Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product
Centanafadine (EB-1020)

Protocol No. 405-201-00037
IND No. 119,361

A Pilot Phase 2a, Multicenter, Open-label, Single-dose Trial to Assess the Pharmacokinetics of Centanafadine Extended-release Capsules After Oral Administration in Pediatric Subjects (9 to 12 years, inclusive) With Attention-deficit Hyperactivity Disorder

Statistical Analysis Plan
Phase 2a

Version: 1.0
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1 Introduction

This statistical analysis plan (SAP) documents the statistical methodology and data analysis algorithms and conventions to be applied for the analysis of clinical trial data of trial 405-201-00037 for centanafadine. The current version of SAP is based on protocol version 3.0 dated on 23 Jul 2019 and final SAP will be consistent with the final version of the protocol.

2 Trial Objectives

Primary Objectives:
To characterize the single-dose concentration-time profile from 0 to 12 hours of centanafadine in pediatric subjects (9 to 12 years, inclusive) with attention-deficit hyperactivity disorder (ADHD).

Other Objectives:

- To assess the safety and tolerability of centanafadine XR in pediatric subjects.
- To assess the ability of pediatric subjects to swallow the centanafadine XR capsule.
- [redacted]
- To assess centanafadine concentrations 24 hours postdose for evaluation of the potential for accumulation following multiple doses.
- To compare the PK of centanafadine after administration of the intact capsules or the capsule contents sprinkled on to applesauce.

3 Trial Design

3.1 Type/Design of Trial

This is a pilot phase 2a, multicenter, open-label, single-dose trial in pediatric subjects (9 to 12 years, inclusive) with a documented history of ADHD and confirmation of an ADHD prescription medication. This trial consists of a screening period (Day −21 to Day −2), check-in (Day −1 or Day 1), 2-day treatment period (Day 1: dosing, Day 2: end of-treatment [EoT]), and a safety follow-up telephone call 7 (+ 2) days after dosing (Day 8). The screening period may be extended if additional time is needed to complete screening procedures, upon discussion with and approval by the medical monitor.

