A Double-blind, Randomized, Placebo-controlled Trial of Adjunctive Suvorexant for Treatment-resistant Insomnia in Patients With Bipolar Disorder

Study Protocol and Statistical Analysis Plan

NCT02527564

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Merck Investigator Studies Program (MISP) Protocol Template	
Requirements for Submitting a Full Proposal	
Section #1 - MISP Protocol Identification	
Study Title:	**A double-blind, randomized, placebo-controlled trial of adjunctive suvorexant for treatment-resistant insomnia in patients with bipolar disorder**
Request Date:	3/30/2015
Institution Name	Stanford University School of Medicine
Investigator Contact Information: – Full address – Phone No. – Fax No. – e-mail address	**Po Wang, MD** **Professor of Psychiatry & Behavioral Sciences** **401 Quarry Road** **Stanford, CA 94305** **P: (650) 723-2483** **wangp0@stanford.edu** **Trisha Suppes, MD, PhD** **Professor of Psychiatry and Behavioral Sciences** **VA Palo Alto Health Care System** **3801 Miranda Ave** [redacted] **Palo Alto, CA 94304** **P: (650) 493-5000** **tsuppes@stanford.edu**

Section #2- Core Protocol	
2.1 Objectives & Hypotheses	2.1 Study Objectives Objective 1. (Hypotheses 1 and 2) To assess the acute (1-week) efficacy of adjunctive (added to existing treatments) suvorexant in patients with bipolar disorder and insomnia despite treatment with traditional hypnotic agents, anxiolytics, atypical antipsychotics, mood stabilizers, and/or antidepressants. Objective 2. (Hypotheses 3 and 4) To assess the subchronic (3-month) efficacy of open adjunctive (added to existing treatments) suvorexant in patients with bipolar disorder and insomnia despite treatment with traditional hypnotic agents, anxiolytics, atypical antipsychotics, mood stabilizers, and/or antidepressants 2.1.1 Clinical Hypotheses. 1. Primary acute efficacy hypothesis – Adjunctive suvorexant 20 mg at bedtime compared to adjunctive placebo for 1 week in patients with insomnia related to bipolar disorder (307.42), despite receiving treatment as usual will yield significantly greater increases in subjective total sleep time (sTST), as assessed by self-report. 2. Secondary acute efficacy hypothesis 1 – Adjunctive suvorexant 20 mg at bedtime compared to adjunctive placebo for 1 week in patients with insomnia related to bipolar disorder (307.42), despite receiving treatment as usual will yield significantly greater increases in objective total sleep time (oTST), as assessed by sleep actigraphy. 3. Secondary subchronic efficacy hypothesis 2 – Adjunctive open suvorexant 20 mg at bedtime for 3 months in patients with insomnia related to bipolar disorder (307.42), despite receiving treatment as usual will yield significant increases in subjective total sleep time (sTST), as assessed by self-report. 4. Secondary subchronic efficacy hypothesis 3 – Adjunctive open suvorexant 20 mg at bedtime for 3 months in patients with insomnia related to bipolar disorder (307.42), despite receiving treatment as usual will yield significant increases in objective total sleep time (oTST), as assessed by sleep actigraphy.
2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data	Insomnia is common in patients with bipolar disorder, not only when hypo/manic, but also when depressed, or even euthymic,[1, 2] and commonly persists despite treatment. Sleep disturbance in remitted bipolar disorder patients may represent a prodrome of an impending mood episode, whereas improvement in sleep quality during an acute mood episode may be an early marker of recovery from the episode.[1] Insomnia therefore represents an important target of treatment in bipolar disorder, regardless of current mood state.[1] Preliminary data from our clinic have been largely consistent with previous literature. Thus, among 89 bipolar disorder patients who achieved recovery from a mood episode and were subsequently followed longitudinally in the Stanford Bipolar Disorders Clinic for at least one year, worse daytime dysfunction, subjective sleep quality, sleep latency, and global sleep disturbance on the Pittsburgh Sleep Quality Index (PSQI)[3] were associated with the presence of subsyndromal mood symptoms.[4] In addition, worse PSQI daytime dysfunction significantly predicted a shorter time to mood episode recurrence.[4] Unfortunately, insomnia associated with bipolar disorder can be challenging to treat. Among 69 Stanford Bipolar Disorders Clinic patients who were already taking at

