICD-9 (295-295.95) or ICD-10 (F20.0-F20.9; F25.1-F25.9) code of schizophrenia in the admission assessment. Separate logistic regression models using generalized estimation equations to adjust for both the clustering of residents in the same NH and in the same state were constructed to examine the association between gender and 1) receipt of antipsychotics (vs. no antipsychotics) and 2) receipt of both antipsychotics and antidepressants (vs. only antipsychotics) in the 7 days before admission assessment. Covariates included in the models were demographics, year of admission, demographics, comorbid psychiatric diagnoses [anxiety, depression, bipolar disorder, other psychosis, post-traumatic stress disorder (PTSD)], number of physical comorbidities [arthritis, diabetes, hypertension, cancer, stroke, congestive heart failure, asthma, pneumonia, hip/other factures, seizure, traumatic brain injury], limitations in activities of daily living (ADL), and cognitive impairment.

Result: We identified 109,920 working-age residents with schizophrenia at NH admission in 2012-16. Over half were 55-64 years old, 44% were women, 63% were non-Hispanic White, and 67% were never married. About 58% had more than one physical comorbidity, 53% experienced moderate to severe limitations in ADL, 23% had mild and 14% had moderate to severe cognitive impairment. The most common psychiatric comorbidity was depression (36%), followed by anxiety (28%) and bipolar disorder (22%). The prevalence of anxiety, depression, and bipolar disorder were higher in women than men. Antipsychotics were received by 84% of both women and men with schizophrenia. After adjusting for covariates, women were 7% more likely than men to receive antipsychotics [adjusted odds ratios (aOR): 1.07, 95% confidence interval (CI): 1.03-1.11]. Among the women who received antipsychotics, 56% also received antidepressants, which was 9% higher than men. Adjusting for covariates, women were 21% more likely than men to receive both antipsychotics and antidepressants than antipsychotics only (aOR: 1.21, 95% CI: 1.17-1.25).

Conclusion: Among newly admitted working-age people with schizophrenia, women were more likely than men to receive antipsychotics (vs. no antipsychotics) and among those receiving antipsychotics, to also receive antidepressants (versus antipsychotics alone). The extent to which gender differences remain in the trajectory of care management for schizophrenia during their NH stay warrants further study.

S40. PHARMACOKINETIC PROFILE OF ASENAPINE TRANSDERMAL SYSTEM HP-3070: THE FIRST ANTIPSYCHOTIC PATCH IN THE US

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Abstract: Background: Asenapine transdermal system HP-3070 (SECUADO®) was developed to effectively deliver asenapine. It is the first antipsychotic patch approved in the US for the treatment of adults with schizophrenia.

Objectives: To characterize the pharmacokinetic (PK) profile of HP-3070.

Methods: Three open-label, randomized, Phase 1 studies were designed to assess the relative bioavailability (BA) of HP-3070 vs sublingual (SL) asenapine (SAPHRIS®); single/multiple-dose PK and dose proportionality; effects of application sites and race on BA; and the effect of external heat on BA. Studies were conducted in healthy subjects with the exception of the multiple dose study which was performed in adults with schizophrenia.

Results: After HP-3070 administration, asenapine concentrations increased gradually over time. Asenapine total daily exposure (AUC) for HP-3070 was well-within the range of that of SL asenapine, whereas peak exposure (Cmax) was significantly lower. AUC of HP-3070 3.8 mg/24h and 7.6 mg/24h doses corresponded to SL asenapine 5 mg and 10 mg BID, respectively. Steady-state plasma concentrations for HP-3070 were achieved approximately 72h after the first application. HP-3070 exhibited low peak-trough fluctuations with a Cmax/Cmin ratio of 1.5. HP-3070 PK at steady-state is dose-proportional in the dose range of 3.8 mg/24 hours to 7.6 mg/24 hours following application. There is no effect on HP-3070 PK with regards to the application site (upper arm, upper back, abdomen, and hip area). The PK of HP-3070 was similar across ethnic groups studied. Direct exposure to external heat increased both the rate and extent of absorption.

Conclusion: Overall, HP-3070 exhibited a consistent, dose-dependent PK profile that was unaffected by site of administration or race. Based on AUC, HP-3070 3.8 mg/24h and 7.6 mg/24h correspond to 5 mg and 10 mg doses BID of SL asenapine, respectively. While AUC was similar to that of SL asenapine, HP-3070 PK exhibits a more predictable absorption profile and lower peak-trough fluctuations. Based on these preferable PK metrics, HP-3070 could address the PK challenges observed with SL asenapine. As the first and only transdermal antipsychotic available in the United States, HP-3070 provides a novel and potentially preferred treatment formulation for persons with schizophrenia.

S41. PHARMACOKINETIC RESULTS OF DOSE PROPORTIONALITY AND FOOD EFFECT STUDY OF A SUBLINGUAL FORMULATION OF CYCLOBENZAPRINE (CBP) HCL (TNX-102 SL)

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Abstract: Objective: TNX-102 SL (TNX) is a sublingual (SL) formulation of CBP, administered as 2 x 2.8 mg tablets, designed for bedtime dosing that is being developed for posttraumatic stress disorder (PTSD) and fibromyalgia (FM). Compared to immediate release and extended release formulations of oral CBP approved for treating muscle spasm, TNX provides transmucosal absorption, rapid systemic exposure, avoidance of first-pass metabolism, and lower exposure to long-lived active major metabolite, norcyclobenzaprine (nCBP)(unpublished). Approved oral CBP products have significant increases in absorption with food and changes in plasma drug levels. Food effects may add unpredictability for patients in terms of therapeutic benefits or side effects. This study evaluated the dose-proportionality of TNX 2.8 mg to 5.6 mg, and the food effect of TNX 5.6 mg.

Design: Sixteen healthy subjects, ages 18-65, were randomized in a 3-way crossover to receive a single dose of TNX 2.8 mg fasted, TNX 5.6 mg fasted, and TNX 5.6 mg fed using a standardized high-fat meal. Thirty-four serial plasma samples were taken up to 360 hours post-dose to compare pharmacokinetic (PK) parameters. CBP and nCBP plasma levels were determined by validated HPLC-MS/MS methods. Safety was assessed by adverse events (AEs), C-SSRS, physical exam, vital signs, ECGs, and laboratory parameters.

Results: Preliminary results show that following a single dose of TNX, the mean Cmax and AUC was 2.5 ng/mL and 64.5 h*ng/mL for CBP, and 0.6 ng/mL and 79.5 h*ng/mL for nCBP, respectively for 2.8 mg under fasting conditions; 5.1 ng/mL and 128.2 h*ng/mL for CBP, and 1.2 ng/mL and 158.2 h*ng/mL for nCBP, respectively for 5.6 mg under fasting conditions; 4.5 ng/mL and 133.2 h*ng/mL for CBP, and 1.1 ng/mL and 156.2 h*ng/mL for nCBP, respectively for 5.6 mg under fed conditions. The Tmax for 2.8 mg fasted, 5.6 mg fasted and 5.6 mg fed were 4.4 h, 4.2 h and 5.1 h for CBP and 61.3h, 62.9h and 61.9h for nCBP, respectively.

No unexpected AEs were observed. Most of the AEs reported were mild in severity and the majority of AEs resolved without treatment. The most frequent AEs reported in the TNX group were mild and transient oral administration site reactions, e.g. tongue or oral numbness.