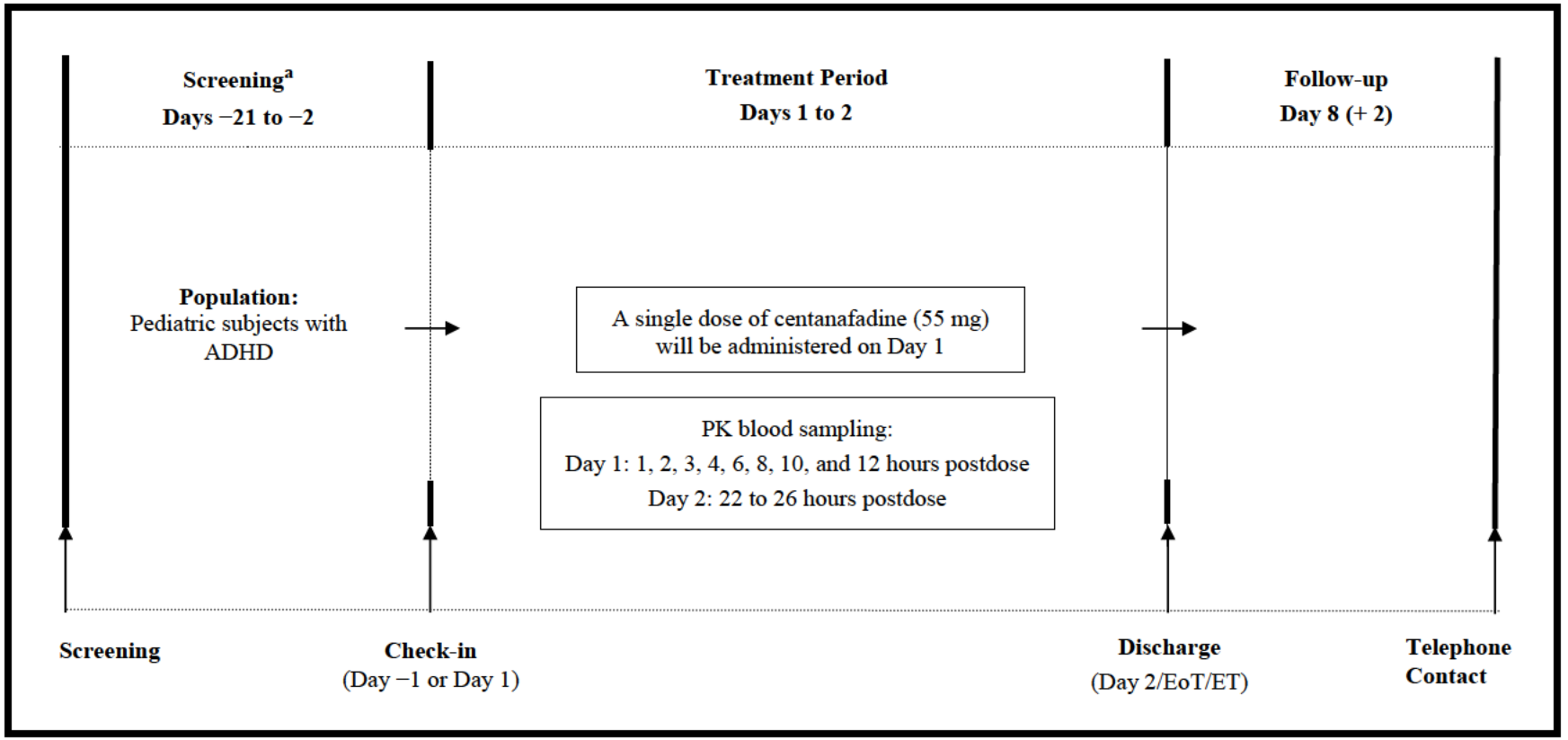
Written informed consent will be freely obtained from all subjects' guardian(s) or legally acceptable representative(s), as applicable for local laws. Written informed assent will be freely obtained from all subjects.

Eligible subjects will check-in either on Day −1 or Day 1, based on the investigator's decision. A single dose of centanafadine will be administered either as intact capsules or the capsule contents sprinkled on a tablespoon of applesauce on Day 1 in the morning. [redacted] Pharmacokinetic and safety assessments will be performed for approximately 24 hours postdose. Subjects may be released from the clinic after PK sample collection at 12 hours postdose to return the following morning or may remain in the clinic until 24 hours postdose, based on the investigator's decision. Subjects released on Day 1 will return to the clinic on Day 2 between 22 to 26 hours postdose for an outpatient visit, which will include EoT assessments and one PK sample. In-clinic subjects may leave the clinic on Day 2 after EoT assessments and PK sampling are complete.

Subjects and/or their caregivers will be contacted by telephone 7 days after dosing to assess any new or ongoing AEs and to record concomitant medications.

The trial design schematic is displayed in Figure 3.1-1.

Figure 3.1-1 Trial Design Schematic



ET = early termination; EoT = end of treatment.
[a] The screening period may be extended if additional time is needed to complete screening procedures, upon discussion with and approval by the medical monitor.

3.2 Trial Treatments

The ability of a subject to swallow the intact capsules will be assessed during the screening period with empty capsules. Based on this assessment, subjects will either be instructed to take the centanafadine capsules intact or the capsule contents sprinkled on a tablespoon of applesauce. An attempt will be made to administer the intact capsules to approximately half of the subjects and approximately half of the subjects will be administered the capsule contents sprinkled on a tablespoon of applesauce.

Centanafadine will be supplied as 1 capsule containing a 50-mg dose as [redacted] beads and 1 capsule containing a 5-mg dose as IR beads for a total centanafadine dose of 55 mg. Both of the intact capsules or the capsule contents sprinkled on a tablespoon of applesauce will be taken orally in the morning [redacted] following a minimum 8-hour fast. [redacted]

3.3 Trial Population

The trial population will consist of males and females, aged 9 to 12 years (inclusive), who have a documented history of ADHD and confirmation of an ADHD prescription medication.

