Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

Centanafadine (EB-1020)

Protocol No. 405-201-00154
IND No. 119361

Protocol Title: A Phase 1, Open-label Trial to Determine the Dose Proportionality and Multiple Dose Pharmacokinetics of Centanafadine Once Daily Extended-release Oral Capsules in Healthy Adults

Protocol Lay Person Short Title: A Study to Test How Different Doses of Centanafadine Given for Multiple Days are Taken up in the Body

Statistical Analysis Plan

Phase 1
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List of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{τ}	area under the plasma concentration-time curve over the dosing interval at steady state
BMI	body mass index
C_{24h}	concentration of drug in plasma at 24 hours
CL_{ss}/F	apparent clearance at steady state
$C_{ss, max}$	maximum (or peak) serum concentration at steady state
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FDA	Food and Drug Administration
ICF	informed consent form
IMP	investigational medicinal product
IND	Investigational New Drug
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
$t_{1/2,z}$	terminal-phase elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time to maximum (or peak) serum concentration
ULN	upper limit of normal
Vz_{ss}/F	volume of distribution at steady state
SOC	system organ class
XR	extended-release

1 Introduction

This statistical analysis plan (SAP) documents the statistical methodology and data analysis algorithms and conventions to be applied for statistical analysis and reporting of safety and pharmacokinetic (PK) data of Trial 405-201-00154.

This SAP is prepared based on the protocol dated 17 Jul 2024.

2 Trial Objectives

Primary Objective

- To assess the dose proportionality and multiple dose PK of centanafadine once daily (QD) extended-release (XR) capsules administered in the fasted state to healthy adults.

Secondary Objective

- To evaluate the safety and tolerability of centanafadine QD XR capsules in healthy adults.

3 Trial Design

3.1 Type/Design of Trial

This is a phase 1, single-center, open-label trial for evaluation of multiple dose PK and dose proportionality of the centanafadine QD XR capsule formulation.

The trial will consist of a screening period (Day −28 to Day −2), check-in (Day −1), an in-clinic treatment and assessment period (Day 1 through discharge on Day 16 or early termination [ET]), and a safety follow-up telephone call on Day 21 (7 [+ 2] days after the last dose of investigational medicinal product [IMP]).

Sixteen healthy adults will be enrolled and administered one 164.4 mg capsule of centanafadine QD XR for 4 days (Days 1 to 4), followed by one 246.6 mg capsule of centanafadine QD XR for 4 days (Days 6 to 9), and then one 328.8 mg capsule of centanafadine QD XR for 4 days (Days 11 to 14). Serial PK samples will be collected over a 48-hour period following dosing on Days 4, 9, and 14 for the determination of centanafadine and metabolite concentrations in plasma. Participants will be discharged on Day 16 after completion of the safety evaluations and collection of the 48-hour PK sample.

See Figure 3.1-1 for schema of the trial design.

