BVR-100

CLINICAL STUDY PROTOCOL BVR100-102

BVR-100 and BES-100 Validation Trial: A Randomized, Double-Blind, Parallel-Group, Controlled Study of Two At-Home Self-Guided Virtual Reality Interventions for Adults with Social Anxiety Disorder

Version 1.00

June 21, 2023

[redacted]

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EMERGENCY CONTACTS

Table 1: Emergency Contact Information

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1. SYNOPSIS

Name of Sponsor/Company: Sunovion Pharmaceuticals Inc.

Device Name: BVR-100 and BES-100

Study Intervention: Virtual Reality Intervention

Study Number: BVR-100-102

Title of Study: BVR-100 and BES-100 Validation Trial: A Randomized, Double-Blind, Parallel-Group, Controlled Study of Two At-Home Self-Guided Virtual Reality Interventions for Adults with Social Anxiety Disorder.

Proposed Indication: Social Anxiety Disorder (SAD)

Study Centers: Approximately 4 clinical sites in the United States (US)

Phase of Development: Pre-Launch

Study Objectives:

The objective of this study is to compare two Virtual Reality (VR)-based interventions, BVR-100 and BES-100, for the treatment of Social Anxiety Disorder (SAD).

Primary:

To evaluate the credibility and expectation of benefit of BVR-100 and BES-100 for subjects with SAD, as measured with the Credibility and Expectancy Questionnaire (CEQ).

Secondary:

- To evaluate subject retention and time-on-task of BVR-100 and BES-100.

Exploratory:

- To explore subjects' experiences and acceptability of BVR-100 and BES-100 in a qualitative interview.
- To evaluate the therapeutic response of the two interventions for SAD on:
  - Fear and avoidance symptoms, as measured by the clinician-administered Liebowitz Social Anxiety Scale (LSAS)
  - Overall symptomatology and functioning, using the Clinical Global Impression Severity scale (CGI-S), the Clinical Global Impression Improvement scale (CGI-I), and the Patient Global Impression Improvement scale (PGI-I).
  - Depression symptoms, measured with the Patient Health Questionnaire (PHQ-9).

Safety:

- To evaluate the safety of BVR-100 and BES-100, as measured by:
  - Incidence of adverse events (AEs),
  - Incidence of serious adverse events (SAEs),
  - Incidence of unanticipated adverse device effects (UADEs), and
  - The Columbia Suicide Severity Rating Scale (C-SSRS).

Study Design:

This is a parallel-group, double-blind (subject and investigators/outcome assessors), randomized, controlled, decentralized, study. The aim of the study is to evaluate the credibility and acceptability, subject retention, and time-on-task of BVR-100 and BES-100 in a sample of subjects with Social Anxiety Disorder (SAD).

The study will include 3 periods as shown in the schematic below.

SCR	RND	Intervention Period (Double-Blind)				
		BSL / W1	W2	W4	W6	W8/EOS/ET
V1	V2	V3	V4	V5	V6	V7
Up to 14 days	Up to 7 days	Days 1-7	Days 8-14	Days 22-28	Days 36-42	Days 50-56

Abbreviations: SCR = Screening; RND = Randomization; BSL = baseline; EOS = end of study; ET = early termination; V = telehealth / call visits; W = week.

Study Visits

Screening and Washout

Informed consent will be obtained from each subject before any study-specific procedures are performed. Subjects will be evaluated for eligibility during a screening phase of up to 14 days. Psychiatric history will be reviewed, and diagnoses will be confirmed by the Principal Investigator (PI) or designee using the Mini-International Neuropsychiatric Interview (MINI). Prior experience with cognitive behavioral therapy (CBT) (ie, including questions about experiences with in-imagination or in-vivo exposure to fearful situations), use of concomitant medications and substance use, and baseline characteristics (ie, social anxiety symptoms measured with the LSAS, depression symptoms as measured by the PHQ-9, and suicidal ideation and behavior measured with the C-SSRS) will be assessed at Screening. Subjects will be asked to wash-out from disallowed psychotropic medications or herbal supplements during the Screening period. A seven-day extension to the Screening period may be allowed with Medical Monitor approval.

Subjects who screen fail due to temporary resolvable medical conditions unrelated to psychiatric entry criteria, or logistical issues with Screening procedures, may be re-screened up to two times if judged appropriate by the Investigator, after discussion and agreement with the Medical Monitor. Re-screened subjects will be re-consented, assigned a new subject number, and all Visit 1 procedures will be repeated.

Randomization

After Screening, subjects deemed eligible by the Investigator will be contacted by investigator site staff to be informed they are qualified to participate in the study. Randomization will occur after confirmation of eligibility and continued subject interest are verified. Subjects will be randomly allocated to either the treatment group (BVR-100) or the control (BES-100) group. Randomization will be assigned via an interactive web responses system (IWRS) in a 1:1 ratio to either BVR-100 or to BES-100. A VR headset pre-loaded with either BVR-100 or BES-100 will be shipped to the subject's address. Subjects will not be informed of their intervention allocation. In order to secure subject blinding, subjects will have no prior experience with CBT. Subjects will be instructed not to share descriptions of the intervention they are receiving with investigator site staff during visits and discouraged from discussing details of the therapy outside the study. The Baseline visit will be scheduled to occur within 5-7 days of the randomization visit, to allow adequate time for VR device delivery/receipt. If, due to delays with device delivery/receipt, an extension beyond the 7 days is necessary, Medical Monitor approval will be required.

Upon confirmation of device delivery, a member of the unblinded site support team will contact the subject to confirm receipt of the device, to establish a relationship, and to remind the subject that they would be the only contact for any device related issues throughout the duration of their participation in the study. After this is confirmed, the Baseline telehealth visit with the investigator site staff can take place.

Intervention Period

Baseline

The Baseline visit will be split into two separate parts. During the first part of the Baseline visit, a telehealth call will be performed with investigator site staff who will administer Baseline visit (Day 1) assessments including clinician-administered outcome measures (C-SSRS, LSAS, CGI-S), collect any adverse events (AEs), concomitant medication changes, and facilitate the delivery of Patient Reported Outcomes (PROs; PHQ-9). During the second part of the Baseline visit, after the call with the investigator site staff is completed, subjects will receive access to a video-guided VR onboarding session providing information to set-up the VR headset, guidance for the initial sign-up, and information about the intervention the subject has been allocated to. This session will be completed by the subject without any involvement of the investigator site staff. However, subjects will be able to reach out to a designated unblinded site support team for any assistance/guidance during the video-guided onboarding session or at any time thereafter. The designated unblinded site support team will ensure that both the video-onboarding and the first VR session are completed. After completing the video-guided onboarding and the first VR session, subjects will be asked to complete the CEQ.

Week 1 – Week 8

During Weeks 1 through 8, subjects will be asked to complete at home self-guided VR sessions. Subjects in both groups will be asked to engage in a minimum of three required VR sessions per week, for a period of 8 weeks. The Baseline visit is the first day of Week 1, and after baseline during the rest of the week, a minimum of two additional VR sessions must be completed by the subject. In addition to the required practices, subjects will be encouraged to also engage with optional content and to review content completed in previous sessions. Engagement with both study interventions will be monitored on a regular basis and notifications will be sent regularly to remind subjects to engage with the interventions. Unscheduled telehealth visits to complete/perform additional safety assessments may be conducted as deemed necessary by the investigator site staff/subject.

During Weeks 1 (aside from the Baseline visit), 3, 5, and 7, there will be no study assessments, or scheduled telehealth calls with investigator site staff completed.

After the VR sessions have been completed, subjects are requested to complete the Patient-Reported Outcomes (PROs) (PHQ-9, PGI-I, and CEQ) as applicable to each particular week, electronically as specified in the Schedule of Assessments. The scales should be reviewed on a bi-weekly basis, to ensure completeness, for any potential AEs that may be reported, and retraining provided to subjects as necessary. During the last 3 days of Weeks 2, 4, 6, and 8 (End of Study [EOS]/Early Termination [ET]), investigator site staff will conduct telehealth study visits to collect clinician-administered outcome measures (C-SSRS, LSAS, CGI-S, CGI-I), AEs and concomitant medication changes. For the Week 8 (EOS/ET) visit, an additional qualitative interview with a member of the unblinded site support team will occur to explore each subjects' experience with their respective interventions (BVR-100 or BES-100). All attempts will be made to ensure that each subject is assessed by the same investigator site staff to minimize confounding bias related to changes in assessor. In the event that subjects require technical support or further program instructions, support will be provided by the unblinded site support team not involved in data collection.

All AE data will be collected by investigator site staff during the check-ins and recorded in the electronic data capture (EDC). Subjects will be provided with contact information in the informed consent form to facilitate ready access to the site/Investigator in order to help address potential safety issues that may arise and to facilitate AE reporting.

Number of Subjects (planned): Approximately 40 subjects are planned (20 subjects per group). Subjects who discontinue early may be replaced at Sponsor discretion to assure that sufficient data for evaluation is collected.

Inclusion and Exclusion Criteria:

Inclusion criteria

1. Subject has provided written informed consent, obtained prior to initiation of any study-specific procedures.
2. Subject is male or female, aged 18 or above.
3. Subject has English fluency and literacy, sufficient to provide consent and follow study instructions as judged by the Investigator.
4. Subject meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5) criteria for Social Anxiety Disorder as established during the Screening visit using the MINI. Subjects may have a comorbid DSM-5 based diagnosis of generalized anxiety disorder and/or a comorbid DSM-5 based diagnosis of specific phobias provided the symptoms of the comorbid disorder(s) are secondary to symptoms of SAD and are considered stable during the 3 months prior to Screening, in the opinion of the Investigator.
5. Subject has a total Liebowitz Social Anxiety Scale (LSAS) score at Screening of ≥ 70.

Exclusion criteria

1. Subject has significant visual, auditory or balance impairment (eg, vertigo, stereoscopic visual impairment).
2. Subject has history of photosensitive epilepsy, seizure disorder or other disorders that may negatively affect the subject's ability to engage with VR and/or their safety.
3. Subject has cognitive, reading or learning disabilities that prevent the comprehension of instructions or is likely to interfere in the subject's ability to engage with the investigational intervention, based on the opinion of the Investigator.
4. Subject has history of motion sickness or medical condition predisposing to nausea or dizziness that is likely to interfere in the subject's ability to engage with the investigational intervention, based on the opinion of the Investigator.
5. Subject has injuries, inflammation or infection affecting the eyes, ears or face that would make the use of the hardware uncomfortable.
6. Subject has, as judged by the Investigator based on intake interview and subject report, current or lifetime history of meeting DSM-5 criteria for schizophrenia spectrum or other psychotic disorder, bipolar or related disorder, major neurocognitive disorder, neurodevelopmental disorder of greater than mild severity or of a severity that impacts the subject's ability to consent, follow study directions, or otherwise safely participate in the study; posttraumatic stress disorder, major depressive disorder (MDD) with psychotic features, borderline or antisocial personality disorder, or any other current comorbid psychiatric disorder that either would be likely to require treatment with prohibited concomitant medications or psychotherapy during this trial, or to confound effectiveness or safety assessments. Prior history of panic disorder or obsessive-compulsive disorder may be acceptable provided subject no longer meets DSM-5 criteria for these disorders. Prior history of MDD (without psychotic features) may be acceptable provided the subject does not currently meet DSM-5 criteria for a major depressive episode.
7. Subject has met DSM-5-based criteria for Alcohol or Substance Use Disorder (other than nicotine or caffeine) within one (1) year prior to Screening based on MINI and opinion of the Investigator.

8. Subject has received ketamine, esketamine, arketamine, or psychedelic therapies (eg, psilocybin, methylenedioxymethamphetamine [MDMA]) for MDD or any psychiatric condition within one (1) year prior to Screening.
9. Subject has lifetime history of suicide attempt, or active suicidal or self-harm ideation in the 6-months prior to Screening based upon the MINI, a score of greater than 0 on item 9 of the PHQ-9, or answers "yes" to "suicidal ideation" item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) or any suicidal behavior on the C-SSRS assessment at the Screening Visit (in the past 6 months) or at Baseline, or at the discretion of the Investigator.
10. Subject has initiated or altered pharmacological treatment regimen, including changes in dose, for any psychiatric indication in the 3 months prior to Screening or is expected to have changes in such therapy during the study.
11. Subject has received treatment with a prohibited psychotropic medication within 3 days or 5 half-lives (whichever is longer) or herbal supplements with CNS-related indications within 3 days prior to randomization or anticipates the need for psychotropic medications or herbal supplements during their participation in this study, with the exception of the medications specified (details provided in the allowed concomitant psychotropic medications section). Herbal supplements/medications without CNS related indications must be discontinued prior to randomization.
12. Subject has lifetime history of receiving Cognitive-Behavioral Therapy (CBT) for any indication or has had any prior exposure to BVR-100, or other VR based intervention for mental health indications, including SAD.
13. Subject has engaged in any form of psychotherapy in the 3 months prior to Screening, or is expected to initiate psychotherapy during the study.
14. In the opinion of the Investigator: (a) study participation may pose a significant or undue risk to the subject; (b) the subject is unlikely to successfully complete all of the requirements of the study per protocol; or (c) study participation may adversely impact the integrity of the data or the validity of the study results.