Up to 12 subjects may be treated in the trial. Subjects who discontinue for a reason other than a safety-related event may be replaced at the discretion of the sponsor.

4 Sample Size

Since this is an exploratory trial, no formal sample size calculations will be performed. Up to 12 subjects may be treated depending on the concentration data and the number of subjects completing through 24 hours.

5 Statistical Analysis Sample

5.1 Enrolled Analysis Set

The enrolled analysis set includes all subjects who have eligibility to enroll in the trial based on screening process.

5.2 Safety Analysis Set

The safety analysis set includes all subjects who receive the single dose of centanafadine.

5.3 Pharmacokinetic (PK) Analysis Set

The PK analysis set includes all subjects who receive the single dose of centanafadine and have at least 1 postdose evaluable plasma concentration.

5.4 Handling of Missing Data

No data imputation will be performed for missing PK data in this trial. The handling of concentrations below the lower limit of quantitation will be according to the sponsor's data handling processes.

6 Primary and Secondary Outcome Variables

6.1 Primary Endpoints

The following primary endpoints will be evaluated:

- C_{max} of centanafadine
- t_{max} of centanafadine
- $AUC_{0\text{-}12h}$ of centanafadine

6.2 Other Outcome Endpoints

The following other endpoints will be evaluated:

- Reported AEs, vital signs, body weight, ECGs, clinical laboratory tests, physical examinations, and the C-SSRS.
- Ability to swallow the centanafadine XR capsule.
- [redacted]

6.3 Other PK Endpoints

The following PK endpoints will be evaluated:

- Centanafadine concentrations at 24 hours postdose
- [redacted]

- PK parameters will be estimated (tmax, Cmax, and [redacted]) for EB 10601 (metabolite of centanafadine) [redacted].
- [redacted]

7 Disposition and Demographic Analysis

7.1 Subject Disposition

The number of subjects who have been screened, the number of subjects who are treated, the number of subjects who discontinue from the trial, and the subjects who complete the trial will be tabulated for total subjects. In addition, the assignment based on capsule swallow test during screening period will also be presented by intact capsule and capsule contents sprinkled on applesauce.

The number and percentage of subjects who discontinue are to be summarized by reason for discontinuation and mode of administration (intact capsules or capsule contents sprinkled on a tablespoon of applesauce) for the enrolled sample.

7.2 Demographic and Baseline Disease Characteristics

Baseline demographic characteristics include age, race, ethnicity, sex, weight, height, and BMI. Baseline disease characteristics include history of ADHD, history of allergy. Summary statistics will consist of mean, median, minimum, maximum, and standard deviation (SD) for continuous variables and tabulations of frequency distributions for categorical variables. The summary will be based on the enrolled sample and by mode of administration (intact capsules or capsule contents sprinkled on a tablespoon of applesauce).

7.3 Medical History

Listings for general medical history, surgical history, ADHD history, and psychiatric history will be provided. The listings will be based on the safety sample and by mode of administration (intact capsules or capsule contents sprinkled on a tablespoon of applesauce).

7.4 Treatment Compliance

The time and dose of each investigation medical product (IMP) administration will be recorded on the source documents and on the eCRF. Treatment compliance will be presented by mode of administration in a listing.

7.5 Concomitant Medication

The proportion of subjects taking concomitant medications will be tabulated by drug classification using WHODrug B3G (March 2019) for all enrolled subjects. Concomitant medications taken prior to dosing, taken on Day 1 dosing, taken after Day 1 dosing will be presented by mode of administration. In addition, listings of concomitant mediations will also be provided.

7.6 Protocol Deviations

Any major protocol deviation will be recorded in the eCRF along with the start date and details of the deviation. A subject listing will be provided describing the deviation date and reason for each subject.

