Honeybrains Biotech

STUDY PROTOCOL
Protocol HB-001

Safety and Efficacy of HB-1 for Panic Disorder: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

Protocol Number:	Protocol HB-001
Phase:	2
Date of Protocol:	02 Dec 2021
Version:	**4.0**
Sponsor:	Honeybrains Biotech 515 W 20th St, Ste 4e New York, NY 10011

INVESTIGATOR PROTOCOL APPROVAL

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to principles of the Declaration of Helsinki and the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice E6 (R2), and all local laws and regulations.

Institution/Clinic: _____

Principal Investigator

Print Name: _____

Signature: _____

Date (dd/mmm/yyyy):_____

SPONSOR PROTOCOL APPROVAL

I have read this protocol and approve the design of this study:

DocuSigned by:
Alon Seifan, MD
8D575C75E61B426...

12/2/2021

Alon Seifan, MD, MS
Chief Medical Officer
Honeybrains Biotech

Date (dd/mmm/yyyy)

CONTACT INFORMATION

Sponsor:

Tomer Seifan, Managing Partner

917-685-1351

Honeybrains Biotech
515 W 20th St, Ste 4e
New York, NY 10011

Dr. Alon Seifan, Chief Medical Officer

786-620-3204

Honeybrains Biotech
515 W 20th St, Ste 4e
New York, NY 10011

PROTOCOL SYNOPSIS

Study Title: Safety and Efficacy of HB-1 for Panic Disorder: A Mulitcenter, Randomized, Double-Blind, Placebo-Controlled Trial

Protocol Number:

HB-001

Phase: 2

HB-1 and Study Rationale:

New treatments that safely improve whole brain functional connectivity could radically transform outcomes for people suffering from Psychiatric Disorders (Tumati S. 2021). Anxiety Disorders (ie, Panic Disorder, Social Anxiety Disorder, Generalized Anxiety Disorder, Obsessive Compulsive Disorder, and Specific Phobia) are a clinically diverse group of disorders that have significant pathophysiological overlap. Anxiety disorders commonly feature disequilibrium in functional connectivity. Specifically, simultaneous alterations within more than one functional brain network, such as default mode, salience and somatomotor networks, are common to these disorders (Kim Y., Yoon H. 2018). Anxiety disorders also commonly feature dysregulations in both adrenergic and angiotensin systems (Winter A. 2019, Killgore W. 2014, Milani A. 2017). For example, patients with Panic Disorder and also patients with Post-Traumatic Stress Disorder display atypical brain connectivity in regions that govern autonomic nervous system regulation (Faravelli C. 1997, Rotella F. 2014, Reiman E. 1984, Owega A. 2001). In fact, successful treatment of symptoms for anxiety disorders is associated with resolution of multiple atypical patterns of regional cerebral connectivity (Zandvakili A. 2020, Lai C. 2013).

Currently, no FDA-approved treatments for anxiety disorders are designed to improve whole brain functional connectivity by targeting the angiotensin and adrenalin systems simultaneously. This is a critical research gap because anxiety disorders are 1) common, 2) debilitating, 3) co-morbid and 4) difficult to treat (Cerda M. 2010). Panic Disorder, for example, is prevalent in 6% of primary care patients (Katon W. 1986). Current FDA-approved treatments, which target symptomatology using neurotransmitter-specific approaches, are limited due to adverse reactions, including abuse potential. For example, current treatments for Panic Disorder include selective serotonin reuptake inhibitors (SSRIs), which have small to medium effects, and benzodiazepines, which are not beneficial for long-term use due to tolerance, dependence, cognitive disturbance, and exacerbation of co-morbid mood disorders (Otto M. 1989, Edwards R. 1980). Regarding future treatments, the drugs currently being tested for Panic Disorder target mechanisms of action similar to currently approved treatments.

This study introduces HB-1, a fixed dose combination of 96 mg telmisartan and 288 mg verapamil, two previously FDA-approved antihypertensives, as a novel therapeutic agent targeting symptoms and quality of life (QoL) for patients with Panic Disorder. HB-1 works by re-equilibrating functional networks within the telencephalon and the mesencephalon brain regions. HB-1 is a promising treatment for Panic Disorder because Panic Disorder is characterized by abnormal physiological stress responses associated with disequilibrium in

more than one functional brain network.

This study hypothesizes that, in patients with Panic Disorder, HB-1 demonstrates a comparable safety profile compared to the safety profiles of the individual agents; and a statistically significant reduction in disease severity, compared to placebo. This study will also examine the effects of HB-1 in treating the most commonly experienced co-morbidities in patients diagnosed with Panic Disorder.

These hypotheses are based on literature that describes relationships between psychosocial stress, emotional intelligence, theories of human motivation, the adrenergic system, functional connectivity, angiotensin receptors, and calcium channels (Lea R. 2019, Zheng Z. 2016, Sagar-Ouriaghli I. 2018, Keller S. 2003). This work builds upon a prior observational pilot study that demonstrated improvement in anxiety and cognitive symptomatology in a diverse group of Neurology & Psychiatry patients who received these co-administered medications in a community-based Neuropsychiatry specialty practice. Regarding safety, adverse events were minimal, and systolic and diastolic blood pressure did not change significantly before and after an average of nine months of treatment observations. Regarding effectiveness, drastic reductions in symptomatology were noted across a broad array of disabling symptoms in patients not only with Panic Disorder but also with common co-morbidities.

Objectives and Endpoints:

Primary Objective
To determine the safety and efficacy of HB-1 versus placebo in male and female adult patients aged 18 to 60 years, inclusive, with Panic Disorder.
Safety Endpoints
Incidence of Treatment Emergent Adverse Events (TEAEs), clinically significant changes in clinical laboratory values, electrocardiogram (ECG), Columbia Suicide Severity Rating Scale (C-SSRS) (Oquendo MA 2003), and orthostatic vital signs.
Efficacy Endpoints
• Change in Panic Disorder Symptom Severity Scale (PDSS) (Furukawa TA. 2009)-primary efficacy endpoint • Number of panic attacks • Change in Clinical Global Impression-Severity Scale (CGI-S) (Guy W. 1976) • Change in Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF) (Endicott J. 1993) • Change in Leibowitz Social Anxiety Scale (LSAS) (Heimberg R. 1999, Baker S. 2002) • Change in Assessment of Overall Sleep Quality -- Question #6 from the Pittsburgh Sleep Quality Index (Buysse DJ. 1989)

Exploratory Objective
To explore the effectiveness of HB-1 on Common Neuropsychiatric Co-Morbidities.
Exploratory Endpoints
• Change in Toronto Alexithymia Scale (TAS-20) (Bagby R. 2020) • Change in Hamilton Anxiety Rating Scale (HAM-A) (Bech P. 1990) • Change in CogScreen Symbol Digit Coding test (SDC) (Kay G. 1995) • Change in Montgomery-Asberg Depression Rating Scale (MADRS) (Fantino B., Moore N. 2009) only for patients with a medical history of depression • Change in Conners' Adult ADHD Rating Scale (CAARS) (Walls B. 2017) only for patients with a medical history of ADHD • Change in The PTSD Checklist for DSM-5 (Blake D. 1995, Blevins C. 2015) only for patients with a medical history of PTSD • Change in Short Form McGill Pain Questionnaire (SF-MPQ) (Melzack R. 1987) only for patients with a medical history of chronic pain • Change in Migraine Disability Assessment Questionnaire (MIDAS) (Lipton R. 2001) only for patients with a medical history of migraine
Abbreviations: ADHD=Attention deficit hyperactivity disorder; AE=adverse event, DSM-5=Diagnostic and Statistical Manual of Mental Disorders 5th edition; ECG=electrocardiogram, PTSD=post traumatic stress disorder

HB-1 Administration:

All patients will receive an oral dose of HB-1 or matching placebo once a day (QD) nightly at bedtime (QHS) with or without food. HB-1 is a proprietary combination of telmisartan and verapamil in a once-daily, extended release formulation.

Study Population:

This study will enroll approximately 80 adult patients who meet DSM-5 criteria for the diagnosis of Panic Disorder.

Study Duration:

The study will consist of a 12-week treatment period and a one-week post-treatment period for safety follow-up.

Study Centers:

Enrollment is anticipated at approximately 8-10 clinical research sites in the United States.

Study Design:

This is a multicenter, randomized, double-blind, placebo-controlled trial. All patients with Panic Disorder, with or without specified co-morbidities, who meet all of the inclusion and

none of the exclusion criteria will be eligible. Patients and researchers will be blinded to their treatment group.

Approximately 80 patients with Panic Disorder will be enrolled and randomized in a 1:1 ratio to HB-1 or placebo.

Assessment of Safety:

Safety will be assessed through the monitoring of TEAEs, clinical laboratory assessments, ECG, Columbia Suicide Severity Rating Scale (C-SSRS) (Oquendo MA 2003), and orthostatic vital signs. Patients will be monitored for safety, from the first dose of study treatment at Visit 2/Week 0 through the Safety Follow-up/End-of-Study (EOS) Visit.

Inclusion Criteria

All patients must meet the following criteria for inclusion:

1. Male or female aged 18 to 60 years old, inclusive, at the time of informed consent.
2. Meets DSM-5 Criteria for Panic Disorder.
3. Documented moderate to severe levels of symptoms at baseline (Panic Disorder Severity Scale of 13 or above) (Furukawa TA. 2009).
4. Medically stable on current medication regimen for at least 3 months (including PRN medications), as determined by Investigator.
5. Willing to remain on current doses of other psychiatric medications throughout the length of the trial.
6. Willing and able to safely stop any of the following medications at least 5 days prior to Visit 2: Inhibitors or inducers of CYP3A4 (erythromycin, ritonavir, telithromycin, rifampin), HMG-CoA Reductase Inhibitors (Simvastatin, Lovastatin, Atorvastatin), Beta Blockers (Timolol eyedrops, Metoprolol), Neuromuscular Blocking Agents (curare-like and depolarizing), Antihypertensive Agents (Prazosin and vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta blockers, alpha agonists), Inhalation Anesthetics, Disopyramide, Flecainide, Quinidine, Cimetidine, Lithium, Carbamazepine, Phenobarbital, Cyclosporine, Aliskiren, Ramipril and Ramiprilat, aspirin, Theophylline, mTOR inhibitors.
7. Willing and able to avoid consumption of grapefruit, grapefruit juice and Seville oranges within two weeks of screening through the last dose of study treatment.
8. Willing and able to limit consumption of alcohol to three servings per day defined as: 1 serving of beer=12 ounces (5% alcohol content); 1 serving of malt liquor=8 ounces (7% alcohol content); 1 serving of wine=5 ounces (12% alcohol content); 1 serving of distilled spirits=1.5 ounces (40% alcohol content).
9. Willing and able to avoid concomitant administration of sensitive P-glycoprotein substrates (digoxin, fexofenadine, dabigatran etexilate, talinolol, loperamide, vinblastine).
10. Fluent in English.
11. Willing to take HB-1 or placebo.

12. Willing and able to provide informed consent indicating an understanding of the requirements of the study and a willingness to comply with scheduled visits and all study procedures.
13. Female patients must be surgically sterile (or have a monogamous partner who is surgically sterile) or be least 2 years postmenopausal or commits to use 2 acceptable forms of birth control (defined as the use of an intrauterine device, a barrier method with spermicide, condoms, or any form of hormonal contraceptives) for the duration of the study and for 4 months following the last dose of study treatment. Male patients must be sterile (biologically or surgically) or commit to the use of a reliable method of birth control (condoms with spermicide) for the duration of the study and for 4 months following the last dose of study treatment. Individuals who are involved exclusively in same-sex relationships are exempt from the birth control requirements but must agree to abide by the recommendations if they do engage in a heterosexual relationship.
14. Female patients who are women of childbearing potential (WOCBP) must have a negative pregnancy test at Screening, within 7 days of dosing with study treatment.

Exclusion Criteria

Patients are to be excluded from the study if they meet any of the following criteria:

1. Severe uncontrolled cardiac disease within 6 months of Screening, including but not limited to uncontrolled hypertension, hypotension (defined as below 90/60); unstable angina; myocardial infarction (MI) or cerebrovascular accident (CVA).
2. Any clinically significant electrocardiogram (ECG) abnormalities at screening.
3. History of atrial flutter, atrial fibrillation or hypertrophic cardiomyopathy.
4. Inadequate hepatic function defined as total bilirubin >1.5 × the upper limit of normal (ULN) ranges of each institution, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >3 × the ULN range of each institution.
5. Inadequate renal function defined as serum creatinine >1.5 × the ULN range of each institution and/or eGFR <60.
6. Any clinically significant abnormalities in clinical laboratory assessments as assessed by the Investigator.
7. Any other systemic conditions or organ abnormalities that in the opinion of the Investigator may interfere with the conduct and/or interpretation of the current study.
8. Unable to complete neuropsychological testing.
9. Diagnosis of Bipolar I, Bipolar II disorder or Schizophrenia.
10. History of suicidal behaviors including ideation.
11. Current treatment with doses of benzodiazepines that are outside the FDA-approved prescriber’s information.
12. Use of tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) is prohibited.
13. Already on treatment with either telmisartan or verapamil or both.
14. Documented prior drug allergy to either telmisartan or verapamil.
15. Documented contraindication to taking telmisartan or verapamil: (eg, Duchenne's muscular dystrophy, myasthenia gravis).
16. Documented moderate to severe substance abuse within the last 6 months (recreational cannabis use is allowed).
17. Pregnant or breastfeeding.