Study Intervention:

BVR-100 is a non-invasive, self-guided, at-home, VR intervention co-developed by BehaVR Inc. and Sunovion Pharmaceuticals, Inc. that is being developed for the treatment of SAD. BVR-100 offers educational modules and immersive environments created using both computer-generated and 360º videos. BVR-100 is delivered via consumer-grade 6 degrees-of-freedom (DoF) VR Head Mounted Device (HMD). The intervention includes immersive and automated VR experiences that guide the user through educational and experiential learning modules.

It is intended as an 8-week program with a recommended minimum frequency of 3 weekly sessions. Each session will be approximately 5-20 minutes long (depending on type and amount of content experienced).

Mode of Administration:

BVR-100 will be delivered via the VR headset. Enrolled subjects in the study will be asked to register in the VR headset using their phone number and to create a log-in PIN code which will be used for subsequent sign-ins.

Duration of Study: The total duration of subject participation in investigational intervention use is approximately 8 weeks (Baseline/Week 1 through Week 8/EOS). Altogether, this study will last approximately 11 weeks from Screening through EOS.

Reference Therapy:

BES-100 is a non-invasive, self-guided, multisession, at-home, VR intervention designed to be used as a sham control condition for the evaluation of BVR-100 in the treatment of SAD. BVR-100 and BES-100 are comparable in all technological, design, and programmatic characteristics, except for the mechanisms of action.

The computer-generated environment will be interactive to increase engagement and provide subjects with a similar interactive experience as BVR-100.

BES-100 is intended as an 8-week program with a recommended minimum frequency of 3 weekly sessions, In addition to the 3 weekly sessions, users can review any already experienced modules or engage with the distraction module at any point during the program. Each session will be approximately 5-20 minutes long.

Concomitant Medications: Prior medications, including the use of psychotropic medication taken during the previous 12 months, and any other medication taken during the previous 3 months will be recorded at Screening. Details on all medications taken prior to Screening (including dosing changes) will be recorded based on subject report.

Thereafter, any changes in concomitant medications or new medications added until the end of study will be recorded. At a minimum, the following information on prior and concomitant medications will be recorded on the case report form (CRF): medication name, dose, frequency, route, start date and time, stop date and time, and indication.

Prohibited Medications

Psychotropic medications and medications with a propensity for psychotropic effects are not permitted during the study participation, except as discussed below (see Allowed Concomitant Psychotropic Medication). Subjects will be requested to refrain from using benzodiazepines (eg, clonazepam and bromazepam) for the duration of their participation in the study. The use of herbal supplements, dietary supplements or other complementary or alternative medications for treating psychiatric indications, as well as nutritional supplements and nonprescription herbal preparations with CNS effects (eg, St. John's Wort, omega-3 fatty acids, kava extracts, gamma-aminobutyric acid supplements, cannabidiol, etc) are not permitted during the study participation. Disallowed psychotropic medications must be washed out during the screening/washout period and fully discontinued a minimum of 3 days or 5 half-lives (whichever is longer) prior to randomization. Disallowed herbal supplements with CNS-related indications must be fully discontinued a minimum of 3 days prior to randomization.

Allowed Concomitant Psychotropic Medications

The use of concomitant psychotropic medications at a stable dose for at least 3 months prior to Screening will be permitted provided they are prescribed for non-exclusionary indications. Pharmacological treatment and dose should not change during trial unless required by physician to adequately treat the subject.

Treatment of Insomnia

Concomitant use of eszopiclone, zaleplon, zolpidem and zolpidem CR is permitted at the discretion of the Investigator with the following restrictions:

- eszopiclone (≤ 3 mg/day), zopiclone (≤ 7.5 mg/day), zaleplon (≤ 20 mg/day), zolpidem (≤ 10 mg/day), and zolpidem CR (≤ 12.5 mg/day) may be administered at bedtime for insomnia, not exceeding 3 instances per week.

Diphenhydramine ≤ 100 mg/day and melatonin ≤ 10 mg/day may be administered at bedtime for insomnia, as needed. Over-the-counter melatonin may be used. Combination melatonin products are not allowed.

Medications that are used for insomnia should be administered no more than once nightly and should not be used in combination.

The date and time of the last dose of any concomitant psychotropic medication(s) taken prior to scheduled effectiveness assessments must be recorded at each visit. Subjects should be encouraged to avoid taking any psychotropic medication (or any agents that may cause sedation) within 12 hours of effectiveness assessments.

Allowed Concomitant Non-Psychotropic Medications

Non-psychotropic medications used to treat stable, chronic medical conditions or for short-term treatment of an acute medical condition may be used during screening and throughout participation. Use of non-prescription pain medications (eg, aspirin, acetaminophen/paracetamol) are allowed during all phases of the study.

Subjects will be requested to refrain from using benzodiazepines (eg, clonazepam and bromazepam) and acute use of beta-blockers (eg, atenolol, propranolol) for the duration of their participation in the study. Individuals who have had a stable use of beta-blockers for cardiac indications are acceptable for this study.

Subjects will be requested to refrain from use of alcohol, tetrahydrocannabinol (THC) for any purpose while taking part in the study.

The use of any concomitant medication or other psychotropic drug use will be assessed and registered during all scheduled telephone visits.

All medications will be coded using the World Health Organization Drug Dictionary (WHO-DD).

Criteria for Evaluation:

Primary Endpoint:

- The measurement of intervention credibility and expectancy of benefit, assessed with the Credibility / Expectancy Questionnaire (CEQ) scores, at Baseline, Week 6, and Week 8/EOS.
    - The Credibility / Expectancy Questionnaire (Devilly-2000) asks about the improvements that subjects believe will be achieved as a result of treatment, and how believable, convincing, and logical the treatment seems. It contains 6 items rated on a 1–9 or a 0%-100% scale. The first three items of the scale load onto the credibility factor and the final three items load onto the expectancy factor.

Secondary Endpoints:

- Subject retention in each group will be assessed by percentage of subjects who remain on the study at Week 6 and Week 8 (EOS). Reasons for dropout will be documented.
- Time-on-task, averaged over all VR sessions, will be assessed at Week 6 and Week 8/EOS. Time on task will be automatically recorded by the VR system after each session.

Other/Exploratory Endpoints:

- The overview of qualitative input obtained during qualitative interviews at Week 8.
- The mean change from baseline in LSAS scores at Week 2, Week 4, Week 6, and Week 8.
- The proportion of "responders", that is, subject who are rated 1 (very much improvement) or 2 (much improvement) in the CGI-I at end-of-treatment (Week 8)
- The mean change from baseline in CGI-S score at Week 2, Week 4, Week 6, and Week 8.
- The mean change from baseline in PGI-I score at Week 2, Week 4, Week 6, and Week 8.
- The mean change from baseline in PHQ-9 score at Week 2, Week 4, Week 6, and Week 8.

Safety Endpoints:

- Incidence of adverse events (AEs).
- Incidence of serious adverse events (SAEs).
- Incidence of unanticipated adverse device effects (UADEs).

- Frequency of subjects with suicidal ideation or suicidal behavior based on the C-SSRS.

Statistical Methods:

All analyses will be based on the modified Intent-to-Treat (mITT) population, which includes all subjects who are randomized, have completed at least one VR session, and have Baseline and at least one post-Baseline effectiveness measurement in CEQ. Additional analysis of the Per-Protocol (PP) population is supportive. The safety assessments will use the Safety population, which includes all subjects who are randomized and have completed at least one VR session.

No formal hypothesis testing relating to primary or exploratory outcomes is planned because this is a pilot study. Baseline demographic and clinical characteristics will be presented descriptively as proportions or as means with standard deviations. Descriptive statistics will be used to estimate group differences in the CEQ at baseline and at Week 6 and Week 8, retention rates at Week 6 and Week 8, and time-on-task at Week 6 and Week 8. Likewise, descriptive statistics will be used to assess differences in the mean change from baseline in the LSAS, CGI-S and PHQ-9 at weeks 2, 4, 6, and 8; differences in the mean change from CGI-S baseline score in the CGI-I and PGI-I at weeks 2, 4, 6, and 8; and proportion of subjects with a "responder" status at the end of treatment at week 8. Single imputation techniques will be employed for all missing data.

Exploratorily, CEQ scores differences between groups will be computed using Student's *t* tests, and associations between CEQ scores and both baseline variables and clinical outcomes will be analyzed. Between-group differences in LSAS and responder status rates will be analyzed using Student's *t* tests and chi-squared tests, respectively. Baseline demographic and clinical characteristics will be compared between groups with the use of the two sample *t*-test and the Mann–Whitney test for continuous measurements with and without normal distribution, respectively.

Safety data regarding AEs (including SAEs and UADEs) will be collected from the start date/time of informed consent form (ICF) consent to the EOS/ET, and summarized by treatment group. Adverse events, AEs leading to discontinuation, serious AEs, and UADEs will be summarized by presenting, for each treatment group, the number and percentage of subjects with any AEs, and AEs by system organ class and preferred term. Adverse events will be further summarized by severity and by relationship to the Investigational Intervention.

Sample Size:

Due to the pilot nature of the study, no formal sample size calculations will be conducted. However, to ensure a reliable estimate of the standard deviations to power a future trial with 90% and an expected effect size between 0.3 and 0.7, fifteen people per arm are recommended (Whitehead-2016). In order to account for a possible attrition rate of 25%, twenty people per arm (total n = 40) will be recruited. In order to ensure adequate data for evaluation, early discontinued subjects may be replaced at Sponsor discretion.

Table 2: Schedule of Assessments

			Investigational Intervention Use Period				
Study Period	**Screen-ing**	**Random-ization**	**Baseline[a]**				
Study Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**
Study Week	**NA**	**NA**	**W1**	**W2**	**W4**	**W6**	**W8 (EOS/ET[b])**
Study Visit Days	**Up to 14 days**	**Up to 7 days**	**1-7**	**8-14**	**22-28**	**36-42**	**50-56**
Procedure							
Obtain Informed Consent	X						
Review Inclusion/Exclusion Criteria	X	X					
Record Demographics and Baseline Characteristics	X						
Record Medical/Psychiatric History	X						
Administer MINI	X						
Randomization[c]		X					
Dispense Investigational Intervention via IWRS [c]		X					
Subject Self-guided Weekly VR Sessions [d]			X	X	X	X	X
Clinician Administers the LSAS	X		X	X	X	X	X
Clinician Administers the C-SSRS	X		X		X		X
Subject Completes the PHQ-9 [e]	X		X	X	X	X	X
Subject Completes the CEQ			X			X	X
Clinician Administers the CGI-I				X	X	X	X
Clinician Administers the CGI-S			X	X	X	X	X

Table 2: Schedule of Assessments (Continued)

			Investigational Intervention Use Period				
Study Period	**Screen-ing**	**Random-ization**	**Baseline[a]**				
Study Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**
Study Week	**NA**	**NA**	**W1**	**W2**	**W4**	**W6**	**W8 (EOS/ET[b])**
Study Visit Days	**Up to 14 days**	**Up to 7 days**	**1-7**	**8-14**	**22-28**	**36-42**	**50-56**
Procedure							
Subject Completes the PGI-I				X	X	X	X
Conduct Qualitative Interview [f]							X
Prior/Concomitant Medications	X	X	X	X	X	X	X
Pretreatment Event and Adverse Event Monitoring	X	X	X	X	X	X	X
Subject Returns Investigational Intervention [f]							X
Telephone Contact [g]	X	X	X	X	X	X	X

Abbreviations: AE = Adverse Event; CEQ = Credibility/Expectation Questionnaire; D = Day; EOS = End of Study; ET = Early Termination; C-SRSS = Columbia Suicide Severity Rating Scale; MINI = Mini-International Neuropsychiatric Interview; CGI-I = Clinical Global Impression – Improvement scale; CGI-S = Clinical Global Impression – Severity scale; LSAS = Liebowitz Social Anxiety Scale; PGI-I = Patient Global Impression – Improvement scale; PHQ-9 = Patient Health Questionnaire; PROs = Patient-Reported Outcomes VR = Virtual Reality; W = Week.

[a] The Baseline visit should be scheduled within 5-7 days of the Randomization visit. The Baseline visit will consist of two parts. The first part will be conducted by investigator site staff via a telehealth call and will include the administration of clinician-administered outcome measures, collection of AEs, concomitant medication, and delivery of the PHQ-9. The second part will be self-administered by the subject and will include the video-guided VR onboarding session, the first self-guided VR session, and the completion of the CEQ.

[b] For subjects who prematurely discontinue from the study, every effort should be made to complete the final evaluation procedures at the early termination (ET) visit within 5 days of the last exposure to the Investigational Intervention, including the PROs if they have not been completed by the subject for the given week.

[c] Randomization cannot occur until the subject has been deemed eligible by the site and Inclusion and Exclusion criteria re-confirmed with the subject via a telehealth contact and after subject interest to participate in this study is confirmed. Upon Randomization using the IWRS, the Investigational Intervention shipment to the subject will be initiated.

[d] The subject self-guided weekly VR sessions begin after the first part of the Baseline visit is completed. During weeks 2, 4, 6 and 8, 3 required VR sessions should be completed prior to the PROs. In addition to the required practices, subjects will be encouraged to also engage with optional content and to review content completed in previous sessions.