Conclusion: TNX 2.8 mg and 5.6 mg were well tolerated in healthy subjects, consistent with prior studies of TNX at these doses. Based on the PK results, the rate and extent of absorption of CBP and nCBP increased in a dose-proportional manner from 2.8 mg to 5.6 mg for TNX. No food effect was observed for CBP or nCBP for TNX 5.6 mg. The absence of a food effect is consistent with transmucosal absorption after sublingual administration, and this is expected to provide more predictable plasma levels compared to oral swallowed forms of CBP.

Together, these data satisfy FDA requirements for the dose-proportionality and food effect assessments needed to support the New Drug Application submission for TNX as a treatment for PTSD and FM.

S42. 3-OH CYPROHEPTADINE FOR NIGHTMARES AND POSTTRAUMATIC STRESS DISORDER

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[1]*Private Practice*

Abstract: Harsch first published on the use of cyproheptadine (Periactin) for nightmares (Harsch HH. Cyproheptadine for recurrent nightmares, Am J Psychiatry 143 (11), 1491-2 Nov 1986). There is “a high prevalence of nightmares in a psychiatric population regardless of the primary diagnosis” (Swart et al. Prevalence of Nightmare Disorder in Psychiatric Outpatients, Psychother Psychosom 82 267-268, 2013). The prevalence was about 30%. However, “nightmares can only be classified as a nightmare disorder if they do not occur exclusively during the course of another mental disorder” or medical condition (DSM5). Michael Brophy found cyproheptadine useful in veterans with PTSD (Cyproheptadine for Combat Nightmares in Post-Traumatic Stress Disorder and Dream Anxiety Disorder, MH Brophy. Mil Med 156 (2), 100-1. Feb 1991). A decade later he participated with A National Center for PTSD in a randomized clinical trial with the Dallas VA

one of the two sites. This study involved standardized instruments for diagnosing PTSD, assessing combat exposure, and Nightmare frequency and severity. It was a double-blind study, a randomized clinical trial, an RCT. The result was negative (Posttraumatic Stress Disorder and Sleep Difficulty by S Jacobs-Rebhun, P P Schnurr, M J Friedman, R Peck, M Brophy, D Fuller, Am J Psychiatry 157 (9), 1525-6. Sep 2000). The statistician, Paula P Schnurr, said that a power statistic could have been derived for the Dallas site predicting a positive result with a higher number of patients. Around fifteen had participated at the Dallas site but the site with a larger number of patients in the Northeast was negative. This was an add-on study, in which cyproheptadine was added on to previous medication for the treatment of PTSD and major depression. At the site in Dallas, trazodone was by far the most common co-administered drug whereas in the Northeast amitriptyline plus other sedative and anxiolytic drugs were used. The co-administered medication, amitriptyline, used at the negative site which use was "suggested against" in the latest VA/ DOD clinical practice guideline. It 'is one of the most potent antihistamines known' (Richelson E. Tricyclic antidepressants and histamine H1 receptors. Mayo Clin Proc. 1979; 54:669–674).

After the negative randomized clinical trial (RCT), Cyproheptadine did not appear as recommended for nightmares in any future treatment recommendations for PTSD or nightmares (VA/ DOD clinical practice guideline for the management of post-traumatic stress disorder and acute stress disorder, June 2017). Nor did cyproheptadine or any metabolites appear as potentially relevant in the future, Gieselmann A, Ait Aoudia M, Carr M, et al. Aetiology and treatment of nightmare disorder: State of the art and future perspectives. J Sleep Res. 28 (4), Aug 2019).

MJ Friedman, the most distinguished co-author of the negative RCT and editor of the Journal of traumatic stress, suggested in a subsequent publication "Future pharmacotherapy for post-traumatic prevention and treatment" (Psychiatr. Clin. North Am. 25: 427 - 441, 2002) "It can be expected in the future greater efficacy may be achieved with more selective serotonergic agents (such as postsynaptic 5-HT1a agonists)." Dr. Brophy showed that the binding of cyproheptadine and 3-OH occurred in nanomolar amounts with the 3 hydroxy cyproheptadine binding more readily(http://3-ohcyproheptadine.blogspot.com/). In "human metabolism of cyproheptadine," C.C. Porter et al. reported that the second most common metabolite was 3 hydroxy cyproheptadine.

I claim the following:

1. 3 hydroxy cyproheptadine will be effective as a drug method for treating nightmares and at a dose of 0.5 to 18 mg at bedtime.

S43. LITHIUM THERAPY AND ITS CLINICAL CORRELATES IN PATIENTS WITH BIPOLAR DISORDER

ABSTRACT NOT INCLUDED

S44. REAL-WORLD EVALUATION OF PATIENT CHARACTERISTICS AND DISEASE MANAGEMENT IN LONG-TERM VALBENAZINE TREATMENT IN ADULTS WITH TARDIVE DYSKINESIA

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Abstract: Objectives: Tardive dyskinesia (TD) is a persistent and often disabling involuntary movement disorder that is associated with long-term exposure to dopamine receptor blocking agents (DRBAs) such as antipsychotics. The long-term efficacy of INGREZZA® (valbenazine) capsules, which was approved in 2017 for treating TD in adults, has been demonstrated in several prospective clinical trials. This multi-center, retrospective chart review will assess the clinical characteristics and overall disease management of adult patients receiving long-term valbenazine treatment for TD in a real-world setting.

Methods: Data from up to 150 patient charts (at 15-20 US clinical sites) will be extracted and entered into a validated electronic data capture (EDC) system. Adult patients (≥18 years) with a clinical diagnosis of DRBA-induced TD and ≥6 consecutive months of valbenazine treatment will be included. Data will be abstracted starting from one month prior to valbenazine initiation, or if applicable, from the last clinical visit prior to initial valbenazine prescription up to the date of data abstraction. Data will be captured pre- and post-valbenazine treatment for the following items: socio-demographics, psychiatric and other comorbid conditions, concomitant medication use, duration/severity of TD, valbenazine treatment patterns, and health care resource utilization. Safety and tolerability will be assessed with adverse events. Changes over time in TD parameters will be evaluated with scatter plots and linear regression models, and predictors of treatment durability will be identified using Cox's proportional hazards models.

Results: Site enrollment is ongoing; interim data will be presented at the meeting.

Conclusions: This retrospective chart review aims to provide insights into the patient characteristics and disease management associated with long-term valbenazine treatment of TD in adult patients and to evaluate real-world decision-making and effects of long-term TD management.

S45. DRIVERS OF ANTIPSYCHOTIC DISCONTINUATION: A RETROSPECTIVE CHART REVIEW STUDY

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Abstract: Background and objectives: First- (FGA) and second-generation antipsychotics (SGA) are the mainstay of pharmacological treatment of schizophrenia spectrum disorders. However, discontinuation rates can be as high as 74% within 18 months (1). Common reasons for antipsychotic discontinuation include adverse reactions (2), but comparative analysis of discontinuation drivers between FGA and SGA have received limited attention hitherto. Thus, the goal of this study was to review and compare reasons for antipsychotic discontinuation between FGA and SGA.