Sample Size Justification

A sample size of 80 patients is planned for the study to be randomized in a 1:1 ratio of active to control.

Assuming a standard deviation of 4.5 in the PDSS, 80 patients will provide for in excess of 95% power to detect a difference in the mean change (from baseline) in the PDSS score of 3.75 at an alpha-level of 0.05. This corresponds to a 50% reduction in mean PDSS scores on HB-1 and a 25% reduction in mean PDSS scores on placebo, assuming baseline mean PDSS scores of 15 for both groups..

In addition, with respect to adverse events, the study has approximately 95% power to detect at

least one patient with an event that occurs in 7.2% of patients in either treatment group.

Statistical Methodology

The study data will be reported using tabular and graphical displays. Baseline information and safety results will be presented for the safety population consisting of patients who received at least one dose of study treatment (active or placebo) during the trial. Effectiveness assessments will be compared on an intent-to-treat basis using the randomized treatment assignment. Demographics and baseline information will be summarized descriptively. Study treatment accountability and exposure will be summarized descriptively. Study drug exposure information will include information of compliance such as the percentage of planned treatment used.

Safety Analyses:

Descriptive summaries of treatment adverse events, laboratory results, and orthostatic vital signs will be provided. C-SSRS (Oquendo MA 2003) results will be provided in a listing.

Efficacy Analyses: Efficacy will be evaluated by comparing change from baseline of HB-1 patients versus placebo patients in gold standard outcome measures for panic disorder and its common co-morbidities. For efficacy, the primary endpoint will be change from baseline in the PDSS.

Descriptive summaries and inferential tests are identified in the analysis section. Significance testing will be at the two-sided 0.05 alpha-level and confidence intervals will be at 95% confidence.

Table 1: Schedule of Assessments

	Screening	Baseline	Treatment Period				Safety Follow-up
Procedure or Assessment	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6/ EOS Visit[k]**	**Safety Follow-up[l]**
Study Week	*Week - 1*	*Week 0*	*Week 2*	*Week 4*	*Week 8*	*Week 12*	*Week 13*
Visit Windows	*V2 within 7 days of V1*		*+/- 3 days*				
Informed Consent	X						
Medical History and Demographics[a]	X						
Eligibility Assessment	X						
Number of Panic Attacks[b]	X	X	X	X	X	X	
Columbia Suicide Severity Rating Scale[c]	X	X	X	X	X	X	
Clinical Laboratory Assessments[d]	X	X	X			X	
Physical Exam	X			X	X	X	
Height/Weight/BMI	X						
Urine Pregnancy Test[e]	X	X	X	X	X	X	
Screening Questionnaires (3)[f]	X						
Orthostatic Vitals[g]	X	X	X	X	X	X	
12-Lead ECG	X			X	X	X	
CogScreen Symbol Digit Coding Test [o]	X						
Weber Test		X				X	
Placebo-Control Reminder Script (PCRS)[n]			X	X	X	X	
Efficacy Endpoint Questionnaires (5)[h]		X	X[m]	X	X	X	
Exploratory Endpoint Questionnaires (8)[i]		X				X	
Study Treatment Dispensation/Return/ Accountability [j]		X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	
Adverse Event Monitoring		X	X	X	X	X	X
Safety Follow-up Phone Call							X[l]

[a] Demographics will include : Age, Sex, Race, Ethnicity, Education, Gender Identity, Lateral Preference Questions, and Parental Education
[b] Number of Panic Attacks. The clinician will ask the patient "How many panic attacks have you had in the last week?" and will confirm the reported panic attack(s) meet DSM-5 criteria (APA 2013).
[c] Columbia Suicide Severity Rating Scale (C-SSRS) (Oquendo MA 2003). At screening, use the Screening/Baseline C-SSRS; at subsequent visits, use the Since Last Visit C-SSRS.
[d] Clinical laboratory assessments will include a comprehensive metabolic panel, CBC including Vitamin B12, urinalysis.
[e] Urine pregnancy test to be administered for women of child-bearing potential (WOCBP) within 7 days prior to Week 0, at Baseline/Week 0, and at each subsequent study visit
[f] Screening Questionnaires will include: Mini International Neuropsychiatric Interview for DSM-5 (MINI) (Sheehan, DV. 1998; Sheehan, DV. 1992-2016), the Clinical Global Impression-Severity Scale (CGI-S) (Guy W. 1976), and the Panic Disorder Symptom Severity Scale (PDSS) (Furukawa TA. 2009).
[g] Orthostatic vital signs should be obtained per Section 6.1.7.
[h] Efficacy Endpoint Questionnaires will include:

- Panic Disorder Symptom Severity Scale (PDSS) (not repeated at Week 0) (Furukawa TA. 2009)
- Clinical Global Impression-Severity Scale (CGI-S) (not repeated at Week 0) (Guy W. 1976)
- Quality of Life Enjoyment and Satisfaction Questionaire Short Form (Q-LES-Q-SF) (Endicott J. 1993)
- Self-Report Leibowitz Anxiety Scale (LSAS) (Heimberg RG. 1999, Baker SL. 2002)
- Assessment of Overall Sleep Quality -- Question #6 from the Pittsburgh Sleep Quality Index (Buysse DJ. 1989)

[i] Exploratory Endpoint Questionnaires will include:

- Toronto Alexithymia Scale (TAS-20) (Bagby RM. 2020)
- Hamilton Anxiety Rating Scale (HAM-A) (Bech P. 1990)
- CogScreen Symbol Digit Coding test (SDC) (Kay G. 1995)
- Montgomery-Asberg Depression Rating Scale (MADRS) (Fantino B., Moore N. 2009) only for patients with a medical history of depression
- Conners' Adult ADHD Rating Scale (CAARS) (Walls BD. 2017) only for patients with a medical history of ADHD
- The PTSD Checklist for DSM-5 (Blake DD. 1995, Blevins CA. 2015) ony for patients with a medical history of PTSD
- Short Form McGill Pain Questionnaire (SF-MPQ) (Melzack R. 1987) only for patients with a medical history of chronic pain
- Migraine Disability Assessment Questionnaire (MIDAS) (Lipton RB. 2001) only for patients with a medical history of migraine

[j] Patients will be randomly assigned to either the HB-1 or placebo treatments groups and will be provided with study drug each month while on treatment. Patients will be instructed to take the study drug once a day (QD) nightly at bedtime (QHS) with or without food, at the same time each day with a glass of water.
[k] Patients who discontinue from the study prior to Week 12: End of study visit (EOS) and all EOS assessments should be performed within 7 days following the discontinuation from the study. Patients who discontinue study treatment prior to Week 12: Patients may discontinue study treatment and remain in the study. Complete the EOS study visit and all EOS assessments within 7 days of study treatment discontinuation. The patient should continue to follow the schedule of assessments through the Safety Follow-Up Phone Call with modified assessments at interim visits including Week 12/Visit 6 as follows:

- Number of Panic Attacks
- C-SSRS (Oquendo MA 2003)
- Efficacy Endpoint Questionnaires
- Exploratory Endpoint Questionanires (when applicable)
- Concomitant Medications
- Adverse Event Monitoring

[l] Safety Follow-up Phone Call is performed approximately 7 days after Visit 6/EOS.
[m] Only the PDSS will be repeated at the Week 2 visit.
[n] Placebo-Control Reminder Script (PCRS) (Cohen, EA. 2021). The PCRS will be administered immediately prior to administering the PDSS at Visits 3-6.
[O] CogScreen Symbol Digit Coding Test (SDC) (Kay G. 1995); SDC to be done twice at Screening/Visit 1 and no passing score is required.

TABLE OF CONTENTS

List of Tables

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADHD	Attention Deficit Hyperactivity Disorder
AE	adverse event
AUC	area under the curve
CAARS	Conners' Adult ADHD Rating Scale
CGI-S	Clinical Global Impression-Severity Scale
c_{max}	maximum serum concentration
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th edition
ECG	Electrocardiogram
eCRF	electronic case report form
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HAM-A	Hamilton Anxiety Scale
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ITT	Intent-to-treat
LSAS	Leibowitz Social Anxiety Scale
MADRS	Montgomery-Asberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MIDAS	Migraine Disability Assessment Questionnaire
MINI	Mini International Neuropsychiatric Interview for DSM-5
OCD	Obsessive Compulsive Disorder
N	number
QD	once a day
QHS	nightly at bedtime
Q-LES-SF	Quality of Life Enjoyment and Satisfaction Scale – Short Form
PCRS	Placebo-Control Reminder Script
PDSS	Panic Disorder Symptom Severity Scale

Abbreviation	Definition
PSQI	Pittsburgh Sleep Quality Index
PTSD	Post-Traumatic Stress Disorder
PCL	PTSD Checklist for DSM-5
PE	physical examination
PI	principal investigator
QoL	Quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SDC	CogScreen Symbol Digit Coding test
SF-MPQ	Short Form McGill Pain Questionnaire
SMC	Safety Monitoring Committee
SSRI	serotonin reuptake inhibitors
TAS-20	Toronto Alexithymia Scale
TEAE	treatment-emergent adverse event
W	week
WOCBP	women of childbearing potential

1. BACKGROUND

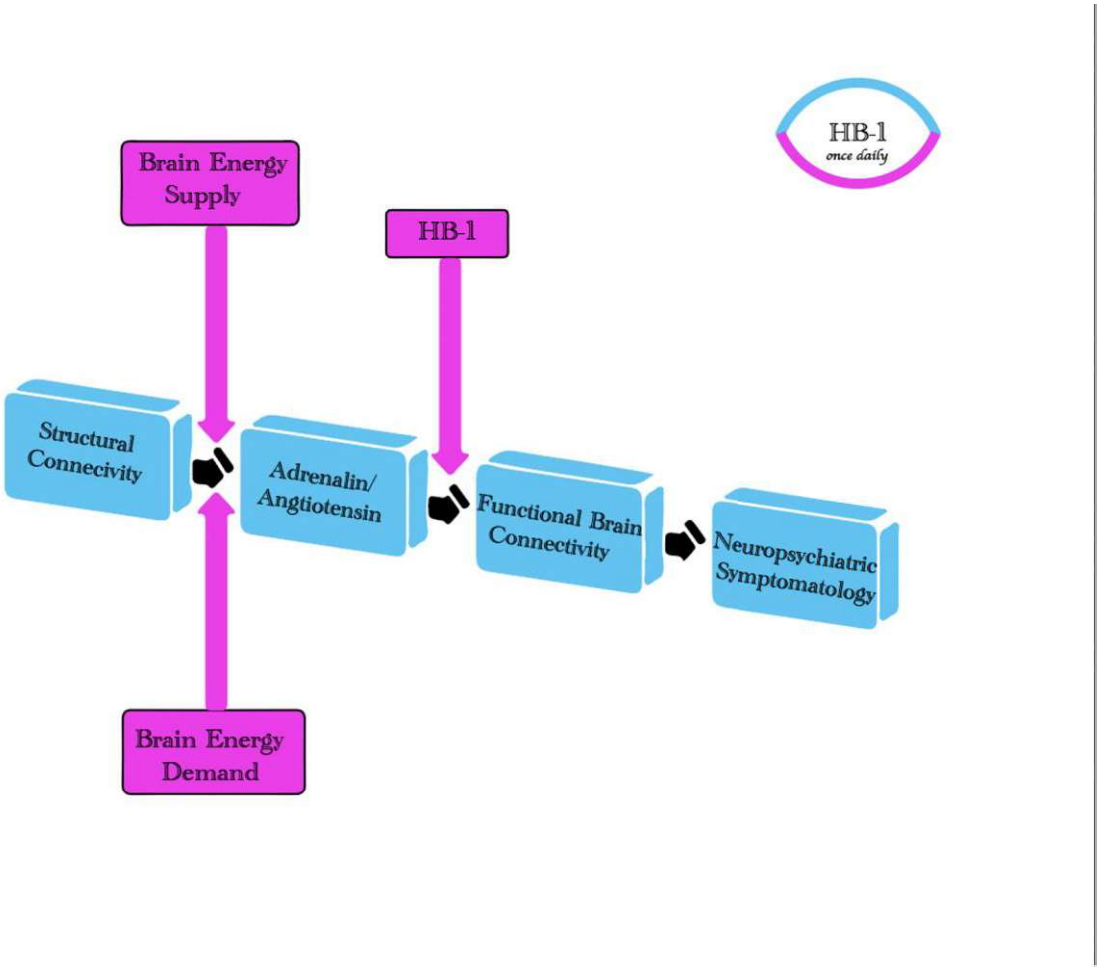
New treatments that safely improve whole brain functional connectivity could radically transform outcomes for people suffering from Psychiatric Disorders (Tumati S. 2021). Anxiety disorders (ie, Panic Disorder, Social Anxiety Disorder, Generalized Anxiety Disorder, Obsessive Compulsive Disorder, Post-traumatic Stress Disorder and Specific Phobia) are a clinically diverse group of disorders that have significant pathophysiological overlap. Anxiety disorders commonly feature disequilibrium in functional connectivity. Specifically, simultaneous alterations within more than one functional brain network, such as default mode, salience and somatomotor networks, are common to these disorders (Kim Y, Yoon H. 2018). Anxiety disorders also commonly feature dysregulations in both adrenergic and angiotensin systems (Winter A. 2019, Killgore W. 2014, Milani A. 2017). For example, patients with Panic Disorder and also patients with Post-Traumatic Stress Disorder display atypical brain connectivity in regions that govern autonomic nervous system regulation (Faravelli C. 1997, Rotella F. 2014, Reiman E. 1984, Owega A. 2001). In fact, successful treatment of symptoms for anxiety disorders is associated with resolution of multiple atypical patterns of regional cerebral connectivity (Zandvakili A. 2020, Lai C. 2013).

