COVER PAGE – STATISTICAL ANALYSIS PLAN (SAP)

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
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SAP Version:	2.0
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STATISTICAL ANALYSIS PLAN

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Protocol Number	812P413
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Study Medication	Qelbree (viloxazine extended-release capsules, SPN-812)
Study Phase	4
Sponsor	Supernus Pharmaceuticals, Inc. 9715 Key West Avenue Rockville, MD 20850 Phone 301.838.2500
SAP Version No.	2.0
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STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURE PAGE

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LIST OF ABBREVIATIONS

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
CGI-C	Clinical Global Impression of Change Scale
CGI-S	Clinical Global Impression of Severity Scale
ClinRO	Clinician-reported Outcome
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual; Fifth edition
eCRF	Electronic Case Report Forms
EOS	End of Study
ER	Extended-release
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
IA	Inattention
MADRS	Montgomery-Åsberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MINI-AS	Mini-International Neuropsychiatric Interview for ADHD Studies
PHQ-8	Patient Health Questionnaire 8-item
PSQI	Pittsburgh Sleep Quality Index
PT	Preferred Term
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
SOP	Standard Operating Procedure
TEAE	Treatment-emergent Adverse Event
WPAI:SHP	Work Productivity and Activity Impairment: Specific Health Problem Questionnaire

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to outline the planned analyses in the study protocol and to provide detailed statistical methods that will be used for the Clinical Study Report (CSR). This SAP is based on Study Protocol 812P413, version 2.0, dated 25Nov2024.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective and Endpoint

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 ADHD Investigator Symptom Rating Scale (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).

2.2. Secondary Objectives and Endpoints

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.	In the Race category, the total of the non-white subcategories does not match the overall non-white value. Are there any categories that are not included
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.
To evaluate the effect of Qelbree as a monotherapy and/or adjunctive therapy 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.

Secondary Efficacy		
OBJECTIVES	**ENDPOINTS**	**JUSTIFICATION FOR ENDPOINTS**
To evaluate the effect of Qelbree as a monotherapy and/or adjunctive therapy 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 as a monotherapy and/or adjunctive therapy on depressive symptoms in adults with ADHD and comorbid mood symptoms as measured by the clinician-rated Montgomery-Åsberg Depression Rating Scale (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 as a monotherapy and/or adjunctive therapy on anxiety symptoms in adults with ADHD and comorbid mood symptoms as measured by the clinician-rated Hamilton Anxiety Rating Scale (HAM-A) (SIGH-A) and the self-rated General Anxiety Disorder 7-item Scale (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 as a monotherapy and/or adjunctive therapy on aspects of functioning in daily life (work productivity and regular activities) as measured by the Work Productivity and Activity Impairment: Specific Health Problem Questionnaire (WPAI:SHP).	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	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 adjunctive therapy 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.

2.3. Exploratory Objective and Endpoint

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

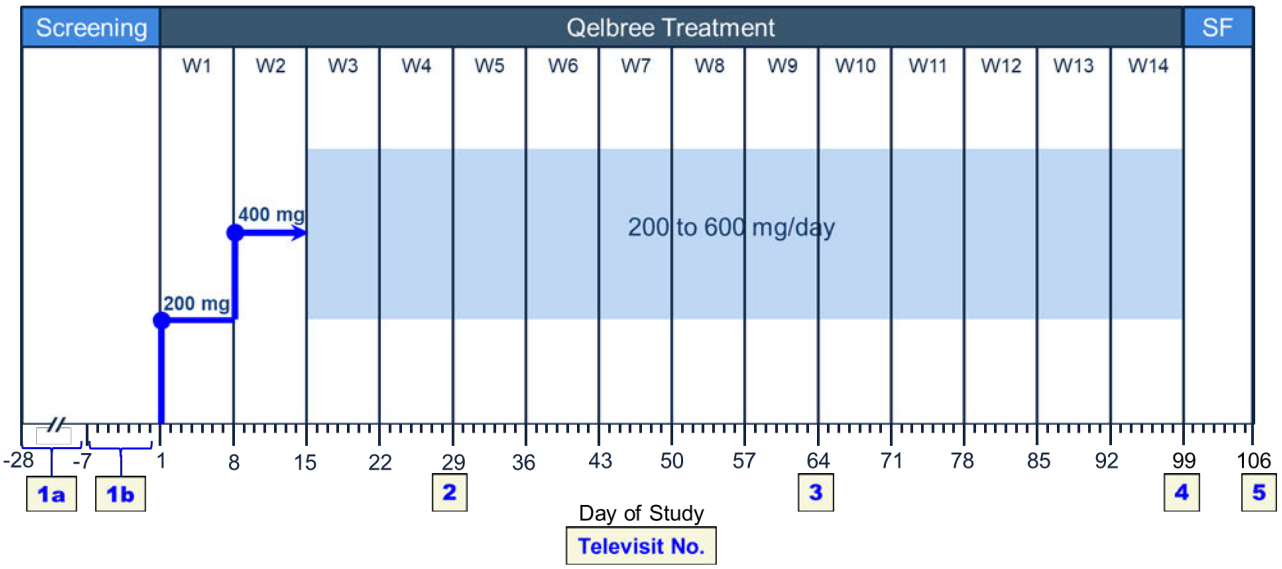
Exploratory		
OBJECTIVES	**ENDPOINTS**	**JUSTIFICATION FOR ENDPOINTS**
[redacted]		

3. STUDY DESCRIPTION

3.1. 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 after each tele-visit with a qualified, trained rater or assessor (Appendix, Table 2).

Figure 1. Protocol Schema



3.2. Schedule of Procedures and Assessments

The Schedule of Procedures and Assessments for the study is presented in Table 1 of the study protocol and it is in Appendix, Table 2 of this document.

3.3. Study Treatment

3.3.1. 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).

3.3.2. Study Treatment Administration

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

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 subject may be instructed to take total daily dose once daily in the evening.

3.4. Randomization

Not applicable for this study.