Methods: We conducted a systematic retrospective chart review in order to extract data on antipsychotic medication discontinuation for patients treated in the inpatient and outpatient units at the Zucker Hillside Hospital, New York between August 2017 and August 2018. Reasons for every discontinuation were independently extracted by two investigators and categorized to: side effects, lack of efficacy, insurance problems, symptom remission, patient preference, poor adherence, and other. Comparisons between FGA vs. SGA were performed using chi-square tests ($\chi 2$) with a significance level of 0.05. Statistical analyses were carried out using IBM SPSS Statistics version 12.0.

Results: 400 charts were reviewed. 233 antipsychotic discontinuations were detected, of which 163 (60.9%) reasons for discontinuation were provided. A total of 71/163 discontinuations (43.6%) were detected in males and 92/163 (56.4%) in females. Further, 113/163 (69.3%) were reported in white subjects, 30/163 (18.4%) in African Americans, 15/163 (9.2%) in Asians, 1/163 patient was of mixed race, whereas in 4/163 (2.5%) cases race was not provided. Regarding type of antipsychotic, 24/163 (14.7%) were FGA discontinuations, whereas 139/163 (85.3%) were SGA discontinuations. No significant differences for reasons for discontinuation based on antipsychotic generation ($\chi 2$= 2.9, p= 0.72). The most common reason for discontinuation overall was side effects, n= 80 (49.1%) followed by patient preference, n= 49 (30.1%) and symptom remission, n=11 (6.7%). Lack of efficacy accounted for 8 (4.9%) of the cases, insurance problems for 3 (1.8%) cases and the remaining 12 (7.4%) cases reported other reasons.

Conclusion: We found no significant differences in reasons for discontinuation between FGA and SGA. Antipsychotic discontinuation was mainly driven by side effects.

Notably, in our study poor adherence was not found to be a major contributing factor to antipsychotic discontinuation in our sample. The fact that our data is based on physician's notes may play a role in these findings, as there may be discordances between physician perceived adherence and real adherence to treatment. Further studies should explore discontinuation differences based on specific side-effects.

S46. PRESCRIBER ATTITUDES, EXPERIENCES, AND PROCLIVITIES TOWARD DIGITAL MEDICINE AND HOW THEY INFLUENCE ADOPTION OF DIGITAL MEDICINE PLATFORMS

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Abstract: Background: Psychiatric prescribers (prescribers) typically assess medication adherence by patient or caregiver self-report (1). A new digital medicine (DM) technology provides objective data on adherence by using an ingestible event monitoring (IEM) sensor embedded within oral medication to track ingestion (2). Despite likely clinical benefit, adoption

by prescribers will in part depend on attitudes toward and experience with digital health technology, learning style preference (LSP), and how the technology's utility and value are described.

Objective: To identify attitudes, experiences, and proclivities toward DM platforms that may affect adoption of the IEM platform and to provide direction on tailoring educational materials to maximize adoption.

Methods: A survey of prescribers treating seriously mentally ill patients was conducted to assess drivers/barriers to IEM adoption. Factor analysis was performed on 13 items representing prior experience with and attitudes toward DM. Factor scores were correlated with prescriber characteristics including attitude and experience with digital technologies, LSP, and level of focus on healthcare cost containment.

Results: A total of 127 prescribers (56% female, 76% physicians, mean age 48.1 yrs.) completed the survey. Over 90% agreed medication adherence is important, visits allow enough time to monitor adherence (84.1%), and tailoring treatment to level of adherence would be beneficial (92.9%). The majority (65.9%) preferred relying upon outcomes data as their learning style while 15.9% preferred recommendations from opinion leaders and 18.3% on information about how the technology would affect practice efficiency.

Factor analysis revealed four underlying dimensions: Level of comfort with EHR; Concern over current ability to monitor medication adherence; Attitudes about value of DM applications; and Benefits vs cost of DM for payers. Women scored higher on attitudes about the value of digital applications ($p<0.01$). Providers who perceive nonadherence as costly, as well as those who believe DM could benefit providers and patients scored higher on attitudes about the value of DM ($p<0.05$). Those whose LSP focuses on improving efficiency and prescribers with a higher proportion of Medicaid/ uninsured patients displayed concern about their ability to monitor adherence ($p<0.05$). Finally, willingness to be a Beta Test site for DM applications was positively correlated with concern about their ability to monitor adherence and attitudes about the value of DM ($p <0.01$).

Conclusions: Prescriber characteristics including LSP, focus on healthcare cost containment, and attitudes toward DM technology may be related to adoption of the IEM platform. Those with more Medicaid/ uninsured patients were more concerned about their ability to monitor adherence while those focused-on cost and benefit to providers and patients viewed DM as part of a solution for managing outcomes and cost. Overall, LSP, patient panel size by payer type, and focus on healthcare cost containment should be considered when developing IEM provider training materials.

S47. INVESTIGATION OF MOBILE HEALTH (MHEALTH) TECHNOLOGIES IN THE MANAGEMENT OF DEPRESSION: ETHICAL, LEGAL, AND REGULATORY CHALLENGES

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Abstract: Background: Mobile Health (mHealth) technologies offer the potential to collect copious amounts of real-time data in "real-world" settings. Data collected include electronic assessments (e.g. questionnaires) known as ecological momentary assessments and passive, continuous data using smartphone sensors or wearable devices (e.g. Fitbit). These mHealth technologies have the potential to revolutionize mental health research and clinical care. However, these tools present ethical, legal, privacy, and regulatory challenges. The present study examines the challenges encountered by our research group in a study using mHealth technologies.
Methods: LifeRhythm, a smart phone app developed by our team, collects location and activity data via smartphone sensors (e.g. GPS, accelerometers) and integrates data gathered from a Fitbit worn by the user. For the mHealth study, a total of 182 participants (58 depressed and 124 non-depressed/controls) were recruited to install the LifeRhythm app on their smart phones and were followed over an 8-month study period. Three sets of data were collected during participant's study participation: sensory data collected by the app, Patient Health Questionnaire (PHQ-9) completed electronically by the participant every two weeks, and clinical assessments conducted by a study clinician. The current study examines the ethical, legal, and regulatory issues encountered during implementation of the mHealth study. This includes challenges encountered during the study regulatory approval process, issues raised by study participants, and issues raised by research team members.

Results: Our app collected passive continuous data based on participant's GPS location, mobility, Internet usage, SMS, and emails. It distinguished the types of internet sites visited (e.g. broad categories of shopping, social media, game, etc.). Statistically significant correlations ($p < 0.05$) were found between specific behavioral features and depression symptomatology. The following ethical, legal, and regulatory issues were identified during the study: 1. Data security during data collection, transportation to the server, storage, and data analyses; 2. Proper anonymization of the data that preserves user privacy while still allowing analysis by the study team; 3. Informed consent, including the participant's understanding of the nature, scope, and granularity of data collected; 4. Liability, including our team's ability to respond to emergent issues (e.g. suicidality expressed in electronic PHQ-9); 5. Security of medical data transmitted from participant's smartphones (e.g. PHQ-9 responses). Results and discussion of these issues will be presented in a descriptive/graphical manner with potential solutions to address these issues. An evidence-informed review of literature pertaining to these issues will be presented.

Conclusions: The mHealth study, using an innovative app developed by our team, showed promise as a potential behavioral biomarker in the management of depression. The study also raised multiple concerns regarding appropriate ethical and legal use of such tools in research settings. These issues will be of even greater significance as mHealth tools become widely adopted in clinical settings.

