COVER PAGE - PROTOCOL

Protocol Number:	812P413
Title:	A Phase IV, Open-label, Decentralized Clinical Trial to Evaluate the Efficacy and Safety of Qelbree® in Adults with Attention-Deficit/Hyperactivity Disorder (ADHD) and Mood Symptoms
Sponsor:	Supernus Pharmaceuticals, Inc. 9715 Key West Avenue Rockville, MD 20850 United States Phone: (301) 838-2500 Fax: (240) 403-0065
Protocol Version:	2.0
Date:	25Nov2024
NCT:	NCT06185985

PROTOCOL

A PHASE IV, OPEN-LABEL, DECENTRALIZED CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF QELBREE® IN ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) AND MOOD SYMPTOMS

Protocol No.:	812P413
Test Article:	Qelbree® (viloxazine extended-release capsules; SPN-812)
Sponsor:	Supernus Pharmaceuticals, Inc. 9715 Key West Avenue, Rockville, MD 20850 United States
Sponsor Representative:	[redacted]
Clinical Research Organization (CRO):	[redacted]
Phase of Study:	Phase IV
Study Design:	Open label, decentralized clinical trial
Country of Implementation:	United States

INVESTIGATOR SIGNATURE PAGE

Protocol Number: 812P413
Version: 2.0
Date: 25-Nov-2024

INVESTIGATOR'S SIGNATURE

I have read the protocol specified above and agree to participate in and comply with the procedures, as outlined herein for the conduct of this clinical trial. I also agree to comply with the applicable US Food and Drug Administration (FDA) regulations and Institutional Review Board (IRB) requirements for testing on human subjects. I agree to ensure that the requirements for obtaining informed consent are met.

_____ _____

Investigator's Signature Date

_____

Printed Name

DOCUMENT HISTORY

Protocol	Approval Date (Version)
Amendment 01	See Sponsor's Protocol Approval Page (Version 2.0)
Original	10 Oct 2023 (Version 1.0)

SPONSOR'S PROTOCOL APPROVAL PAGE

Protocol Number: 812P413
Version: 2.0
Date: 25-Nov-2024

I have read the protocol specified above and agree to comply with the procedures, as outlined herein for the conduct of this clinical trial. The signature below indicates the sponsor's approval of this protocol.

Contents

1. LIST OF ABBREVIATIONS 8

2. PROTOCOL SYNOPSIS 10

3. INTRODUCTION AND BACKGROUND 15

3.1 Study Rationale 15

3.2 Background 15

3.2.1 ADHD and Mood Symptoms 15

3.2.2 Adult ADHD Qelbree Clinical Trial Findings 17

3.3 Risk/Benefit Assessment 18

3.3.1 Known Potential Risks 18

3.3.2 Known Potential Benefits 19

3.3.3 Assessment of Potential Risks and Benefits 19

4. STUDY OBJECTIVES AND ENDPOINTS 20

5. RECRUITMENT AND PRE-SCREENING 23

6. STUDY DESIGN 24

6.1 Screening Period 24

6.1.1 Televisit #1a: 24

6.1.2 Televisit #1b: 25

6.2 Treatment Period 25

6.3 End of Study 26

6.4 Safety Follow-up (SF) Televisit 27

7. STUDY POPULATION 30

7.1 Inclusion Criteria 30

7.2 Exclusion Criteria 31

7.3 Screen Failures 32

7.4 Recruitment and Retention 32

8. STUDY TREATMENT 32

8.1 Study Treatment Description 32

8.2 Study Treatment Administration 32

8.2.1 Study Medication 32

8.2.2 Dosing 32

8.2.3 Mode of Administration 33

8.3 Study Product Preparation/Handling/Storage/Accountability 33

8.4 Concomitant Diets, Treatments, and Medications 33
8.4.1 Contraindications 33

9. STUDY ASSESSMENTS AND PROCEDURES 34

9.1 Screening Assessments 34
9.1.1 Psychiatric Diagnostic Instruments 34
9.1.1.1 Mini-International Neuropsychiatric Interview for ADHD Studies (MINI-AS) 34

9.2 Efficacy Assessments 35
9.2.1 Clinician-Rated Outcomes (ClinROs) 35
9.2.1.1 Adult ADHD Investigator Symptom Rating Scale (AISRS) 35
9.2.1.2 Clinical Global Impressions of Severity/Change (CGI-S/C) Scales 35
9.2.1.3 Montgomery–Åsberg Depression Rating Scale (MADRS) 36
9.2.1.4 Hamilton Anxiety Rating Scale (HAM-A) 36
9.2.2 Patient-Reported Outcomes (PROs) 37
9.2.2.1 Adult ADHD Self-Report Scale v1.1 Symptom Checklist (ASRSv1.1-SC) 37
9.2.2.2 Patient Health Questionnaire (PHQ-8) 38
9.2.2.3 General Anxiety Disorder-7 item (GAD-7) Scale 38
9.2.2.4 Behavior Rating Inventory of Executive Function–Adult Version (BRIEF-A) 38
9.2.2.5 Work Productivity and Activity Impairment: Specific Health Problem (WPAI:SHP) 40
9.2.2.6 Pittsburgh Sleep Quality Index (PSQI) 40

9.3 Questionnaires 41
9.3.1 Reproductive/Menstrual Cycle History (RMCH) Questionnaire 41

9.4 Safety Assessments 41
9.4.1 Adverse Events 41
9.4.2 Blood Pressure/Pulse Rate and Weight 41
9.4.3 Columbia-Suicide Severity Rating Scale (C-SSRS) 41

9.5 Adverse Events 42
9.5.1 Definition of Adverse Events 42
9.5.2 Definition of Serious Adverse Events 42
9.5.3 Adverse Event Reporting 42
9.5.4 Serious Adverse Event Reporting 43
9.5.5 Adverse Event Severity and Causality Assessments 43
9.5.6 Serious Adverse Event Follow-Up 45
9.5.7 Pregnancy Reporting 45

10. STUDY COMPLETION AND DISCONTINUATION 45

10.1 Study Completion 45

10.2 Study Discontinuation 46

10.3 Lost to Follow-up 46

11. DATA MANAGEMENT 47

11.1 Data Collection 47

11.2 Data Handling 47
11.3 Data Entry 47
11.4 Computerized Logical Checks 47
11.5 Audit Trail 48
12. STATISTICAL METHODS 48
12.1 General Considerations 48
12.2 Populations for Analyses 48
12.3 Determination of Sample size 48
12.4 Patient Disposition 49
12.5 Demographics and Baseline Analysis 49
12.6 Study Medication Exposure and Compliance 49
12.7 Concomitant Medications 49
12.8 Efficacy Analysis 49
12.8.1 Primary Endpoint(s) 49
12.8.2 Secondary Endpoint(s) 49
12.9 Safety Analysis 50
12.10 Exploratory Analysis 50
13. QUALITY CONTROL AND ASSURANCE 51
13.1 Acceptability of Case Report Forms (Source Documents) 51
13.2 Modification of Protocol 51
13.3 Reporting Protocol Deviations 52
13.4 Monitoring 52
13.5 Audits and Inspections 52
14. ETHICS AND REGULATORY REQUIREMENTS 53
14.1 Institutional Review Board/Independent Ethics Committee 53
14.2 Investigator Responsibilities 53
14.3 Informed Consent Process 53
15. STUDY CLOSURE 54
16. PUBLICATION PLAN 54
17. REFERENCES 56

1. List of Abbreviations

Abbreviation	TERM/DEFINITION
ADHD	Attention-Deficit/Hyperactivity Disorder
AE	Adverse Event
AISRS	Adult ADHD Investigator Symptom Rating Scale
ASRSv1.1-SC	Adult ADHD Self-Report Scale v1.1 Symptoms Checklist
ATC	Anatomical Therapeutic Chemical
BP	Blood pressure
BRI	Behavioral Regulation Index
BRIEF-A	Behavior Rating Inventory of Executive Function–Adult Version
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change Scale
CGI-S	Clinical Global Impression of Severity Scale
ClinRO	Clinician-reported outcome
COACH	Clinical Oversight and Coordination Hub
CPM	Clinical Project Manager
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual; fifth edition
EC	Ethics Committee
eCRF	Electronic Case Report Forms
EDC	Electronic data capture
eIC	Electronic informed consent
EOS	End of study
ER	Extended-release
FDA	Food and Drug Administration
FOCP	Female of childbearing potential
GAD	General Anxiety Disorder
GAD-7	General Anxiety Disorder 7-item scale
GCP	Good Clinical Practice
GEC	Global Executive Composite
HAM-A	Hamilton Anxiety Rating Scale
HI	Hyperactivity/Impulsivity
ICH	International Council on Harmonisation
IA	Inattention
IRB	Institutional Review Board
IUD	Intrauterine device
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	Monoamine oxidase inhibitors
MDD	Major Depression Disorder
MedDRA	Medical Dictionary for Regulatory Activities

mg	Milligrams
MI	Metacognition Index
MINI-AS	Mini-International Neuropsychiatric Interview for ADHD Studies
NRI	Norepinephrine reuptake inhibitor
OCD	Obsessive compulsive disorder
PHQ-8	Patient Health Questionnaire-8 item
PI	Principal Investigator
PRO	Patient-reported outcome
PSQI	Pittsburgh Sleep Quality Index
PT	Preferred Term
PTSD	Post-traumatic stress disorder
QA	Quality Assurance
QC	Quality Control
OCD	Obsessive Compulsive Disorder
QD	Once a day
RMCH	Reproductive/Menstrual Cycle History Questionnaire
SAE	Serious Adverse Event
SIGH-A	Structured Interview Guide for the Hamilton Anxiety Scale
SIGMA	Structured Interview Guide for the Montgomery-Åsberg Depression Rating Scale
SM	Study medication
SOC	System Organ Class
SOE	Schedule of Events
SOP	Standard Operating Procedure
Sub-I	Sub-Investigator
TEAE	Treatment-emergent Adverse Event
UAP	Unanticipated problems
US	United States
WPAI:SHP	Work Productivity and Activity Impairment: Specific Health Problem Questionnaire

2. Protocol Synopsis

Title
A Phase IV, Open-label, Decentralized Clinical Trial to Evaluate the Efficacy and Safety of Qelbree in Adults with Attention-Deficit/Hyperactivity Disorder (ADHD) and Mood Symptoms

Study Description:
This is a Phase IV, open-label, decentralized clinical trial to evaluate the efficacy and safety of Qelbree in adults with ADHD and mood symptoms. Adults 18 years and older will be recruited into this study. Participants will be recruited using digital and social media advertising, and referrals from physicians' existing patient pool. Individuals who are pre-qualified will be sent an email invitation to download the study app and contacted to schedule a screening televisit. Once eligibility is confirmed and participants are enrolled, study medication will be shipped. The treatment period will last for up to a total of 14 weeks. Participants will be assessed for compliance and specific outcomes during the treatment period

Study Objectives

Primary Efficacy Objective

The primary objective of this study is to evaluate the efficacy of Qelbree as a monotherapy and/or as an adjunctive therapy for ADHD symptoms in adults with ADHD and comorbid mood symptoms as measured by the clinician-rated ADHD Investigator Symptom Rating Scale (AISRS).

Secondary Efficacy Objectives

The secondary objectives of this study are to evaluate the effect of Qelbree as a monotherapy and/or as an adjunctive therapy in adults with ADHD and comorbid mood symptoms on:

- Inattention and Hyperactivity/Impulsivity symptoms as measured by the clinician-rated AISRS.
- ADHD symptoms as measured by self-rated Adult ADHD Self-Report Scale Symptoms Checklist (ASRSv1.1-SC).
- Inattention and Hyperactivity/Impulsivity symptoms as measured by the self-rated ASRSv1.1-SC
- Global severity of ADHD symptoms as measured by Clinical Global Impression of Severity (CGI-S) scale
- Global change of ADHD symptoms as measured by the Clinical Global Impression of Change (CGI-C) scale
- Depressive symptoms as measured by the clinician-rated Structured Interview Guide for the Montgomery and Åsberg Depression Rating Scale (SIGMA) and by the self-rated Patient Health Questionnaire 8-Item (PHQ-8)

- Anxiety symptoms as measured by the clinician-rated Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A) and the self-rated General Anxiety Disorder 7-Item (GAD-7)
- Executive Function as measured by the Behavior Rating Inventory of Executive Function–Adult Version (BRIEF-A), Self-Report
- Aspects of functioning in daily life (work productivity and regular activities) as measured by the Work Productivity and Activity Impairment: Specific Health Problem (WPAI:SHP) Questionnaire
- Sleep as measured by the self-rated Pittsburgh Sleep Quality Index (PSQI)

Secondary Safety Objective

To evaluate the safety of Qelbree as a monotherapy and/or as an adjunctive therapy in adults with ADHD and comorbid mood symptoms.

Exploratory Objective

[redacted]

Study Endpoints

Primary Efficacy Endpoint

- Change from baseline in AISRS Total score by visit

Secondary Efficacy Endpoints

- Change from baseline in AISRS Inattention and Hyperactivity/Impulsivity Subscale scores by visit
- Change from baseline in ASRSv1.1-SC Total score by visit
- Change from baseline in ASRSv1.1-SC Inattention and Hyperactivity/Impulsivity Subscale scores by visit
- Change from baseline in CGI-S score by visit
- CGI-C score by visit
- Change from baseline in MADRS Total Score at Week 14/EOS
- Change from baseline in PHQ-8 Total Score by visit
- Change from baseline in HAM-A Total Score at Week 14/EOS
- Change from baseline in GAD-7 Total Score by visit
- Change from baseline at Week 14/EOS in BRIEF-A T-score for:
  i. Global Executive Composite (GEC)
  ii. Behavioral Regulation Index (BRI)
  iii. Metacognition Index (MI)

- Change from baseline in the WPAI:SHP:
  - absenteeism percentage by visit
  - presenteeism percentage by visit
  - work productivity percentage by visit
  - regular activity percentage by visit
- Change from baseline at Week 14/EOS in the PSQI global score

Secondary Safety Endpoints

- Adverse events (AEs)
- Change from baseline in blood pressure, pulse rate, and weight
- Suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS)

Exploratory Endpoints

[redacted]

Study Population

Adults ≥18 years of age with ADHD (primary diagnosis) and Mood Symptoms will be screened for eligibility. Up to 750 adults will be enrolled (defined as having signed ICF and taken at least 1 dose of Qelbree). Based on a dropout rate of 33%, up to 500 participants will complete the study.

Study Sites

Single, decentralized site in the United States

Study Duration

Following the Screening Period (up to 4 weeks), eligible participants will be treated with Study medication for up to 14 weeks (Treatment Period). The total study duration between informed consent and the end of the Treatment Period is approximately 18 weeks.