3.5. Blinding

This is an open label, non-randomized, study; therefore, treatment blinding is not applicable.

3.6. Sample Size

Approximately 750 participants will be dosed in this study, to obtain 500 completed (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.

4. STUDY VARIABLES

4.1. Primary Efficacy Variable

- The primary efficacy variable is the change from baseline (CFB) in **AISRS Total** score by visit. The AISRS consists of 18 items that directly correspond to the 18 symptoms of ADHD and is further subdivided into two subscales: Inattention (9 items) and Hyperactivity/Impulsivity (9 items). The severity of each symptom is rated on a 4-point scale (0-3; where 0 = None, 1 = Mild, 2 = Moderate, and 3 = Severe) based on participants behavior in the past week. The sum of all 18 items yields the Total score (range 0-54). Higher scores indicate more severe ADHD symptoms. A CFB in AISRS Total score <0 represents a better outcome (reduction in ADHD symptoms).

4.2. Secondary Efficacy Variables

The following are the list of secondary efficacy variables.

- CFB in **AISRS Inattention Subscale** score by visit: The sum of all 9 Inattention items (odd numbered items) yields the Inattention Subscale score (range 0-27). Higher scores indicate more severe Inattention symptoms. A CFB in Inattention Subscale score <0 represents a better outcome (reduction in Inattention symptoms).
- CFB in **AISRS Hyperactivity/Impulsivity Subscale** score by visit: The sum of all 9 Hyperactivity/Impulsivity items (even numbered items) yields the Hyperactivity/Impulsivity Subscale score (range 0-27). Higher scores indicate more severe Hyperactivity/Impulsivity symptoms. A CFB in Hyperactivity/Impulsivity Subscale score <0 represents a better outcome (reduction in Hyperactivity/Impulsivity symptoms).
- CFB in **ASRSv1.1-SC Total** score by visit: 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 (9 items) and Hyperactivity/Impulsivity (9 items). Participants rate the frequency of each symptom on a 5-point scale (0-4, where 0 = Never, 1 = Rarely, 2 = Sometimes, 3 = Often, and 4 = Very Often) based on participant's experience in the past week. The sum of all 18 items yields the Total score (range 0-72). Higher scores indicate more severe ADHD symptoms. A CFB in ASRSv1.1-SC Total score <0 represents a better outcome (reduction in ADHD symptoms).
- CFB in **ASRSv1.1-SC Inattention Subscale** score by visit: The sum of all 9 Inattention items (Item #1, 2, 3, 4, 7, 8, 9, 10, 11) yields the Inattention Subscale score (range 0-36). Higher scores indicate more severe Inattention symptoms A CFB in Inattention Subscale score <0 represents a better outcome (reduction in Inattention symptoms).
- CFB in **ASRSv1.1-SC Hyperactivity/Impulsivity Subscale** score by visit: The sum of all 9 Hyperactivity/Impulsivity items (Item #5, 6, 12, 13, 14, 15, 16, 17, 18) yields the Hyperactivity/Impulsivity Subscale score (range 0-36). Higher scores indicate more severe Hyperactivity/Impulsivity symptoms. A CFB in Hyperactivity/Impulsivity Subscale score <0 represents a better outcome (reduction in Hyperactivity/Impulsivity symptoms).

- CFB in **CGI-S** score by visit: The CGI-S scale is a single item clinician's rating of the severity of the ADHD symptoms in relation to the clinician's total experience with subjects with ADHD. The CGI-S is a single item 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. A CFB in CGI-S score <0 represents a better outcome (reduction in severity).
- The **CGI-C** score by visit: The CGI-C scale is a single item clinician's 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.
- CFB in **MADRS Total** Score at Week 14/EOS: The MADRS consists of 10 items. Each item/symptom is rated on a 7-point scale (0 to 6 continuum, where 0=no abnormality to 6=severe). The sum of all 10 items yields the MADRS Total score (range 0 to 60). A total score ranging from 0-6 indicates that the subject is in the normal range (no depression), a score ranging from 7-19 indicates "mild depression", 20 to 34 indicates "moderate depression", a 35 to 60 indicates "severe depression". A CFB in MADRS Total score <0 represents a better outcome (reduction in depression symptoms).
- CFB in **PHQ-8 Total** Score by visit: The PHQ-8 is a 8-item depression module, which the patient scores each on 4-point Likert scale (0-3), where 0 = not at all; 1 = several days, 2 = more than half the days, and 3 = nearly every day. The sum of all 8 items yields the PQH-8 Total score (range 0 to 24). A PHQ-8 Total score ≥10 indicates major depression and ≥20 indicates severe major depression. A CFB in PHQ-8 Total score <0 represents a better outcome (reduction in depression symptoms).
- CFB in **HAM-A Total** Score at Week 14/EOS: The HAM-A consists of 14 items. Each item is rated/scored on a 5-point Likert scale, where 0 = Not present, 1 = Mild, 2 = Moderate, 3 = Severe, and 4 = Very severe. The HAM-A (SIGH-A) Total score is the sum of all 14 items 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." A CFB in HAM-A Total score <0 represents a better outcome (reduction in depression symptoms).
- CFB in **GAD-7 Total** score by visit: The GAD-7 scale is a self-reported 7-item questionnaire for screening and measuring the severity of generalized anxiety disorder. The patient scores each 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 GAD-7 Total Score is the sum of all 7 items ranging from 0 to 21, where a total score of 0 to 4 = None/Minimal anxiety, 5 to 9 = Mild anxiety, 10 to 14 = Moderate anxiety, and ≥ 15 = Severe anxiety. A CFB in GAD-7 Total score <0 represents a better outcome (reduction in anxiety symptoms).