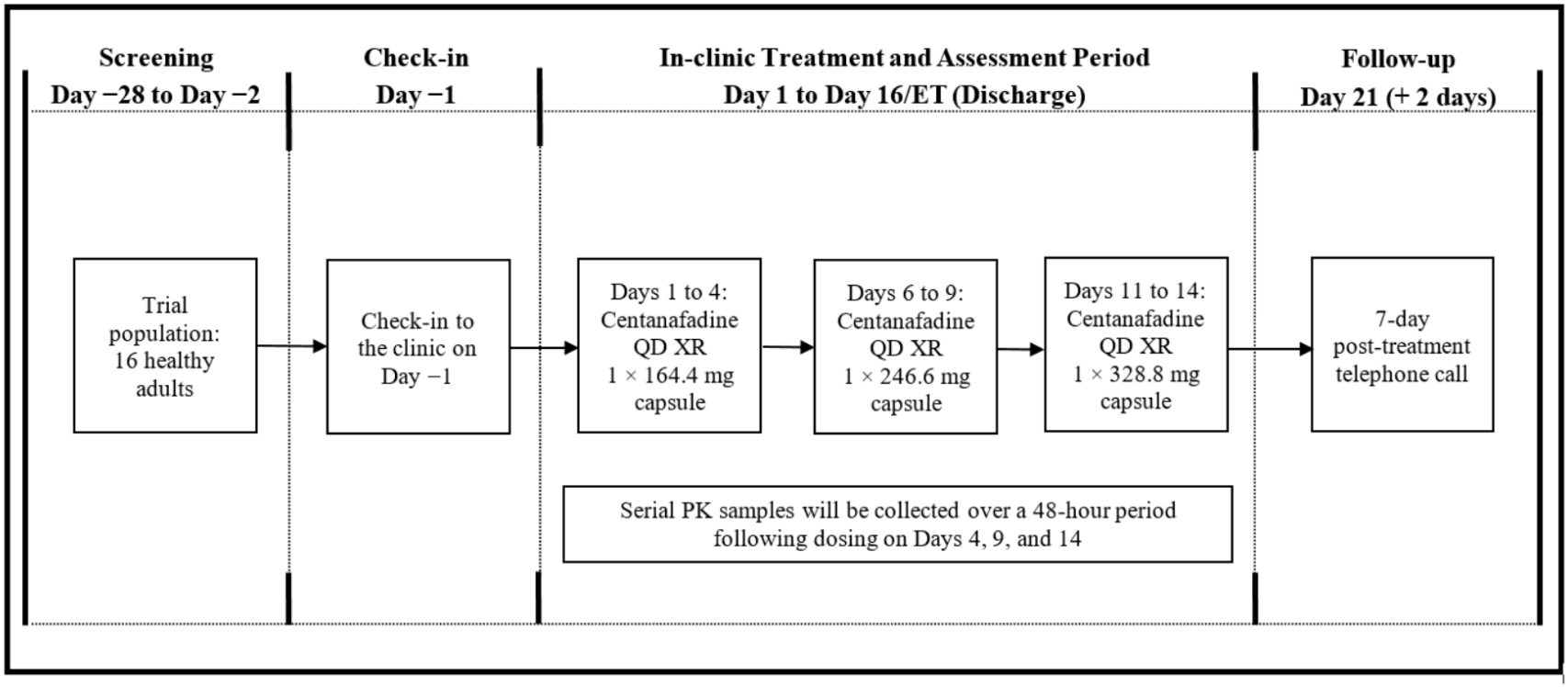


Figure 3.1-1 Trial Design Schematic

ET = early termination; PK = pharmacokinetics; QD = once daily; XR = extended-release.

3.2 Trial Treatments

Trial interventions are all prespecified IMPs intended to be administered to participants during the conduct of the trial.

The IMP will be provided as 164.4, 246.6, and 328.8 mg to-be-marketed centanafadine QD XR oral capsules. On Days 1 to 4, all participants will receive one 164.4 mg capsule of centanafadine QD XR. On Days 6 to 9, all participants will receive one 246.6 mg capsule of centanafadine QD XR. On Days 11 to 14, all participants will receive one 328.8 mg capsule of centanafadine QD XR.

On serial PK sampling days, the IMP will be administered in the morning with approximately 240 mL of water. No additional water will be permitted from 1 hour prior to IMP administration through 1-hour postdose. Participants will fast for at least 10 hours the night prior to the first day of serial PK sampling for each dose, and no food will be permitted until after 4 hours postdose on the first day of serial PK sampling for each dose. On non-serial PK sampling days, the IMP will be administered in the morning with approximately 240 mL of water at least 1 hour prior to breakfast.

3.3 Trial Population

An appropriate number of participants will be screened in order to enroll and treat up to 16 healthy males and females between 18 and 55 years of age, inclusive. Neither sex will comprise more than 60% of the trial participants. Discontinued participants may be replaced at the sponsor’s discretion.

4 Sample Size

The sample size of 16 enrolled participants was chosen empirically based on practical considerations and variability observed in previous trials using centanafadine QD XR capsules.

5 Statistical Analysis Sets

5.1 Enrolled Analysis Set

The Enrolled Analysis Set includes all participants who signed informed consent form (ICF) and enrolled in the trial.

5.2 Safety Analysis Set

The Safety Analysis Set includes all participants who are administered at least one dose of IMP.

5.3 Pharmacokinetic Analysis Set

The PK Analysis Set includes all participants who are administered at least one dose of IMP and have evaluable plasma concentration data and PK parameters.

5.4 Handling of Missing Data

5.4.1 Missing Data

Both the PK and safety analyses will be based on observed (non-missing) data and no data imputation will be performed in this trial. The handling of concentrations below the lower limit of quantitation will be according to the sponsor's data handling processes.

5.4.2 Incomplete Dates

The general rule for imputing incomplete dates in Safety Analysis Sets when the year is present is to use January if only the month is missing and the first day of a month if only the day is missing. If both month and day are missing but the year is available, January 1 is imputed. If the year is unknown, the date will be considered as missing.