Description of Study Treatment

Study Medication (SM): Qelbree [viloxazine extended-release capsules; SPN-812] 100 mg, 150 mg, and 200 mg capsules.

Dosing: 200 mg once daily (QD) during Week 1; and 400 mg QD Week 2 onwards. Dosage may be adjusted/titrated in increments of up to 200 mg weekly to the maximum recommended dosage of 600 mg once daily, depending on response and tolerability.

Reference Therapy: None

Route of administration: Orally, with or without food. Can be swallowed intact (whole) or contents of the capsule can be sprinkled over a teaspoonful of pudding/applesauce that is consumed entirely. See Section 8.2 for further details.

Inclusion Criteria

To be eligible for participation in this study, a participant must meet all of the following criteria:

1. Is male or female, ≥18 years of age.
2. Is willing and capable of providing and signing electronic informed consent.
3. Has a primary diagnosis of ADHD based on the Diagnostic and Statistical Manual of Mental Disorders; Fifth Edition, Text Revision (DSM-5-TR) as confirmed with the Mini-International Neuropsychiatric Interview for ADHD Studies (MINI-AS).
4. Has an AISRS Total score ≥24 at Screening.
5. Has a CGI-S score ≥3 at Screening.
6. Has a MADRS (SIGMA) Total score >22 at Screening and/or HAM-A (SIGH-A) Total score >22 at Screening.
7. If potential participant is a biological female, one of the following (a, b, or c) must be met:
   a. Has undergone menopause, defined as a biological female who reports amenorrhea for at least 12 consecutive months prior to providing informed consent.
   b. Is a non-pregnant Female of Childbearing Potential (FOCP) who is not seeking fertility treatment during the study and agrees to use one of the following acceptable birth control methods beginning 14 days prior to the first dose of study medication, throughout the study while taking study medication, and for 7 days following the last dose of study medication:
      i. Hormonal contraceptive
      ii. Barrier method: simultaneous use of male condom and diaphragm or cervical cap with spermicidal foam/gel/film/cream/suppository
   c. Has had bilateral tubal ligation, hysterectomy, bilateral oophorectomy (permanently sterilized) at least 6 months prior to providing informed consent.
8. If potential participant is a biological male, one of the following must be met:
   a. Is capable of having children and agrees to use 2 methods of contraception beginning 14 days prior to the first dose of study medication, throughout the study while taking study medication, and for 7 days following the last dose of study medication.
   b. Has had sterilization surgery (permanently sterilized) at least 6 months prior to providing informed consent.
9. Owns a functioning smartphone device, has access to an internet connection (Wi-Fi or data plan), is willing to download and use the study mobile app throughout the study, and is willing to have visual telemedicine appointments (televisits) at times designated in the study protocol.

Exclusion Criteria

A participant who meets any of the following criteria will be excluded from participation in the study:

1. Has a history of substance use disorder (alcohol, opioids, etc.) within the last 6 months prior to providing informed consent with exception of nicotine and cannabis.
2. Is currently taking or has taken Qelbree for treatment of ADHD in the last 3 months or is currently taking another non-stimulant medication for treatment of ADHD, like atomoxetine (Strattera), Clonidine (Catapres, Kapvay) or Guanfacine (Tenex, Intuniv). Stimulant medications for ADHD and most medications for mood symptoms (symptoms of depression and/or anxiety) are allowed.
3. Is taking a prohibited concomitant medication per the Qelbree prescribing information.
4. Is a FOCP who is pregnant, nursing, sexually active with a male partner and not willing to use one of the acceptable birth control methods throughout the study and/or is seeking fertility treatment.
5. Has a history of moderate or severe head trauma or other neurological disorder or systemic medical disease that, in the Investigator's opinion, is likely to affect central nervous system functioning. This would include participants with:
   a. A current diagnosis of a major neurological disorder; or
   b. Seizures, seizure disorder or seizure-like events; or a history of seizure disorder within the immediate family (siblings, parents); or
   c. Encephalopathy
6. Has attempted suicide within the 6 months prior to the C-SSRS assessment at Screening, or is at significant risk of suicide, either in the opinion of the Investigator or defined as a "yes" to suicidal ideation questions 4 or 5 or answering "yes" to suicidal behavior on the C-SSRS within the 6 months prior to the C-SSRS assessment at Screening.
7. Is currently participating in another clinical trial or has participated in a clinical trial within the 60 days prior to providing informed consent.
8. Has any history of schizophrenia, schizoaffective disorder, or bipolar disorder, or has any other psychiatric disorders in the Investigator's clinical judgement would interfere with their ability to participate in the study.
9. Has any unstable, clinically significant cardiovascular condition that in the Investigator's clinical judgement would preclude their participating in the study.
10. Has any disease or taking any medication that could, in the Investigator's opinion, interfere with the assessments of safety, tolerability, or efficacy, or interfere with study conduct or interpretation of results.
11. History of unexplained loss of consciousness, unexplained syncope, unexplained irregular heartbeat or palpitations or near drowning with hospital admission.
12. In the Investigator's opinion, is unlikely to comply with the protocol or is unsuitable for any other reason.

3. Introduction and Background

3.1 Study Rationale

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood disorders that can continue through to adolescence and into adulthood. Symptoms include difficulty staying focused and paying attention, difficulty controlling behavior, and hyperactivity (over-activity). The overall prevalence of ADHD in adults is between 2.5% and 6.7% with it being more common in men than women (Abdelnour et al., 2022). A majority of adults with ADHD also experience psychiatric comorbidities, particularly mood disorder symptoms, like depression and anxiety (Kessler et al., 2006; Kolar et al., 2008). Medication treatment for both ADHD and any comorbid psychiatric disorders can be challenging.

While there is no cure for ADHD, available treatments aim to reduce symptoms and improve functioning. Qelbree, viloxazine extended-release capsules (SPN-812), is a selective norepinephrine reuptake inhibitor indicated for the treatment of ADHD in adults and pediatric patients 6 years and older. It is the first novel, non-stimulant option FDA-approved for adults with ADHD in the last twenty years.

The active substance in Qelbree is viloxazine, whose mechanism of action is still not fully understood. Viloxazine was previously marketed in several European countries as an antidepressant in an immediate-release (IR) product (Findling et al., 2021). The efficacy and safety of Qelbree was evaluated for the treatment of ADHD in children (Johnson et al., 2020; Nasser et al., 2020; Nasser et al., 2021a), in adolescents (Nasser et al., 2021b; Nasser et al., 2021c) and in adults (Nasser et al., 2022). In these trials including the adult trial, participants were excluded for other psychiatric disorders, including depression and anxiety.

To date no evaluation of Qelbree has been conducted in adults with ADHD and mood symptoms, as well as those receiving concurrent medication treatment for mood symptoms. This study will evaluate the efficacy and safety of Qelbree in adults with ADHD and mood symptoms in an open-label, real-world setting.

3.2 Background

3.2.1 ADHD and Mood Symptoms

ADHD, a childhood-onset neurodevelopmental condition, is a frequent and disabling condition in adults (Magnin and Maurs, 2017). In adulthood, the clinical presentation, as in childhood, involves the symptom triad of inattention, hyperactivity, and impulsivity (Weibel et al., 2020). However, in adults, hyperactivity is more often internalized, symptoms of inattention may be masked by anxiety symptoms or obsessive-like compensation strategies (Weibel et al., 2020).

Several studies in adults with ADHD have reported its association with comorbid depression, anxiety, bipolar disorder, and substance use disorder. The National Comorbid Survey found that adults with ADHD are three times more likely to develop major depressive disorder (MDD), six times more likely to develop dysthymia, and more than four times more likely to have any mood disorder (Kessler et al., 2006). These comorbidities present important clinical

challenges since their co-occurrence results in greater disease burden and more severe illness courses than ADHD or mood and anxiety disorders alone (Katzman et al., 2017). Furthermore, the World Federation of ADHD International Consensus Statement reports that many large epidemiologic and clinical studies show that ADHD often co-occurs with other psychiatric disorders, especially depression, bipolar disorder, autism spectrum disorders, anxiety disorders, oppositional defiant disorder, conduct disorder, eating disorders, and substance use disorders; and their presence does not rule out a diagnosis of ADHD (Faraone et al., 2021).

An important treatment consideration is the potential for the effective treatment of ADHD to improve functional outcomes in people with comorbid conditions. For instance, many studies have reported improvements in comorbid psychiatric symptoms when ADHD is effectively treated. Atomoxetine has been associated with improvements in both ADHD and comorbid anxiety and depressive symptoms; and the efficacy of co-administration of SSRIs or SNRIs with stimulants on functional outcomes in ADHD with comorbid anxiety or depressive symptoms (Katzman et al., 2017).

Furthermore, data suggests that early and optimal treatment of ADHD has the potential to alter the trajectory of psychiatric morbidity by preventing the emergence of psychiatric comorbidities such as mood and anxiety disorders or substance use disorders (Katzman et al., 2017). In a 10-year longitudinal study of male youths with ADHD, Biederman et al., (2009) found that those who were treated with stimulants had a significantly lower risk of developing comorbid depressive and anxiety disorders as adults and were also significantly less likely to have impaired functional outcomes, than those who were not treated (Katzman et al., 2017).

The burden of associated mood disorders with ADHD in adulthood affects multiple areas of a person's life, and may result in serious functional impairment, in various domains, leading to academic, social, vocational, and familial consequences (Weibel et al., 2020). Furthermore, adults with ADHD have shown lower self-esteem, greater sleep disturbances, and an increased risk of mortality and comorbidities such as depression, anxiety, and substance use disorders compared with non-ADHD adults (Weibel et al., 2020). Accordingly, the cumulative negative consequences of living with ADHD in adulthood can substantially impact an individual's social, emotional, educational, professional, and economic well-being (Weibel et al., 2020). The considerable disability and the poorer quality of life among adults with ADHD, therefore, warrants optimal evaluation and management (Weibel et al., 2020).

Management often employs common psychological approaches such as psycho-education and cognitive-behavioral therapy with a specific focus on emotional regulation (Weibel et al., 2020). Current pharmacological treatments for ADHD include stimulant and nonstimulant medications (Groom and Cortese, 2022). Psychostimulants are commonly used to treat ADHD and although their safety and tolerance are satisfactory, their long-term clinical benefit is still under discussion (Weibel et al., 2020; Groom and Cortese, 2022). Alternatively, when response or tolerability to psychostimulants is poor, or when certain comorbid disorders are present, nonstimulants stand to play an important role in the management of ADHD (Weibel et al., 2020; Groom and Cortese, 2022).

3.2.2 Adult ADHD Qelbree Clinical Trial Findings

The efficacy and safety of Qelbree for the treatment of ADHD in adults was assessed in a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel group, two-arm, 6-week trial (Study 812P306) (Qelbree® Prescribing Information [PI]; Nasser et al., 2022). Eligible adults aged 18 to 65 years were randomized 1:1 to viloxazine extended-release (ER) (flexible dose of 200–600 mg/day) or matched placebo. Participants took Qelbree 200 mg or matching placebo QD during Week 1 and Qelbree 400 mg or matching placebo QD during Week 2. Based on efficacy and tolerability, the Investigator could adjust dose by 200mg/day per week at Week 3 and Week 4 visits. Treatments were administered as a once daily single dose. The primary efficacy endpoint was the change from baseline in the AISRS Total score at end of study (EOS; Week 6). The key secondary endpoint was the change from baseline in the CGI-S score at EOS. Other secondary measures included CGI-I score at EOS and change from baseline at EOS in the AISRS inattention and hyperactivity/impulsivity subscale scores, BRIEF-A T-scores, and GAD-7 total score.

A total of 374 adults were randomized, 372 were dosed and 267 completed the study. At end of study, the mean viloxazine ER dose was 504 mg. In this study (Nasser et al., 2022):

- The reduction in the change from baseline AISRS Total score (least-square means ± standard error) at EOS was greater in participants treated with viloxazine ER (−15.5 ± 0.91; n=175) compared with placebo (−11.7 ± 0.90; n=179), and the difference (-3.7 ± 1.28) was statistically significant (p = 0.0040).
- The reduction in the change from baseline CGI-S score at EOS was also greater in participants treated with viloxazine ER (−1.4 ± 0.10; n=175) compared with placebo (−1.0 ± 0.10; n=179), and the difference (-0.4 ± 0.14) was statistically significant (p = 0.0023).
- The viloxazine ER group demonstrated significantly greater improvements (mean difference [lower95%CI, upper95%CI]) in the AISRS Inattention (−2.5 [−4.0, −0.9]; p = 0.0015) and Hyperactivity/Impulsivity (−1.4 [−2.7, −0.1]; p = 0.0380) subscales, the CGI-I (−0.3 [−0.6, -0.1]; p = 0.0076), and the BRIEF-A Global Executive Composite (−2.4 [−4.8, 0.0]; p = 0.0468) and Metacognition Index (−3.3 [−5.9, −0.8]; p = 0.0100).
- Analysis of categorical secondary endpoints revealed that the AISRS 30% response rate (defined as the percent of participants with a 30% or more reduction in AISRS Total Score) at Week 6 was significantly higher in the viloxazine ER group compared with placebo (12.4 [0.6, 23.8]; p = 0.0395); all other comparisons were not significant.

In terms of safety, the most common adverse reactions of Qelbree (occurring at ≥5% and at least twice the placebo rate) were insomnia, headache, somnolence, fatigue, nausea, decreased appetite, dry mouth, and constipation (Qelbree PI). Adverse events (AEs) leading to discontinuation of Qelbree treatment were fatigue, insomnia, constipation, and headache. Adverse reactions that occurred in at least 2% of patients treated with Qelbree (n=189) and more frequently in Qelbree-treated patients than in placebo-treated patients were: insomnia (23% vs 7%), headache (17% vs 7%), nausea (12% vs 3%), dry mouth (10% vs 2%), fatigue (12% vs 3%), decreased appetite (10% vs 3%), and tachycardia (4% vs 1%).

3.3 Risk/Benefit Assessment

3.3.1 Known Potential Risks

The safety of Qelbree has been evaluated in 189 adult participants (18 to 60 years of age) with ADHD exposed to one or more doses ranging from 200 mg to 600 mg QD in a short-term (6 week), randomized, double-blind, placebo-controlled trial (Study 812P306). Approximately 9% of the 189 participants receiving Qelbree discontinued treatment due to an adverse reaction. The adverse reactions most commonly associated with discontinuation of Qelbree were fatigue (n=4), insomnia (n=3), constipation (n=3), and headache (n=2). The most commonly reported adverse reactions (occurring at ≥5% and at least twice the placebo rate of Qelbree) were insomnia, headache, somnolence, fatigue, nausea, decreased appetite, dry mouth, and constipation (Qelbree PI).