  WPAI:SHP scales will be derived from these 6 questions:

Q1 = currently employed;

Q2 = hours missed due to specified problem;

Q3 = hours missed other reasons;

Q4 = hours actually worked;

Q5 = degree problem affected productivity while working; where 0 = "My ADHD symptoms had no effect on my work" and 10 = "My ADHD symptoms completely prevented me from working"

Q6 = degree problem affected regular activities, other than work at a job; where 0 = "My ADHD symptoms had no effect on my daily activities" and 10 = "My ADHD symptoms completely prevented me from doing my daily activities"

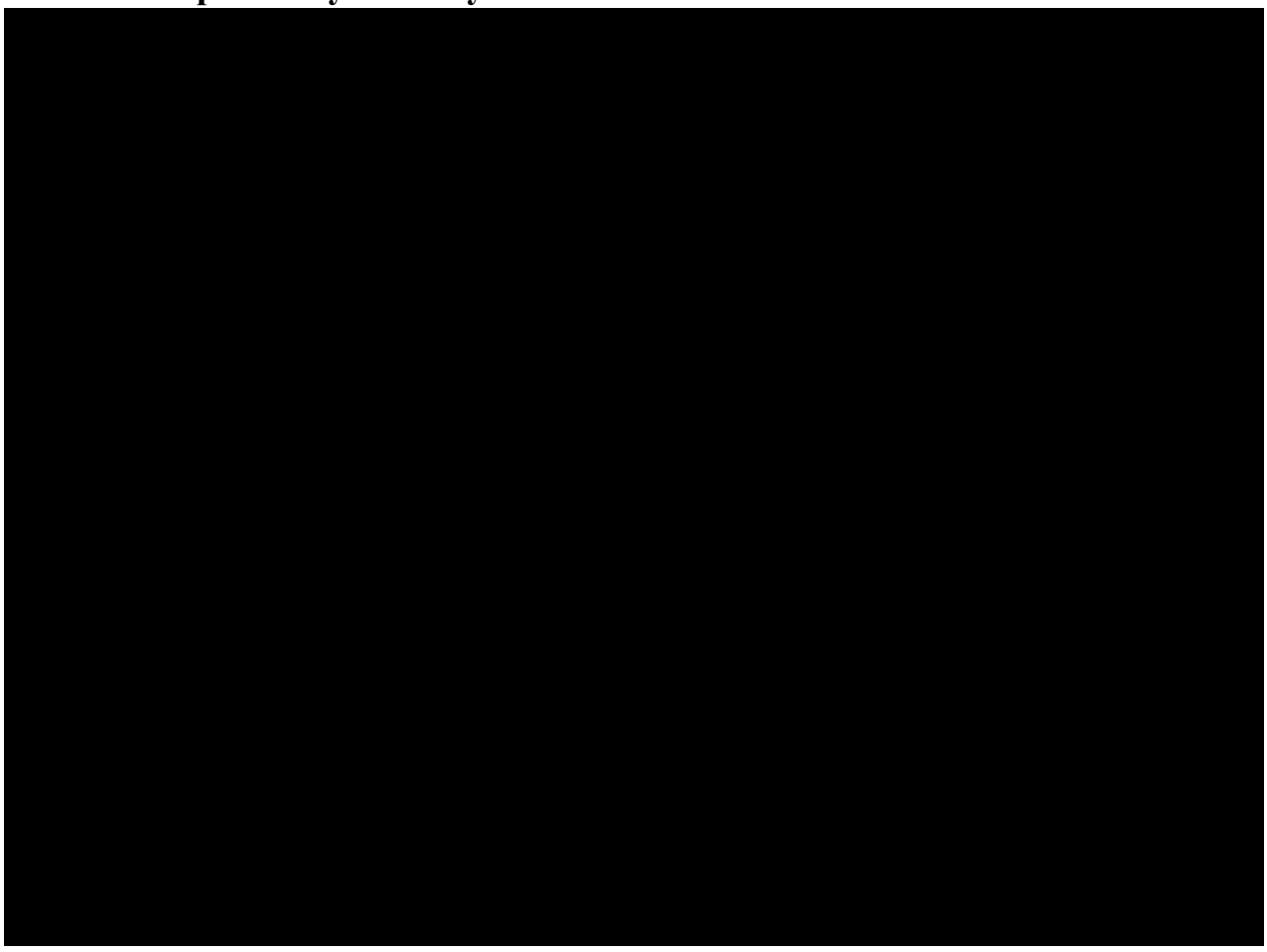
- CFB in **WPAI:SHP Absenteeism** percentage by visit: The WPAI:SHP questionnaire consists of 6 items that ask about the number of hours missed from work or regular activities due to the specific health problem, and the degree of impairment while working or performing regular activities. WPAI outcomes are expressed as impairment percentages. Percent work time missed due to problem (absenteeism) is calculated using the following formula: [Q2/(Q2+Q4)]×100 (range 0 to 100%). A higher percentage indicates greater impairment and less productivity. A CFB in percentage <0 represents a better outcome.
- CFB in **WPAI:SHP Presenteeism** percentage by visit: Percent impairment while working due to problem (presenteeism) is calculated using the following formula: [Q5/10]×100 (range 0 to 100%). A higher percentage indicates greater impairment and less productivity. A CFB in percentage <0 represents a better outcome.
- CFB in **WPAI:SHP Work Productivity** percentage by visit: Percent overall work impairment due to problem is calculated using the following formula: [Q2/(Q2+Q4)+((1-(Q2/(Q2+Q4)))×(Q5/10))]×100 (range 0 to 100%). A higher percentage indicates greater impairment and less productivity. A CFB in percentage <0 represents a better outcome.
- CFB in **WPAI:SHP Regular Activity** percentage by visit: Percent activity impairment due to problem is calculated using the following formula: [Q6/10]×100 (range 0 to 100%). A higher percentage indicates greater impairment and less productivity. A CFB in percentage <0 represents a better outcome.
- **The BRIEF-A** is a standardized 75-item self-rating scale that assesses overall functioning (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. Raw GEC scores, BRI, MI and their subscales (individual scales) will be converted to T-scores (T-score ≥ 65 is considered abnormally elevated) using Appendix A of the BRIEF-A Professional Manual and change from baseline in T-scores will be calculated. A lower change from baseline GEC T-score (<0) represents a better outcome.
- CFB in **BRIEF-A Global Executive Function (GEC)** T-Score at Week 14/EOS:

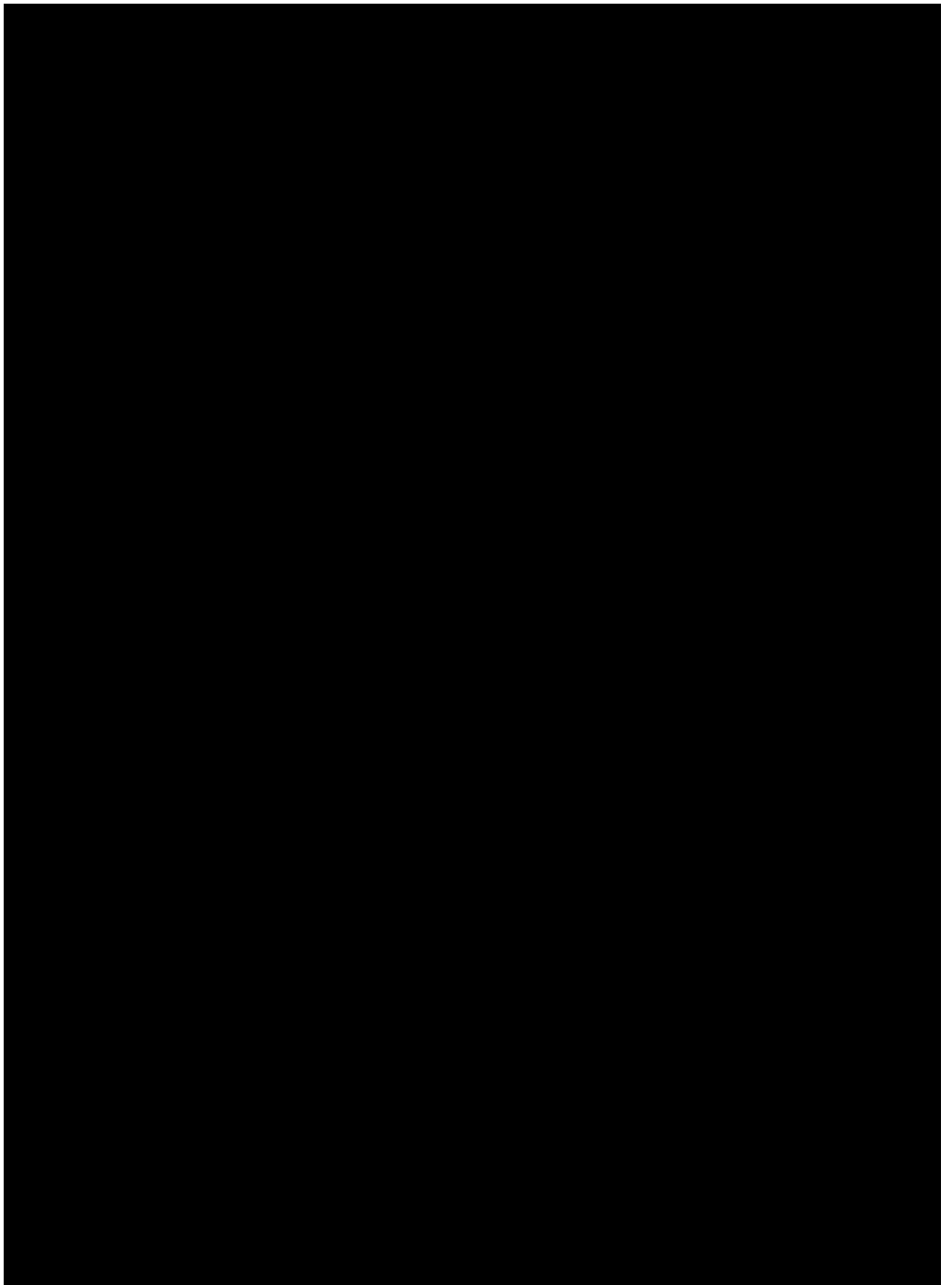
  Behavioral Regulation Index [BRI]) that assess aspects of executive function and problems with self-regulation from the perspective of the individual. Subjects rate each