S48. DEVELOPMENT AND VALIDATION OF AI-DRIVEN MONITORING OF INTENTIONAL MEDICATION NON-ADHERENCE IN CLINICAL TRIALS

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[1]AiCure

Abstract: Introduction: Intentional non-adherence through false reporting is a component of overall medication non-adherence in clinical trials [1]. Remote visual monitoring of medication adherence has previously allowed for tracking of adherence [2], but it is unclear if such methods are robust to intentional non-adherence through deceitful mock-ingestion during administration of medication. In the current study, we evaluate the accuracy of remote human visual evaluation by expert raters of adherence and non-adherence and evaluate the accuracy of a novel artificial intelligence (AI) based computer vision (CV) algorithm in detecting adherence and intentional non-adherence compared to expert human evaluation. This is the first extensive validation of a remote AI driven adherence monitoring platform's ability to visually monitor adherence and intentional non-adherence.

Methods: 2.1 – Manual labeling of intentional non-adherence

Videos from n = 133,033 dosing administrations captured remotely through smartphones from 1,393 participants across 22 clinical trials were manually labeled for intentional non-adherence at the following levels:

- Green: Medication adherence confirmed
- Yellow: Missing information necessary to confirm medication adherence
- Orange: Suspicious behavior without visual confirmation of intentional non-adherence
- Red: Strong visual evidence of intentional non-adherence

2.2 – Assessing accuracy of manual labeling

To validate the accuracy of the labels, their ability to predict whether a PK sample would be above or below lower limit of quantification (LLOQ) was assessed using 6-fold cross validation (n = 694).

2.3 – CV-based labeling of intentional non-adherence

A CV classification algorithm to predict non-adherence labels was trained on n = 94,415 manually labelled videos. It was then tested on two hold-out datasets; n = 31,427 for the first set and n = 7,191 for the second set.

2.4 – Comparison of manual and CV-based labeling

To further validate the performance of the algorithm against human raters, Cohen's Kappa was utilized to assess pairwise comparisons between two trained human raters and the CV algorithm.

Results: 3.1 – Accuracy of manual labeling

When compared with PK levels thresholded at LLOQ, labels signifying strong visual evidence of intentional non-adherence were able to predict drug levels in the blood with AUC = 0.91, SE = 8x10-4. This showed that manual labeling was able to identify intentional non-adherence with high accuracy.

3.2 – Accuracy of CV-based labeling

The CV algorithm was able to predict green and red labels in the first dataset with AUC = 0.92 and AUC = 0.93 respectively and in the second dataset with AUC = 0.94 and AUC = 0.87. This showed that the CV algorithm is able to label intentional non-adherence with high accuracy when compared to manual review.

3.3 – Comparison of manual and CV-based labeling

The two trained human raters demonstrated acceptable consistency with each other when classifying red, orange, yellow, and green labels with Kappa = 0.74. The CV algorithm also showed consistency with both human raters with Kappa = 0.72 and Kappa = 0.76 for reviewer 1 and reviewer 2 respectively.

Conclusion: The high accuracy of remote manual labeling and AI-driven labeling, both of which are able to identify intentional non-adherence, supports the validity of automated remote monitoring of medication adherence. Both methodologies greatly increase the scalability of directly observed medication treatment.

S49. COMPARISON OF DIFFERENT DURATION REGIMENS FOR INTRAVENOUS RACEMIC KETAMINE: 100-MINUTE VERSUS 40-MINUTE INFUSIONS FOR REFRACTORY UNIPOLAR OR BIPOLAR DEPRESSION

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Abstract: Aims: Meta-analytic data demonstrate that IV ketamine is effective for treatment-refractory unipolar or bipolar depression (TRD), usually using 40-minute infusions. Precise biomarker or clinical predictors of response are unknown. One potential clinical biomarker of response may be duration of infusion, which may influence both response and side effect profile. Methods: To evaluate biomarkers, we are conducting a multi-site clinical trial of IV ketamine for TRD, administering three acute infusions within 11 days. Both 100-minute and 40-minute infusions have been administered, enabling comparison of efficacy, side effects, safety, and tolerability. Remission was defined as MADRS scores ≤9.

Results: To date, 66 of a proposed 100 subjects have completed the three acute phase infusions. Twenty-two participants have had additional maintenance infusions, yielding 160 individual infusions of 100-minutes and 116 individual infusions of 40 minutes. Participants have a mean age of 43.59 years (SD ± 13.15) and most are female (65%). Mean MADRS score at baseline was 27.6. Preliminary efficacy data show that the change in MADRS scores for single 100-min infusion, (N=46) pre & 24-hrs post were 13 points (M=12.54, SD=9.25), and MADRS scores for single 40-min infusion, (N=20) pre & 24-hrs post were 12 points (M=11.65, SD=8.12), a

nonsignificant difference; t (64) = .988, p-value =0.710. Comparisons of side effects between the two infusion types were also nonsignificant.

Conclusion: There was no efficacy difference in depression resolution when comparing 40 and 100 minute infusions of IV ketamine. In addition, occurrence of side effects shows little advantage for a slow 100-minute infusion.

S50. ACCUMULATION OF NEUROMELANIN IN BRAINS OF PATIENTS WITH SCHIZOPHRENIA: A SYSTEMATIC REVIEW

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Abstract: Objectives: A growing body of evidence pointed out the utility of examining the accumulation of neuromelanin (NM), which is a byproduct of the synthesis of monoamine neurotransmitters like dopamine (DA), as a proxy of DA scanned by positron emission tomography (PET) that is still not widely available because of its high production costs and the short half-life of radioligands. This concept has already been applied in Parkinson's disease but rarely for any psychiatric disorders such as schizophrenia (Sz). The aim of this study was to synthesize data of published studies that investigated the accumulation of NM in patients with Sz. Methods: We conducted a systematic literature search for studies examining the pigmentation or signal alteration of NM in patients with Sz compared to healthy controls on January 15, 2020, using PubMed and Embase with the following search terms: (neuromelanin or NM) AND (schizophrenia* or schizoaffective or psychosis or psychotic). Cross-reference and hand searches were also performed.

Results: An initial search yielded 880 studies; of these, seven articles that consisted of 12 studies were identified to be relevant. All these studies examined the NM signal intensity (SI) or contrast ratio (CR) of the NM-related signal using NM sensitive MRI (NM-MRI) (5 studies), or the density of NM pigmentation on a post-mortem human brain specimen with immunohistochemistry (1 study) or microdensitometer (1 study), and compared them between Sz patients and healthy controls (HC). The most frequently investigated region was substantia nigra (SN) (7 studies), followed by locus ceruleus (LC) (4 studies), and ventral tegmental area (VTA) (1 study). Cassidy et al. (2019) revealed that highly psychotic patients (PANSS positive scores>19) had significantly higher contrast-to-noise ratio (CNR) in the SN, while no difference was detected in the LC. Mabry et al. (2019) found slight, but not significant, the lower optical density of NM in the SN in the patient group. Yamashita et al. (2016) showed the SI of the VTA in Sz was significantly decreased whereas there was no change in the SN. Watanabe et al. (2014) demonstrated increases in both SI and CR of the SN in Sz patients but no significant difference in the LC. According to Sasaki et al. (2010), there was no change in the SN nor LC of Sz. Shibata et al. (2008) found that the CR of the SN was significantly higher in Sz patients than in HC, but no change was observed in the LC. Kaiya (1980) noted that no significant difference in melanin content between medicated and control brains was seen. In summary, 3 out of the 7 studies showed an increase in the NM accumulation of the SN (3 with NM-MRI), while the others exhibited no change (2 with NM-MRI;

2 with the other methods). Besides, an increased CR in the SN was observed in 3 out of 5 studies when confined to MRI studies. All the four studies concerning the LC demonstrated no significant change in signal alteration nor pigmentation of NM. In the VTA, a decreased SI was observed.