Adverse Events of concern include (Qelbree PI):

- Suicidal Thoughts and Behavior: Among 189 adults treated with Qelbree, a total of three participants (1.6%) reported suicidal ideation on the C-SSRS, versus 0 of 183 adults treated with placebo. No adults treated with either Qelbree or placebo reported suicidal behavior on the C-SSRS in the study. No attempted or completed suicides occurred in the trial. Participants treated with Qelbree had higher rates of insomnia and irritability. Although a causal link between the emergence of insomnia and irritability and the emergence of suicidal impulses has not been established, there is a concern that these and other symptoms such as depressed mood, anxiety, agitation, akathisia, mania, hypomania, panic attacks, impulsive behavior, and aggression may represent precursors to emerging suicidal ideation or behavior.
- Blood Pressure and Heart Rate Increases: In a clinical study in adult participants (18 to 60 years of age), 52/178 (29%) of participants treated daily with Qelbree (200 mg to 600 mg) had a >20 beat per minute (bpm) increase in pulse rate at any time point in the clinical trial, compared to 23/181 (13%) of participants who received placebo. Of participants treated daily with Qelbree (200 to 600 mg), 23/178 (13%) had a ≥ 15 mmHg increase in diastolic blood pressure at any time in the clinical trial, compared to 16/181 (9%) of participants in the placebo group.
- Somnolence and Fatigue: In adults, somnolence was reported in 6% of Qelbree-treated participants versus 2% in placebo-treated participants. Fatigue was reported in 12% of Qelbree-treated participants versus 3% of placebo-treated participants.
- Activation of Mania or Hypomania: Noradrenergic drugs, such as Qelbree, may induce a manic or mixed episode in participants with bipolar disorder.

The safety of Qelbree has also been evaluated in 159 adults (18 to 60 years of age) with ADHD [e.g., completed the adult Phase 3 trial (812P306)] who were exposed to one or more doses ranging from 200 mg to 600 mg QD in a long-term (up to 156 weeks; 3 years), open-label extension safety trial (Study 812P311). All participants initiated Qelbree at 200 mg once daily (first 58 participants were instructed to titrate up to 400 mg after 1 week; for all subsequent participants, any dose adjustment following Visit 1 did not occur until end of Week 2 at Visit 2). All participants completed 3 visits during the first 12 weeks (Optimization Phase) in which Investigator adjusted participant's dose based on efficacy and tolerability to

optimal dose. Following the Optimization Phase, participants completed regular study visits to assess safety/efficacy every 8 weeks for up to another 144 weeks (~3 years total); maximum exposure was 124 weeks.

Adverse Events were reported in 115 (72.3%) participants. The most frequently reported AEs were insomnia, nausea, headache, fatigue, corona virus infection, anxiety, dry mouth, and vomiting. AEs for most participants were considered mild [n=42 (26.4%)] or moderate [n=64 (40.3%)] in severity and related to study medication [n=82 (51.6%)] by the Investigator. AEs leading to permanent study medication discontinuation occurred in 28 (17.6%) participants. SAEs were reported in 2 (1.3%) participants (syncope/fall/spinal column injury; deep vein thrombosis/pulmonary embolism); neither were considered related to the study medication by the Investigator. No deaths occurred during the study.

3.3.2 Known Potential Benefits

Qelbree is the first non-stimulant approved for adult ADHD in over 20 years. Qelbree has been proven to significantly reduce ADHD symptoms, including symptoms of inattention and hyperactivity/impulsivity as early as Week 2. Qelbree is dosed once-daily, can be taken with or without food, and its extended-release formula provides 24-hour exposure. Studies with Qelbree have shown no evidence of abuse potential and its once-daily dosing minimizes the risk of treatment abuse, misuse, or diversion. Furthermore, studies have not reported withdrawal symptoms or signs of dependence reported as AEs in clinical trials (Qelbree HCP, n.d.).

3.3.3 Assessment of Potential Risks and Benefits

Viloxazine extended-release capsules (Qelbree) is a novel nonstimulant that is US FDA approved for the treatment of ADHD in patients 6 years of age and older based on positive results from three pediatric pivotal phase III trials and one adult phase III trial. In adults, treatment with viloxazine ER resulted in a statistically significant improvement on the AISRS, indicating an improvement in ADHD symptoms and associated functional impairment after only 2 weeks of treatment, and was demonstrable until the end of the study. Furthermore, safety data provided in adults with ADHD indicate viloxazine ER was tolerated with no reported serious AEs and <10% of viloxazine ER-treated participants discontinuing as a result of an AE. Viloxazine ER was generally regarded as safe with most reported TEAEs being assessed by Investigators as “mild” or “moderate” in severity.[4]

This study aims to confirm the findings reported in controlled clinical trials in a real-world setting. Given the findings reported during Qelbree’s clinical development, participants of this study are expected to receive improvement in ADHD symptoms, executive functioning, and overall clinical improvement.

Given the known risks of treatment with Qelbree, this study will closely monitor participants for AEs. This study will closely monitor participants using standardized and validated clinical-rated scales for behavior change or worsening of behavior. Participants will be shipped a BP/PR cuff for monitoring potential increases in blood pressure and pulse rate. Participants will also be monitored for mania or hypomania while on treatment. Participants will be advised to exercise caution when driving or operating hazardous machinery due to the potential for somnolence and fatigue with treatment.

4. Study Objectives and Endpoints

Primary Efficacy		
OBJECTIVES	**ENDPOINTS**	**JUSTIFICATION FOR ENDPOINTS**
The primary objective of this study is to evaluate the efficacy of Qelbree as a monotherapy and/or as an adjunctive therapy for ADHD symptoms in adults with ADHD and comorbid mood symptoms as measured by the clinician-rated AISRS.	Change from baseline in AISRS Total score by visit.	The AISRS is a clinician-rated scale that was validated for evaluating ADHD symptoms in adults in clinical trials per criteria outline in the DSM-5. The AISRS has been used in other clinical trials to evaluate the efficacy/safety of ADHD treatments, including the clinical trials of Qelbree in adults (Studies 812P306 and 812P311).

Secondary Efficacy		
OBJECTIVES	**ENDPOINTS**	**JUSTIFICATION FOR ENDPOINTS**
To evaluate the effect of Qelbree as a monotherapy and/or as an adjunctive therapy on Inattention (IA) and Hyperactivity/Impulsivity (HI) symptoms in adults with ADHD and comorbid mood symptoms as measured by the clinician-rated AISRS.	Change from baseline in AISRS Inattention and Hyperactivity/Impulsivity Subscale scores by visit.	The AISRS is a clinician-rated scale that was validated for evaluating ADHD symptoms in adults in clinical trials per criteria outline in the DSM-5. The AISRS has been used in other clinical trials to evaluate the efficacy/safety of ADHD treatments, including the clinical trials of Qelbree in adults (Studies 812P306 and 812P311).
To evaluate the effect of Qelbree as a monotherapy and/or as an adjunctive therapy for ADHD symptoms in adults with ADHD and comorbid mood symptoms as measured by the self-rated ASRSv1.1-SC.	Change from baseline in ASRSv1.1-SC Total score by visit.	The ASRSv1.1-SC is a self-report scale that was validated for evaluating ADHD symptoms in adults in clinical trials per criteria outline in the DSM-5. The ASRSv1.1-SC and similar endpoints have been used in other clinical trials that evaluated efficacy and safety of ADHD treatments.
To evaluate the effect of Qelbree as a monotherapy and/or as an adjunctive therapy on IA and HI symptoms in adults with ADHD and comorbid mood symptoms as measured by the self-rated ASRSv1.1-SC.	Change from baseline in ASRSv1.1-SC Inattention and Hyperactivity/Impulsivity Subscale scores by visit.	The ASRSv1.1-SC is a self-report scale that was validated for evaluating ADHD symptoms in adults in clinical trials per criteria outline in the DSM-5. The ASRSv1.1-SC and similar endpoints have been used in other clinical trials that evaluated efficacy and safety of ADHD treatments.

Secondary Efficacy		
OBJECTIVES	**ENDPOINTS**	**JUSTIFICATION FOR ENDPOINTS**
To evaluate the effect of Qelbree on global severity of ADHD symptoms in adults with ADHD and comorbid mood symptoms as measured by the clinician-rated CGI-S scale.	Change from baseline in the CGI-S score by visit.	The clinician-rated CGI-S scale is commonly used in most clinical trials, especially ADHD.
To evaluate the effect of Qelbree on global change in ADHD symptoms in adults with ADHD and comorbid mood symptoms as measured by the clinician-rated CGI-C scale.	CGI-C score by visit.	The clinician-rated CGI-C scale is commonly used in most clinical trials, especially ADHD.
To evaluate the effect of Qelbree on depressive symptoms in adults with ADHD and comorbid mood symptoms as measured by the clinician-rated MADRS (SIGMA) and by the self-rated PHQ-8.	Change from baseline in: • MADRS (SIGMA) Total Score at Week 14/EOS • PHQ-8 Total score by visit	The clinician-rated MADRS (SIGMA) and self-report PHQ-8 are commonly used to assess symptoms of depression in clinical trials.
To evaluate the effect of Qelbree on anxiety symptoms in adults with ADHD and comorbid mood symptoms as measured by the clinician-rated HAM-A (SIGH-A) and the self-rated GAD-7.	Change from baseline in: • HAM-A (SIGH-A) Total score at Week 14/EOS • GAD-7 Total score by visit	The clinician-rate HAM-A (SIGH-A) and self-report GAD-7 are commonly used to assess symptoms of anxiety in clinical trials.
To evaluate the effect of Qelbree on executive function in adults with ADHD and comorbid mood symptoms as measured by the BRIEF-A, Self-Report.	Change from baseline at Week 14/EOS in BRIEF-A T-score for the: • Global Executive Composite (GEC) • Behavioral Regulation Index (BRI) • Metacognition Index (MI)	ADHD-associated impairments in executive function in ADHD is well known. The BRIEF-A is a self-report scale that was validated for evaluating global and aspects of executive function in adults with ADHD. It has been administered in other clinical trials that evaluated the efficacy and safety of ADHD treatments.
To evaluate the effect of Qelbree on aspects of functioning in daily life (work productivity and regular activities) as measured by the WPAI:SHP.	Change from baseline in the WPAI:SHP absenteeism percentage by visit, presenteeism percentage by visit, work productivity percentage by visit, and regular activity percentage by visit.	ADHD-associated functional impairments is well known. The WPAI:SHP is a self-report scale that was validated for evaluating functional impairment in aspects of daily life. It has been administered to assess the impact of ADHD and ADHD treatments on work productivity and regular activities in adults with ADHD.

Secondary Efficacy		
OBJECTIVES	**ENDPOINTS**	**JUSTIFICATION FOR ENDPOINTS**
To evaluate the effect of Qelbree on sleep in adults with ADHD and comorbid mood symptoms as measured by the self-rated PSQI.	Change from baseline at Week 14/EOS in the PSQI global score.	Sleep and/or circadian-related disturbances (e.g., insomnia, daytime sleepiness, delayed sleep phase disorder) have been documented in participants diagnosed with ADHD and in individuals receiving treatment with psychiatric and psychostimulant medication. The PSQI is commonly used in clinical trials to assess changes in sleep parameters (quality, timing, duration, latency, etc.) and overall daytime functioning.

Secondary Safety		
OBJECTIVES	**ENDPOINTS**	**JUSTIFICATION FOR ENDPOINTS**
To evaluate the safety of Qelbree as a monotherapy and/or as an adjunctive therapy in adults with ADHD and comorbid mood symptoms	Safety endpoints are: • Adverse events (AEs) • Change from baseline in blood pressure, pulse rate, and weight • Suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS)	These endpoints were chosen to assess safety parameters related to caution and/or warnings in Qelbree Prescribing Information.

Exploratory		
OBJECTIVES	**ENDPOINTS**	**JUSTIFICATION FOR ENDPOINTS**
[redacted]		

Exploratory		
OBJECTIVES	**ENDPOINTS**	**JUSTIFICATION FOR ENDPOINTS**
[redacted]		
[redacted]		

5. Recruitment and pre-screening

Adults 18 years and older will be recruited into this study. Participants will be recruited using digital tools including advertising, and referrals from physicians' existing patient pool. Potential participants will be directed to a landing page that will provide basic information about the study and those interested will be requested to provide their contact information and answer pre-qualifying study specific questions. Those who pass the pre-qualifying criteria will be contacted by the study team to arrange the screening televisit and sent an email invitation to download the study app on their smartphone using the contact details they provided.

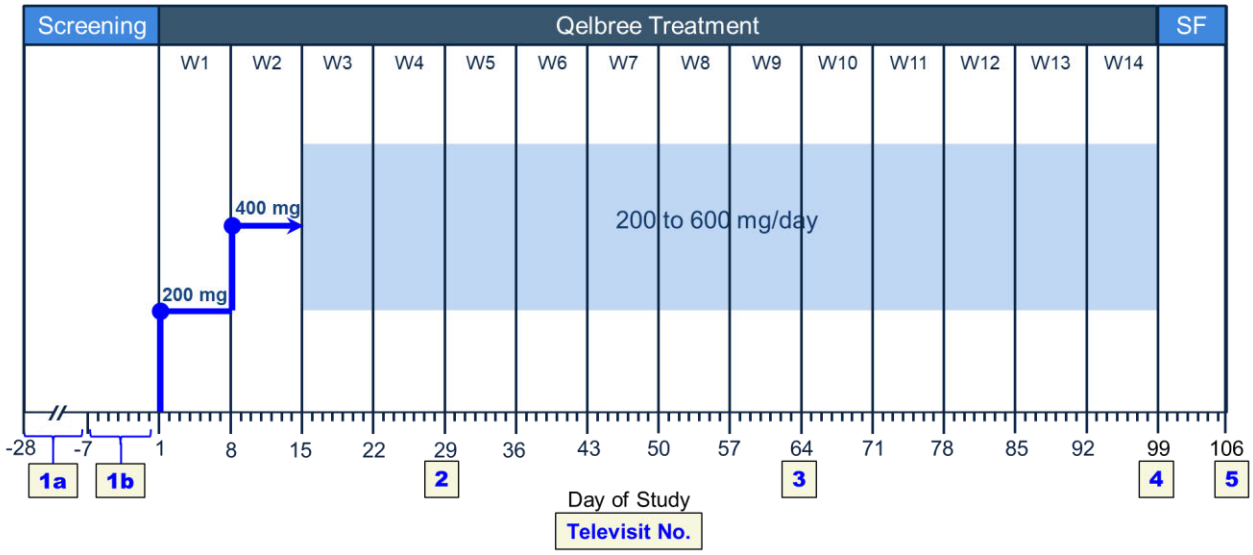
Those who download the mobile app will receive details about the study, be presented with an electronic informed consent (eIC) to read prior to the televisit, and contact information for the Principal Investigator (PI) / virtual clinical trial support team (e.g. CRO) to address any questions or concerns during the eIC process and throughout the study duration.