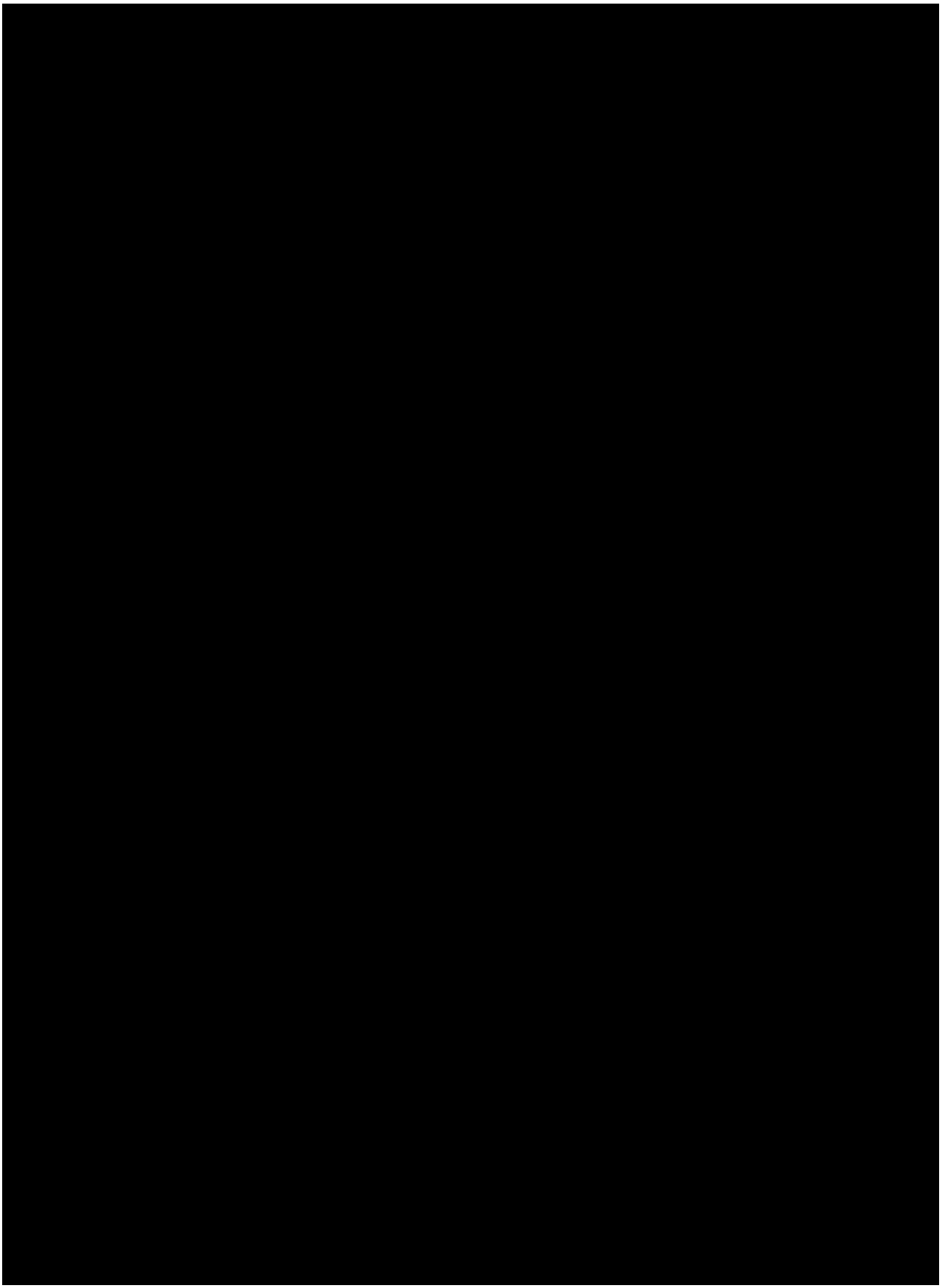
item on a 3-point scale (1=Never, 2=Sometimes, or 3=Often) based on their experience in past month. The sum of 70 items yields the GEC raw score (range: 70-210).

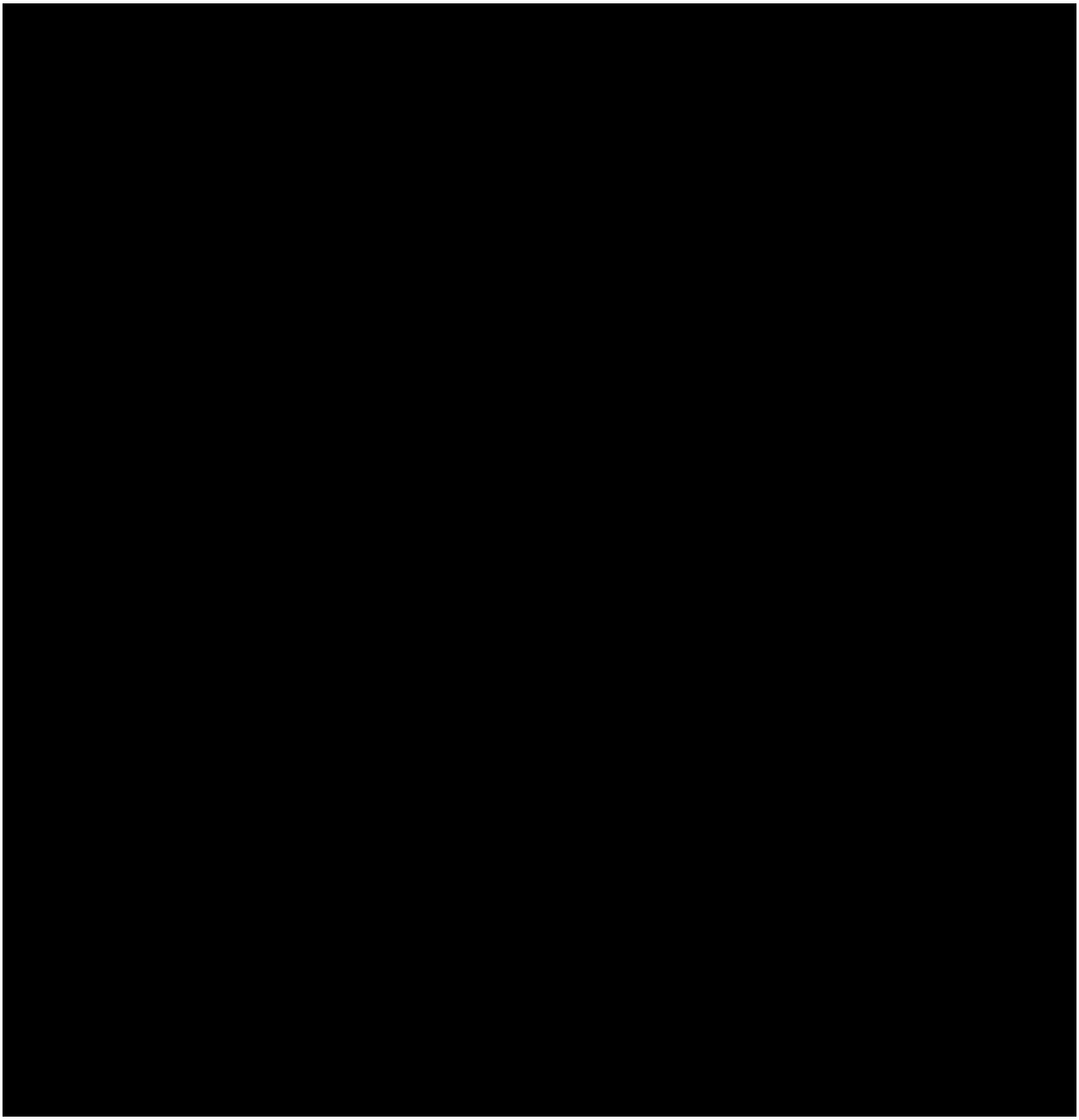
- CFB in the **BRIEF-A Behavioral Regulation Index (BRI)** T-score at Week 14/ EOS: The BRI captures the ability to maintain appropriate regulatory control of one's own behavior and emotional responses. The sum of 30 items yields the BRI raw score (range: 30-90).
- CFB in the **BRIEF-A Metacognitive Index (MI)** T-score at Week 14/ EOS: MI reflects individual's ability to problem solve (includes initiate activity, generate ideas, sustain working memory, plan/organize approaches, monitor success/failure, and organize materials/environment). The sum of 40 items (list can be found in the BRIEF-A manual) yields the MI raw score (range: 40-120).
- CFB in **PSQI Global** score at Week 14/EOS: The PSQI is a 19-item questionnaire that generates a Global score 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 7 areas of sleep. Scoring of the answers is based on a 0 to 3 scale, where a score of 3 reflects the negative extreme on the Likert Scale and 0 better on the individual scales. The sum of all the 7 components scores yields the global score (range 0-21); a global sum of "5" or greater indicates a "poor" sleeper.