No date imputation will be performed for PK sampling.

6 Primary and Secondary Outcome Variables

6.1 Primary Endpoints

The following PK parameters will be determined for centanafadine after multiple doses:

- Maximum (or peak) serum concentration at steady state ($C_{ss,max}$)
- Area under the plasma concentration-time curve over the dosing interval at steady state (AUC_{τ})
- Apparent clearance at steady state (CL_{ss}/F)
- Volume of distribution at steady state (Vz_{ss}/F)

6.2 Secondary Endpoints

The following PK parameters will be determined for centanafadine after multiple doses:

- Time to maximum (peak) plasma concentration (t_{max})
- Terminal-phase elimination half-life ($t_{1/2, z}$)
- Concentration of drug in plasma at 24 hours (C_{24h})

For the metabolite, the same PK parameters may be calculated (except CL_{ss}/F and Vz_{ss}/F) as supported by the data.

6.3 Safety Endpoints

- Reported adverse events(AEs)
- Clinical laboratory assessments
- Vital signs
- 12-lead electrocardiograms (ECGs)
- Columbia-Suicide Severity Rating Scale (C-SSRS)

7 Disposition and Demographic Analysis

7.1 Participant Disposition

The number of participants who are screened, enrolled, treated, discontinue from the trial, and complete the trial will be tabulated.

The number and percentage of participants who discontinue from the trial are to be summarized by discontinuation reason and treatment for the Enrolled Analysis Set.

7.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics (age, sex assigned at birth, race, ethnicity, weight, height, and body mass index [BMI]) will be summarized using descriptive statistics (number of participants, mean, standard deviation [SD], median, minimum, and maximum for continuous variables, and the proportion of participants for categorical variables). The summary will be based on the Enrolled Analysis Set.

7.3 Medical History

Listings for general medical history based on the Safety Analysis Set will be provided.

7.4 Treatment Compliance

The time and dose of each IMP administration will be recorded on the electronic case report form (eCRF). A listing of treatment compliance for each participant based on the Safety Analysis Set will be provided.

7.5 Prior and Concomitant Medications

The count and proportion of participants taking concomitant medications will be tabulated by drug classification using the latest version of World Health Organization Drug Dictionary for the Enrolled Analysis Set. The concomitant medications tabulation will be summarized as follows: prior to start of IMP, during IMP, and post IMP for the Enrolled Analysis Set. During IMP is designed as if the participant takes any medication

between Day 1 and Day 16. Concomitant medications during IMP will be summarized by treatment.

In addition, listings of concomitant mediations will be provided.

7.6 Protocol Deviations

Major protocol deviation data will be summarized by type of deviation (eg, violation of informed consent process, IMP dispensing or participant dosing error, treatment assignment error, participant enrolled in violation of eligibility criteria or concomitant medication criteria) for the Enrolled Analysis Set. In addition, a participant listing will be provided describing the major deviations for each participant.

8 Safety Analyses

All safety analyses will be conducted based upon the Safety Analysis Set. Safety variables to be analyzed include treatment exposure, AEs, clinical laboratory tests, physical examinations, vital signs, ECGs, and suicidality via the C-SSRS.

8.1 Extent of Exposure

Extent of exposure to IMP will be provided with descriptive statistics (n, percentage) by day and treatment. A listing recording date, time, and dosage will be provided as well.

8.2 Adverse Events

All treatment-emergent adverse events (TEAEs) will be coded by Medical Dictionary for Regulatory Activities (MedDRA; Version 26.0 or later), System Organ Class (SOC), and MedDRA preferred term.

Treatment-emergent adverse events are defined as those AEs with an onset date on or after the start of IMP treatment, or if the event was continuous from baseline and was worsening, serious, IMP related, or resulted in death, discontinuation, interruption, or reduction of IMP.

Newly acquired, nontraumatic skin eruptions are considered as AESIs. The following examples would not be considered as AESIs: contact dermatitis, insect bites and stings, poison plant intoxication (eg, poison ivy), skin reactions to ECG electrodes or similar adhesive tape, or chemical or thermal burns. Some examples of AESIs should include, but are not limited to, newly acquired maculopapular, macular, papular, papulosquamous, urticarial, acneiform, mucosal, cutaneous, mucocutaneous, vesicular, pustular, bullous, squamous, exfoliative, pruritic or non-pruritic, erythematous, exanthematous also known

as morbilliform rashes or skin eruptions which are localized or generalized, regardless of severity (mild, moderate, severe) or seriousness (i.e., nonserious lesions are also eligible).