	least one scheduled (i.e. non-PRN) prescription sedative-hypnotic agent at the time of initial assessment, 55.0% (N=38) complained of insomnia on at least one day within the prior week (unpublished data). Thus, treatment-resistant insomnia is both highly prevalent and associated with poorer longitudinal outcomes in bipolar disorder. More effective treatments for insomnia associated with bipolar disorder are urgently needed. Suvorexant is a novel hypnotic agent that promotes sleep via orexin receptor antagonism.[5] A phase 3 randomized, double-blind, placebo-controlled study has demonstrated the efficacy and safety of suvorexant, in doses of 10mg to 20mg at bedtime, for the treatment of insomnia in healthy adults.[6] We propose conducting a randomized, double-blind, placebo-controlled study assessing the efficacy of adjunctive (added to existing treatments) suvorexant in depressed or euthymic (but not hypo/manic) patients with bipolar disorder (Type I, Type II, or Type Not Otherwise Specified) and insomnia despite treatment with traditional hypnotic agents, anxiolytics, atypical antipsychotics, mood stabilizers, and/or antidepressants.
2.3 Study Design	Patients with bipolar disorder (Type I, Type II, or Type Not Otherwise Specified) who are currently euthymic or have current syndromal or subsyndromal depressive (but not hypo/manic) symptoms (i.e. have Young Mania Rating Scale [YMRS][7] total score < 12), and with insomnia related to bipolar disorder (307.42), with subjective total sleep time (sTST) < 6 hours on at least 1 night during the prior week, will be randomized to receive either adjunctive double-blind placebo or adjunctive double-blind suvorexant 10 mg at bedtime for 3 nights, which as necessary and tolerated then may be increased to 20 mg at bedtime for 4 nights. In all patients, there will be an attempt to increase Suvorexant/Placebo dose from 10 to 20 mg at bedtime after three nights (although Suvorexant/Placebo dose may remain at 10 mg if the patient prefers to do so, though this is expected to be uncommon). Following the 1-week randomized controlled phase, all patients will receive open suvorexant 10 mg at bedtime for 3 nights, which as necessary and tolerated then may be increased to 20 mg at bedtime for 3 months. All patients (i.e. those in both the active drug and placebo group) will revert back to the 10mg dose at the start of the open treatment phase in order to protect the blind. Inclusion Criteria: 1. Adult outpatients (age 18 years and older) meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)[8] criteria for bipolar I disorder (296.70), bipolar II disorder (296.89), or bipolar disorder not otherwise specified (296.80), with concurrent insomnia related to bipolar disorder (307.42). 2. Currently taking ≥ 1 prescription psychotropic medication (hypnotic agents, anxiolytics, atypical antipsychotics, mood stabilizers, and/or antidepressants) for management of bipolar disorder. 3. Subjective total sleep time (sTST) < 6 hours on ≥ 1 night during the prior week, assessed at baseline visit using the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) Clinical Monitoring Form (CMF).[9] Exclusion Criteria: 1. Current hypo/manic symptoms, as evidenced by YMRS total score ≥ 12, assessed at baseline visit. 2. Current (past 6 months) alcohol or substance use disorder, as determined by assessment with the Mini-International Neuropsychiatric Interview (MINI)[10] at baseline visit. 3. Current psychosis, as determined by assessment with the MINI at baseline visit.

4. Women who are currently pregnant or breastfeeding.
5. Clinically significant abnormalities on baseline laboratory tests (comprehensive metabolic panel, fasting lipid panel, CBC with differential, thyroid stimulating hormone).
6. Presence of any unstable and/or potentially confounding neurological and/or medical disorder.

2.4 Study Flow

	Baseline	Week 0	Week 1	Month 1	Month 2	Month 3
ADE	**X**					
MINI	**X**					
DSM-IV-TR 307.42 checklist	**X**					
CMF	**X**	**X**	**X**	**X**	**X**	**X**
YMRS	**X**	**X**	**X**	**X**	**X**	**X**
MADRS	**X**	**X**	**X**	**X**	**X**	**X**
sTST	**X**	**X**	**X**	**X**	**X**	**X**
oTST		**X**	**X**	**X**	**X**	**X**
FISER/ GRSEB		**X**	**X**	**X**	**X**	**X**
CMP	**X**					
FLP	**X**					
CBC	**X**					
TSH	**X**					
Upreg	**X**					