8 Pharmacokinetic Analysis

A noncompartmental analysis will be performed. Plasma concentrations of centanafadine and metabolite(s) will be summarized by time point and mode of administration (intact capsules or capsule contents sprinkled on a tablespoon of applesauce). The PK parameters will be summarized by analyte and mode of administration using descriptive statistics.

No inferential statistical analysis will be conducted.

The following PK parameters will be summarized:

- Maximum (peak) plasma concentration (C_{max}) of centanafadine
- Time to maximum concentration (t_{max}) of centanafadine
- Area under the concentration-time curve from time 0 to 12 hours postdose (AUC_{0-12h}) of centanafadine
- Centanafadine concentration at 24 hours postdose

[redacted]

10 Safety Analyses

All the following safety analyses will be performed for the safety sample.

10.1 Extent of Exposure

A table displaying the number of subjects who took 1 day of study medication will be presented by mode of administration (intact capsules or capsule contents sprinkled on a tablespoon of applesauce). The summary will be based on the Safety analysis Set.

10.2 Adverse Events

All treatment-emergent adverse events (TEAEs) will be coded by Medical Dictionary for Regulatory Activities (MedDRA; Version 21 or later) system organ class and preferred term. Treatment-emergent adverse events are defined as those AEs that occur after administration of IMP or events that worsen relative to baseline.

Newly acquired skin eruptions that are nontraumatic will be considered AEs of special interest (AESIs). These may include but are not limited to eruptions such as skin rashes, skin irritations, skin reactions, or acneiform lesions. This does not include localized contact irritation at ECG lead sites due to application/removal of lead adhesive. Preferred terms from AE database will be reviewed by Otsuka medical team to determine the list to be included in AESIs table.

The incidence of the following events will be summarized:

- TEAEs
- TEAEs by severity
- TEAEs potentially causally related to the IMP
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of study
- AESIs.

All TEAEs will be presented in a listing. The listing of death due to AEs, serious AEs, AEs leading to discontinuation, and AESIs will also be provided.

10.3 Clinical Laboratory Data

Clinical hematology, chemistry, and urinalysis are tested at screening, check-in (Day -1 or Day 1), and Day 2/ET.

For clinical laboratory tests data, baseline is defined as the last non-missing value obtained before dosing. The predose assessment will be performed either on Day −1 or

Day 1 depending on investigator's decision. If the predose assessment is missing, the baseline value will be based on the screening visit.

Clinical laboratory tests (observed and change from baseline data) will be summarized by time point and mode of administration (intact capsules or capsule contents sprinkled on a tablespoon of applesauce). The incidence of potentially clinically relevant clinical laboratory tests as defined in Appendix 1 will be summarized by mode of administration. Laboratory results that are potentially clinically relevant will also be listed out by subjects.

When laboratory test is repeated, the last repeat value will be used in the summary for that visit. Unscheduled laboratory data will not be summarized in the change from baseline table but will be included in incidence table.

10.4 Vital Sign Data

Vital signs, including systolic and diastolic blood pressure and heart rate, will be assessed at check-in, predose (within 2 hours before dosing) on Day 1, and 3 hours postdose on Day 1.

The baseline of vital sign is defined as data collected within 2 hours before dosing on Day 1. If a parameter is missing on Day 1 then the screening data collected at check-in will be used.

Change from baseline in vital signs will be summarized for post-baseline assessment. The incidence of potentially clinical relevant vital signs, as defined in Appendix 2 will be summarized by time point and mode of administration. Vital sign data that are potentially clinically relevant will also be listed out by subject.

When vital sign is repeated, the last repeat value will be used in the summary for that visit. Unscheduled vital sign data will not be summarized in the change from baseline table but will be included in incidence table.

10.5 Physical Examination Data

A complete physical examination will be performed at screening, check-in (Day -1 or Day 1), and Day 2/ET. A complete physical examination will consist of measurement of height and weight and an assessment of the following body systems: head, eyes, ears, nose, and throat; thorax; abdomen; extremities; neurological; and skin and mucosae. Any abnormalities considered by the investigator to be clinically significant are to be recorded as AEs on the AE eCRF.

