# CLINICAL STUDY PROTOCOL

## *A Randomized, Multicenter, Double-Blind, Flexibly-dosed, Efficacy and Safety Study of Escitalopram in the Treatment of Children and Adolescents With Generalized Anxiety Disorder*

| | |
|---|---|
| **Protocol Number:** | SCT-MD-60 |
| **EudraCT Number:** | Not Applicable |
| **IND Number:** | 058380 |
| **Investigational Product:** | Escitalopram |
| **Phase:** | Phase 3 |
| **Sponsor:** | Allergan<br>5 Giralda Farms<br>Madison, NJ 07940<br>United States |
| **Contract Research Organization:** | Syneos Health<br>1030 Sync Street<br>Morrisville, NC 27560<br>United States |
| **Protocol Date:** | Protocol Version 1.0: 27 Nov 2018<br>Protocol Version 2.0: 15 Mar 2019<br>Protocol Version 3.0: 30 June 2020 |
| **Protocol Version:** | Version 3.0 |

## 1 PROTOCOL APPROVAL SIGNATURES

**Protocol Title:** A Randomized, Multicenter, Double-Blind, Flexibly-dosed, Efficacy and Safety Study of Escitalopram in the Treatment of Children and Adolescents With Generalized Anxiety Disorder

**Protocol Number:** SCT-MD-60

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for current Good Clinical Practice (cGCP) and applicable regulatory requirements.

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In May 2020, AbbVie completed its acquisition of Allergan. Allergan remains sponsor of this study. AbbVie is used for the addressess of sponsor signatories and sponsor personnel.

## 3 SYNOPSIS

**Protocol Number:**

SCT-MD-60

**Title:**

A Randomized, Multicenter, Double-Blind, Flexibly-dosed, Efficacy and Safety Study of Escitalopram in the Treatment of Children and Adolescents With Generalized Anxiety Disorder

**Investigational Product**:

Escitalopram

**Study Centers:**

Approximately 40 centers in the United States

**Phase:**

Phase 3

**Objectives:**

The primary objective of this study is to assess the safety and efficacy of escitalopram relative to placebo in the acute treatment of children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) who meet criteria for generalized anxiety disorder (GAD) as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

The secondary objective of this study is to characterize the pharmacokinetic (PK) profile of escitalopram in the pediatric population (aged 7 through 17 years).

The exploratory objective of this study is to assess the exposure/dose-response relationship.

**Study Design:**

This is a randomized, multicenter, double-blind, flexibly-dosed, placebo-controlled parallel group study.

During the coronavirus disease 2019 (COVID-19) pandemic, remote study visits are possible to avoid missing efficacy data, but not preferred over clinic visits.

**Number of Subjects:**

Approximately 430 subjects will be screened and a total of approximately 256 subjects are planned to be randomized in a 1:1 ratio to either escitalopram or placebo. The randomization schedule will be stratified by age at randomization (grouped as 7–11 years vs. 12–17 years) and sex, and blocked. The sample size may be increased based on the outcome of a blinded interim analysis but the number of subjects in each treatment arm will be capped at 160.

**Treatment:**

Subjects will begin with a 10 mg/day dose of escitalopram (taken orally) or matching placebo for the first 2 weeks of double-blind treatment. At the end of Week 2, subjects who can tolerate the current dose of 10 mg/day may have a dose escalation to 20 mg/day of escitalopram or matching placebo. Dose escalation will be at the investigator's discretion taking into account the Clinical Global Impression of Severity (CGI-S) score. Subjects who remain on the 10 mg/day dose of escitalopram or matching placebo will be evaluated again at Week 4 for a possible dose escalation to 20 mg/day at the investigator's discretion. The dose may be decreased from 20 mg/day to 10 mg/day following discussion with the medical director if the subject does not tolerate the 20 mg/day dose.

**Study Duration:**

The study design incorporates an up to 3-week screening period, an 8-week double-blind, acute treatment period, and a 1-week double-blind down taper period with a follow-up telephone contact 1 week after the end of the double-blind down taper period.

**Study Population:**

Key inclusion criteria:

- Subjects, male or female, must be between 7 and 17 years old, inclusive, at the time of consent/assent and at the Baseline Visit.

- Subject meets DSM-5 criteria for a primary diagnosis of GAD at Screening established by a comprehensive psychiatric evaluation and confirmed/supported using the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI Kid).

- Diagnosis of moderate or greater severity of GAD as determined by the following:

    a. Presence of ≥4 symptoms identified on the generalized anxiety subsection of the Pediatric Anxiety Rating Scale (PARS) symptom checklist, 2 of which are "excessive worry" and "dread or fearful anticipation" (nonspecific) at the Screening and Baseline Visits.

    b. PARS severity score of ≥15 at the Screening and Baseline Visits for symptoms identified on the generalized anxiety subsection of PARS symptom checklist, derived by summing 5 of the 7 severity/impairment/interference items (2, 3 5, 6, and 7).

    c. Clinical Global Impression of Severity (CGI-S) rating of ≥4 at the Screening and Baseline Visits.

- Male subjects who are sexually active with a partner of childbearing potential must use, with their partner, a condom plus an approved method of highly effective contraception from the time of informed consent until 14 days after the last dose of study drug. The following methods are acceptable:

    a. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

        i. oral

        ii. intravaginal

        iii. transdermal

    b. Progestogen-only hormonal contraception associated with inhibition of ovulation

        i. oral

        ii. injectable

        iii. implantable intrauterine device

        iv. intrauterine hormone-releasing system

    c. Surgical sterilization (vasectomy or bilateral tubal occlusion)

- Female subjects who are not of childbearing potential do not need to use any methods of contraception. This includes preadolescent and adolescent females who have not reached menarche.

- Female subjects who are sexually active and are of childbearing potential must use, with their partner, an approved method of highly effective contraception from the time of informed consent until 14 days after the last dose of study drug. In this patient population, a subject would be

considered sexually active if they participate in any behaviors which may result in pregnancy. The following methods are acceptable:

a. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation and a barrier method (ie, condom for male partner):
    i. oral
    ii. intravaginal
    iii. transdermal

b. Progestogen-only hormonal contraception associated with inhibition of ovulation and a barrier method (ie, condom for male partner):
    i. oral
    ii. injectable
    iii. implantable intrauterine device
    iv. intrauterine hormone-releasing system

c. Surgical sterilization (vasectomy or bilateral tubal occlusion)

- Strict abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, they, with their partner, must comply with the contraceptive requirements detailed above.

- Female subjects of childbearing potential must have a negative serum beta-human chorionic gonadotropin pregnancy test at the Screening Visit, a negative urine pregnancy test at the Baseline Visit, and must not be breastfeeding.

- Subject must be in general good health, weigh at least 20 kg and be within the 3rd to 97th percentile for gender specific body mass index (BMI)-for-age from the Centers for Disease Control and Prevention growth charts at the Screening and Baseline Visits.

Key exclusion criteria:

- Current diagnosis of a major depressive episode, or lifetime diagnosis of attention-deficit/hyperactivity disorder, bipolar disorder, psychotic depression, schizophrenia or other psychotic disorder, feeding and/or eating disorder, obsessive-compulsive disorder, conduct disorder, oppositional defiant disorder, post-traumatic stress disorder, panic disorder, or pervasive development disorder.

- Suspected or previously diagnosed intellectual disability disorder.

- DSM-5-defined substance use disorder within a year (12 months) prior to Screening Visit.

- Any secondary DSM-5 disorder that requires pharmacologic treatment or would be a potential confound to the study assessments or ability to participate in all study procedures, as determined by the investigator.

- Environmental stressor (current or historic – eg, history of abuse/trauma, significant change in psychosocial status, significant injury) that, in the opinion of the investigator, may confound assessments or subject's ability to complete all protocol requirements.

- One or more first-degree relatives with diagnosed bipolar I disorder.

- Subject answers "yes" to "Suicidal Ideation" item 3 (active suicidal ideation with any methods, not plan, without intent to act), item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) within the past 6 months and/or a lifetime history of suicidal behavior, as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS).
- Subject is currently considered at risk for suicide in the opinion of the investigator.
- Lack of response to 2 or more adequate trials of antidepressants or other anti-anxiety medications at a clinically appropriate dose for a minimum of 4 weeks for GAD at the time of screening or, in the judgement of the investigator, the patient had treatment-resistant GAD.
- Change to psychotherapy (start, stop, or change in type, intensity, or frequency) in the 6 weeks prior to the Screening Visit.
- History of seizure disorder (other than febrile seizures).
- History of electroconvulsive therapy at any time during the subject's lifetime.
- Serious or unstable medical illness, or clinically significant laboratory or electrocardiogram (ECG) result that, in the opinion of the investigator, would compromise participation in the study, confound results, or be likely to lead to hospitalization during the course of the study.
- Hypo- or hyperthyroidism, unless stabilized on appropriate pharmacotherapy with no change in dosage for at least 3 months before the Screening Visit. If thyroid-stimulating hormone (TSH) is abnormal, the subject must have a normal triiodothyronine (T3) and thyroxine (T4).
- Use of biotin as a dietary supplement at more than 2.5 mg total per day within 7 days of the Screening Visit.
- Initiated or discontinued hormone therapy (including oral contraceptives for female subjects) within 3 months prior to screening.
- Taking any medications that are contraindicated to escitalopram (escitalopram oxalate).
- Treatment with any investigational drug within 30 days or 5 half-lives (whichever is longer) prior to study entry.

**Primary Endpoint:**

The primary efficacy endpoint is the change from baseline to acute treatment endpoint (Week 8) in the PARS severity score.

The PARS severity score for GAD is assessed for all symptoms identified in the generalized anxiety section of the PARS symptom checklist. The PARS severity score for GAD will be derived by summing 5 of 7 severity/impairment/interference items (2, 3, 5, 6, and 7).

**Secondary Endpoints:**

The secondary efficacy endpoints are as follows:

- Response rate on the PARS at acute treatment endpoint (Week 8)
    - Response is defined as a 50% improvement on the PARS severity score for GAD.
- Remission rate on the PARS at acute treatment endpoint (Week 8)

  - Remission is defined as PARS severity score for GAD ≤8 (using 6 PARS items: 2, 3, 4, 5, 6, and 7)
- Change on the CGI-S from baseline to acute treatment endpoint (Week 8)
  - Remission rate on CGI-S at acute treatment endpoint (Week 8). Remission rate is defined as the percentage of subjects having a CGI-S score ≤2 at endpoint.
- Change on the Children's Global Assessment Scale (CGAS) from baseline to acute treatment endpoint (Week 8)
  - Remission rate on the CGAS at acute treatment endpoint (Week 8). Functional remission is defined as CGAS >70.
- COVID-19 impact assessment score at each visit.

The safety endpoints during the double-blind treatment period are as follows:

- Incidence of treatment-emergent adverse events.
- Observed values and change from baseline in vital signs (blood pressure, pulse rate, temperature, respiration rate, height, weight, BMI, height percentile, weight percentile, and BMI percentile); incidence of vital sign potentially clinically significant (PCS) values.
- Observed values and changes from baseline in ECG intervals and interpretation; incidence of ECG PCS values.
- Observed values and changes from baseline in clinical laboratory assessments (hematology, chemistry, and urinalysis); incidence of clinical laboratory PCS values.
- Incidence of suicidal ideation and/or suicidal behavior as determined by the C-SSRS.

The PK endpoint is as follows:

- PK parameters of escitalopram using a nonlinear mixed effects approach.

The exposure/dose-response endpoints are as follows:

- Relationship between efficacy parameters and plasma exposure using a nonlinear mixed effects approach. The relationship between safety parameters and plasma exposure may also be explored.

**Efficacy Assessments:**

The efficacy assessments include the PARS severity score for GAD, CGI-S, the CGAS, and a global COVID-19 impact assessment.

**Safety Assessments:**

The safety assessments include adverse events, vital signs, physical examination, ECGs, laboratory assessments, and the C-SSRS.

**Pharmacokinetic Assessments:**

Plasma concentrations of escitalopram and S-demethylcitalopram.

**Statistical Analysis:**

For the analysis of the primary efficacy endpoint (change from baseline in PARS severity score), a mixed model for repeated measures (MMRM) will be used for the comparison of escitalopram to placebo at Week 8. The significance test for the difference in means at Week 8 will be based on least squares means using a 2-sided α of 0.05.

The secondary efficacy endpoints of response rate on the PARS, and remission rates on the PARS, CGI-S, and CGAS, will be analyzed using a repeated measures model for categorical outcomes. The change from baseline in CGI-S and CGAS will be analyzed using the same methodology described for the primary efficacy endpoint. The COVID-19 impact assessment score will be summarized at each visit.

The safety endpoints will be analyzed descriptively.

PK parameters of escitalopram will be derived using a nonlinear mixed effects approach. The exposure/dose-response relationship for efficacy and potentially safety parameters will be explored using a nonlinear mixed effects approach.

## 4 TABLE OF CONTENTS

## 5 LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| AST | aspartate aminotransferase |
| AUC | area under the plasma concentration-time curve |
| BMI | body mass index |
| CDC | Centers for Disease Control and Prevention |
| CGAS | Children's Global Assessment Scale |
| cGCP | current Good Clinical Practice |
| CGI-S | Clinical Global Impression of Severity |
| Cmax | maximum plasma concentration |
| COVID-19 | coronavirus disease 2019 |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| FDA | Food and Drug Administration |
| GAD | generalized anxiety disorder |
| ICF | informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IRB | institutional review board |
| IXRS | Interactive Response System |
| LOCF | last observation carried forward |
| LS | least squares |
| MDD | major depressive disorder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MINI Kid | Mini-International Neuropsychiatric Interview for Children and Adolescents |
| mITT | modified Intent-to-Treat |
| MMRM | mixed-effects model for repeated measures |
| MMRM-CAT | categorical MMRM |
| n | number of observations |
| NEAE | newly emergent adverse event |
| PARS | Pediatric Anxiety Rating Scale |
| PCS | potentially clinically significant |
| PK | pharmacokinetic |
| PT | preferred term |
| QTcB | Bazett's correction of QT interval |
| QTcF | Fridericia's correction of QT interval |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SID | subject identification |
| SOC | system organ class |
| SSRI | selective serotonin reuptake inhibitor |
| SUSAR | suspected unexpected serious adverse reaction |
| T3 | triiodothyronine |

| | |
|---|---|
| T4 | thyroxine |
| TEAE | treatment-emergent adverse event |
| TSH | thyroid-stimulating hormone |
| ULN | upper limit of normal |
| WHO | World Health Organization |

## 6 INTRODUCTION

Generalized anxiety disorder (GAD) is one of the most frequently occurring childhood anxiety disorders[1]. In the United States, an estimated 2.2% of adolescents (aged 13 through 18 years) had GAD, with an estimated 0.9% having severe impairment based on data published in 2010. The prevalence of GAD among adolescents was higher for females (3.0%) than for males (1.5%)[2].

An anxiety disorder such as GAD in children and adolescents increases the risk for substance abuse and suicidal ideation and suicide attempts, and also increases the risk for anxiety or depressive disorders in adulthood[3,4,5]. However, anxiety disorders are often untreated in children and adolescents[6].

There is increasing evidence to suggest that selective serotonin reuptake inhibitors (SSRIs) are effective treatments for youth with GAD and are generally well tolerated[7].

Escitalopram, the S-enantiomer of racemic citalopram, is an SSRI primarily responsible for the serotonin reuptake inhibition produced by citalopram. Escitalopram binds preferentially to the serotonin transporter and has very low or no affinity for neurotransmitter receptors or for the dopamine and norepinephrine transporters. The mechanism of antidepressant action of escitalopram is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from its inhibition of central nervous system neuronal reuptake of serotonin (5-hydroxytryptamine).

Five clinical studies evaluating the efficacy and safety of escitalopram in adult patients with GAD have been completed. Three of the 5 studies were placebo-controlled; one was an open-label extension study; and one was a relapse-prevention study. The efficacy of escitalopram in the acute treatment of GAD was demonstrated in the three, 8-week, flexible-dose, placebo-controlled studies. In all 3 studies, escitalopram showed statistically significant greater mean improvement compared to placebo on the Hamilton Anxiety Scale. Results from the relapse-prevention study showed that treatment with escitalopram at 20 mg/day significantly reduced the risk of relapse of GAD.

The most commonly observed adverse reactions in the placebo-controlled double-blind studies in adult escitalopram patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia.

Escitalopram has not been evaluated in pediatric patients in clinical studies in GAD. In pediatric patients (aged 6 through 17 years) in studies in major depressive disorder (MDD), the overall profile of adverse reactions was generally similar to that seen in adult studies. However, the following adverse reactions were reported at an incidence of at least 2% for escitalopram and greater than placebo: back pain, urinary tract infection, vomiting, and nasal congestion.

The single- and multiple-dose pharmacokinetics (PK) of escitalopram are linear and dose-proportional in a dose range of 10 to 30 mg/day. The mean terminal half-life is about 27 to 32 hours. Following a single oral dose (20 mg tablet or solution) of escitalopram, peak blood levels occur at about 5 hours. With once-daily dosing, steady state plasma concentrations are achieved within approximately one week. Escitalopram is metabolized to S-demethylcitalopram and S-didemethylcitalopram. At steady state, the concentration of S-demethylcitalopram in plasma is approximately one-third that of escitalopram. The level of S-didemethylcitalopram was not detectable in most subjects[8].

In a single-dose study of 10 mg escitalopram, the area under the plasma concentration-time curve (AUC) of escitalopram decreased by 19%, and the maximum plasma concentration (Cmax) increased by 26% in healthy adolescent subjects (12 to 17 years of age) compared to adults[8]. Following multiple dosing of 40 mg/day citalopram, steady state Cmax and AUC were similar in adolescent patients with MDD (12 to 17 years of age) compared to adult patients[8].