This study introduces HB-1, a fixed dose combination of 96 mg telmisartan and 288 mg verapamil, two previously FDA-approved antihypertensives, as a novel therapeutic agent targeting symptoms and quality of life (QoL) for patients with Panic Disorder. HB-1 works by re-equilibrating functional networks within the telencephalon and the mesencephalon brain regions. HB-1 is a promising treatment for Panic Disorder because Panic Disorder is characterized by abnormal physiological stress responses associated with disequilibrium in more than one functional brain network.

This study hypothesizes that, in patients with Panic Disorder, HB-1 demonstrates a comparable safety profile compared to the safety profiles of the individual agents; and a statistically significant reduction in disease severity, compared to placebo. This study will also examine the effects of HB-1 in treating the most commonly experienced co-morbidities in patients diagnosed with Panic Disorder.

These hypotheses are based on real-world clinical observation of significant improvement in anxiety and cognitive symptomatology in a diverse group of Neurology & Psychiatry patients who received these co-administered medications at a community-based Neuropsychiatry specialty practice. Regarding safety, adverse events were minimal, and systolic and diastolic blood pressure did not change significantly before and after an average of nine months of treatment observations. Regarding effectiveness, drastic reductions in symptomatology were noted across a broad array of disabling symptoms in patients not only with Panic Disorder but also with common co-morbidities. This hypothesis is also based on an extensive body of literature that describes relationships between psychosocial stress, emotional intelligence, theories of human motivation, quality of life, the adrenergic system, functional connectivity, angiotensin receptors and calcium channels (Lea R. 2019, Zheng Z. 2016, Sagar-Ouriaghli I. 2018, Keller S. 2003) (see Figure 1).

Figure 1: HB-1



1.1. Unmet Need

Currently, no FDA-approved treatments for anxiety disorders are designed to improve whole brain functional connectivity by targeting the angiotensin and adrenalin systems simultaneously. This is a critical research gap because anxiety disorders are 1) common, 2) debilitating, 3) co--morbid and 4) difficult to treat (Cerda M. 2010). Panic Disorder, for example, is prevalent in 6% of primary care patients (Katon W. 1986). Current FDA-approved treatments, which target symptomatology using neurotransmitter-specific approaches, are limited due to adverse reactions, including abuse potential. For example, current treatments for Panic Disorder include selective serotonin reuptake inhibitors (SSRIs), which have a small to medium effects, and benzodiazepines, which are not beneficial for long-term use due to tolerance, dependence, cognitive disturbance, and exacerbation of co-morbid mood disorders (Otto M. 1989, Edwards R. 1980). Regarding future treatments, the drugs currently being tested for Panic Disorder target mechanisms of action similar to currently approved treatments.

Whereas many of the anxiety disorders feature hundreds of novel treatment options in development, Panic Disorder represents an important disorder with fewer options in

development. There are few planned or active Phase 2 or 3 studies for the treatment of Panic Disorder in adults.

1.2. HB-1 for the Treatment of Panic Disorder

The Sponsor plans to develop a single dosage formulation therapy of verapamil and telmisartan for the treatment of Panic Disorder in adults. HB-1 contains telmisartan and verapamil, two products previously approved by the FDA for the treatment of cardiovascular conditions. Telmisartan (Micardis®) was approved by the FDA in 1998 and Verapamil (Verelan® PM) was approved in the United States in 1981. HB-1 is dosed using a specific ratio of verapamil to telmisartan which leads to its unique clinical effects. HB-1 treatment is expected to help patients achieve greater reductions in specific symptomatology, faster psychosocial advancement, and higher quality of life, with a mechanism of action related to normalization of asymmetric cerebral blood flow patterns that cause disability.

At this time, Honeybrains has conducted an IRB-approved, observational cohort study of a diverse group of neurology and psychiatry patients who received combination therapy with telmisartan and verapamil from 2019 to March 2020. The trial included a total of 102 patients, ages 18 to 70, with clinically diagnosed panic disorder, social anxiety disorder, ADHD, and other co-morbidities such as PTSD, migraine, and/or chronic musculoskeletal pain. Overall, the treatment appeared to significantly reduce symptomatology without causing adverse symptomatology or changes to vital signs. Specifically, the average self-reported symptom severity was significantly reduced in eight of the 10 cardinal neuropsychiatric symptoms (ie, anxiety, depression, irritability, apathy, body pain, insomnia, headache, cognitive difficulty) post treatment compared to baseline. Effect sizes were largest for anxiety, apathy, cognitive difficulty and overall neuropsychiatric disability. Psychosocial outcomes (NIH Toolbox General Life Satisfaction) were significantly better after combination treatment. Post-treatment systolic and diastolic blood pressure measurements did not change significantly from baseline. The effect of combination therapy on vital signs was no different than the effect of individual telmisartan or individual verapamil. The Overall Medical Review of Symptoms score was not significantly higher at one month or last observation; in fact, it was lower. Also, the rate of adverse symptoms from combination treatment was similar to known rates of adverse symptoms from verapamil and telmisartan. Importantly, the lateralization of the Weber test, which indicates the dominant side of activity of the auditory functional network, changed significantly when patients went on or off treatment, suggesting that the mechanisms of action is acting on reversible patterns of functional connectivity.

In summary, this study suggested that in terms of safety HB-1 was well tolerated, with an adverse event profile that is no different than those of the individual agents, and as a novel therapeutic agent HB-1 is hypothesized to significantly reduce disease severity in patients with panic disorder and ADHD. An extensive body of literature supports the use of this co-administration and describes relationships between psychosocial stress, the adrenergic system, functional connectivity, cerebral blood flow, angiotensin receptors and calcium channels (Kikuchi K. 2020, Jennings JR. 2009). Collectively, findings from the clinical data and from prior research suggest that treatments that normalize cerebral blood flow may lead to more complete relief of inter-related neuropsychiatric symptoms (anxiety, depression, irritability, body

pain, fatigue, headache, apathy, cognitive difficulty, psychosis, insomnia) that are germane to different neurological and behavioral health disorders.

1.3. HB-1

HB-1, a fixed dose combination of 96 mg telmisartan and 288 mg verapamil, two previously FDA-approved antihypertensives, is a novel therapeutic agent targeting symptoms and QoL for patients with Panic Disorder. HB-1 treatment is expected to help patients achieve greater reductions in specific symptomatology, faster psychosocial advancement, and higher QoL, with a mechanism of action related to normalization of asymmetric cerebral blood flow patterns that cause disability. HB-1 is a new treatment which modulates the brain renin angiotensin system (RAS) and adrenergic system simultaneously, resulting in a central hemodynamic that improves outcomes in different neuropsychiatric disorders. The use of treatments that target central mechanisms common to more than one co-morbidity could radically improve the quality of outcomes in neurological and behavioral disorders.

1.4. Telmisartan

Telmisartan, an angiotensin II type 1 receptor (AT1) blocker, is approved for the treatment of hypertension. The pro-inflammatory properties of angiotensin II as well as its anti-inflammatory effects are well-established (Fan X. 2017). Poor adaptation to stress, alterations in cerebrovascular function and excessive brain inflammation play critical roles in the pathophysiology of many psychiatric and neurological disorders (Saavedra JM. 2012). AT1 blockade may have a therapeutic effect in these types of disorders.

1.5. Verapamil Hydrochloride

Verapamil is a calcium channel antagonist used in cardiovascular diseases such as hypertension, angina, and certain arrythmias. It is used clinically as a racemic mixture that contains equal amounts of (R)- verapamil and (S)- verapamil. Its antihypertensive effects result from causing a decrease in peripheral vascular resistance. It specifically blocks the L-type calcium channel along with other, lesser characterized, calcium channels (T-, P-, and possibly N- and Q-type Ca (2+) channels) (Tfelt-Hansen P. 2009, Dobrev D. 1999).

P-glycoprotein function, which is involved in verapamil BBB efflux, is associated with several neurodegenerative and psychiatric diseases (van Assema DM. 2012). Measures of psychiatric morbidity in patients taking verapamil tended to improve, such as measurements of cognitive scores and psychiatric comorbidity scores (Palmer A. 1990). Multiple studies found verapamil to be well tolerated in patients with bipolar disorder with therapeutic effects in mania comparable to amitriptyline, prazosin and propranolol (Cipriani A. 2016). Other psychiatric clinical measures have shown significant improvement with verapamil therapy such as the Brief Psychiatric Rating Scale (BPRS) and general impression.

1.6. Study Overview

This multicenter, randomized, double-blind, placebo-controlled trial will assess the safety of HB-1 and effectiveness of HB-1 versus placebo for the treatment of Panic Disorder. This study will enroll approximately 80 patients who meet DSM-5 criteria for the diagnosis of Panic Disorder recruited from approximately eight clinical research sites. All patients will receive an oral dose

of HB-1 or matching placebo once a day. HB-1 is a proprietary combination of telmisartan and verapamil in a once-daily, extended release formulation.

2. OBJECTIVES

2.1. Primary Objective

To determine the safety and efficacy of HB-1 versus placebo in male and female adult patients aged 18 to 60 years, inclusive, with Panic Disorder.

2.2. Exploratory Objective

To compare the effectiveness of HB-1 on Common Neuropsychiatric Co-Morbidities.

3. ENDPOINTS

3.1. Safety Endpoints

Incidence of Treatment Emergent Adverse Events (TEAEs), clinically significant changes in clinical laboratory values, changes in electrocardiogram (ECG), and Columbia Suicide Severity Rating Scale (C-SSRS) (Oquendo MA 2003), and orthostatic vital signs.

3.2. Efficacy Endpoints

- Change in Panic Disorder Symptom Severity Scale (PDSS) (Furukawa T. 2009) - primary efficacy endpoint.
- Number of panic attacks
- Change in Clinical Global Impression-Severity Scale (CGI-S) (Guy W. 1976)
- Change in Quality of Life Enjoyment and Satification Questionaire Short Form (Q-LES-Q-SF) (Endicott J. 1993)
- Change in Leibowitz Anxiety Scale (LSAS) (Heimberg R. 1999, Baker S. 2002)
- Change in Assessment of Overall Sleep Quality -- Question #6 from the Pittsburgh Sleep Quality Index (Buysse DJ. 1989)

3.3. Exploratory Endpoints

- Change in Toronto Alexithymia Scale (TAS-20) (Bagby R. 2020)
- Change in Hamilton Anxiety Rating Scale (HAM-A) (Bech P. 1990)
- Change in Montgomery-Asberg Depression Rating Scale (MADRS) (Fantino B., Moore N. 2009) only for patients with a medical history of depression
- Change in CogScreen Symbol Digit Coding test (SDC) (Kay G. 1995)
- Change in Conners' Adult ADHD Rating Scale (CAARS) (Walls B. 2017) only for patients with a medical history of ADHD
- Change in The PTSD Checklist for DSM-5 (Blake DD. 1995, Blevins CA. 2015) only for patients with a medical history of PTSD

- Change in Short Form McGill Pain Questionnaire (SF-MPQ) (Melzack R. 1987) only for patients with a medical history of chronic pain
- Change in Migraine Disability Assessment Questionnaire (MIDAS) (Lipton RB. 2001) only for patients with a medical history of migraine

4. STUDY DESIGN AND DESCRIPTION

4.1. Study Design

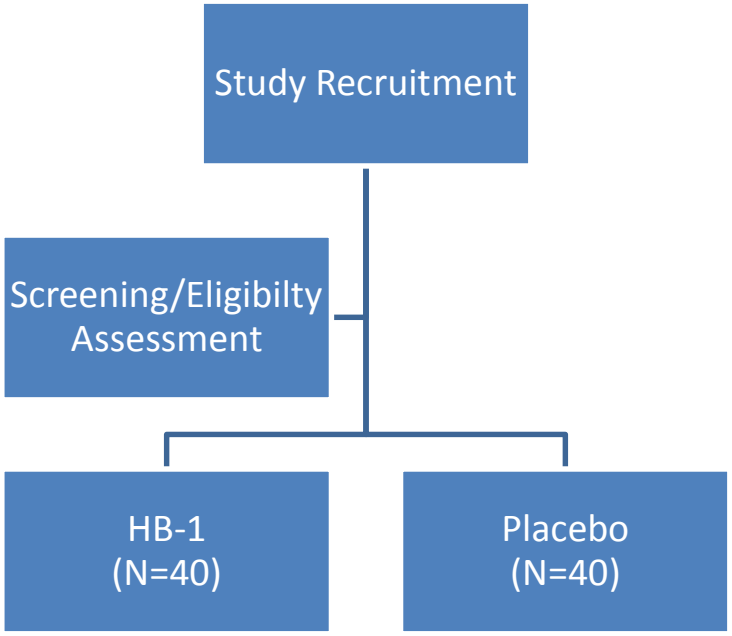
This is a multicenter, randomized, double-blind, placebo-controlled trial. All patients with Panic Disorder, with or without specified co-morbidities, who meet all of the inclusion and none of the exclusion criteria will be eligible. Patients and researchers will be blinded to their treatment group.

