Document Type: Statistical Analysis Plan

Protocol Title: An Open-Label Study to Assess the Long-term Safety and Efficacy of AXS-05 in Subjects with Treatment Resistant Depression

ClinicalTrials.gov Identifier: NCT04634669

Document Date: February 21, 2022

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STATISTICAL ANALYSIS PLAN

VERSION: FINAL
DATE: FEBRUARY 21, 2022

STUDY DRUG:

AXS-05 (dextromethorphan-bupropion)

PROTOCOL NUMBER:

AXS-05-TRD-202

STUDY TITLE:

An Open-Label Study to Assess the Long-term Safety and Efficacy of AXS-05 in Subjects with Treatment Resistant Depression

SPONSOR:

Axsome Therapeutics

[redacted]

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

SIGNATURE PAGE

This document has been prepared and/or reviewed by:

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
AXS	Axsome Therapeutics
BID	Twice Daily (bis in die)
BUP	Bupropion
CGI-I	Clinical Global Impression of Improvement of Illness
CGI-S	Clinical Global Impression of Severity of Illness
CPFQ	Cognition and Physical Functioning Questionnaire
CRF	Case Report Form
C-SSRS	Columbia – Suicide Severity Rating Scale
DM	Dextromethorphan
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
HAM-A	Hamilton Anxiety Rating Scale
ITT	Intent-to-Treat Population
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified Intent-to-Treat Population
QIDS-SR-16	Quick Inventory of Depressive Symptomatology-Self- Rated
QD	Once Daily (quoque die)
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCID-5-CT	Structured Clinical Interview for DSM-5, Clinical Trials Version
SD	Standard Deviation
SDS	Sheehan Disability Scale
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Events

USA	United States of America
VAMS	Visual Analog Mood Scale

2. INTRODUCTION

This statistical analysis plan (SAP) is based on Protocol AXS-05-TRD-202, Amendment 2 Version dated November 08, 2021.

The purpose of this document is to provide details on study populations and on how the variables will be derived, how missing data will be handled, as well as details on statistical methodologies to be used to analyze the safety and efficacy data from the study. SAP may be revised, for example, due to protocol amendments or regulatory feedback. Each approved SAP will be numbered sequentially as Version I. The final approved SAP to be implemented for the analyses must be documented before database lock and should be label as "Version: Final" with a date. Methodologies described in the Final version will be carried out. Deviations from the Final version, if any, will be discussed in the Clinical Study Report (CSR).

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of this study is to evaluate the long-term safety of AXS-05 for the treatment of treatment resistant depression (TRD).

3.2. Secondary Objective

The secondary objective of this study is to evaluate the long-term clinical efficacy outcomes of AXS-05 for the treatment of TRD.

4. STUDY DESIGN

This study is a multi-center, open-label trial to evaluate the long-term safety and efficacy of AXS-05 in subjects with TRD. Eligible subjects must have either completed Study AXS-05-TRD-201 immediately prior to enrollment in this study or must meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for MDD without psychotic features. Eligible subjects receive AXS-05 [redacted] twice daily for up to 15 months. Subjects return to clinic every week for 2 weeks, then every 2 weeks for the next 6 weeks, then monthly thereafter (Months 3-15). At all visits, subjects are assessed for safety by adverse events (AE), vital signs, and the Columbia - Suicide Severity Rating Scale (C-SSRS). At Visit 1, and at Months 3, 6, 9, 12, and 15, clinical laboratory examinations, electrocardiograms (EGCs), and physical examinations are also performed. Subject- and clinician-reported assessments including the Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impression of Severity (CGI-S), Hamilton Anxiety Scale (HAM-A), Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ), the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF), and the Sheehan Disability Scale (SDS) are assessed at Visit 1, Week 1, Week 2, Week 4, Week 6, and Months 2, 3, 6, 9, 12, and 15. The Clinical Global Impression of Improvement (CGI-I) is assessed at Week 1, Week 2, Week 4, Week 6, and Months 2, 3, 6, 9, 12, and 15.