[e] The PROs will be completed by the subject during the Telehealth contact, for Screening and Baseline Visits, as applicable, in an unassisted manner. During Weeks 2, 4, 6, and 8, these are to be completed after the self-guided at home VR sessions.

[f] The W8/EOS/ET assessments will consist of three parts. The first part will be the Subject's at home completion of the required 3 VR modules and electronic PRO assessments. The second part will include the telehealth visit with the investigator site staff to complete all applicable assessments. The third part will be conducted by the unblinded site support team where the Qualitative Interview will be completed as the final study assessment on the same day or within 48 hours. During this visit, the unblinded site support team will instruct the subject to return the device and provide any necessary guidance.

[g] The Telehealth contact during weeks 2, 4, 6, and 8, to collect concomitant mediation and/or AEs, clinician administered C-SRSS, LSAS, CGI-S, CGI-I, and other applicable assessments, should be completed on the last 3 days of each week. At any point in the study, an unscheduled Telehealth contact can be performed if requested by the investigator site staff/subject.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The abbreviations and the definition of key study terms used in the clinical study protocol are shown in Table 3 and Table 4.

Table 3: List of Abbreviations

Abbreviation	Full Form
AE	Adverse event
CBT	Cognitive behavioral therapy
CEQ	Credibility/Expectation Questionnaire
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
CRF	Case report form
CRO	Contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
DoF	Degrees of Freedom
DTx	Digital therapeutics
DXE	Dynamic Experience Engine
EDC	Electronic data capture
EOS	End of study
ET	Early termination
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HMD	Head-mounted Device
ICF	Informed consent form
ICH	International Council for Harmonisation
ISO	International Organization for Standardization
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IRB	Institutional Review Board
IWRS	Interactive web responses system
mITT	Modified intention-to-Treat
LSAS	Liebowitz Social Anxiety Scale

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
MedDRA	Medical Dictionary for Regulatory Activities
MDD	Major Depressive Disorder
MINI	Mini-International Neuropsychiatric Interview
PGI-I	Patient Global Impression - Improvement
PHQ-9	Patient Health Questionnaire
PI	Principal Investigator
PP	Per Protocol
PROs	Patient-Reported Outcomes
RCT	Randomized controlled trials
SAD	Social Anxiety Disorder
SAE	Serious adverse event
SOC	System organ class
UADE	Unanticipated Adverse Device Effects
US	United States
VR	Virtual Reality
VRET	Virtual Reality Exposure Therapy
VR-CORE	Virtual Reality Clinical Outcomes Research Experts

Table 4: Definition of Key Study Terms

Terms	Definition of terms
CRF	A printed, optical, or electronic document designed to record all of the protocol required information to report to the Sponsor for each study subject.
Screened Subject	Any subject who signed the study specific informed consent and completed at least one study related procedure.
Screen Failures	Any subject who signed the study specific informed consent but either failed to meet study requirements during screening or met study requirements at screening but was not enrolled.
Investigational Device Use Period	The period of the study in which the investigational device is administered.
Enrolled Subject	Any subject who was successfully screened and enrolled into the study.
Completed Subject	Any subject who participated throughout the duration of the study.
Early Termination Subject	Any subject who was successfully screened and enrolled into the investigational device use period of the study but did not complete the study.
End of Study	The day that the subject completes the study per the study design.

4. INTRODUCTION

The objective of this study is to compare two Virtual Reality (VR)-based interventions, BVR-100 and BES-100, for the treatment of Social Anxiety Disorder (SAD).

4.1. Background

Social anxieties and fears exist along a continuum of intensity, ranging from mild phenomena such as shyness to psychopathological levels of fear and anxiety that can be classified as social anxiety disorder (SAD) (McNeil-2014). SAD is characterized by overwhelming anxiety and excessive self-consciousness in everyday social situations, which causes significant distress and often leads to impairment in important areas of functioning (American Psychiatric Association-2013). It affects 7% of the population and has a high comorbidity with other anxiety, affective, and substance-use disorders (Kessler-2005). SAD is associated with increased healthcare utilization and a range of indirect costs relating to reduced productivity, social impairment, and reduction in quality of life (Konnopka-2000).

SAD can be a chronic and naturally unremitting disorder if not treated adequately. Despite the extent of suffering and impairment, only about half of adults with the disorder ever seek treatment (Grant-2005). Guidelines from the National Institute for Health and Care Excellence recommend individual Cognitive Behavioral Therapy (CBT) as the first-line treatment for adults with social anxiety (Mayo-Wilson-2014). Standard treatment guidelines and evidence-based CBT tools for social anxiety include exposure, cognitive restructuring, social skills training and relaxation training (Mayo-Wilson- 2014; National Collaborating Centre for Mental Health (UK)-2015). Studies of group, individual, and internet-based CBT for the treatment of SAD have demonstrated response rates between 58 and 75% (Blanco-2010; Butler-2021; Dryman-2017; Loerinc-2015) and remission rates around 40% (Springer-2018). Despite the demonstrable efficacy of CBT, and in particular exposure therapy, only a minority of individuals receive this treatment (Freiheit-2004; McAleavey-2014; Pittig-2019; Sars-2015).

Virtual reality (VR) technology offers a unique opportunity to disseminate CBT and exposure therapy. Studies indicate that patients prefer to receive VR exposure therapy (VRET) to traditional exposure therapy (Garcia-Palacios-2007). VRET has large effect sizes (Kampmann-2016; Wechsler-2019) and may be particularly useful for those who show reluctance toward completing in vivo or imaginal exposure. VRET may be useful in addressing the shortcomings of established methods of exposure, particularly in relation to cost-effectiveness, convenience, treatment acceptability, treatment availability and accessibility, and difficulties with patients visualizing scenes during imaginal exposure (Emmelkamp-2020; Morina-2021).

While the use of VRET has been extensively researched, delivering cognitive components of CBT using VR is a novel and promising approach (Bolinski-2021; Lindner-2019). Combining the use of immersive and self-guided interventions, patients can learn effective cognitive techniques to counter automatic anxious thoughts, a central cause of anxiety maintenance and treatment according to cognitive perspectives (Clark-1999). Similarly, mindfulness and acceptance-based therapies have emerged as effective interventions for SAD, often combined with traditional CBT techniques (Liu-2021; Norton-2015). Because of its potential to shield subjects' attention from distraction and induce strong feelings of presence, VR can enhance the

practices of mindfulness and facilitate emotion regulation therefore reducing symptoms of anxiety (Navarro-Haro-2019; Seabrook-2020). Furthermore, VR may be combined with engaging game-design mechanics to deliver highly automated unguided interventions, thus showing an enormous potential for improving public health due to its cost-effectiveness and scalability.

The current study will test BVR-100, a VR-based multi-session, self-led intervention for social anxiety symptoms including CBT techniques against BES-100, a VR-based intervention intended as a control-arm for BVR-100.

4.2. Study Conduct Rationale

Digital therapeutics (DTx) are evidence-based software products used to prevent, manage, or treat medical conditions. DTx need to adhere to the same standards of evidence and regulatory oversight as prescription medications and traditional medical devices. However, DTx face additional challenges to establishing appropriate control conditions that support evidence-generation in randomized controlled trials (RCT). In particular, DTx interventions are subject to "digital placebo" effects, involving technology-related non-specific effects (eg, beliefs about technology, design of the hardware and software, information provided, medium of delivery, time-on-task, etc.), that are not present in drug trials (Torous-2016). Furthermore, DTx delivering psychological interventions such as CBT are faced with the additional challenge of controlling for more complex placebo effects that typically occur in the context of psychotherapy, such as the effect of the frequency and intensity of therapist–patient interactions. While the FDA acknowledges that "*it may be challenging to construct a placebo control that appears to function like the investigational device but delivers no therapy*" (Center for Devices & Radiological Health, n.d.), it is still recommended that Sponsors evaluate placebos in terms of their face-validity (ie, time-on-task), blinding, and subject retention. Pilot testing BVR-100 against a "sham" control such as BES-100 will provide the Sponsors with the opportunity to test the face-validity of the BES-100, preliminarily assess the effectiveness of BVR-100 and BES-100, and inform the subsequent large-scale RCT.

4.3. Intervention Use Justification

The present pilot study is set to inform a subsequent RCT evaluating the clinical effectiveness and safety of BVR-100 intended to support registration. Key design parameters of the present pilot study will be generally aligned with that of the subsequent planned RCT, including the study duration, main effectiveness outcomes, inclusion and exclusion criteria, study visits, and subject monitoring.

The present study aims to evaluate the credibility and expectation of benefit of BES-100 vs BVR-100 as a proxy for subject blinding. In line with FDA recommendations, study endpoints will also include an evaluation of time-on-task and drop-out rates (also referred to as subject retention) at end-of-study (EOS). Like the subsequent RCT, this 8-week, 2-arm, double-blinded pilot RCT will compare both BES-100 and BVR-100 interventions. Subjects meeting the diagnostic criteria for SAD and a Liebowitz Social Anxiety Scale (LSAS) score at Screening of ≥ 70 will be randomly allocated to the BVR-100 or BES-100 groups and asked to complete an at-home, self-guided VR intervention for 8-weeks. In order to obtain preliminary evidence of effectiveness in a manner that is aligned with the primary and secondary endpoints planned in

the subsequent RCT, SAD fear and avoidance symptoms and overall symptom improvement will be assessed using the LSAS and the CGI scales, in addition to the self-reported PGI-I. Self-reported and clinician-administered assessments will be administered at Baseline, Week 2, Week 4, Week 6, and Week 8 (EOS).

Because of the exploratory nature of the study, no formal hypothesis testing will be used to assess clinical benefit (or lack thereof). The sample size is intended to support the reliable evaluation of treatment credibility, time-on-task, and drop-out rates across study arms.

Justification for Intervention Parameters

Given the scientific rigor required in a pivotal RCT and the novelty of the VR-based BVR-100 intervention, we chose to design a stringent control condition –as opposed to less stringent controls such as waitlist controls– that allows us to more appropriately control for expectation effects and minimize subject unblinding. The BES-100 has been specifically developed as a "sham" for BVR-100. A sham is a medical device that is thought to be ineffective and is equivalent of a placebo control in pharmacological trials. FDA guidance indicates that sham- or placebo-controlled trials provide internal evidence of assay sensitivity and allow to interpret differences between intervention and sham groups without reference to external findings, thus providing robust evidence of effectiveness: "*where there may be a placebo effect with the use of a device, the comparison of the results of use of the device with an ineffective device used under conditions designed to resemble the conditions of use under investigation as far as possible*" (Center for Devices & Radiological Health, n.d.; Center for Drug Evaluation & Research, n.d.).

In order to design an inert sham intervention with no or minimal therapeutic effects, the critical mechanisms of action in BVR-100 will not be present in BES-100.

On the other hand, and in line with the best practice framework by the Virtual Reality Clinical Outcomes Research Experts (VR-CORE) committee (Birckhead-2019), BES-100 will mirror BVR-100 in terms of device and digital format. Both BES-100 and BVR-100 will use the same VR headset and controllers and have a similar user interface and graphic quality thus ensuring that usability does not differ substantially across interventions. As BVR-100, BES-100 will offer a combination of non-immersive 2D audiovisual content as well as fully immersive and active VR experiences. Thus, BES-100 will control for critical factors related to the user experience in VR while offering a similar look and feel as BVR-100. Special care will be taken to ensure that BES-100 has a similar amount and variety of prescribed content as BVR-100, such that expected time-on-task during the intervention is similar across conditions.

The combination of modules delivering educational content (general health and neuroscience clips) and interactive and immersive activities are expected to result in a minimally therapeutic yet credible intervention that results in a similar usage and subject retention during the intervention, ultimately promoting subject blinding to the treatment assignment.

4.4. Benefit-Risk

While there may not be any direct benefit of BVR-100/BES-100 for subjects in this study, it is expected that the results of this study will help inform potential future treatments for SAD, and thus may provide an indirect benefit to patients with SAD in the future.

The VR interventions are non-invasive, and risks associated with exposure to the interventions are generally expected to be transitory.

Potential risks of VR include, but are not limited to: motion sickness, blurry vision, eye strain, headaches, dizziness, fatigue, and nausea. The use of VR can cause loss of situational awareness leading to a potential for injury.

The study VR intervention is intended to engage subjects with stimuli that may elicit some discomfort . As a result, these stimuli may cause anxiety. While considered unlikely, it is possible that the stimuli could trigger a panic attack in some subjects. In such cases, subjects will be instructed to temporarily remove the VR headset.

VR-related effects as well as anxiety elicited by the stimuli are expected to be transitory in nature. Should the VR experience become too uncomfortable, subjects can remove the VR headset and disengage from the VR intervention.

Any such events would be subject to standard adverse event (AE) reporting practices. Subjects are free to withdraw consent from participation in the study at any time. Similarly, should the Investigator determine that it is unsafe for a subject to continue in the study at any time, the subject should be discontinued.

5. STUDY OBJECTIVES

The objective of this study is to compare two Virtual Reality (VR)-based interventions, BVR-100 and BES-100, for the treatment of Social Anxiety Disorder (SAD).

