1.0 TITLE PAGE

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PROTOCOL VLZ-MD-23

An Open-label Long-term Safety Study of Vilazodone in Pediatric Patients With Major Depressive Disorder

STATISTICAL ANALYSIS PLAN

Final: 10 Feb 2016

2.0 TABLE OF CONTENTS

2.1 LIST OF IN-TEXT TABLES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ALP	alanine phosphatase
BP	blood pressure
CDR-S	Children's Depression Rating Scale–Revised
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
C-SSRS	Columbia Suicide Severity Rating Scale
ECG	Electrocardiogram
ITT	Intent-to-Treat
LLN	lower limit of normal
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NEAE	newly emergent adverse event
PCS	potentially clinically significant
SAE	serious adverse event
SAP	Statistical Analysis Plan
SI	*Le Système International d'Unités* (International System of Units)
SOC	system organ class
TBL	total bilirubin
TEAE	treatment emergent adverse event
ULN	upper limit of normal

4.0 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and/or specified in the protocol of Study VLZ-MD-23. Specifications of tables, figures, and data listings are contained in a separate document. The statistical analysis for pharmacokinetic parameters will be specified in a separate document.

Study VLZ-MD-23 will be an open-label, long-term safety study in pediatric patients, ages 7 to 17 years with major depressive disorder (MDD). Eligible patients will include de novo patients meeting the inclusion/exclusion criteria and patients who completed the lead-in study (VLZ-MD-22). Study centers will enroll either de novo patients or patients who completed the lead in study. Patients who complete Study VLZ-MD-22 will have the option to participate in Study VLZ-MD-23.

The study will be approximately 28 weeks in duration, including approximately a 1-week screening/washout period, a 26-week open-label treatment period, and a 1-week down-taper period. During the open-label treatment period, study visits will be conducted after 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26 weeks of treatment (see Table 4–1). Safety and efficacy assessments will be performed at the designated visits. Patients prematurely discontinuing from the study, regardless of cause, will be seen for a final evaluation.

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses for efficacy and safety assessments as outlined and/or specified in the final study protocol (version dated 15 Dec 2014). Specifications of tables, figures, and data listings are contained in a separate document.

Table 4–1. SCHEDULE OF EVALUATIONS: Study VLZ-MD-23

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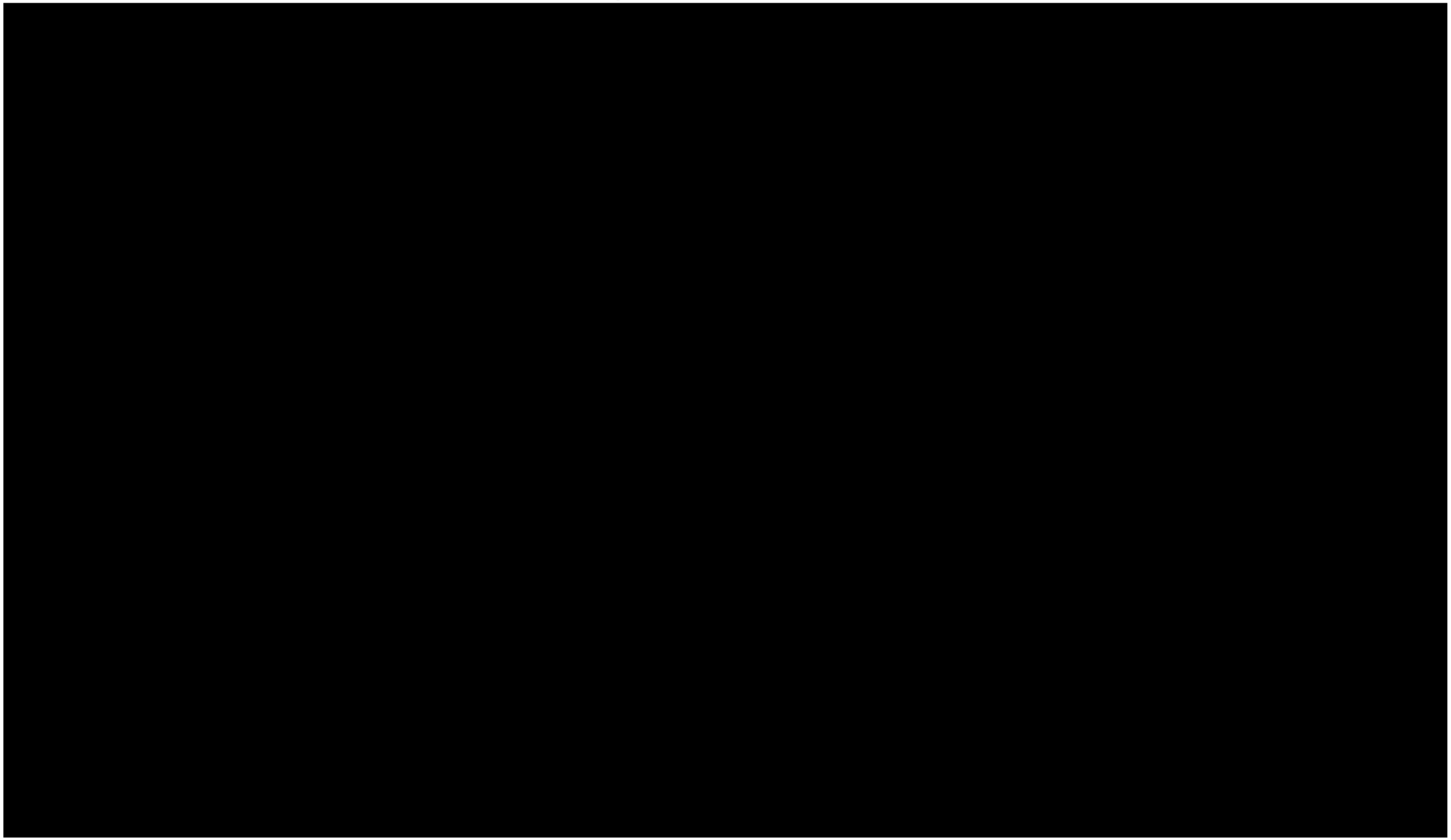