Escitalopram is approved in the United States (under the trade name Lexapro®) for the acute and maintenance treatment of MDD in adults (aged 18 through 65 years) and adolescents (aged 12 through 17 years) and the acute treatment of GAD in adults at once-daily doses of 10 to 20 mg. Outside the United States, escitalopram is approved for the treatment of MDD, GAD, panic disorder, obsessive-compulsive disorder, and social anxiety disorder under the trade names Cipralex® and Esertia® at a dosage of 5 to 20 mg/day.

The United States Food and Drug Administration (FDA) required a Post-Marketing Requirement (PMR) study in the pediatric population for the treatment of GAD under the Pediatric Research Equity Act (PREA).

The current study is designed to evaluate the safety, efficacy, and PK of (10 to 20 mg/day) escitalopram in pediatric subjects (aged 7 through 17 years) for the treatment of GAD.

For further details of nonclinical and clinical studies, PK, and toxicology, please see the package insert for escitalopram[8].

# 7 STUDY OBJECTIVES

## 7.1 Primary Objective

The primary objective of this study is to assess the safety and efficacy of escitalopram relative to placebo in the acute treatment of children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) who meet criteria for GAD as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

## 7.2 Secondary Objective

The secondary objective of this study is to characterize the PK profile of escitalopram in the pediatric population (aged 7 through 17 years).

## 7.3 Exploratory Objective

The exploratory objective of this study is to assess the exposure/dose-response relationship.

# 8 INVESTIGATIONAL PLAN

## 8.1 Overall Study Design and Plan: Description

This is a randomized, multicenter, double-blind, flexibly-dosed, placebo-controlled parallel group study of escitalopram in the treatment of children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) with GAD.

The study design incorporates an up to 3-week screening period, an 8-week double-blind, acute treatment period, and a 1-week double-blind down taper period.

Approximately 430 subjects will be screened and a total of approximately 256 subjects are planned to be randomized in a 1:1 ratio to either escitalopram or placebo. The randomization schedule will be stratified by age at randomization (grouped as 7-11 years vs. 12–17 years) and sex, and blocked.

Subjects will begin with a 10 mg/day dose of escitalopram (taken orally) or matching placebo for the first 2 weeks of double-blind treatment. At the end of Week 2, subjects who can tolerate the current dose of 10 mg/day may have a dose escalation to 20 mg/day of escitalopram or matching placebo. Dose escalation will be at the investigator's discretion taking into account the Clinical Global Impression of Severity (CGI-S) score. Subjects who remain on the 10 mg/day dose of escitalopram or matching placebo will be evaluated again at Week 4 for a possible dose escalation to 20 mg/day at the investigator's discretion. Dose escalations cannot be made at any other time during the study. The dose may be decreased from 20 mg/day to 10 mg/day following discussion with the medical director if the subject does not tolerate the 20 mg/day dose. At the end of the treatment period or at early withdrawal, subjects will enter a 1-week double-blind down taper period with a follow-up telephone contact 1 week after the end of the double-blind down taper period.

A blinded interim analysis will be conducted when 75% of randomized subjects have either completed or discontinued the study in order to check the assumptions in the sample size calculation. Based on this, the sample size may be increased to ensure an adequate power. However, due to the difficulties in recruiting pediatric subjects with GAD, the number of subjects in each treatment arm will be capped at 160.

The study design is shown in Figure 1.

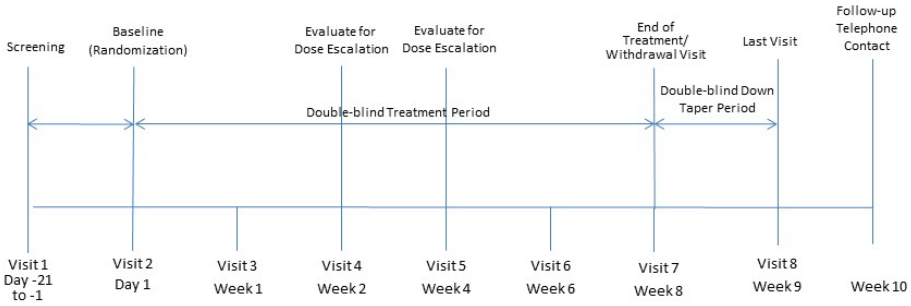
The coronavirus disease 2019 (COVID-19) pandemic (and any other naming conventions used) developed after this study began and this protocol has been amended to account for study procedures that need to be modified in association with adhering to local safety guidelines or regulations.

During the COVID-19 pandemic, remote study visits, in which data are collected via telephone or videoconference, are possible but not preferred. Nearly all scheduled safety assessments, with exception of the Columbia-Suicide Severity Rating Scale (C-SSRS), are not possible by remote visit and must be collected in person via clinic visits. To

accommodate changes sites may need to implement during the pandemic, Section 8.1.2 outlines the conduct of study assessments during in-clinic visits, which is the preferred method of conducting the study, while study assessments for remote visits are included in Section 8.1.3.

### 8.1.1 Study Design

**Figure 1 Flow Chart of the Study**



### 8.1.2 Schedule of Assessments

| Period | Screening Period | Double-blind Acute Treatment Period | | | | | | Double-blind Down Taper Period | Follow-up |
|---|---|---|---|---|---|---|---|---|---|
| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7/ET[a] | 8[b] | Telephone Contact |
| Day/Week | Day -21 to -1 | Baseline Day 1 | Week 1[c] | Week 2[c] | Week 4[c] | Week 6[c] | Week 8/ET[c] | Week 9[c] | Week 10[c] |
| Subject Informed Consent/Assent | X | | | | | | | | |
| Parent Informed Consent | X | | | | | | | | |
| Inclusion/Exclusion Criteria | X | X | | | | | | | |
| Demographics | X | | | | | | | | |
| Medical History | X | | | | | | | | |
| Psychiatric History | X | | | | | | | | |
| Medication History | X | | | | | | | | |
| MINI Kid | X | | | | | | | | |
| Physical Examination | X | | | | | | X | | |
| Body Mass Index (BMI) | X | | | | X | | X | | |
| Randomization | | X | | | | | | | |
| Vital Signs[d] | X | X | X | X | X | X | X | X | |
| Electrocardiogram (ECG) | X | | | | | | X | | |
| Urine Drug Screen | X | | | | | | X | | |
| Screen for HBsAg, HCVAb, HIV | X | | | | | | | | |
| Clinical Chemistry including Thyroid | X[e] | | | | | | X | | |
| Hematology | X | | | | | | X | | |
| Urinalysis | X | | | | | | X | | |
| Pregnancy Test[f] | X | X | | | | | X | | |
| C-SSRS | X | X | X | X | X | X | X | X | |
| CGAS | X | X | X | X | X | X | X | | |
| PARS | X | X | | X | | | X | | |
| CGI-S | X | X | | X | | | X | | |
| Global COVID-19 Impact Assessment[g] | X | X | X | X | X | X | X | | |
| Evaluate for Dose Escalation[h] | | | | X | X | | | | |
| PK Blood Samples[i] | | | | | X | | X | | |
| Dispense Study Drug | | X[j] | X | X | X | X | X | | |
| Study Drug Accountability | | | X | X | X | X | X | X | |
| Adverse Events | | ◄---------- | | | | | | | ----------► |

| Period | Screening Period | Double-blind Acute Treatment Period | | | | | | Double-blind Down Taper Period | Follow-up |
|---|---|---|---|---|---|---|---|---|---|
| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7/ET[a] | 8[b] | Telephone Contact |
| Day/Week | Day -21 to -1 | Baseline Day 1 | Week 1[c] | Week 2[c] | Week 4[c] | Week 6[c] | Week 8/ET[c] | Week 9[c] | Week 10[c] |
| Concomitant Medications | ◄---------- | | | | | | | | ----------► |

Abbreviations: BMI = body mass index; CGAS = Children's Global Assessment Scale; CGI-S = Clinical Global Assessment of Severity; COVID-19 = coronavirus disease 2019; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ET = End of Treatment; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; HIV = human immunodeficiency virus; MINI Kid = Mini-International Neuropsychiatric Interview for Children and Adolescents; PARS = Pediatric Anxiety Rating Scale; PK = pharmacokinetic.

[a] End of Treatment or Early Withdrawal.

[b] If a site becomes aware of any adverse events after study completion (occurring outside of a defined study visit, including any contact up to 30 days after receiving the last dose of study drug), all adverse events reported by the patient or patient representative or observed or otherwise identified by the investigator or other study personnel must be documented.

[c] Visit window ± 3 days. Refer to Section 8.2.2.1, Table 1 for visit windows for safety assessments (physical examination, BMI, vital signs, ECG, urine drug screen, clinical chemistry including thyroid, hematology, urinalysis, pregnancy test) and/or PK assessments missed due to remote visits.

[d] Vital signs (blood pressure, pulse rate, temperature, and respiration rate) will be recorded at every visit. Height and weight will be recorded at Visit 1 (Screening), Visit 5 (Week 4), and Visit 7 (Week 8/ET) only.

[e] Fasting blood sample.

[f] A serum pregnancy test will be performed at Visit 1 (Screening); a urine pregnancy test will be performed at Visit 2 (Baseline) and Visit 7 (Week 8/ET) for females of childbearing potential.

[g] To be completed last after all other study assessments.

[h] Subjects who can tolerate the current dose of 10 mg/day may have a dose escalation to 20 mg/day at the investigator's discretion taking into account the CGI-S score.

[i] For PK blood sampling for assented/consented subjects at Visit 5 (Week 4) and Visit 7 (Week 8/ET), 2 blood samples per subject will be collected at each of these visits for escitalopram and S-demethylcitalopram analysis at the following times: Visit 5 (Week 4): for subjects receiving dose in the morning, at 0 h (predose) and ≥ 1 h postdose and for subjects receiving dose in the evening, 2 samples at random times during the visit (ie, postdose from the dose received the previous evening), collected at least 2 hours apart from each other; and Visit 7 (Week 8/ET): 2 samples at random times during the visit (ie, postdose from the dose received in the morning or the previous evening), collected at least 2 hours apart from each other.

[j] Subjects should take their first dose of study drug in clinic.

### 8.1.3 Schedule of Assessments that Can Be Done Remotely

| Period | Double-blind Acute Treatment Period | | | | | | Double-blind Down Taper Period | Follow-up |
|---|---|---|---|---|---|---|---|---|
| Visit | 2 | 3 | 4 | 5 | 6 | 7/ET[a] | 8[b] | Telephone Contact |
| Day/Week | Baseline Day 1 | Week 1[c] | Week 2[c] | Week 4[c] | Week 6[c] | Week 8/ET[c] | Week 9[c] | Week 10[c] |
| Inclusion/Exclusion Criteria | X | | | | | | | |
| Randomization | X | | | | | | | |
| C-SSRS | X | X | X | X | X | X | X | |
| CGAS | X | X | X | X | X | X | | |
| PARS | X | | X | | | X | | |
| CGI-S | X | | X | | | X | | |
| Global COVID-19 impact assessment[d] | X | X | X | X | X | X | X | |
| Evaluate for Dose Escalation[e] | | | X | X | | | | |
| Dispense Study Drug[f] | X[g] | X | X | X | X | X | | |
| Study Drug Accountability | | X | X | X | X | X | X | |
| Adverse Events | ◄---------- | | | | | | | ----------► |
| Concomitant Medications | ◄---------- | | | | | | | ----------► |

Abbreviations: CGAS = Children's Global Assessment Scale; CGI-S = Clinical Global Assessment of Severity; COVID-19 = coronavirus disease 2019; C-SSRS = Columbia-Suicide Severity Rating Scale; ET = End of Treatment; PARS = Pediatric Anxiety Rating Scale; PK = pharmacokinetic.

Notes for Remote Study Visits:

- The Baseline Visit can be remote but it is not preferred. For all female subjects of childbearing potential, the Baseline Visit must take place as an in-clinic visit with all assessments outlined in Section 8.1.2.
- Subject data are collected via telephone or telehealth video calls using a technology provider (see Appendix 17.3). Sites should remain consistent with either methods (video or telephone) for each subject.
- In-clinic safety and PK assessments missed due to remote visits may be collected per Section 8.2.2.1, Table 1.

[a] End of Treatment or Early Withdrawal.

[b] If a site becomes aware of any adverse events after study completion (occurring outside of a defined study visit, including any contact up to 30 days after receiving the last dose of study drug), all adverse events reported by the patient or patient representative or observed or otherwise identified by the investigator or other study personnel must be documented.

[c] Visit window ± 3 days.

[d] To be completed last after all other study assessments.

[e] Subjects who can tolerate the current dose of 10 mg/day may have a dose escalation to 20 mg/day at the investigator's discretion taking into account the CGI-S score.

[f] For remote visits study drug will be sent to subjects via curbside (preferred) or courier.

[g] In case of a remote Baseline Visit, subjects will receive and take their first dose of study drug via curbside (preferred) or they will receive it by courier and take it at home.

## 8.2 Discussion of Study Design

### 8.2.1 Study Design

This study will be performed in pediatric subjects (aged 7 through 17 years) with GAD in order to assess safety and efficacy in this patient population.

In order to standardize the subject population and to make it as homogeneous as possible, all subjects must meet the DSM-5 criteria for diagnosis of GAD and have at least moderate severity of GAD assessed using standard rating scales. In addition, the randomization schedule will be stratified so that there is treatment balance within the age group and sex group strata.

There is a known placebo effect in this indication[9] so this study will use a parallel-group design with a placebo-control arm. As some of the endpoints (eg, safety, clinical assessments) are potentially subjective, this study will be performed in a double-blind manner.

Subjects randomized to the escitalopram treatment arm will receive escitalopram at an initial dose of 10 mg/day with the possibility to increase the dose to 20 mg/day after 2 weeks and 4 weeks. The dose can only be increased if the subject tolerates the current dose. Further details on the selection of doses in this study are provided in Section 8.4.5.

A double-blind treatment period of 8 weeks was selected because it is expected to see a treatment effect within this period and the efficacy of escitalopram in the treatment of GAD beyond 8 weeks has not been systematically studied. The study includes a 1-week double-blind down taper period at the End of Treatment to minimize symptoms associated with discontinuation of escitalopram.

Analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal ideation and behavior (suicidality) in children, adolescents, and young adults (aged 18 through 24 years) with MDD and other psychiatric disorders. In order to monitor this, the C-SSRS will be completed at the Screening, Baseline, and each study visit (see Section 10.1.2.1 for further details).

### 8.2.2 Quality Management and Risk Evaluation

This protocol was evaluated to identify risks to those processes and data that are critical to assure human subject protection and reliability of study results. To mitigate these risks, on-site and remote risk-based monitoring standard operating procedures will be employed to ensure site compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) current Good Clinical Practice (cGCP). Concurrent medical review by the contract research organization represents an integral component of the study's centralized monitoring

activities by monitoring subject safety and ensuring scientific integrity of the study data through the assessment of critical study data identified during the risk assessment for the study. Issues identified during on-site or remote monitoring or during medical review that may affect subject safety, data quality and/or the study's scientific integrity will be communicated to the study team triggering increased frequency of site communication until issues are remediated.

#### 8.2.2.1 COVID-19 Specific Processes

To promote subject safety and data quality during the COVID-19 pandemic, the following processes will be implemented:

- Exclusion of subjects whose anxiety is significantly impacted by COVID-19 as assessed by investigator (see Section 8.3.3).
- Global COVID-19 impact assessment (see Section 10.1.1.4).
- Visit conduct options allowing remote visits as outlined below:

  During remote study visits data are collected via telephone or videoconference (see Appendix 17.3).

  Any clinical assessment (including physical examination, vital signs, urine, or blood tests) necessary as part of evaluation of a reported adverse event (AE) must be performed immediately. If the study site is closed or the subject is unable to travel to the study site, alternate arrangements for in-person clinical assessment should be secured.

Option 1: In-Clinic Visits

This is the preferred option. All study visits are performed as in-clinic visits with all assessments outlined in the Schedule of Assessments in Section 8.1.2.

Option 2: Remote Visits (except Screening for all subjects and Baseline Visit for female subjects of childbearing potential)

This option is only to be used if local guidance and regulations are preventing the site or subject from completing an in-clinic visit. Screening must take place as an in-clinic visit with all assessments outlined in the Schedule of Assessments in Section 8.1.2. The Baseline Visit must take place as an in-clinic visit for all female subjects of childbearing potential with all assessments outlined in the Schedule of Assessments in Section 8.1.2 (including pregnancy test). All other visits can be completed remotely with the assessments outlined in Section 8.1.3.

Table 1 outlines allowed visit windows if a subject comes into the clinic to complete physical examination, body mass index (BMI), vital signs, electrocardiogram (ECG),

urine drug screen, safety lab (clinical chemistry including thyroid, hematology, urinalysis), pregnancy test, and/or PK.

All attempts should be made to collect all safety assessments within 6 weeks of the Visit 7 date, if logistically possible.

If a subject is able to switch from remote visits to in-clinic visits, the investigator should contact the study monitor for guidance.

**Table 1 Visit Windows for Safety and PK Assessments Missed due to Remote Visits**

| *Visit* | *Assessment* | *Limits for allowance of out-of-window collection* |
|---|---|---|
| Visit 5/Week 4 | PK | up to 3 weeks early or late (± 21 days) (Section 10 1.3) |
| | BMI | up to 3 weeks late (+ 21 days) |
| Visit 7/Week 8 or ET | PK | up to 1 week late (+ 7 days) (Section 10.1.3) |
| | Clinical chemistry, hematology, urine drug screen | up to 1 week late (+ 7 days)* |
| | Physical examination, BMI, vital signs, ECG, urinalysis, pregnancy test | up to 1 week late (+ 7 days)* |
| Visit 8/Week 9 | Vital signs | up to 1 week late (+ 7 days)* |

Abbreviations: BMI = body mass index; ECG = electrocardiogram; ET = End of Treatment; PK = pharmacokinetic.
Note, if subjects cannot do the assessments within these timeframes, it will be noted as missing assessment(s) for that visit.
NOTE: PK assessments outside the above visit windows should not be done at all.
* For purposes of including as safety endpoints, these assessments will be included in the safety analysis if collected up to 1 week late. Any safety data collected 8 days to 42 days late will be considered missing for analysis purposes. The 6-week window is allowed to capture any follow-up safety data on the participant and will be noted in the final study report (see also Section 11.6).