Approximately 80 patients with Panic Disorder will be enrolled and randomized in a 1:1 ratio to HB-1 or placebo using a central randomization.

The study design is presented in Figure 2. A schedule of assessments is presented in Table 1.

Figure 2: Study Design

Safety and Effectiveness of HB-1 for Panic Disorder



4.2. Justification for Study Design, Dose, and Endpoints

This study was designed as a pragmatic trial because in real-world conditions most panic disorder patients have multiple neuropsychiatric co-morbidities and are usually taking one or more medications. Pragmatic trial design was chosen because pragmatic trials are useful to

address questions related to generalizability and variability in response. Pragmatic trials can be useful to evaluate the effectiveness of an intervention in real-world setting, ie, in patients who may not be adherent to treatment and/or who have co-morbid conditions. Pragmatic trials focus on a wide range of outcomes, such as symptoms, mechanisms, functional status, quality of life, and costs.

A pragmatic study design that enables wider inclusion of patients, regardless of whether they have co-morbidities, or are already on treatment, was also important in order to increase the recruitability of patients (reduce exclusionary criteria). A pragmatic design is enabled by the fact that the drug does not interact with most common psychiatric treatments.

4.3. Dosing Frequency

HB-1 and placebo are dosed once a day (QD), nightly at bedtime (QHS) with or without food.

4.4. Monitoring of Adverse Events

Safety will be assessed through the monitoring of Adverse Events (AEs), Treatment Emergent Adverse Events (TEAEs), clinical laboratory assessments, ECGs, Columbia Suicide Severity Rating Scale (C-SSRS) (Oquendo MA 2003), and orthostatic vital signs. Patients will be monitored for safety from the first dose of HB-1 or placebo at study Week 0 through the Safety Follow-up visit. Serious adverse events (SAEs) will be reported immedidately to the sponsor and recorded in the eCRF.

Table 2 below provides guidance on the management of known toxicities that have been associated with verapamil or telmisartan monotherapy. If any of the following criteria are met, the subject will have study treatment discontinued and the Medical Monitor must be informed immediately. Subjects may discontinue study treatment, however, and remain in the study (see Section 4.5). The stopping criteria listed below will also be captured as adverse events (see Section 8).

Table 2: Subject Specific Stopping Criteria

Cardiac Disorders	
Hypotension	• SBP <90 mmHg and DBP <60 mmHg for three consecutive readings 10 minutes apart
Orthostatic Hypotension	• Decline of ≥20mm Hg in systolic or ≥10 mm Hg in diastolic blood pressure after 3 minutes of standing.
New-onset 2nd or 3rd degree AV block	• Grade 1 or higher per CTCAE V5.0*
Sick sinus syndrome	• Grade 1 or higher per CTCAE V5.0
Atrial flutter	• Grade 1 or higher per CTCAE V5.0
Atrial fibrillation	• Grade 1 or higher per CTCAE V5.0
New-onset bradycardia	• Resting heart rate below 50
New-onset tachycardia	• Resting heart rate above 120

Onset of angina pectoris	• Grade 1 or higher per CTCAE V5.0
Congestive heart failure	• Grade 1 or higher per CTCAE V5.0
Pulmonary edema	• Grade 1 or higher per CTCAE V5.0
Peripheral edema	• Grade 2 or higher per CTCAE V5.0
General Disorders	
Urticaria	• Grade 2 or higher per CTCAE V5.0
Hyperkalemia	• Potassium values that are 2X the ULN for the local lab normal refences ranges. • Values may be repeated and confirmed.
Gout exacerbation	• Hyperuricemia Grade 1 or higher per CTCAE V5.0 • Values may be repeated and confirmed.
Impaired hepatic function	• ALT, AST, ALP values that are twice the upper or lower limit of local lab normal reference range. • Values may be repeated and confirmed.
Impaired renal function	• Doubling in creatinine value. • Values may be repeated and confirmed.
Thrombocytopenia	• Platelet count values below 150,000/mL • Values may be repeated and confirmed.

*Common Terminology Criteria for Adverse Events (CTCAE) V5 dated 27Nov2017

Women who are using oral contraceptives will be monitored for adverse events associated with overexposure at each study visit. This should include signs and symptoms of myocardial infarction, stroke, and venous thromboembolism.

4.5. Treatment Discontinuation

Patients who discontinue from study treatment prior to Week 12/Visit 6 should complete an End of Study (EOS) visit. The EOS visit should be conducted within 7 days from the last dose of study treatment. Patients may discontinue study treatment and remain in the study. If a patient discontinues study treatment for any reason, the patient should continue to follow the schedule of assessments through the Safety Follow-Up Phone Call with modified assessments at interim visits including Week 12/Visit 6 as follows:

- Number of Panic Attacks
- Columbia Suicide Severity Rating Scale (C-SSRS) (Oquendo MA 2003)
- Efficacy Endpoint Questionairres
- Exploratory Endpoint Questionanires (when applicable)
- Concomitant Medications
- Adverse Event Monitoring

Patients will be discontinued from treatment for any of the following reasons:

- An AE that requires permanent discontinuation of study treatment*
- Noncompliance to the protocol
- Investigator decision for any medically appropriate reason or belief that further treatment is undesirable or the risk-benefit profile has become unfavorable
- Patient becomes pregnant
- Patient lost to follow-up
- Termination of the study by the Sponsor
- Voluntary withdrawal of consent by patient

* *AEs leading to the discontinuation of study treatment will be followed until resolution, resolution to baseline or until the event is considered stable or chronic.*

4.6. Study Discontinuation

Patients are free to withdraw from participation in the study at any time, for any reason, and without prejudice. The Investigator must withdraw any patient from the study if the patient withdraws consent and requests to stop participating in the study.

In the event the patient withdraws from the study, if possible, an End of Study (EOS) Visit should occur within 7 days after the last dose of study treatment. Patients may discontinue study treatment and remain in the study (see Section 4.5).

5. STUDY POPULATION

5.1. Inclusion Criteria

All patients must meet the following criteria for inclusion:

1. Male or female, aged 18 to 60 years old, inclusive, at the time of informed consent.
2. Meets DSM-5 Criteria for Panic Disorder.
3. Documented moderate to severe levels of symptoms at baseline Panic Disorder Severity Scale of 13 or above (Furukawa TA. 2009).
4. Medically stable on current medication regimen for at least 3 months (including PRN medications), as determined by clinician.
5. Willing to remain on current doses of other psychiatric medications throughout the length of the trial trial.
6. Willing and able to safely stop any of the following medications at least 5 days prior to Visit 2: Inhibitors or inducers of CYP3A4 (erythromycin, ritonavir, telithromycin, rifampin), HMG-CoA Reductase Inhibitors (Simvastatin, Lovastatin, Atorvastatin), Beta Blockers (Timolol eyedrops, Metoprolol), Neuromuscular Blocking Agents (curare-like and depolarizing), Antihypertensive Agents (Prazosin and vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta blockers, alpha agonists), Inhalation Anesthetics, Disopyramide, Flecainide, Quinidine, Cimetidine, Lithium, Carbamazepine, Phenobarbital, Cyclosporine,, Aliskiren, Ramipril and Ramiprilat, aspirin, Theophylline, mTOR inhibitors.
7. Willing and able to avoid consumption of grapefruit, grapefruit juice and Seville oranges within two weeks of screening through the last dose of study treatment.
8. Willing and able to limit consumption of alcohol to three servings per day defined as: 1 serving of beer=12 ounces (5% alcohol content); 1 serving of malt liquor=8 ounces (7% alcohol content); 1 serving of wine=5 ounces (12% alcohol content); 1 serving of distilled spirits=1.5 ounces (40% alcohol content).
9. Willing and able to avoid concomitant administration of sensitive P-glycoprotein substrates (digoxin, fexofenadine, dabigatran etexilate, talinolol, loperamide, vinblastine).
10. Fluent in English.
11. Willing to take HB-1.
12. Willing and able to provide informed consent indicating an understanding of the requirements of the study and a willingness to comply with scheduled visits and all study procedures.
13. Female patients must be surgically sterile (or have a monogamous partner who is surgically sterile), or be at least 2 years postmenopausal, or commits to use 2 acceptable forms of birth control (defined as the use of an intrauterine device (IUD), a barrier method with spermicide, condoms, or any form of hormonal contraceptives) for the duration of the study and for 4 months following the last dose of study treatment. Male patients must be sterile (biologically or surgically) or commit to the use of a reliable

method of birth control (condoms with spermicide) for the duration of the study and for 4 months following the last dose of study treatment . Individuals who are involved exclusively in same-sex relationships are exempt from the birth control requirements but must agree to abide by the recommendations if they do engage in a heterosexual relationship.

14. Female patients who are women of childbearing potential (WOCBP) must have a negative pregnancy test at Screening within 7 days of dosing with study treatment.

5.2. Exclusion Criteria

Patients are to be excluded from the study if they meet any of the following criteria:

1. Severe uncontrolled cardiac disease within 6 months of Screening, including but not limited to uncontrolled hypertension, hypotension (defined as below 90/60); unstable angina; myocardial infarction (MI) or cerebrovascular accident (CVA).
2. Any clinically significant electrocardiogram (ECG) abnormalities at screening.
3. History of atrial flutter, atrial fibrillation or hypertrophic cardiomyopathy.
4. Inadequate hepatic function defined as total bilirubin >1.5 × the upper limit of normal (ULN) ranges of each institution, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >3 × the ULN range of each institution.
5. Inadequate renal function defined as serum creatinine >1.5 × the ULN range of each institution and/or eGFR <60.
6. Any clinically significant abnormalities in clinical laboratory assessments as assessed by the investigator.
7. Any other systemic conditions or organ abnormalities that in the opinion of the Investigator may interfere with the conduct and/or interpretation of the current study.
8. Unable to complete neuropsychological testing.
9. Diagnosis of Bipolar I, Bipolar II disorder or Schizophrenia.
10. History of suicidal behaviors including ideation.
11. Current treatment with doses of benzodiazepines that are outside the FDA-approved prescriber’s information.
12. Use of tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) is prohibited.
13. Already on treatment with either telmisartan or verapamil or both.
14. Documented prior drug allergy to either telmisartan or verapamil.
15. Documented contraindication to taking telmisartan or verapamil (eg, Duchenne's muscular dystrophy, myasthenia gravis).
16. Documented moderate to severe substance abuse within the last 6 months (recreational cannabis use is allowed).
17. Pregnant or breastfeeding.

6. STUDY PROCEDURES AND ASSESSMENTS

Time points for assessments to be collected throughout the study can be found in the Schedule of Assessments (Table 1). A brief description of each assessment can be found below.

6.1. Screening and Treatment Procedures and Assessments

6.1.1. Informed Consent Form

An ICF must be signed by prospective patients prior to initiating any study-specific procedures. Standard of care assessments performed prior to ICF signing may fulfill study eligibility requirements if performed within the screening period.

6.1.2. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria (Section 5.1 and Section 5.2, respectively) will be reviewed for each potential patient. Eligibility assessments will include the Mini International Neuropsychiatric Interview for DSM-5 (MINI) (Sheehan DV. 1998; Sheehan DV. 1992-2016) and Panic Disorder Symptom Severity Scale (PDSS) (Furukawa T. 2009). Eligibility will be documented in the electronic case report form (eCRF).

6.1.3. Medical History, Demographics, Neurological and Behavioral Health History

Complete medical history will be obtained, including demographics, neurological and behavioral health information. Demographics will include: Age, Sex, Race, Ethnicity, Education, Gender Identity, Lateral Preference Questions, and Parental Education.

6.1.4. Concomitant Medications and Procedures

At Screening, concomitant medications will be recorded. Assessment of any change in concomitant medications or procedures since the last visit will occur at all further patient visits through safety follow-up.

6.1.5. Physical Exam

Physical exams will be conducted at the time points specified in the Schedule of Assessments (Table 1). The physical examination at screening will consist of the following body systems:

- **Head, eyes, ears, nose, and throat exam**: inspection, palpation ,and testing, as appropriate.
- **Cardiovascular evaluation**: Auscultation of the carotid arteries and left anterior chest to evaluate heart sounds and possible murmurs.
- **Respiratory assessment**: Observation of inspiration and expiration. Auscultation of breath sounds both anterior and posterior chest.
- **Musculosketal assessment**: Muscles, bones, and joints are assessed by functional grouping using techniques of inspection, palpation, and manipulation while the clinician observes responses and reactions.
- **Neurological exam**: Observation of mental awareness. Testing of gross motor function and reflexes.

- **Skin and lymph node check**: Skin tone/pallor and lymph nodes are inspected.