The virtual clinical trial support team assists participants throughout the study, playing a key role in recruitment, retention, compliance, and monitoring. Communication may occur through the chat function of the mobile app, email, or telephone with the support team.

6. Study Design

This is a Phase IV, open-label, fully decentralized clinical trial to evaluate the efficacy and safety of Qelbree in adults with ADHD and Mood Symptoms (Figure 1). Participants will complete patient-reported outcome (PRO) measures on the study mobile app, and participate in televisits with a qualified, trained rater or assessor (Table 1).

Figure 1. Protocol Schema



6.1 Screening Period

The duration of the screening period is up to 4 weeks (28 days) starting from the date of Screening televisit (e.g. Televisit #1a) after obtaining informed consent. The Screening Period includes two virtual televisits. The first televisit should occur within 3 weeks after the date of obtaining informed consent. If a potential participant is still considered eligible after Televisit 1a, the second screening televisit will be scheduled; Televisit 1b should occur tentatively no later than a week prior to participant taking first dose of study medication. If participants prefer, Televisit #1a and #1b can be combined and completed in a single visit (Table 1).

6.1.1 Televisit #1a:

After signing the eIC, the following will be administered/obtained/collected by a trained assessor at televisit, unless otherwise noted (Table 1):

- Demographic information and Height
- Medical/Psychiatric/Social History
- Reproductive/Menstrual Cycle History Questionnaire; biological females only
- MINI-AS
- Prior Medications (past 12 months) and Concomitant Medications
- C-SSRS '*Baseline/Screening*' Version
- Review Inclusion and Exclusion Criteria

6.1.2 Televisit #1b:

The following will be administered/obtained/collected by a qualified/trained rater or assessor during televisit (Table 1):

- AISRS
- CGI-S
- SIGMA
- SIGH-A
- C-SSRS '*Since Last Visit*' Version
- Review Concomitant Medications
- Review Inclusion and Exclusion Criteria

If participant is still considered eligible:

1. The participant will complete the following via the study mobile app:
   - Training Module
   - ASRSv1.1-SC
   - PHQ-8
   - GAD-7
   - WPAI:SHP
   - PSQI
   - BRIEF-A
2. Schedule next televisits (Week 4, 9, and 14).
3. The following items will be shipped to participant's home address:
   - Blood pressure cuff to measure and report blood pressure and pulse rate
   - Urine Pregnancy Test (UPT) for females of childbearing potential (FOCP). A negative pregnancy test is required to continue participation in the study.
   - First shipment of study medication

Once the shipment has been received, participants will report their first blood pressure and pulse rate reading and UPT result (FOCPs only) in the study mobile app. At all other timepoints in the study this information will be reported during the televisit (Table 1).

6.2 Treatment Period

The first shipment will contain sufficient medication for the first 4 weeks of the study, after which, two more shipments will be triggered for ongoing treatment based on participant response and PI or designee's prescription.

Once study medication is received, the participant will confirm receipt and administration of the first dose within the study mobile app. At all other timepoints, dosing information will be captured during the televisit.

A televisit will be scheduled 4 weeks (28 days), 9 weeks (63 days) and 14 weeks (98 days) after date of first dose (Table 1, Figure 1). Participants will need to continue to take study medication as per the instructions provided by the Investigator during the Treatment Period.

During the Televisit #2 and #3 (Weeks 4 and 9), the following will be administered, obtained or collected by a qualified/trained rater or assessor (ClinRO efficacy assessments should not be administered if participant is discontinuing and has not taken daily dose of Qelbree for >7 consecutive days prior to the televisit):

- AISRS
- CGI-S
- CGI-C
- C-SSRS '*Since Last Visit*' Version
- Review AEs
- Review Concomitant Medications
- Report systolic/diastolic blood pressure, pulse rate, and weight
- Report UPT results (FOCPs only)
- RMCH Questionnaire's Menstrual-Question #5 (FOCPs only)
- SM accountability; Report the number of remaining capsules in bottle
- Confirm or reschedule next virtual visit (Week 9 and Week 14, as applicable)

In addition, at Weeks 4 and 9, the participant will complete the following via the study mobile app (PRO efficacy assessments should not be administered if participant is discontinuing and has not taken daily dose of Qelbree for >7 consecutive days prior to attempting them):

- SM administration mode/time query; report admin method and average admin time
- ASRSv1.1-SC
- PHQ-8
- GAD-7
- WPAI:SHP

During the treatment period, participants should continue all current medications or other treatment regimens as prescribed by their primary care physician. Their primary care physician will determine changes to these regimens according to routine clinical practice, but participants should be reminded to report changes in concomitant medications (e.g., new medication started, current medication discontinued, or dose reduced, etc.) to the study staff between televisits. Participants may withdraw consent or PI/designee can discontinue a participant if they feel it is no longer in the best interest of the participant to continue in the study. If the participant's participation ends prior to Week 14 of treatment, the reason for discontinuation will be captured by the study staff.

6.3 End of Study

During the Televisit #4 (Week 14/EOS), the following will be administered, obtained or collected by a qualified/trained rater (Table 1; ClinRO efficacy assessments should not be administered if participant has not taken daily dose of Qelbree for >7 consecutive days prior):

- AISRS
- CGI-S
- CGI-C
- SIGMA

- SIGH-A
- C-SSRS '*Since Last Visit*' Version
- Review AEs
- Review Concomitant Medications
- Report systolic/diastolic blood pressure, pulse rate, and weight
- Report UPT results (FOCPs only)
- RMCH Questionnaire's Menstrual-Question #5 (FOCPs only)
- SM accountability; report the number of remaining capsules in bottle
- Schedule safety follow-up televisit

In addition, at Week 14/EOS, the participant will complete or report the following via the study mobile app (efficacy assessments should not be administered if participant has not taken daily dose of Qelbree for >7 consecutive days prior):

- SM administration mode/time query; report admin method and average admin time
- ASRSv1.1-SC
- PHQ-8
- GAD-7
- WPAI:SHP
- PSQI
- BRIEF-A

If participant discontinues early (Early-Termination), perform Week 14 assessments; however, ClinRO/PRO efficacy assessments should not be administered if participant has not taken daily dose of Qelbree for >7 consecutive days prior.

6.4 Safety Follow-up (SF) Televisit

A week following participant's last dose of study medication, a safety follow-up televisit will be conducted to review AEs and Concomitant Medications (Table 1).

Table 1. Schedule of Events

Study Period	Screening Period			Treatment Period			EOS[10]	SF
Week of Study	–	–	–	–	4	9	14	15
Televisit[1] No.	1a	1b	–	–	2	3	4	5
Day of Study	- 28 to -1		- 7 to -1	1	29	64	99	106
Window (days)	–	–	–	–	± 3	± 3	± 3	± 3
Informed Consent	X							
Schedule Next Televisit	X	X			X	X	X	
Review Inclusion/Exclusion Criteria	X	X						
Demographics	X							
Medical/Psychiatric/Social History	X							
RMCH Questionnaire	X[2]	X[2]			X[3]	X[3]	X[3]	
Review Prior Medications[4]	X							
Review Concomitant Medications	X	X			X	X	X	X
Review Adverse Events					X	X	X	X
Ship BP/PR cuff[5]	X							
Ship UPT (FOCP only)[5]	X							
Confirm Negative UPT (FOCP only)	X				X	X	X	
BP/PR and Weight[5,6]	X				X	X	X	
Height[7]	X							
MINI-AS (DSM-5-TR)	X							
AISRS *(ClinRO)*		X			X	X	X	
CGI-S *(ClinRO)*		X			X	X	X	
CGI-C (*ClinRO*)					X	X	X	
SIGMA *(ClinRO)*		X					X	
SIGH-A *(ClinRO)*		X					X	
C-SSRS (Baseline/Screening version)	X							
C-SSRS (Since Last Visit version)		X			X	X	X	
Mobile App Training Module (PROs)		X						
Dispense SM			X		X	X		
First Dose of Qelbree[8]				X				
ASRSv1.1-SC *(PRO)* [9]		X			X	X	X	
PHQ-8 *(PRO)* [9]		X			X	X	X	

Study Period	Screening Period			Treatment Period			EOS[10]	SF
Week of Study	–	–	–	–	4	9	14	15
Televisit[1] No.	1a	1b	–	–	2	3	4	5
Day of Study	- 28 to -1		- 7 to -1	1	29	64	99	106
Window (days)	–	–	–	–	± 3	± 3	± 3	± 3
GAD-7 *(PRO)*[9]		X			X	X	X	
WPAI:SHP *(PRO)*[9]		X			X	X	X	
PSQI *(PRO)*[9]		X					X	
BRIEF-A *(PRO)*[9]		X					X	
SM Administration Mode/Time[9]					X	X	X	
SM Accountability					X	X	X	
Participant Ship/Return Unused SM[10]							X	

Abbreviations: AISRS = Adult ADHD Investigator Symptom Rating Scale; ASRSv1.1-SC = Adult ADHD Self-Report Scale Version 1.1 Symptom Checklist; BRIEF-A = Behavior Rating Inventory of Executive Function–Adult Version; BP = Blood Pressure (systolic/diastolic); CGI-S = Clinical Global Impression Scale of Severity; CGI-C = Clinical Global Impression Scale of Change; C-SSRS = Columbia Suicide Severity Rating Scale; ClinRO = Clinician-Reported Outcomes; EOS = end of study; FOCP = Females of Childbearing Potential; GAD-7 = General Anxiety Disorder-7 item; MINI-AS = Mini International Neuropsychiatric Interview for ADHD Studies; PHQ-8 = Patient Health Questionnaire 8-item; PRO = Patient-Reported Outcomes; PSQI = Pittsburgh Sleep Quality Index; PR = Pulse Rate; RMCH = Reproductive/Menstrual Cycle History; RMCH mQ5 = RMCH Questionnaire (Menstrual-Question #5); SF = Safety follow-up; SIGH-A = Structured Interview Guide for the Hamilton Anxiety Scale; SIGMA = Structured Interview Guide for the Montgomery and Åsberg Depression Rating Scale; SM = study medication; UPT = Urine Pregnancy Test; WPAI:SHP = Work Productivity and Activity Impairment: Specific Health Problem Questionnaire.

Footnotes:

1. Virtual televisits will last between 45 to 120 minutes. Consent will occur on or before Telehealth Visit 1a.
2. Administer full/entire RMCH Questionnaire (1 up to 8 items) to biological females at Screening only (if not administered at Televisit #1a, administer at Televisit #1b).
3. Only administer the RMCH mQ5 to FOCPs at Televisit #2, #3, and #4 during Treatment [Week 4, Week 9, and Week 14/EOS, respectively].
4. All medications (especially stimulant or non-stimulant ADHD medications) taken 12 months prior to Screening.
5. BP/PR cuff (and UPT) will be shipped once participant is determined eligible. Prior to taking first dose, participant will measure and record BP/PR and weight (and confirm a negative UPT).
6. Weight will be collected with shoes off. BP/PR will be measured in a seated position. Self-reported by the participant to the study team on Day 1 and thereafter reported during scheduled televisits.
7. Height (with shoes off) will be self-reported to the study team.
8. Participant will need to report time, date, and dose of SM within the study mobile app on Day 1
9. PROs and questions about SM administration method and timing will be completed in the study mobile app.
10. At Week 14 the participant will be required to return all SM to Sponsor for destruction upon confirmation of proper SM accountability.
11. If participant discontinues early (Early-Termination), perform Week 14 assessments; however, ClinRO/PRO efficacy assessments should not be administered if participant has not taken daily dose of Qelbree for >7 consecutive days prior.

7. Study Population

7.1 Inclusion Criteria

To be eligible for participation in this study, a participant must meet all of the following criteria:

1. Is male or female, ≥18 years of age.
2. Is willing and capable to provide and sign electronic informed consent.
3. Has a primary diagnosis of ADHD based on the Diagnostic and Statistical Manual of Mental Disorders; Fifth Edition, Text Revised (DSM-5-TR) as confirmed with the Mini-International Neuropsychiatric Interview for ADHD Studies (MINI-AS).
4. Has an AISRS Total score ≥24 at Screening.
5. Has a CGI-S score ≥3 at Screening.
6. Has a MADRS (SIGMA) Total score >22 at Screening and/or HAM-A (SIGH-A) Total score >22 at Screening.
7. If potential participant is a biological female, one of the following (a, b, or c) must be met:
   a. Has undergone menopause, defined as a biological female who reports amenorrhea for at least 12 consecutive months prior to providing informed consent.
   b. Is a non-pregnant Female of Childbearing Potential (FOCP) who is not seeking fertility treatment during the study and agrees to use one of the following acceptable birth control methods beginning 14 days prior to the first dose of study medication, throughout the study while taking study medication, and for 7 days following the last dose of study medication:
      i. Hormonal contraceptive
      ii. Barrier method: simultaneous use of male condom and diaphragm or cervical cap with spermicidal foam/gel/film/cream/suppository.
   c. Has had bilateral tubal ligation, hysterectomy, bilateral oophorectomy (permanently sterilized) at least 6 months prior to providing informed.
8. If potential participant is a biological male, one of the following must be met:
   a. Is capable of having children and agrees to use 2 methods of contraception beginning 14 days prior to the first dose of study medication, throughout the study while taking study medication, and for 7 days following the last dose of study medication.
   b. Has had sterilization surgery (permanently sterilized) at least 6 months prior to providing informed consent.
9. Owns a functioning smartphone device, has access to an internet connection (Wi-Fi or data plan), is willing to download and use the study mobile app throughout the study,

and is willing to have visual telemedicine appointments (televisits) at times designated in the study protocol.