5.0 OBJECTIVE

The objective of this study is to evaluate the long-term safety and tolerability of vilazodone for the treatment of MDD in pediatric outpatients (7-17 years).

6.0 PATIENT POPULATIONS

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

6.1 SCREENED POPULATION

The Screened Population will consist of all patients who signed informed consent for this study.

6.2 ENROLLED POPULATION

The Enrolled Population will consist of all patients in the Screened Population who were dispensed investigational product.

6.3 SAFETY POPULATION

The Safety Population will consist of all patients who took at least 1 dose of open-label investigational product.

6.4 INTENT-TO-TREAT POPULATION

The Intent-to-Treat (ITT) Population will consist of all patients in the Safety Population who had a baseline and at least 1 postbaseline assessment of the Children's Depression Rating Scale–Revised (CDRS-R) total score.

7.0 PATIENT DISPOSITION

The number of patients in the Screened Population will be summarized overall by study center. The number of patients in the Enrolled, Safety, and ITT populations will be summarized by study center.

Screen failures (ie, patients who were screened but not included in the Enrolled Population) and the associated reasons for failure will be tabulated. The number and percentage of patients who complete the open-label treatment period and of patients who prematurely discontinue during the same period will be presented. The reasons for premature discontinuation from the open-label treatment period as recorded on the disposition pages of the electronic case report forms will be summarized (number and percentage) for the Safety Population. All patients who prematurely discontinue during the open-label treatment period will be listed by discontinuation reason for the Safety Population.

All summaries in this section will be presented by patient cohort (rollover patients from Study VLZ-MD-22 or *de novo* patients) and overall. The rollover patients from Study VLZ-MD-22 will be summarized by lead-in treatment group.

8.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters (age, sex, race, ethnicity) and other baseline characteristics (weight, height, body mass index) will be summarized descriptively by cohort and by lead-in treatment group for the Safety and ITT populations, respectively. Baseline efficacy variables will be summarized by cohort and by lead-in treatment group for the ITT Population.

Continuous variables will be summarized by number of patients and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients.

Medical and surgical history/physical findings will be classified by system organ class (SOC) and preferred term using the *Medical Dictionary for Regulatory Activities*, version 17.0 or newer. The number and percentage of patients with abnormalities in medical and surgical histories in each SOC and preferred term will be summarized by cohort and by lead-in treatment group for the Safety Population. Psychiatric history of MDD, other psychiatric history, prior treatment with psychotropic medication, and non-drug psychiatric treatment history will also be summarized by cohort and by lead-in treatment group for the Safety Population.

The *World Health Organization Drug Dictionary*, version March 2014 or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name.

Prior medication is defined as any recorded medication taken before the date of the first dose of open-label investigational product. *Concomitant medication* is defined as any medication taken on or after the date of the first dose of open-label investigational product.

9.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.1 EXTENT OF EXPOSURE

Exposure to open-label investigational product for the Safety Population during the open-label treatment period will be summarized in terms of treatment duration, calculated as the number of days from the date of the first dose of open-label investigational product to taken the date of the last dose of open-label investigational product taken during the open-label treatment period, inclusive. Descriptive statistics (number of patients, mean, SD, median, minimum, and maximum) will be presented by cohort and by lead-in treatment group. The number and percentage of patients by exposure will be presented for specific intervals by cohort.

[redacted]

9.2 MEASUREMENT OF TREATMENT COMPLIANCE

[redacted]

10.0 EFFICACY ANALYSES

All efficacy analyses will be based on the ITT Population. For patients who completed the lead-in study (VLZ-MD-22), the baseline for efficacy from the lead-in study will be used as the baseline for this study. For de novo patients, the latest nonmissing evaluation of efficacy variables (at or prior to Visit 2) before the first dose of open-label investigational product will be used as baseline. Descriptive statistics for each efficacy parameter (n, mean, SD, SEM, median, minimum, and maximum) will be presented for each visit, by cohort and by lead-in treatment group for continuous variables using observed case (OC) approach. At a specific visit, only patients in the ITT Population with both baseline and post-baseline values will be included in the summary.