Any abnormal change from the initial screening physical examination must be assessed by the investigator as not clinically significant (NCS) or clinically significant (CS) and recorded in the source document and eCRF.

Any CS change after Visit 2, as determined by the investigator, will be recorded as an AE in source documentation and on the AE eCRF.

6.1.6. Height, Weight, and BMI

Height, weight, and BMI will be collected at screening.

6.1.7. Orthostatic Vital Signs

Orthostatic vital signs check will be performed at the time points specified in the Schedule of Assessments (Table 1). Orthostatic vital signs should include the following steps based up the Agency for Healthcare Research and Quality procedure (Tool3F):

1. Instruct the patient on the process of orthostatic blood pressure measurement and its rationale.
2. Assess by verbal report and observation the patient's ability to stand.
3. Have patient lie in bed with the head flat for a minimum of 3 minutes.
4. Measure the blood pressure and the pulse while the patient is supine.
5. Instruct patient to sit for 1 minute.
    a. Ask patient about dizziness, weakness, or visual changes associated with position change. Note diaphoresis or pallor.
    b. Check sitting blood pressure and pulse.
    c. If the patient has symptoms associated with position change or sitting blood pressure ≤ 90/60, put patient back to bed.
6. Instruct patient to stand.
    a. Ask patient about dizziness, weakness, or visual changes associated with position change. Note diaphoresis or pallor.
    b. If patient is unable to stand, sit patient upright with legs dangling over the edge of the bed.
    c. The patient should be permitted to resume a supine position immediately if syncope or near syncope develops.
7. Measure the blood pressure and pulse 3 minutes after patient stands. Support the forearm at heart level when taking the blood pressures to prevent inaccurate measurement.
8. Assist patient back to bed in a position of comfort.
9. Document vital signs and other pertinent observations on the nursing flowsheet or in the medical record. Note all measurements taken and the position of the patient during each reading.

Subtract values 3 minutes after standing (or if patient cannot stand, then sitting) from lying values. A decline of ≥20mm Hg in systolic or ≥10 mm Hg in diastolic blood pressure after 3 minutes of standing indicates orthostatic hypotension. Clinically significant orthostatic hypotension should be treated per standard of care and the Medical Monitor should be contacted.

6.1.8. Clinical Laboratory Tests

The following laboratory parameters will be measured at the time points specified in the Schedule of Assessments (Table 1) and will be analyzed locally:

- Pregnancy test should be administered for women of child-bearing potential (WOCBP) within 7 days prior to Week 0 and then at each subsequent study visit.
- Comprehensive Metabolic Panel (CMP): albumin, blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine, creatinine phosphokinase, glucose, potassium, sodium, total bilirubin, total protein, alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST)
- Complete Blood Count (CBC): white blood cell count, red blood cell count, hematocrit, hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglaobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution (RDW), platemet cont, mean platelet volume (MPV), Vitamin B12
- Urinalysis:microscopic examination, specific gravity, pH, protein, glucose, ketones, blood and urobilinogen

6.1.9. Study Treatment Administration

Detailed instructions on the administration of study treatment can be found in Section 7.

6.1.10. Adverse Events (AEs)

All AEs should be captured on the eCRF from Visit 2/Week 0 through the Safety Follow-up visit. Adverse events considered at least possibly related to study treatment should be followed until resolution, return to baseline, or deemed chronic or stable.

All serious adverse events (SAEs) will be immediately reported to the Sponsor from the time of Visit 2/Week 0 (dosing) through the Safety Follow-up/End of Study Visit.

See Section 8.2 for a full description of the collection and reporting of AEs during this study.

6.1.11. Electrocardiogram (ECG)

At Visit 1/Screening, Visit 4/Week 4, Visit 5/Week 8 and Visit 6/Week 12 a standard 12-lead ECG will be conducted. following an approximate 10-minute rest period in all patients and will be interpreted by the Investigator to assess clinical significance.

6.1.12. Weber Test

A Weber Test will be conducted at Baseline/Visit 2 and Visit 6/Week 12. The Weber test is a test of lateralization of auditory function. Tap the tuning fork strongly on your palm and then press the butt of the instrument on the top of the patient's head in the midline and ask the patient where they hear the sound. Normally, the sound is heard in the center of the head or equally in both ears. If there is a conductive hearing loss present, the vibration will be louder on the side with the conductive hearing loss. If the patient does not hear the vibration at all, attempt again, but press the butt harder on the patient's head.

Weber Test results will be documented on the eCRF.

6.1.13. Assessments and Questionnaires

6.1.13.1. Mini International Neuropsychiatric Interview for DSM-5 (MINI)

The Mini International Neuropsychiatric Interview (MINI) is a brief, structured diagnostic interview for the major psychiatric disorders in DSM-5 (Sheehan DV. 1998; Sheehan DV. 1992-2016). It is routinely used to assess psychiatric diagnoses in clinical trials. The Standard MINI with the additional Attention Deficit Hyperactivity Disorder (ADHD) module will be used at Screening.

6.1.13.2. Placebo-Control Reminder Script (PCRS)

Placebo-Control Reminder Script (PCRS) (Cohen, EA. 2021) will be administered immediately prior to administering the PDSS at Visits 3-6.

6.1.13.3. Panic Disorder Symptom Severity Scale (PDSS)

The PDSS is a brief clinician rating scale designed to rate severity and treatment progress in individuals diagnosed with Panic Disorder (Furukawa TA. 2009).

6.1.13.4. Number of Panic Attacks

The patient will be asked "How many panic attacks have you had in the last week?" at Visits 1-6. The clinician will confirm the reported panic attack(s) meet DSM-5 criteria (APA 2013).

6.1.13.5. Assessment of Overall Sleep Quality

The patient will be asked "During the past month, how would you rate your sleep quality overall?" at Visit 2 and Visits 4-6. This is question #6 from the Pittsburgh Sleep Quality Index (Buysse DJ. 1989).

6.1.13.6. Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS) (Oquendo MA 2003) is a suicidal ideation rating scale. The scale identifies behaviors and thoughts that are associated with an increased risk of suicidal actions in the future. The C-SSRS Baseline/Screening version will be conducted at Screening. The C-SSRS Since Last Visit version will be conducted at each post-Screening visit, including Baseline.

If the investigator determines that a patient is at risk of suicide or self-harm, appropriate measures to ensure the patient's safety and obtain mental health evaluation must be implemented. Patients who meet criteria will be referred to a local psychiatrist for prompt evaluation and also to the National Suicide Prevention Hotline. The patient must immediately be discontinued from the study. The event should be recorded as either an AE or SAE as determined by the investigator and reported within 24 hours to the Sponsor.

6.1.13.7. Clinical Global Impression-Severity Scale (CGI-S)

The CGI-S scale is a tool used by clinicans to assess the severity of illness in relation to the clinicans previous experience with other patients with that diagnosis (Guy W. 1976).

6.1.13.8. Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF)

The Quality of Life Enjoyment and Satisfaction Scale – Short Form (Q-LES-SF) is a 16-item, self-administered questionnaire that captures an individual's satisfaction with and enjoyment of life. Item scores range from 1 to 5 (Endicott J. 1993). The Total Score is reported as the percentage of the maximum possible score (Raw Score – Minimum Possible Score / Maximum Possible Score – Minimum Possible Score).

6.1.13.9. Self Report Leibowitz Anxiety Scale (LSAS)

The LSAS questionnaire is a self report rating scale used to assess social anxiety in individuals and has been validated for use as self-report (Heimberg R. 1999, Baker S. 2002).

6.1.13.10. Toronto Alexithymia Scale (TAS-20)

The TAS-20 is a self-administered assessment looking at how one identifies and describes emotions (Bagby RM. 2020).

6.1.13.11. Hamilton Anxiety Rating Scale (HAM-A)

The Hamilton Anxiety Scale (HAM-A) is a 14-item, clinician-administered scale that measuresseverity of anxiety (Bech P. 1990). Symptoms assessed include those associated with mental agitation,psychological distress, and physical complaints related to anxiety. Items are scored along a rangefrom 0 to 4; the Total Score (sum of all item scores) ranges from 0 to 56. Higher scores reflectgreater severity of anxiety symptoms.

6.1.13.12. Montgomery-Asberg Depression Rating Scale (MADRS)

The Montgomery-Asberg Depression Rating Scale (MADRS) is a 10-item, clinician administered interview assessing severity of depressive symptoms (Fantino B., Moore N. 2009). Item scores range from 0 to 6, with the Overall Score (sum of all item scores) ranging from 0 – 60. Higher scores reflect greater severity of depressive symptoms. This assessment should only be administered to patients with a medical history of depression.

6.1.13.13. CogScreen Symbol Digit Coding test (SDC)

The CogScreen Symbol Digit Coding test (SDC) is a computer-based digit symbol substitution task administered by trained study staff (Kay G. 1995). SDC measures attention, visual scanning, working memory, and speed of information processing.

6.1.13.14. Conners' Adult ADHD Rating Scale (CAARS)

The Conners' Adult ADHD Rating Scale (CAARS) is a self-report assessment evaluating symptoms and behaviors in adults with ADHD (Walls B. 2017). This assessment should only be administered to patients with a medical history of ADHD.

6.1.13.15. The PTSD Checklist for DSM-5

The PTSD Checklist for DSM-5 (PCL) is a 20-item self-report measure of the DSM-5 symptoms of PTSD (Blake D. 1995, Blevins C. 2015). This assessment should only be administered to patients with a history of PTSD.

6.1.13.16. Short Form McGill Pain Questionnaire (SF-MPQ)

The SF-MPQ is a short self-report assessment evaluating pain using sensory and affective subscales from the longer original MPQ assessment (Melzack R. 1987). This assessment should only be administered to patients with a medical history of chronic pain.

6.1.13.17. Migraine Disability Assessment Questionnaire (MIDAS)

The MIDAS questionnaire is a self-report measure that assesses the impact, level of pain, and disability due to an individuals headaches (Lipton R. 2001). This assessment should only be administered to patients with a medical history of migraine.

6.1.14. Safety Follow-Up Phone Call

All patients will have a Safety Follow-Up Phone call approximately 7 days after the last study visit (Visit 6 or EOS), unless the patient withdraws from the study prematurely. During this safety follow-up phone call, information on ongoing and new AEs will be collected.

6.2. Concomitant Medications

6.2.1. Other Concomitant Therapies

Any other medication that is considered necessary for the patient's welfare, including medications for neuropsychiatric disorders (such as SSRI's, benzodiazepines, stimulant medications, antipsychotics, mood stabilizers) and that is not expected to interfere with the evaluation of HB-1 may be given at the discretion of the Investigator. Patients are expected to remain stable on their psychiatric medications throughout the duration of the trial.

Treatment with doses of benzodiazepines that are outside the FDA-approved prescriber's information are excluded.

The following concomitant medications are also excluded per protocol: Inhibitors or inducers of CYP3A4 (erythromycin, ritonavir, telithromycin, rifampin), HMG-CoA Reductase Inhibitors (Simvastatin, Lovastatin, Atorvastatin), Beta Blockers (Timolol eyedrops, Metoprolol), Neuromuscular Blocking Agents (curare-like and depolarizing), Antihypertensive Agents (Prazosin and vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta blockers, alpha agonists), Inhalation Anesthetics, Disopyramide, Flecainide, Quinidine, Cimetidine, Lithium, Carbamazepine, Phenobarbital, Cyclosporine, Aliskiren, Ramipril and Ramiprilat, aspirin, Theophylline, mTOR inhibitors; sensitive P-glycoprotein substrates (digoxin, fexofenadine, dabigatran etexilate, talinolol, loperamide, vinblastine); grapefruit, grapefruit juice and Seville oranges within two weeks of screening through the last dose of study treatment.

Additionally, patients are required to limit consumption of alcohol to three servings per day defined as: 1 serving of beer=12 ounces (5% alcohol content); 1 serving of malt liquor=8 ounces

(7% alcohol content); 1 serving of wine=5 ounces (12% alcohol content); 1 serving of distilled spirits=1.5 ounces (40% alcohol content

6.2.2. Contraception and Pregnancy

The effects of HB-1 on conception, pregnancy, and lactation are unknown.

Note: According to the information available in the Micardis® (telmisartan) label, telmisartan belongs to p*regnancy categories C (first trimester) and D (second and third trimesters). When pregnancy is detected, discontinue telmisartan as soon as possible, as it can cause fetal harm when administered to a pregnant woman.*

According to the information available in Verelan® PM (verapamil hydrochloride) label, verapamil belongs to pregnancy category C, there are no adequate and well-controlled studies in pregnant women. Verapamil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery.

At Screening, all female patients who are not surgically sterile or postmenopausal must agree to use at least 2 acceptable methods of birth control (defined as the use of an IUD, a barrier method with spermicide, condoms, or any form of hormonal contraceptives,) for the duration of the study and for 4 months after the last dose of study treatment.

At Screening, all male patients who are not sterile (biologically or surgically) must commit to the use of a reliable method of birth control (condoms with spermicide) for the duration of the study and for 4 months after the last dose of study treatment. Male patients should not donate sperm for 4 months following the last dose of study treatment.

Individuals who are involved exclusively in same-sex relationships are exempt from the birth control requirements but must agree to abide by the recommendations if they do engage in a heterosexual relationship.