7.2 Exclusion Criteria

A participant who meets any of the following criteria will be excluded from participation in the study:

1. Has a history of substance use disorder (alcohol, opioids, etc.) within the last 6 months prior to providing informed consent with exception of nicotine and cannabis.
2. Is currently taking or has taken Qelbree for treatment of ADHD in the last 3 months or is currently taking another non-stimulant medication for treatment of ADHD, like atomoxetine (Strattera), Clonidine (Catapres, Kapvay) or Guanfacine (Tenex, Intuniv). Stimulant medications for ADHD and most medications for mood symptoms (symptoms of depression and/or anxiety) are allowed.
3. Is taking a prohibited concomitant medication per the Qelbree Prescribing Information.
4. Is a FOCP who is pregnant, nursing, sexually active with a male partner and not willing to use one of the acceptable birth control methods throughout the study and/or is seeking fertility treatment.
5. Has history of moderate or severe head trauma or other neurological disorder or systemic medical disease that, in the Investigator's opinion, is likely to affect central nervous system functioning. This would include participants with:
    a) A current diagnosis of a major neurological disorder; or
    b) Seizures, seizure disorder or seizure-like events; or a history of seizure disorder within the immediate family (siblings, parents); or
    c) Encephalopathy
6. Has attempted suicide within the 6 months prior to the C-SSRS assessment at Screening, or is at significant risk of suicide, either in the opinion of the Investigator or defined as a "yes" to suicidal ideation questions 4 or 5 or answering "yes" to suicidal behavior on the C-SSRS within the 6 months prior to the C-SSRS assessment at Screening.
7. Is currently participating in another clinical trial or has participated in a clinical trial within the 60 days prior to providing informed consent.
8. Has any history of schizophrenia, schizoaffective disorder, or bipolar disorder, or has any other psychiatric disorders in the Investigator's clinical judgement would interfere with their ability to participate in the study.
9. Has any unstable, clinically significant cardiovascular condition that in the Investigator's clinical judgement would preclude their participating in the study.
10. Has any disease or taking any medication that could, in the Investigator's opinion, interfere with the assessments of safety, tolerability, or efficacy, or interfere with study conduct or interpretation of results.
11. History of unexplained loss of consciousness, unexplained syncope, unexplained irregular heartbeat or palpitations or near drowning with hospital admission.

12. In the Investigator's opinion, is unlikely to comply with the protocol or is unsuitable for any other reason.

7.3 Screen Failures

Participants who are consented to participate in the clinical trial, who do not meet one or more criteria required for participation in the trial during the screening procedures, are considered screen failures.

On a case-by-case basis, participants who previously screened for this study (e.g., provided informed consent), but were not dispensed SM may be allowed to rescreen for this study, but only after receiving written permission from sponsor and medical monitor.

7.4 Recruitment and Retention

Participants will be targeted for recruitment using digital and social media advertisements, and referrals from physicians' existing patient pool, within the contiguous US. A sufficient number of individuals will be screened to obtain up to 750 participants who will be dosed. An anticipated attrition rate of 33% is expected to result in the completion of up to 500 participants through the treatment period (14 weeks). Participants will have completed the study upon completion of all study procedures, assessments, and observations through the end of Week 14 of treatment.

8. Study Treatment

8.1 Study Treatment Description

Qelbree (viloxazine extended-release capsules) is a selective norepinephrine reuptake inhibitor indicated for the treatment of ADHD in adults and pediatric patients 6 years and older. Qelbree received marketing approval in the US in 2021 for pediatric patients 6-17 years of age, and in 2022 for adults ≥18 years of age (Qelbree PI).

8.2 Study Treatment Administration

8.2.1 Study Medication

Qelbree (viloxazine extended-release capsules) is supplied in 100 mg, 150 mg, and 200 mg capsules (Qelbree PI).

8.2.2 Dosing

Participants will be instructed to take Qelbree 200 mg once daily (QD) in the morning during Week 1 and 400 mg QD in the morning during Week 2 onwards until next contact with Investigator. The investigator may adjust/titrate dosage in increments of up to 200 mg weekly to the maximum recommended dosage of 600 mg once daily, depending on response and tolerability. At the discretion of the Investigator based on tolerability, the participant may be

instructed to take total daily dose once daily in the evening. See full prescribing information for Qelbree regarding participants who have severe renal impairment.

8.2.3 Mode of Administration

Qelbree is administered orally, with or without food. Qelbree capsules should not be cut, crushed, or chewed. Qelbree capsules should be swallowed whole, and if swallowing the capsule(s) whole is difficult, the capsule(s) can be opened, and the entire contents can be sprinkled over a teaspoonful or tablespoonful of pudding or applesauce. This mixture must be consumed entirely, without chewing, within 15 minutes for pudding or within 2 hours for applesauce. This mixture must not be stored for future use.

At Week 4, 9 and 14, participant will report the method of oral administration that was used during the past 4-5 weeks of treatment, e.g., in the past 4 or 5 weeks: (a) I swallowed intact capsule whole each time; (b) I swallowed food mixture each time; or (c) I used both methods to swallow study medication. In addition, at Week 4, 9 and 14, the participant will report the average clock time (hh:mm AM/PM) or time of day range that he/she took their daily dose of study medication during past 4-5 weeks.

For warnings and precautions, refer to full prescribing information for Qelbree.

8.3 Study Product Preparation/Handling/Storage/Accountability

Qelbree (viloxazine extended-release capsules) are available in the following strengths and colors:

- 100mg (yellow capsule printed with “SPN” on capsule cap and “100” on capsule body with edible black ink).
- 150mg (lavender capsule printed with “SPN” on capsule cap and “150” on capsule body with edible black ink).
- 200mg (light green capsule printed with “SPN” on capsule cap and “200” on capsule body with edible black ink).

Storage and Handling

- Qelbree should be stored at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F).

8.4 Concomitant Diets, Treatments, and Medications

8.4.1 Contraindications

Qelbree is contraindicated in participants:

- receiving concomitant treatment with monoamine oxidase inhibitors (MAOI), or within 14 days following discontinuing an MAOI, because of an increased risk of hypertensive crisis.

- receiving concomitant administration of sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range.

For drug interactions, refer to full prescribing information for Qelbree.

Furthermore, participants that are currently undergoing treatment for substance use disorder (if participant is stable/in recovery; with or without medication-assisted treatment), may be allowed to participate in this study on a case-by-case basis with Sponsor input.

All concomitant medications will be recorded in the eCRF. If a participant is taking a stimulant medication that is commercially available in a **short-acting** (immediate-release) and a **long-acting** (extended-release, prolonged release, etc.) formulation, also record in parentheses next to the name of stimulant in ConMeds page in participant's eCRF whether the participant's stimulant medication is either a short-acting [e.g., methylphenidate (IR), amphetamine [IR], etc.] or a long-acting [i.e., methylphenidate (ER), amphetamine [XR], etc.) formulation.

9. Study Assessments and Procedures

9.1 Screening Assessments

9.1.1 Psychiatric Diagnostic Instruments

9.1.1.1 Mini-International Neuropsychiatric Interview for ADHD Studies (MINI-AS)

The Mini International Neuropsychiatric Interview (MINI) was developed and designed as a brief structured diagnostic interview for the major psychiatric disorders in DSM-III-R, DSM-IV and DSM-5 and ICD-10 (Sheehan et al., 1997; Lecrubier et al., 1997; Sheehan et al., 1998). Validation and reliability studies have shown that the MINI has similar reliability and validity properties to similar instruments, however administration duration of time of the MINI is much shorter than the other diagnostic instruments. The standard MINI assesses the 17 most common mental health disorders (e.g., current prevalence rates of 0.5% or higher in the general population in epidemiology studies) using branching tree logic. Compared to the standard MINI, the MINI-AS version has a more detailed set of questions for each of the nine Psychotic Disorders. It is suitable for clinical and research settings where Psychotic Disorders are a focus of interest and where it is important to differentiate between the different psychotic disorders (e.g., schizophrenia vs schizoaffective disorder). The standard MINI does assess both Major Depressive Disorder with Psychotic Features and Bipolar I Disorder with Psychotic Features. Otherwise, all the other modules are similar to the standard MINI.

As outlined in Section 6.1.1, a diagnosis of ADHD is confirmed via MINI-AS by trained central assessor/psychiatrist.

9.2 Efficacy Assessments

9.2.1 Clinician-Rated Outcomes (ClinROs)

As outlined in Section 6.1.2, once a diagnosis of ADHD is confirmed, all clinician-rated outcome assessments will be administered by trained central raters or psychiatric nurse practitioners for reliability of data captured. ClinRO efficacy assessments should not be administered if participant is discontinuing and has not taken daily dose of Qelbree for >7 consecutive days prior to televisit.

9.2.1.1 Adult ADHD Investigator Symptom Rating Scale (AISRS)

The adult ADHD Investigator Symptom Rating Scale (AISRS) was developed to better measure the presence and severity of ADHD symptoms based on DSM-IV diagnostic criteria in adult participants (Spencer et al., 2010). It is a semi-structured clinical interview with suggested prompts for each item to improve interrater reliability. The scale consists of 18 items that directly correspond to the 18 symptoms of ADHD and are further subdivided into two subscales: Inattention (9 items) and Hyperactivity/Impulsivity (9 items). During the interview with the participant, the clinician/Investigator rates the frequency and severity of each symptom on a 4-point Likert-type scale, where 0 = *None*, 1 = *Mild*, 2 = *Moderate*, and 3 = *Severe*, with a maximum total score of 54 points and maximum subscale score of 27 points. The scale allows the assessment of functional impairments linked to each symptom dimension. The AISRS Total score is the sum of all 18 items (or sum of the Inattention and Hyperactivity/Impulsivity subscale scores). The AISRS is being used in this study to assess efficacy of Qelbree in the treatment of ADHD in adults with mood disorders. The AISRS Totals and Subscale scores are the primary outcome measures for this study.

9.2.1.2 Clinical Global Impressions of Severity/Change (CGI-S/C) Scales

The Clinical Global Impression scale was developed to provide a brief, stand-alone assessment of the clinician's view of a participant's global functioning prior to and after administration of SM (Guy, 1976). The Clinical Global Impression of Severity (CGI-S) scale is a single item clinician rating of clinician's assessment of the severity of the ADHD symptoms in relation to the clinician's total experience with patients with ADHD. The CGI-S is evaluated on a 7-point scale with 1 = *Asymptomatic, no symptoms*, 2 = *Borderline*, 3 = *Mild*, 4 = *Moderate*, 5 = *Marked*, 6 = *Severe*, and 7 = *Among the most extreme*. Successful therapy is indicated by a lower overall score in subsequent testing. The Clinical Global Impression of Change (CGI-C) scale is a single item clinician assessment of how much the patient's ADHD symptoms have changed (improved, worsened or no change) during treatment relative to his/her baseline state prior to the beginning of treatment. The CGI-C is evaluated on a 7-point scale with 1 = *Very much improved*, 2 = *Much improved*, 3 = *Minimally improved*, 4 = *No change*, 5 = *Minimally worse*, 6 = *Much worse*, and 7 = *Very much worse*. Successful therapy is indicated by a score <4 in subsequent testing. The CGI is being used in this study to assess efficacy of Qelbree in the treatment of ADHD in adults with mood disorders. The CGI-S/C scores are secondary outcome measures for this study.

9.2.1.3 Montgomery–Åsberg Depression Rating Scale (MADRS)

The Montgomery–Åsberg Depression Rating Scale (MADRS) is a 10-item investigator-rated diagnostic questionnaire used to measure the severity of depressive episodes in participants with mood disorders and is designed to be sensitive to changes brought on by treatment (Montgomery and Åsberg, 1979). A structured interview guide for the Montgomery–Åsberg Depression Rating Scale (SIGMA) was developed to improve consistency on how the scale is administered among clinicians/raters across study sites or clinical trials and to improve the reliability of the ratings (Williams and Kobak, 2008). The questionnaire assesses the severity of the following 10 symptoms: (1) Apparent sadness; (2) Reported sadness; (3) Inner tension; (4) Reduced sleep; (5) Reduced appetite; (6) Concentration difficulties; (7) Lassitude; (8) Inability to feel; (9) Pessimistic thoughts; (10) Suicidal thoughts. Nine of the items are based upon patient report, and one is on the rater's observation during the rating interview. Each MADRS item/symptoms is rated on a 7-point Likert scale (0–6 continuum, where 0=no abnormality to 6=severe); point can be defined rating (0, 2, 4, 6) or points between them (1, 3, 5). The overall score ranges from 0 to 60. A higher MADRS total score indicates more severe depression; total score ranges of 0 to 6 indicate normal/symptom absent, 7 to 19 indicate mild depression, 20 to 34 indicate moderate depression, >34 indicate severe depression (Snaith et al., 1986; Herrmann et al., 1998; Müller et al., 2000). It takes about 25-45 minutes to complete the SIGMA. The MADRS is being used in this study to assess symptoms of depression during Qelbree treatment in adults with ADHD. The MADRS Total score is a secondary outcome measure for this study.

9.2.1.4 Hamilton Anxiety Rating Scale (HAM-A)

The Hamilton Anxiety Rating Scale (HAM-A) is a rating scale developed to assess/measure the severity of an individual's anxiety (Hamilton, 1959). The HAM-A is used to assess severity of anxiety in children, adolescents and adults in both clinical and research settings (Hamilton, 1959; Maier et al., 1988; Borkovec and Costello, 1993). The HAM-A consists of 14 items or parameters, each defined by a series of symptoms. It measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). The original HAM-A does not provide any standardized probe questions. Therefore, a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH-A) was developed to instructions for administration and clear anchor points for the assignment of severity ratings (Shear et al., 2001). Each item on the HAM-A is rated/scored on a 5-point Likert scale, where 0 = *Not present*, 1 = *Mild*, 2 = *Moderate*, 3 = *Severe*, and 4 = *Very severe*. The ratings/scores of all 14 items are summated to yield a total score (ranging from 0 to 56), where ≤ 17 indicates "mild anxiety severity," 18 to 24 indicates "moderate anxiety severity," 25 to 30 indicates "moderate to severe anxiety severity," and ≥ 31 indicates "severe anxiety." It takes 25 to 35 minutes to complete the HAM-A. The HAM-A is being used in this study to assess symptoms of anxiety during Qelbree treatment in adults with ADHD. The HAM-A Total score is a secondary outcome measure for this study.

9.2.2 Patient-Reported Outcomes (PROs)

As outlined in Section 6.1.2, once a diagnosis of ADHD is confirmed and ClinROs have been completed, eligible participants will complete patient-reported outcome assessments via the study mobile app prior to first dose (e.g., during virtual visit #2, if necessary). During the Treatment Period, following first dose, the PRO efficacy assessments should not be administered if participant is discontinuing and has not taken daily dose of Qelbree for >7 consecutive days prior.