Physical examination data will be presented in a listing.

10.6 Electrocardiogram (ECG) Data

Descriptive statistics of change from baseline in heart rate and ECG intervals of PR, QRS, QT, and QTcF, will be provided by time point and mode of administration. The incidence of potentially clinically relevant ECGs, as defined in Appendix 3 will be summarized by time point and mode of administration. ECG data that are potentially clinically relevant will also be listed out by subject.

When ECG assessment is repeated, the last repeat value will be used in the summary for that visit. Unscheduled ECG value will not be summarized in the change from baseline table but will be included in incidence table.

10.7 Potential Serious Hepatotoxicity

A listing will be provided to present the incidence of subjects who experience an elevation in AST or ALT that is ≥ 3 times the ULN.

10.8 Other Safety Data

The “Baseline/Screening” version of the C-SSRS will be completed at the screening visit and the “Since Last Visit” version of the C-SSRS will be completed at check-in (Day −1 or Day 1) and EoT/ET (Day 2).

The incidence of suicidal behavior and suicidal ideation will be summarized by time point and mode of administration.

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Appendix 1 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria (Normal Ranges) for Subjects 9 - 12 Years Old[a,b]
Chemistry	
AST	≥ 2 × ULN
ALT	≥ 2 × ULN
ALP	≥ 2 × ULN
BUN	≥ 24 mg/dL (≤ 4 mg/dL or ≥ 24 mg/dL)
Creatinine	≥ 0.7 mg/dL (≤ 0.2 mg/dL or ≥ 0.7 mg/dL)
Uric acid	≥ 6.7 mg/dL (≤ 1.6 mg/dL or ≥ 6.7 mg/dL)
Bilirubin (total)	≥ 1.6 mg/dL (≤ 0.2 mg/dL or ≥ 1.6 mg/dL)
CPK	≥ 2 × ULN
Prolactin	≥ 21.00 ng/dL (≤ 2.63 ng/dL or ≥ 21.00 ng/dL)
Hematology	
Hematocrit	≤ 33% (≤ 33% or ≥ 44%)
Hemoglobin	≤ 11.2 g/dL (≤ 11.2 g/dL or ≥ 15.5 g/dL)
White blood count	≤ 4.35×10^3/μL (≤ 4.35×10^3/μL or ≥ 13.65×10^3/μL)
Eosinophils	≥ 4.8%
Neutrophils	≤ 40.5% (≤ 40.5% or ≥ 75.0%)
Absolute neutrophil count	≤ 1.00×10^3/μL or ≥ 9.00×10^3/μL
Platelet count	≤ 130×10^3/μL (≤ 130×10^3/μL or ≥ 570×10^3/μL)
Urinalysis	
Protein	Change from baseline
Glucose	Presence
Additional Criteria	
Chloride	≤ 94 mEq/L or ≥ 112 mEq/L
Potassium	≤ 3.3 mEq/L or ≥ 5.2 mEq/L
Sodium	≤ 132 mEq/L or ≥ 148 mEq/L
Calcium	≤ 8.3 mg/dL or ≥ 10.9 mg/dL
Glucose	
Fasting	≥ 100 mg/dL (≤ 70 mg/dL or ≥ 100 mg/dL)
Nonfasting	≥ 139 mg/dL (≤ 59 mg/dL or ≥ 139 mg/dL)
Total cholesterol, fasting	≥ 217 mg/dL (≤ 97 mg/dL or ≥ 217 mg/dL)
LDL cholesterol, fasting	≥ 130 mg/dL
HDL cholesterol, fasting	≤ 34 mg/dL (≤ 34 mg/dL or ≥ 75 mg/dL)
Triglycerides, fasting	≥ 131 mg/dL (≤ 30 mg/dL or ≥ 131 mg/dL)

[a]The recommended criteria represented in this table are intended to identify on-treatment outside of normal values that could potentially be clinically relevant. Variations based on local laboratory ranges may need to be considered.