Women who are using oral contraceptives will be monitored for adverse events associated with overexposure at each study visit. This should include signs and symptoms of myocardial infarction, stroke, and venous thromboembolism.

7. HB-1 MATERIALS AND MANAGEMENT

The Sponsor plans to develop HB-1 as a single dosage formulation of telmisartan and verapamil which will be administered orally once a day (QD) nightly at bedtime (QHS) with or without food. The Sponsor plans to dose HB-1 at 96 mg telmisartan and 288 mg verapamil with extended-release technology to distribute the components as evenly as possible throughout a 24 hour day. The proposed dosages to be used in HB-1 are within FDA-approved PK parameters [maximum serum concentration (C_{max}) and area under the curve (AUC)] and are based on the safety and efficacy of the combination treatment of telmisartan and verapamil in the Sponsor's completed observational study.

7.1. HB-1

7.1.1. Description of HB-1

HB-1 will be supplied as oval, white to off-white dual active pharmaceutical ingredient (API) tablet and will be packaged with 35 tablets per HDPE bottle with 1g of desiccants and a child resistant closure.

Telmisartan

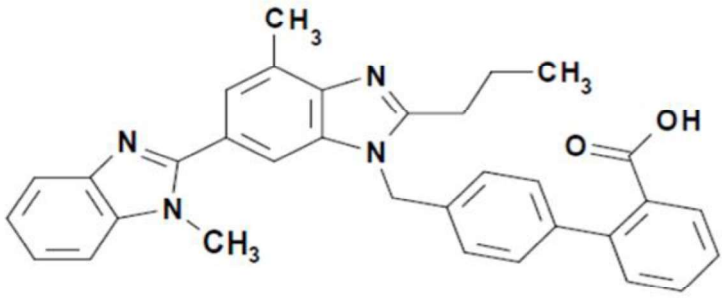
Generic name: telmisartan (immediate release)

Chemical name: [1,1`-Biphenyl]-2-caboxylic acid, 4`-[(1,4`-dimethyl-2`-propyl[2,6`-bi-1H-benzimidazol]-1`-yl) methyl]-

CAS Registry Number: 144701-48-4

Formula: $C_{33}H_{30}N_4O_2$

Figure 3: Structure of Telmisartan



Molecular Weight: 514.62

Appearance: White to slightly yellowish crystalline powder

Solubility: Practically insoluble in water, slightly soluble in methanol, sparingly soluble in methylene chloride

Verapamil Hydrochloride

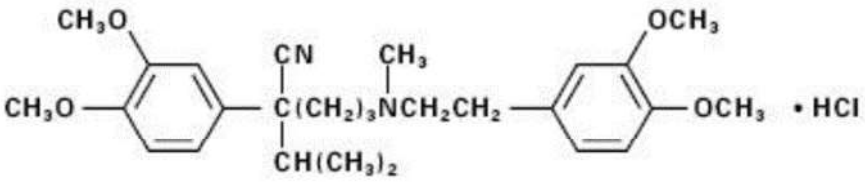
Generic name: verapamil hydrochloride (extended release)

Chemical name: Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)-ethyl]methylamino]propyl]-3,4-dimethoxy-α-(1-methylethyl), monohydrochloride

CAS Registry Number: 52-53-9

Formula: $C_{27}H_{36}N_2O_4 \cdot HCl$

Figure 4: Structure of Verapamil Hydrochloride



Molecular weight: 491.07

Appearance: An almost white, crystalline powder

Solubility: Soluble in water, chloroform, and methanol

7.1.2. Dosage and Administration

All patients will receive an oral dose of HB-1 or matching placebo once a day (QD) nightly at bedtime (QHS) with or without food. HB-1 is a proprietary combination of telmisartan and verapamil in a once-daily, extended release formulation.

7.1.3. Storage and Handling

All study drug must be transported, received, stored, and handled in accordance with the container or product label, the instructions supplied to the site and its designated pharmacy personnel, the site's standard operating procedures (SOPs), and applicable regulations.

Appropriate storage and transportation conditions will be maintained for study treatment from the point of manufacture up to delivery to the clinical sites. All shipments of study treatment will include a temperature monitoring device that records required storage conditions for the bottles at regular intervals for the entire time the shipment is in transit.

Upon receipt by the site, the designated site personnel will examine the shipment and temperature monitoring devices to verify the study treatment bottles were received in acceptable condition. If not received in acceptable condition, the site must notify their Clinical Research Associate and the site should quarantine the study drug until a decision has been made by Honeybrains regarding its use. Once inspected, bottles should be stored at USP Controlled Room Temperature Conditions, 20°C to 25°C in a locked, limited access area.

7.2. Drug Accountability

The Investigator or designee is responsible for taking an inventory of each shipment of drug received and comparing it with the accompanying drug order form. All unused drug will be retained at the site. After full drug accountability and reconciliation, the Investigator will dispose of any drug at the clinical trial site per site procedures, or if necessary, all drug will be returned to the Sponsor or its designee. Disposition of all drug should be documented, including any drug that is lost or damaged.

7.3. Assignment to Treatment

Once enrolled, each patient will be assigned a unique subject identification number. This number will be recorded on the patient's eCRF pages and used to identify the patient throughout the study. Once a subject number is assigned, it cannot be reassigned to any other patient. All patients will either be assigned to receive HB-1 or placebo using a central randomization system.. Patients and Investigators will be blinded to the study treatment assignment.

Study treatment will be dispensed to patients in blinded bottles. Bottle 1 will be dispensed at Visit 2/Week 0; patient will bring it back for accountability at Visit 3/Week 2 and will take it back home; patient will return Bottle 1 at Visit 4/Week 4 and will be dispensed Bottle 2 (with return of Bottle 2 at Visit 5/Week 8); then Bottle 3 will be dispensed at Visit 5/Week 8 (and returned at Visit 6/Week 12).

7.4. Unblinding Procedure

The study drug blind shall not be broken by the Investigator unless information concerning the study drug is necessary for the medical treatment of the subject. All study assessments and assignment of causality for AEs should be performed, if possible, prior to unblinding. In the event of a medical emergency, if possible, the medical monitor should be contacted before the study drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the study drug blind can be broken via the central randomization system.

The sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded, study drug must be stopped immediately and the subject must be withdrawn from the study.

No change should be made to any prior assessments or data of any subject after unblinding of his/her treatment assignment.

8. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

The Medical Monitor will perform an ongoing blinded review of safety and tolerability and will advise on whether it is safe to continue study treatment. Safety will be assessed through the monitoring of TEAEs, clinical laboratory assessments, ECG, Columbia Suicide Severity Rating Scale (C-SSRS) (Oquendo MA 2003), and orthostatic vital signs.

8.1. Adverse Events

8.1.1. Definition of an Adverse Event (AE)

An AE is defined as any untoward medical occurrence associated with the use of a drug, or with study participation, whether or not consider related to study treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.

AEs include worsening of a pre-existing medical condition as well as clinically significant changes from baseline laboratory values/conditions. Worsening of the preexisting medical condition (eg, diabetes, hypertension) means that it has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study is not considered an AE.

8.1.2. Definition of Treatment Emergent Adverse Event (TEAE)

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the drug treatment or any event already present that worsens in either intensity or frequency following exposure to the drug treatment.

8.1.3. Definition of Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization.
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF (as documented as medical history on the eCRF) is not considered an SAE
    - Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience, is not considered an SAE
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect
- Is considered an important medical event

- If an AE does not meet one of the serious criteria, but the Investigator or Sponsor considers an event to be clinically important, the event could be classified as an SAE under the criterion of "Important medical event."

8.2. Procedures for Recording and Reporting Adverse Events

8.2.1. Recording Adverse Events

Patients will be instructed to report all AEs and will be asked a general health status question at each study visit. All AEs and SAEs occurring in patients will be recorded in the eCRF from Visit 2/Week 0 through the Saftey Follow-up Visit after the last dose of drug. An AE will be followed until it is either resolved, has returned to baseline, or is determined to be a stable or chronic condition. All SAEs will be processed as outlined in Section 8.2.2.

At each required visit during the trial, all AEs that have occurred since the previous visit must be reviewed by the Investigator. The Investigator must determine if the AE is serious or non-serious.

The Investigator must assign the following AE attributes:

- AE diagnosis or syndrome(s) if known
  - If not known at time of the report, record the signs and/or symptoms as AEs and provide an updated report with diagnosis when obtained
- Dates of onset and resolution
- Severity as defined per protocol
- Assessment of relatedness to drug
- Action taken with drug as a result of the AE

In general, an AE that is the primary cause of subsequent events should be identified by the primary cause (eg, for dehydration due to diarrhea, the AE would be diarrhea). However, AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events (eg, sepsis secondary to pneumonia, both events should be recorded).

8.2.1.1. Relationship to Study Treatment

The Investigator must assess whether the AE may be related to study drug or study mandated procedure, when applicable. The relationship is defined below:

Relationship assessments that indicate the event is "Not Drug Related":

- None: The event is related to an etiology other than the study product administration (the alternative etiology must be documented in the study patient's medical record).
- Remote: The event is unlikely to be related to the study product and likely to be related to factors other than study product.

Relationship assessments that indicate the event is "Drug Related":

- Possible: There is an association between the event and the administration of drug, and there is a plausible mechanism for the event to be related to the study product; but there

may also be alternative etiology, such as characteristics of the patient's clinical status or underlying disease.

- Probable: There is an association between the event and the administration of drug, there is a plausible mechanism for the event to be related to the study product, and the event could not be reasonably explained by known characteristics of the patient's clinical status or an alternative etiology is not apparent.
- Definite: There is an association between the event and the administration of drug, there is a plausible mechanism for the event to be related to the study product and causes other than drug have been ruled out and/or the event re-appeared on re-exposure to drug.

8.2.1.2. Adverse Event Severity

The Investigator will assess the Grade of the AE using the criteria below:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Note: it is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity, whereas seriousness is classified by the criteria based on the regulatory definitions as described in Section 8.1.3 above.

8.2.2. Reporting of Serious Adverse Events

SAEs will be reported to the sponsor immediately and recorded on the appropriate eCRF and SAE Report Form within 24 hours of the Investigator's first knowledge of the event, even if the experience does not appear to be related to drug, from the Visit 2/Week 0 through the Safety Follow-up visit after the last dose of study drug.

The initial SAE eCRF must be as complete as possible, including details of the current illness and SAE, and an assessment of the relationship between the event and drug. Additional information relating to a previously reported SAE must also be reported within 24 hours of the Investigator's first knowledge of information. The Investigator may also be asked, by the Sponsor or designee, to provide clarifications or additional information.

8.2.2.1. Reporting of Serious Adverse Events to Regulatory Authorities and Institutional Review Board

The Sponsor or designee will determine expectedness of the Sponsor's product for each reported SAE based on the appropriate reference safety information per local requirements. The Sponsor

or designee shall notify regulatory authorities of serious, unexpected, and related AEs or other AEs, per local requirements.

The Sponsor or designee shall notify the Investigator of serious, related, and unexpected AE(s) submitted to the regulatory agencies, per local country requirements.

The Investigator will notify the appropriate IRB of serious, related, and unexpected AE(s), or significant risks to patients, per local country requirements. The Investigator must keep copies of all AE information on file, including correspondence with the Sponsor or IRBs.

9. STATISTICAL METHODS

9.1. General Considerations

This is a multicenter, randomized, double-blind placebo-controlled trial. All patients will be randomized in a 1:1 ratio to receive an oral dose of HB-1 or matching placebo once a day. Study data will be provided in listings and sorted by patient number, study period, and assessment time. The study results will be displayed using descriptive summary tables and inferential analyses completed as described below. Summaries will be displayed by treatment group for all tables. For measurements that have multiple intermediate visits, results for observed data will be summarized for each time point.

Standard numeric descriptive statistics include number of patients or records observed (N), mean, standard deviation (std), median, minimum (min), and maximum (max) values. Standard categorical descriptive statistics include the count and percentages of patients with a level of the variable summarized. Hypothesis tests will assess the null hypothesis that there is no difference between HB-1 and placebo treatment arms. Testing will be done at the 0.05 alpha-level. Any confidence intervals provided will be at 95% confidence.

All summaries, statistical analyses, and individual patient data listings described below will be completed using Version 9.4 or later of the SAS Statistical Analysis System (SAS Institute, Inc. Cary, NC).

Additional details regarding estimands, including handling of intercurrent events will be provided in a separate statistical analysis plan (SAP) to be finalized prior to completion of the study and unblinding.

Determination of Sample Size

A sample size of 80 patients is planned for the study to be randomized in a 1:1 ratio of active to control.

Assuming a standard deviation of 4.5 in the PDSS, 80 patients will provide for in excess of 95% power to detect a difference in the mean change (from baseline) in the PDSS score of 3.75 at an alpha-level of 0.05 at 12 weeks. This corresponds to a 50% reduction in mean PDSS scores on HB-1 and a 25% reduction in mean PDSS scores on placebo, assuming baseline mean PDSS scores of 15 for both groups.

In addition, with respect to adverse events, the study has approximately 95% power to detect at least one patient with an event that occurs in 7.2% of patients in either treatment group.