9.2.2.1 Adult ADHD Self-Report Scale v1.1 Symptom Checklist (ASRSv1.1-SC)

The Adult ADHD Self-Report Scale v1.1 Symptom Checklist (ASRSv1.1-SC) was developed in conjunction with the World Health Organization (WHO) and the Workgroup on Adult ADHD to help screen for ADHD in adult participants based on DSM-IV diagnostic criteria (Kessler et al., 2005; Adler et al., 2006; Adler et al., 2019). The ASRSv1.1-SC consists of 18 items that correspond to the 18 DSM-IV symptoms of ADHD, which are further subdivided into two subscales: Inattention (IA; 9 items: 1 to 4 and 7 to 11) and Hyperactivity/Impulsivity (HI; 9 items; 5, 6, and 12 to 18) to allow assessment of functional impairments linked to each symptom dimension. Individuals rate the frequency of each symptom on a 5-point scale (where 0 = *Never*, 1 = *Rarely*, 2 = *Sometimes*, 3 = *Often*, and 4 = *Very Often*) based on their experience over an indicated period of time (e.g., in the past week). The ASRSv1.1-SC ratings can be evaluated as a categorical (Screener and ADHD Presentation Type) or continuous variable (Total and Subscale scores) as follows:

- As a categorical variable, absolute ratings (0-4) are first converted to a binary score (1 or 0). For instance, for items 1 to 3, 9, 12, 16, and 18 ratings of *Sometimes*, *Often*, and *Very Often* are assigned a value of 1 and ratings of *Never* and *Rarely* are assigned a value of 0. For the remaining 11 items (4 to 8, 10 and 11, 13 to 15, and 17) ratings of *Often* and *Very Often* are assigned a value of 1 and ratings of *Never, Rarely*, and *Sometimes* are assigned a value of 0. For the Screener, if the sum of the binary scores for six items (items 1 to 6) is ≥4 then the patient is considered to have symptoms highly consistent with ADHD in adults. For ADHD Presentation Type, if sum of the binary score of the 9 IA items or the 9 HI items is ≥ 6 then the patient is considered to be symptomatic for AI and/or HI, respectively.
- As a continuous variable, the sum of absolute rating (0-4) of all18 items yields the absolute Total score (range 0 to 72: the higher the score, the more severe the ADHD symptoms). The sum of the absolute rating of the 9 IA items or the 9 HI items yields absolute Subscale score (range 0 to 36: the higher the score, the more severe the IA or HI symptoms, respectively).

It takes approximately 5 minutes to complete the ASRSv1.1-SC. The ASRSv1.1-SC is being used in this study to characterize ADHD symptoms at baseline (categorical) prior to treatment and to assess efficacy (continuous variable)of Qelbree in the treatment of ADHD in adults. The absolute ASRSv1.1-SC Totals and Subscale scores are secondary outcome measures for this study.

9.2.2.2 Patient Health Questionnaire (PHQ-8)

The Patient Health Questionnaire (PHQ) is a multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression (Spitzer et al., 1999; Spitzer et al., 2000; Kroenke et al., 2001). The initial 9-item version (PHQ-9) incorporates DSM-IV depression diagnostic criteria with other leading major depressive symptoms into a brief self-report tool. It is one of the most validated tools in mental health which can assist clinicians with diagnosing depression and assist researchers with monitoring treatment response. Research has shown that certain scores on the PHQ-9 are strongly correlated with a subsequent major depression diagnosis. However, not everyone with an elevated PHQ-9 is certain to have major depression. The PHQ-9 is a self-administered version of the PRIME-MD diagnostic instrument for common mental disorders (Kroenke et al., 2001). Since the C-SSRS is being administered at screening and follow up during treatment in this study, the PHQ-8 will be administered in this study (e.g., 8-item depression scale with item #9 for suicide risk omitted). The PHQ-8 has been validated as a diagnostic and severity measure for depressive disorders in large clinical studies (Kroenke et al., 2009). The PHQ-8 is the depression module, which the patient scores each on 4-point Likert scale, including 0 = *not at all*; 1 = *several days*, 2 = *more than half the days*, and 3 = *nearly every day*; sum of all items yields total score (0-24). PHQ-8 total scores ≥10 indicate major depression and ≥20 indicate severe major depression. The PHQ-8 takes less than 5 minutes to complete. The PHQ is being used in this study to assess self-reported symptoms of depression during Qelbree treatment in adults with ADHD. The PHQ-8 Total score is a secondary outcome measure for this study.

9.2.2.3 General Anxiety Disorder-7 item (GAD-7) Scale

Generalized Anxiety Disorder 7 scale (GAD-7) is a self-reported 7-item questionnaire for screening and measuring the severity of generalized anxiety disorder (Spitzer et al., 2006). The GAD-7 measures the severity of various symptoms of generalized anxiety disorder over the past 2 weeks according to reported response categories with assigned points. The patient scores each GAD-7 item on 4-point Likert scale, where 0 = *Not at all*, 1 = *Several days*, 2 = *Over half the days*, and 3 = *Nearly every day*. The clinician/Investigator can obtain the total score by summating all 7 items. GAD 7 total scores range from 0 to 21, where a total score of 1 to 4 = None/Minimal anxiety, 5 to 9 = Mild anxiety, 10 to 14 = Moderate anxiety, and ≥ 15 = Severe anxiety. It takes less than 5 minutes to complete the GAD-7. The GAD-7 is being used in this study to assess self-reported symptoms anxiety during Qelbree treatment in adults with ADHD. The GAD-7 Total score is a secondary outcome measure for this study.

9.2.2.4 Behavior Rating Inventory of Executive Function–Adult Version (BRIEF-A)

The Behavior Rating Inventory of Executive Function–Adult Version (BRIEF-A; Self report) is a standardized rating scale that captures views of an individual's executive functions into everyday behaviors in adults ages 18 to 90 years (Roth et al., 2005; Roth et al., 2013). It has been utilized in clinical trials to assess changes in executive function with treatment for neurological and psychiatric disorders, including ADHD (Adler et al., 2014). The self-report

provides the insight of the individual's viewpoint of their own difficulties in self-regulation. The BRIEF-A is a 75-item self-rating scale that assesses overall functioning (Global Executive Function [GEC]) and 9 non-overlapping scales among 2 summary index scales. (Metacognition Index [MI] and Behavioral Regulation Index [BRI]) that assess aspects of executive function and problems with self-regulation from the perspective of the individual. Description of the nine BRIEF-A scales (Roth et al., 2013) by summary index scale:

1. The Behavioral Regulation Index (BRI) captures the ability to maintain appropriate regulatory control of one's own behavior and emotional responses. The BRI is broken down into the following four scales within the BRIEF-A:
   - Inhibit: Control impulses; appropriately stop verbal, attentional, physical behavior at the proper time
   - Shift: Move freely from one situation, activity, or aspect of a problem to another as the situation demands; think flexibly to aid problem-solving
   - Emotional control: Modulate one's emotional responses appropriately
   - Self-Monitor: Recognize the effect of one's own behavior on others
2. The Metacognition Index (MI) reflects the individual's ability to initiate activity and generate problem-solving ideas, to sustain working memory, to plan and organize problem-solving approaches, to monitor success and failure in problem solving, and to organize one's materials and environment. The MI is broken down into the following four scales within the BRIEF-A:
   - Initiate: Begin a task or activity without external prompting; independently generate ideas
   - Working memory: Hold information in mind in order to complete a task; stay with, or stick to, an activity
   - Plan/organize: Anticipate future events; set goals; develop steps ahead of time to carry out a task; organize information and behavior to achieve and objective; carry out tasks in a systematic manner
   - Task Monitor: Assess performance during or after finishing a task for mistakes
   - Organization of Materials: Keep workspace and living areas in an orderly manner; keep track of materials needed for tasks

Participants rate each item on a 3-point scale (1=*Never*, 2=*Sometimes*, or 3=*Often*) based on their experience within the last month. The sum of 70 items yields the GEC raw score (range: 70-210), the sum of 40 items yields the MI raw score (range: 40-120), the sum of 30 items yields the BRI raw score (range: 30-90), the sum of 8 items yields the "Inhibit" raw score (range: 8-24), the sum of 6 items yields the "Shift" raw score (range: 6-18), the sum of 10 items yields the "Emotional Control" raw score (range: 10-30), sum of 6 items yields the "Self-Monitor" raw score (range: 6-18), sum of 8 items yields the "Initiate" scale raw score (range: 8-24), the sum of 10 items yields the "Plan/Organize" raw score (range: 10-30), the sum of 6 items yields the "Task Monitor" raw score (range: 6-18), the sum of 8 items yields the

"Organization of Material" raw score (range: 8-24), and the sum of 8 items yields the "Working Memory" raw score (range: 8-24). Raw scores are converted to a T-score (normative population mean=50 and standard deviation=10; T-score ≥ 65 is considered abnormally elevated). It takes 15-20 minutes to complete the BRIEF-A. The BRIEF-A is being used in this study to assess self-reported executive function during Qelbree treatment in adults with ADHD. The BRIEF-A T-scores for GEC, BRI, MI and the nine individual scales are secondary outcome measures for this study.

9.2.2.5 Work Productivity and Activity Impairment: Specific Health Problem (WPAI:SHP)

The Work Productivity and Activity Impairment (WPAI) Questionnaire is a self-assessment questionnaire that measures the impact of health problems on work productivity and regular activities (Reilly et al., 1993). There are WPAI versions that assesses based on a general health problem (WPAI:GH) or based on specific health problem (WPAI:SHP; e.g., ADHD). The WPAI:SHP will be used in this study. The WPAI questionnaire has been used to clinical research to assess the impact of ADHD and ADHD treatments on work productivity and regular activities in adults with ADHD (Pawaskar et al., 2020; Spaulding et al., 2022; Schein et al., 2023; Lee et al., 2023). The WPAI:SHP questionnaire consists of six questions that ask about employment status (Q1), the number of hours missed from work or regular activities due to the specific health problem or other reasons (Q2, Q3), the number of hours actually worked (Q4), and the degree of impairment while working or performing regular activities (Q5, Q6) on an 11-point scale (where 0 = "*PROBLEM (My ADHD symptoms) had no effect on my work/ daily activities*" and 10 = "*PROBLEM (My ADHD symptoms) completely prevented me from doing my work/ daily activities* . The WPAI:SHP questionnaire can be used to calculate four outputs: Absenteeism percentage , Presenteeism percentage, Work Productivity Loss percentage, and Activity Impairment percentage. It takes 2-3 minutes to complete the WPAI:SHP. The WPAI:SHP scores/percents are secondary outcome measures for this study.

9.2.2.6 Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index (PSQI) is a validated and effective instrument used to measure the quality and patterns of sleep in adults (Buysse et al., 1989). The PSQI is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval. It is a 19-item questionnaire out of which generate 7 component scores (or domains): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. The individual rates each of these seven areas of sleep. Scoring of the answers is based on a 0 to 3 scale, whereby 3 reflects the negative extreme on the Likert Scale. A global sum of "5" or greater indicates a "poor" sleeper. Although there are several questions that request the evaluation of the client's bedmate or roommate, these are not scored, nor reflected in the attached instrument. An updated scoring was established from original scoring algorithm: *if*

5J is not complete or the value is missing, it now counts as a "0". It takes 10-15 minutes to complete the PSQI. The PSQI is being used in this study to assess self-reported sleep behavior and daytime function during Qelbree treatment in adults with ADHD. The PSQI global [redacted] scores are secondary outcome measures for this study.

9.3 Questionnaires

9.3.1 Reproductive/Menstrual Cycle History (RMCH) Questionnaire

All biologically female participants will be asked about timing of menarche, history of pregnancies, and current reproductive status at Screening. Those biologically female participants who are of childbearing potential will also be asked questions about their menstrual cycle in the past year at Screening. Those biologically female participants who are not of childbearing potential will be asked questions about when their menses stopped and the reason at Screening. At each Televisit FOCPs will report the date of their last menses (RMCH Questionnaire's Menstrual-Question #5).

9.4 Safety Assessments

The safety endpoints measured during this study are AEs, blood pressure/pulse rate, weight, and the Columbia Suicide Severity Rating Scale (C-SSRS).

9.4.1 Adverse Events

Adverse events will be captured and/or recorded from the time the participant administers the first dose of study medication and until 30 days after last dose of study medication has been administered. Adverse events will be assessed/captured by assessor at every contact/televisit with participant.

9.4.2 Blood Pressure/Pulse Rate and Weight

Blood pressure/pulse rate (BP/PR) and weight will be measured using BP/PR cuffs and weight scale, respectively. BP/PR cuffs will be shipped to participants. All participants will use the same BP/PR device for measurement consistency . Although the BP/PR device records each measurement/reading, systolic/diastolic BP and PR values will be captured by participant in study app at Screening and by assessor in eCRF during all other televisits during the 14-week treatment period.

9.4.3 Columbia-Suicide Severity Rating Scale (C-SSRS)

Assessment of suicidal ideation and behavior will be conducted using the Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011). The C-SSRS is an FDA-recommended prospective assessment instrument that directly classifies suicidal ideation and behavior events into 11 preferred categories, including 5 levels of suicidal ideation, 5 levels of suicidal behavior, and the category of self-injurious behaviors with no suicidal intent.

The instrument has been validated used successfully in adult participants with various psychiatric disorders that do not involve cognitive impairment. The C-SSRS outcomes that can be used for clinical management and safety monitoring are suicidal lethality rating, suicidal ideation score, and suicidal ideation intensity rating. The C-SSRS is a short questionnaire that can be administered quickly and consists of simple questions to assess the severity and immediacy of suicide risk. The C-SSRS will be administered by trained assessor during televisits during screening (*Baseline/Screening* version) and treatment (*Since Last Visit* version) periods.

9.5 Adverse Events

9.5.1 Definition of Adverse Events

An AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

The use of the term "AE" does not imply a relationship with the study product or with the clinical study. AEs will be defined as falling into the categories "non-serious AE" and "SAE".

The AE may be a new illness, worsening of a concomitant illness, an effect of the study product, or a combination of two or more of these factors.

9.5.2 Definition of Serious Adverse Events

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (21 CFR 312.32 (a)).

9.5.3 Adverse Event Reporting

For the purposes of this study, the period of observation for collection of AEs begins after the first dose is administered and continues through the completion of the study at Week 14 (end of treatment). Any health changes prior to first dose will be recorded as medical history.

All AEs occurring during the study will be individually assessed by the Investigator, reported, and recorded, regardless of seriousness or relationship to the study product.

The following information will be documented in each case:

- Participant ID
- AE Term

- Start Date of event
- End Date of event or Ongoing
- Severity or Intensity
- Seriousness
- Action taken with study product
- Action taken to treat event
- Outcome
- Relationship to study product
- Participant's health status

9.5.4 Serious Adverse Event Reporting

Documentation of an SAE requires that in addition to AE information provided in Section 9.5.3, the Investigator or designee will provide:

- Seriousness criteria: life threatening, hospitalization, persistent/significant disability, congenital anomaly/birth defect, death [if marked, then date of death]
- Event Description: where a narrative would capture the details of the event
- Relevant Medical History: any medical history pertinent to the event
- Other situations:
    - Medical or scientific judgment will be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant, and/or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

In addition, the Sponsor (via the Investigator or designee) will be notified of SAE via email within 24 hours of identifying it (e.g. recorded in the SAE form). SAE meeting the Institutional Review Board (IRB) criteria for reporting will be reported to the IRB within the required timeline. SAEs which result in death or are life-threatening must be reported to IRB and Sponsor immediately.