In addition, by-visit analyses using the last-observation-carried-forward (LOCF) approach will be presented for each efficacy parameters. For the LOCF approach, only the postbaseline total score of a parameter will be imputed; individual item scores will not be carried forward to derive the total score. Baseline total score will be carried forward only for the intermittent missing scores immediately after baseline. If all the postbaseline values are missing, the baseline value will not be carried forward.

The efficacy parameters will include the following at selected postbaseline visits:

- Change from baseline in CDRS-R total score
- Change from baseline in Clinical Global Impressions – Severity (CGI-S) score
- Clinical Global Impressions – Improvement (CGI-I) score

11.0 SAFETY ANALYSES

The safety analysis will be performed for the open-label treatment period and down-taper period separately using the Safety Population. The safety analyses will be presented by patient cohort (rollover patients from Study VLZ-MD-22 and *de novo* patients) and overall. The rollover patients from Study VLZ-MD-22 will also be presented by lead-in treatment group.

The safety parameters will include adverse events (AEs), clinical laboratory parameters, vital sign measurements, electrocardiogram (ECG) parameters, Columbia Suicide Severity Rating Scale (C-SSRS) evaluations, and the change from baseline in the age- and gender-adjusted height (evaluation of growth). For patients who completed the lead-in study (VLZ-MD-22), the baseline for safety parameters from the lead-in study will be used as the baseline for this study. For *de novo* patients, the latest nonmissing evaluation of safety parameters before the first dose of open-label investigational product will be used as the baseline.

11.1 ADVERSE EVENTS

AEs will be coded by SOC and preferred term using the *Medical Dictionary for Regulatory Activities,* version 17.0 or newer.

For patients who completed the lead-in study (VLZ-MD-22), an AE (classified by preferred term) that occurs during the open-label treatment period or during the down-taper period will be considered a treatment-emergent adverse event (TEAE) if it was not present before the date of the first dose of double-blind investigational product in the lead-in study or if it was present before the date of the first dose of double-blind investigational product in the lead-in study and increased in severity during the open-label treatment period or during the down-taper period. If more than 1 AE is reported before the date of the first dose of double-blind investigational product in the lead-in study and coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs occurring during the open-label treatment period or during the open-label down-taper period that were also coded to that preferred term. An AE that occurs more than 30 days after the date of the last dose of investigational product will not be counted as a TEAE.

For *de novo* patients, an AE (classified by preferred term) that occurs during the open-label treatment period or during the open-label down-taper period will be considered a TEAE if the AE was not present before the date of the first dose of open-label investigational product or if it was present before the date of the first dose of open-label investigational product and increased in severity during the open-label treatment period or during the open-label down-taper period. If more than 1 AE is reported before the date of the first dose of open-label investigational product and coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs occurring during the open-label treatment period or during the open-label down-taper period that were also coded to that preferred term. An AE that occurs more than 30 days after the date of the last dose of investigational product will not be counted as a TEAE.

For patients who completed the lead-in study (VLZ-MD-22), an AE (classified by preferred term) occurring during the open-label treatment period will be considered a newly emergent adverse event (NEAE) if the AE was not present before the first dose of the open-label treatment period investigational product or it was present before the first dose of the open-label treatment period investigational product and increased in severity during the open-label treatment period. If more than 1 AE was reported before the first dose of the open-label investigational product and coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs occurring during the open-label treatment period that were also coded to that preferred term.

An AE occurring during the open-label down-taper period will be considered an NEAE if it was not present before the start of the down-taper period or was present before the start of the down-taper period but increased in severity during the down-taper period. An AE that occurs more than 30 days after the date of the last dose of investigational product will not be counted as a NEAE.

The number and percentage of patients reporting TEAEs during the open-label treatment period and during the open-label down-taper period will be tabulated by SOC and preferred term, for both the open-label treatment period and the open-label down-taper period, separately. If more than 1 AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the greatest severity and strictest causality 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 separately for the open-label treatment period and the open-label down-taper period.

A common TEAE during the open-label treatment period will be summarized in 2 ways: ≥ 1% of patients and ≥ 2% of patients in any cohort or any lead-in treatment group. The incidence of common TEAEs will be summarized separately by preferred term and cohort and lead-in treatment group and will be sorted by decreasing frequency for the total group.