Analysis Populations

Analyses will be performed comparing treatment groups for each of the following populations:

All Patients – all patients who sign informed consent and are assigned a unique patient identification number.

Intent-to-Treat (ITT) – all patients who are successfully randomized to either the HB-1 or control treatment groups. This will be the primary population used for efficacy analyses. Patients will be analyzed according to randomized treatment group.

Safety Population – patients who are randomized and receive at least one dose of study drug. This will be the primary population used to summarize all safety data. Safety summaries will be based on the treatment that patients actually receive.

Handling of Missing Data

Data may be missing either because an assessment is not completed or if patients have withdrawn consent from further participation in the study. Additional details for handling missing data will be dependent on the extent of missing data and will be specified in the SAP.

Adjustments of Multiplicity

To control for multiplicity of select analyses, a hierarchical approach will be used to test the following endpoints in order, each at the 0.05 alpha-level. These endpoints are 1) PDSS (primary efficacy endpoint), 2) mean number of panic attacks, 3) CGI-S. Irrespective, of the significance of these specific measures, planning for future studies will be based on the totality of safety and efficacy data and nominal p-values will be reported for all inferential tests.

Interim Analyses

Interim analyses are not planned for this study.

Patient Disposition

Patient disposition will be summarized for the All Patients population and summarized by treatment group and overall for all patients. The number and percentage of patients who are screened, screen-failed, randomized, and completed the treatment period, follow-up period, or discontinued the study (including reasons for discontinuation) will be presented.

Demographics and Baseline Characteristics

Demographics information will be summarized using descriptive statistics. For gender, race, and ethnicity the summarization of those categorical values will be performed using percentages and frequency. Age, height, weight, and BMI will be summarized using descriptive statistics as total number of patient observed (n), mean, median, minimum, and maximum. Listings and summaries of demographics, baseline characteristics, and medical history, will be summarized by treatment group for the Safety population.

Extent of Exposure to Study Medications and Treatment Compliance

All patients will receive an oral dose of HB-1 or matching placebo once a day for a total of 12 weeks. One (1) bottle will be dispensed to the patient at Visits 2, 4 and 5. Study drug accountability will be performed at Visits 3 – 6 and study drug bottles will be returned at Visits 4-6.

Drug exposure and compliance will be summarized by treatment for the safety population. Drug exposure (in days) will be calculated as: last dose date - first dose date + 1. Exposure will be summarized as a continuous variable for the treatment period. Percent compliance will be calculated by visit and overall for the treatment period. Compliance will be summarized as a continuous variable.

Prior and Concomitant Therapies

All patients with Panic Disorder, with or without co-morbidities will be eligible, as long as they are stable on their current psychiatric medications for at least three months as determined by Investigator and are willing to remain on current doses of other psychiatric medications throughout the length of the trial. Concomitant medications will be summarized categorically by treatment group for the safety population by visit and overall for the treatment period.

Efficacy and Exploratory Analyses

All efficacy and exploratory analyses shall be conducted by treatment group on the ITT population. These endpoints are based on measurement scales collected over the visits of the study. Each of the scales may have domains or subdomains.

A mixed model repeated measures (MMRM) approach, with fixed effects for treatment, visit, the treatment-by-visit interaction, baseline, baseline-by-visit, will be used to analyze continuous endpoints. The outcome is the change from baseline to each on-treatment time point. All protocol-scheduled time points will be included in the model. The model will use the unstructured or Toeplitz (whichever has a better fit by AICC value) within-subject variance-covariance matrix. The denominator degrees of freedom will be according to the method of Kenward-Roger. The estimated least square (LS) means and their standard errors as well as the estimated treatment effect (differences between treatments at each time point) will be summarized by treatment. In addition, the 95% confidence intervals of the LS means and the difference between treatments, p-values for treatment comparisons will be provided. For endpoints without a baseline measurement, baseline and the visit-by-baseline interaction will be omitted from the model. The primary analysis timepoint will be at 12 weeks.

Efficacy Endpoint Analyses

Scales of interest Panic Disorder are the:

- Panic Disorder Symptom Severity Scale (PDSS) (Furukawa TA. 2009)
- Number of panic attacks
- Clinical Global Impression-Severity Scale (CGI-S) (Guy W. 1976)
- Quality of Life Enjoyment and Satisfaction Questionaire Short Form (Q-LES-Q-SF) (Endicott J. 1993)
- Self-Reported Leibowitz Anxiety Scale (LSAS) (Heimberg R. 1999, Baker S. 2002)
- Assessment of Overall Sleep Quality—Question #6 from the Pittsburgh Sleep Quality Index (Buysse DJ. 1989)

Exploratory Endpoint Analyses

The objective of all exploratory endpoints is to compare the effectiveness of HB-1 versus placebo on common neuropsychiatric comorbidities. Analyses will be conducted in the same manner as efficacy endpoints. The questionnaires which will be used for exploratory endpoints include:

- Toronto Alexithymia Scale (TAS-20) (Bagby RM. 2020)
- Hamilton Anxiety Rating Scale (HAM-A) (Bech P. 1990)
- Montgomery-Asberg Depression Rating Scale (MADRS) (Fantino B., Moore N. 2009) only for patients with a medical history of depression
- CogScreen Symbol Digit Coding test (SDC) (Kay G. 1995)
- Conners' Adult ADHD Rating Scale (CAARS) (Walls B. 2017) only for patients with a medical history of ADHD
- The PTSD Checklist for DSM-5 (Short Form McGill Pain Questionnaire (SF-MPQ) (Blake D. 1995, Blevins C. 2015) only for patients with a medical history of PTSD
- Migraine Disability Assessment Questionnaire (MIDAS) (Lipton R. 2001) only for patients with a medical history of migraine
- Short Form McGill Pain Questionnaire (SF-MPQ) (Melzack R. 1987) only for patients with a history of chronic pain.

Safety Analyses

Safety endpoints include TEAEs, clinical laboratory abnormalities, changes in ECG, and orthostatic vital signs between treatment groups. C-SSRS (Oquendo MA 2003) results will be provided in a listing. All summaries of safety and tolerability will be performed on data from the safety population using descriptive statistics only unless otherwise specified.

Adverse Events

All adverse events will be summarized descriptively by group without comparison between the groups. An overall summary of aderse events should be provided to the show the the number and percentage of patients with at least one TEAEs, at least one serious TEAEs, at least one drug related event, and at least one serious drug-related event. The total number of each event type will also be summarized along the severity and relatedness distribution of all events.

Summaries of the number and percentage of patients in the safety population with at least one adverse event, classified according to preferred term and/or body system using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) will be provided for the following types of AEs:

- TEAEs
- Drug Related TEAEs
- SAEs

- Drug Related SAEs
- AEs by severity (mild, moderate, severe, life-threatening, death)
- AEs by relationship (not related, remote, possible, probable, definite)

Clinical Laboratory Evaluations

Clinical laboratory results will be collected at screening and at each visit specified in the Schedule of Assessments table. Clinical laboratory test results for pregnancy, comprehensive metabolid panel, complete blood count, and urinalysis, will be summarized by treatment group and presented in tabular and graphic formats where appropriate. Descriptive summaries of the change from baseline calculations will be provided along with 95% CIs for the mean change from baseline within each group will be provided, but no formal statistical tests are planned between treatment groups. Any abnormal finding or clinically significant changes will be captured as AEs.

Vital Signs and ECGs

Vital signs check and ECGs will be performed at the time points specified in the Schedule of Assessments. Vital signs parameters (including blood pressure and pulse rate after 3 minutes of lying flat in a supine position; followed by blood pressure and pulse rate after standing for 3 minutes) and ECG results will be summarized by treatment group and presented in tabular and graphic formats where appropriate. Descriptive summaries of the change from baseline calculations will be provided along with 95% CIs for the mean change from baseline to detect potentially significant changes in vital sign values or ECG results. ECG abnormalities will be summarized by timepoint and for post-baseline assessments, the number and percentage of patients with new abnormalities will be summarized.

Physical Examinations

Physical examination findings will be listed for each patient at each assessment time point as specified in the Schedule of Assessments. Any abnormal change from the initial screening physical examination must be assessed by the investigator as not clinically significant or clinically significant and recorded in the source document and eCRF. Clinically significant new findings and adverse changes in physical examination findings will be captured as AEs or pretreatment events. Body systems which will be inspected for physical examinaions include: head, eyes; ears, nose, throat; cardiovascular system; respiratory system; musculoskeletal system; neurological exam; skin; lymph nodes.

10. STUDY ADMINISTRATION

10.1. Good Clinical Practice Statement

This study is to be performed in accordance with the protocol, the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) E6 (R2), and all applicable local laws and regulatory requirements.

10.2. Informed Consent (ICF)

The Sponsor or designee will provide a sample patient informed consent form (ICF) for modification, as appropriate, by the Investigator. The ICF must include all elements required by ICH and GCP and must adhere to the IRB/IEC requirements and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator or designee will explain the nature of the study, its purpose and associated procedures, the expected duration, and the potential risks involved to the patient prior to enrollment. The Investigator or designee will obtain written, informed consent. The patient will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Following the discussion regarding the study, a patient will be asked if they are willing to sign and personally date a statement of informed consent. Only if the patient voluntarily agrees to sign the informed consent statement and has done so, may he/she enter the study. A copy of the signed and dated ICF will be provided to the patient. The original signed ICF is to remain in the Investigator's file, per local requirements.

The ICF and any other written information provided to the patients will be revised whenever important new information becomes available that may be relevant to the patient's consent, or if there is an amendment to the protocol which necessitates a change to the content of the patient's informed consent. The Investigator will inform the patients of changes in a timely manner and will ask the patients to confirm continuation of their participation in the study by their signature on the revised ICF (if applicable). Any written ICF and written information must receive the approval/favorable opinion of the IRB in advance of use. Any additional approvals from the initial ICF should be forwarded to the Sponsor.

10.3. Patient Confidentiality

The written ICF will explain that study data will be stored in a database, maintaining confidentiality in accordance with national data legislation. All data processed by the Sponsor or its representative(s) will be identified by patient number and study code.

The written ICF will also explain that for data verification purposes, authorized representatives of the Sponsor, a regulatory authority, and an IRB may require direct access to parts of the hospital or clinic records relevant to the study that include the patient's medical history.

The Investigator must ensure that the patients' anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor, patients should not be identified by their names, but by their assigned patient number and study code. Documents not for submission to the Sponsor, such as signed ICF, should be maintained in strict confidence by the Investigator.

10.4. Institutional Review Board Requirements

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an institutional review board (IRB) at each clinical trial site. The Principal Investigator must submit written approval from the IRB to the Sponsor before he or she can enroll any patient into the study.

The Principal Investigator is responsible for informing the IRB of any amendment to the protocol. In addition, the IRB must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB annually or as required by the IRB, regulations, and guidelines.

Progress reports and notifications of SAEs will be provided to the IRB according to regulations and guidelines.

10.5. Case Report Forms and Source Documentation

eCRFs will be provided for the recording of all data. The Principal Investigator or designee will record data from all observations, tests, and assessments specified in the protocol on the eCRFs provided by the Sponsor.

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Honeybrains and should not be made available in any form to third parties without written permission from Honeybrains.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, and /or source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts. In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site, as well as at Honeybrains and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

10.6. Sponsor Monitoring

Before the first patient signs consent to participate in the study, a representative of the Sponsor will perform a qualification visit (either in person or remotely) to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to the protocol and the responsibilities of the Sponsor

- Confirm that the Investigator(s) (and other personnel involved with the study) have not invoked sanctions or demonstrated any scientific misconduct or fraud

During the conduct of the study, a representative of the Sponsor will have regular contact with the clinical trial site, and have regular visits (either in person or remotely) with the clinical site to:

- Provide information and support the Investigator
- Confirm that the facilities remain acceptable
- Confirm that the study team is adhering to the protocol, data are being accurately recorded in the eCRFs, and the study drug is being properly maintained and accountability records are current
- Perform source data verification with access to all original clinical records for each patient

10.7. Quality Assurance

In compliance with GCP and regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, regulatory agencies or IRB may conduct quality assurance audits at any time during or following a study. The Investigator must agree to allow auditors direct access to all study-related documents, including source documents, and must agree to allocate his or her time and the time of his or her study staff to the auditors in order to discuss findings and issues.

10.8. Study or Clinical Site Termination

The Sponsor, or designee, reserves the right to terminate the study or a clinical trial site at any time. Conditions that may warrant termination of the study include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- The decision on the part of the Sponsor to suspend or discontinue testing the study treatment
- Failure of the Investigator to comply with GCP
- Submission of knowingly false information from the clinical trial site to the Sponsor or regulatory authorities
- Insufficient adherence to protocol requirements

If terminating the study, the Sponsor and the Investigator(s) will assure that adequate consideration is given to the protection of the patients' interests.

10.9. Records Retention

All correspondence related to this clinical study should be kept in appropriate study files. Records of patients, source documents, eCRFs, drug inventory, IRB, and Sponsor correspondence pertaining to this study must be kept on file. All study documents must be kept secured for a period of 2 years after a marketing application is approved for drug, or until 2 years

after shipment and delivery of the drug for investigational use is discontinued or as long as required by local regulations, whichever is longer. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing or relocating study records for any reason.