5.1. Primary Objective(s)

The primary objective of this study is to evaluate the credibility and expectation of benefit of BVR-100 and BES-100 for subjects with SAD, as measured with the Credibility and Expectancy Questionnaire (CEQ).

5.2. Secondary Objective(s)

The secondary objective of this study is to evaluate subject retention and time-on-task of BVR-100 and BES-100.

5.3. Exploratory Objective(s)

This study will pursue the following exploratory objectives:

- To explore subjects' experiences and acceptability of BVR-100 and BES-100 in a qualitative interview
- To evaluate the therapeutic response of the two interventions for SAD on:
    - Fear and avoidance symptoms, as measured by the clinician-administered Liebowitz Social Anxiety Scale (LSAS)
    - Overall symptomatology and functioning, using the Clinical Global Impression Severity scale (CGI-S), the Clinical Global Impression Improvement scale (CGI-I), and the Patient Global Impression Improvement scale (PGI-I)
    - Depression symptoms, measured with the Patient Health Questionnaire (PHQ-9).

5.4. Safety Objective(s)

This study will evaluate the safety of BVR-100 and BES-100, as measured by:

- Incidence of adverse events (AEs),
- Incidence of serious adverse events (SAEs),
- Incidence of unanticipated adverse device effects (UADEs), and
- The Columbia Suicide Severity Rating Scale (C-SSRS).

6. STUDY ENDPOINTS

6.1. Primary Endpoint(s)

The primary endpoint of this study is the measurement of intervention credibility and expectancy of benefit, assessed with the Credibility / Expectancy Questionnaire (CEQ) scores, at Baseline, Week 6, and Week 8/EOS.

The CEQ (Devilly-2000) asks about the improvements that subjects believe will be achieved as a result of treatment, and how believable, convincing, and logical the treatment seems. It contains 6 items rated on a 1–9 or a 0%-100% scale. The first three items of the scale load onto the credibility factor and the final three items load onto the expectancy factor.

6.2. Secondary Endpoint(s)

Secondary endpoints for this study include:

- Subject retention in each group will be assessed by percentage of subjects who remain on the study at Week 6, and Week 8/EOS. Reasons for dropout will be documented.
- Time-on-task, averaged over all VR sessions, will be assessed at Week 6 and Week 8/EOS. Time on task will be automatically recorded by the VR system after each session.

6.3. Exploratory Endpoint(s)

- The overview of qualitative input obtained during qualitative interviews at Week 8.
- The mean change from baseline in LSAS scores at Week 2, Week 4, Week 6, and Week 8.
- The proportion of "responders", that is, subject who are rated 1 (very much improvement) or 2 (much improvement) in the CGI-I at end-of-treatment (Week 8)
- The mean change from baseline in CGI-S score at Week 2, Week 4, Week 6, and Week 8.
- The mean change from baseline in PGI-I score at Week 2, Week 4, Week 6, and Week 8.
- The mean change from baseline in PHQ-9 score at Week 2, Week 4, Week 6, and Week 8.

6.4. Safety Endpoint(s)

- Incidence of AEs.
- Incidence of SAEs.
- Incidence of UADEs.
- Frequency of subjects with suicidal ideation or suicidal behavior based on the C-SSRS.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a parallel-group, double-blind (subject and investigators/outcome assessors), randomized, controlled, decentralized, study. The aim of the study is to evaluate the credibility and acceptability, subject retention, and time-on-task of BVR-100 and BES-100 in a sample of subjects with Social Anxiety Disorder (SAD).

The study will include 3 periods as shown in Table 5 below.

Table 5: Study Schematic

SCR	RND	Intervention Period (Double-Blind)				
		BSL / W1	W2	W4	W6	W8/EOS/ET
V1	V2	V3	V4	V5	V6	V7
Up to 14 days	Up to 7 days	Days 1-7	Days 8-14	Days 22-28	Days 36-42	Days 50-56

Abbreviations: SCR = Screening; RND = Randomization; BSL = baseline; EOS = end of study; ET = early termination; V = telehealth / call visits; W = week.

Details of the study assessments and other procedures to be performed at each week are presented in Table 2, Schedule of Assessments, and Section 11 , Study Assessments. The total study duration will be approximately 11 weeks from Screening through EOS (Week 8).

Screening and Washout

Informed consent will be obtained from each subject before any study-specific procedures are performed. Subjects will be evaluated for eligibility during a screening phase of up to 14 days: Psychiatric history will be reviewed, and diagnoses will be confirmed by the Principal Investigator (PI) or designee using the Mini-International Neuropsychiatric Interview (MINI). Prior experience with CBT therapy (ie, including questions about experiences with in-imagination or in-vivo exposure to fearful situations), use of concomitant medications and substance use, and baseline characteristics (ie, social anxiety symptoms measured with the LSAS, depression symptoms as measured by the PHQ-9, and suicidal ideation and behavior measured with the Columbia Suicide Severity Rating Scale [C-SSRS]) will be assessed at Screening. Subjects will be asked to wash-out from disallowed psychotropic medications or herbal supplements during the screening period. A seven-day extension to the screening period may be allowed with Medical Monitor approval.

Subjects who screen fail due to temporary resolvable medical conditions unrelated to psychiatric entry criteria, or logistical issues with Screening procedures, may be re-screened up to two times if judged appropriate by the Investigator, after discussion and agreement with the Medical Monitor. Re-screened subjects will be re-consented, assigned a new subject number, and all Visit 1 procedures will be repeated.

Randomization

After Screening, subjects deemed eligible by the Investigator will be contacted by investigator site staff to be informed they are qualified to participate in the study. Randomization will occur after confirmation of eligibility and continued subject interest are verified. Subjects will be randomly allocated to either the treatment group (BVR-100) or the control (BES-100) group. Randomization will be assigned via an interactive web responses system (IWRS) in a 1:1 ratio to either BVR-100 or to BES-100. A VR headset pre-loaded with either BVR-100 or BES-100 will be shipped to the subject's address. Subjects will not be informed of their intervention allocation. In order to secure subjects blinding, subjects will have no prior experience with CBT. Subjects will be instructed not to share descriptions of the intervention they are receiving with investigator site staff during visits and discouraged from discussing details of the therapy outside the study. The Baseline visit will be scheduled to occur within 5-7 days of the randomization visit, to allow adequate time for VR device delivery/receipt. However, it could occur earlier if the device is received earlier. If, due to delays with device delivery/receipt, an extension beyond the 7 days is necessary, Medical Monitor approval will be required.

Upon confirmation of device delivery, a member of the unblinded site support team will contact the subject to confirm receipt of the device, to establish a relationship, and remind the subject that they would be the only contact for any device related issues throughout the duration of their participation in the study. After this is confirmed, the Baseline telehealth visit with the investigator site staff can take place.

Intervention Period

Baseline

The Baseline visit will be split into two separate parts. During the first part of the Baseline visit, a telehealth call will be performed with the investigator site staff who will administer Baseline visit (Day 1) assessments including clinician-administered outcome measures (C-SSRS, LSAS, CGI-S), collect any adverse events (AEs), concomitant medication changes, and facilitate the delivery of Patient Reported Outcomes (PROs; PHQ-9). During the second part, after the call with the investigator site staff is completed, subjects will receive access to a video-guided VR onboarding session providing information to set-up the VR headset, guidance for the initial sign-up, and information about the intervention the subject has been allocated to. This session will be completed by the subject without any involvement of the investigator site staff. However, subjects will be able to reach out to an unblinded site support team for any assistance/guidance during the video-guided onboarding session or at any time thereafter. The unblinded site support team will ensure that both the video-onboarding and the first VR session are completed. After completing the video-guided onboarding and the first VR session, subjects will be asked to complete the CEQ.

Week 1- Week 8

During Weeks 1 through 8, subjects will be asked to complete at home self-guided VR sessions. Subjects in both groups will be asked to engage in a minimum of three required VR sessions per week, for a period of 8 weeks. The Baseline visit is the first day of Week 1, and after baseline during the rest of the week, a minimum of two additional VR sessions must be completed by the subject. In addition to the required practices, subjects will be encouraged to also engage with optional content and to review content completed in previous sessions. Engagement with both

study interventions will be monitored on a regular basis and notifications will be sent regularly to remind subjects to engage with the interventions. Unscheduled telehealth to complete/perform additional safety assessments be conducted as deemed necessary by the investigator site staff/subject.

During Weeks 1 (aside from the Baseline visit), 3, 5, and 7, there will be no study assessments, or scheduled telehealth calls with investigator site staff completed.

After the VR sessions have been completed, subjects are requested to complete the PROs (PHQ-9, PGI-I, and CEQ) as applicable to each particular week, electronically as specified in the Schedule of Assessments. The scales should be reviewed on a bi-weekly basis, to ensure completeness, for any potential AEs that may be reported, and retraining provided to subjects as necessary. During the last 3 days of Weeks 2, 4, 6, and 8 (EOS/ET), investigator site staff will conduct telehealth study visits to collect clinician-administered outcome measures (C-SSRS, LSAS, CGI-S, CGI-I), AEs and concomitant medication changes. For the Week 8 (EOS/ET) visit, an additional qualitative interview with a member of the unblinded site support team will occur to explore each subjects' experience with their respective interventions (BVR-100 or BES-100). All attempts will be made to ensure that each subject is assessed by the same investigator site staff to minimize confounding bias related to changing assessor. In the event that subjects require technical support or further program instructions, support will be provided by the unblinded site support team not involved in data collection.

All AE data will be collected by investigator site staff during the check-ins and recorded in the electronic data capture (EDC). Subjects will be provided with contact information in the informed consent form to facilitate ready access to the site/Investigator in order to help address potential safety issues that may arise and to facilitate AE reporting.

7.2. Treatment Assignment and Blinding

7.2.1. Treatment Assignment

All enrolled subjects will be randomly assigned to either the treatment (BVR-100) or control (BES-100) group. After Screening, subjects deemed eligible by the Investigator will be contacted by investigator site staff to be informed they are qualified to participate in the study. Randomization will occur after confirmation of eligibility and continued subject interest are verified. Subjects will be randomly allocated to either the treatment group (BVR-100) or the control (BES-100) group. Randomization will be assigned via an interactive web responses system (IWRS) in a 1:1 ratio to either BVR-100 or to BES-100.

Once a randomization number has been assigned, it cannot be reused. The randomization schedule will be generated by an independent, non-study biostatistician.

7.2.2. Blinding

Subjects, Investigators, investigator site staff, persons performing the assessments, clinical operations personnel, data analysts, will remain blinded to the identity of the VR intervention from the time of randomization until database lock and unblinding, using the following methods:

- Randomization data are kept strictly confidential until the time of unblinding in the IWRS, and will not be accessible by anyone else involved in the study with the

following exceptions: Unblinded site support team to support the subjects with any technical VR device issues and performing qualitative interview, pharmacovigilance department for evaluation and reporting of UADEs, SAEs, and any other AEs of clinical interest.

- The identity of the interventions will be concealed by the use of VR headsets that are all identical in packaging, labeling, schedule of administration and appearance.

In order to secure subject blinding, subjects will have no prior experience with CBT. Subjects will be instructed and reminded on an ongoing basis not to share descriptions of the intervention they are receiving in any capacity with investigator site staff (with the exception of the unblinded site support team) during visits or at any point during study participation and discouraged from discussing details of the therapy outside the study.

Investigator site staff will not be provided the details of the study intervention and various components/experiences within the program beyond the broad overview that is presented in this protocol to minimize any chance of unblinding. The VR device allocated to each subject upon randomization will be shipped directly to the subject's address from the depot and any activities, including subject training/tech support related to the VR intervention will be managed by the unblinded site support team external to the site, removing the investigator site staff from the entire process to minimize any chance of unblinding.

Actual subject identity revealing actual study treatment will not be disclosed before database lock and study unblinding unless an emergency unblinding becomes necessary.

7.2.3. Emergency Unblinding Procedures

In the case of a medical emergency, where knowledge of study intervention by the Investigator or an authorized delegate is essential for immediate medical management, a 24-hour code-break service will be available via the IWRS. The date and reason for unblinding are to be documented. Any subject for whom the intervention assignment was unblinded is to be discontinued from further study participation and ET assessments completed. The identity of those individuals at the study site who gain access to the unblinded treatment assignment must be documented. It is mandatory that all personnel who are involved in the unblinding, and who have access to the unblinded intervention assignment, maintain the confidentiality of the information and do not divulge the intervention assignment.

7.3. Rationale

7.3.1. Rationale for the Study Design

The present pilot study is set to inform a subsequent RCT evaluating the clinical effectiveness and safety of BVR-100 intended to support registration. Key design parameters of the present pilot study will be generally aligned with that of the subsequent planned RCT, including the study duration, main effectiveness outcomes, inclusion and exclusion criteria, study visits, and subject monitoring.