Conclusion: Our finding suggested the clinical feasibility of NM in SN using NM-MRI as a potential diagnostic biomarker for Sz, whereas that in LC seems to be of no use. However, several limitations remain to be considered. The number of studies was small. Employed analysis techniques were heterogeneous. Subjects included in these studies were not always well characterized in terms of the diagnosis and the severity of illness; especially, no study has examined in patients with treatment-resistant Sz (TRS) to date, which we are now conducting.

S51. MEDIATION OF THE RELATIONSHIP BETWEEN SUICIDE AND SLEEP BY PERSONALITY

ABSTRACT NOT INCLUDED

S52. AN MRS STUDY IN PEOPLE WITH REMITTED PSYCHOTIC DEPRESSION COMPARED TO CONTROLS PLUS EXAMINATION OF EFFECTS OF OLANZAPINE VS. PLACEBO: A PRELIMINARY ANALYSIS

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Abstract: Introduction: The neurobiological effects of antipsychotics on brain function are not fully understood. Historically, dopamine has been the focus of antipsychotics, although recent magnetic resonance spectroscopy (MRS) studies also suggest that antipsychotics decrease glutamate (Glu) in the frontal cortex (Goto, 2012) and increase myo-inositol (mI) in the thalamus (Szulc, 2005). In the present study, we compared the brain metabolite concentration between patients with remitted psychotic depression and healthy individuals. Moreover, we examined if the use of olanzapine was related to metabolite level change in comparison with placebo.

Methods: MRS data was obtained from a nested, multi-site multimodal neuroimaging study examining patients with psychotic depression (Study of the Pharmacotherapy of Psychotic Depression (STOP-PD) II). All patients in the STOP-PD II randomized controlled trial were treated with sertraline and olanzapine for 12 to 20 weeks and were then randomly assigned to continue sertraline plus olanzapine or switch to sertraline plus placebo. Baseline MRS acquisitions were obtained for 77 patients at the time of randomization. Follow-up scans were collected either

at the time of relapse or once sustained remission was achieved 36 weeks after their baseline scan. 91 controls also completed an MRS scan. For the MRS acquisition, a PRESS sequence was acquired at 3 Tesla. We used data from two sites (CMH and MAS) which acquired water-scaled metabolite concentrations. Acquisition parameters were as follows: TR = 2000 ms, TE = 35 ms (CMH) or 30 ms (MAS), 128 averages. The voxels were placed in the left dorsolateral prefrontal cortex (L-DLPFC) (30 x 30 x 15 mm (CMH) or 25 x 25 x 15 mm (MAS)) and bilateral supragenual anterior cingulate cortex (SACC) (30 x 20 x 15 mm). Water-scaled Glu, glutamate + glutamine (Glx), glycerophosphocholine + phosphocholine (Cho), mI, N-acetylaspartate + N-acetylaspartylglutamate (NAA), and creatine + phosphocreatine (Cr) concentrations were estimated with a corresponding basis set provided by LCModel and were corrected for water concentrations of the CSF, GM, and WM compartments. Linear regression models were used to compare metabolite levels between patient and control groups at baseline, and to examine changes in brain metabolites between olanzapine and placebo groups. We analyzed data from each site separately and then meta-analyzed them as a standardized mean difference (SMD).

Results: We proceeded with baseline MRS data for 40 remitted patients with psychotic depression and 45 controls after quality assurance. The mean and standard deviation of age in patients and controls were 53.3 ± 13.9 and 42.6 ± 16.7 years (P = 0.002), respectively, and the number of males was 14 (35.0%) and 25 (56.8%) (P = 0.08), respectively. When the data were meta-analyzed, remitted patients with psychotic depression demonstrated higher Cho (SMD = 0.82; 95% CI, 0.37–1.28; P = 0.0004) and mI (SMD = 0.69; 95% CI, 0.24–1.15; P = 0.0028) in the L-DLPFC and higher mI (SMD = 0.54; 95% CI = 0.10–0.99; P = 0.017) in the SACC after adjusting for age and sex. Among the patients, longitudinal data were available for 15 in the olanzapine and 18 in the placebo groups. Those randomized to placebo showed a decrease in mI (SMD = 0.96; 95% CI = 0.21–1.71; P = 0.012) and Cr (SMD = 1.08; 95% CI, 0.33–1.84; P = 0.005) in the SACC compared to those randomized to continue on olanzapine. No differences between groups were present in L-DLPFC.

Conclusions: Cho and mI in remitted patients with psychotic depression were higher than controls. Moreover, olanzapine may maintain mI and Cr levels. Additional statistical modeling of the data will also be pursued to disentangle the effects of medication vs. effects of illness on Cho and mI.

S53. VALIDATION OF A COMPUTERIZED ADAPTIVE ASSESSMENT TOOL FOR SEVERITY OF PSYCHOTIC SYMPTOMS AND DIAGNOSTIC PREDICTION

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Abstract: Introduction: Unlike other areas of medicine, psychiatry is highly dependent on patient and family reports to assess the presence and severity of disease. Thus, impairment level is determined by a total score on a rating scale, which requires that the same items of a given assessment tool need to be administered to all respondents, interpreted and coded. Hence, rating scales are time consuming and require trained raters, limiting the widespread use of measurement-

based approaches in the routine clinical management of schizophrenia. One alternative to the administration of a full traditional assessment is adaptive testing, in which individuals may receive different scale items that are targeted to their specific impairment level, reducing administration time and increasing measurement efficiency and scalability. When computational algorithms automatically match questionnaire takers with the most relevant questions for them, this is called Computer Adaptive Testing (CAT). This study aimed to test the psychometric properties and predictive power of a self-administered computerized adaptive testing tool for psychosis (CAT-Psychosis).

Methods: Patients from the inpatient and outpatient units at The Zucker Hillside Hospital, New York, rated themselves with the self-administered CAT-Psychosis which yields a current psychotic severity score. The CAT-Psychosis is based on a multidimensional extension of traditional Item Response Theory (IRT)-based CAT that is suitable for complex traits and disorders such as psychosis. The Brief Psychiatric Rating Scale (BPRS) was administered to test convergent validity wit CAT-Psychosis self-report. Subjects were re-tested within 7 days to assess test-retest reliability. Generalized linear mixed models and Pearson product moment correlation coefficients were used to test for correlations between individual ratings and average CAT-Psychosis severity scores respectively and the BPRS. Intraclass correlation coefficients (ICCs) were used to test for reliability. Generalized linear and non-linear (logistic) mixed models were used to estimate diagnostic discrimination capacity (lifetime ratings) and to estimate diagnostic sensitivity, specificity and area under the ROC curve with 10-fold cross validation.

Results:200 subjects (160 patients with psychosis and 40 healthy controls) were included in the study. The CAT-Psychosis self-report showed convergent validity against BPRS scores (r=0.690; 95% confidence interval (CI): 0.609-0.756). CAT-Psychosis self-report showed test-retest reliability (ICC=0.815; 95% CI: 0.741-0.871). CAT-Psychosis self-report was able to discriminate psychosis from healthy controls (Area Under the ROC Curve (AUC)= 0.850, 95% CI: 0.807-0.894). Median length of assessment was 1 minute, 20 seconds (interquartile range (IQR): 0:57min-2:09min).