## 8.3 Selection of Study Population

### 8.3.1 Number of Planned Subjects

A total of approximately 430 subjects will be screened and approximately 256 subjects (128 per treatment arm) are planned to be randomized in approximately 40 centers in the United States. It is assumed that approximately 115 subjects per treatment arm will be evaluable (ie, have at least one postbaseline assessment).

A blinded interim analysis will be conducted when 75% of randomized subjects have either completed or discontinued the study in order to check the assumptions in the sample size calculation. Based on this, the sample size may be increased to ensure an adequate power due to variance assumption deviation as well as increased variance due to COVID-19 remote visits. However, due to the difficulties in recruiting pediatric

subjects with GAD, the number of subjects in each treatment arm will be capped at 160 (see Section 11.8).

Re-screening of subjects who do not meet the entry criteria is not allowed, except for the reasons outlined in Section 8.3.4. A subject can only be re-screened once.

The statistical considerations on which the sample size is based are provided in Section 11.9.

### 8.3.2 Inclusion Criteria

To be eligible for study entry subjects must satisfy all of the following criteria:

1. Subject's parent/legal representative must give written informed consent, including privacy authorization, prior to study participation. The subject will complete an informed assent prior to study participation.

2. Subject's parent/legal representative and the subject, if capable, are judged to be reliable by the investigator to keep all appointments for clinical visits, tests, and procedures required by the protocol.

3. Subject's parent/legal representative and the subject, if capable, must have a degree of understanding such that they can communicate intelligently with the investigator and study coordinator.

4. Subjects, male or female, must be between 7 and 17 years old, inclusive, at the time of consent/assent and at the Baseline Visit.

5. Subject meets DSM-5 criteria for a primary diagnosis of GAD at Screening established by a comprehensive psychiatric evaluation and confirmed/supported using the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI Kid).

6. Diagnosis of moderate or greater severity of GAD as determined by the following:

    a. Presence of ≥4 symptoms identified on the generalized anxiety subsection of the Pediatric Anxiety Rating Scale (PARS) symptom checklist, 2 of which are "excessive worry" and "dread or fearful anticipation" (nonspecific) at the Screening and Baseline Visits.

    b. PARS severity score of ≥15 at the Screening and Baseline Visits for symptoms identified on the generalized anxiety subsection of PARS symptom checklist, derived by summing 5 of the 7 severity/impairment/interference items (2, 3 5, 6, and 7).

c. CGI-S rating of ≥4 at the Screening and Baseline Visits.

7. Male subjects who are sexually active with a partner of childbearing potential must use, with their partner, a condom plus an approved method of highly effective contraception from the time of informed consent until 14 days after the last dose of study drug. The following methods are acceptable:

    a. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

        i. oral

        ii. intravaginal

        iii. transdermal

    b. Progestogen-only hormonal contraception associated with inhibition of ovulation

        i. oral

        ii. injectable

        iii. implantable intrauterine device

        iv. intrauterine hormone-releasing system

    c. Surgical sterilization (vasectomy or bilateral tubal occlusion)

8. Female subjects who are not of childbearing potential do not need to use any methods of contraception. This includes preadolescent and adolescent females who have not reached menarche.

9. Female subjects who are sexually active and are of childbearing potential must use, with their partner, an approved method of highly effective contraception from the time of informed consent until 14 days after the last dose of study drug. In this patient population, a subject would be considered sexually active if they participate in any behaviors which may result in pregnancy. The following methods are acceptable:

    a. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation and a barrier method (ie, condom for male partner):

        i. oral

ii. intravaginal

iii. transdermal

b. Progestogen-only hormonal contraception associated with inhibition of ovulation and a barrier method (ie, condom for male partner):

i. oral

ii. injectable

iii. implantable intrauterine device

iv. intrauterine hormone-releasing system

c. Surgical sterilization (vasectomy or bilateral tubal occlusion)

10. Strict abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, they, with their partner, must comply with the contraceptive requirements detailed above.

11. Female subjects of childbearing potential must have a negative serum beta-human chorionic gonadotropin pregnancy test at the Screening Visit, a negative urine pregnancy test at the Baseline Visit, and must not be breastfeeding.

12. Subject must have venous access sufficient to allow blood sampling and be compliant with blood draws as per the protocol.

13. Subject must be in general good health (defined as the absence of any clinically relevant abnormalities as determined by the investigator) based on screening physical and neurological examinations, vital signs, medical history, and clinical laboratory values (hematology, chemistry, and urinalysis). Note: If any of the hematology, chemistry, or urinalysis results are not within the laboratory's reference range, then the subject may be included only if the investigator determines the deviations to be not clinically relevant.

14. Subject weighs at least 20 kg and is within the 3rd to 97th percentile for gender specific BMI-for-age from the Centers for Disease Control and Prevention (CDC) growth charts at the Screening and Baseline Visits.

15. Subject's living environment is determined to be stable by the investigator.

### 8.3.3 Exclusion Criteria

Subjects will be excluded from the study if one or more of the following criteria is applicable:

1. Current diagnosis of a major depressive episode, or lifetime diagnosis of attention-deficit/hyperactivity disorder, bipolar disorder, psychotic depression, schizophrenia or other psychotic disorder, feeding and/or eating disorder, obsessive-compulsive disorder, conduct disorder, oppositional defiant disorder, post-traumatic stress disorder, panic disorder, or pervasive development disorder.

2. Suspected or previously diagnosed intellectual disability disorder.

3. DSM-5-defined substance use disorder within a year (12 months) prior to Screening Visit.

4. Any secondary DSM-5 disorder that requires pharmacologic treatment or would be a potential confound to the study assessments or ability to participate in all study procedures, as determined by the investigator.

5. Environmental stressor (current or historic – eg, history of abuse/trauma, significant change in psychosocial status, significant injury) that, in the opinion of the investigator, may confound assessments or subject's ability to complete all protocol requirements.

6. One or more first-degree relatives with diagnosed bipolar I disorder.

7. Subject answers "yes" to "Suicidal Ideation" item 3 (active suicidal ideation with any methods, not plan, without intent to act), item 4 (active suicidal ideation with some intent to act, without specific plan), or item 5 (active suicidal ideation with specific plan and intent) within the past 6 months and/or a lifetime history of suicidal behavior, as assessed by the C-SSRS.

8. Subject is currently considered at risk for suicide in the opinion of the investigator.

9. Lack of response to 2 or more adequate trials of antidepressants or other anti-anxiety medications at a clinically appropriate dose for a minimum of 4 weeks for GAD at the time of screening or, in the judgement of the investigator, the patient had treatment-resistant GAD.

10. Change to psychotherapy (start, stop, or change in type, intensity, or frequency) in the 6 weeks prior to the Screening Visit.

11. History of seizure disorder (other than febrile seizures).

12. History of electroconvulsive therapy at any time during the subject's lifetime.

13. Had a positive urine drug screen for any substances of abuse or excluded medication.

14. Known hypersensitivity to escitalopram (escitalopram oxalate) or citalopram or any of the inactive ingredients, or had frequent or severe allergic reactions to multiple medications.

15. Have used escitalopram (at a minimum required dose and duration per FDA approval) and had a suboptimal effect as determined by the investigator.

16. Serious or unstable medical illness, or clinically significant laboratory or ECG result that, in the opinion of the investigator, would compromise participation in the study, confound results, or be likely to lead to hospitalization during the course of the study.

17. Hypo- or hyperthyroidism, unless stabilized on appropriate pharmacotherapy with no change in dosage for at least 3 months before the Screening Visit. If thyroid-stimulating hormone (TSH) is abnormal, the subject must have a normal triiodothyronine (T3) and thyroxine (T4).

18. Use of biotin as a dietary supplement at more than 2.5 mg total per day within 7 days of the Screening Visit.

19. Initiated or discontinued hormone therapy (including oral contraceptives for female subjects) within 3 months prior to screening.

20. Taking any medications that are contraindicated to escitalopram (escitalopram oxalate).

21. Inability to speak, read, or understand English well enough to complete the assessments.

22. Treatment with any investigational drug within 30 days or 5 half-lives (whichever is longer) prior to study entry.

23. Unlikely to comply with study requirements or unsuitable for any reason, including any indication the subject may be significantly impacted by the COVID-19 (or associated virus) pandemic, based on investigator judgement.

24. Employees or relatives of employees of investigational site, Syneos Health, or Allergan.

25. Family members or individuals living in the same household as the study subject.

### 8.3.4 Re-screening

Re-screening is allowed only under the following exceptional circumstances. Note a subject can only be re-screened once.

- Logistical reasons (eg, scheduling of visits).
- Subjects who have not yet completed washout of fluoxetine at screening can be re-screened once washout is completed. The medical monitor is to be contacted in these cases.
- For subjects who failed screening according to the BMI criteria based on World Health Organization (WHO) growth charts.
- Screen failures due to a recruitment hold. Subjects can be re-screened once the recruitment hold is lifted.

### 8.3.5 Removal of Subjects From the Study

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Withdrawal of consent
- Use of non-permitted concurrent therapy
- Noncompliance with the study drug or study schedule
- Lost to follow-up
- Adverse event
- Investigator request
- Intercurrent illness
- Protocol deviation
- Pregnancy
- Sponsor request
- Lack of efficacy
- Due to the COVID-19 pandemic
- Death

Subjects who do not complete the study will not be replaced.

Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the electronic case report form (eCRF).

Subjects withdrawing from the study will be encouraged to complete the same final evaluations as subjects completing the study according to this protocol, particularly

safety evaluations. The aim is to record data in the same way as for subjects who completed the study.

Subjects who withdraw early from the study should complete the End of Treatment Visit and enter the 1-week down taper period.

Subjects should be monitored for the following symptoms when discontinuing treatment: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (eg, paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. A gradual reduction in dose rather than abrupt cessation is recommended, whenever possible.

Reasonable efforts will be made to contact subjects who are lost to follow-up (eg, 3 attempts to contact the subject by telephone/letter). These efforts must be documented in the subject's file.

The sponsor has the right to terminate the study at any time in case of serious adverse events (SAEs) or if special circumstances concerning the investigational product or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

**Pregnancy**

Subjects will be instructed that known or suspected pregnancy occurring during the study, in subjects or female partners of male subjects, should be confirmed and reported to the investigator, who will then withdraw the subject from the study after appropriate safety follow-up. The investigator should discuss down tapering with the medical director for any subject being withdrawn as a result of pregnancy.

The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be immediately reported to the sponsor by the investigator. All pregnancies will be followed to term by the investigator, and pregnancy outcome, as well as the health status of mother and child will be reported to the sponsor.

Full details will be recorded on the withdrawal page of the eCRF, and a pregnancy form will be completed (see Section 10.1.2.2.2).

## 8.4 Investigational Products

### 8.4.1 Investigational Products Administered

Subjects randomized to the escitalopram arm will receive escitalopram 10 mg/day for the first 2 weeks. At the end of Week 2, subjects who can tolerate the current dose of 10 mg/day may have a dose escalation to 20 mg/day. Dose escalation will be at the

investigator's discretion taking into account the CGI-S score. Subjects who remain on 10 mg/day will be evaluated again at Week 4 for a possible dose escalation to 20 mg/day at the investigator's discretion. Dose escalations cannot be made at any other time during the study. The dose may be decreased from 20 mg/day to 10 mg/day following discussion with the medical director if the subject does not tolerate the 20 mg/day dose.

At the end of the 8-week double-blind acute treatment period, or at withdrawal, the subject will enter a 1-week double-blind down taper period.

For subjects receiving escitalopram 10 mg/day, the doses given during the double-blind down taper period will be as follows:

- Week 9: Subjects will receive placebo.

For subjects receiving escitalopram 20 mg/day, the doses given during the double-blind down taper period will be as follows:

- Week 9: Subjects will receive 10 mg/day.

Subjects randomized to the placebo arm will receive matching placebo during the double-blind treatment period. Subjects will be evaluated at the end of Week 2 and Week 4 and subjects tolerating 10 mg/day matching placebo may be indicated for dose escalation by the investigator but in a blinded fashion will continue to receive matching placebo. Subjects receiving placebo will follow a similar down tapering schedule at the end of the double-blind treatment period.

For details on overdose of escitalopram, please see Section 10.1.2.2.5.

### 8.4.2 Identity of Investigational Products

Escitalopram (S-(+)-1-[3-dimethyl-aminopropyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile oxalate) is the S-enantiomer of racemic citalopram.

Encapsulated escitalopram 10 mg tablets will be provided for both the 10 mg and 20 mg doses. The active study medication will be provided in single-dose capsules that are identical in appearance, and contain one 10 mg tablet for the 10 mg dose, or two 10 mg tablets for the 20 mg dose. Escitalopram tablets are film-coated, round tablets containing escitalopram oxalate in strengths equivalent to 10 mg escitalopram base.

Matching placebo capsules are similar but do not contain active escitalopram.

Investigational products should be stored at 25 °C (77 °F); excursions to 15 °C to 30 °C (59 °F to 86 °F) are permitted.

### 8.4.3 Packaging and Labeling

The investigational product will be provided in 10 count bottles.

All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

### 8.4.4 Method of Assigning Subjects to Treatment Groups

After successfully meeting study entry criteria, subjects will be randomized in a 1:1 ratio to escitalopram or placebo. The randomization schedule will be stratified by age at randomization (grouped as 7–11 years vs. 12–17 years) and sex, and blocked. Approximately 430 subjects will be screened and a total of approximately 256 subjects are planned for randomization.

An Interactive Response System (IXRS) will be used to manage the randomization, assignment of treatment during the study, and if necessary emergency unblinding of subjects during the study conduct. The IXRS will assign a randomization number, distinct from the subject number, at the time of randomization.

### 8.4.5 Selection of Doses in the Study

In this study in GAD, the initial dose will be 10 mg/day with a possible increase to 20 mg/day after a minimum of 2 weeks for both pediatric subjects (aged 7 through 11 years) and adolescents (aged 12 through 17 years). Clinical assessment at the Week 2 Visit may provide information for the investigator to increase the dose at that time. There is no standard of care for when doses should be adjusted. As there is no Week 3 Visit, allowing an evaluation for dose escalation at the Week 2 Visit is an ideal option.

### 8.4.6 Selection and Timing of Dose for Each Subject

Subjects will be randomly allocated to receive escitalopram or placebo.

For in-clinic visits according to Option 1 in Section 8.2.2.1:

Subjects will receive their first dose of study drug on site on Day 1. Subjects will then self-administer the investigational product on an outpatient basis once a day. Subjects should be instructed to administer investigational product at approximately the same time each day including on days when clinic visits occur. Subjects may take the investigational product with or without food. To allow for PK sampling during in-clinic visits, subjects receiving study drug in the morning will be instructed to withhold taking the morning dose on the day of the Week 4 Visit (Visit 5) and to bring their study drug to the visit. Subjects receiving study drug in the evening should take their dose in the evening before the visit.

For remote visits according to Option 2 in Section 8.2.2.1:

Subjects will receive and take their first dose of study drug on Day 1 via curbside (preferred) or they will receive it by courier and take it at home. Subjects will then self-administer the investigational product on an outpatient basis once a day. Subjects should be instructed to administer investigational product at approximately the same time each day including on days when remote visits are scheduled. Subjects may take the investigational product with or without food.

Details of dose escalation and down tapering are provided in Section 8.4.1.

### 8.4.7 Blinding

The escitalopram and placebo capsules are the same in appearance. The investigators, study center staff, subjects, study contract research organization staff, and study sponsor staff will be blinded to the treatment assignments. The only planned unblinding will be at the conclusion of the study, when the database has been cleaned, statistical populations have been defined, and approval for database lock has been given by Allergan.

The blind for a specific subject can be broken by the investigator (emergency code breaking) only if the investigator considers the information indispensable to the safety of the subject. Any subject whose treatment is unblinded by the investigator will be withdrawn at the moment of unblinding, with the reason for unblinding given as the reason for discontinuation from the study.

Bioanalytical representatives will be unblinded for PK sample bioanalysis during the conduct of the study. The unblinding of bioanalytical representatives will be carried out in a secure manner following the sponsor's standard operating procedures. Extreme care and diligence will be taken to ensure no other individuals outside the bioanalytical team will be unblinded.

### 8.4.8 Prior and Concomitant Therapy

#### 8.4.8.1 Prohibited Medication/Therapy

Subjects must stop all antidepressant treatment (except for fluoxetine) at least 14 days prior to randomization. Antidepressant treatment includes SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), bupropion, and tricyclic antidepressants.

Subjects must stop fluoxetine at least 28 days prior to randomization. If the subject is taking fluoxetine at the time of screening, the subject may need to be screen failed and then re-screened once the washout is complete. Please contact the medical monitor for guidance (see Section 8.3.4).

Subjects should not have initiated or discontinued hormone therapy (including oral contraceptives for female subjects) within the 3 months prior to screening.

A table listing prohibited concomitant medications during the study is presented in Appendix 17.2.

### 8.4.9 Treatment Compliance

Compliance with study medication will be monitored at each visit during treatment. Subjects will be instructed to bring all unused study medication with them to each visit. At the investigator's discretion, noncompliance could result in termination of the subject from the study.

## 9 TIMING OF STUDY PROCEDURES

Each subject will complete an informed assent and the subject's parent/legal representative will provide written informed consent before any study-related procedures are performed.

The planned study assessments are in Section 8.1.2.