[redacted]

4.1. Sample Size Justification

This study planned to enroll approximately 150 subjects. This sample size allows for an assessment of the long-term safety and efficacy in patients with TRD.

5. STUDY DURATION AND VISIT SCHEDULE

Eligible subjects are treated with open-label AXS-05 for up to 15 months. The visit schedule is outlined in Table 2.

Table 2: Schedule of Assessments

Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19 / ETV
Study Day/Week	**D1[f]**	**Wk 1 (± 2d)**	**Wk 2 (± 2d)**	**Wk 4 (± 3d)**	**Wk 6 (± 3d)**	**Mo 2 (± 7d)**	**Mo 3 (± 7d)**	**Mo 4 (± 7d)**	**Mo 5 (± 7d)**	**Mo 6 (± 7d)**	**Mo 7 (± 7d)**	**Mo 8 (± 7d)**	**Mo 9 (± 7d)**	**Mo 10 (± 7d)**	**Mo 11 (± 7d)**	**Mo 12 (± 7d)**	**Mo 13 (± 7d)**	**Mo 14 (± 7d)**	**Mo 15 (± 7d)**
Informed Consent	X																		
Inclusion/Exclusion Criteria	X																		
Physical Examination	X*						X			X			X			X			X
ECG[d]	X*						X			X			X			X			X
Serum Chemistry	X*						X			X			X			X			X
Vital Signs, Height/Weight[a]	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[b]	X*			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
MADRS	X*	X	X	X	X	X	X			X			X			X			X
CGI-I		X	X	X	X	X	X			X			X			X			X
CGI-S	X*	X	X	X	X	X	X			X			X			X			X
HAM-A	X	X	X	X	X	X	X			X			X			X			X
CPFQ	X	X	X	X	X	X	X			X			X			X			X
Q-LES-Q-SF	X	X	X	X	X	X	X			X			X			X			X
SDS	X	X	X	X	X	X	X			X			X			X			X
C-SSRS	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensation[c]	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Accountability		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

*Conducted as part of the End of Study (EOS) visit during Study AXS-05-TRD-201

Abbreviations: C-SSRS = Columbia - Suicide Severity Rating Scale; CGI-I =Clinical Global Impression of Improvement; CGI-S =Clinical Global Impression of Severity; D = day; CPFQ = Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire; ECG = electrocardiogram; ETV = early termination visit; HAM-A = Hamilton Anxiety Scale; MADRS =Montgomery-Åsberg Depression Rating Scale; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; SDS = Sheehan Disability Scale; Wk = week.

a Vital signs, including blood pressure, pulse, respiratory rate, and oral body temperature, is measured after the subject has been in a seated position for at least 5 minutes. Weight willbe measured at each visit and height will only be measured at Visit 1.

b Required only for females of childbearing potential.

c Study drug can be re-dispensed, when appropriate.

d Subjects should rest in the supine position for at least 2 minutes prior to performing ECG.

[redacted]

6. CLINICAL ASSESSMENTS

6.1. Efficacy

6.1.1. Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS [1] is a clinician-rated scale used to assess depressive symptomatology during the previous week. Subjects are rated on 10 items to assess feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty concentrating and lack of interest. Each item is scored on a 7-point scale. A score of 0 indicates the absence of symptoms, and a score of 6 indicates symptoms of maximum severity. Total scores range from 0 to 60, with higher scores representing more severe depression.

6.1.2. MADRS-6 Subscale (Core Symptoms)

The MADRS-6 is a 6-item subscale of the MADRS evaluating the core symptoms of depression – apparent sadness, reported sadness, inner tension, lassitude, inability to feel, and pessimistic thought. Total scores range from 0 to 36, with higher scores representing more severe core symptoms of depression.

6.1.3. MADRS-5 Subscale (Anhedonic Symptoms)

The MADRS-5 is a 5-item subscale of the MADRS evaluating the anhedonic symptoms of depression – apparent sadness, reported sadness, concentration difficulties, lassitude, and inability to feel. Total scores range from 0 to 25, with higher scores representing more severe anhedonia symptoms of depression.