ADE = Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) Affective Disorders Evaluation[11]; MINI = Mini-International Neuropsychiatric Interview[10]; DSM-IV-TR 307.42 checklist = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision[8] criteria for insomnia related to bipolar disorder (307.42); CMF = STEP-BD Clinical Monitoring Form[9]; YMRS = Young Mania Rating Scale[7]; MADRS = Montgomery-Asberg Depression Rating Scale[12]; sTST = subjective Total Sleep Time (assessed with STEP-BD CMF at baseline visit, and with electronic self-report sleep diary at subsequent visits); oTST = objective Total Sleep Time (assessed with Actigraph device); FISER/GRSEB = Frequency and Intensity of Side Effects Ratings/Global Rating of Side Effects Burden[13]; CMP = comprehensive metabolic panel; FLP = fasting lipid panel; CBC = complete blood count with differential; TSH = thyroid stimulating hormone; Upreg = Urine pregnancy test (only for women of reproductive potential).

2.5 Study Procedures

Patients will have the following assessments:

1. <u>Baseline (1 week prior to randomization)</u>

Due to COVID-19 restrictions, all assessments will be done remotely via Zoom with clinician and study coordinator. Only the lab tests will be done in person. Medication and Actigraph will be mailed out to participant

Diagnostic assessments

- Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) Affective Disorders Evaluation (ADE)[11]
- MINI
- DSM-IV-TR insomnia related to bipolar disorder (307.42) checklist

Clinical symptom assessments

- STEP-BD CMF, including subjective Total Sleep Time (sTST)
- YMRS
- Montgomery-Asberg Depression Rating Scale (MADRS)[12]

	Laboratory tests • Comprehensive metabolic panel • Fasting lipid panel • Complete blood count with differential • Thyroid stimulating hormone • Urine pregnancy test (only for women of reproductive potential) 2. Controlled Week-0 (Randomization; prior to one week of double-blind, placebo-controlled adjunctive suvorexant) **Due to COVID-19 restrictions, all assessments will be done remotely via Zoom with clinician and study coordinator. Medication and Actigraph will be mailed out to participant** Clinical symptom assessments • STEP-BD CMF • YMRS • MADRS • Electronic self-report sleep diary, including subjective Total Sleep Time (sTST) • Sleep actigraphy, including objective Total Sleep Time (oTST) assessed with Actigraph device • Frequency and Intensity of Side Effects Ratings/Global Rating of Side Effects Burden (FISER/GRSEB)[13] 3. Controlled Week-1 (after one week of double-blind, placebo-controlled adjunctive suvorexant) **Due to COVID-19 restrictions, all assessments will be done remotely via Zoom with clinician and study coordinator. Medication and Actigraph will be mailed out to participant** Clinical symptom assessments • STEP-BD CMF • YMRS • MADRS • Electronic self-report sleep diary, including subjective Total Sleep Time (sTST) • Sleep actigraphy, including objective Total Sleep Time (oTST) assessed with Actigraph device • FISER/GRSEB 4. Open Month-1 (after one month of open suvorexant) **Due to COVID-19 restrictions, all assessments will be done remotely via Zoom with clinician and study coordinator. Medication and Actigraph will be mailed out to participant** Clinical symptom assessments • STEP-BD CMF • YMRS • MADRS • Electronic self-report sleep diary, including subjective Total Sleep Time (sTST) • Sleep actigraphy, including objective Total Sleep Time (oTST) assessed with Actigraph device • FISER/GRSEB