### 9.1 Pre-treatment

#### 9.1.1 Screening Visit (Visit 1)

- Assess for eligibility (against the inclusion and exclusion criteria).
- Collect full medical history, including concomitant illnesses/diseases and concomitant medications.
- Collect psychiatric history.
- Record demographic data, such as ethnic origin, race, year of birth, and sex.
- Record historical disease data and diagnostic information (including MINI Kid).
- Complete Children's Global Assessment Scale (CGAS), PARS, and CGI-S.
- Complete C-SSRS.
- Complete global COVID-19 impact assessment.
- Record vital signs (blood pressure, pulse rate, temperature, respiration rate, height, and weight).
- Record BMI.
- Perform a physical examination (including neurological examination).
- Perform an ECG.
- Collect samples for hematology, clinical chemistry including thyroid (fasting sample), urinalysis, and pregnancy (if applicable) tests.
- Collect samples for hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCVAb), and human immunodeficiency virus (HIV) tests.

- Collect urine sample for drug screening (alcohol, opioids, benzodiazepines, tetrahydrocannabinol, barbiturates, and amphetamines).

### 9.1.2 Baseline Visit (Visit 2)

The following procedures will be performed at the Baseline Visit:

- Reassess for eligibility against the inclusion and exclusion criteria.
- Randomization will take place for eligible subjects and each will receive a randomization number.
- Record any AEs that have occurred since the previous visit and any changes in concomitant medications.
- Complete CGAS, PARS, and CGI-S.
- Complete C-SSRS.
- Complete global COVID-19 impact assessment.
- Record vital signs (blood pressure, pulse rate, temperature, and respiration rate).
- Perform a urine pregnancy test, if applicable.

When all the baseline procedures have been performed and the investigator has confirmed the subject's eligibility for the study, the study drug will be dispensed to the subject. Subjects should take their first dose of study drug in clinic on Day 1.

Refer to Section 8.1.3 for procedures and assessments if Visit 2 is done remotely. For remote visits, subjects will receive and take their first dose of study drug via curbside (preferred) or they will receive it by courier and take it at home.

## 9.2 Treatment Period

### 9.2.1 Week 1 (Visit 3)

The Week 1 Visit (Visit 3) will take place 7 days ± 3 days after the Baseline Visit. The following procedures will be performed at Visit 3:

- Perform an accountability check on any remaining study drug as well as empty study drug bottles.
- Record any AEs that have occurred since the previous visit and any changes in concomitant medications.
- Complete CGAS.
- Complete C-SSRS.
- Complete global COVID-19 impact assessment.
- Record vital signs (blood pressure, pulse rate, temperature, and respiration rate).

When all of these procedures have been performed, the study drug will be dispensed and the next visit scheduled.

Refer to Section 8.1.3 for assessments if Visit 3 is done remotely. Study drug will be delivered to subjects via curbside (preferred) or courier.

### 9.2.2 Week 2 (Visit 4)

The Week 2 Visit (Visit 4) will take place 14 days ± 3 days after the Baseline Visit. The following procedures will be performed at Visit 4:

- Perform an accountability check on any remaining study drug as well as empty study drug bottles.
- Record any AEs that have occurred since the previous visit and any changes in concomitant medications.
- Complete CGAS, PARS, and CGI-S.
- Complete C-SSRS.
- Complete global COVID-19 impact assessment.
- Record vital signs (blood pressure, pulse rate, temperature, and respiration rate).
- Assess the subject for dose escalation: subjects who can tolerate the current dose may have a dose escalation at the investigator's discretion, taking into account the CGI-S score.

When all of these procedures have been performed, and the dose has been confirmed, the study drug will be dispensed and the next visit scheduled. Subjects receiving study drug in the morning will be instructed to withhold taking the morning dose on the day of the Week 4 Visit (Visit 5) and to bring their study drug to the visit.

Refer to Section 8.1.3 for assessments if Visit 4 is done remotely. Study drug will be delivered to subjects via curbside (preferred) or courier.

### 9.2.3 Week 4 (Visit 5)

The Week 4 Visit (Visit 5) will take place 4 weeks ± 3 days after the Baseline Visit. The following procedures will be performed at Visit 5:

- Perform an accountability check on any remaining study drug as well as empty study drug bottles.
- Record any AEs that have occurred since the previous visit and any changes in concomitant medications.
- Complete CGAS.
- Complete C-SSRS.
- Complete global COVID-19 impact assessment.
- Record vital signs (blood pressure, pulse rate, temperature, respiration rate, height, and weight).
- Record BMI.
- Subjects on morning dosing:

  - Collect a predose PK blood sample.
  - Administer study drug.
  - Collect a PK blood sample at ≥ 1 hour postdose.
- Subjects on evening dosing:
  - Collect 2 PK blood samples at random times during the visit (ie, postdose from the dose received the previous evening), at least 2 hours apart from each other.
- Assess the subject for dose escalation: subjects who can tolerate the current dose may have a dose escalation at the investigator's discretion, taking into account the CGI-S score.

When all of these procedures have been performed, the study drug will be dispensed and the next visit scheduled.

Refer to Section 8.1.3 for assessments and to Table 1 for assessment windows if Visit 5 is done remotely. Study drug will be delivered to subjects via curbside (preferred) or courier.

### 9.2.4 Week 6 (Visit 6)

The Week 6 Visit (Visit 6) will take place 6 weeks ± 3 days after the Baseline Visit. The following procedures will be performed at Visit 6:

- Perform an accountability check on any remaining study drug as well as empty study drug bottles.
- Record any AEs that have occurred since the previous visit and any changes in concomitant medications.
- Complete CGAS.
- Complete C-SSRS.
- Complete global COVID-19 impact assessment.
- Record vital signs (blood pressure, pulse rate, temperature, and respiration rate).

When all of these procedures have been performed, the study drug will be dispensed and the next visit scheduled.

Refer to Section 8.1.3 for assessments if Visit 6 is done remotely. Study drug will be delivered to subjects via curbside (preferred) or courier.

### 9.2.5 Week 8 End of Treatment or Early Withdrawal (Visit 7)

The Week 8 End of Treatment or Early Withdrawal Visit (Visit 7) will take place 8 weeks ± 3 days after the Baseline Visit or at early withdrawal. The following procedures will be performed at Visit 7:

- Perform an accountability check on any remaining study drug as well as empty study drug bottles.
- Record any AEs that have occurred since the previous visit and any changes in concomitant medications.
- Complete CGAS, PARS, and CGI-S.
- Complete C-SSRS.
- Complete global COVID-19 impact assessment.
- Record vital signs (blood pressure, pulse rate, temperature, respiration rate, height, and weight).
- Record BMI.
- Record any changes from baseline in physical examination.
- Perform an ECG.
- Collect samples for hematology, clinical chemistry including thyroid, and urinalysis tests.
- Collect urine sample for drug screening (alcohol, opioids, benzodiazepines, tetrahydrocannabinol, barbiturates, and amphetamines).
- Perform a urine pregnancy test, if applicable.
- Collect 2 PK blood samples at random times during the visit (ie, postdose from the dose received in the morning or the previous evening), at least 2 hours apart from each other.

When all of these procedures have been performed, the study drug for the down taper period will be dispensed and the next visit scheduled.

Refer to Section 8.1.3 for assessments and to Table 1 for assessment windows if Visit 7 is done remotely. Study drug will be delivered to subjects via curbside (preferred) or courier. All attempts should be made to collect safety labs within 6 weeks of the Visit 7 date.

## 9.3 Down Taper Period

### 9.3.1 Week 9 (Visit 8)

The Week 9 Visit (Visit 8) will take place 9 weeks ± 3 days after the Baseline Visit. The following procedures will be performed at Visit 8:

- Perform an accountability check on any remaining study drug as well as empty study drug bottles.
- Record any AEs that have occurred since the last visit and any changes in concomitant medications.
- Complete C-SSRS.
- Record vital signs (blood pressure, pulse rate, temperature, and respiration rate).
- Schedule a follow-up telephone contact in 1 week's time.

Refer to Section 8.1.3 for assessments and to Table 1 for assessment windows if Visit 8 is done remotely.

### 9.4 Follow-up

#### 9.4.1 Week 10 (Follow-up Telephone Contact)

The follow-up telephone contact to review subject safety will take place at Week 10 (10 weeks ± 3 days after the Baseline Visit).

### 9.5 Unscheduled Visits

Unscheduled visits can be performed if safety concerns arise and at the discretion of the investigator. Additional examinations may be performed as necessary to ensure the safety and well-being of the subjects during the study.

### 9.6 Duration of Treatment

The duration of treatment will be up to 9 weeks (an 8-week double-blind, acute treatment period, and a 1-week double-blind down taper period).

### 9.7 End of Study

A subject will have fulfilled the requirements for study completion when the subject has completed all study periods, including the last scheduled follow-up telephone contact at Week 10 as indicated in the Schedule of Assessments in Section 8.1.2.

The end of the study will be the last subject's last scheduled follow-up telephone contact at Week 10 as indicated in the Schedule of Assessments in Section 8.1.2.

## 10 EFFICACY, SAFETY, AND PHARMACOKINETIC ASSESSMENTS

The planned Schedule of Assessments is in Section 8.1.2.

The modified Schedule of Assessments in conjunction with the COVID-19 pandemic is in Section 8.1.3 and the options for conducting remote visits are outlined in Section 8.2.2.1. For any efficacy or safety assessment data that are collected during a remote visit, the appropriately trained study center staff may conduct the assessment by telephone or videoconference. Sites should remain consistent with the method used for each subject.

## 10.1 Efficacy, Safety, and Pharmacokinetic Assessments

### 10.1.1 Efficacy Assessments

The efficacy assessments will be completed by the investigator or appropriately qualified study center staff. Every effort should be made to ensure that each instrument is completed by the same assessor at each visit.

#### 10.1.1.1 Pediatric Anxiety Rating Scale

The PARS is a clinician-rated instrument for assessing the severity of anxiety symptoms associated with common anxiety disorders including GAD in children[10,11].

The PARS severity score for GAD will be assessed for all symptoms identified in the generalized anxiety section of the PARS symptom checklist and the scores recorded on the eCRF.

#### 10.1.1.2 Clinical Global Impression of Severity

The CGI-S was developed for use in clinical trials to provide an assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication[12,13].

The CGI-S will be completed using a 7-point scale and the scores recorded on the eCRF.

#### 10.1.1.3 Children's Global Assessment Scale

The CGAS can be used as a measure of global functioning and impairment[14].

The CGAS will be completed by the clinician using a 100-point scale ranging from 1 to 100, with higher scores indicating better functioning. The scores will be recorded on the eCRF.

#### 10.1.1.4 Global COVID-19 Impact Assessment

A global COVID-19 impact assessment will be used to evaluate the impact of the coronavirus disease pandemic on the severity of the subject's GAD during the last 1 week. The rating will include scores from 0 (not applicable, subject not enrolled in the trial during the pandemic) to 7 (extreme impact). Raters will also evaluate whether the impact was an improvement or worsening of the subject's GAD. The global COVID-19 impact assessment will be completed last after all study assessments by appropriately qualified study center staff and the scores recorded on the eCRF. Every effort should be made to ensure that the assessments are completed by the same assessor at each visit.

### 10.1.2 Safety Assessments

#### 10.1.2.1 Columbia-Suicide Severity Rating Scale

The C-SSRS is an instrument designed to systematically assess and track suicidal ideation and behavior[15]. The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior.

The C-SSRS will be completed by the investigator or appropriately qualified study center staff and the scores recorded on the eCRF. Every effort should be made to ensure that the assessments are completed by the same assessor at each visit.

Any positive score should be reported to the medical director and immediate subject care should be implemented and documented. Any positive score should be recorded as an AE or SAE, as appropriate.

In addition to the planned assessments, the investigator must continually evaluate suicidality risk throughout the subject's participation in the study.

#### 10.1.2.2 Adverse Events

**Adverse Event Definition**

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AEs will be elicited by asking the subject a nonleading question, for example, "Have you experienced any new or changed symptoms since we last asked/since your last visit?". AEs should be reported on the appropriate page of the eCRF.

**Assessment of Severity**

Each AE will be assigned a category by the investigator as follows:

| | |
|---|---|
| Mild: | An AE that is easily tolerated by the subject, causes minimal discomfort and does not interfere with everyday activities. |
| Moderate: | An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed. |
| Severe: | An AE that prevents normal everyday activities; treatment or other intervention usually needed. |

If there is a change in severity of an AE, it must be recorded as a separate event.

**Assessment of Causality**

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study drug. Causality should be assessed using the categories presented in the following table:

| | |
|---|---|
| Unrelated: | Clinical event with an incompatible time relationship to study drug administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the study drug. |
| Unlikely: | Clinical event whose time relationship to study drug administration makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals. |
| Possible: | Clinical event with a reasonable time relationship to study drug administration, but that could also be explained by concurrent disease or other drugs or chemicals. |
| Probable: | Clinical event with a reasonable time relationship to study drug administration, and is unlikely to be attributed to concurrent disease or other drugs or chemicals. |
| Very Likely/Certain: | Clinical event with plausible time relationship to study drug administration, and that cannot be explained by concurrent disease or other drugs or chemicals. |

**Action Taken**

The investigator will describe the action taken in the appropriate section of the eCRF, as follows:

- None
- Study drug stopped

- Study drug temporarily interrupted
- Concomitant medication
- Other, specify.

**Follow-up of Adverse Events**

All investigators should follow up subjects with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF.

**Documentation and Reporting of Adverse Events**

All AEs from the signing of the informed consent form (ICF) until 30 days after receiving the last dose of study drug will be collected according to the procedures outlined above at the timepoints specified in the Schedule of Assessments (Section 8.1.2/8.1.3), and as observed or reported spontaneously by study participants.

AEs should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant eCRF pages. The following data should be documented for each AE:

- Description of the symptom event
- Classification of 'serious' or 'not serious'
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship
- Outcome of event (unknown, recovered, recovering, not yet recovered, recovered with sequelae, death [with date and cause reported]).

**10.1.2.2.1 Serious Adverse Events**

**Serious Adverse Event Definition**

An SAE is any untoward medical occurrence or effect that, at any dose,

- Results in death.
- Is life-threatening (an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred, ie, it does not include a reaction that might have caused death if it had occurred in a more serious form).
- Requires or prolongs inpatient hospitalization. (Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non-worsening condition is not, however, considered an AE. The details of such

hospitalizations must be recorded on the medical history or physical examination page of the eCRF).
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions).
- Results in a congenital anomaly/birth defect.

In addition, medical and scientific judgement is required to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any event that the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the subject or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the investigational product.

**Reporting of Serious Adverse Events**

Any SAEs from the signing of the ICF until 30 days after receiving the last dose of study drug will be collected according to the procedures outlined above at the timepoints specified in the Schedule of Assessments (Section 8.1.2/8.1.3), and as observed or reported spontaneously by study participants, whether or not the SAE is considered to be related to the investigational product.

The sponsor is required to inform worldwide regulatory authorities of SAEs that meet specific criteria. Therefore, the sponsor must be notified immediately regarding any SAE that occurs after informed consent is obtained.

Within 24 hours of learning of any AE that meets one of the criteria for an SAE, the study center personnel must report the event to Global Drug Safety on the SAE Form for Clinical Trials. The medical director may also be notified by telephone, however, notification of the medical director by telephone does not substitute for reporting of the event to the sponsor by email/fax of the SAE form for Clinical Trials within the required time period.

If, during follow-up, any nonserious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The study center must transmit the SAE Form for Clinical Trials to the SAE email address or fax number shown below. Even if an initial report is made by telephone, the SAE Form for Clinical Trials completed with all available details must still be faxed or emailed within 24 hours of knowledge of the event at the study center.

Supplemental information should be submitted as soon as available and may include laboratory results, radiology reports, progress notes, hospital admission and emergency

room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

The investigator is expected to take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the subject's eCRF. All SAEs are to be followed by the study staff until resolution or until the SAE is deemed stable. ***The sponsor may contact the study center to solicit additional information or follow up on the event.***

Fax or email the SAE Form for Clinical Trials to the following SAE fax number/email address:

Fax Number: +1-714-796-9504 (back-up fax number: +1-714-246-5295)

Email: IR-Clinical-SAE@allergan.com

**10.1.2.2.2 Reporting of Pregnancies Occurring During the Study**

Study site personnel must report every pregnancy from the time the subject signs the ICF until 30 days after receiving the last dose of study drug. Within 24 hours of learning of the pregnancy, the study site personnel must report the event to the sponsor's Global Patient Safety department on the Clinical Trial Pregnancy Form and fax/email it to the following SAE/pregnancy fax number/email address, even if no AE has occurred:

Fax Number: +1-714-796-9504 (back-up fax number: +1-714-246-5295)

Email: IR-Clinical-SAE@allergan.com

Pregnancies in female partners of male subjects occurring during the time frame described above must also be reported.

The pregnancy must be followed to term and the outcome reported by completing a follow-up Clinical Trial Pregnancy Form. If the pregnancy is associated with an SAE (eg, if the mother is hospitalized for hemorrhage), a separate SAE Form for Clinical Trials must be filed with the appropriate serious criterion (eg, hospitalization) indicated in addition to the Clinical Trial Pregnancy Form.

**10.1.2.2.3 Unexpected Adverse Reactions**

**Unexpected Adverse Reaction Definition**

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the study drug at any dose that is not consistent with the applicable product information (eg, investigators brochure for an unauthorized investigational medicinal product or summary of product characteristics for an authorized product).

All suspected unexpected serious adverse reactions (SUSARs) will be the subject of expedited reporting. The sponsor shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and institutional review board (IRB) within 7 days after knowledge by the sponsor of such a case and that relevant follow-up information is communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and IRB within 15 days after knowledge by the sponsor of such a case. All investigators should follow up SUSARs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Post study SUSARs that occur after the subject has completed the clinical study must be reported by the investigator to the sponsor.

**10.1.2.2.4 Warnings and Precautions**

Clinical Worsening/Suicide Risk: subjects should be monitored for clinical worsening, suicidality and unusual change in behavior, especially at the start of therapy or at times of dose changes. (See Section 10.1.2.1 for use of the C-SSRS).