6.1.4. Clinical Global Impression – Improvement (CGI-I)

The CGI-I scale [2] is a one item, clinician-rated scale that is used to rate total improvement or worsening of mental illness regardless of whether the clinician considers it to be a result of drug treatment or not. The subject is rated on a scale from 1 to 7, with 1 indicating that the subject is very much improved and 7 indicating that the subject is very much worse.

6.1.5. Clinical Global Impression – Severity (CGI-S)

The CGI-S scale [2] is a one-item, clinician-rated scale used to rate the severity of the subject's current state of mental illness compared with a subject population with TRD. The subject is rated on a scale from 1 to 7, with 1 indicating a "normal state" and 7 indicating "among the most extremely ill subjects".

6.1.6. Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q LES Q SF)

The Q-LES-Q-SF [3] is a patient-reported, 16-item questionnaire designed to measure of the degree of enjoyment and satisfaction experienced by subjects in various areas of daily

functioning. Each item is scored from 0 (very poor) to 5 (very good). The total raw score is the sum of the first 14-items, ranging from 14 to 70. The raw total score is transformed into a percentage maximum possible score using the following formula:

(raw total score − minimum score [14]) /
(maximum possible raw score [70] − minimum score).

The percent of maximum score ranges from 0% to 100%, with higher scores represent better quality of life.

6.1.7. Sheehan Disability Scale (SDS)

The SDS [4] is a 3-item patient-reported questionnaire used to evaluate impairments in areas of the subject's life. The scale evaluates 3 domains: work, social life/leisure, and family life/home responsibility. Each domain is rated on an 11-point continuum (0 = no impairment to 10 = most severe). The total score is the sum of the 3 domains, ranging from 0 to 30, with higher scores representing greater disability.

6.1.8. Hamilton Rating Scale for Anxiety (HAM-A)

The HAM-A [5] is a 14-item, clinician-administered scale to evaluate symptoms of anxiety. Each item is rated on a five-point scale ranging from 0 (not present) to 4 (very severe). The total score is the sum of each item, scores range from 0 to 56, where higher scores representing greater severity of anxiety.

6.1.9. Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ)

The CPFQ [6] is a 7-item, patient-rated scale used to measure cognitive and executive dysfunction in mood and anxiety disorders and was developed to assess clinically relevant cognitive and physical symptoms that could emerge or persist during long-term treatment for depression. Subjects grade the perceived quality of both their physical and cognitive functioning. The CPFQ is comprised of 7 distinct items: motivation/enthusiasm, wakefulness/alertness, energy, focus/attention, recall, ability to find words, and sharpness/mental acuity. Each item is scored from 1 (greater than normal) to 6 (totally absent). The total scores ranges from 7 to 42, with higher scores indicating worsening effects on cognition and physical functioning.

The CPFQ is comprised of two dimensions, physical and cognitive. The physical dimension assesses sleepiness and fatigue, and the cognitive dimension assesses apathy, inattention, forgetfulness, word-finding difficulties, and mental slowness.

6.2. Safety

Safety assessments include the evaluation of treatment-emergent adverse events (TEAEs), clinical laboratory test results, ECGs, vital sign measurements, and C-SSRS. Clinically significant physical examination findings are recorded as adverse events.

6.3. Adverse Events

The definitions, management of, and special considerations for AEs are provided in Section 10 of the protocol.

6.3.1. Clinical Laboratory Safety Assessments

The following clinical laboratory assessments are collected:

- Serum Chemistry: Albumin, total bilirubin, direct bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, random glucose, sodium, potassium, and chloride.

- Urine Pregnancy Test: For females of childbearing potential. A test will be performed on site at each study visit.

6.3.2. Vital Signs

Vital signs include seated blood pressure, pulse, respiratory rate, and oral body temperature. Blood pressure is measured after the subject has been in a sitting position for 5 minutes. Height is only collected at Visit 1 and weight is collected at all study visits.