The present study aims to evaluate the credibility and expectation of benefit of BES-100 vs BVR-100 as a proxy for subject blinding. In line with FDA recommendations, study endpoints will also include an evaluation of time-on-task and drop-out rates at end-of-study. Like the

subsequent RCT, this 8-week, 2-arm, double-blinded pilot RCT will compare both BES-100 and BVR-100 interventions. Subjects meeting the diagnostic criteria for SAD and a LSAS score at Screening of ≥ 70 will be randomly allocated to the BVR-100 or BES-100 groups and asked to complete an at-home, self-guided VR intervention for 8-weeks. In order to obtain preliminary evidence of effectiveness in a manner that is aligned with the primary and secondary endpoints planned in the subsequent RCT, SAD fear and avoidance symptoms and overall symptom improvement will be assessed using the LSAS and the CGI scales, in addition to the self-reported PGI-I. Self-reported and clinician-administered assessments will be administered at Baseline, Week 2, Week 4, Week 6, and Week 8 (end of study).

Because of the exploratory nature of the study, no formal hypothesis testing will be used to assess clinical benefit (or lack of it). The sample size is intended to support the reliable evaluation of treatment credibility, time-on-task, and drop-out rates across study arms.

7.3.2. Rationale for the Device

BehaVR Inc.'s proprietary platform and VR environments can help serve to reduce the logistical, social, and psychological barriers to traditional CBT, such as a shortage of trained clinicians, cost of treatment, resources needed to access treatment, stigma, or negative beliefs about CBT and exposure (Wolitzky-Taylor-2018). Also, VR avatars can provide a supportive learning community for self-guided learners who need structure when establishing a new routine such as regular mindfulness practice. An additional benefit of VR is that it is more scalable and disseminable compared with human therapists and usual "brick and mortar" treatment environments. Given recent technological advances and associated decrease in the cost of VR hardware, VR may be readily accessed in a variety of environments. The ability for a user to have treatment continuity in the home environment may facilitate repetition of skill practice, consolidating learning and potentially boosting therapeutic neuroplasticity (Boeldt-2019).

In that regard, the premise of this application is that delivering BVR-100 via BehaVR's platform will provide an efficacious and highly disseminable form of this evidence-based intervention to improve outcomes. In addition to overcoming implementation barriers, VR in conjunction with BehaVR's Dynamic Experience Engine (DXE,) can aid in CBT and exposure therapy by removing sensory distractions that may otherwise hinder the learning process, personalizing patient experience with machine learning, and encouraging interaction and imagination in an immersive virtual environment. Through these features, VR can increase the perceived usability of the intervention (Garcia-Palacios-2007; Huang-2016) helping to bridge the gap between in-person and digital treatment environments and increasing treatment engagement (Boeldt-2019; Graham-2019).

Novel evidence-based interventions are needed to improve and increase access to treatment for patients with SAD. CBT is an empirically supported therapeutic approach that has demonstrated efficacy in reducing SAD symptoms. However, barriers to treatment accessibility may hinder widespread implementation of CBT. Combining CBT and VR with the advanced BehaVR DXE platform, will increase patient access to an array of potent behavioral and cognitive techniques with demonstrated efficacy, while delivering a personally tailored intervention that adapts to the current needs of the patient.

7.4. Prevention of Missing Data

In an effort to minimize the number of subjects who are terminated from the study prior to study completion and/or missed assessments, the following study design and conduct elements are implemented:

- Study centers are trained on the importance of continued follow-up and on the informed consent process, ensuring subjects understand the commitment they are making, including the intent to complete the trial.
- Bi-weekly scheduled touchpoints between subjects and investigator site staff.
- Weekly reminders to all subjects to complete all required VR modules and PROs as per protocol.
- Data collection is regularly monitored at the site level for adherence during the study.

See Section 15.4.4 for statistical considerations related to missing data.

8. SELECTION OF SUBJECTS

8.1. Subject Inclusion Criteria

To qualify for participation, subjects must meet all the following inclusion criteria:

1. Subject has provided written informed consent, obtained prior to initiation of any study-specific procedures.
2. Subject is male or female, aged 18 or above.
3. Subject has English fluency and literacy, sufficient to provide consent and follow study instructions as judged by the Investigator.
4. Subject meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5) criteria for Social Anxiety Disorder as established during the Screening visit using the MINI. Subjects may have a comorbid DSM-5 based diagnosis of generalized anxiety disorder and/or a comorbid DSM-5 based diagnosis of specific phobias provided the symptoms of the comorbid disorder(s) are secondary to symptoms of SAD and are considered stable during the 3 months prior to Screening, in the opinion of the Investigator.
5. Subject has a total Liebowitz Social Anxiety Scale (LSAS) score at Screening of ≥ 70.

8.2. Subject Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible to participate in the study:

1. Subject has significant visual, auditory or balance impairment (eg, vertigo, stereoscopic visual impairment).
2. Subject has history of photosensitive epilepsy, seizure disorder or other disorders that may negatively affect the subjects's ability to engage with VR and/or their safety.
3. Subject has cognitive, reading or learning disabilities that prevent the comprehension of instructions or is likely to interfere in the subject's ability to engage with the investigational intervention, based on the opinion of the Investigator.
4. Subject has history of motion sickness or medical condition predisposing to nausea or dizziness that is likely to interfere in the subject's ability to engage with the investigational intervention, based on the opinion of the Investigator.
5. Subject has injuries, inflammation or infection affecting the eyes, ears or face that would make the use of the hardware uncomfortable.
6. Subject has, as judged by the Investigator based on intake interview and subject report, current or lifetime history of meeting DSM-5 criteria for schizophrenia spectrum or other psychotic disorder, bipolar or related disorder, major neurocognitive disorder, neurodevelopmental disorder of greater than mild severity or of a severity that impacts the subject's ability to consent, follow study directions, or otherwise safely participate in the study; posttraumatic stress disorder, major depressive disorder (MDD) with psychotic features, Borderline or antisocial personality disorder, or any other current comorbid psychiatric disorder that either would be likely to require treatment with prohibited

concomitant medications or psychotherapy during this trial, or to confound effectiveness or safety assessments. Prior history of panic disorder or obsessive-compulsive disorder may be acceptable provided subject no longer meets DSM-5 criteria for these disorders. Prior history of MDD (without psychotic features) may be acceptable provided the subject does not currently meet DSM-5 criteria for a major depressive episode.

7. Subject has met DSM-5-based criteria for Alcohol or Substance Use Disorder (other than nicotine or caffeine) within one (1) year prior to Screening based on MINI and opinion of the Investigator.
8. Subject has received ketamine, esketamine, arketamine, or psychedelic therapies (eg, psilocybin, methylenedioxymethamphetamine [MDMA]) for MDD or any psychiatric condition within one (1) year prior to Screening.
9. Subject has lifetime history of suicide attempt, or active suicidal or self-harm ideation in the 6-months prior to Screening based upon the MINI, a score of greater than 0 on item 9 of the PHQ-9, or answers “yes” to “suicidal ideation” item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) or any suicidal behavior on the C-SSRS assessment at the Screening Visit (in the past 6 months) or at Baseline, or at the discretion of the Investigator.
10. Subject has initiated or altered pharmacological treatment regimen, including changes in dose, for any psychiatric indication in the 3 months prior to Screening or is expected to have changes in such therapy during the study.
11. Subject has received treatment with a prohibited psychotropic medication within 3 days or 5 half-lives (whichever is longer) or herbal supplements with CNS-related indications within 3 days prior to randomization or anticipates the need for psychotropic medications or herbal supplements during their participation in this study, with the exception of the medications specified (details provided in the allowed concomitant psychotropic medications section). Herbal supplements/medications without CNS related indications must be discontinued prior to randomization.
12. Subject has lifetime history of receiving Cognitive-Behavioral Therapy (CBT) for any indication or has had any prior exposure to BVR-100, or other VR based intervention for mental health indications, including SAD.
13. Subject has engaged in any form of psychotherapy in the 3 months prior to Screening, or is expected to initiate psychotherapy during the study.
14. In the opinion of the Investigator: (a) study participation may pose a significant or undue risk to the subject; (b) the subject is unlikely to successfully complete all of the requirements of the study per protocol; or (c) study participation may adversely impact the integrity of the data or the validity of the study results.

9. STUDY MATERIALS AND MANAGEMENT

9.1. Description of Investigational Intervention

BVR-100 is a non-invasive, self-guided, at-home, VR intervention co-developed by BehaVR Inc. and Sunovion Pharmaceuticals, Inc. that is being developed for the treatment of SAD. BVR-100 offers educational modules and immersive environments created using both computer-generated and 360º videos. BVR-100 is delivered via consumer-grade 6 degrees-of-freedom (DoF) VR Head Mounted Device (HMD). The intervention includes immersive and automated VR experiences that guide the user through educational and experiential learning modules.

It is intended as an 8-week program with a recommended minimum frequency of 3 weekly sessions. Each session will be approximately 5-20 minutes long (depending on type and amount of content experienced).

Like BVR-100, BES-100 is a non-invasive, self-guided, multisession, at-home, VR intervention designed to be used as a sham control condition for the evaluation of BVR-100 in the treatment of SAD. BVR-100 and BES-100 are comparable in all technological, design, and programmatic characteristics, except for the mechanisms of action.

The computer-generated environment will be interactive to increase engagement and provide subjects with a similar interactive experience as BVR-100.

Like BVR-100, BES-100 is intended as an 8-week program with a recommended minimum frequency of 3 weekly sessions, In addition to the 3 weekly sessions, users can review any already experienced modules or engage with the distraction module at any point during the program. Each session will be approximately 5-20 minutes long.

9.2. Study Intervention Packaging and Labeling

The label will have the following language:

- Sponsor name and that it is for investigational use only for this study.
- The software will have its own unique identifier and a kit Number will be on the device box.
- Instructions will be included in the kit and a video for onboarding.

9.3. Dispensing Investigational Intervention

An Interactive Web Response System (IWRS) will be used to manage subject screening and randomization.

BVR-100 and BES-100 VR device kit Numbers will be assigned by the IWRS based on the treatment schedule.

The assigned study device will be shipped directly from the depot to the subject, and the delivery/receipt will be confirmed by the unblinded site support team during the introductory call. The VR intervention subject onboarding will be completed independently by the subject during the second part of the Baseline visit via an onboarding video and ongoing technical support provided by unblinded site support team external to the site.

Subjects will engage with the VR intervention for at least 3 VR sessions per week, for a period of 8 weeks.

9.4. Study Intervention Accountability

The unblinded site support team external to the investigator site is responsible for maintaining adequate and up to date records of VR device accountability documentation that includes the date of shipment out of the depot, delivery/receipt by subject, and shipment back to depot/receipt at depot in the study records for each subject. The contract research organization (CRO) will maintain a master accountability log.

10. TREATMENT OF SUBJECTS

10.1. Investigational Intervention

BVR-100 or BES-100 will be shipped directly to the address of eligible subjects. Onboarding and training videos will be provided electronically.

10.2. Compliance with the Investigational Intervention

Use of BVR-100 or BES-100 will be recorded electronically and closely monitored by the unblinded site support team for protocol compliance. Weekly reminders will be sent out to study subjects, and they will be followed up with as necessary.

10.3. Concomitant Medications and Therapies

Prior medications, including the use of psychotropic medication taken during the previous 12 months, and any other medication taken during the previous 3 months will be recorded at Screening. Details on all medications taken prior to Screening (including dosing changes) will be recorded based on subject report.

Thereafter, any changes in concomitant medications or new medications added until the end of study will be recorded. At a minimum, the following information on prior and concomitant medications will be recorded on the case report form (CRF): medication name, dose, frequency, route, start date and time, stop date and time, and indication.

Prohibited Medications

Psychotropic medications and medications with a propensity for psychotropic effects are not permitted during the study participation, except as discussed below (see Allowed Concomitant Psychotropic Medication). Subjects will be requested to refrain from using benzodiazepines (eg, clonazepam and bromazepam) for the duration of their participation in the studyThe use of herbal supplements, dietary supplements or other complementary or alternative medications for treating psychiatric indications, as well as nutritional supplements and nonprescription herbal preparations with CNS effects (eg, St. John’s Wort, omega-3 fatty acids, kava extracts, gamma-aminobutyric acid supplements, cannabidiol, etc) are not permitted during the study participation. Disallowed psychotropic medications must be washed out during the screening/washout period and fully discontinued a minimum of 3 days or 5 half-lives (whichever is longer) prior to randomization. Disallowed herbal supplements with CNS-related indications must be fully discontinued a minimum of 3 days prior to randomization.

Allowed Concomitant Psychotropic Medications

The use of concomitant psychotropic medications at a stable dose for at least 3 months prior to Screening will be permitted provided they are prescribed for non-exclusionary indications. Pharmacological treatment and dose should not change during trial unless required by physician to adequately treat the subject.

Treatment of Insomnia

Concomitant use of eszopiclone, zaleplon, zolpidem and zolpidem CR is permitted at the discretion of the Investigator with the following restrictions:

- eszopiclone (≤ 3 mg/day), zopiclone (≤ 7.5 mg/day), zaleplon (≤ 20 mg/day), zolpidem (≤ 10 mg/day), and zolpidem CR (≤ 12.5 mg/day) may be administered at bedtime for insomnia, not exceeding 3 instances per week.

Diphenhydramine ≤ 100 mg/day and melatonin ≤ 10 mg/day may be administered at bedtime for insomnia, as needed. Over-the-counter melatonin may be used. Combination melatonin products are not allowed.

Medications that are used for insomnia should be administered no more than once nightly and should not be used in combination.