Serotonin Syndrome: serotonin syndrome has been reported with SSRIs, including escitalopram, when taken alone, but especially when co-administered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort). Serotonin syndrome symptoms may include mental status changes (eg, agitation, hallucinations, delirium, and coma), autonomic instability (eg, tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, and hyperthermia), neuromuscular symptoms (eg, tremor, rigidity, myoclonus, hyperreflexia, and incoordination) seizures, and/or gastrointestinal symptoms (eg, nausea, vomiting, and diarrhea). If symptoms of serotonin syndrome occur, escitalopram should be discontinued and supportive treatment initiated.

Hyponatremia: hyponatremia may occur as a result of treatment with SSRIs, including escitalopram. Subjects taking diuretics or who are otherwise volume depleted may be at greater risk. Discontinuation of escitalopram should be considered in subjects with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Caution should be used when escitalopram is taken in combination with other centrally acting drugs.

Full details of the Warnings and Precautions associated with escitalopram are available in the prescribing information.

**10.1.2.2.5 Overdose**

Symptoms most often accompanying escitalopram overdose, alone or in combination with other drugs and/or alcohol, include convulsions, coma, dizziness, hypotension,

insomnia, nausea, vomiting, sinus tachycardia, somnolence, and ECG changes (including QT prolongation and very rare cases of torsade de pointes). Acute renal failure has been very rarely reported accompanying overdose.

In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

#### 10.1.2.2.6 Potential Hy's Law Cases

Criteria for potential Hy's law cases are as follows:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 × upper limit of normal (ULN) AND
- Total bilirubin ≥ 2 × ULN AND
- Alkaline phosphatase < 2 × ULN

Study site personnel must report every subject who meets these criteria. Typically, all 3 analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period. This requirement applies from the time the subject signs the ICF for the study until 30 days after receiving the last dose of study drug.

A laboratory alert for potential Hy's laws cases will be in place, and the laboratory must notify investigators and the sponsor immediately when the above criteria have been met. A potential Hy's law case must be reported to the sponsor on an SAE form as soon as possible (within 24 hours of learning of the potential Hy's law case) to the SAE/pregnancy fax number, even if no AE has occurred. The eCRF for potential Hy's law cases must be completed within 7 calendar days. Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in conjunction with the Study Medical Monitor and in accordance with the FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009. The patient should return to the study site and be evaluated as soon as possible, preferably within 48 hours from the time the investigator becomes aware of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical examination.

### 10.1.2.3 Clinical Laboratory Evaluation

The hematology, clinical chemistry, urinalysis, and other laboratory variables analyses (see Section 10.1.2.3.1) will be performed at a central laboratory. Reference ranges will be used by the investigator to assess the laboratory data for clinical significance and pathological changes. The following laboratory safety tests will be performed at the times outlined in the Schedule of Assessments in Section 8.1.2. Information on

collection, processing, and shipping of samples will be provided in the Laboratory Manual.

**Hematology**

Hemoglobin, hematocrit, white blood cell count (total and differential), red blood cell count, platelet count, mean cell volume, mean cell hemoglobin (MCH), and MCH concentration.

**Clinical Chemistry**

Creatinine, urea (or blood urea nitrogen), aspartate transferase, alanine transferase, gamma glutamyltransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin, albumin, total protein, sodium, potassium, chloride, glucose, uric acid, calcium, phosphorus, TSH, T3, and T4.

**Urinalysis**

pH, glucose, ketones, blood, protein, and microscopy.

#### 10.1.2.3.1 Other Laboratory Variables

Screening for pregnancy using serum β-HCG will be performed at the Screening Visit. Urine pregnancy tests will be performed at the Baseline Visit and the Week 8/End of Treatment Visit (Visit 7).

Urine drug screen (alcohol, opioids, benzodiazepines, tetrahydrocannabinol, barbiturates, amphetamines) will be performed at the Screening Visit and the Week 8/End of Treatment Visit (Visit 7).

Screening for HBsAg, HCVab, and HIV will be performed at the Screening Visit only.

### 10.1.2.4 Vital Signs

Vital signs (blood pressure, pulse rate, temperature, and respiration rate) will be recorded in a standardized manner (ie, after the subject has rested in the sitting position for 5 minutes). Height, weight, and BMI will also be recorded at specified visits. The times of assessment are outlined in the Schedule of Assessments in Section 8.1.2.

### 10.1.2.5 Physical Examination

A complete physical examination (including neurological examination) will be performed at the Screening Visit (Visit 1) and at the end of Week 8/ET (Visit 7) by a professionally trained physician or health professional listed on Form FDA 1572 and licensed to perform physical examinations. Any untoward clinically relevant changes will be recorded as AEs.

#### 10.1.2.6 Electrocardiogram

A 12-lead single trace ECG will be performed at the times outlined in the Schedule of Assessments in Section 8.1.2 in a standardized manner (ie, after the subject has rested in the semi-supine position for at least 5 minutes). Measurements will include ventricular heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc interval. The QTc interval will be calculated using both the Bazett correction (QTcB = QT/(RR)½) and the Fridericia correction (QTcF = QT/(RR)⅓).

The ECGs will be centrally read. The date and an overall interpretation of the ECG will be recorded in the eCRF. Any abnormalities will be assessed as clinically significant or not clinically significant and recorded on the eCRF.

### 10.1.3 Pharmacokinetic Assessments

#### 10.1.3.1 Study Drug Concentration Measurements

PK blood samples for measurement of escitalopram and S-demethylcitalopram plasma concentrations will be collected from assented/consented subjects at Visit 5 (Week 4) and Visit 7 (Week 8). For subjects who cannot go the site for scheduled visits due to the COVID-19 pandemic, PK sample collection can occur at the times specified in Section 8.2.2.1, Table 1. Two PK blood samples per subject will be collected at each of these visits at the following times:

Visit 5:

- For subjects receiving dose in the morning, at 0 hour (predose) and ≥ 1 hour postdose
- For subjects receiving dose in the evening, 2 samples at random times during the visit (ie, postdose from the dose received the previous evening), collected at least 2 hours apart from each other

Visit 7:

- For subjects receiving dose in the morning or in the evening, 2 samples at random times during the visit (ie, postdose from the dose received in the morning or the previous evening), collected at least 2 hours apart from each other

To allow for a predose sampling, subjects on a morning dosing schedule should be instructed to withhold their daily dose on the morning of Visit 5 and take study drug when instructed at the study center.

The actual date and clock times of the dose on the PK sampling date as well as the 2 doses taken prior to the PK sampling date, and the actual date and clock times of all blood draws, will be recorded in the eCRF. Blood samples will be collected in prechilled 6 mL Vacutainer® tubes containing lithium heparin as an anticoagulant and processed, stored, and shipped as specified in the Laboratory Manual.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded. Bioanalytical representatives will be unblinded for PK sample bioanalysis during the conduct of the study. The unblinding of bioanalytical representatives will be carried out in a secure manner following the sponsor's standard operating procedures. Extreme care and diligence will be taken to ensure no other individuals outside the bioanalytical team will be unblinded.

#### 10.1.3.2 Handling of Biological Specimens

PK samples obtained from subjects will be stored at the centralized clinical laboratory until ready for PK analyses by the bioanalytical laboratory using a validated method.

### 10.2 Appropriateness of Measurements

The efficacy and safety assessments planned for this study are widely used and generally recognized as reliable, accurate, and relevant to the disease condition.

## 11 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

### 11.1 Subject Populations

Five populations will be considered in the statistical analysis of the study, as specified below.

#### 11.1.1.1 Screened Population

The Screened Population will consist of all subjects who underwent a Screening Visit and received a subject number, and signed the ICF.

#### 11.1.1.2 Randomized Population

The Randomized Population will consist of all subjects in the Screened Population who are randomized to a treatment group in the study.

#### 11.1.1.3 Safety Population

The Safety Population will consist of all subjects in the Randomized Population who took at least one dose of study medication.

#### 11.1.1.4 Modified Intent-to-Treat (mITT) Population

The modified Intent-to-Treat (mITT) Population is defined as all subjects who are randomized and receive at least one dose of study medication, and have both baseline and at least one postbaseline primary efficacy measure (ie, PARS severity score). The mITT population will be used for all of the efficacy analyses.

#### 11.1.1.5 Pharmacokinetic Population

The PK Population is defined as all subjects in the Safety Population with at least one evaluable plasma concentration of escitalopram or S-demethylcitalopram.

### 11.2 Disposition

The number of subjects in the Screened Population will be summarized overall by study center. The number of subjects in the Randomized, Safety, and mITT Populations will be summarized by treatment group and study center. Subjects whose disposition status was impacted by the COVID-19 pandemic will also be summarized.

Screen failures (ie, subjects who were screened but not included in the Randomized Population) and the associated reasons for failure will be tabulated overall. The reasons for premature discontinuation from the double-blind treatment period as recorded on the termination pages of the eCRF will be summarized (number and percentage) by treatment group for the Safety Population.

The number and percentage of subjects with significant protocol deviations will be summarized overall and by treatment group for the Randomized Population. Deviations related to the following categories will be included:

- inclusion or exclusion criteria
- withdrawal criteria
- treatment or dose
- concomitant medications

These and any additional significant protocol deviations will be reviewed and documented before database lock and unblinding of treatment codes.

Protocol deviations that occur due to COVID-19 will be summarized and listed separately.

### 11.3 Demographic and Other Baseline Characteristics

Demographic parameters (eg, age, age group [7-11 vs. 12-17 years], sex, race, ethnicity, weight, weight z-score, height, height z-score, BMI, BMI z-score) and other baseline characteristics will be summarized by treatment group for the Safety and mITT Populations. Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for continuous variables, and frequency distributions (counts and percentages) will be presented for categorical variables.

Medical history terms will be encoded using the latest available Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Summaries of medical history will be produced by system organ class (SOC) and preferred term (PT).

Psychiatric history and results from the MINI Kid will be summarized descriptively.

Prior and concomitant medications, including prior treatment for GAD, will be coded using the latest available WHO Drug dictionary. Drug classes and preferred names will be summarized by randomized treatment.

### 11.4 Extent of Exposure and Treatment Compliance

#### 11.4.1 Extent of Exposure

##### 11.4.1.1 Investigational Product

Total exposure to double-blind investigational product for the Safety Population during the double-blind treatment period will be summarized, calculated as the number of days from the date of the first dose of double-blind investigational product taken to the date of the last dose taken through the Week 8 End of Treatment or Early Withdrawal Visit, inclusive. Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented by treatment group. Similarly, the treatment duration in the down taper period, defined as the first dose in the down taper period to the last dose in the down taper period, inclusive, will be summarized. The total duration of double-blind investigational product exposure, defined as the sum of the treatment duration through Week 8 and the duration in the down taper period will be summarized.

The number and percentage of subjects who had their dosage escalated at Week 2 from 10 mg/day to 20 mg/day will be summarized by treatment group. The denominator will be the number of subjects who had study medication dispensed at Week 2. Similarly, the number and percentage of subjects who had their dosage escalated at Week 4 from 10 mg/day to 20 mg/day will be summarized by treatment group. The number of subjects who required a dose reduction from 20 mg/day to 10 mg/day will be summarized by treatment group. The number of days from first date of escalation to 20 mg/day to the dose reduction will be summarized using descriptive statistics.

The weekly and overall mean daily dose of investigational product will be summarized by treatment group for the Safety Population.

#### 11.4.1.2 Prior and Concomitant Medication

Prior medication is defined as any recorded medication taken before the date of the first dose of double-blind investigational product. Concomitant medication is defined as any recorded medication used on or after the date of the first dose of double-blind investigational product. A medication may be classified as both a prior medication and concomitant medication.

Prior and concomitant medications, used for treatment of GAD and for other indications, will be summarized by the number and proportion of subjects in each treatment group receiving each medication within each therapeutic class for the Safety Population. Multiple medication use by a subject will only be counted once. Any recorded medications started after last dose of double-blind investigational product will not be summarized but will be included in listings.

### 11.4.2 Measurement of Treatment Compliance

Dosing compliance for a specified period will be defined as the total number of capsules actually taken by a subject during that period divided by the number of capsules prescribed to be taken for the same period multiplied by 100. This information will be obtained from the investigational product record of the subject's eCRF.

The total number of capsules actually taken during a specific time period is calculated based on the study medication record. The number of capsules prescribed to be taken for a specific treatment period will be calculated by multiplying the number of days in that period by the number of capsules to be taken per day.

Descriptive statistics for investigational product compliance will be presented by treatment group for each period between 2 consecutive visits, as well as for the entire double-blind treatment period, the period from first dose to the Week 8 End of Treatment or Early Withdrawal Visit, and the down taper period.

## 11.5 Efficacy Analysis

The efficacy analyses will be based on the mITT Population. Baseline for efficacy is defined as the last non-missing efficacy assessment recorded at or before the date of the first double-blind dosing. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance. For efficacy analyses in which study center is a factor, a small center will be defined as a center with less than 2 subjects in at least 1 treatment group in the mITT Population. A pooling algorithm for the pooling of small centers will be specified in the statistical analysis plan (SAP). By-visit analysis based on the

mixed-effects model for repeated measures (MMRM) using the observed case approach will be performed for all continuous efficacy parameters.

#### 11.5.1.1 Primary Efficacy Analysis

The primary efficacy endpoint is the change from Baseline to Week 8 in the PARS severity score.

The PARS severity score for GAD is assessed for all symptoms identified in the generalized anxiety section of the PARS symptom checklist. The PARS severity score for GAD will be derived by summing 5 of 7 severity/impairment/interference items (2, 3, 5, 6, and 7).

The primary analysis will be performed using an MMRM with treatment group, age group strata (7-11 vs. 12-17 years), sex, study center, visit, and treatment group-by-visit interaction as the fixed effects and the baseline value and baseline value-by-visit interaction as the covariates. An unstructured covariance matrix will be used to model the covariance of within-subject scores. The Kenward-Roger approximation[16] will be used to estimate denominator degrees of freedom for the unstructured covariance matrix. If the model convergence for the unstructured covariance matrix fails, then the Fisher scoring algorithm will be used to provide better initial values of the covariance parameters. In the event that the model still does not converge after using those initial values, simplified covariance structures will be used to fit the model in the following order until the model converges: (1) ante-dependence, (2) heterogeneous autoregressive, (3) Toeplitz, and (4) compound symmetry. If a structured covariance is used, then a robust sandwich estimator will be used for estimating the variance of the treatment effect estimate.

The MMRM analysis will be performed based on all post-baseline scores using only the observed cases without imputation of missing values.

The significance test for the difference in means at Week 8 will be based on least squares (LS) means using a 2-sided α of 0.05. Differences between treatments at the other post-baseline visits will also be estimated based on LS means.

Sensitivity analyses will be conducted on the primary efficacy endpoint to assess the missing at random assumption of the MMRM model and the impact of COVID-19 using remote home assessments. Details will be provided in the SAP.

#### 11.5.1.1.1 Estimand for the Primary Efficacy Analysis

The following describes the estimand approach for the primary efficacy analysis described in ICH E9 (R1) (2017)[17].

**Target Population**

As noted above in Section 11.5, the target population is the mITT population.

**Variable**

The variable is the same as the definition of the primary efficacy analysis described in Section 11.5.1.1.

**Accounting for Intercurrent Events**

The primary analysis will treat measurements after study withdrawal as missing in the MMRM modeling, leading to an estimate of the treatment effect while on treatment. The impact of the missing at random assumption of MMRM will be assessed using 2 different approaches. The first will be a simple last observation carried forward (LOCF) approach. The second will be a sensitivity analysis using a pattern-mixture model. The details of this sensitivity analyses will be provided in detail in the SAP.

**Population-level Summary**

The population-level summary for the primary endpoint is the difference in primary variable means between the escitalopram group and placebo, while remaining on the study treatment.

### 11.5.1.2 Secondary Efficacy Parameters

Inferential testing for the secondary endpoints will be reported with nominal p-values. No adjustments for multiplicity will be made. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

The secondary efficacy endpoints are as follows:

- Response rate on the PARS at acute treatment endpoint (Week 8)
  - Response is defined as a 50% improvement on the PARS severity score for GAD.
- Remission rate on the PARS at acute treatment endpoint (Week 8)
  - Remission is defined as PARS severity score for GAD $\leq$8 (using 6 PARS items: 2, 3, 4, 5, 6, and 7)
- Change on the CGI-S from baseline to acute treatment endpoint (Week 8)

  - Remission rate on CGI-S at acute treatment endpoint (Week 8). Remission rate is defined as the percentage of subjects having a CGI-S score ≤2 at endpoint.

- Change on the CGAS from baseline to acute treatment endpoint (Week 8)
  - Remission rate on the CGAS at acute treatment endpoint (Week 8). Functional remission is defined as CGAS >70.

- COVID-19 impact assessment score at each visit.

The response rate of the PARS will be analyzed using a repeated measures model for categorical outcomes. Modeling will be completed using a categorical MMRM (MMRM-CAT) approach, in which a pseudo-likelihood-based repeated measures analysis will be used and implemented in SAS procedure GLIMMIX. A binary distribution with logit link will be used for the dependent variable. Classification variables for treatment, age group, sex, visit (as a categorical variable), treatment-by-age group interaction, treatment-by-sex interaction, treatment-by-visit interaction, and treatment-by-age group-by-sex interaction, and baseline score as a covariate will be considered in the modeling.

#### 11.5.1.2.1 Analysis of Remission in PARS

The remission rate on the PARS will be analyzed using the same MMRM-CAT as the response rate on the PARS.

#### 11.5.1.2.2 Change on the CGI-S from Baseline to Acute Treatment Endpoint (Week 8)

The change in the CGI-S will be analyzed using the same methodology described for the primary efficacy endpoint. The analysis of the remission rate for the CGI-S will use the same methodology described for the analysis of the response rate on the PARS.

#### 11.5.1.2.3 Change on the CGAS from Baseline to Acute Treatment Endpoint (Week 8)

The change in the CGAS will be analyzed using the same methodology described for the primary efficacy endpoint. The analysis of the remission rate for the CGAS will use the same methodology described for the analysis of the response rate on the PARS.