6.3.3. Electrocardiogram (ECG)

A 12-lead ECG is conducted after the subject has been resting (supine) for at least 2 minutes. At a minimum, the following parameters should be collected; PR interval, QRS duration, and QTcF.

The date and time of last dose prior to each ECG is recorded.

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

The C-SSRS [7] is a clinician-rated scale that reports the severity of both suicidal ideation and behavior. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent).

If the subject reports active suicidal ideation, the C-SSRS captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt). More than 1 classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts.

At all visits the C-SSRS is completed with a recall period since the last visit.

7. DEFINITIONS AND CONVENTIONS

7.1. General Considerations

Continuous data will be summarized using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Frequencies and percentages will be used to summarize categorical (discrete) data. Presentations of categorical data will generally suppress percentages for items where the count is zero in order to draw attention to the nonzero counts. In general, mean, standard deviation (SD), median, minimum, maximum, and percentages will be presented with one decimal.

Data listings will present all data collected on case report forms (CRFs) by group, center, and subject number.

7.2. Subject Grouping

The study is enrolling two groups of subjects: Rollover Group (subjects who previously participated in Study AXS-05-TRD-201), and Direct Entry Group (subjects who had not previously participated in AXS-05-TRD-201). The Rollover Group will be further noted as "Rollover AXS-05" or "Rollover Placebo". In general, data will be presented by Group (Rollover AXS-05, Rollover Placebo, and Direct Entry) and Overall.

7.3. Baseline

Unless otherwise stated, the last observed measurement prior to or on the date of enrollment will be considered the baseline measurement.

7.4. Analysis Populations

7.4.1. Safety Population

The Safety population will include all subjects who have received at least one dose of study medication. All safety analyses will use the safety population.

7.4.2. mITT Population

The modified Intent-to-Treat (mITT) population will consist of all who are enrolled, take at least 1 dose of study drug, and have at least 1 post-baseline efficacy assessment.

7.5. Data Quality Assurance

Accurate and reliable data collection is ensured by verification and cross check of the CRFs against the investigator's records by the study monitor (source document verification) and by the maintenance of a drug–dispensing log by the investigator. Collected data is entered into a computer database and subject to electronic and manual quality assurance procedures.

8. DESCRIPTION OF THE STUDY POPULATIONS

All tables, figures, and listings will include a population descriptor (e.g., mITT or Safety) in the titles.

8.1. Subject Disposition

Subject disposition summaries will be presented by group and overall. The summaries will include the number of subjects enrolled and the number of subjects in the safety and mITT populations, as well as the number and percentage of subjects who complete the study. The summaries will also include the reasons for early discontinuation from the study.

8.2. Demographics and Baseline Characteristics

A summary of demographics and baseline characteristics will be presented by group and overall for the Safety and mITT populations. The demographic characteristics will, at a minimum, consist of age, sex, ethnicity, and race using descriptive statistics.

Clinical baseline characteristics summarized for the Safety and mITT populations will include, at minimum, psychiatric history.

8.3. Medical History

A listing of medical history (both ongoing and past conditions) will be presented for the Safety population.

8.4. Prior and Concomitant Medication

All medications recorded on the CRFs will be coded using the WHO Drug Dictionary Version March 2021. Prior and concomitant medications will be summarized by group and overall for the Safety population by anatomical therapeutic chemical (ATC) Class Level 4 and WHO Drug base substance preferred name.

Prior medications are defined as medications with stop dates occurring before the date of first administration of any study treatment. Concomitant medications are defined as medications with start dates occurring on or after the date of first administration of any study treatment and no more than 30 days after the last study visit. Medications with start and stop dates that bracket the date of first administration of a study treatment will be summarized as both prior and concomitant medications.

Medications that were clearly stopped prior to the date of first administration of study treatment will be included in the prior medications table, and medications that were clearly started on or after the date of first administration of study treatment will be included in the concomitant medications table. All other medications will be included in both the prior and concomitant medications tables.

8.5. Identification and Summary of Protocol Deviations

Major protocol deviations will be summarized as far as they can be extracted from numeric or coded study data. All protocol deviations (major and minor) will be presented in a listing.