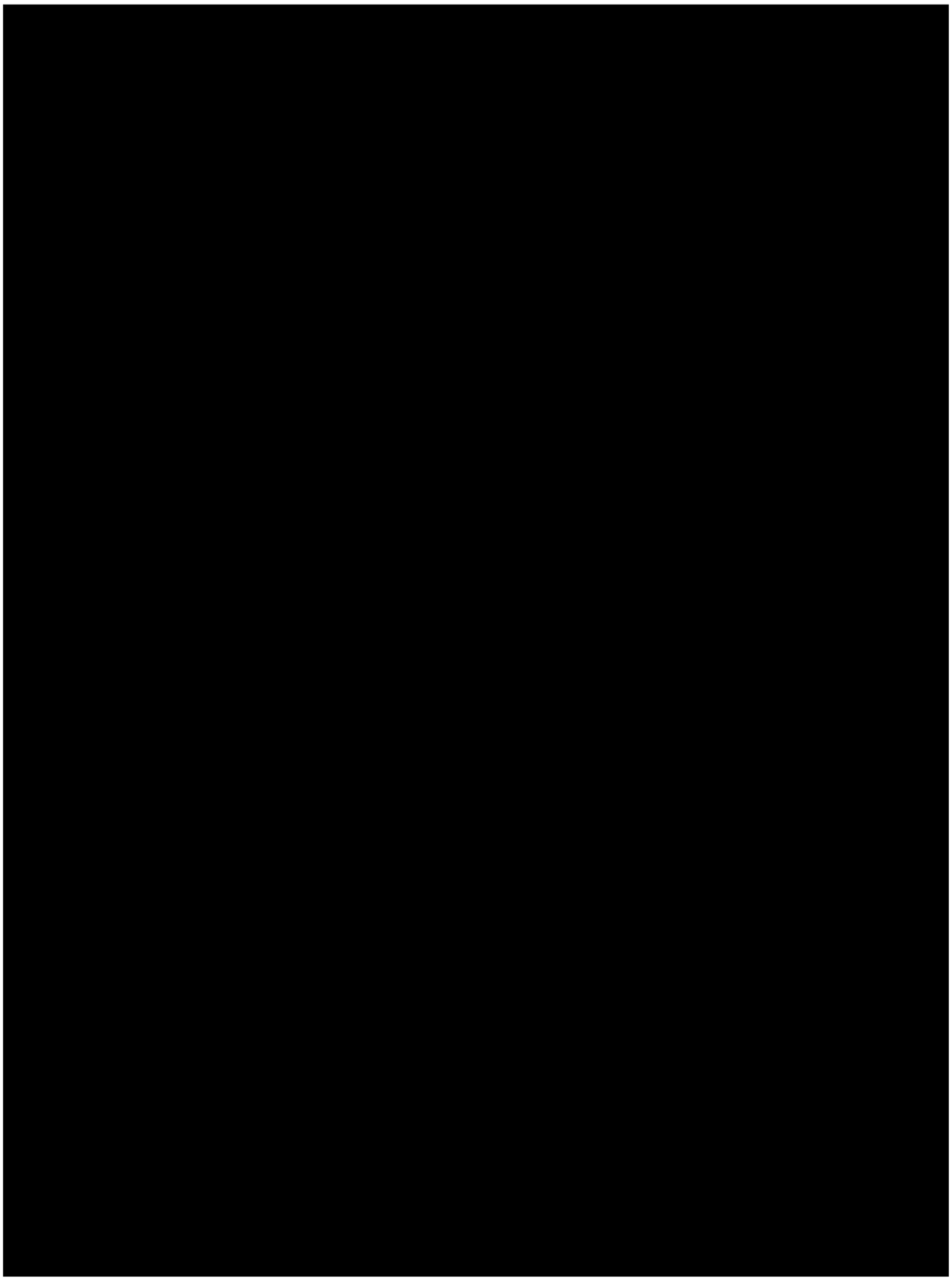
NEAEs reported during the open-label treatment period and the during open-label down-taper period will be summarized separately by body system and preferred term.

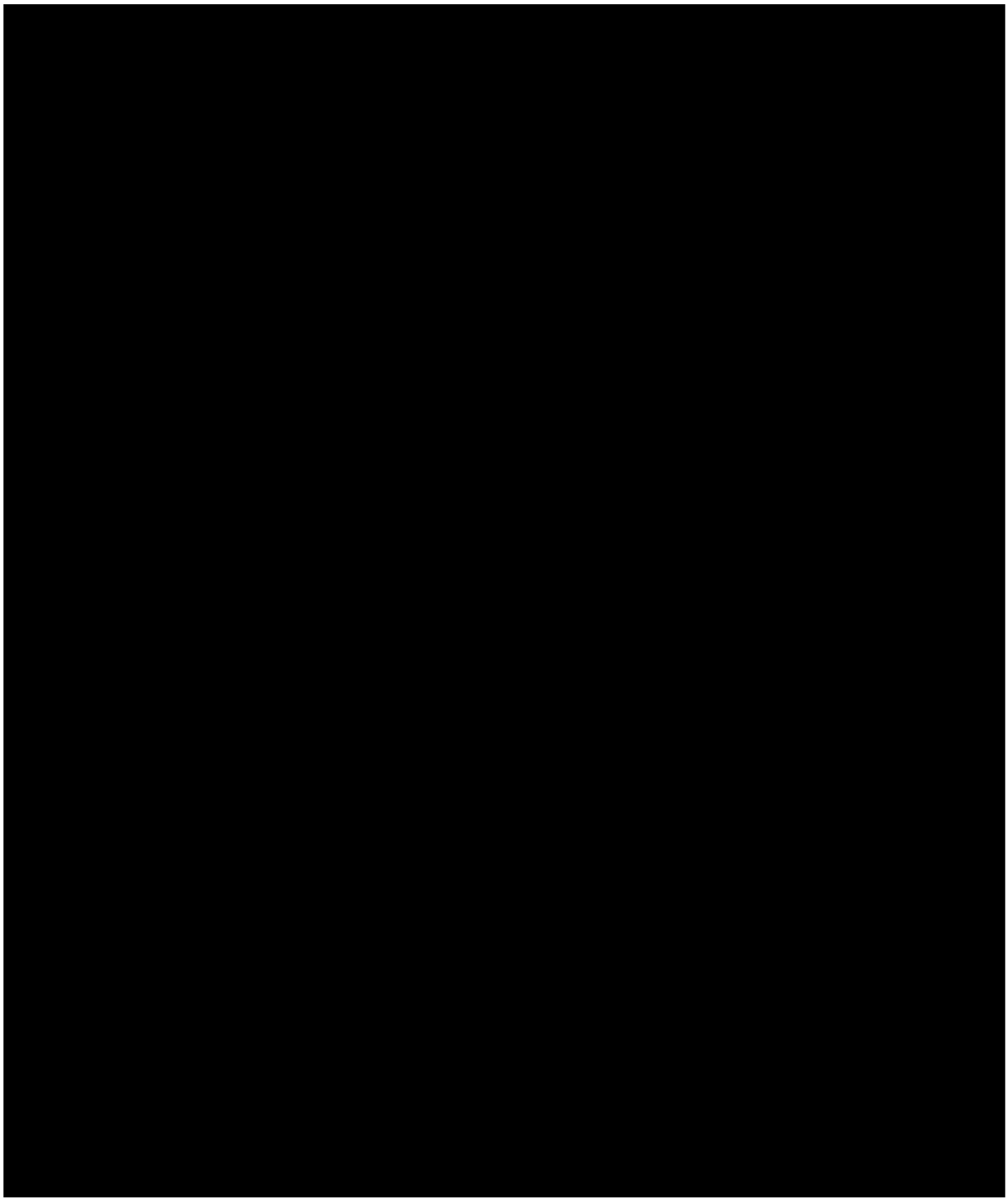
A serious adverse event (SAE) that occurred between the date of the first dose of open-label investigational product and 30 days after the date of the last dose of open-label investigational product in the study, inclusive, will be considered an on-therapy SAE. The incidence of SAEs and AEs leading to premature discontinuation of the study will also be summarized by study period, SOC and preferred term. Listings will be presented for patients with SAEs, patients with AEs leading to premature discontinuation, and patients who died (if any). All patients with SAEs, including those reported during the screening period or more than 30 days after the date of the last dose of the open-label investigational product, and patients discontinuing due to AEs before the start of open label investigational product will be included in these listings.