#### 11.5.1.2.4 COVID-19 Impact Assessment Score at each Visit

The COVID-19 impact assessment score will be summarized at each visit.

## 11.6 Safety Analysis

The safety analysis will be performed for the double-blind treatment period and double-blind down taper period separately using the Safety Population. The safety parameters will include AEs, clinical laboratory parameters, vital sign measurements, and ECG parameters. For each safety parameter, the last assessment made before the first dose of double-blind investigational product will be used as the baseline for all analyses of that safety parameter.

Safety data collected outside of planned visit windows but within allowance limits (up to 1 week late for Visits 7 and 8) will be included in the summary tables. Safety data collected outside of planned visit windows and outside of the allowance limits (>1 week to 6 weeks late for Visits 7 and 8) will be listed, but will not be included in the summary tables. Subgroup analyses may be performed to assess the impact of COVID-19 on the safety analyses.

The safety endpoints during the double-blind treatment period are as follows:

- Incidence of treatment-emergent adverse events (TEAEs).
- Observed values and change from baseline in vital signs (blood pressure, pulse rate, temperature, respiration rate, height, weight, BMI, height percentile, weight percentile, and BMI percentile); incidence of vital sign potentially clinically significant (PCS) values.
- Observed values and changes from baseline in ECG intervals and interpretation; incidence of ECG PCS values.
- Observed values and changes from baseline in clinical laboratory assessments (hematology, chemistry, and urinalysis); incidence of clinical laboratory PCS values.
- Incidence of suicidal ideation and/or suicidal behavior as determined by the C-SSRS.

#### 11.6.1.1 Adverse Events

AEs will be coded to an SOC and PT using the latest available version of MedDRA. An AE (classified by PT) not present before the date of the first dose of the double-blind treatment period or during the double-blind down taper period or that was present before the first dose but increased in severity or seriousness will be considered a TEAE. An AE that starts more than 30 days after the date of the last dose of double-blind investigational product will not be counted as a TEAE.

An AE that starts during the double-blind down taper period or that increases in severity or seriousness during the double-blind down taper period will be considered a newly emergent AE (NEAE). The NEAEs during the double-blind down taper period will be summarized by SOC, PT, and treatment group for all subjects who enter the double-blind down taper period.

The number and percentage of subjects reporting TEAEs in each treatment group will be tabulated by SOC and PT; by SOC, PT, and severity; and by SOC, PT, and causal relationship to the investigational product. If more than one AE is coded to the same PT for the same subject, the subject will be counted only once for that PT using the most severe and most related occurrence for the summarization by severity and by causal relationship to the investigational product, respectively.

The distribution of TEAEs by severity and causal relationship to the investigational product will be summarized by treatment group. The incidence of common (≥ 2% of subjects in any treatment group) TEAEs during the double-blind treatment period will be summarized by PT and treatment group.

An SAE that occurred between the date of the first dose of double-blind investigational product and 30 days after the date of the last dose of double-blind investigational product in the study, inclusive, will be considered an on-therapy SAE. The incidence of SAEs and AEs leading to premature discontinuation of the study will also be summarized by study period (separately for double-blind treatment period and double-blind down taper period), SOC, PT, and treatment group. Listings will be presented for subjects with SAEs, subjects with AEs leading to premature discontinuation, and subjects who died. All subjects with SAEs, including those reported during the screening period or more than 30 days after the date of the last dose of the double-blind investigational product, and subjects discontinuing due to AEs before the start of double-blind investigational product will be included in these listings.

Each AE summary described above will be presented as all AEs, AEs that are associated with the COVID-19 pandemic (as determined by the investigator), and AEs that are not associated with the COVID-19 pandemic. AEs associated with the COVID-19 pandemic will be listed separately.

#### 11.6.1.2 Vital Signs

Descriptive statistics for vital signs (ie, blood pressure, pulse rate, temperature, respiration rate, height, weight, BMI, height percentile, weight percentile, and BMI percentile) and changes from baseline values at each visit and at end of study will be presented by treatment group. Height, weight, and BMI z-scores will be calculated based on CDC growth charts.

Vital sign values will be PCS if they meet both the observed-value criteria and the change from baseline-value criteria. The criteria for PCS vital sign values will be detailed in the SAP. The percentages will be calculated relative to the number of subjects with baseline values and at least one postbaseline assessment. The numerator will be the total number of subjects with available baseline values and at least one PCS postbaseline value. A supportive listing of subjects with PCS postbaseline values will be provided, including the subject identification (SID) number, study center number, and

baseline and postbaseline values. A listing of all AEs for subjects with PCS vital sign values will also be provided.

#### 11.6.1.3 Electrocardiograms

Descriptive statistics for ECG parameters (ie, ventricular heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc interval) and changes from baseline values at each assessment time point will be presented by treatment group. The QTc interval is calculated using both the Bazett (QTcB = QT/(RR)½) and Fridericia (QTcF = QT/(RR)⅓) corrections. The number and percentage of subjects with PCS postbaseline ECG values will be tabulated by treatment group. The criteria for PCS ECG values will be detailed in the SAP. The percentages will be calculated relative to the number of subjects with available non-PCS baseline values and at least one postbaseline assessment. The numerator will be the total number of subjects with available non-PCS baseline values and at least one PCS postbaseline value. A supportive listing of subjects with PCS postbaseline values will be provided, including the SID number, study center number, and baseline and postbaseline values. A listing of all AEs for subjects with PCS ECG values will also be provided.

A listing of subjects with postbaseline clinically significant ECG abnormalities, as reported by the investigator or by the central cardiologist, will also be provided.

The number and percentage of subjects with an increase >30 msec but ≤60 msec, and with an increase >60 msec in QTcB or QTcF will be tabulated. A supportive listing of subjects with postbaseline QTcB or QTcF increases >30 msec will be provided, including the SID number, study center, and all QTcB and QTcF values (including changes from baseline). A listing of all AEs for subjects with postbaseline QTcB or QTcF increases >30 msec will also be provided.

#### 11.6.1.4 Clinical Laboratory Evaluations

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each assessment time point will be presented by treatment group for each clinical laboratory parameter. The number and percentage of subjects with PCS postbaseline clinical laboratory values will be tabulated by treatment group. The criteria for PCS laboratory values will be detailed in the SAP. The percentages will be calculated relative to the number of subjects with available non-PCS baseline values and at least one postbaseline assessment. The numerator will be the total number of subjects with available non-PCS baseline values and at least one PCS postbaseline value. A supportive listing of subjects with PCS postbaseline values will be provided, including the SID number, study center number, and baseline and postbaseline values. A listing of all AEs for subjects with PCS laboratory values will also be provided.

#### 11.6.1.5 Columbia-Suicide Severity Rating Scale

For the C-SSRS, the number and percentage of subjects with suicidal ideation or suicidal behavior as recorded on the C-SSRS scale will be presented by treatment group. The distribution of responses for most severe suicidal ideation and suicidal behavior during the lifetime history, the double-blind treatment period and the down taper period will also be presented by treatment group for the Safety Population. Supportive listings will be provided and will include the SID number, treatment group, visit number, lifetime history, and postbaseline values for each patient. Intensity of ideation, suicidal behavior type, and lethality of suicidal behavior will also be included in these listings.

### 11.7 Pharmacokinetic and Exposure-Response Evaluation

Escitalopram and S-demethylcitalopram plasma concentrations will be listed.

Escitalopram concentrations will be analyzed using a nonlinear mixed effects approach. Population PK parameters, inter-subject, and residual variability will be determined. The effect of covariates on the escitalopram PK will also be investigated. The exposure/dose-response relationship between efficacy parameters and plasma exposure and potentially safety parameters and plasma exposure will be explored using a nonlinear mixed effects approach. The analysis results will be provided in a separate report.

### 11.8 Interim Analyses

A blinded interim analysis will be conducted when 75% of randomized subjects have either completed or discontinued the study to obtain an estimate of the pooled standard deviation on change from baseline in the PARS score to Week 8 of the double-blind treatment period. If the estimated pooled standard deviation is larger than the assumed pooled standard deviation in the sample size calculation due to assumption deviation as well as COVID-19 remote visits (see Section 11.9), sample sizes in placebo and escitalopram treatment groups may be increased to ensure an adequate power. However, due to the difficulties in recruiting pediatric subjects with GAD, the number of subjects in each treatment arm will be capped at 160.

### 11.9 Determination of Sample Size

The sample size estimate was constructed using a simulation approach as described in Lu K. (2012)[18].

The primary efficacy parameter will be the change from baseline to Week 8 of the double-blind treatment period in PARS total score. To detect an effect size (treatment group difference of 2.30 units relative to pooled standard deviation of 5.79[19]) of 0.39, a sample size of 128 subjects in the escitalopram treatment group and 128 subjects in the placebo group will provide 85% power based on an MMRM model using simulation

method. The simulation assumed a correlation of 0.7 between the repeated measures, and a common dropout rate of 14%, based on historical data of escitalopram in pediatric subjects.

### 11.10 Protocol Deviations

Deviations from the protocol will be documented on an ongoing basis based on monitoring reports (eg, failure of eligibility criteria). Protocol deviations may also be identified by data management checks or statistical programming (eg, study treatment compliance, duration of study treatment, study completion, prohibited medications based on drug codes).

## 12 QUALITY ASSURANCE AND QUALITY CONTROL

### 12.1 Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

### 12.2 Monitoring

Data for each subject will be recorded on an eCRF. Data collection must be completed for each subject who signs an ICF/assent and is administered study drug.

In accordance with cGCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

The investigator must permit the monitor, the IRB, the sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs.

### 12.3 Data Management and Coding

Syneos Health will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures of the data management and biostatistics departments of Syneos Health.

Study centers will enter data directly into an electronic data capture (EDC) system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly

on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be FDA CFR 21 Part 11 compliant.

Medical coding will use MedDRA for concomitant diseases and AEs and WHO Drug for medications.

Missing or inconsistent data will be queried in writing to the investigator for clarification. Subsequent modifications to the database will be documented.

### 12.4 Quality Management and Risk Evaluation

Details are provided in Section 8.2.2.

# 13 RECORDS AND SUPPLIES

## 13.1 Drug Accountability

On receipt of the study drug (including rescue medication, if relevant), the investigator (or deputy) will conduct an inventory of the supplies and verify that study drug supplies are received intact and in the correct amounts before completing a supplies receipt. The investigator will retain a copy of this receipt at the study center and maintain the original receipt in the site investigator file. The monitor may check the study supplies at each study center at any time during the study.

It is the responsibility of the study monitor to ensure that the investigator (or deputy) has correctly documented the amount of the study drug received, dispensed, and returned on the dispensing log that will be provided. A full drug accountability log will be maintained at the study center at all times. In addition, sites will be provided a separate Investigational Product Curbside Pickup and Shipment Tracking Form to document pertinent study drug dispensing information each time a new shipment of study drug is shipped directly to a subject's residence, dispensed curbside at the site, or delivered to a subject's residence via site personnel. Sites will be instructed to submit this form to Syneos Health any time study drug is dispensed using these methods. The study monitor will arrange collection of unused study drug returned by the subject. All used and unused bottles will be returned to the sponsor. The study monitor will also perform an inventory of study drug at the close-out visit to the study center. All discrepancies must be accounted for and documented.

## 13.2 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between Syneos Health and the sponsor.

# 14 ETHICS

## 14.1 Institutional Review Board

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.

## 14.2 Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

## 14.3 Ethical Conduct of the Study

The investigators and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, cGCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

## 14.4 Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to cGCP.

The investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before that subject has given written informed consent to participate in the study.

The investigator or designated personnel will inform the subject and their parent/legal representative of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The subject and their parent/legal representative should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the subject and their parent/legal representative will be given ample time to consider the study. Subjects

and their parent/legal representative will be required to sign and date the ICF/assent. There will be a separate ICF/assent for the PK part of the study. After signatures are obtained, the ICF/assent will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the ICF/assent will be provided to the subject and their parent/legal representative.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF/assent will be approved by the IRBs (and regulatory authorities, if required). The study subjects and their parent/legal representative will be informed about this new information and reconsent will be obtained.

### 14.5 Subject Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IRBs approving this research, and the United States FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act[20], applicable to national and/or local laws and regulations on personal data protection.

## 15 REPORTING AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the study center when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study-related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately.

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## 17 APPENDICES

## 17.1 Prohibited Medications

| **Drugs Allowed (Y) and Drugs Not Allowed (N) as Concomitant Medications** | | | |
|---|---|---|---|
| *Drug Class* | *Episodic Use (p.r.n)* | *Chronic Use* | *Restrictions* |
| Analgesics | Y | Y | Non-narcotic analgesics only |
| Anesthetics<br>General<br>Local | <br>N<br>Y | <br>N<br>N | |
| Anorexics | N | N | |
| Antacids | Y | Y | |
| Antiacne | Y | Y | Topical agents only; Accutane (isotretinoin) is not allowed. |
| Antianginal Agents | N | N | |
| Antiarrhythmics | N | N | |
| Antibiotics | Y | (Call[a]) | Zyvox (linezolid) is prohibited |
| Anticoagulants | N | Y | Only aspirin (maximum 325 mg/day) is allowed as chronic anti-platelet treatment. |
| Anticonvulsants | N | N | |
| Antidepressants | N | N | |
| Antidiarrheal Preparations | Y | N | Only Imodium (loperamide hydrochloride), Pepto-Bismol, and kaolin preparations are allowed. |
| Antifungal Agents<br>Systemic<br>Topical | <br>N<br>Y | <br>N<br>Y | |
| Antihistamines | Y | (Call[a]) | Only Allegra (fexofenadine), Claritin (loratadine), Clarinex (desloratadine), and Zyrtec (cetirizine) are allowed. See Cough and Cold Preparations for combination products. |
| Antihypertensives | N | Y[b] | Diupres (reserpine), Catapres (clonidine), Minipress (prazosin), Inderal (propranolol), Wytensin (guanabenz), Tenex (guanfacine), and Aldomet (methyldopa) are not allowed. |
| Anti-impotence Medications | (Call[a]) | N | |
| Anti-inflammatory Drugs | Y | Y[c] | Indocin (indomethacin) and systemic corticosteroids are not allowed. |
| Migraine | (Call[a]) | N | Ergotamine or ergot derivatives are not allowed. Call[a] for use of triptans. |
| Antinauseants | Y | N | Only phosphoric acid preparations (Emetrol, Emecheck), Pepto-Bismol and cola syrup are allowed. |

| **Drugs Allowed (Y) and Drugs Not Allowed (N) as Concomitant Medications** | | | |
|---|---|---|---|
| *Drug Class* | *Episodic Use (p.r.n)* | *Chronic Use* | *Restrictions* |
| Antineoplastics | N | N | |
| Antiobesity | N | Y[c] | Only Xenical (orlistat) is allowed |
| Anti-Psoriatic Treatments | Y | Y | Soriatane (acitretin) is not allowed |
| Antipsychotics | N | N | |
| Antiviral Agents | Y | Y[b] | Only Zovirax, Valtrex, and Famvir are allowed |
| Anxiolytics | N | N | |
| Biotin | N | N | Biotin supplement > 2.5 mg total per day is not allowed.<br>Biotin supplement ≤ 2.5 mg total per day is allowed. |
| Cough/Cold Preparations | Y | (Call[a]) | Use of cough and cold preparations containing pseudoephedrine are not permitted. Decongestants containing narcotics are not permitted. See Antihistamines. |
| Diuretics | Y | Y[b] | Episodic use of diuretics is restricted to treatment of premenstrual symptoms. |
| $H_2$ Blockers/Proton pump inhibitors | Y | Y[b] | Tagamet (cimetidine) is not allowed. |
| Hormones | N | Y | Only thyroid hormone replacement, oral contraceptives, patch contraceptives, estrogen and progesterone replacement therapy are allowed. Hormone therapy (including oral contraceptives for female subjects) should not be initiated or discontinued within the 3 months prior to screening. |
| Hormone Suppressants | N | Y[b] | Only Proscar (finasteride) is allowed. |
| Hypoglycemic Agents | Y | Y | |
| Hypolipidemics | N | Y[b] | Only Mevacor (lovastatin), Zocor (simvastatin), Pravachol (pravastatin), Lipitor (atorvastatin), and Lescol (fluvastatin) are allowed. |
| Insulin | N | N | |
| Laxatives | Y | Y[c] | Only fiber-based products and Colace (docusate sodium) are allowed. |
| Muscle Relaxants | N | N | |

| **Drugs Allowed (Y) and Drugs Not Allowed (N) as Concomitant Medications** | | | |
|---|---|---|---|
| *Drug Class* | *Episodic Use (p.r.n)* | *Chronic Use* | *Restrictions* |
| Psychotropic drugs not otherwise specified (including herbal products) | N | N | No drugs with psychomotor effects or with anxiolytic, stimulant, antipsychotic, or sedative properties are allowed. |
| Sedatives/Hypnotics | Y | N | Only Ambien (zolpidem) or Sonata (zaleplon) (no more than 3 times per week), at a maximum dose of 10 mg/day, is permitted if required for sleep. |
| Steroids | | | |
| - Systemic | N | N | |
| - Topical | Y | Y | |
| - Inhalant | Y | Y | |
| Vaccines | Y | N/A | |

Abbreviations: N = No; N/A = not applicable; p.r.n. = pro re nata; Y = yes.
a Call the medical director to discuss.
b If being taken for at least 6 months before study and dose is stabilized.
c If being taken before admission to the study.

### 17.2 Investigator Signature Page

**Protocol Title:** A Randomized, Multicenter, Double-Blind, Flexibly-dosed, Efficacy and Safety Study of Escitalopram in the Treatment of Children and Adolescents With Generalized Anxiety Disorder
**Protocol Number:** SCT-MD-60

**Confidentiality and cGCP Compliance Statement**

I, the undersigned, have reviewed this protocol, including appendices, and I will conduct the study as described in compliance with this protocol, cGCP, and relevant ICH guidelines.