4.3. Exploratory Efficacy Variables









5. STATISTICAL CONSIDERATIONS

5.1. General Statistical Methods

All statistical analysis will be performed using SAS version 9.4 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, interquartile range (Q1 and Q3), minimum, and maximum. Standard error may be added if it is needed for the display and interpretation of some efficacy results. Summary statistics for categorical variables will be presented in terms of frequencies and percentages. Participant data listing to support summaries will be provided.

Unscheduled measurements (unless defined as baseline or otherwise specified) will be excluded from descriptive statistics performed by visits in summary tables but will be included in data listings and other analyses that not performed by visit. For assessments that are repeated, unless otherwise specified, the non-missing values from the first assessment will be used for generating summary statistics.

Mean (±SE) profiles and Mean (±SE) CFB for AISRS total score, MADRS, HAM-A and GAD-7 will be plotted by visit.

5.2. Baseline Definitions

Baseline is defined as the last non-missing assessment measured prior to the start of SM.

5.3. Analysis Populations

Safety Population: This includes all subjects who received at least one dose of Qelbree.

Full Analysis Set: This includes a subset of subjects in the Safety Population who have a valid AISRS at baseline (prior to first dose) and at least one valid AISRS post-baseline assessment.

5.4. Adjustments for Covariates

No covariates adjustments analyses are planned for this study.

5.5. Hypotheses and Test Statistic

No formal hypotheses are planned for this study.

5.6. Handling of Missing data

5.6.1. Missing Efficacy Endpoints

Missing efficacy variables will be handled using the following rules:

- For AISRS Total Score and subscales Inattention & Hyperactivity/Impulsivity, if more than 3 items are missing then the total score will be set to missing. If ≤3 items are missing then the values for the missing items will be imputed using the mean of the non-missing items rounded to the nearest integer.
- For ASRSv1.1 Total Score and subscales Inattention & Hyperactivity/Impulsivity, if more than 3 items are missing then the total score will be set to missing. If ≤3 items are missing then the values for the missing items will be imputed using the mean of the non-missing items rounded to the nearest integer.

- For the following scales, if 1 of the individual item score is missing, either the total or subscale score will be set to missing. GAD-7 Total Score, HAM-A Total Score, BRIEF-A GEC Total Raw Score, BRIEF-A BRI Raw Score, BRIEF-A MI Raw Score, all the 9 non-overlapping BRIEF-A subscales.
- For WPAI:SHP, if Q1 = No, questions 2-5 are not applicable. If Q1 = Yes, questions 2 through 6 (Q2-Q6) are not allowed to be missing. If these questions are missing, then any scores calculated using the missing questions are also set to missing. For example, Absenteeism (hours) is derived from questions 2 and 4 (Q2 and Q4), if either Q2 or Q4 is missing, then Absenteeism will be set to missing. The same logic applies to the three-remaining score.
- For PSQI, questions 1 through 9 (Q1-Q9) are not allowed to be missing. If these questions are missing, then any scores calculated using missing questions are also set to missing. For example, "Sleep Latency" is derived based on Q2 and Q5a, if either Q2 or Q5a is missing, the "Sleep Latency" score will be set to missing, and the same logic applies to the other remaining scales. If a range is given for an answer (for example, '30 to 60' is written as the answer to Q2, minutes to fall asleep), use the mean.

5.6.2. Missing Safety Endpoints

Missing dates for AEs or concomitant medications will be imputed as described using the following rules:

- Partial start date:
  - Missing day only: Impute the first dose date if the year and the month of the AE start date are identical to those of the first dose date and also the AE end date is not prior to the first dose date; otherwise, impute the first day of the month.
  - Missing both day and month: Impute the first dose date if the year of the AE start date is identical to the year of the first dose date and also the AE end date is not prior to the first dose date; otherwise impute 1st January.
- Partial end date:
  - Missing day only: Impute/use the last day of the month or the last study date, whichever is earlier.
  - Missing day and month – Impute/use 31st December or the last study date, whichever is earlier.
- Completely missing start and end date or missing year: No imputation will be done.

5.7. Analysis Visit Windows

Unless otherwise specified, data will not be analyzed using visit windows; instead, nominal visits will be used. Each visit per study schedule will be mapped to analysis visit for summary tables. Early termination visits will be mapped to next schedule visit and summarized.

5.8. Interim Analysis

No formal interim analysis is planned for this study.

6. STUDY SUBJECTS AND EXPOSURE

6.1. Subjects Disposition

Subject disposition will be summarized descriptively. It will include tabulations of the number and percentage of subjects in the categories listed below.

- Number of subjects consented
- Number of subjects in the "specified population" (e.g., Safety population)
- Number (%) of subjects who completed the study
- Number (%) of subjects who discontinued study
- Primary reasons of discontinuation may include any of the following
    - Withdrawal of consent
    - Adverse events
    - Lack of efficacy
    - Noncompliance with study procedures
    - Lost to follow-up
    - Other

Inclusion and exclusion criteria met/not met and reasons for screen failures will be summarized in a separate table.