	5. Open Month-2 (after two months of open suvorexant) **Due to COVID-19 restrictions, all assessments will be done remotely via Zoom with clinician and study coordinator. Medication and Actigraph will be mailed out to participant** Clinical symptom assessments • STEP-BD CMF • YMRS • MADRS • Electronic self-report sleep diary, including subjective Total Sleep Time (sTST) • Sleep actigraphy, including objective Total Sleep Time (oTST) assessed with Actigraph device • FISER/GRSEB 6. Open Month-3 (after three months of open suvorexant) **Due to COVID-19 restrictions, all assessments will be done remotely via Zoom with clinician and study coordinator. Medication and Actigraph will be mailed back to study team using prepaid shipping label.** Clinical symptom assessments • STEP-BD CMF • YMRS • MADRS • Electronic self-report sleep diary, including subjective Total Sleep Time (sTST) • Sleep actigraphy, including objective Total Sleep Time (oTST) assessed with Actigraph device • FISER/GRSEB
2.6 Study Duration	Estimated length of time required to recruit patients and complete the study is 6 years, from September 1, 2015 to August 31, 2021.
2.7 Statistical Analysis and Sample Size Justification	The investigator will analyze the study data. The blind will be maintained using blinded medication and matching placebo provided by the sponsor. For the final analysis, the clinical database will not be unblinded until medical/scientific review has been completed, protocol violators have been identified (if appropriate), and data has been declared complete. Data will then be unblinded, data analysis will be completed, and the manuscripts will be prepared for publication. Variables/Time Points of Interest Primary outcome – subjective total sleep time (sTST), according to self-report, assessed at Controlled Week-0, Controlled Week-1, Open month-1, Open month-2, and Open month-3. Secondary outcome – objective total sleep time (oTST), according to Actigraph, assessed at Controlled Week-0, Controlled Week-1, Open month-1, Open month-2, and Open month-3. Statistical Methods For the randomized controlled phase, the primary outcome (change in sTST from Controlled Week-0 to Controlled Week-1) for adjunctive suvorexant versus adjunctive placebo will be assessed using a Mixed-Effect Model Repeated Measure (MMRM), with a significance threshold of $p < 0.05$.

	For this 1-week, double-blind, placebo-controlled trial, assuming a two-tailed alpha of .05, a sample of 50 patients (25 patients taking double-blind adjunctive suvorexant, and 25 patients taking adjunctive placebo) would be required to detect an adjunctive suvorexant treatment effect (compared to adjunctive placebo) of 0.70, with a power of approximately .80, as described in greater detail below. For the open extension study, the key efficacy outcome will be change in sTST from Controlled Week-0 to Open Month-3, stratified by acute treatment arm (i.e., blind adjunctive suvorexant followed by open adjunctive suvorexant, and blind adjunctive placebo followed by open adjunctive suvorexant), using a paired Mixed-Effect Model Repeated Measure (MMRM) analysis, with a significance threshold of $p < 0.05$. Additional secondary analyses include evaluation of change in oTST from Controlled Week-0 to Controlled Week-1 for adjunctive suvorexant versus adjunctive placebo, using MMRM with a significance threshold of $p < 0.05$; and change in oTST from Controlled Week-0 to Open Month-3, stratified by acute treatment arm (i.e., blind adjunctive suvorexant followed by open adjunctive suvorexant, and blind adjunctive placebo followed by open adjunctive suvorexant), using a paired MMRM analysis, with a significance threshold of $p < 0.05$. There are no adjustments for dropout, as we expect no more than 5% dropout by the end of week 1. <u>Multiplicity</u> No correction for multiple comparisons will be used. <u>Power/Sample Size:</u> Based on pooled results in Table 1 of Herring, et al.,[14] we expect baseline mean (SD) sTST in minutes of 317 (64). We expect a robust sTST benefit with suvorexant (60 min increase) compared to placebo (15 minute increase) - admittedly this is a more marked suvorexant-placebo difference (60-15 = 45 minutes, which yields an effect size of 0.70) than in Herring et al. Supplemental Table S1,[14] which had a pooled suvorexant-placebo difference of 33-15 = 18 minutes, which yielded a pooled effect size of only 0.28. Thus, for the primary outcome of the randomized controlled phase, based upon a sample size of n=25 patients per group, and a two-tailed alpha of 0.05, this study has 80% power to detect an effect difference in change in sTST for suvorexant versus placebo of 0.70.
2.8 Specific Drug Supply Requirements	Suvorexant 10 mg tablets, 20mg tablets, and matching placebo will be supplied by Merck. <u>Drug Supply Requirements:</u> Drug Name: Suvorexant 10 mg tablets. Amount: 3 tabs for days 1-3 of 1-week, randomized, controlled treatment phase (a total of <u>150 tabs</u> for 50 double-blind suvorexant patients), then 3 tabs for days 1-3 of 3-month open treatment phase (a total of <u>300 tablets</u> for 100 open suvorexant patients). Total **<u>450 Suvorexant 10 mg tablets</u>**. Drug Name: Suvorexant 20 mg tablets. Amount: 4 tabs for days 4-7 of 1-week, randomized, controlled treatment phase (a total of <u>200 tabs</u> for 50 double-blind suvorexant patients), then 87 tabs for days 4-90