Listings will be presented for patients with SAEs, patients with AEs leading to discontinuation, and patients who die (if any).

11.2 CLINICAL LABORATORY PARAMETERS

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each assessment time point (including the end of the open-label treatment period) will be presented for the following laboratory parameters:





11.3 VITAL SIGNS

Descriptive statistics for vital signs (ie, sitting radial pulse rate, sitting systolic and diastolic blood pressure (BP), body weight, and height) and changes from baseline values at each visit and at the end of the open-label treatment period will be presented. In addition, height and weight z scores will be calculated based on growth charts.

11.4 ELECTROCARDIOGRAM (ECG)

Descriptive statistics for ECG parameters (ie, ventricular heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc) and changes from baseline values at each assessment time point will be presented. The QTc is calculated using both the Bazett and Fridericia corrections.

11.5 OTHER SAFETY PARAMETERS

Other safety parameters include C-SSRS and growth.

11.5.1 Suicidality Assessment

For the C-SSRS, the number and percentage of patients with any suicidal ideation or suicidal behavior will be presented by cohort, separately for the lifetime history, the open-label treatment period and the open-label down-taper period. The distribution of responses for the most severe suicidal ideation and suicidal behavior will be summarized by cohort and by lead-in treatment group, separately for the lifetime history, the open-label treatment period, and the open-label down-taper period. Supportive listings will be provided and will include the patient identification 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. A listing of all AEs occurring in patients who have suicidal ideation or suicidal behavior will also be provided.

11.5.2 Growth Evaluation

Weight and height will be presented in raw score and standardized z-scores adjusted for gender and age, using the LMS method (Cole TJ, 1990).

Descriptive statistics for raw scores of height and weight, age-and-gender-adjusted height and weight, and changes from baseline values at each visit and at the end of the open-label treatment group will be presented.

12.0 HEALTH OUTCOME ANALYSES

Not applicable.

13.0 INTERIM ANALYSIS

No interim analysis is planned for this study.

14.0 DETERMINATION OF SAMPLE SIZE

This is a long-term open-label study of the safety and tolerability of vilazodone in pediatric patients with MDD. [redacted] approximately 250 patients are planned for enrollment in this study [redacted]

15.0 COMPUTER METHODS

Statistical analyses will be performed [redacted]

16.0 DATA HANDLING CONVENTIONS

16.1 VISIT TIME WINDOWS

Table 16.1–1 below presents the visits assigned for efficacy and safety analyses corresponding to the range of treatment days (window) in the open-label treatment period during which an actual visit may have occurred.

[redacted]

16.2 DERIVED EFFICACY VARIABLES

The total score at a particular visit will be calculated using (sum of nonmissing items) × (total number of items) / (number of nonmissing items) only if the number of missing items is ≤ 2 for the CDRS-R score.