An overall summary of the AEs by treatment will be provided. The incidence and percentage of participants with the following events will be summarized by SOC, MedDRA preferred term, severity, and treatment:

- TEAEs
- TEAEs by severity
- TEAEs potentially causally related to the IMP
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP
- AESIs
- Non serious TEAEs of at least 5%

All TEAEs will be presented in listings. The listings of death, serious AEs, AEs leading to discontinuation of the IMP, and AESIs will also be provided as well.

8.3 Clinical Laboratory Data

For clinical laboratory tests data, the baseline value is defined as the last non-missing value obtained before dosing for the first IMP of the trial.

The potentially clinically relevant laboratory test abnormalities will be listed by participant and by test. Clinical laboratory tests (observed and change from baseline data) will be summarized by visit. The incidence of potentially clinically relevant clinical laboratory tests as defined in Appendix 1 will be summarized. Shift tables will be produced assessing status (low-normal-high) changes from baseline using the laboratory reference range provided by the site lab.

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 the incidence table. All clinical laboratory test results will be presented in a listing.

8.4 Vital Sign Data

Blood pressure and pulse measurements will be made in the supine and standing positions after the participant has been in each position for at least 3 minutes. The supine measurements will be performed first followed by the standing measurements.

The baseline of vital signs is defined as the last non-missing value obtained before the first IMP of each treatment. If the predose assessment before first IMP of a treatment is missing, the baseline value will be based on the check-in visit on Day -1.

Vital signs data (observed and change from baseline data) will be summarized by time point and treatment. The incidence of potentially clinically relevant vital signs, as defined in Appendix 2 will be summarized by treatment as well. The potentially clinically significant vital signs abnormalities will be listed by participant. All vital signs test results will be presented in a listing.

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

8.5 Physical Examination Data

Physical examination data will be presented in a listing.

8.6 Electrocardiogram Data

Baseline value will be the average of the triplicate assessments on Day -1. If all assessments are not available on Day -1, the baseline value will be based on the screening value.

Descriptive statistics of ECG values (observed and change from baseline data) will be provided by visit. The incidence of potentially clinically relevant ECGs will be summarized by visit as well. Criteria for Identifying ECG Measurements of Potential Clinical Relevance are provided in Appendix 3. All ECG test results will be presented in a listing.

8.7 Potential Serious Hepatotoxicity

A listing will be provided to present the incidence of participants who experience an elevation in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) that is ≥ 3 times the upper limit of normal (ULN) and total bilirubin that is ≥ 2 times the ULN.

8.8 Columbia-Suicide Severity Rating Scale

Suicidality will be assessed based on C-SSRS data. Data for the “Baseline/Screening” version of the C-SSRS and the “Since Last Visit” version of the C-SSRS will be summarized descriptively and presented in a listing.

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 all other time

points. Baseline and post-baseline C-SSRS data will be summarized using the Safety Analysis Set to report the incidence of:

- Suicidality
- Suicidal behavior (and its 4 types)
- Suicidal ideation (and its 5 types)

Suicidality is defined as reporting at least 1 occurrence of any suicidal behavior or suicidal ideation. Suicidal behavior is defined as reporting any type of suicidal behaviors (actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior). Suicidal ideation is defined as reporting any type of suicidal ideation. In addition to these 3 incidences, C-SSRS data collected post-baseline will also be summarized using SAS to report the incidence of:

- Completed suicide
- Emergence of suicidal ideation
- Emergence of serious suicidal ideation
- Worsening of suicidal ideation
- Emergence of suicidal behavior

Any completed suicide is considered as complete suicidality. Emergence of suicidal ideation is defined as having no suicidal ideation at screening and baseline and reporting any type of ideation during treatment. Emergence of serious suicidal ideation is defined as having no suicidal ideation at screening and baseline and reporting any type of suicidal ideation with ideation severity rating of 4 or 5 during treatment. Worsening of suicidal ideation is defined as occurring when the most severe suicidal ideation rating during treatment is more severe than its worst rating at screening and baseline. Emergence of suicidal behavior is defined as having no suicidal behavior at screening and baseline and reporting any type of suicidal behavior during treatment.

9 Pharmacokinetics Analysis

9.1 Primary Pharmacokinetics Analysis

The primary analysis variables are the centanafadine PK parameters $C_{ss,\,max}$, AUC_{τ}, CL_{ss}/F, and Vz_{ss}/F. Pharmacokinetic parameters will be summarized by treatment and analyte using descriptive statistics (mean, median, standard deviation, percentage coefficient of variation [%CV], minimum, maximum, and geometric mean).