	of 3-month open treatment phase (a total of 8700 tablets for 100 open suvorexant patients). Total **8900 Suvorexant 20 mg tablets**. Drug Name: Placebo tablets (to match suvorexant 10mg tablets). Amount: 3 tabs for days 1-3 of 1-week, randomized, controlled phase (a total of 150 tablets for 50 double-blind placebo patients). Total **150 placebo tablets (to match suvorexant 10mg tablets)**. Drug Name: Placebo tablets (to match suvorexant 20mg tablets). Amount: 4 tabs for days 4-7 of 1-week, randomized, controlled phase (a total of 200 tablets for 50 double-blind placebo patients). Total **200 placebo tablets (to match suvorexant 20mg tablets)**. Note: At conclusion of the study or upon drug expiration, the Merck GRS will be responsible for issuing a Drug Disposition Letter to the investigator for US based studies. The investigator will be responsible for the destruction of the supplies at the study center pursuant to the ICH/GCP Guidelines, local regulations and the investigator's institutional policies. Clinical supplies will be received by Dr. Shefali Miller at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies will be dispensed in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies, the amount dispensed to and returned by the patients, and the disposition at the end of the study.
2.9 Adverse Experience Reporting	Adverse experience reporting will be conducted as outlined by the Model Study Agreement.
2.10 Itemized Study Budget	A preliminary study budget is provided with the initial proposal to give guidance to the MISP Review Committee as to the expected study costs. A refined itemized budget detailing the costs associated with the study will be provided with the final protocol or included in the study agreement as Exhibit B.
2.11 References	1. Plante DT, Winkelman JW. Sleep disturbance in bipolar disorder: therapeutic implications. Am J Psychiatry 2008;165:830-843. 2. Gruber J, Harvey AG, Wang PW, et al. Sleep functioning in relation to mood, function, and quality of life at entry to the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). J Affect Disord 2009;114:41-49. 3. Buysse DJ, Reynolds CF, 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193-213. 4. Cretu JB, Culver JL, Ketter TA. Sleep disturbance/daytime dysfunction, subsyndromal symptoms, and time to relapse in recovered patients with bipolar disorder. (in preparation). 5. Merck. Belsomra (suvorexant) prescribing information, updated August 2014. http://www.merck.com/product/usa/pi_circulars/b/belsomra/belsomra_pi.pdf (accessed March 4, 2015). 6. Michelson D, Snyder E, Paradis E, et al. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet Neurol 2014;13:461-471.

	7. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978;133:429-435. 8. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). Washington: American Psychiatric Association; 2000. 9. Sachs GS, Guille C, McMurrich SL. A clinical monitoring form for mood disorders. Bipolar Disord 2002;4:323-327. 10. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59:22-33. 11. Sachs GS, Thase ME, Otto MW, et al. Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry 2003;53:1028-1042. 12. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382-389. 13. Wisniewski SR, Rush AJ, Balasubramani GK, et al. Self-rated global measure of the frequency, intensity, and burden of side effects. J Psychiatr Pract 2006;12:71-79. 14. Herring WJ, Connor KM, Ivgy-May N, et al. Suvorexant in patients with insomnia: results from two 3-Month randomized controlled clinical trials. Biol Psychiatry 2014 (epub ahead of print).
2.12 Publication Plan	• Publication plan – We anticipate two publications – 1. The primary paper (describing the 1-week double-blind placebo controlled trial; and 2. The key secondary paper (describing the 3-month open continuation study) • Projected target date for manuscript submission is November 30, 2017 for both papers, which will be submitted to the Journal of Affective disorders. • We anticipate two abstracts – as describe for the two anticipated publications above. • We anticipate presenting the two abstracts at the American Psychiatric Association Annual Meeting in New York, NY (May 5-10, 2018).
2.13 Curriculum Vitae	Curriculum vitae for Dr. Terence Ketter and Dr. Shefali Miller are attached.
2.13 Protocol Submission for Investigator-Initiated Studies	This protocol will be submitted by the investigators directly or through the Global Research Specialist at www.merckiisp.com