Once the protocol has been approved by the IRB, I will not modify this protocol without obtaining prior approval of Allergan and of the IRB. I will submit the protocol amendments and/or any ICF modifications to Allergan and IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all eCRFs, laboratory samples, or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by Allergan, to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

Investigator Signature Date

Printed Name

Institution

### 17.3 Telehealth

For remote study visits subject data are collected via telephone or telehealth video calls using the technology provider.

**Overall Design**

In order to support the subject's education, engagement and activity completion in the study, subjects will participate by using their own mobile telephone. If the subject's own mobile telephone model and/or operating system does not meet the minimum technology requirements, if the subject does not have a device or chooses not to do video conferencing then regular telephone contact will be allowed. Sites should remain consistent with either methods for each subject.

If the subject decides to use their own mobile device, the subject will be provided with a study-specific mobile application (app) to support reminders/notifications, activity completion, etc. This mobile app will be downloaded by the subject on their own mobile telephone from the Apple (iOS device) or Google Play Store (Android device) upon their receipt of a study-specific email with download hyperlink and unique study access code.

The study-specific mobile application (app) will support the subject to complete study-specific activities such as:

- Receive notifications for an ad-hoc telehealth call.
- Conducting Telehealth Virtual Visits with the investigator and/or authorized site representative.

### 17.4 Protocol Amendment Summary

Protocol version 2.0 dated 15 Mar 2019 is being amended to create protocol version 3.0 dated 30 June 2020. This amended version of the protocol supersedes protocol version 2.0.
This amendment is in reaction to the COVID-19 pandemic and it implements processes to mitigate COVID-19 risks and ensure subject and data quality.
These changes and their rationale are described in detail in the following table.
Minor consistency and administrative changes have also been made.

**Table 2 Protocol SCT-MD-60 Amendment 2.0 dated 30 June 2020 Table of Changes**

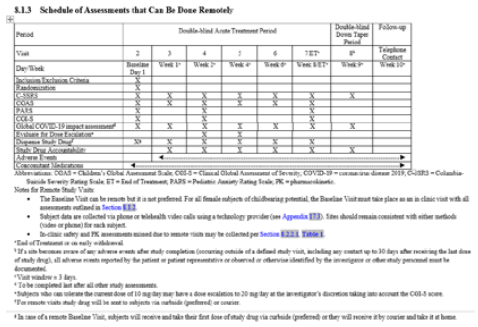
| Location in Amended Protocol | Original Text (Final Protocol Version 2.0 dated 15 Mar 2019) | Revised Text in Amended Protocol (Protocol Version 3.0 dated 30 June 2020) | Rationale for Change |
|---|---|---|---|
| Title page | Syneos Health<br>3201 Beechleaf Court<br>Suite 600<br>Raleigh, NC 27604-1547<br>United States | Syneos Health<br>1030 Sync Street<br>Morrisville, NC 27560<br>United States | Address of contract research organization updated |
| 1 Protocol approval signatures | [redacted], MD PhD<br>Vice President, Clinical Development CNS<br>Allergan<br>5 Giralda Farms<br>Madison, NJ 07940<br>United States<br><br>[redacted]<br>Associate Vice President, Clinical Pharmacology<br>Allergan<br>5 Giralda Farms<br>Madison, NJ 07940<br>United States | [redacted], MS MD<br>Vice President, Neuroscience Development<br>AbbVie<br>[redacted]<br>1 North Waukegan Road<br>North Chicago, IL 60064<br>United States<br><br>[redacted], PhD DABT<br>Vice President, Non-Clinical and Translational Sciences<br>AbbVie<br>2525 Dupont Drive<br>Irvine, CA 92612<br>United States | Sponsor signatories updated |
| 2 Study personnel | Allergan<br>2525 Dupont Drive<br>Irvine, CA 92612<br>United States<br><br>[redacted], PhD<br>Director, Biostatistics | AbbVie<br>2525 Dupont Drive<br>Irvine, CA 92612<br>United States<br><br>[redacted] PhD<br>Director, Biostatistics<br><br>In May 2020, AbbVie completed its acquisition of Allergan. Allergan remains sponsor of this | Updates to account for changes in sponsor personnel and for acquisition of Allergan by AbbVie. |

| Location in Amended Protocol | Original Text (Final Protocol Version 2.0 dated 15 Mar 2019) | Revised Text in Amended Protocol (Protocol Version 3.0 dated 30 June 2020) | Rationale for Change |
|---|---|---|---|
| | | study. AbbVie is used for the addressess of sponsor signatories and sponsor personnel. | |
| 2 Study personnel | Syneos Health<br>3201 Beechleaf Court<br>Suite 600<br>Raleigh, NC 27604-1547<br>United States | Syneos Health<br>1030 Sync Street<br>Morrisville, NC 27560<br>United States | Address of medical director from contract research organization updated |
| 3 Synopsis | | Study design<br>During the coronavirus disease 2019 (COVID-19) pandemic, remote study visits are possible to avoid missing efficacy data but not preferred over clinic visits. | Addition of visit conduct options in response to COVID-19 pandemic |
| 3 Synopsis | Study duration<br>The study design incorporates a 1 to 2 week screening period, … | Study duration<br>The study design incorporates an up to 3-week screening period, … | Screening window extended to allow for more time for safety results and medical records |
| 3 Synopsis | Key inclusion criteria<br>• Subject must be in general good health, weigh at least 20 kg and be within the 3rd to 97th percentile for gender specific body mass index (BMI)-for-age from the World Health Organization growth charts at the Screening and Baseline Visits. | Key inclusion criteria<br>• Subject must be in general good health, weigh at least 20 kg and be within the 3rd to 97th percentile for gender specific body mass index (BMI)-for-age from the Centers for Disease Control and Prevention growth charts at the Screening and Baseline Visits. | Change from WHO (global) to CDC (US-specific) criteria to be more reflective of subject population in the US |
| 3 Synopsis | Key exclusion criteria<br>• Current diagnosis of major depressive disorder, attention-deficit/hyperactivity disorder, or lifetime diagnosis of bipolar disorder, psychotic depression, schizophrenia or other psychotic disorder, feeding and/or eating disorder, obsessive-compulsive disorder, conduct disorder, oppositional defiant disorder, post- | Key exclusion criteria<br>• Current diagnosis of a major depressive episode, or lifetime diagnosis of attention-deficit/hyperactivity disorder, bipolar disorder, psychotic depression, schizophrenia or other psychotic disorder, feeding and/or eating disorder, obsessive-compulsive disorder, conduct disorder, oppositional defiant disorder, post- | Clarification of exclusion criteria |

| Location in Amended Protocol | Original Text (Final Protocol Version 2.0 dated 15 Mar 2019) | Revised Text in Amended Protocol (Protocol Version 3.0 dated 30 June 2020) | Rationale for Change |
|---|---|---|---|
| | traumatic stress disorder, panic disorder, or pervasive development disorder.<br>• Subject answers "yes" to "Suicidal Ideation" item 3 (active suicidal ideation with any methods, not plan, without intent to act), item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) and/or a lifetime history of suicidal behavior, as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS). | traumatic stress disorder, panic disorder, or pervasive development disorder.<br>• Subject answers "yes" to "Suicidal Ideation" item 3 (active suicidal ideation with any methods, not plan, without intent to act), item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) within the past 6 months and/or a lifetime history of suicidal behavior, as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS). | |
| 3 Synopsis | | Secondary Endpoints<br>…<br>• COVID-19 impact assessment score at each visit. | Assessment of COVID-19 impact |
| 3 Synopsis | Efficacy assessments<br>The efficacy assessments include the PARS severity score for GAD, CGI-S, and the CGAS. | Efficacy assessments<br>The efficacy assessments include the PARS severity score for GAD, CGI-S, the CGAS, and a global COVID-19 impact assessment. | Addition of COVID-19 specific assessment |
| 3 Synopsis | Statistical Analysis<br>… The change from baseline in CGI-S and CGAS will be analyzed using the same methodology described for the primary efficacy endpoint. | Statistical Analysis<br>… The change from baseline in CGI-S and CGAS will be analyzed using the same methodology described for the primary efficacy endpoint. The COVID-19 impact assessment score will be summarized at each visit. | Addition of COVID-19 specific assessment |
| 5 List of Abbreviations | | ALT alanine aminotransferase<br>AST aspartate aminotransferase<br>CDC Centers for Disease Control and Prevention | Abbreviations updated |

| Location in Amended Protocol | Original Text (Final Protocol Version 2.0 dated 15 Mar 2019) | Revised Text in Amended Protocol (Protocol Version 3.0 dated 30 June 2020) | Rationale for Change |
|---|---|---|---|
| | | COVID-19 coronavirus disease 2019<br>ULN upper limit normal | |
| | DSMB Data Safety Monitoring Board<br>MAOI monoamine oxidase inhibitor<br>PP per protocol | | Correction, deletion of abbreviations not used |
| 8.1 8.1 Overall Study Design and Plan: Description | The study design incorporates a 1 to 2 week screening period,… | The study design incorporates an up to 3-week screening period,…<br>The coronavirus disease 2019 (COVID-19) pandemic (and any other naming conventions used) developed after this study began and this protocol has been amended to account for study procedures that need to be modified in association with adhering to local safety guidelines or regulations.<br>During the COVID-19 pandemic, remote study visits, in which data are collected via telephone or videoconference, are possible but not preferred. Nearly all scheduled safety assessments, with exception of the Columbia-Suicide Severity Rating Scale (C-SSRS), are not possible by remote visit and must be collected in person via clinic visits. To accommodate changes sites may need to implement during the pandemic, Section 8.1.2 outlines the conduct of study assessments during in-clinic visits, which is the preferred method of conducting the study, while study assessments for remote visits are included in Section 8.1.3. | Screening window extended to allow for more time for safety results and medical records<br>Explanation of COVID-19 specific study processes |
| 8.1.1 Study Design | | Changing the screening period from 2 to 3 weeks in study flow chart (Figure 1). | Screening window extended to allow for more time for safety results and medical records |

| Location in Amended Protocol | Original Text (Final Protocol Version 2.0 dated 15 Mar 2019) | Revised Text in Amended Protocol (Protocol Version 3.0 dated 30 June 2020) | Rationale for Change |
|---|---|---|---|
| 8.1.2 Schedule of Assessments | Screening period Day -14 to -1 | Screening period Day -21 to -1 | Screening window extended to allow for more time for safety results and medical records |
| | | Global COVID-19 impact assessment added for Visits 1, 2, 3, 4, 5, 6, 7/ET including footnote g: To be completed last after all other study assessments | Addition of COVID-19 specific process in line with Section 8.2.2.1 |
| | b If a site becomes aware of any adverse events after study completion (occurring outside of a defined study visit, including any contact up to 30 days after study completion),… | b If a site becomes aware of any adverse events after study completion (occurring outside of a defined study visit, including any contact up to 30 days after receiving the last dose of study drug), … | Harmonization of language for follow-up of adverse events in line with 10.1.2.2 |
| | c Visit window ± 3 days after Visit 2 (Baseline). | c Visit window ± 3 days. Refer to Section 8.2.2.1, Table 1 for visit windows for safety assessments (physical examination, BMI, vital signs, ECG, urine drug screen, clinical chemistry including thyroid, hematology, urinalysis, pregnancy test) and/or PK assessments missed due to remote visits. | Correction and clarification |
| | i Subjects should take their first dose of study drug on site. | j Subjects should take their first dose of study drug in clinic. | Clarification |

| Location in Amended Protocol | Original Text (Final Protocol Version 2.0 dated 15 Mar 2019) | Revised Text in Amended Protocol (Protocol Version 3.0 dated 30 June 2020) | Rationale for Change |
|---|---|---|---|
| 8.1.3 Schedule of Assessments for Remote Visits | | Schedule of Assessments added for visits that can be done remotely<br>  | Introduction of optional remote visits in reaction to the impact of COVID-19 pandemic and to ensure subject safety and data quality |
| 8.2.2.1 COVID-19 Specific Processes | | 8.2.2.1 COVID-19 Specific Processes<br>To promote subject safety and data quality during the COVID-19 pandemic, the following processes will be implemented:<br>• Exclusion of subjects whose anxiety is significantly impacted by COVID-19 as assessed by investigator (see Section 8.3.3).<br>• Global COVID-19 impact assessment (see Section 10.1.1.4).<br>• Visit conduct options allowing remote visits as outlined below:<br>During remote study visits data are collected via telephone or videoconference (see Appendix 17.3).<br>Any clinical assessment (including physical examination, vital signs, urine or blood tests) necessary as part of evaluation of a reported | Introduction of COVID specific processes and visit conduct options in reaction to COVID-19 pandemic and to ensure subject safety and data quality |

| Location in Amended Protocol | Original Text (Final Protocol Version 2.0 dated 15 Mar 2019) | Revised Text in Amended Protocol (Protocol Version 3.0 dated 30 June 2020) | Rationale for Change |
|---|---|---|---|
| | | adverse event (AE) must be performed immediately. If the study site is closed or the subject is unable to travel to the study site, alternate arrangements for in person clinical assessment should be secured.<br><u>Option 1: In-Clinic Visits</u><br>This is the preferred option. All study visits are performed as in-clinic visits with all assessments outlined in the Schedule of Assessments in Section 8.1.2.<br><u>Option 2: Remote Visits (except Screening for all subjects and Baseline Visit for female subjects of childbearing potential)</u><br>This option is only to be used if local guidance and regulations are preventing the site or subject from completing an in-clinic visit. Screening must take place as an in-clinic visit with all assessments outlined in the Schedule of Assessments in Section 8.1.2. The Baseline Visit must take place as an in clinic visit for all female subjects of childbearing potential with all assessments outlined in the Schedule of Assessments in Section 8.1.2 (including pregnancy test). All other visits can be completed remotely with the assessments outlined in Section 8.1.3.<br>Table 1 outlines allowed visit windows if a subject comes into the clinic to complete physical examination, body mass index (BMI), vital signs, electrocardiogram (ECG), urine drug screen, safety lab (clinical chemistry including | |

| Location in Amended Protocol | Original Text (Final Protocol Version 2.0 dated 15 Mar 2019) | Revised Text in Amended Protocol (Protocol Version 3.0 dated 30 June 2020) | Rationale for Change |
|---|---|---|---|
| | | thyroid, hematology, urinalysis), pregnancy test and/or PK.<br>All attempts should be made to collect all safety assessments within 6 weeks of the Visit 7 date, if logistically possible.<br>If a subject is able to switch from remote visits to in clinic visits, the investigator should contact the study monitor for guidance.<br>**Table 1 Visit windows for safety and PK assessments missed due to remote visits**<br>*Visit* / *Assessment* / *Limits for allowance of out-of-window collection*<br>Visit 5/Week 4 / PK / up to 3 weeks early or late (± 21 days) (Section 10.1.3)<br>/ BMI / up to 3 weeks late (+ 21 days)<br>Visit 7/Week 8 or ET / PK / up to 1 week late (+ 7 days) (Section 10.1.3)<br>/ Clinical chemistry, hematology, urine drug screen / up to 1 week late (+ 7 days)*<br>/ Physical examination, BMI, vital signs, ECG, urinalysis, pregnancy test / up to 1 week late (+ 7 days)*<br>Visit 8/Week 9 / Vital signs / up to 1 week late (+ 7 days)*<br>Abbreviations: BMI = body mass index; ECG = electrocardiogram; ET = End of Treatment; PK = pharmacokinetic.<br>Note, if subjects cannot do the assessments within these timeframes, it will be noted as missing assessment(s) for that visit.<br>NOTE: PK assessments outside the above visit windows should not be done at all.<br>* For purposes of including as safety endpoints, these assessments will be included in the safety analysis if collected up to 1 week late. Any safety data collected 8 days to 42 days late will be considered missing for analysis purposes. The 6-week window is allowed to capture any follow-up safety data on the participant and will be noted in the final study report (see also Section 11.0). | |
| 8.3.1 Number of Planned Subjects | … Based on this, the sample size may be increased to ensure an adequate power. ….<br><br>Re-screening of subjects who do not meet the entry criteria is not allowed. Re-screening may be performed for logistical reasons (eg, scheduling of visits), but a subject can only be re-screened once. | … Based on this, the sample size may be increased to ensure an adequate power due to variance assumption deviation as well as increased variance due to COVID-19 remote visits….<br>Re-screening of subjects who do not meet the entry criteria is not allowed, except for the reasons outlined in Section 8.3.4. A subject can only be re-screened once. | Updates on re-screening in reaction to the COVID-19 pandemic |
| 8.3.2 Inclusion Criteria | 14. Subject weighs at least 20 kg and is within the 3rd to 97th percentile for gender specific body mass index (BMI)-for-age from the World | 14. Subject weighs at least 20 kg and is within the 3rd to 97th percentile for gender specific BMI-for-age from the Centers for Disease | Changed from WHO (global) to CDC (US-specific) criteria to be more |

| Location in Amended Protocol | Original Text (Final Protocol Version 2.0 dated 15 Mar 2019) | Revised Text in Amended Protocol (Protocol Version 3.0 dated 30 June 2020) | Rationale for Change |
|---|---|---|---|
| | Health Organization (WHO) growth charts at the Screening and Baseline Visits. | Control and Prevention (CDC) growth charts at the Screening and Baseline Visits. | reflective of subject population in the US |
| 8.3.3 Exclusion Criteria | 1. Current diagnosis of MDD, attention-deficit/hyperactivity disorder, or lifetime diagnosis of bipolar disorder, psychotic depression, schizophrenia or other psychotic disorder, feeding and/or eating disorder, obsessive-compulsive disorder, conduct disorder, oppositional defiant disorder, post-traumatic stress disorder, panic disorder, or pervasive development disorder. | 1. Current diagnosis of a major depressive episode, or lifetime diagnosis of attention deficit/hyperactivity disorder, bipolar disorder, psychotic depression, schizophrenia or other psychotic disorder, feeding and/or eating disorder, obsessive-compulsive disorder, conduct disorder, oppositional defiant disorder, post-traumatic stress disorder, panic disorder, or pervasive development disorder. | Clarification of exclusion criterion |
| | 7. Subject answers “yes” to “Suicidal Ideation” item 3 (active suicidal ideation with any methods, not plan, without intent to act), item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) and/or a lifetime history of suicidal behavior, as assessed by the C-SSRS. | 7. Subject answers “yes” to “Suicidal Ideation” item 3 (active suicidal ideation with any methods, not plan, without intent to act), item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) within the past 6 months and/or a lifetime history of suicidal behavior, as assessed by the C-SSRS. | Clarification of exclusion criterion |
| | 23. Unlikely to comply with study requirements or unsuitable for any reason, based on investigator judgement. | 23. Unlikely to comply with study requirements or unsuitable for any reason, including any indication the subject may be significantly impacted by the COVID-19 (or associated virus) pandemic, based on investigator judgement. | Addition of precautions for screening in response to COVID-19 pandemic |
| | | 25. Family members or individuals living in the same household as the study subject. | Addition to avoid data bias |