[b]Information adapted from: 1. Soghier L, Pham K, Rooney S. Reference Range Values for Pediatric Care. The American Academy of Pediatrics. 2014; 2. Hughes HK, Kahl LK. The Johns Hopkins Hospital: The Harriet Lane Handbook. 21st edition. 2015; 3. Covance central laboratory reference ranges, 2019.

Appendix 2 Criteria for Potential Clinically Significant Vital Signs

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart rate at rest[b]	< 60 bpm or > 110 bpm	Increase or decrease of ≥ 15 bpm
Systolic blood pressure[c]		
School-age (6 to 9 years old)	< 85 mmHg or > 115 mmHg	Increase or decrease of ≥ 20 mmHg
Preadolescent (10 to 12 years old)	< 90 mmHg or > 120 mmHg	Increase or decrease of ≥ 15 mmHg
Diastolic blood pressure[c]		
School-age (6 to 9 years old)	< 50 mmHg or > 80 mmHg	Increase or decrease of ≥ 15 mmHg
Preadolescent (10 to 12 years old)	< 60 mmHg or > 80 mmHg	Increase or decrease of ≥ 15 mmHg
Orthostatic hypotension	≥ 30 mmHg decrease in systolic blood pressure and/or a decrease of ≥ 20 mmHg in diastolic blood pressure after at least 3 minutes of standing compared to the previous supine blood pressure	Not applicable (baseline status not considered)
Orthostatic tachycardia	≥ 25 bpm increase in heart rate from supine to standing	Not applicable (baseline status not considered)
Weight	Not applicable	Increase or decrease of ≥ 25%

bpm = beats per minute.

[a]The criterion value and change relative to baseline represented in this table are intended to identify on-treatment values outside of normal changes and that could potentially be clinically relevant. In order to be identified as potentially clinically relevant, the on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column. When evaluating these values, the emotional state of the subject must be taken into consideration (eg, crying, screaming) and documented as applicable.

[b]Information adapted from: Hughes HK, Kahl LK. The Johns Hopkins Hospital: The Harriet Lane Handbook. 21st edition. 2015.

[c]Information adapted from: Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents: American Academy of Pediatrics Subcommittee on Screening and Management of High Blood Pressure in Children. Pediatrics. 2017;140(3):1-72.

Appendix 3 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Rhythm		
Sinus tachycardia[b]	≥ 110 bpm	increase of ≥ 15 bpm
Sinus bradycardia[c]	≤ 60 bpm	decrease of ≥ 15 bpm
Supraventricular premature beat	all	not present → present
Ventricular premature beat	all	not present → present
Supraventricular tachycardia	all	not present → present
Ventricular tachycardia	all	not present → present
Atrial fibrillation	all	not present → present
Atrial flutter	all	not present → present
Conduction		
1 atrioventricular block	PR ≥ 200 msec	increase of ≥ 50 msec
2 atrioventricular block	all	not present → present
3 atrioventricular block	all	not present → present
Left bundle-branch block	all	not present → present
Right bundle-branch block	all	not present → present
Pre-excitation syndrome	all	not present → present
Other intraventricular conduction block[d]	QRS ≥ 120 msec	increase of ≥ 20 msec
Infarction		
Acute or subacute	all	not present → present
Old	all	not present → present ≥ 12 weeks post trial entry
ST/T Morphological		
Myocardial ischemia	all	not present → present
Symmetrical T-wave inversion	all	not present → present
Increase in QTc		
< 12 years old	QTcF ≥ 450 msec	increase of 60 msec
≥ 12 years old	QTcF ≥ 460 msec	from baseline