9.5.5 Adverse Event Severity and Causality Assessments

Assessment of Severity

The severity of AEs will be defined by the following criteria.

- *Mild:* Symptoms hardly perceived, only slight impairment of general well-being
- *Moderate:* Clearly noticeable symptoms, but tolerable without immediate relief
- *Severe*: Overwhelming discomfort

Assessment of Causality

The Investigator or designee will assess the possibility of a link between the study product and an AE on the basis of the following criteria:

- *Unrelated*
  - There is an evident other explanation for the AE
  - The AE is in accordance with the effect or adverse effect of the concomitant medication being taken by participant
  - The AE occurred prior to the administration of the study product
- *Unlikely relation*
  - Reasonable temporal relationship with the intake of the study product, although there is another plausible explanation for the occurrence of the AE
- *Possible relation*
  - Reasonable temporal relationship with the intake of the study product, although there are a number of other factors that could have caused the AE
- *Probable relation*
  - Reasonable temporal relationship with the intake of the study product although other plausible reasons point to a causal relationship with the study product
- *Definite relation*
  - Reasonable temporal relationship with the intake of the study product, and
  - There is no other explanation for the AE, and
  - Subsidence or disappearance of the AE on withdrawal of the study product (discontinuation), and
  - Recurrence of the symptoms on reintroduction of the study product

Expected Adverse Events

Expected AEs are known AEs based on previous findings from use of the products or procedures used in this study. The most commonly observed adverse reactions in adults are insomnia, headache, somnolence, fatigue, nausea, decreased appetite, dry mouth and constipation (Qelbree PI).

Adverse events of concern include (1) suicidal thoughts and behavior, (2) blood pressure and pulse rate increases, (3) activation of mania or hypomania, and (4) somnolence and fatigue (Qelbree PI).

Unanticipated Problems

Definition

Unanticipated problems (UAP) involving risks to particpants or others includes, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Notification to Regulatory Authorities and IRBs

The Investigator or designee will report UAPs to the IRB per required timelines, and the Sponsor will notify the FDA as applicable.

9.5.6 Serious Adverse Event Follow-Up

The Investigator or designee will continue to follow all AEs and SAEs until the completion of the study (Week 14). All communication between the Investigator or designated study team members and participants regarding the treatment and outcome of the AE will be documented and included as part of the study database.

If a participant is withdrawn at any stage during the study due to an AE, the Investigator or designee will advise the participant of appropriate follow-up with a local doctor, if needed. If a participant's involvement in the study ends prior to resolution of an event, the event will be marked as ongoing and the Investigator or designee will advise the participant of appropriate follow-up (e.g., to provide follow-up information/referral to the participant's primary care physician). The status of the AE at the last follow-up will be documented.

Notification to Regulatory Authorities and IRBs

The Investigator or designee will report UAPs to the IRB per required timelines, and the Sponsor will notify the FDA as applicable.

9.5.7 Pregnancy Reporting

Participants who self-report pregnancy will be excluded from the study at screening. If the participant reports being pregnant after enrollment, they will be withdrawn from the study and a Pregnancy Reporting Form will be filled out by the PI or designee and the Sponsor will be alerted of the pregnancy. Participants that become pregnant after enrollment and have taken at least one dose of Qelbree, will be followed until the outcome of the pregnancy is known.

10. Study Completion and Discontinuation

10.1 Study Completion

Participants that take study medication until Week 14/EOS and complete most study procedures (e.g. safety and ClinROs) by the end of the 14-week treatment period will be

considered to have completed the study. Participants that choose to discontinue study medication prior to Week 14, will be withdrawn from the study and reasons for discontinuation will be noted in the eCRF.

10.2 Study Discontinuation

The participant may withdraw themselves from the study at any time by notifying the study team. Participants may be discontinued from the study by the Investigator or designee if study procedures have not been followed or if the Investigator or designee determines the participant is not able to safely continue with the study due to an AE or other health-related issue.

Reasons for participant's study discontinuation may include:

- Withdrawal of consent (the reason for withdrawal of consent should be captured)
- Adverse event(s)
- Lack of efficacy
- Noncompliance with study procedures
- Lost to follow-up (the Investigator will document efforts to attempt to reach the participant by phone, email, and chat via study mobile app prior to considering that participant lost to follow-up)
- Other

After a participant has been discontinued, they will not be allowed to re-screen for enrollment in the study, unless there is a technical issue. The reasons for discontinuation will be documented in the participant's study record. Participants enrolled in error may be discontinued from the study with agreement from the Investigator and Sponsor.

If a participant is discontinued for any reason other than lost to follow-up, Week 14 procedures should be completed, and any outstanding data recorded in their record. If a participant is withdrawn at any stage during the study due to an AE, the Investigator or designee will advise the participant of appropriate follow-up with a local doctor, if needed. If a participant's involvement in the study ends prior to resolution of an event, the event will be marked as ongoing and the Investigator or designee will advise the participant of appropriate follow-up (e.g., to provide follow-up information/referral to the participant's primary care physician). The status of the AE at the last follow-up will be documented. The reason for discontinuation and efforts to follow participants who discontinue because of AEs will be fully documented.

10.3 Lost to Follow-up

A participant can be considered lost to follow-up if they fail to comply with scheduled visits and are unable to be contacted by the Investigator or designated study personnel on three separate documented attempts. The date of study termination will be the last scheduled visit contact with the participant. If, at any point, contact is re-established with the participant, they

may be allowed to continue in the study at the discretion of the Investigator and with prior written approval from the Sponsor.

11. Data Management

11.1 Data Collection

Study data will be collected in the study mobile app and study's Electronic Data Capture (EDC) Platform.

All questionnaire responses/assessment ratings will be directly captured in the study's EDC platform, with the exception of the MINI-AS that is completed separately, and select portions are captured in the study's EDC platform.

Management of clinical data will be performed in accordance with applicable standards and procedures with oversight by the Sponsor to ensure integrity of the data.

To protect the privacy of participants, no personal information [including the name(s) or initial(s)] is to be recorded in the eCRF or as part of the query text. Identifiable data are isolated to specific members of the study team and these data will not be transferred/available to the Sponsor.

The Sponsor will be provided with all associated study data, as applicable, at the completion of the study.

11.2 Data Handling

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance. Any changes or corrections to data will be performed in the study's EDC Platform, and it will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by the Investigator.

The study mobile app and associated management system are fully validated and 21 CFR Part 11 complaint. Release notes and validation certificates are held by CRO.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and any concomitant medications terms (if applicable) will be coded using the medication dictionary, WHODrug.

11.3 Data Entry

Once consent is obtained, the participants will complete the required information via the study mobile app. In addition to the participant entered information, the decentralized site staff will be entering data into an EDC.

11.4 Computerized Logical Checks

The database will incorporate the needed programmed logical checks to ensure consistent and complete data entry. The data management team will perform logical manual checks, and queries will be raised for the decentralized site staff to address.

11.5 Audit Trail

The Clinical Data Management System complies with Good Clinical Practice (GCP) predicated rule requirements, laws, and regulations (Personal data protection) for clinical trials and allows an audit of actions performed by users.

All original entries and changes made in the database will be captured by an audit trail which will include the date and time of the entry or change, and the individual making the entry or change who will be identified via their unique user ID.

12. Statistical Methods

12.1 General Considerations

All statistical analysis will be performed using SAS version 9.4 or higher or R version 4.03 or higher. All statistical analyses will be presented using descriptive statistics. Summary statistics for continuous variables will include sample size (N), mean, median, standard deviation, first quartile (Q1), third quartile (Q3), minimum, and maximum. Summary statistics for categorical variables will be presented in terms of frequencies and percentages. Participant data listing to support summaries will be provided. More details will be provided in the Statistical Analysis Plan (SAP).

Baseline is defined as the last non-missing assessment recorded before receiving the first dose of study medication.

12.2 Populations for Analyses

Safety Analysis Set: This set includes all participants who provided informed consent and took at least one dose of Qelbree. The safety analyses will be conducted using the Safety Analysis Set. Safety data will be summarized based on the Safety Analysis Set.

Efficacy Analysis Set: For each secondary efficacy outcome measure, the summary will be based on a subset of participants in the Safety Analysis Set who have a valid AISRS at baseline (prior to first dose) and at least one valid AISRS post-baseline (following first dose) assessment.

12.3 Determination of Sample size

Up to 750 participants will be dosed in this study, to obtain up to 500 competed (through the end of Week 14 of treatment) participants, with an anticipated attrition rate of 33%. There is no consideration for power for the sample size determination in this decentralized, open label study.

12.4 Patient Disposition

The number and percentage of participants in the Safety Analysis Set, the Efficacy Analysis Set, who completed the study and discontinued from the study and the primary reason for early discontinuation will be summarized.

12.5 Demographics and Baseline Analysis

Demographic/baseline variables will be presented in descriptive summaries that include age, age group, sex, ethnicity, race, height and weight at baseline, BMI, and other baseline efficacy end points using descriptive statistics for continuous variables and using counts and percentages for categorical variables.

12.6 Study Medication Exposure and Compliance

Duration of exposure is defined as the total number of days a patient is exposed to Qelbree. This will be calculated for each patient by taking the difference between the date of last dose minus the date of the first dose, plus 1 (date of last dose minus date of first dose +1). Duration of SM exposure will be summarized by duration category (defined in the SAP) and will also be summarized using descriptive statistics.

Percent of SM compliance is defined as {(number of capsules dispensed minus number of capsules returned) /number of capsules instructed to take * 100%. SM compliance will be summarized by compliance category (<80%, 80-120%, and >120%) and number and percent of participants in each compliance category. Study medication compliance will also be summarized as a continuous variable using descriptive statistics.

12.7 Concomitant Medications

Concomitant medications will be assigned an 11-digit code using the WHO-DD drug codes. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. A tabular summary of concomitant medications by drug class will be presented for the Safety population.

12.8 Efficacy Analysis

12.8.1 Primary Endpoint(s)

- The primary efficacy endpoint is change from baseline in AISRS Total score by visit. The observed (raw) and change from baseline Total score will be summarized by study visit using descriptive statistics as described above. The summary will be based on Efficacy Analysis Set.

12.8.2 Secondary Endpoint(s)

The following secondary endpoints will be analyzed in a similar manner to the primary endpoint.

- Change from baseline in AISRS Inattention and Hyperactivity/Impulsivity Subscale scores by visit
- Change from baseline in ASRSv1.1-SC Total score by visit
- Change from baseline in ASRSv1.1-SC Subscale (Inattention and Hyperactivity/Impulsivity) scores by visit
- Change from baseline CGI-S score by visit
- CGI-C score by visit
- Change from baseline in MADRS Total Score at Week 14/EOS
- Change from baseline in PHQ-8 Total Score by visit
- Change from baseline in HAM-A Total Score at Week 14/EOS
- Change from baseline in GAD-7 Total Score by visit
- Change from baseline at Week 14/EOS in BRIEF-A T-score for the:
    i. Global Executive Composite (GEC)
    ii. Behavioral Regulation Index (BRI)
    iii. Metacognition Index (MI)
- Change from baseline in the WPAI:SHP absenteeism percentage by visit, presenteeism percentage by visit, work productivity percentage by visit, and regular activity percentage by visit
- Change from baseline at Week 14/EOS in the PSQI global score

The observed (raw) and the change from baseline (except CGI-C) score/value will be summarized by study visit for each secondary efficacy outcome measure (total/global score and subscale scores) using descriptive statistics as described above. For each secondary efficacy outcome measure, the summary will be based on Efficacy Analysis Set.

12.9 Safety Analysis

Safety analyses will be performed based on the safety analysis set.

AEs will be classified into standardized medical terminology from the Verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA) and Preferred Term (PT).

The incidence rate, severity, and relationship to Qelbree for all AEs will be summarized for each System Organ Class (SOC) and PT. The absolute and change from baseline for blood pressure, pulse rate, and weight will be presented will be summarized using descriptive statistics by study visit.

Columbia Suicide Severity Rating Scale (C-SSRS) outcomes will be summarized using number and percent of participants by categories for suicidal ideation, suicidal behavior and suicidal ideation or behavior.

12.10 Exploratory Analysis

[redacted]

13. Quality Control and Assurance

13.1 Acceptability of Case Report Forms (Source Documents)

A case report form (CRF) is a printed, optical, or electronic document designed to record the protocol required information to be reported to the sponsor on each trial participant.

Management of clinical data will be performed in accordance with CRO's applicable standards and procedures with oversight from the Sponsor to ensure integrity of the data.

To protect the privacy of participants, no personal information (including the name or initials) is to be recorded in the eCRF or as part of the query text.

All eCRF pages should be completed during a participant's assessment when the eCRF has been designated as the source.

The Sponsor will obtain and retain all eCRFs and associated study data as applicable at the completion of the study.

Any identifiable data accessible to a designated team at CRO will not be transferred/available to the Sponsor except if needed during routine monitoring, regulatory audit, and/or inspection.

Before enrolling any participants in the study, the Sponsor or its designee and the Investigator will review the protocol, the eCRF and eCRF instructions, the procedure for obtaining informed consent, and the procedure for reporting AEs.

13.2 Modification of Protocol

All additions or changes to the study protocol must be approved by the Sponsor. The IRB must be notified of all subsequent additions or changes in the study protocol for review and approval as necessary.

The Investigator will not make any changes to this protocol without prior written consent from the Sponsor and the subsequent approval by the IRB. Any permanent change to the protocol, whether it is an overall change or a specific change, must be handled as a protocol amendment. The written amendment must be submitted to the chairperson of the IRB identified with this responsibility. Except for ''administrative amendment'', Investigators must

await IRB approval of protocol amendments before implementing the change(s). Administrative amendments are defined to have no effect on the safety of the research participants, scope of the investigation, or quality of the trial. However, a protocol change intended to eliminate an apparent immediate hazard to participants should be implemented immediately, and the IRB notified as per stipulated timeline within five days.

When, in the judgment of the reviewing IRB, the Investigators and/or Sponsor, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the participant, the currently approved written informed consent form will require similar modification. In such cases, informed consent will be re-obtained from participants enrolled in the study before expecting continued participation.

13.3 Reporting Protocol Deviations

A protocol deviation is any non-compliance with the clinical study protocol or International Conference on Harmonization Good Clinical Practice (ICH GCP). The non-compliance may be either on the part of the participant, the Investigator, or the study staff. It is the responsibility of the Investigator to identify and report deviations per IRB requirements.

13.4 Monitoring

This study will be monitored on an ongoing basis.

The Sponsor or its designated study monitor may perform ongoing review of the eCRFs in accordance with the monitoring plan, to confirm that data entered into the eCRF by authorized site personnel is accurate, complete, and verifiable from source documents (as applicable); that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. At the end of the trial the monitor will make a study site close-out visit to ensure that all documentation is complete. In all cases, it is the responsibility of the CPM / monitor to maintain participant confidentiality.