Conclusions: CAT-Psychosis self-report provides valid severity ratings and can reliably discriminate psychotic patients from healthy controls, yielding a dramatic reduction in administration time, while maintaining reliable psychometric properties. The availability of a scalable, valid and reliable self-administered instrument would be of enormous value, both for research and for routine clinical management of psychotic disorders. Independent replication of our findings in other patient populations and in other languages is needed to ensure worldwide scalability.

S54. PATIENT-REPORTED BARRIERS LIMITING MENTAL HEALTH CARE AMONG ADULTS WITH MAJOR DEPRESSIVE DISORDER: A NATIONWIDE ANALYSIS USING NATIONAL SURVEY ON DRUG USE AND HEALTH DATA

ABSTRACT NOT INCLUDED

S55. ESTIMATING INDIVIDUALIZED TREATMENT RULES FOR REDUCING RECIDIVISM AMONG CRIMINAL JUSTICE-INVOLVED ADULTS WITH MENTAL ILLNESS

ABSTRACT NOT INCLUDED

S56. METFORMIN FOR COMORBID GLUCOSE DYSREGULATION AND SCHIZOPHRENIA SPECTRUM DISORDERS: A PILOT DOUBLE-BLIND RANDOMIZED CONTROL STUDY

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Abstract: Background: Patients with severe mental illness (SMI) loose 15-20 years of life due to cardiovascular disease. Much of the metabolic risk, including high rates of type 2 diabetes (T2D) is accrued early on in the illness, highlighting the need for early intervention strategies to target modifiable cardiovascular risk factors. There is however an astounding paucity of studies in SMI examining interventions outside of weight loss.

Methods: Thirty participants with schizophrenia spectrum disorders and co-morbid prediabetes or T2D were randomly assigned, in a double-blind fashion to 1500mg/d of metformin or placebo (2:1 ratio; n=21 metformin and n=9 placebo). Patients had to be overweight/obese, <40 years old, and receiving a stable dose of antipsychotics. The primary outcome measures were improvements in glycemia (HbA1c, fasting glucose), and insulin sensitivity (Matsuda-derived from glucose tolerance tests and HOMA-IR). Secondary outcomes included changes in weight, fat distribution (MRI quantification of hepatic and visceral fat), cognition, and hippocampal volume (MRI). Data were analyzed using mixed-models methods and intention to treat analysis.

Results: Twenty-two patients (n=14 metformin; n=8 placebo) completed the 4-month trial. The metformin group had a significant decrease in the HOMA-IR (p=0.043), and fasting blood glucose (p=0.007) vs. placebo. There were no differences between treatment groups in the Matsuda index, HBA1c ,or secondary outcome measures. Weight loss among all participants correlated significantly with decreased subcutaneous, but not visceral adipose tissue.

Conclusions: Independently of weight loss, metformin effectively improves dysglycemia and insulin sensitivity in a population at very high risk for early CV mortality.

S57. THE IMPACT OF MAJOR DEPRESSIVE DISORDER AND SUICIDAL IDEATION OR SUICIDE ATTEMPTS ON CAREGIVERS: A COMPARISON OF DIRECT AND

INDIRECT COSTS AND ABSENCES USING OBJECTIVELY MEASURED REAL WORLD DATA

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Abstract: Background: Major depressive disorder (MDD) is one of the most prevalent psychiatric disorders in the United States(1) and a significant risk factor for suicidal ideation and suicide attempts (SI/SA). Over 50% of those who attempt suicide have MDD(2). The economic impact of MDD and SI/SA on patients is documented in the literature, but the impact on caregivers has not been well documented.

Aims: To compare costs (direct/indirect) and absences among employed caregivers of patients with MDD-Alone (without SI/SA) only versus MDD+SI/SA versus controls (without MDD).

Methods: Patients (aged ≥18 years) with MDD-Alone (first diagnosis for MDD-defined index date), patients with MDD and SI/SA (first SI/SA-event-defined index date), and non-MDD controls (no MDD or SI/SA diagnoses, randomly generated index date) were identified by ICD-9 and ICD-10 codes in the Human Capital Management Services (HCMS) employer database. Patients required a caregiver (employed spouse/partner) in the HCMS data for each pair. Twenty controls and 20 MDD-Alone patients were matched to each MDD+SI/SA patient on caregiver age, gender, and index year. Medical and prescription drug (Rx) claims and absenteeism (payment/time) in the HCMS employer database from January 2010 to August 2019 were retrospectively analyzed for the 3 cohorts. All employee/patient pairs had 6 months pre-/postindex-date information and met additional inclusion/exclusion criteria. Costs were adjusted to September 2019 US dollars. Outcomes included direct costs (medical, Rx), indirect costs (absence payments by benefit type), and absence time. Each outcome analyzed used separate two-part (logistic followed by general linear), stepwise regression models, controlling for demographics, job-related variables, region, index year, and Charlson Comorbidity Index.

Results: A total of 570 MDD+SI/SA patient (mean age 44.1 years, 67.5% female) and caregiver (mean age 44.6 years, 32.3% female) pairs along with matching cohort pairs of MDD-Alone (n=11,400) and non-MDD (n=11,400) controls were identified. Annual average salaries of caregivers of MDD+SI/SA cohort ($75,536) and non-MDD controls ($80,006) were similar (P>0.05), and MDD+SI/SA and control cohorts significantly differed from MDD-Alone ($86,548) (P<0.0001). Caregivers in the MDD+SI/SA and MDD-Alone cohorts had significant differences in selected mental health conditions compared with non-MDD controls. Caregivers of patients with MDD+SI/SA had higher total direct costs ($6,983) compared with the MDD-Alone cohort and non-MDD controls. Specifically, higher medical and Rx costs were observed among the caregivers of patients with MDD+SI/SA and MDD-Alone compared with non-MDD controls ($5,131 and $4,548 versus $3,885, respectively P<0.0001). Additionally, the prescription Rx drug costs were the highest in the MDD+SI/SA cohort ($1,852, P<0.001). Caregivers of patients with MDD+SI/SA had higher total indirect costs. Total health-related work absence days were also

highest among caregivers of patients with MDD+SI/SA compared with MDD-Alone and non-MDD controls (3.11 versus 1.72 versus 1.75, respectively).

Conclusions: Caregivers of patients with MDD+SI/SA had significantly greater direct and indirect costs compared with caregivers of the MDD-Alone and non-MDD control cohorts.