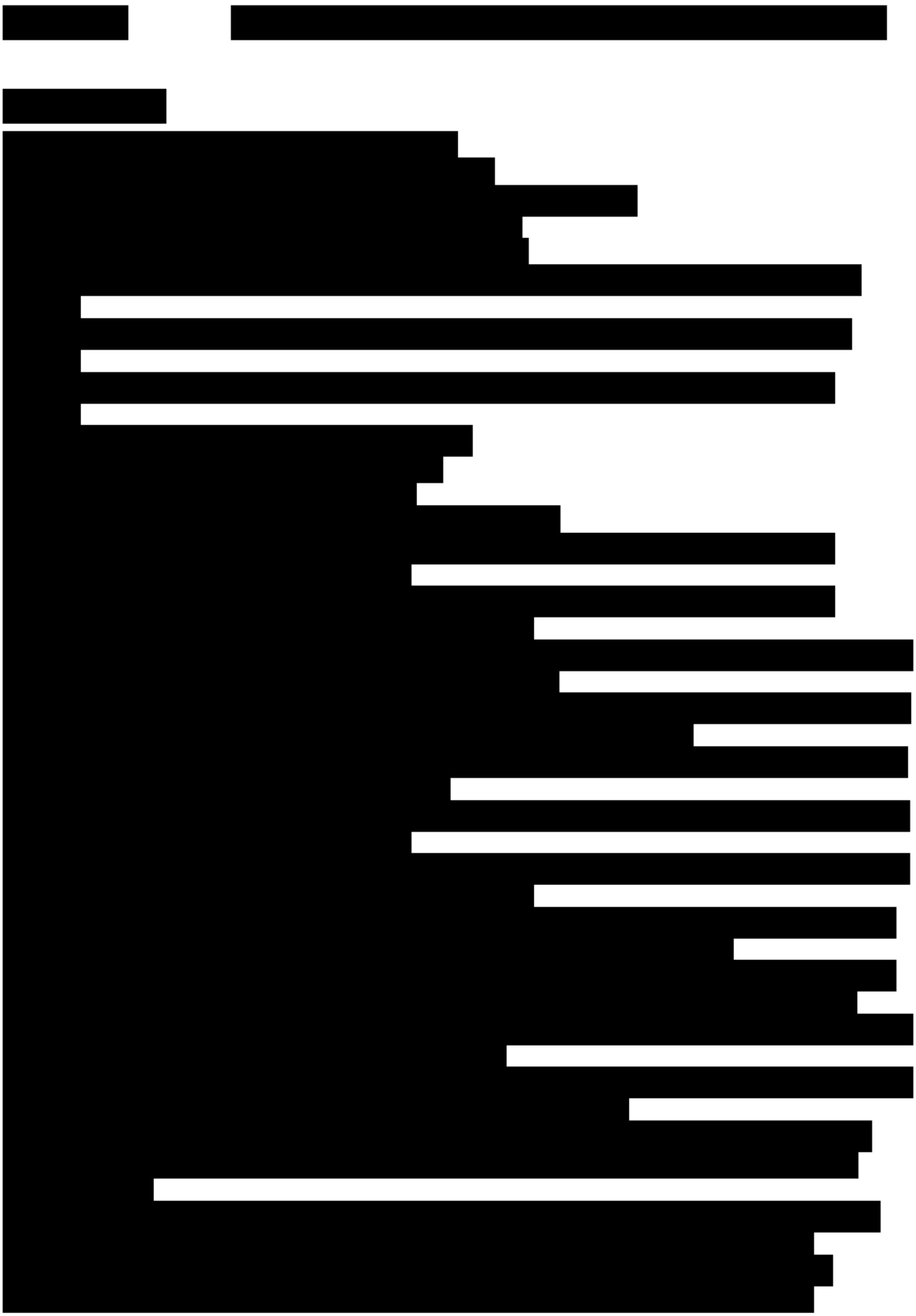
QTc = corrected QT interval.

[a]The criterion value and change relative to baseline represented in this table are intended to identify on-treatment values outside of normal changes and that could potentially be clinically relevant. In order to be identified as potentially clinically relevant, the on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column. When evaluating these values, the emotional state of the subject must be taken into consideration (eg, crying, screaming) and documented as applicable.

[b]No current diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, or other rhythm abnormality.

[c]No current diagnosis of atrial fibrillation, atrial flutter, or other rhythm abnormality.

[d]No current diagnosis of left bundle branch block or right bundle branch block.



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