13.5 Audits and Inspections

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance assessment and/or audit of the study records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit, or inspection, CRO will grant advisor(s), auditor(s), and inspector(s) access as per agreed upon terms to relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

CRO will notify the Sponsor or its agents immediately of any regulatory inspection notification in relation to the study.

The Sponsor will be available to help CRO prepare for an inspection.

14. Ethics and Regulatory Requirements

14.1 Institutional Review Board/Independent Ethics Committee

The study protocol will be submitted by the Investigator for examination by the IRB. Commencement of the clinical study is not permitted without written approval of the IRB.

The study will be initiated after approval from the IRB which follows the guidance of US regulatory bodies, general GCP regulations, and standards set by the ICH.

This study will be conducted according to the principles and rules laid down in the Declaration of Helsinki and its subsequent amendments.

14.2 Investigator Responsibilities

The Investigator or designee is responsible for the following:

- Obtaining the written and dated approval of the applicable IRB and other regulatory agency, if any, prior to the conduct of the study
- Selecting participants in accordance with the inclusion and exclusion criteria after the eIC is signed
- Maintaining confidentiality and safety of participants in accordance with the Declaration of Helsinki
- Adhering to the study protocol and the spirit of GCP
- Following procedure if modification becomes necessary. The PI or designee will provide a rationale in a protocol amendment, which is signed by the Investigator and Sponsor for submission to the IRB. After the protocol amendment approval, participants still active in the study must re-sign the eIC to remain in the study
- Providing accurate, complete, and timely data reported to the Sponsor
- Providing participants with any newly available information that may be relevant to them during the study
- Identifying AEs and notifying the Sponsor, IRB, and health authorities, as applicable
- Cooperating in the case of an audit and/or regulatory inspections, providing direct access to data and/or documents.

14.3 Informed Consent Process

Informed consent will be obtained from the participants using the IRB-approved electronic Informed Consent (eIC) method before any study-related procedures are performed or any data are collected and will be done in accordance with all applicable regulatory requirements.

The informed consent form (ICF) used during the informed consent process must be the current IRB approved ICF. The IRB/Ethics Committee (EC) will approve the eIC language. Any amendments to these documents must be approved by the IRB/EC prior to distribution or use.

Before any protocol-required procedures are performed, the participant must:

- Be informed of all aspects of the study (risks and benefits)
- Be given time to ask questions and time to consider the decision to participate
- Voluntarily agree to participate in the study
- Sign and date an IRB approved eIC

The Investigator and/or designee will be available to answer questions about all aspects of the study before the participant decides they want to participate.

The decision of the participant to participate in the study is entirely voluntary. It will be clearly stated to the participant within the eIC language that the consent to participate can be withdrawn at any time without penalty or loss of benefits to which the participant is otherwise entitled.

15. Study Closure

Premature Termination of Study

Should it prove necessary to discontinue the study permanently prior to completion, the Sponsor will notify CRO and the IRB of the rationale. Participants will be informed by CRO or its designee. All relevant study documents and data will then be returned to the Sponsor.

Termination of Study

After the completion or termination of the study, all relevant study documents and data will be sent to the Sponsor by the CRO. The Investigator will inform the IRB of the end of the study and a certificate of study closure will be issued.

16. Publication Plan

Any presentation or publication of data collected as a direct or indirect result of this trial will be considered as a joint publication by the Investigator(s) and the appropriate personnel at the Sponsor's site. Authorship will be determined by mutual agreement. All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the Sponsor, prior to submission for publication or presentation. No publication or presentation with respect to the study shall be made until all Sponsor comments on the proposed publication or presentation have been addressed to the Sponsor's satisfaction.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be outlined in the agreement between each Investigator and the Sponsor or designee.

17. References

Abdelnour E, Jansen MO, Gold JA. ADHD Diagnostic Trends: Increased Recognition or Overdiagnosis? Mo Med. 2022 Sep-Oct;119(5):467-473.

Adler LA, Clemow DB, Williams DW, Durell TM. Atomoxetine Effects on Executive Function as Measured by the BRIEF-A in Young Adults with ADHD: A Randomized, Double-Blind, Placebo-Controlled Study. PLoS One. 2014 Aug 22;9(8):e104175.

Adler LA, Faraone SV, Sarocco P, Atkins N, Khachatryan A. Establishing US norms for the Adult ADHD Self-Report Scale (ASRS-v1.1) and characterizing symptom burden among adults with self-reported ADHD. Int J Clin Pract. 2019;73(1):e13260.

Adler LA, Spencer T, Faraone SV, Kessler RC, Howes MJ, Biederman J, Secnik K. Validity of pilot Adult ADHD Self- Report Scale (ASRS) to rate adult ADHD symptoms. Ann Clin Psychiatry. 2006;18(3):145-148.

Attention-Deficit/Hyperactivity Disorder (ADHD). NIH. Available online: https://www.nimh.nih.gov/health/statistics/attention-deficit-hyperactivity-disorder-adhd (Accessed on 26JUL2023).

Biederman J, Monuteaux MC, Spencer T, Wilens TE, Faraone SV. Do stimulants protect against psychiatric disorders in youth with ADHD? A 10-year follow-up study. Pediatrics. 2009;124(1):71–78.

Borkovec T and Costello E. Efficacy of applied relaxation and cognitive behavioral therapy in the treatment of generalized anxiety disorder. J Clin Consult Psychol. 1993;61(4):611-619.

Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989 May;28(2):193-213.

Faraone SV, Banaschewski T, Coghill D, Zheng Y, et al. The World Federation of ADHD International Consensus Statement: 208 Evidence-based conclusions about the disorder. Neurosci Biobehav Rev. 2021;128:789-818.

Findling RL, Candler SA, Nasser AF, Schwabe S, Yu C, Garcia-Olivares J, O'Neal W, Newcorn JH. Viloxazine in the Management of CNS Disorders: A Historical Overview and Current Status. CNS Drugs. 2021 Jun;35(6):643-653.

Groom MJ and Cortese S. Current Pharmacological Treatments for ADHD. Curr Top Behav Neurosci. 2022;57:19-50.

Guy W, 1976. Clinical global impressions. *ECDEU Assessment manual for Psychopharmacology*, Rockville, MD: US National Institutes of Health, Psychopharmacology Research Branch.

Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959;32:50-55.

Herrmann N, Black S, Lawrence J, Szekely C, Szalai J. The Sunnybrook stroke study: A prospective study of depressive symptoms and functional outcomes. Stroke. 1998; 29:618-624.

Johnson JK, Liranso T, Saylor K, Tulloch G, Adewole T, Schwabe S, Nasser A, Findling RL, Newcorn JH. A Phase II Double-Blind, Placebo-Controlled, Efficacy and Safety Study of SPN-812 (Extended-Release Viloxazine) in Children With ADHD. J Atten Disord. 2020 Jan;24(2):348-358.

Katzman MA, Bilkey TS, Chokka PR, Fallu A, Klassen LJ. Adult ADHD and comorbid disorders: clinical implications of a dimensional approach. BMC Psychiatry. 2017 Aug 22;17(1):302.

Kessler RC, Adler L, Ames M, Demler O, Faraone S, Hiripi E, et al. The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. Psychol Med. 2005;35(2):245-256.

Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, Faraone SV, Greenhill LL, Howes MJ, Secnik K, Spencer T, Ustun TB, Walters EE, Zaslavsky AM. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry. 2006 Apr;163(4):716-723.

Kolar D, Keller A, Golfinopoulos M, Cumyn L, Syer C, Hechtman L. Treatment of adults with attention-deficit/hyperactivity disorder. Neuropsychiatr Dis Treat. 2008 Apr;4(2):389-403.

Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001 Sep;16(9):606-613.

Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord. 2009 Apr;114(1-3):163-173.

Lecrubier Y, Sheehan D, Weiller E, Amorim P, Bonora I, Sheehan K, Janavs J, Dunbar G. The MINI International Neuropsychiatric Interview (M.I.N.I.) A Short Diagnostic Structured Interview: Reliability and Validity According to the CIDI. European Psychiatry. 1997;12: 224-231.

Lee L, Arunajadai S, Mikl J, Erensen JG, Goodman DW. The Burden of Attention-Deficit/Hyperactivity Disorder in Adults: A Real-World Linked Data Study. Prim Care Companion CNS Disord. 2023 Mar 14;25(2):22m03348.

Magnin E and Maurs C. Attention-deficit/hyperactivity disorder during adulthood. Rev Neurol (Paris). 2017 Jul-Aug;173(7-8):506-515.

Maier W, Buller R, Philipp M, Heuser I. The Hamilton Anxiety Scale: reliability, validity and sensitivity to change in anxiety and depressive disorders. J Affect Disord. 1988;14(1):61-68.

Montgomery SA and Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134(4):382-389.

Müller MJ, Szegedi A, Wetzel H, Benkert O. Moderate and severe depression. Gradations for the Montgomery-Asberg Depression Rating Scale. J Affect Disord. 2000 Nov;60(2):137-140.

Nasser A, Liranso T, Adewole T, Fry N, Hull JT, Chowdhry F, Busse GD, Cutler AJ, Jones NJ, Findling RL, Schwabe S. A Phase III, Randomized, Placebo-controlled Trial to Assess the Efficacy and Safety of Once-daily SPN-812 (Viloxazine Extended-release) in the Treatment

of Attention-deficit/Hyperactivity Disorder in School-age Children. Clin Ther. 2020 Aug;42(8):1452-1466.

Nasser A, Liranso T, Adewole T, Fry N, Hull JT, Chowdhry F, Busse GD, Melyan Z, Cutler AJ, Findling RL, Schwabe S. Once-Daily SPN-812 200 and 400 mg in the treatment of ADHD in School-aged Children: A Phase III Randomized, Controlled Trial. Clin Ther. 2021a Apr;43(4):684-700.

Nasser A, Liranso T, Adewole T, Fry N, Hull JT, Busse GD, Chowdhry F, Cutler AJ, Jones NJ, Findling RL, Schwabe S. A Phase 3, Placebo-Controlled Trial of Once-Daily Viloxazine Extended-Release Capsules in Adolescents With Attention-Deficit/Hyperactivity Disorder. J Clin Psychopharmacol. 2021b;41(4):370-380.

Nasser A, Liranso T, Adewole T, Fry N, Hull JT, Chowdhry F, Cutler AJ, Melyan Z, Findling RL, Schwabe S. A Phase 3 Placebo-Controlled Trial of Once-Daily 400-mg and 600-mg SPN-812 (Viloxazine Extended-Release) in Adolescents with ADHD. Psychopharmacol Bull. 2021c Mar 16;51(2):43-64.

Nasser A, Hull JT, Chaturvedi SA, Liranso T, Odebo O, Kosheleff AR, Fry N, Cutler AJ, Rubin J, Schwabe S, Childress A. A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Assessing the Efficacy and Safety of Viloxazine Extended-Release Capsules in Adults with Attention-Deficit/Hyperactivity Disorder. CNS Drugs. 2022 Aug;36(8):897-915.

Pawaskar M, Fridman M, Grebla R, Madhoo M. Comparison of Quality of Life, Productivity, Functioning and Self-Esteem in Adults Diagnosed With ADHD and With Symptomatic ADHD. J Atten Disord. 2020 Jan;24(1):136-144.

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011 Dec;168(12):1266-1277.

Qelbree® (viloxazine extended-release capsules), for oral use. Prescribing Information.

Qelbree® For US Healthcare Professionals only. Available online: https://www.qelbreehcp.com/efficacy/adults (Accessed on 26JUL2023).

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993 Nov;4(5):353-365.

Roth R. M., Isquith P. K., Gioia G. A. Behavior Rating Inventory of Executive Function - Adult Version (BRIEF-A) Lutz, FL: Psychological Assessment Resources; 2005.

Roth RM, Lance CE, Isquith PK, Fischer AS, Giancola PR. Confirmatory factor analysis of the Behavior Rating Inventory of Executive Function-Adult version in healthy adults and application to attention-deficit/hyperactivity disorder. Arch Clin Neuropsychol. 2013 Aug;28(5):425-434.

Schein J, Cloutier M, Gauthier-Loiselle M, Bungay R, Guerin A, Childress A. Symptoms associated with ADHD/treatment-related adverse side effects and their impact on quality of life and work productivity in adults with ADHD. Curr Med Res Opin. 2023 Jan;39(1):149-159.

Shear MK, Vander Bilt J, Rucci P, Endicott J, Lydiard B, Otto MW, Pollack MH, Chandler L, Williams J, Ali A, Frank DM. Reliability and validity of a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH-A). Depress Anxiety. 2001;13(4):166-178.

Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Janavs J, Weiller E, Bonara LI, Keskiner A, Schinka J, Knapp E, Sheehan MF, Dunbar GC. Reliability and Validity of the MINI International Neuropsychiatric Interview (M.I.N.I.): According to the SCID-P. European Psychiatry. 1997; 12:232-241.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22-33;quiz 34-57.

Snaith R, Harrop F, Newby D, Teale C. Grade scores of the Montgomery- Åsberg Depression and the Clinical Anxiety Scales. Brit J Psychiatry. 1986 May; 148:599-601.

Spalding W, Farahbakhshian S, Maculaitis MC, Peck EY, Goren A. The Association of Oral Stimulant Medication Adherence with Work Productivity among Adults with ADHD. J Atten Disord. 2022 Apr;26(6):831-842.

Spencer TJ, Adler LA, Meihua Q, Saylor KE, Brown TE, Holdnack JA, Schuh KJ, Trzepacz PT, Kelsey DK. Validation of the adult ADHD investigator symptom rating scale (AISRS). J Atten Disord. 2010 Jul;14(1):57-68.

Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006 May 22;166(10):1092-1097.

Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA. 1999 Nov 10;282(18):1737-1744.

Spitzer RL, Williams JB, Kroenke K, Hornyak R, McMurray J. Validity and utility of the PRIME-MD patient health questionnaire in assessment of 3000 obstetric-gynecologic patients: the PRIME-MD Patient Health Questionnaire Obstetrics-Gynecology Study. Am J Obstet Gynecol. 2000 Sep;183(3):759-769.

Weibel S, Menard O, Ionita A, Boumendjel M, Cabelguen C, Kraemer C, Micoulaud-Franchi JA, Bioulac S, Perroud N, Sauvaget A, Carton L, Gachet M, Lopez R. Practical considerations for the evaluation and management of Attention Deficit Hyperactivity Disorder (ADHD) in adults. Encephale. 2020 Feb;46(1):30-40.

Williams JBW and Kobak KA. Development and reliability of a structured interview guide for the Montgomery– Åsberg Depression Rating Scale (SIGMA). Brit J Psychiatry. 2008 Jan; 192:52-58.