Dose proportionality of the $C_{ss,max}$ and AUC_{τ} values for 164.4 mg, 246.6 mg, and 328.8 mg doses of centanafadine QD XR at steady state (Days 4, 9, and 14, respectively) will

be explored using the random intercept power model, with participant as a random effect, using the following equation:

$$\ln(\text{PK parameter}) = \alpha + \beta \ln(\text{dose})$$

where α is the intercept and β is the slope parameter. The slope (exponent) of the power model and its 90% CI will be presented.

For all analyses, only individuals that have PK parameters determined will be included.

9.2 Secondary Pharmacokinetic Endpoint Analyses

The secondary pharmacokinetic endpoint parameters listed in Section 6.2 will be summarized using descriptive statistics in a similar way of the primary pharmacokinetic endpoints. T_{max} will be summarized by median, min and max only.

Individual plasma concentrations of centanafadine and its metabolite(s) will be summarized by analyte, treatment, and time point using descriptive statistics.

Noncompartmental PK analysis will be performed to estimate the PK parameters for centanafadine (and metabolite) and summarized using descriptive statistics for concentrations, except for t_{max} which will be reported as median. Other parameters may be calculated as supported by the data collected.

For the dose proportionality analysis of C_{24h}, the same random intercept power model as for the primary endpoint analysis will be used.

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[redacted]

12 Interim Analysis

There is no interim analysis for this trial.

13 Changes in the Planned Analyses

The safety dataset and PK dataset described in Section 9.2 of the Protocol are referred to as the Safety Analysis Set and PK Analysis Set in this SAP.

Appendix 1 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria
Chemistry	
AST	≥ 3 × ULN
ALT	≥ 3 × ULN
Alkaline phosphatase	≥ 3 × ULN
Blood urea nitrogen	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Bilirubin	≥ 2.0 mg/dL
Creatine kinase	> 3 × ULN
Hematology	
Hematocrit	
Males	≤ 37% and decrease of ≥ 3 percentage points from baseline
Females	≤ 32% and decrease of ≥ 3 percentage points from baseline
Hemoglobin	
Males	≤ 11.5 g/dL
Females	≤ 9.5 g/dL
Leukocyte count	≤ 2,800 mm^3 or ≥ 16,000 mm^3
Platelet	≤ 75,000/mm^3 or ≥ 700,000/mm^3
Urinalysis	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥ 2 units
Additional Criteria	
Potassium	≤ 2.5 mEq/L or ≥ 6.5 mEq/L
Sodium	≤ 126 mEq/L or ≥ 156 mEq/L
Calcium	≤ 8.2 mg/dL or ≥ 12 mg/dL
Glucose	
Fasting	≥ 100 mg/dL
Nonfasting	≥ 200 mg/dL
Cholesterol, fasting	≥ 240 mg/dL
Triglycerides, fasting	≥ 150 mg/dL

ULN=upper limit of normal, AST= Aspartate aminotransferase, ALT= alanine transaminase.

Appendix 2 Criteria for Identifying Vital Signs of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart rate[b]	> 90 bpm < 50 bpm	≥ 10 bpm increase ≥ 10 bpm decrease
SBP[b]	> 140 mmHg Supine ≤ 90 mmHg	≥ 20 mmHg increase ≥ 20 mmHg decrease
DBP[b]	> 90 mmHg Supine < 60 mmHg	≥ 10 mmHg increase ≥ 10 mmHg decrease
Orthostatic hypotension	≥ 30 mmHg decrease in SBP and/or a decrease of ≥ 20 mmHg in DBP 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	–	≥ 7% increase ≥ 7% decrease

SBP= Systolic blood pressure, DBP= diastolic blood pressure.

[a]In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the participant's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

[b]As defined in "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original New Drug Application Submission and for Organizing Information in Periodic Safety Updates," FDA Division of Neuropharmacological Drug Products draft (2/27/87).

Appendix 3 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Conduction		
1 atrioventricular block	PR ≥ 200 msec	increase of ≥ 50 msec
Other intraventricular conduction block[b]	QRS ≥ 120 msec	increase of ≥ 20 msec
ST/T Morphological		
Increase in QTc	QTcF > 450 msec (males) QTcF > 470 msec (females)	

QTc = corrected QT interval.

[a]In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the participant's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

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

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