9. EFFICACY

This is a long-term and open-label safety study, and safety evaluation is the primary objective. The efficacy assessments are secondary and will be analyzed appropriately. Efficacy analyses will be performed on the mITT population.

9.1. Efficacy Variables

The following efficacy variables will be summarized by group and overall. Week 6 is the primary timepoint, and Weeks 1 and 2 are key secondary timepoints:

- Change from baseline in MADRS total score over time
- Percentage of subjects achieving clinical response on MADRS total score (≥50% improvement from baseline) over time
- Percentage of subjects achieving clinical remission on the MADRS total score (≤10) over time.
- Change from baseline in MADRS-6 score over time
- Percentage of subjects achieving clinical response on MADRS-6 score (≥50% improvement from baseline) over time
- Change from baseline in MADRS-5 score over time
- Percentage of subjects achieving clinical response on MADRS-5 score (≥50% improvement from baseline) over time
- Change from baseline on the CGI-S over time
- [redacted]
- [redacted]
- CGI-I over time
- [redacted]
- Change from baseline in HAM-A over time. *The HAM-A was added during protocol Amendment 1, and therefore only subjects who have a baseline HAM-A will be included in this analysis.*

- Percentage of subjects achieving a response on the HAM-A (≥50% improvement from baseline) over time. *The HAM-A was added during protocol Amendment 1, and therefore only subjects who have a baseline HAM-A will be included in this analysis.*

- Percentage of subjects achieving remission on the HAM-A (≤7) over time

- Change from baseline in CPFQ over time. *The CPFQ was added during protocol Amendment 1, and therefore only subjects who have a baseline CPFQ will be included in this analysis.*

- Percent of subjects achieving an at least 1 category change from baseline in the CPFQ based on the following categories (*The CPFQ was added during protocol Amendment 1, and therefore only subjects who have a baseline CPFQ will be included in this analysis)*:

    - ≤7: Greater than normal functioning
    - 8–14: Normal functioning
    - 15–21: Minimally diminished functioning
    - 22–28: Moderately diminished functioning
    - 29–35: Markedly diminished functioning
    - 36–42: Totally absent functioning

- Change from baseline in Q-LES-Q over time

- Change from baseline in SDS total score over time

- Change from baseline in each SDS domain over time

- [redacted]

- [redacted]

- [redacted]

- [redacted]

- Percentage of subjects achieving remission on both the MADRS and HAM-A (MADRS total score ≤10 and HAMA total score ≤7) over time

- Percentage of subjects achieving remission on both the MADRS and SDS (MADRS total score ≤10 and SDS total score ≤6) over time

Unless otherwise stated, the changes will be derived in such a manner so that a positive change is indicative of improvement. For example, since the higher the MADRS, the greater impairment, the change for MADRS will be derived as baseline - post baseline. Change from baseline related variables will be analyzed using paired t-tests. Between treatment differences may be performed when appropriate (e.g., sufficient sample size).

10. SAFETY AND TOLERABILITY

Safety analyses will be performed for the Safety population. Safety evaluations will be based on the incidence, severity, relatedness, and type of adverse events, as well as on clinically significant changes in the subject's ECGs, vital signs, clinical labs, and C-SSRS.

10.1. Extent of Exposure

Summary statistics of exposure to study drug will be summarized for the Safety population. Exposure is defined as last dosing date – first dosing date + 1. The exposure will be summarized by summary statistics as well as by weekly frequency.

10.2. Adverse Events

Each AE and SAE term will be recorded as a verbatim term on the case report forms (CRFs). All AEs and SAEs will be coded by primary system organ class (SOC) and mapped to a preferred term using the MedDRA dictionary Version 22. The investigator will assess AE severity and relationship to the study treatment.

All AEs will be listed. However, only treatment emergent adverse events (TEAEs) will be included in the AE summaries. A TEAE is defined as any AE with an onset date in the interval between the first study treatment dosing date and 7 days after the last study treatment dosing date. In addition, any AEs occurring after the first dose that the investigators deem to be treatment related will also be considered TEAEs and will be included in the AE summaries.