S58. CO-PRESCRIBED BENZODIAZEPINES IN OLDER ADULTS RECEIVING ANTIDEPRESSANTS FOR ANXIETY AND DEPRESSIVE DISORDERS: ASSOCIATION WITH TREATMENT OUTCOMES

ABSTRACT NOT INCLUDED

S59. A MINDFULNESS AND PEER MENTORING PROGRAM TO IMPROVE ADHERENCE TO MEDICATION ASSISTED TREATMENT FOR OPIOID USE DISORDERS (THE MIND AND MENTORS PROGRAM [MIMP])

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Abstract: Although medication assisted therapy (MAT) for opioid use disorders (OUD) is safe and effective and is currently considered the gold standard for treating OUD, adherence to MAT regimens remains a challenge. Initial studies have demonstrated efficacy of mindfulness-based interventions as adjunctive treatment for substance use disorders (SUD) while reducing substance use and cravings. Additionally, non-randomized pilot studies suggest that mindfulness-based interventions may be effective in reducing symptoms of depression and anxiety in individuals undergoing MAT for OUD. In addition, peer recovery support services delivered by individuals in recovery from SUD have also been found to be effective in reducing relapse rates, increasing treatment retention, and improving relationships with treatment providers and social supports.6 Nonetheless, recent studies that have used a combination of therapy and MAT have yielded mixed results, thereby necessitating further exploration. 7-8 Several factors, including depression, anxiety, stress, and cravings affect adherence to MAT and other SUD treatment regimens because they increase likelihood of relapse.9-12 Additionally, physiologic stress reactivity and drug cue reactivity, often measured by the hormone cortisol, have been shown to be predictors of relapse.
The goal of our present study is to determine the effectiveness of a mindfulness-based intervention that also utilizes peer mentors in addition to professional substance abuse therapists (the Minds and Mentors program [MiMP]) in improving adherence to MAT for OUD and reducing relapse rates in a sample of individuals with OUD who are also on MAT versus a twelve-step facilitation (TSF) program. This study was recently funded by the National Institutes of Health's National Center for Complementary and Integrative Health (NCCIH) under the Helping to End Addiction Long-term (HEAL) Initiative. The MiMP is a 12-week intervention that uses group therapy and meets once a week for about an hour and half. We hypothesize that participants in MiMP will demonstrate better adherence (primary outcomes measures), reduced relapse and cravings reduced depression, anxiety, and stress, and improved social support (secondary outcomes measures), and

reduced cortisol levels and reactivity to drug cues (exploratory outcome measures). This study will utilize an individually randomized group treatment design. Data collection will occur at baseline (T0), end of treatment (T1), and at 3 (T2), 6 (T3), and 12 (T4) months follow-up.

The findings of the study have the potential to impact policy and practice changes related to treatment of OUD and strategies to improve adherence to MAT. This intervention has the potential to ultimately decrease morbidity and mortality in individuals with OUD by decreasing relapse and other comorbid psychosocial outcomes such as depression, anxiety, and stress. Furthermore, this study may help in the identification of individuals who are more reactive to stress, and who may need treatments that incorporate additional elements focused on stress reduction.

S60. CORTISOL, ESTRADIOL AND INTERLEUKIN-6 ALTERATIONS IN PERIPARTUM WOMEN VETERANS FROM PREGNANCY TO POSTPARTUM: A PILOT INVESTIGATION

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Abstract: Background: The population of reproductive-age women veterans is growing, as is their use of maternity benefits. Women veterans are twice as likely as their non-pregnant counterparts to have mental health issues, such as anxiety, depression and posttraumatic stress disorder (PTSD). Women are known to have significant alterations in hormonal and inflammatory signaling during both pregnancy and postpartum, also known as the peripartum period. A recent study determined increased IL-6 in women with postpartum depressive symptoms compared to healthy controls (1). Methods: We recruited 28 pregnant women veterans for a psychological assessment battery, and we have previously characterized the frequency of depression (Edinburgh Postnatal Depression Scale, or EPDS); PTSD symptoms (PTSD Checklist for DSM-5, or PCL-5); and suicidal ideation (Columbia Suicide Severity Rating Scale, or C-SSRS) in this cohort (2). We assessed the women during the 3rd trimester of pregnancy (mean 36 weeks, range 31-40 weeks) and in the early postpartum period (mean 7 weeks, range 5-14 weeks). We additionally obtained blood for determination of cortisol, estradiol, and interleukin-6 (IL-6) by enzyme-linked immunosorbent assay (ELISA).

Results: As measured by an EPDS of 13 or greater, the frequency of clinically meaningful depressive symptoms was 25% and 30% during pregnancy and postpartum, respectively. For PTSD assessment, presumptive PTSD (i.e., PCL-5 of 33 or greater) occurred in 25% of the pregnant veterans, which increased to 34.5% in the postpartum period. As determined from the C-SSRS, two veterans had passive suicidal thoughts during pregnancy, and one veteran had active suicidal thoughts – intent but no plan – in the postpartum. None of the veterans acted on suicidal thoughts during the course of this study (2). As anticipated, we observed significant decreases in cortisol (229.82 ng/mL, versus 86.34 ng/mL) and estradiol (6666.04 pg/mL, versus 114.86 pg/mL) from the 3rd trimester of pregnancy to postpartum. However, we did not determine any difference in the average level of IL-6 during pregnancy (2.33 pg/mL) versus postpartum (2.41 pg/mL). We

did not find any significant differences in cortisol, estradiol, or IL-6 in the peripartum veterans with depressive or PTSD symptoms as compared to those without.

Conclusion: Women veterans are at higher risk compared to their civilian counterparts to develop mental health issues, especially in the setting of pregnancy and postpartum. The results presented here add to our currently limited understanding of depressive and PTSD symptoms in this vulnerable population. Surprisingly, we did not find any changes in the absolute level of IL-6 from pregnancy to postpartum, nor did we determine alterations in the women veterans with depressive or PTSD symptoms. These hormone and cytokine analyses add to the ongoing discourse regarding hormonal and inflammatory changes in depression during the peripartum period. However, these results must be interpreted with caution due to the small sample size. Further investigation is warranted to examine the significance of inflammatory changes in pregnancy and postpartum in relation to depressive and PTSD symptomatology.

S61. TSPAN5 REGULATES SEROTONIN AND KYNURENINE LEVELS: PHARMACOGENOMIC MECHANISMS RELATED TO ALCOHOL USE DISORDER AND ACAMPROSATE TREATMENT RESPONSE

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Abstract: Background: We previously reported that TSPAN5 SNPs were associated with plasma serotonin concentrations which were themselves correlated with selective serotonin reuptake inhibitor treatment outcomes in patients with major depressive disorder (MDD), and with alcohol use disoder (AUD) risk. A recent genome-wide association study (GWAS) of alcohol consumption in UK Biobank participants identified a series of genome-wide significant variants on chromosome 4. Strikingly, several of those SNPs (rs3114045, rs193099203 and rs9991733) are trans-eQTLs in the brain for TSPAN5 which maps to chromosome 4 (1). When the UK Biobank study results were stratified by sex, the rs114026228 SNP in TSPAN5 (p=3.60E-13) was the top signal associated with alcohol consumption in men. In addition, a recent GWAS meta-analysis demonstrated that TSPAN5 SNPs were associated with AUD risk in an African American population (2). It should also be pointed out that the TSPAN5 rs11947402 SNP which was originally identified from our GWAS for baseline plasma 5-HT concentrations in MDD patients was also associated with AUD risk (p=0.017) in that same AUD GWAS meta-analysis (2). As a result of this growing body of evidence that TSPAN5 may play a role in AUD risk, the present study was designed to explore the biological function of TSPAN5 with a focus on the tryptophan pathway using human iPSC-derived CNS cells exposed to either ethanol (EtOH) or acamprosate—an FDA approved medication for the treatment of AUD.

Methods: Functional genomic studies were performed using five human induced pluripotent stem cell (iPSC) lines. The Mayo Clinic Center for the Individualized Treatment of Alcoholism recruited 443 AUD subjects with clinical data, and DNA samples were obtained at baseline and

after 3 months of acamprosate treatment. Specifically, 300 European American subjects have their 3-month acamprosate treatment outcomes available.