| Location in Amended Protocol | Original Text (Final Protocol Version 2.0 dated 15 Mar 2019) | Revised Text in Amended Protocol (Protocol Version 3.0 dated 30 June 2020) | Rationale for Change |
|---|---|---|---|
| 8.3.4 Re-screening | | 8.3.4 Re-screening<br>Re-screening is allowed only under the following exceptional circumstances. Note a subject can only be re-screened once.<br>• Logistical reasons (eg, scheduling of visits).<br>• Subjects who have not yet completed washout of fluoxetine at screening can be re-screened once washout is completed. The medical monitor is to be contacted in these cases.<br>• For subjects who failed screening according to the BMI criteria based on WHO growth charts.<br>• Screen failures due to a recruitment hold. Subjects can be re-screened once the recruitment hold is lifted. | Addition of rescreen criteria in line with other amendment changes |
| 8.3.5 Removal of Subjects From the Study | | • Due to the COVID-19 pandemic | COVID-19 specific update |
| 8.4.6 Selection and Timing of Dose for Each Subject | …<br>Subjects will receive their first dose of study drug on site on Day 1. Subjects will then self-administer the investigational product on an outpatient basis once a day. Subjects should be instructed to administer investigational product at approximately the same time each day including on days when clinic visits occur. Subjects may take investigational product with or without food. To allow for PK sampling, subjects receiving study drug in the morning | For in-clinic visits according to Option 1 in Section 8.2.2.1:<br>Subjects will receive their first dose of study drug on site on Day 1. Subjects will then self-administer the investigational product on an outpatient basis once a day. Subjects should be instructed to administer investigational product at approximately the same time each day including on days when clinic visits occur. Subjects may take the investigational product with or without food. To allow for PK sampling | Addition of text on remote visits in line with Section 8.2.2.1 |

| Location in Amended Protocol | Original Text (Final Protocol Version 2.0 dated 15 Mar 2019) | Revised Text in Amended Protocol (Protocol Version 3.0 dated 30 June 2020) | Rationale for Change |
|---|---|---|---|
| | will be instructed to withhold taking the morning dose on the day of the Week 4 Visit (Visit 5) and to bring their study drug to the visit. Subjects receiving study drug in the evening should take their dose in the evening before the visit. | during in clinic visits, subjects receiving study drug in the morning will be instructed to withhold taking the morning dose on the day of the Week 4 Visit (Visit 5) and to bring their study drug to the visit. Subjects receiving study drug in the evening should take their dose in the evening before the visit.<br>For remote visits according to Option 2 in Section 8.2.2.1:<br>Subjects will receive and take their first dose of study drug on Day 1 via curbside (preferred) or they will receive it by courier and take it at home. Subjects will then self-administer the investigational product on an outpatient basis once a day. Subjects should be instructed to administer investigational product at approximately the same time each day including on days when remote visits are scheduled. Subjects may take the investigational product with or without food. | |
| 8.4.8.1 Prohibited Medication/ Therapy | | Subjects must stop all antidepressant treatment (except for fluoxetine) at least 14 days prior to randomization. Antidepressant treatment includes SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), bupropion, and tricyclic antidepressants.<br>Subjects must stop fluoxetine at least 28 days prior to randomization. If the subject is taking fluoxetine at the time of screening, the subject may need to be screen failed and then re-screened once the washout is complete. Please | Clarification of washout of antidepressant treatments |

| Location in Amended Protocol | Original Text (Final Protocol Version 2.0 dated 15 Mar 2019) | Revised Text in Amended Protocol (Protocol Version 3.0 dated 30 June 2020) | Rationale for Change |
|---|---|---|---|
| | | contact the medical monitor for guidance (see Section 8.3.4). | |
| 9.1.1 Screening Visit | | • Complete global COVID-19 impact assessment. | Addition of global COVID-19 impact assessment in line with Section 8.2.2.1 |
| 9.1.2 Baseline Visit | Subjects should take their first dose of study drug on site on Day 1 | • Complete global COVID-19 impact assessment.<br>Subjects should take their first dose of study drug in clinic on Day 1.<br>Refer to Section 8.1.3 for procedures and assessments if Visit 2 is done remotely. For remote visits, subjects will receive and take their first dose of study drug via curbside (preferred) or they will receive it by courier and take it at home. | Addition of global COVID-19 impact assessment in line with Section 8.2.2.1<br>Clarification<br>Addition of language for remote visits. |
| 9.2.1 Week 1 (Visit 3) | | • Complete global COVID-19 impact assessment.<br>Refer to Section 8.1.3 for assessments if Visit 3 is done remotely. Study drug will be delivered to subjects via curbside (preferred) or courier. | Addition of global COVID-19 impact assessment in line with Section 8.2.2.1<br>Addition of language for remote visits. |
| 9.2.2 Week 2 (Visit 4) | | • Complete global COVID-19 impact assessment.<br>Refer to Section 8.1.3 for assessments if Visit 4 is done remotely. Study drug will be delivered to subjects via curbside (preferred) or courier. | Addition of global COVID-19 impact assessment in line with Section 8.2.2.1<br>Addition of language for remote visits. |

| Location in Amended Protocol | Original Text (Final Protocol Version 2.0 dated 15 Mar 2019) | Revised Text in Amended Protocol (Protocol Version 3.0 dated 30 June 2020) | Rationale for Change |
|---|---|---|---|
| 9.2.3 Week 4 (Visit 5) | | • Complete global COVID-19 impact assessment.<br><br>Refer to Section 8.1.3 for assessments and to Table 1 for assessment windows if Visit 5 is done remotely. Study drug will be delivered to subjects via curbside (preferred) or courier. | Addition of global COVID-19 impact assessment in line with Section 8.2.2.1<br>Addition of language for remote visits. |
| 9.2.4 Week 6 (Visit 6) | | • Complete global COVID-19 impact assessment.<br><br>Refer to Section 8.1.3 for assessments if Visit 6 is done remotely. Study drug will be delivered to subjects via curbside (preferred) or courier. | Addition of global COVID-19 impact assessment in line with Section 8.2.2.1<br>Addition of language for remote visits. |
| 9.2.5 Week 8 (Visit 7) | | • Complete global COVID-19 impact assessment.<br><br>Refer to Section 8.1.3 for assessments and to Table 1 for assessment windows if Visit 7 is done remotely. Study drug will be delivered to subjects via curbside (preferred) or courier. All attempts should be made to collect safety labs within 6 weeks of the Visit 7 date. | Addition of global COVID-19 impact assessment in line with Section 8.2.2.1<br>Addition of language for remote visits. |
| 9.3.1 Week 9 (Visit 8) | | Refer to Section 8.1.3 for assessments and to Table 1 for assessment windows if Visit 8 is done remotely. | Addition of language for remote visits. |
| 9.7 End of Study | | 9.7 End of Study<br>A subject will have fulfilled the requirements for study completion when the subject has completed all study periods, including the last scheduled follow-up telephone contact at Week | Clarification and definition of end of study |

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| | | 10 as indicated in the Schedule of Assessments in Section 8.1.2.<br>The end of the study will be the last subject's last scheduled follow-up telephone contact at Week 10 as indicated in the Schedule of Assessments in Section 8.1.2. | |
| 10 Efficacy, Safety, and Pharmacokinetic Assessments | | The modified Schedule of Assessments in conjunction with the COVID-19 pandemic is in Section 8.1.3 and the options for conducting remote visits are outlined in Section 8.2.2.1. For any efficacy or safety assessment data that are collected during a remote visit, the appropriately trained study center staff may conduct the assessment by telephone or videoconference. Sites should remain consistent with the method used for each subject. | Explanation |
| 10.1.1.4 Global COVID-19 Impact Assessment | | 10.1.1.4 Global COVID-19 Impact Assessment<br>A global COVID-19 impact assessment will be used to evaluate the impact of the coronavirus disease pandemic on the severity of the subject's GAD during the last 1 week. The rating will include scores from 0 (not applicable, subject not enrolled in the trial during the pandemic) to 7 (extreme impact). Raters will also evaluate whether the impact was an improvement or worsening of the subject's GAD. The global COVID-19 impact assessment will be completed last after all study assessments by appropriately qualified study center staff and the scores recorded on the eCRF. Every effort should be | Addition of coronavirus disease specific process in line with Section 8.2.2.1 |

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| | | made to ensure that the assessments are completed by the same assessor at each visit. | |
| 10.1.2.2 Adverse Events | Follow-up of Adverse Events<br>All investigators should follow up subjects with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF.<br>Subjects should be followed up for 30 days after receiving the last dose of study drug, and any AEs that occur during this time should be reported according to the procedures outlined above.<br>Documentation and Reporting of Adverse Events | Follow-up of Adverse Events<br>All investigators should follow up subjects with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF.<br>Documentation and Reporting of Adverse Events<br>All AEs from the signing of the informed consent form (ICF) until 30 days after receiving the last dose of study drug will be collected according to the procedures outlined above at the timepoints specified in the Schedule of Assessments (Section 8.1.2/8.1.3), and as observed or reported spontaneously by study participants. | Harmonization of language for follow-up of adverse events |
| 10.1.2.2.1 Serious Adverse Events | Any SAE must be reported by the investigator if it occurs during the clinical study or within 30 days of receiving the study drug, whether or not the SAE is considered to be related to the investigational product. | Any SAEs from the signing of the ICF until 30 days after receiving the last dose of study drug will be collected according to the procedures outlined above at the timepoints specified in the Schedule of Assessments (Section 8.1.2/8.1.3), and as observed or reported spontaneously by study participants, whether or not the SAE is | Harmonization of language for follow-up of adverse events |

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| | | considered to be related to the investigational product. | |
| 10.1.2.2.2 Reporting of Pregnancies Occurring During the Study | Study site personnel must report every pregnancy from the time the subject signs the informed consent form (ICF) until 30 days following the last dose of investigational product. | Study site personnel must report every pregnancy from the time the subject signs the ICF until 30 days after receiving the last dose of study drug. | Harmonization of language for follow-up of adverse events |
| 10.1.2.2.6 10. Potential Hy's Law Cases | | 10.1.2.2.6 Potential Hy's Law Cases<br>Criteria for potential Hy's law cases are as follows:<br>• Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 × upper limit of normal (ULN) AND<br>• Total bilirubin ≥ 2 × ULN AND<br>• Alkaline phosphatase < 2 × ULN<br>Study site personnel must report every subject who meets these criteria. Typically, all 3 analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period. This requirement applies from the time the subject signs the ICF for the study until 30 days after receiving the last dose of study drug.<br>A laboratory alert for potential Hy's laws cases will be in place, and the laboratory must notify investigators and the sponsor immediately when the above criteria have been met. A potential Hy's law case must be reported to the sponsor on an SAE form as soon as possible (within 24 hours of learning of the potential Hy's law case) to the SAE/pregnancy fax number, even if no AE | Addition for subject safety |

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| | | has occurred. The eCRF for potential Hy's law cases must be completed within 7 calendar days. Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in conjunction with the Study Medical Monitor and in accordance with the FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009. The patient should return to the study site and be evaluated as soon as possible, preferably within 48 hours from the time the investigator becomes aware of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical examination. | |
| 10.1.3.1 Study Drug Concentration Measurements | | For subjects who cannot go the site for scheduled visits due to the COVID 19 pandemic, PK sample collection can occur at the times specified in Section 8.2.2.1, Table 1. | Addition to align with changes in Section 8.2.2.1 |
| 11.2 Disposition | | Subjects whose disposition status was impacted by the COVID-19 pandemic will also be summarized. | Update to consider COVID-19 impact in disposition data |
| | Screen failures (ie, subjects who were screened but not included in the Randomized Population) and the associated reasons for failure will be tabulated overall. Subjects completing the Week 8 assessment will be considered completers. | Screen failures (ie, subjects who were screened but not included in the Randomized Population) and the associated reasons for failure will be tabulated overall.<br><br>Protocol deviations that occur due to COVID-19 will be summarized and listed separately. | |

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| 11.5.1.1 Primary Efficacy Analysis | | Sensitivity analyses will be conducted on the primary efficacy endpoint to assess the missing at random assumption of the MMRM model and the impact of COVID-19 using remote home assessment. Details will be provided in the SAP. | Addition to consider COVID-19 impact in efficacy data |
| 11.5.1.1.1 Estimand for the Primary Efficacy Analysis | The second will be a sensitivity analysis using a pattern-mixture model. The commonly applied "copy reference" method may be employed. | The second will be a sensitivity analysis using a pattern-mixture model. | Correction |
| 11.5.1.2 Secondary Efficacy Parameters | | • COVID-19 impact assessment score at each visit. | Additional secondary endpoint for assessment of COVID-19 impact |
| 11.5.1.2.4 COVID-19 Impact Assessment Score at each Visit | | 11.5.1.2.4 COVID-19 Impact Assessment Score at each Visit<br>The COVID-19 impact assessment score will be summarized at each visit. | Addition to align with additional secondary endpoint |
| 11.6 Safety Analysis | | Safety data collected outside of planned visit windows but within allowance limits (up to 1 week late for Visits 7 and 8) will be included in the summary tables. Safety data collected outside of planned visit windows and outside of the allowance limits (>1 week to 6 weeks late for Visits 7 and 8) will be listed, but will not be included in the summary tables. Subgroup analyses may be performed to assess the impact of COVID-19 on the safety analyses. | Addition to align with changes in Section 8.2.2.1 |
| 11.6.1.1 Adverse Events | | Each AE summary described above will be presented as all AEs, AEs that are associated with the COVID-19 pandemic (as determined by | Addition to consider COVID-19 impact in summary of safety data |

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| | | the investigator), and AEs that are not associated with the COVID-19 pandemic. AEs associated with the COVID-19 pandemic will be listed separately. | |
| 11.8 Interim Analyses | If the estimated pooled standard deviation is larger than the assumed pooled standard deviation in the sample size calculation (see Section 11.9), sample sizes in placebo and escitalopram treatment groups may be increased to ensure an adequate power. | If the estimated pooled standard deviation is larger than the assumed pooled standard deviation in the sample size calculation due to assumption deviation as well as COVID-19 remote visits (see Section 11.9), sample sizes in placebo and escitalopram treatment groups may be increased to ensure an adequate power. | Additional language to account for remote visits |
| 13.1 Drug Accountability | | In addition, sites will be provided a separate Investigational Product Curbside Pickup and Shipment Tracking Form to document pertinent study drug dispensing information each time a new shipment of study drug is shipped directly to a subject's residence, dispensed curbside at the site, or delivered to a subject's residence via site personnel. Sites will be instructed to submit this form to Syneos Health any time study drug is dispensed using these methods. | Additional language for remote visits. |
| 17.1 Clinical Global Impression of Severity | 1. Normal—not at all ill, symptoms of disorder not present past 7 days<br>2. Borderline mentally ill—subtle or suspected pathology<br>3. Mildly ill—clearly established symptoms with minimal, if any, distress or difficulty in social and occupational function<br>4. Moderately ill—overt symptoms causing noticeable, but modest, functional | | Deleted for consistency as no other assessments are included in the protocol appendix. |

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| | impairment or distress; symptom level may warrant medication<br>5. Markedly ill—intrusive symptoms that distinctly impair social/occupational function or cause intrusive levels of distress<br>6. Severely ill—disruptive pathology, behavior and function are frequently influenced by symptoms, may require assistance from others<br>7. Among the most extremely ill patients—pathology drastically interferes in many life functions; may be hospitalized | | |
| 17.1 Prohibited Medication | Hormones<br>Only thyroid hormone replacement, oral contraceptives, patch contraceptives, estrogen and progesterone replacement therapy are allowed. | Hormones<br>Reference to footnote b removed<br>Hormone therapy (including oral contraceptives for female subjects) should not be initiated or discontinued within the 3 months prior to screening. | Update to align with changes in Section 8.4.8.1 for washout of antidepressant medication. |
| 17.3 Telehealth | | 17.3 Telehealth<br>For remote study visits subject data are collected via telephone or telehealth video calls using the technology provider.<br>Overall Design<br>In order to support the subject's education, engagement and activity completion in the study, subjects will participate by using their own mobile telephone. If the subject's own mobile telephone model and/or operating system does not meet the minimum technology requirements, if the subject does not have a device or chooses not to do video conferencing then regular | Addition of information on data collection via telephone or video calls for remote visits. |

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| | | telephone contact will be allowed. Sites should remain consistent with either methods for each subject.<br>If the subject decides to use their own mobile device, the subject will be provided with a study-specific mobile application (app) to support reminders/notifications, activity completion, etc. This mobile app will be downloaded by the subject on their own mobile telephone from the Apple (iOS device) or Google Play Store (Android device) upon their receipt of a study-specific email with download hyperlink and unique study access code.<br>The study-specific mobile application (app) will support the subject to complete study-specific activities such as:<br>• Receive notifications for an ad-hoc telehealth call.<br>• Conducting Telehealth Virtual Visits with the investigator and/or authorized site representative. | |