10.10. Publications

Publication by the clinical trial site(s) of any data from this study must be carried out in accordance with the Clinical Trial Agreement.

11. LIST OF REFERENCES

1. Kim YK, Yoon HK. Common and Distinct Brain Networks Underlying Panic and Social Anxiety Disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2018 Jan 3;80(Pt B):115-122. doi: 10.1016/j.pnpbp.2017.06.017. Epub 2017 Jun 19.

2. Winter A, Ahlbrand R, Sah R. Recruitment of Central Angiotensin II Type 1 Receptor Associated Neurocircuits in Carbon Dioxide Associated Fear. Prog Neuropsychopharmacol Biol Psychiatry. 2019 Jun 8;92:378-386. doi: 10.1016/j.pnpbp.2019.02.007. Epub 2019 Feb 16.

3. Killgore WD, Britton JC, Schwab ZJ, Price LM, Weiner MR, Gold AL, Rosso IM, Simon NM, Pollack MH, Rauch SL. Cortico-Limbic Responses to Masked Affective Faces Across PTSD, Panic Disorder, and Specific Phobia. Depress Anxiety. 2014 Feb;31(2):150-9. doi: 10.1002/da.22156. Epub 2013 Jul 16. PMID: 23861215

4. Milani AC, Hoffmann EV, Fossaluza V, Jackowski AP, Mello MF. Does Pediatric Post-Traumatic Stress Disorder Alter the Brain? Systematic Review and Meta-Analysis of Structural and Functional Magnetic Resonance Imaging Studies. Psychiatry Clin Neurosci. 2017 Mar;71(3):154-169. doi: 10.1111/pcn.12473. Epub 2017 Jan 6. PMID: 27778421

5. Faravelli C, Marinoni M, Spiti R, Ginanneschi A, Serena A, Fabbri C, Di Matteo C, Del Mastio M, Inzitari D. Abnormal Brain Hemodynamic Responses During Passive Orthostatic Challenge in Panic Disorder. Am J Psychiatry 1997;154(3):378-383.

6. Rotella F, Marinoni M, Lejeune F, Alari F, Depinesi D, Cosci F, Faravelli C. Brain Circulation during Panic Attack: A Transcranial Doppler Study with Clomipramine Challenge. Psychiatry J 2014;2014:296862.

7. Reiman EM, Raichle ME, Butler FK, Herscovitch P, Robins E. A Focal Brain Abnormality in Panic Disorder, A Severe Form of Anxiety. Nature 1984;310(5979):683-685.

8. Owega A, Sabri O, Klingelhofer J, Albers M. Cerebral Blood Flow Velocity in Untreated Panic Disorder Patients: A Transcranial Doppler Ultrasonography Study. Biol Psychiatry 2001;50(4):299-304.

9. Zandvakili A, Swearingen HR, Philip NS. Changes in Functional Connectivity After Theta-Burst Transcranial Magnetic Stimulation for Post-Traumatic Stress Disorder: A

Machine-Learning Study. Eur Arch Psychiatry Clin Neurosci. 2020 Jul 27. doi: 10.1007/s00406-020-01172-5. Online ahead of print. PMID: 32719969

10. Lai CH, Wu YT. Changes in Regional Homogeneity of Parieto-Temporal Regions in Panic Disorder Patients Who Achieved Remission with Antidepressant Treatment. J Affect Disord. 2013 Nov;151(2):709-14. doi: 10.1016/j.jad.2013.08.006. Epub 2013 Aug 19. PMID: 23993443

11. Cerdá M, Sagdeo A, Johnson J, Galea S. Genetic and Environmental Influences on Psychiatric Comorbidity: A Systematic Review. J Affect Disord. 2010 Oct;126(1-2):14-38. doi: 10.1016/j.jad.2009.11.006. Epub 2009 Dec 11. PMID: 20004978

12. Furukawa TA, Katherine Shear M, Barlow DH, Gorman JM, Woods SW, Money R, Etschel E, Engel RR, Leucht S. Evidence-Based Guidelines for Interpretation of the Panic Disorder Severity Scale. Depress Anxiety. 2009;26(10):922-9. doi: 10.1002/da.20532. PMID: 19006198

13. Guy, W. Clinical Global Impression, in ECDEU Assessment Manual for Psychopharmacology, W. Guy, Editor. 1976, National Institute of Mental Health: Rockville, MD. p. 218-21.

14. Kikuchi K, Fujita Y, Shen X, et al. Interaction between Angiotensin Receptor and β-Adrenergic Receptor Regulates the Production of Amyloid β-Protein. Biol. Pharm. Bull. 43, 731-735 (2020).

15. Bagby RM, Parker JDA, Taylor GJ. Twenty-five Years with the 20-item Toronto Alexithymia Scale. J Psychosom Res. 2020 Jan 23;131:109940. doi: 10.1016/j.jpsychores.2020.109940.

16. Palmer A, Fletcher A, Hamilton G, Muriss S, & Bulpitt C. A Comparison of Verapamil and Nifedipine on Qualtity of Life. Br. J. clin. Pharmac. (1990), 30, 35-370.

17. Heimberg RG, Horner KJ, Juster HR, Safren SA, Brown EJ, Schneier FR, Liebowitz MR. Psychometric properties of the Liebowitz Social Anxiety Scale. Psychol Med 1999;29(1):199-212.

18. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane TM. The development of a Clinician-Administered PTSD Scale. J Trauma Stress 1995;8(1):75-90.

19. Melzack R. The Short-Form McGill Pain Questionnaire. Pain 1987;30(2):191-197.

20. Lipton RB, Stewart WF, Sawyer J, Edmeads JG. Clinical Utility of an Instrument Assessing Migraine Disability: the Migraine Disability Assessment (MIDAS) questionnaire. Headache 2001;41(9):854-861.

21. Walls BD, Wallace ER, Brothers SL, Berry DT. Utility of the Conners' Adult ADHD Rating Scale Validity Scales in Identifying Simulated Attention-Deficit Hyperactivity Disorder and Random Responding. Psychol Assess 2017;29(12)1437-1446.

22. Tumati S, Paulus MP, Northoff G. Out-of-step: Brain-heart Desynchronization in Anxiety Disorders. Mol Psychiatry. 2021 Jan 27. doi: 10.1038/s41380-021-01029-w. Online ahead of print.PMID: 33504952.

23. Sieciński S, Kostka PS, Tkacz EJ. Heart Rate Variability Analysis on Electrocardiograms, Seismocardiograms and Gyrocardiograms on Healthy Volunteers. Sensors (Basel). 2020 Aug 13;20(16):4522. doi: 10.3390/s20164522.

24. Baker SL, Heinrichs N, Kim HJ, Hofmann SG. The Liebowitz Social Anxiety Scale as a Self-report Instrument: A Preliminary Psychometric Analysis. Behav Res Ther. 2002 Jun;40(6):701-15. doi: 10.1016/s0005-7967(01)00060-2.

25. Blevins CA, Weathers FW, Davis MT, et al. The Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5): Development and Initial Psychometric Evaluation. Trauma Stress. 2015 Dec;28(6):489-98. doi: 10.1002/jts.22059. Epub 2015 Nov 25.

26. Saavedra JM. Angiotensin II AT1 Receptor Blockers Ameliorate Inflammatory Stress: A Beneficial Effect for the Treatment of Brain Disorders. Cell Mol Neurobiol. 2012 July ; 32(5): 667–681. doi:10.1007/s10571-011-9754-6.

27. Cipriani A, Saunders K, Attenburrow M-J, Stefaniak J, Panchal P, Stockton S, Lane TA, Tunbridge EM, Geddes JR, and Harrison PJ. A Systematic Review of Calcium Channel Antagonists in Bipolar Disorder and Some Considerations for their Future Development. Molecular Psychiatry (2016) 21, 1324-1332.

28. Dobrev D, Milde AS, Andreas K, and Ravens U. The Effects of Verapamil and Diltiazem on N-, P- and Q-type Calcium Channels Mediating Dopamine Release in rat Striatum. British Journal of Pharmacology (1999) 127, 576-582.

29. van Assema DM, Lubberink M, Bauer M, van der Flier WM, Schuit RC, Windhorst AD, Comans EFI, Hoetjes NJ, Tolboom, N, Langer O, Muller M, Scheltens P, Lammertsma AA, and van Berckel BNM. Blood-Brain Barrier P-glycoprotein Function in Alheimer's Disease. Brain 2012: 135; 181–189.

30. Tfelt-Hansen P, and Tfelt-Hansen J. Verapamil for Cluster Headache. Clinical Pharmacology and Possible Mode of Action. Headache 2009;49:117-125.

31. Fan X, Song X, Zhao M, Jarskog LF, Natarajan R, Shukair N, Freudenreich O, Henderson DC, and Goff DC. The Effect of Adjunctive Telmisartan Treatment on Psychopathology and Cognition in Patients with Schizophrenia. Acta Psychiatr Scand. 2017 November ; 136(5): 465–472. doi:10.1111/acps.12799.

32. Otto MW, Tuby KS, Gould RA, McLean RY, Pollack MH. An Effect-Size Analysis of the Relative Efficacy and Tolerability of Serotonin Selective Reuptake Inhibitors for Panic Disorder. Am J Psychiatry. 2001 Dec;158(12):1989-92. doi: 10.1176/appi.ajp.158.12.1989.

33. Edwards RA, Medlicott RW. Advantages and Disadvantages of Benzodiazepine Prescription. N Z Med J. 1980 Nov 12;92(671):357-9.

34. Lea RG, Davis SK, Mahoney B, Qualter P. Does Emotional Intelligence Buffer the Effects of Acute Stress? A Systematic Review. Front Psychol. 2019 Apr 17;10:810. doi: 10.3389/fpsyg.2019.00810. eCollection 2019.

35. Zheng Z, Gu S, Lei Y, Lu S, Wang W, Li Y, Wang F. Safety Needs Mediate Stressful Events Induced Mental Disorders. Neural Plast. 2016;2016:8058093. doi: 10.1155/2016/8058093. Epub 2016 Sep 21.

36. Sagar-Ouriaghli I, Lievesley K, Santosh PJ. Propranolol for Treating Emotional, Behavioural, Autonomic Dysregulation in Children and Adolescents with Autism Spectrum Disorders. Psychopharmacol. 2018 Jun;32(6):641-653. doi: 10.1177/0269881118756245. Epub 2018 Feb 27.PMID: 29484909.

37. Keller S, Frishman WH. Neuropsychiatric Effects of Cardiovascular Drug Therapy. Cardiol Rev. 2003 Mar-Apr;11(2):73-93. doi: 10.1097/01.CRD.0000053453.89776.2D.PMID: 12620132.

38. Katon W. Panic Disorder: Epidemiology, Diagnosis, and Treatment in Primary Care. J Clin Psychiatry. 1986 Oct;47 Suppl:21-30.PMID: 3531189 Review.

39. .Jennings JR, Zanstra Y. Is the Brain the Essential in Hypertension? Neuroimage. 2009 Sep;47(3):914-21. doi: 10.1016/j.neuroimage.2009.04.072. Epub 2009 May 4.PMID: 19410005

40. Endicott J., Nee J., Harrison W., Blumenthal R. Quality of Life Enjoyment and Satisfaction Questionnaire: A New Measure. Psychopharmacol Bull. 1993;29(2):321-6.PMID: 8290681

41. Tool 3F: Orthostatic Vital Sign Measurement. Content last reviewed January 2013. Agency for Healthcare Research and Quality, Rockville, MD. https://www.ahrq.gov/patient-safety/settings/hospital/fall-prevention/toolkit/orthostatic-vital-sign.html

42. Bech P. Psychometric developments of the Hamilton scales: the spectrum of depression, dysthymia, and anxiety. Psychopharmacol Ser. 1990;9:72-9. doi: 10.1007/978-3-642-75373-2_9.PMID: 2204923

43. Kay G. *Cogscreen Aeromedical Edition Professional Manual*. Psychological Assessment Resources, Inc.; Odessa, FL: 1995.

44. Fantino B., Moore N. The self-reported Montgomery-Asberg Depression Rating Scale is a useful evaluative tool in Major Depressive Disorder. BMC Psychiatry. 2009 May 27;9:26. doi: 10.1186/1471-244X-9-26.PMID: 19473506

45. American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5). American Psychiatric Publishing: Washington, DC.

46. Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.

47. Buysse D.J., Reynolds C.F., Monk T.H., Berman S.R., & Kupfer D.J. (1989). The Pittsburgh Sleep Quality Index (PSQI): A new instrument for psychiatric research and practice. Psychiatry Research, 28(2), 193-213.

48. Cohen E.A., Hassman H.H., Ereshefsky L. *et al.* Placebo response mitigation with a participant-focused psychoeducational procedure: a randomized, single-blind, all placebo study in major depressive and psychotic disorders. *Neuropsychopharmacol.* 46, 844–850

49. . Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar G: The Mini International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview. *J. Clin Psychiatry*, 1998;59(suppl 20): 22-33. http://www.psychiatrist.com/JCP/article/Pages/1998/v59s20/v59s2005.aspx

50. Sheehan, D.V. (1992 - 2016). Mini International Psychiatric Interview, English Version 7.0.2 for DSM-5. Harm Research Institute.