If a patient misses a postbaseline visit or if his/her postbaseline visit is outside of the visit time window, a record for the scheduled visit will be imputed using the last observed nonmissing value immediately before the missing value. If the missing value occurs at Week 2, the baseline value will be carried forward for Week 2, provided that at least 1 subsequent postbaseline assessment is available. For a composite scale such as CDRS-R total score, individual items of the rating scale will not be carried forward. Only total scores will be carried forward using the LOCF approach.

16.3 AGE-AND-GENDER_CORRELATED VALUES FOR WEIGHT AND HEIGHT

To adjust weight (kg) and height (cm) for sex and age, one needs to compare them to standard reference values for the same sex and age group, which are available in the United States Growth Charts and can be downloaded from:
http://www.cdc.gov/growthcharts/percentile_data_files.htm

The z-score is calculated as below

$$z = \frac{(X/M)^L - 1}{SL}, \text{ if L} \neq 0 \text{ and}$$

$$z = \frac{\ln(X/M)}{S}, \text{ if } L = 0,$$

where X is the physical measurement (eg weight and height) and L, M, and S are the values from the appropriate table corresponding to the age in months (or length/stature) and sex (1 = male; 2 = female). X must be in metric measurements (kilograms or meters). This is called LMS method (Cole TJ, 1990), and parameters L, M, and S are the Box-Cox transformation power, median, and SD, respectively, in the reference data, which are provided in the reference data tables.

16.4 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

For roll-over patients, the corresponding baseline of the double-blind lead-in study will be used. If a de novo patient has repeated assessments before the date of the first dose of open-label investigational product, the results from the final nonmissing assessment made before the date of the first dose of open-label investigational product will be used as baseline. If the end-of-open-label-treatment period assessments are repeated or if unscheduled visits occur, the last nonmissing postbaseline assessment during the open-label treatment period will be used as the end-of-open-label-treatment-period assessment for generating summary statistics. Likewise, if the end of open-label down-taper period assessments are repeated or if unscheduled visits occur, the last non-missing assessment during the open-label down-taper period will be used as the end-of-open-label-down-taper-period assessment for generating summary statistics. However, all postbaseline assessments will be used to determine PCS values for laboratory parameters, vital signs and ECG parameters, and to determine most severe suicidal ideation and most severe suicidal behavior from C-SSRS. All assessments will be presented in the data listings.

16.5 MISSING DATE OF INVESTIGATIONAL PRODUCT

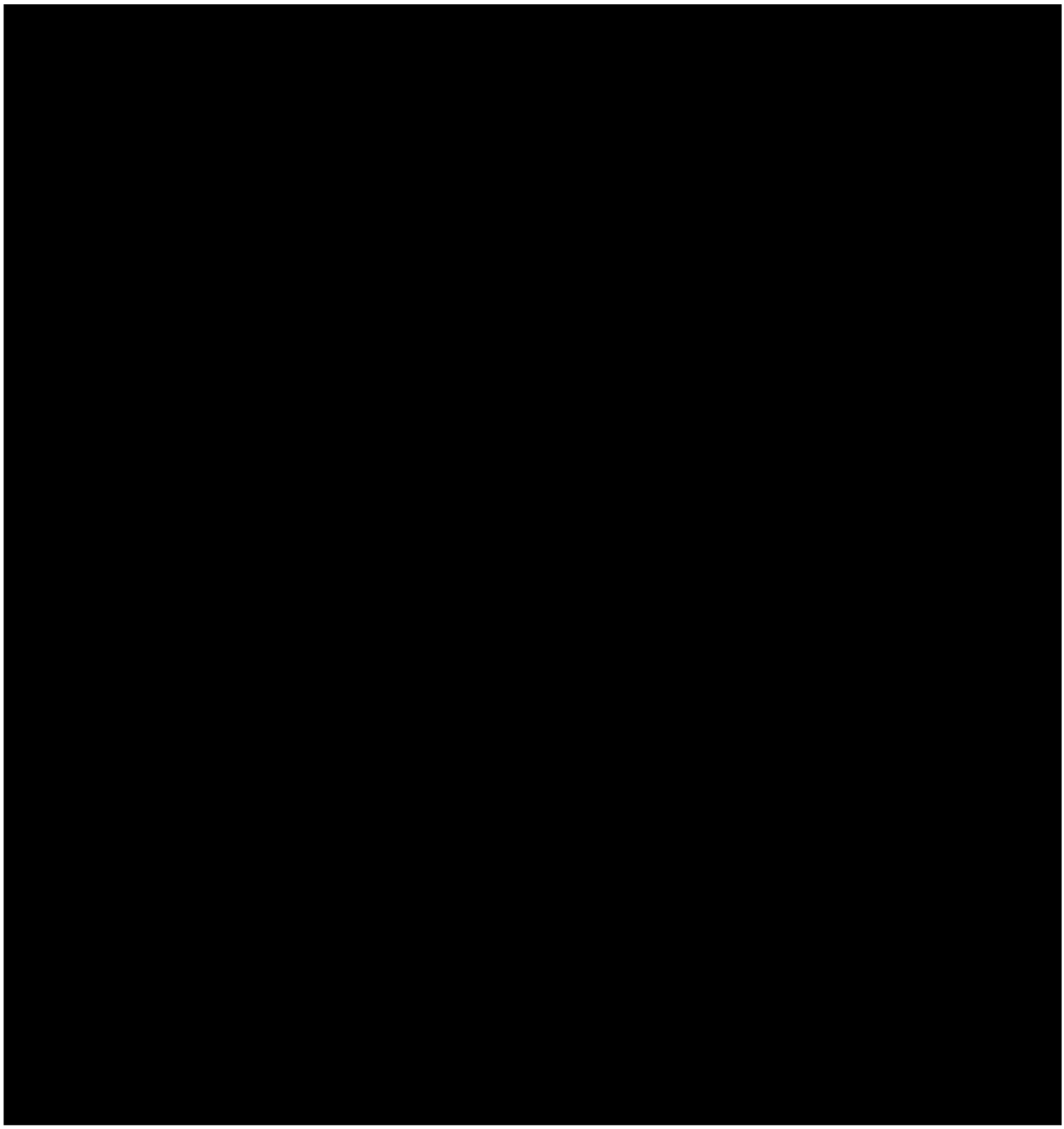
When the date of the last dose of the open-label investigational product during the study treatment period is missing for a patient in the Safety Population, all efforts should be made to obtain the date from the Investigator. If it is still missing after all efforts have been made, then the last available dosing record date will be used as the last dose date.