The date and time of the last dose of any concomitant psychotropic medication(s) taken prior to scheduled effectiveness assessments must be recorded at each visit. Subjects should be encouraged to avoid taking any psychotropic medication (or any agents that may cause sedation) within 12 hours of effectiveness assessments.

Allowed Concomitant Non-Psychotropic Medications

Non-psychotropic medications used to treat stable, chronic medical conditions or for short-term treatment of an acute medical condition may be used during screening and throughout participation. Use of non-prescription pain medications (eg, aspirin, acetaminophen/paracetamol) are allowed during all phases of the study.

Subjects will be requested to refrain from using benzodiazepines (eg, clonazepam and bromazepam) and acute use of beta-blockers (eg, atenolol and propranolol) for the duration of their participation in the study. Individuals with a stable history of beta-blockers for cardiac indications are permissible for this study.

Subjects will be requested to refrain from use of alcohol, tetrahydrocannabinol (THC) for any purpose while taking part in the study.

The use of any concomitant medication or other psychotropic drug use will be assessed and registered during all scheduled telephone visits.

Information on the format and version of the coding dictionary is provided in the Data Management Plan (DMP). All medications will be coded using World Health Organization Drug Dictionary (WHO-DD).

11. STUDY ASSESSMENTS

All study assessments will be conducted/performed remotely. A study schematic is presented in Table 5. A Schedule of Assessments to be performed each week is presented in Table 2.

11.1. Demographics and Baseline Characteristics

Demographics will be recorded, including: year of birth and age, sex assigned at birth, ethnic identity, and racial identity.

11.2. Medical and Psychiatric History

Medical and psychiatric history will also be recorded. Psychiatric history will be reviewed, and diagnoses will be confirmed by PI using the MINI. Prior experience with CBT (ie, including questions about experiences with in-imagination or in-vivo exposure to fearful situations) and use of concomitant medications and substance use will be reviewed. Only relevant/significant medical history and recurrence of any condition will be collected.

The MINI (Sheehan-1998) is a short diagnostic structured interview to explore 17 disorders based on DSM-V criteria. There are one or two questions for each disorder, which can be ruled out as diagnoses based on negative responses. All eligible Subjects must meet the MINI criteria for Social Anxiety Disorder for study inclusion.

11.3. Effectiveness Assessments

All assessments will be administered as outlined in Table 2, Schedule of Assessments. Descriptions of each assessment are outlined below.

11.3.1. Credibility/Expectation Questionnaire

The Credibility/Expectation Questionnaire (CEQ), (Devilly-2000) asks about the improvements that subjects believe will be achieved as a result of treatment, and how believable, convincing, and logical the treatment seems. It contains six items rated on a 1–9 or a 0%-100% scale. The first three items of the scale load onto the credibility factor and the final three items load onto the expectancy factor.

11.3.2. Liebowitz Social Anxiety Scale

The LSAS (Liebowitz-1987) is a clinician administered instrument that assesses both fear and avoidance across a number of social situations. This measure has been frequently used in pharmacological studies of social phobia and in cognitive behavioral studies.

The scale consists of 24 items each depicting different social situations. The fear scale ratings range from 0 (no fear) to 3 (severe fear). The avoidance ratings also range from 0 to 3 and are based on the percent of time avoiding the particular situation [0 = never; 1 = occasionally (10%); 2 = often (33–67%); and 3 = usually (67–100%)]. The clinician has the flexibility to ask additional questions beyond these ratings and may adjust the ratings accordingly. In addition to the fear and avoidance subscales, the LSAS is further divided into two subscales for scoring, including social interaction (11 items) and performance situations (13 items). Thus, an overall score is derived along with six additional scores based on fear and avoidance: total fear, fear of

social interaction, fear of performance situations, total avoidance, avoidance of social interaction, and avoidance of performance situations.

11.3.3. Clinical Global Impression - Severity

The severity of illness for each subject will be rated using the CGI-S (Guy-1976). The CGI-S is a standardized, clinician-administered global rating scale that measures disease severity on a 7-point Likert scale. A higher score on the CGI-S represents a higher severity of disease. To perform this assessment, the rater or investigator will answer the following question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" Response choices include: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients.

11.3.4. Clinical Global Impression - Improvement

The efficacy of trial treatment will be rated for each subject using the CGI-I (Guy-1976). The rater or investigator will rate the subject's total change compared to the subject's condition at baseline, whether or not it is due entirely to study treatment. Response choices include: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.

11.3.5. Patient Health Questionnaire

The PHQ (Spitzer-1999) is a self-administered version of the PRIME-MD diagnostic instrument for common mental disorders. The PHQ-9 is the depression module, which scores each of the 9 DSM criteria as "0" (not at all) to "3" (nearly every day).

11.3.6. Patient Global Impression Improvement

The PGI-I (Guy-1976) will ask subjects to rate their perceived improvement of their condition from treatment initiation to present, based on the following seven-point scale: 1=very much improved since the initiation of treatment; 2=much improved; 3=minimally improved; 4=no change from baseline (the initiation of treatment); 5=minimally worse; 6= much worse; 7=very much worse since the initiation of treatment.

11.3.7. Qualitative Interview

At the conclusion of the study (EOS) or early termination (ET), a member of the unblinded site support team will complete a qualitative interview within 48 hours of the final clinical assessments outlined above. This interview will explore subjects' experiences, perceptions, and acceptability of BVR-100 and BES-100. This interview will last for approximately 45 minutes.

11.4. Safety Assessments

The Investigator or appropriate designee will review results of safety assessments on a regular basis and the Sponsor must be kept fully informed of any clinically significant findings either at Screening or subsequently during study conduct. Subjects will be provided a contact telephone number to report safety concerns (eg, AEs). This telephone number will be the study site's phone number and also documented on the informed consent form (ICF).

Safety assessments will be administered according to the Schedule of Assessments in Table 2.

11.4.1. Adverse Events

Adverse events will be collected for each subject. Subjects should be queried in a non-leading manner, without specific prompting (eg, "Has there been any change in your health status since your last visit?"). See Section 12, Safety Reporting.

All AEs will be monitored throughout the study by spontaneous subject reports and by the investigator site staff soliciting AEs at each scheduled telephone contact.

11.4.2. Columbia Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale (C-SSRS) will be administered by investigator site staff.

The C-SSRS is a tool designed to systematically assess and track suicidal adverse events (suicidal behavior and suicidal ideation) throughout the trial. The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior. The scale takes approximately 5 minutes to administer (Posner-2011). The C-SSRS will be administered by a trained rater at the site. Subjects with Type 4 or Type 5 suicidal ideation at the Screening or Baseline visit will be excluded from entry into the study. Subjects with Type 4 or Type 5 suicidal ideation during the study will be discontinued from the study and referred to a mental health professional. At the Screening visit/Visit 1, the "Baseline/Screening" version of C-SSRS will be used. For all applicable visits onward, the "Since Last Visit" version of the C-SSRS will be used.

If a subject answers "yes" to "Suicidal Ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on any post-Baseline C-SSRS assessment, the subject must be discontinued from the study, referred to the Investigator for follow-up evaluation, and followed until the event resolves; in addition, an associated AE must be reported.

11.5. Study Visits and Assessments

This study is a decentralized trial, and thus all 'visits' will occur via telehealth. All assessments will be completed in accordance with the schedule outlined in Table 2.

11.5.1. Visit 1 - Screening: (Up to 14 Days)

Subjects will be evaluated at Screening (up to 14 days prior to Randomization) to determine their eligibility to randomize in the study.

The following study-related procedures will be performed by investigator site staff in order of the site's clinical preference:

- Obtain informed consent**. (MUST occur first)**
- Review inclusion and exclusion criteria.
- Record demographics and baseline characteristics.
- Record medical/psychiatric history.

- Administer the MINI.
- Clinician administers the LSAS.
- Clinician administers the C-SSRS.
- Subject completes the PHQ-9.
- Review prior/concomitant medications.
- Review pretreatment adverse event monitoring.

For subjects that wish to participate in the study and are currently taking disallowed psychotropic medications or herbal supplements, subjects will be asked to wash-out from these medicaments during the Screening period.

11.5.2. Visit 2 - Randomization (up to 7 days)

After Screening, subjects deemed eligible by the Investigator will be contacted by investigator site staff to be informed they are qualified to participate in the study. Visit 2 will occur up to 7 days prior to Baseline, including the following study-related procedures to be performed by investigator site staff:

- Review Inclusion and Exclusion criteria.
- Confirm continued Subject interest in study participation.
- Review prior/concomitant medications.
- Pretreatment adverse event monitoring
- Randomization via an interactive web responses system (IWRS) in a 1:1 ratio to either treatment (BVR-100) or control (BES-100) intervention
- Schedule Baseline visit within 5-7 days of the Randomization visit.

Remind the subject that neither the investigator site staff nor the subject will know which treatment group they have been assigned to throughout the duration of their participation, and that they must not discuss anything regarding the intervention with the investigator site staff.

Remind the subject that they will be contacted by a designated member of the unblinded site support team to provide guidance shortly after device delivery.

After randomization to either treatment group, the VR headset–pre-loaded with BVR-100 or BES-100 will be shipped out to the subject's address from the depot.

Subjects will be blinded to their intervention assignment, and they will be instructed on an ongoing basis to refrain from sharing any details about their intervention with anyone beyond the unblinded site support team assigned to the study.

11.5.3. Visit 3 - Baseline: (Week 1)

The Baseline visit will be scheduled to occur within 5-7 days of the randomization visit, to allow adequate time for VR device delivery/receipt. However, if the device is received earlier and the Baseline visit occurs earlier, this will be acceptable. If, due to delays with device

delivery/receipt, an extension beyond the 7 days is necessary, approval by the Medical Monitor is required.

Upon confirmation of device delivery, a member of the unblinded site support team will contact the subject to confirm receipt of the device, to establish a relationship, and again remind the subject that they would be the only contact for any device related issues throughout the duration of their participation in the study. After this is confirmed, the Baseline visit with the investigator site staff could take place.

The Baseline visit is the first day of Week 1, and it will be split into two separate parts, expected to occur on the same day. During the first part of the Baseline visit, a telehealth call will be performed with the investigator site staff who will administer Baseline visit (Day 1) assessments including the following procedures:

PART 1 (investigator site staff during telehealth Visit 3):

- Clinician administers C-SSRS.
- Clinician administers LSAS.
- Clinician administers CGI-S.
- Collect any AEs.
- Review concomitant medication changes.
- Subject completes PHQ-9.
- Prior to ending the telehealth visit, remind the subject regarding Part 2 of the visit, which is completed independently at home by the subject, where they will be responsible for three activities:
  - Viewing the video for VR onboarding, a link for which will be sent immediately following the conclusion of Baseline, Part 1;
  - Completing the first VR session; and
  - Completing (electronically) the CEQ.

Remind the subject that throughout the duration of their study participation, they must not discuss anything regarding the intervention with the investigator site staff and that they could reach out to the designated unblinded site support team at any time.

PART 2 (Independently at home by Subject):

- Shortly after the conclusion of Baseline, Part 1, and on the same day, subjects will receive access to complete a video-guided VR onboarding session providing information to set-up the VR headset and information about the intervention.
- Subjects will be able to reach out to a designated, unblinded site support team for any assistance/guidance during the video-guided onboarding session or at any time thereafter.
- After successful video onboarding, subjects will complete the first VR session.

- Then, after completion of the first VR session, subjects complete the CEQ electronically.

The designated, unblinded site support team will ensure that the video-onboarding, the first VR session, and the CEQ are completed all *within the same day as Baseline, Part 1*.

- During the rest of Week 1 (days 2-7), subjects will be expected to continue their engagement with the VR intervention and to complete a minimum of two additional VR sessions for a weekly total of three completed VR sessions.
- Subjects are also encouraged to engage with the optional VR content.

11.5.4. Intervention period (Weeks 2, 4, 6, and 8/EOS)

These intervention weeks will be split into multiple parts: Part 1, independent at-home activities completed by the subjects, Part 2, a telehealth visit with investigator site staff, and for Week 8/EOS ONLY, an additional Part 3, where after the telehealth call, a qualitative interview with a member of the unblinded site support team will take place. The details are further outlined below:

PART 1 (Independently at home by Subject):

- Minimum of 3 required VR sessions (Must be completed prior to PROs).
- Subject electronically completes PHQ-9.
- Subject electronically completes PGI-I.
- Subject electronically completes CEQ (Week 6 and Week 8 ONLY).
- Subjects are encouraged to engage with optional content and to review content completed at any time.
- In the event that subjects require technical support or further VR program instructions, support will be provided by a designated unblinded site support team (ie, personnel external to the site and not involved in data collection).

The scales should be reviewed upon their completion on a bi-weekly basis, to ensure completeness, for any potential AEs that may be reported, and retraining provided to subjects as necessary. Weekly reminders to all study subjects to complete their modules and PROs will be sent out. Subjects that fail to complete weekly content requirements will be contacted directly by the unblinded site support team, who will closely monitor intervention compliance for both groups.