6.2. Protocol Deviations

A protocol deviation is defined as any change, divergence, or departure from the study design or procedures defined in the protocol. An important protocol deviation (IPD) is defined as a protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

Prior to the database lock, PDs recorded in the EDC will be reviewed for the determination of IPDs, these will be summarized descriptively and listed. Protocol deviations will be provided in subject data listings.

6.3. Demographic and Baseline Characteristics

The summaries of demographic data and baseline characteristics will be provided for the Safety Populations. Subject demographic data (age, age group, sex at birth, gender, ethnicity, race, marital status, dependents, residence status, residence duration, level of education, annual household income, student status, employment status [contracted status/not employed status], hours worked per day, hours worked per week, days worked per week, work schedule [same shift/rotating shifts/split shifts]) and baseline characteristics (body weight, height, AISRS, CGI-S, MADRS, HAM-A, PHQ-8, GAD-7, WPAI:SHP, PSQI, and BRIEF-A) will be summarized descriptively.

Baseline Characteristics per ASRSv1.1-SC: The following **ASRS.v1.1-SC** measures at baseline will be included in the Demography and Baseline Characteristics summary table by counts and percentages.

- Total ASRS Score ≥ 24
- ASRS Screener: ADHD Symptoms Present
- ADHD Presentation type (based on ASRS)
    - Hyperactive/Impulsive (HI) ADHD Presentation Type
    - Inattentive (IA) ADHD Presentation Type
    - Combined (HI and IA) ADHD Presentation Type
    - Neither (HI or IA) ADHD Presentation Type

The measures for the ASRS v1.1-SC baseline characteristics will be derived as follows:

Step 1: Transform Ratings for ASRS at Baseline (screening tele-visit):

For Items 1, 2, 3, 9, 12, 16, and 18, ratings of: "Sometimes", "Often", and "Very Often" are assigned a value of 1; "Never" and "Rarely" are assigned a value 0.

For Items 4, 5, 6, 7, 8, 10, 11, 13, 14, 15, and 17, ratings of: "Often" and "Very Often" are assigned a value of 1 "Never", "Rarely", and "Sometimes" are assigned a value of 0.

Step 2: Sum and generate categorical (count and frequencies) summary for the following:

ASRS Screener: ADHD Symptoms Present. Sum transformed items #s 1-6 (range 0-6); Score ≥4 is considered highly consistent with symptoms of ADHD present.

ADHD Presentation Type (based on ASRS):

- HI Subscale = Sum of 9 transformed items: #s 5, 6, 12, 13, 14, 15, 16, 17, 18 (range 0-9); Score ≥6 implies HI is present.
- IA Subscale = Sum of 9 transformed items: #s 1, 2, 3, 4, 7, 8, 9, 10, 11 (range 0-9); Score ≥6 implies: IA is present.
- Summarize number and percentage of subjects with:
    - HI ADHD Presentation Type only at Baseline (HI Score ≥6 and IA Score <6)
    - IA ADHD Presentation Type only at Baseline (HI Score <6 and IA Score ≥6)
    - Combined (HI and IA) ADHD Presentation Type at Baseline (HI Score ≥6 and IA Score ≥6)
    - Neither (HI or IA) present at Baseline (HI Score <6 and IA Score <6)

6.4. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 or the available version at the time of database lock. The number and percent of subjects reporting various medical, family, and psychiatric histories, grouped by system organ class (SOC) and preferred term (PT), will be summarized descriptively for the Safety Population. The table will be sorted by descending frequency of SOC and then PT within SOC.

All medical and psychiatric history will be listed. Nicotine, caffeine, and cannabis/marijuana use and responses on the Reproductive Menstrual Cycle History Questionnaire will be summarized.

6.5. Prior and Concomitant Medication

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD) version Global September 2023, and will be summarized descriptively by

the fourth level anatomical therapeutic chemical (ATC) classification and Preferred Name (PN), if applicable, using counts and percentages for the Safety Population. ATC fourth (ATC4) level is for the chemical, pharmacological or therapeutic subgroup. If an ATC4 level classification is not available for a coded term, the lowest available ATC level code will be substituted.

Prior medications are defined as those taken prior to first dose of study medication. Concomitant medications are those taken on or after start of study medication.

If a medication starts prior to the first dose and continues after the first dose it will be considered both prior and concomitant. Prior and concomitant medications will also be listed.

6.6. Study Treatment Exposure and Compliance

Duration of exposure is defined as the total number of days a subject is exposed to any study medication and defined as:

Duration of Treatment Exposure = date of last dose – date of first dose + 1.

Duration of treatment exposure will be summarized using descriptive statistics and by duration category:

- 1 to <= 29 Days
- 30 to <= 64 Days
- 65 to <= 99 Days
- >=100 Days

Analysis of exposure will also be explored by presenting the exposure using the modal total daily dose (most frequent dose, that is a dose with the longest exposure) over the treatment period. If two or more doses have the same exposure days, the average will be taken. The modal dose will be categorized into the following dosing intervals/groups:

Low, Medium, and High (200 mg, 300 to 400 mg and 500 mg to 600 mg).

This analysis will be repeated by using the “last dose” that a subject was on prior to either completing or discontinuing the study.

The starting date for a new dose will be the date when a subject confirms the receiving of a new shipment of SM.

Compliance:

Percentage compliance will be calculated by the overall treatment period. Percentage compliance will be calculated using the following derivations.

- Total Dispensed Dosage (mg) =Sum of the # of Capsules Dispensed × Dose per Capsule (mg)
- Total Returned Dosage (mg) = Sum of the # of Capsules Returned × Dose per Capsule (mg)
- Total Missed or Lost Dosage (mg) = Sum of the # of Capsules Missed or Lost × Dose per Capsule (mg)
- Total Dose (mg) Taken = Total dispensed dosage (mg) – [Total returned dosage (mg) +

Total missed or lost dosage (mg)]

- Total Planned Dose (mg) = Sum of planned dose (mg) at each day

SM Compliance = [(Total dose taken (mg))/Total planned dose (mg)]×100%.