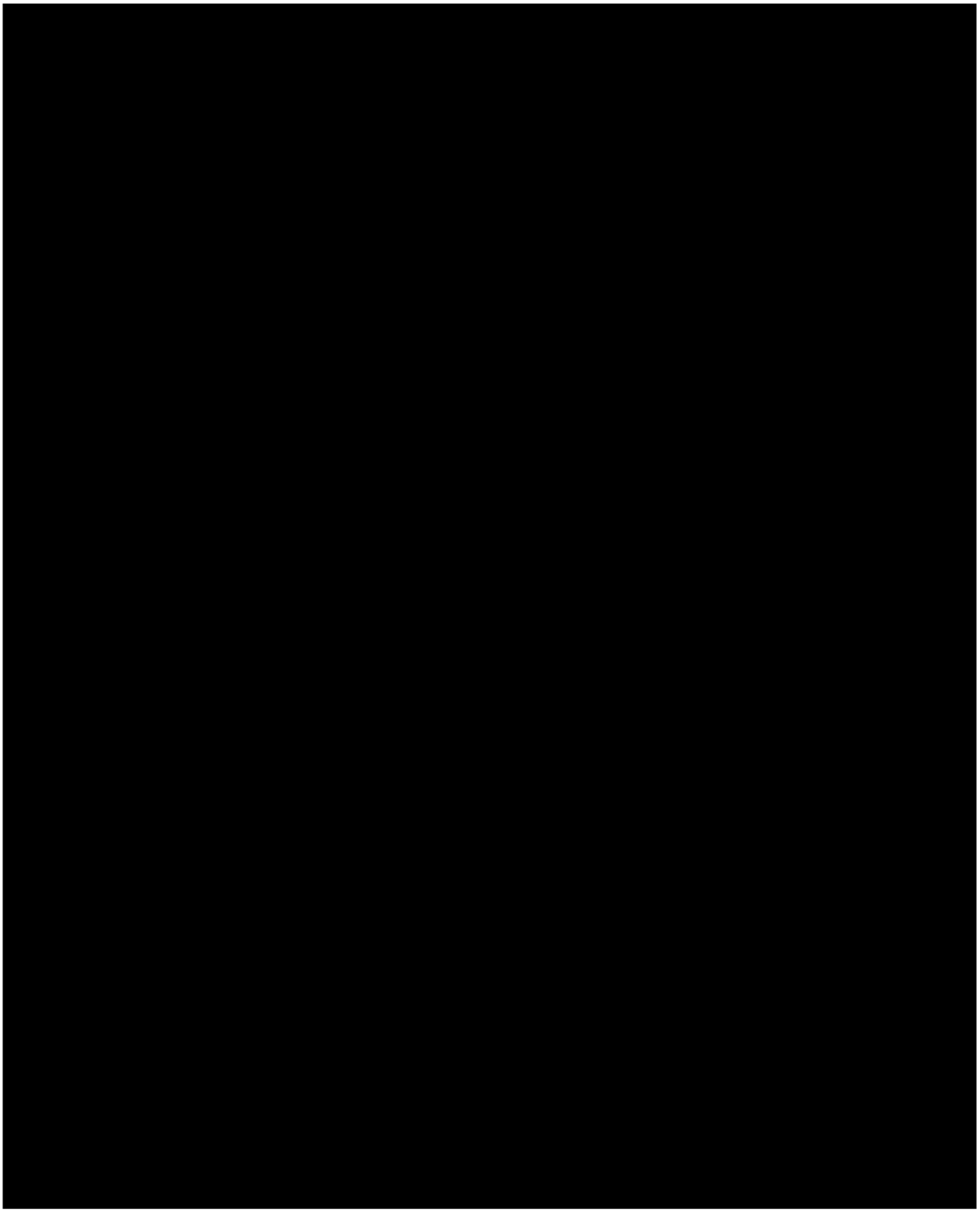
16.6 MISSING SEVERITY TO INVESTIGATIONAL PRODUCT IN ADVERSE EVENTS

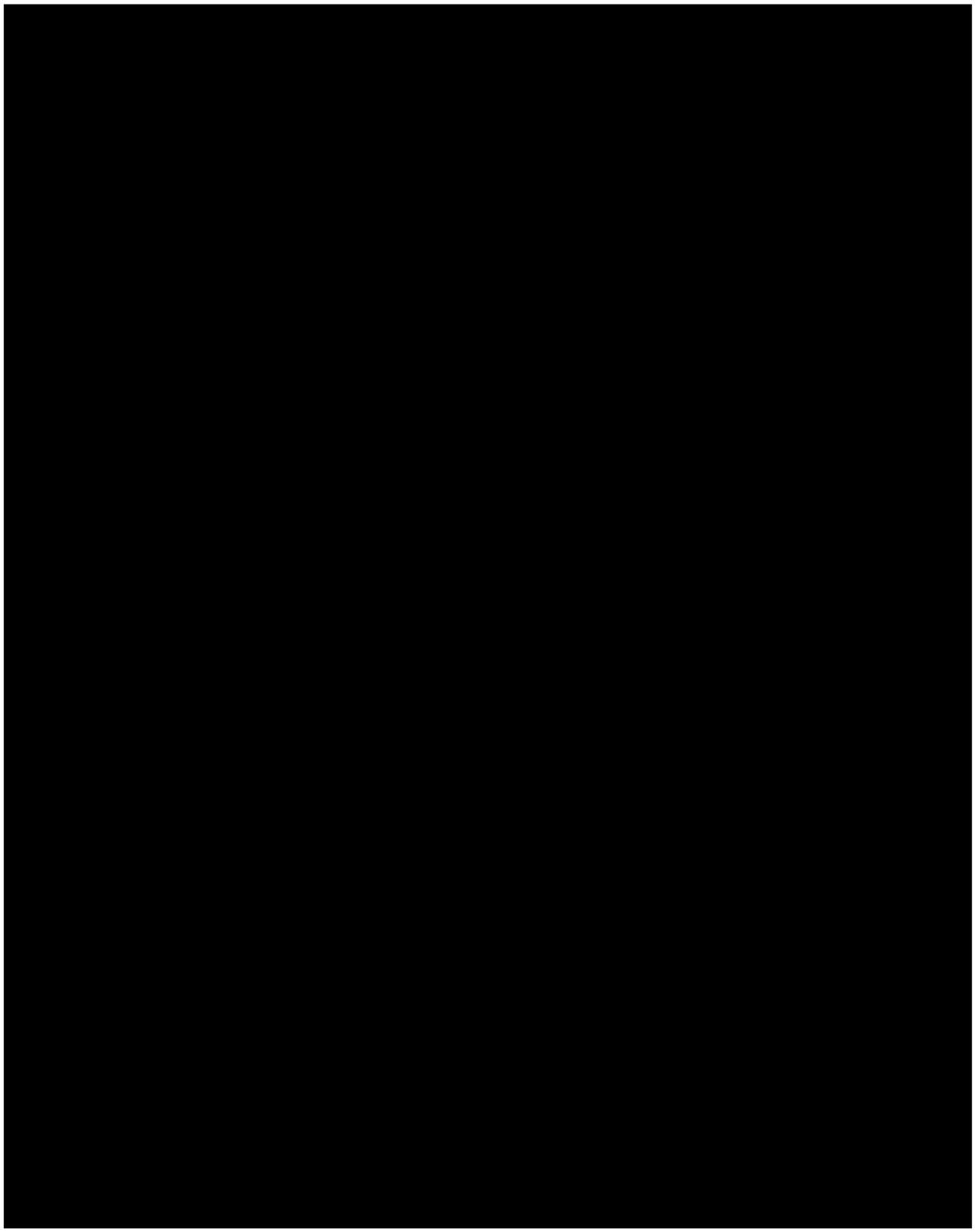
If the severity is missing for an AE started on or after the date of the first dose of the open-label investigational product, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summary, while the actual values should be presented in data listings.

16.7 MISSING RELATIONSHIP TO INVESTIGATIONAL PRODUCT FOR ADVERSE EVENTS

If the relationship to the investigational product is missing for an AE started on or after the date of the first dose of the open-label investigational product, a causality of "Related" will be assigned. The imputed values for relationship to the investigational product will be used for incidence summary, while the actual values should be presented in data listings.







16.10 CHARACTER VALUES OF CLINICAL LABORATORY PARAMETERS

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table due, for example, to the fact that a character value is reported for a parameter of the numerical type, a coded value needs to be appropriately determined and used in the statistical analyses. However, the actual values as reported in the database will be presented in data listings.

17.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

No major changes have been made to the original protocol dated 15 Dec 2014.

18.0 REFERENCES

Cole TJ. The LMS method for constructing normalized growth standards. *Eur J Clin Nutr.*1990, 44: 45-60.

19.0 APPENDICES

APPENDIX I. REPORTING SELECTED LABORATORY PARAMETERS IN CONVENTIONAL UNIT

All clinical laboratory parameters will be reported in the International System (SI) units as standard practice. In addition, descriptive statistics for values and changes from baseline in conventional units at all assessed visits will be reported for selected laboratory parameters [redacted]

[redacted]