For the purpose of calculating treatment emergence and inclusion in summary tables, incomplete onset dates will be imputed using the method described in Appendix 1.

AEs will be summarized by the number and percentage of subjects in each primary SOC and preferred term. Subjects will be counted only once for each primary SOC and each preferred term. Summary tables of AEs by primary SOC, preferred term and severity will be provided. If a subject has more than one AE coded to the same preferred term, the subject will be counted only once for that preferred term by using the event with the highest severity. Similarly, if a subject has more than one AE within a primary SOC category, the subject will be counted only once in that SOC category by using the event with the highest severity. AEs by primary SOC, preferred term and relationship to study drug will be provided as well. In addition, serious adverse events (SAEs) by primary SOC and preferred term will be provided. Deaths and SAEs will be summarized similarly to AEs. All adverse event tables will also include the total number of events, counting multiple events per Subject.

In the AE summary, preferred terms within each SOC will appear in frequency order.

Frequencies for deaths and hospitalizations will also be summarized by treatment group and overall.

10.3. Clinical Laboratory Tests

Clinical laboratory tests will include serum chemistry and urine pregnancy tests. Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for each laboratory value for each of the scheduled visits. Shift tables will also be presented.

10.4. ECG

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from Baseline will be calculated for each ECG parameter.

10.5. Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, oral body temperature, and weight. Changes in weight will be further presented by the percentage of subjects with a 7-10%, >10% to 15%, and ≥ 15% weight change from baseline over time.

10.6. Physical Exam

Physical exam data for each subject will be presented in a listing.

11. REFERENCES

1. Montgomery, S.A. and M. Asberg, *A new depression scale designed to be sensitive to change.* Br J Psychiatry, 1979. **134**: p. 382-9.

2. Guy, W., *ECDEU Assessment Manual for Psychopharmacology*. 1976, Rockville, MD: US Department of Heath, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration.

3. Endicott, J., et al., Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. Psychopharmacol Bull, 1993. **29**(2): p. 321-6.

4. Sheehan, D.V., K. Harnett-Sheehan, and B.A. Raj, *The measurement of disability.* Int Clin Psychopharmacol, 1996. **11 Suppl 3**: p. 89-95.

5. Hamilton, M., *The assessment of anxiety states by rating.* Br J Med Psychol, 1959. **32**(1): p. 50-5.

6. Fava, M., et al., A cross-sectional study of the prevalence of cognitive and physical symptoms during long-term antidepressant treatment. J Clin Psychiatry, 2006. **67**(11): p. 1754-9.

7. Posner, K., et al., The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry, 2011. **168**(12): p. 1266-77.

APPENDIX 1. IMPUTATION ALGORITHM FOR PARTIAL AND MISSING DATES

This section describes missing date imputation methods.

For Adverse Events

If onset date is completely missing, onset date is set to date of first dose.

If (year is present and month and day are missing) or (year and day are present and month is missing):

- If year = year of first dose, then set month and day to month and day of first dose
- If year < year of first dose, then set month and day to December 31.
- If year > year of first dose, then set month and day to January 1.
- If month and year are present and day is missing:
- If year = year of first dose and
- If month = month of first dose then set day to day of first dose
- If month < month of first dose then set day to last day of month
- If month > month of first dose then set day to first day of month
- If year < year of first dose then set day to last day of month
- If year > year of first dose then set day to first day of month

For all other cases, set onset date to date of first dose.

For Concomitant Medications

Start Date: If start date is completely missing and end date is not prior to date of first dose, then the medication will be classified as concomitant. If start date is completely missing and end date is prior to date of first dose, then the medication will be classified as prior.

If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to January 1. If year and month are present and day is missing then set day to first day of month.

End Date: If end date is completely missing then the medication will be classified as concomitant.

If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to December 31. If year and month are present and day is missing then set day to last day of the month.

Note: that if both start and end dates are missing then the medication will be classified as concomitant.