Results: TSPAN5 mRNA expression was downregulated by ethanol and by acamprosate—an FDA approved drug for AUD therapy, resulting in decreased serotonin concentrations in iPSC-derived neuron culture media and the down-regulation of DDC, MAOA, MAOB, TPH1, and TPH2. Strikingly, these results were compatible with results obtained after the knockdown of TSPAN5 expression in neurons. Very similar observations were also made in iPSC-derived astrocytes. Mass spectrometry identified proteins related to clathrin and other vesicle related proteins which interacted physically with TSPAN5, indicating that TSPAN5 might play a role in vesicular function in addition to regulating genes associated with serotonin biosynthesis and metabolism. RNA-seq data demonstrated that TSPAN5 knockdown in iPSC-derived astrocytes also significantly influenced kynurenine concentrations as well as the expression of genes associated with immune related pathways. Finally, we also determined that genetic variants that are associated with TSPAN5 expression might be biomarkers for abstinence length in AUD patients enrolled in the Mayo Clinic Center for the Individualized Treatment of Alcoholism clinical trial.

Conclusions: TSPAN5 is an alcohol responsive gene that plays a role in the regulation of 5HT and kynurenine concentrations. The functional genomic data from iPSC-derived CNS cells open a new avenue for understanding the biological role of TSPAN5 in AUD as well as acamprosate's mechanism of action. Our results highlight novel pharmacogenomic mechanisms underlying response to acamprosate therapy.

S62. KETAMINE MODULATES FRONTO-STRIATAL CIRCUITRY IN DEPRESSED AND HEALTHY INDIVIDUALS

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Abstract: Ketamine improves motivation-related symptoms in depression, but simultaneously elicits similar symptoms in healthy individuals, suggesting that it might have different effects in health and disease. Here we examine if ketamine affects the brain's reward system, which is well established in driving motivational behavior. We also tested whether inflammatory mechanisms, known to influence neural and behavioral motivational processes, may underlie some of these changes. These questions were explored in the context of a double-blind, placebo-controlled, crossover trial of ketamine in 33 treatment-resistant depressed patients (TRD) and 25 healthy controls. Resting-state functional magnetic resonance imaging was acquired two days post-ketamine and post-placebo infusions and was used to probe fronto-striatal circuitry with striatal seed-based functional connectivity. Ketamine increased fronto-striatal functional connectivity in TRD patients towards levels observed in healthy individuals, while shifting the connectivity profile in healthy individuals towards a state that was similar to depressed patients under placebo. These effects were observed largely in the absence of inflammatory (C-reactive protein) changes and were associated with both acute and sustained improvements in symptoms in the TRD group. These findings highlight the potential importance of fronto-striatal circuitry in ketamine's

mechanism of action and may be particularly relevant for understanding ketamine-induced shifts in motivational symptoms.

F63. LONG-TERM EVALUATION OF OPEN-LABEL PIMAVANSERIN SAFETY AND TOLERABILITY IN PARKINSON'S DISEASE PSYCHOSIS

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Abstract: *Background:* Pimavanserin is a selective 5-HT2A inverse agonist/antagonist. Previous results from randomized, double-blind, placebo-controlled studies showed pimavanserin to be generally safe, and well tolerated.
Methods: This multi-year, open-label study assessed the long-term safety and tolerability of pimavanserin 34 mg for treating Parkinson's disease psychosis (PDP). Patients with PDP who previously completed randomized, double-blind, placebo-controlled studies and/or an earlier open-label extension (OLE) study enrolled in this 11-year OLE study (NCT00550238). Study evaluations included adverse events, motor symptoms, clinical laboratory results, and other safety measures, as well as the Caregiver Burden Scale (CBS) and the Clinical Global Impressions-Severity (CGI-S) scale.
Results: Among 459 participants, mean age was 71.2 years, 61.7% were male, and 458 (99.8%) had a previous psychiatric history. The median duration of treatment was 454.0 days (range: 1 to 3270 days), with a total exposure of 914.8 patient-years. 392 (85.4%) patients experienced at least 1 treatment-emergent adverse event (TEAE); the majority were of mild to moderate intensity, with falls, urinary tract infection, and hallucinations being most commonly reported. Serious TEAEs were experienced by 188 (41.0%) patients, most often pneumonia, urinary tract infection, aspiration pneumonia, and hip fracture. TEAEs that resulted in discontinuation were experienced by 133 (29.0%) patients. Sixty-one patients died, 59 (12.9%) of whom experienced a TEAE with a fatal outcome during treatment or within 30 days after the last dose of study drug; the observed mortality rate was 6.45 patients per 100 patient-years of exposure. Serious TEAEs, TEAEs leading to discontinuation, and death were more common in patients aged ≥81 years. Mean scores for the CGI-S scale and CBS remained generally stable over 192 weeks (>3.5 years) of the study period.
Conclusions: Long-term study showed pimavanserin treatment to be generally safe and well tolerated over 192 weeks. No new or unexpected safety findings were observed.

F64. IMPROVEMENT AND DURABILITY IN SAPS-PD ASSESSMENT OVER 10 WEEKS OF PIMAVANSERIN TREATMENT FOR PARKINSON'S DISEASE PSYCHOSIS

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Abstract: *Background:* Parkinson's disease psychosis (PDP) affects up to 60% of patients with PD. Pimavanserin, a selective 5-HT2A inverse agonist/antagonist, demonstrated efficacy for PDP in a randomized, placebo-controlled study. We evaluated the efficacy and tolerability of open-label pimavanserin for an additional 4 weeks following the completion of a 6-week double-blind, placebo-controlled study.

Method: Patients completing pimavanserin or placebo treatment in the 6-week randomized Core Study (CS) (NCT01174004) could enroll in a 4-week open-label extension (OLE) (NCT00550238) and receive pimavanserin 34 mg once daily. Patients remained blinded to previous treatment and underwent the same blinded CS assessments at Week 4 with the Scale for the Assessment of Positive Symptoms (SAPS) PD and hallucinations + delusions (H+D) scales, Clinical Global Impression Improvement (CGI-I) and Severity (CGI-S) scales and Caregiver Burden Scale (CBS). Adverse events (AEs) were collected at each visit.

Results: Of 199 CS patients, 171 entered the OLE, and 148 (86.5%) completed Week 4. Mean (SE) change from OLE baseline to OLE Week 4 for the SAPS-PD was -0.43 (-0.8) for prior pimavanserin-treated patients and -3.4 (0.7) for prior placebo-treated patients. Mean change from CS baseline to OLE Week 4 for SAPS-PD was similar among prior pimavanserin and prior placebo-treated participants (-6.9 vs. -6.3). CGI-I, CGI-S, CBS, and SAPS H+D also improved from CS baseline to OLE week 4 in prior placebo-treated patients. During the OLE, AEs were reported by 92 (53.8%) patients; 2 (1.2%) had serious AEs.

Conclusion: During the 4-week OLE, prior pimavanserin-treated patients maintained improvements observed in the 6-week CS, and prior placebo-treated patients exhibited significant improvements from OLE baseline, with improvements from CS baseline comparable to those in prior pimavanserin-treated patients. No new safety concerns were identified over 10 weeks of pimavanserin treatment.