PART 2 (<u>investigator site staff</u> during telehealth Visit 4 (W2)/ Visit 5 (W4) / Visit 6 (W6)/ Visit 7 (W8/EOS)):

During the last 3 days of Weeks 2, 4, 6, and 8, the investigator site staff will conduct telehealth study visits to complete the following assessments:

- Clinician administers C-SSRS. (Week 4 and Week 8 ONLY)
- Clinician administers LSAS.
- Clinician completes CGI-S.
- Clinician completes CGI-I.

- Collect AEs and concomitant medication changes.

All attempts will be made to ensure that each subject is assessed by the same study staff to minimize confounding bias due to changing assessors.

Unscheduled telehealth visits to complete/perform additional safety assessments, may be conducted as deemed necessary by the investigator site staff/subject.

After the completion of the telehealth portion of visit 7 with investigator site staff, the second part of the visit will be conducted separately by a member of the unblinded site support team where the Qualitative Interview will be completed as the final study assessment on the same day or within no later than 48 hours. During this visit, the unblinded site support team will instruct the patient to return the device and provide any necessary guidance/instructions.

11.5.5. Intervention Period (Weeks 3, 5, and 7)

Independently at home by subject:

- Minimum of 3 required VR sessions.
- Subjects are encouraged to engage with optional content and to review content completed at any time.
- In the event that subjects require technical support or further VR program instructions, support will be provided by a designated unblinded site support team (ie, personnel external to the site and not involved in data collection).

There are no telehealth visits scheduled during these weeks; however, unscheduled telehealth visits to complete/perform additional safety assessments, may be conducted as deemed necessary by the investigator site staff/subject.

11.5.6. Early Termination

For subjects who prematurely discontinue from the study, every effort should be made to complete the final evaluation procedures, as described in Section 11.5.4 and including clinical and PRO assessments , as well as the Qualitative Interview outlined in Section 11.3.7 at the ET visit. This ET visit should occur within 5 days of the last exposure to the Investigational Intervention, including the qualitative interview and PROs if they have not been completed by the subject for the given week.

12. SAFETY REPORTING

12.1. Definitions

12.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence associated with the use of an investigational intervention in humans, whether or not considered related to the intervention.

Untoward medical occurrences that occur after the time of signing the Informed Consent Form (ICF) and prior to the first VR session are a subset of AEs referred to in analysis as pre-treatment events. Those that occur after first VR session are considered AEs. Importantly, all AEs, including pre-treatment events, are collected via the same form by investigator site staff, who will complete the AE form in the EDC, which will then immediately notify both the CRO and Sponsor.

An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease occurring after the administration of an investigational intervention, whether or not considered related to the investigational intervention. AEs may include the onset of new illness and the exacerbation of pre-existing conditions. AEs will be collected from after first use of the investigational intervention to the EOS/ET.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

12.1.2. Serious Adverse Events

A serious adverse event (SAE) is an AE that meets one or more of the following criteria:

- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the subject or may require a medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

The term "severe" is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction) (see Section 12.2); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning as defined by the criteria above.

During the study, if a subject has a hospitalization or procedure (eg, elective surgery) that was scheduled before the study entry, ie, before informed consent for an event/condition that occurred before the study, the hospitalization is considered a therapeutic intervention and not the result of a SAE. However, if the event/condition worsens during the study, it should be reported as an AE (or SAE, if the event/condition results in a serious outcome such as prolongation of hospitalization).

Life-threatening means that the subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that had it occurred in a more severe form might have caused death.

SAE criteria information will be captured on the CRF.

12.1.3. Unanticipated Adverse Device Effects

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

12.2. Collection and Recording of Adverse Events

All pre-treatment events and AEs including UADEs must be recorded in the subject's study records/source documents in accordance with the Investigator's normal clinical practice. All pre-treatment events and AEs must be recorded on the CRF.

All AEs will be followed until resolution, stabilization of the condition, the event is otherwise explained, the completion of the study, or the subject is lost to follow-up.

Each AE is to be evaluated for duration, severity, frequency, seriousness, action taken with the investigational intervention, outcome, and causal relationship to the investigational intervention. Definitions for severity, frequency, action taken with the investigational intervention, outcome, and causal relationship to the investigational intervention are presented below.

The severity of AE:

- **Mild** - Ordinarily transient symptoms that do not influence performance of subject's daily activities. Other treatment is not ordinarily indicated.
- **Moderate** - Marked symptoms sufficient to make the subject uncomfortable. Moderate influence on performance of subject's daily activities. Other treatment may be necessary.
- **Severe** - Symptoms cause considerable discomfort. Substantial influence on subject's daily activities. May be unable to continue the study, and other treatment may be necessary.

The frequency of AE:

- **Once** – an isolated episode.
- **Intermittent** – occurs on two or more separate occasions.

- **Continuous** – does not abate from date of onset to date of resolution.

The action taken with the investigational intervention:

- **None**
- **Removed temporarily**
- **Removed permanently**
- **Replaced**
- **Action taken with component(s)**
- **Unknown**

The outcome of the AE:

- **Recovered/Resolved**
- **Recovering/Resolving**
- **Not Recovered/Not Resolved**
- **Recovered/Resolved with Sequelae**
- **Fatal**
- **Unknown**

The causal relationship of the AE to the investigational intervention:

- **Not related: -** Improbable temporal relationship and is plausibly related to other drugs/products or underlying disease.
- **Related**
  - **Possible** - occurred in a reasonable time after the use of the intervention, but could be related to concurrent drugs or underlying disease.
  - **Probable** - occurred in a reasonable time after use, is unlikely to be attributable to concurrent drugs or underlying disease, and there is a plausible mechanism to implicate the intervention.
  - **Definite** - occurred in a reasonable time after use and cannot be explained by concurrent drugs or underlying disease. The adverse event should respond to dechallenge/rechallenge, however, this is not mandatory before assigning a definite causality.

The Medical Monitor is the initial contact person for protocol related questions or discussion of AEs. The contact information for the Medical Monitor as well as other emergency contact information can be found in Table 1 of this protocol.

12.3. Immediately Reportable Events

The following medical events must be immediately reported to the Sponsor by completing the AE form in the EDC:

- SAEs
- UADEs

Emergency contact information can be found in Table 1.

12.3.1. Serious Adverse Events

When a SAE has occurred, the site will enter the SAE into the EDC without delay after awareness, and the Sponsor/designee will receive an email notification of the SAE.

The site will complete the SAE form and file it in the subject's study records.

Upon notification, the CRA will reach out to the site staff to collect additional information related to the event.

The site will report the SAE to the IRB per their Safety Reporting Requirements and provide the submission form and Acknowledgement of Receipt to the CRA.

The site will follow up on the SAE during each subject contact until resolution, lost to follow-up, stabilization of condition, study completion, or the event is otherwise explained. Any updates to the SAE will be entered into the EDC.

The Sponsor or designee will promptly notify all study centers and Investigators of an SAE that is determined to be a risk for other/all subjects.

12.3.2. Unanticipated Adverse Device Effects

The investigator or study staff must determine if an incident, experience, outcome, or adverse event that meets all the criteria for a UADE requires prompt reporting to the Sponsor and the IRB. The assessment of whether an incident, experience, outcome, or adverse event is unexpected (in terms of nature, severity, or frequency) should consider the following: the research procedures that are described in the protocol-related documents, such as the informed consent document, IRB approved research protocol, and the characteristics of the subject population being studied.

In assessing whether an incident, experience, outcome, or adverse event is related to the intervention, the investigator should consider the intervention being administered, and the underlying disorder or condition of the subject, and other circumstances unrelated to either the intervention or any underlying disorder.

UADEs and adverse events that are determined to be at least partially caused by the intervention are considered related to participation in the study, whereas adverse events determined to be solely caused by a subject's underlying disorder or other circumstances unrelated to the trial are considered unrelated to participation in the study.

The investigator is required to submit a report of a UADE to the Sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event. UADEs that require remedial action to prevent an unreasonable risk of substantial harm to the public should be reported by the Investigator within 5 calendar days. The investigator is also responsible for providing progress reports on anticipated and unanticipated adverse device effects at regular intervals, but at least annually, to Sponsors, monitors, and IRBs. On the other hand, the Sponsor must immediately conduct an evaluation of a UADE and must

report the results of the evaluation to FDA (if applicable), all reviewing IRBs, and participating investigators within 10 working days after the Sponsor first receives notice of the effect. If a Sponsor determines that a UADE presents an unreasonable risk to subjects, the Sponsor must terminate all investigations within 5 days of the Sponsor making this determination.

13. TERMINATION OF SUBJECT FROM STUDY

Subjects may be prematurely terminated from the study participation at any time for any of the following reasons:

- Adverse Event (including UADE)
- Lost to follow-up (specify)
- Withdrawal of consent (specify)
- Death
- Protocol deviation (specify)
- Other (specify)

The reason for termination of study participation and information on the epoch will be recorded on the appropriate CRF. In case of death, the date of death should be captured on the CRF.

Subjects who discontinue early may be replaced at Sponsor discretion to assure that sufficient data for evaluation is collected.

14. STUDY TERMINATION

The Sponsor reserves the right to discontinue the study at this study center for safety or administrative reasons at any time while safeguarding that early termination does not compromise subjects' safety or well-being. Should the study be terminated and/or the study center closed for whatever reason, all documentation and study materials pertaining to the study must be returned to the Sponsor or its representative.

If, in the opinion of the Investigator, clinical observations suggest it may be unsafe to continue, the Investigator may terminate part or the entire study after consultation with the Sponsor.

In the event of study or site termination, subjects will be required to complete study assessments scheduled for the EOS/Early Termination (Week 8; see Table 2).

15. STATISTICS

15.1. Sample Size

Due to the pilot nature of the study, no formal sample size calculations will be conducted. However, to ensure a reliable estimate of the standard deviations to power a future trial with 90% and an expected effect size between 0.3 and 0.7, fifteen people per arm are recommended (Whitehead-2016). In order to account for a possible attrition rate of 25%, twenty people per arm (total n = 40) will be recruited. In order to ensure adequate data for evaluation, early discontinued subjects may be replaced at Sponsor discretion.

15.2. Analysis Populations

The effectiveness analyses will be based on the modified Intent-to-Treat (mITT) population, which includes all subjects who are randomized, have completed at least one VR session, and have a Baseline and at least one post-Baseline effectiveness measurement in CEQ. Additional analysis of the Per-Protocol (PP) population (defined as all subjects who have completed the 8-week intervention period without any important protocol deviations) is supportive, while the mITT population will be the primary analysis population. The primary effectiveness endpoint must achieve significance in the mITT to preserve type I error for the secondary endpoint.

The safety assessments will use the Safety population, which includes all subjects who are randomized and have completed at least one VR session.

15.3. Data Analysis

Continuous outcomes will be summarized for the number of subjects, mean, standard deviation, median, minimum, maximum, 25th percentile, and 75th percentile. For categorical outcomes, the number and percentage of subjects will be presented.

For analyses of change from baseline, baseline will generally be defined as the first day of Week 1. Single imputation techniques will be employed for all missing data. All data from the CRFs, as well as any derived variables, will be presented in data listings.

SAS® Version 9.2 or higher will be used for all analyses.

15.3.1. Subject Disposition

Subject disposition will be summarized and presented for the number and percentage of subjects, who were screened, entered the study, randomized, completed the study, and discontinued early (including reasons for discontinuations).

15.3.2. Compliance with BVR-100 and BES-100

Compliance with BVR-100 and BES-100 will be summarized descriptively, as described by time-on-task , number of sessions, and subject retention. A data listing, by subject, will also be provided.

15.3.3. Important Protocol Deviations

Important protocol deviations (IPDs) will be identified and documented based on a review of potential IPDs prior to database lock. The potential IPDs will be identified through programmatic checks of study data , as well as through review of selected data listings. The potential IPDs to be reviewed include, but are not limited to, subjects who:

- Did not meet inclusion/exclusion criteria.
- Did not properly use BVR-100 or BES-100.
- Received any disallowed concomitant medication.

Individual IPDs will be presented in a data listing. The number and percentage of subjects with IPDs will be summarized by type of deviation and treatment group.

15.4. Demographic and Baseline Characteristics

All analyses will be based on mITT population as described in Section 15.2, as well as a secondary analysis of the PP and Safety populations.

Baseline demographic and clinical characteristics will be presented descriptively as proportions or as means with standard deviations. Baseline demographic and clinical characteristics will be compared between groups with the use of the two-sample *t*-test and the Mann–Whitney test for continuous measurements with and without normal distribution, respectively.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 or higher and will be summarized for the safety population by presenting the number and percentage of subjects with at least one condition in each system organ class (SOC) and preferred term (PT).

15.4.1. Concomitant Medications

All medications will be coded to indication-specific ATC (Anatomical Therapeutic Chemical) classification (ie, ATC level 3) and preferred name using the World Health Organization Drug Dictionary (WHO-DD) Enhanced extended with WHODrug Global.

Any medications taken during the course of the study, with a start date on or after the date of the first use of BVR-100/BES-100 and with a start date prior to, and an end date on or after, the date of the first use of BVR-100/BES-100 will be considered concomitant medications. Medications that ended prior to the date of the first use of BVR-100/BES-100 will be considered prior medications. Prior and Concomitant medications will be summarized for the number and percentage of subjects using each medication by dosage form and overall by the drug class and preferred name for the safety population.