SM compliance will be summarized descriptively. SM compliance will also be categorized as <80%, 80 to 120%, and >120%. The number and percent of subjects in each compliance category will be summarized descriptively.

7. EFFICACY ANALYSES

All efficacy endpoints will be summarized descriptively using the FAS.

7.1. Primary Efficacy Analysis

The primary efficacy endpoint is CFB in AISRS Total score by visit. The observed and change from baseline in Total score will be summarized by study visit using descriptive statistics. A comparison of Week 14/EOS vs Baseline difference in CFB; a nominal p-value from one sample t-test and associated 95% CI will be presented.

7.2. Secondary Efficacy Analysis

The following secondary endpoints will be analyzed in a similar manner to the primary endpoint. A comparison of Week 14/EOS vs Baseline difference in CFB with a nominal p-value from one sample t-test and associated 95% CI for any of the secondary endpoints may be explored as needed.

- CFB in AISRS Inattention Subscale score by visit
- CFB in AISRS Hyperactivity/Impulsivity Subscale score by visit
- CFB in ASRSv1.1-SC Total score by visit
- CFB in ASRSv1.1-SC Inattention Subscale score by visit
- CFB in ASRSv1.1-SC Hyperactivity/Impulsivity Subscale score by visit
- CFB in CGI-S score by visit
- CGI-C score by visit
- CFB in MADRS Total Score at Week 14/EOS
- CFB in PHQ-8 Total Score by visit
- CFB in HAM-A Total Score at Week 14/EOS
- CFB in GAD-7 Total Score by visit
- CFB in the WPAI:SHP:
    - Absenteeism percentage by visit
    - Presenteeism percentage by visit
    - Work Productivity percentage by visit
    - Regular Activity percentage by visit
- CFB in BRIEF-A T-score at Week 14/EOS for the
    - GEC
    - BRI
    - MI
- CFB in PSQI global score at Week 14/EOS

7.3. Exploratory Efficacy Analysis

8. SAFETY ANALYSES

The assessment of overall safety and tolerability will be based on adverse events, vital signs (blood pressure, pulse rate, and weight) and C-SSRS.

All safety analyses will be performed using the safety population.

8.1. Adverse Events

All adverse events (AEs) will be coded using the MedDRA Version 27.0 or current version.

A treatment-emergent adverse event (TEAE) is defined as an AE with a start date on or after the first dose of study medication, or that worsened in severity following the first dose of study medication. Any event that is present at baseline but worsens in severity will be determined by the Investigator and entered in the eCRF as a new AE. Thus, AEs that occurred on or after the first dose of study medication are TEAEs.

The incidence of TEAEs (number and percent of subjects) will be summarized by System Organ Class (SOC), preferred term (PT), and treatment groups. It will be sorted by decreasing frequency for the overall active treatment groups. A subject with multiple occurrences of an AE with the same PT will be counted only once in the AE category per SOC and PT for summary tables. In addition, for TEAE tables that are summarized by PT and treatment group, the sorting will be based on the decreasing frequency within the PT.

Based on the investigator's determination, the severity of TEAEs will be classified as mild, moderate or severe. For summaries by severity, a patient experiencing multiple AEs in the same PT with different intensities will only be counted once with the maximum severity. If severity is missing, then the maximum severity will be assumed for the analysis (i.e., severity = severe).

The relationship between the study medication and a TEAE is determined by the investigator and will be classified as unrelated (i.e., unlikely related or not related) or related (possibly related, probably related or definitely related). TEAEs with missing relatedness will be counted as definitely related. For summaries by relationship, a patient experiencing multiple AEs in the same PT with different relationship will only be counted once with the most related occurrence.

An overview of TEAEs will include summaries of incidence rates of subjects who had at least one TEAE, serious TEAE, TEAE leading to death, TEAE by maximum severity, TEAE by relationship, TEAE leading to withdrawal of study medication and related serious TEAE.

In addition to the overview of TEAE summary, the following summary tables will be provided:

- Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Most Common (≥ 5%) Treatment-Emergent Adverse Events by Preferred Term
- Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity
- Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Medication
- Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Treatment-Emergent Adverse Events Leading to Withdrawal of Study Medication by System Organ Class and Preferred Term

In addition, listings will be provided for TEAEs, SAEs, TEAEs Leading to Withdrawal of Study Medication, and Deaths. If no SAEs or Deaths occurred, a blank listing with "No SAE (or Deaths) were reported on this study" will be indicated in the listing.

8.2. Vital Signs

8.2.1. Absolute Value and Change from Baseline

Change from baseline in vital sign variables (blood pressure, pulse rate and weight) will be calculated for each post-dose visit.

Observed values and change from baseline will be summarized descriptively by visit.

8.2.2. Shift in Vital Signs

Compared to the reference range, each of the three vital signs variables (diastolic blood pressure, systolic blood pressure and pulse rate) values will be classified as low, normal, high or missing. Shift tables for the change from baseline to all study visits will be summarized using number and percentage of subjects by visit.

Vital sign normal ranges are presented in Table 1.

Table 1. Vital Signs Normal Ranges

Parameter	Low	High
Diastolic blood pressure (mmHg)	60	90
Systolic blood pressure (mmHg)	90	140
Pulse rate	50	100

8.3. Columbia Suicide Severity Rating Scales (C-SSRS)

The number and percentage of subjects with a response of "Yes" by categories for suicidal ideation, suicidal behavior and suicidal ideation or behavior will be summarized descriptively by visit. The listing for C-SSRS will be provided.

9. CHANGES FROM THE PROTOCOL

There are no changes from the planned analyses in the study protocol.

10. REFERENCES

Protocol 812P413 Version 2.0, dated 25NOV2024: 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.

11. APPENDICES

Table 2. Schedule of Procedures and Assessments

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 cut (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/BR 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.