15.4.2. Effectiveness Analyses

No formal hypothesis testing relating to primary, secondary, or exploratory outcomes is planned because this is a pilot study.

15.4.2.1. Analysis of Primary Endpoint

Descriptive statistics will be used to estimate group differences in the CEQ at Baseline and at Weeks 6 and 8. Exploratorily, CEQ scores differences between groups will be computed using Student's *t* tests will be analyzed.

15.4.2.2. Analysis of Secondary Endpoints

Descriptive statistics will be used to estimate group differences in retention rates and time-on-task at Weeks 6 and 8. Associations determined through Student's *t* tests between the primary endpoint (CEQ scores) and both baseline variables and clinical outcomes will be analyzed.

15.4.2.3. Analysis of Other Effectiveness Endpoints

N/A

15.4.2.4. Analysis of Exploratory Endpoints

Likewise, descriptive statistics will be used to assess differences in the mean change from baseline in the LSAS, CGI-S and PHQ-9 at Weeks 2, 4, 6, and 8; differences in the mean change from CGI-S baseline score in the CGI-I and PGI-I at Weeks 2, 4, 6, and 8; and proportion of subjects with a "responder" status at the end of treatment at Week 8. Between-group differences in LSAS and responder status rates will be analyzed using Student's *t* tests and chi-squared tests, respectively.

15.4.3. Safety Analyses

Safety data including AEs, SAEs and, UADEs will be collected from the start date/time of Investigational Intervention, defined as the engagement with first intervention session, to the EOS/ET, and summarized by treatment group. Adverse events, AEs leading to discontinuation, serious AEs, and UADEs will be summarized by presenting, for each treatment group, the number and percentage of subjects with any AEs, and AEs by system organ class and preferred term. Adverse events will be further summarized by severity and by relationship to the Investigational Intervention.

AEs are defined as untoward medical occurrences that started at the same time of or after the first VR session. Untoward medical occurrences that started prior to the first VR session, but after signing the ICF are pre-treatment events.

Whenever available, the time information should be accounted for in the derivation of AEs vs. pre-treatment events. In the case where time is not available, untoward medical occurrences that started on or after the day of the first VR session will be considered AEs; those that started before the day of the first VR session, but after signing the ICF, will be considered pre-treatment events. The identification of AEs versus pre-treatment events will be determined programmatically, and not at the site level.

15.4.3.1. Adverse Events

All AEs will be coded using MedDRA version 26.0 or higher. AEs are untoward medical occurrences:

- that occurred on or after the first BVR-100/BES-100 use,
- with a missing start date and a stop date on or after the first BVR-100/BES-100 use, or
- with both a missing start and stop date.

AEs will be summarized by MedDRA SOC and PT.

The following AEs will be summarized and presented by MedDRA SOC and PT for the Safety population:

- All AEs (including number of events and subject incidence).
- AEs by severity (mild, moderate, severe).
- AEs by relationship to the investigational intervention (related, or not related).

The following conventions will be followed in summarizing AEs:

- For subject incidence summaries, each subject will be counted only once within each SOC and within each preferred term.
- If a subject reports more than one AE within a preferred term and/or a body system, the AE with the highest known severity within each body system and within each preferred term will be included in the summaries by severity.
- For summaries by relationship to the investigational intervention, AEs will be grouped as "related" or "not related." AEs assessed as "possible," "probable," or "definite," will be grouped as "related." If a subject reports more than one AE within, SOC and PT, and any are related, it will be summarized as related. AEs whose relationship to the investigational intervention is assessed as "not related" or "unlikely" will be grouped as "not related."

A listing of AEs, as well as a listing of deaths, SAEs, UADEs, or AEs leading to discontinuation, will be presented.

15.4.3.2 Suicidality Measure

Frequency and severity of suicidal ideation and suicidal behavior as measured by the C-SSRS scale will be summarized by treatment for the overall post-Baseline period and by visit.

15.4.4. Treatment of Missing Data

Missing observations will be treated as missing at random, and no data imputation will be performed.

16. PROCEDURE FOR CLINICAL STUDY QUALITY CONTROL /DATA COLLECTION, MANAGEMENT, AND QUALITY ASSURANCE

16.1. Protected Health and Information and Confidentiality

The investigator and members of the Investigational Review Board (IRB)/Independent Ethics Committee (IEC) of record shall consider all data or findings generated during the conduct of the study, other than information to be disclosed by law, as confidential. Disclosure of such data or findings to any third party shall not occur without the prior written consent of the Sponsor.

All reports and communications relating to subjects in the study will identify subjects by their subject ID number only.

16.2. Data Management

Every effort will be taken to ensure the accuracy and reliability of data including the selection of qualified investigators as appropriate study centers, review of protocol procedures with the investigators and associated personnel before the study commences, and periodic remote monitoring visits by the Sponsor or their representative, as deemed appropriate by the Sponsor. Guidance for eCRF completion will be provided and reviewed with the investigator site personnel prior to the start of the study. The Sponsor or designee will review eCRFs for accuracy and completeness and any discrepancies will be resolved with the investigator or designee, as appropriate.

16.3. Electronic Case Report Forms

Investigator Site staff, as indicated in the Delegation Log, who will use the EDC system will have adequate training in order to perform assigned tasks. Training will be conducted by the Sponsor's qualified designated appointee as part of the Site Initiation Visit or as needed.

Data (such as Medical History, ICF, concomitant medication, assessment of I/E Criteria, and safety events and C-SSRS) collected during the conduct of the study will be entered into a 21 CFR Part 11 compliant eCRF database. Accuracy and data quality will be ensured through implementation of data edit checks.

Most clinical scales (LSAS, CGI-I, CGI-S) and PROs (CEQ, PGI-I, PHQ-9) will be administered electronically.

The Diagnostic scale MINI will be done on paper.

Once the study is closed and all data has been monitored and signed by study investigators, the database will be locked and analyzed for statistical evaluation and reporting.

16.4. Study Monitoring

The study will be monitored from Initiation through study closure by Sponsor or its representatives.

The study will be monitored regularly by trained clinical trial monitors to ensure the protection of the Subject rights and safety, as well as data quality and integrity in compliance with 21 CFR paragraph 812 Subpart C.

The monitor will remotely verify information entered into the eCRFs against source documents and the subject's medical records to ensure validity of the data.

On the occasion that a monitor requests additional data or clarification of data for the eCRF, the request must be addressed appropriately prior to the next monitoring visit. Once completed eCRF data are verified against source data, the study monitor will electronically sign off to indicate that data has been monitored for correctness. The investigator must sign all eCRFs prior to site close out.

There will be a remote site close out visit to ensure all documentation is in place and all outstanding items have been addressed. Record retention policies will be reviewed, and post-study investigator responsibilities discussed.

16.5. Audits

The study may be subject to audit by the Sponsor/designee or any regulatory body. If such an audit occurs, the Investigator must agree to allow access to all study related documentation for inspection. Investigators will immediately notify the Sponsor upon learning of announced audits or inspections by regulatory agencies.

The Investigator will promptly notify the Sponsor/CRO of all requests to inspect a Sunovion-sponsored study by government agencies and will promptly forward a copy of all such inspection reports.

16.6. Study Documentation

A source document is defined as any handwritten or computer-generated document that contains medical information or test results that have been collected for or are in support of the protocol specifications.

Investigators are required to record and maintain adequate and accurate case histories for all subject observations, assessments and data pertinent to the study conduct.

The investigator and Institution will be responsible for providing direct access to source data to Sponsor, their designated representatives and to appropriate authorities for the purposes of monitoring, audit, IRB/IEC review or regulatory inspection. Subjects will be notified of such access to study records as part of the consenting process.

16.7. Record Retention and Storage

Sponsor will retain all study documentation for a period of at least five (5) years or in accordance with Good Clinical Practice (GCP) regulations in force in the Sponsor's jurisdiction, whichever is greater, following formal discontinuation of the study.

The investigator shall retain all study documentation for a period of at least three (3) years or in accordance with retention policies of the IRB/IEC of record, whichever is longer.

17. ETHICAL AND REGULATORY OBLIGATIONS

17.1. Study Conduct

The Investigator will assure proper implementation and conduct of the study including those study-related duties delegated to other appropriately qualified individuals. The Investigator will assure that study staff cooperate with monitoring and audits.

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council for Harmonization (ICH) guidelines on GCP, International Organization for Standardization (ISO)14155:2020 and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human Subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study Subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

The Investigator must sign and return to Sponsor/CRO the “Investigator Approval" page.

The Investigator must provide a copy of current curriculum vitae (including a copy of a current medical license), ICH-GCP Certificate and financial disclosure information.

The Investigator must sign and return a completed Investigator Agreement to Sponsor/CRO.

17.2. Institutional Review Board/Independent Ethics Committee

Before the start of data collection, the participating physician (or Sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, protocol amendments
- Sponsor-approved ICF (and any other written materials to be provided to the Subjects)
- Participating physicians’ curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding the name of the Sponsor, institutional affiliations, and potential conflicts of interest
- Any other documents that the IEC/IRB requests to fulfill its obligations.

Where appropriate, as required by local regulations, this study will be undertaken only after the IEC/IRB has given full approval of the final protocol, protocol amendments (if any, excluding those that are purely administrative, with no consequences for data collection), and the ICF, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the participating physician (or Sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding those that are purely administrative, with no consequences for data collection)
- Revision(s) to the ICF and any other written materials to be provided to subjects
- If applicable, new or revised Subject recruiting materials approved by the Sponsor
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB
- Reports of AEs that are serious, unlisted/unexpected, and temporally associated with the Procedures under study
- New information that may adversely affect the safety of the Subjects or the conduct of the study
- Report of deaths of Subjects under the participating physician's care
- Notification if a new participating physician is responsible at the participating site
- Any other requirements of the IEC/IRB.

All protocol amendments and any applicable revisions to the ICF will follow the appropriate review and approval process, in accordance with local regulations.

At the end of the study, where required by local regulations, the participating physician or authorized designee (or Sponsor where required) will notify the IEC/IRB about the study completion.

17.3. Informed Consent

Each subject must sign an ICF allowing data collection and source data verification in accordance with local requirements and Sponsor policy. The ICF must be signed before collection of any subject data.

The ICF that is/are used must be reviewed and approved in accordance with local regulations, applicable regulatory requirements, and Sponsor policy, and must be in a language that the subject can read and understand.

Prior to participation, each prospective subject will be given a full explanation of the study, allowed to read the approved informed consent form and be provided ample time and the opportunity to ask any questions that may arise. Once all questions have been answered and the Investigator is assured that the prospective subject understands the implications of participating in the study, the prospective subject will be asked to give consent to participate in the study by signing the informed consent form. As part of the consent process, each prospective subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection. It should be clearly explained to each prospective subject that participation in each and every study contact and assessment is expected. The Investigator will provide a copy of the signed informed consent form to each subject, and will record the date of the informed consent on the CRF.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or if important new information becomes available that may be relevant to the subject’s consent,

the informed consent form must be revised, submitted to the IRB/IEC for review and approval or favorable opinion. The revised informed consent form must be used to obtain consent from a subject currently enrolled in the study if he or she is affected by the amendment. The revised informed consent form must be used to obtain consent from any new subjects who are enrolled into the study after the date of the approval or favorable opinion of the protocol amendment.

17.4. Protocol Amendments and Emergency Deviations

All revisions and/or amendments to this protocol must be approved in writing by the Sponsor and the appropriate IRB/IEC. The Investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from the Sponsor and the IRB/IEC, except where necessary to eliminate an apparent immediate hazard to a study subject.

Emergency deviations or modifications must be reported to the Sponsor/CRO and the IRB/IEC within five business days of the occurrence, or in accordance with applicable regulatory requirements.

17.5. Financial Disclosure

By signing this protocol, the Investigator agrees to provide to the Sponsor prior to start of study accurate financial information to allow the Sponsor to submit complete and accurate certification and disclosure statements as required by the US FDA regulations (21 CFR Part 54). The Investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by the Sponsor. The Investigator will update this information if there are any relevant changes during the conduct of the study and for one year after completion of the study.

The Investigator also consents to the transmission of this information to the Sponsor for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

17.6. Publication Policy

Any formal presentation or publication of data collected as a direct or indirect result of the study will be considered a joint publication by the Investigators and the appropriate personnel of the Sponsor. For multicenter studies, it is mandatory that the first publication is based on all data obtained from all analyses as stipulated in the protocol. Investigators participating in multicenter studies must agree not to present data gathered individually or by a subgroup of centers before the full, initial publication, unless this has been agreed to by all other Investigators and by the Sponsor.

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19. INVESTIGATOR APPROVAL

I have read the protocol, BVR-100-102, Version 1.00, "BVR-100 and BES-100 Validation Trial: A Randomized, Double-Blind, Parallel-Group, Controlled Study of Two At-Home Self-Guided Virtual Reality Interventions for Adults with Social Anxiety Disorder", and agree that it contains all necessary details for conducting the study and to conduct the study in strict accordance with the specifications outlined herein.

I agree that no additional procedure(s) will be added during the conduct of the study except through protocol amendment by Sunovion Pharmaceuticals Inc. and after documentation of IRB approval.

Investigator Signature: _____

Print Investigator Name: _____

Date: _____