NCT #NCT04366726

STATISTICAL ANALYSIS PLAN

A Prospective, Single Arm Study to Evaluate the PK, PD and Usability of Abaloparatide-sMTS in Postmenopausal Women with Low Bone Mineral Density

Protocol BA058-05-022

Protocol Version and Date: Amendment 1 (18 March 2019)

Name of Test Drug: Abaloparatide-sMTS

Phase: Phase 1

Methodology: Prospective, Single Arm, Open-Label

Sponsor: Radius Health, Inc.

[redacted]

Tel: 617-551-4000
Fax: [redacted]

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Confidentiality Statement

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Protocol Title: A Prospective, Single Arm Study to Evaluate the PK, PD and Usability of Abaloparatide-sMTS in Postmenopausal Women with Low Bone Mineral Density

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Study Drug: Abaloparatide-sMTS

SAP Version: Version 1.0 (19 Jun 2019)

Prepared By:

[redacted] Date

Radius Health, Inc.

REVIEWED AND APPROVED BY:

[redacted] Date

Radius Health, Inc.

[redacted] Date

[redacted]

Radius Health, Inc.

[redacted] Date

[redacted]

Radius Health, Inc.

[redacted] Date

[redacted]

Radius Health, Inc.

[redacted] Date

[redacted]

Radius Health, Inc.

[redacted] Date

[redacted]

Radius Health, Inc.

[redacted] Date

Radius Health, Inc.

[redacted] Date

Radius Health, Inc.

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LIST OF ABBREVIATIONS

Abbreviation	Term
µg	Microgram
AE	Adverse event
AESI	Adverse event of special interest
cAMP	Cyclic adenosine monophosphate
ATC	Anatomical therapeutic chemical
BMD	Bone mineral density
bpm	Beats per minute
CSR	Clinical study report
CTMS	Clinical trial management system
DBP	Diastolic blood pressure
DXA	Dual energy X-ray absorptiometry
ECG	Electrocardiogram
eCRF	Electronic case report form
EOT	End of treatment
FSH	Follicle-stimulating hormone
IU	International Unit
MedDRA	Medical dictionary for regulatory activities
msec	Millisecond
PAP	Pharmacometric analysis plan
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Prothrombin time
PTH	Parathyroid hormone
PTHrP	Parathyroid hormone related peptide
PTT	Partial thromboplastin time
QT	Total depolarization and repolarization time
QTc	Total depolarization and repolarization time corrected with heart rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
sMTS	Solid microstructured transdermal system
SOC	System organ class
SD	Standard deviation
SE	Standard error
SI	Standard international

Abbreviation	Term
s-PINP	Serum procollagen type 1 N propeptide
TEAEs	Treatment emergent adverse events
TMF	Trial master file
TSQM	Treatment satisfaction questionnaire for medication
WHO	World Health Organization

1 BACKGROUND

This Statistical Analysis Plan (SAP) describes the statistical methods for Study BA058-05-022 to analyze usability, pharmacodynamic and safety data. The method for analyzing the pharmacokinetic data will be described in the Pharmacometric Analysis Plan (PAP) as a separate document.

1.1 Study Objectives

The primary objective of this study, as stated in Section 2 of the protocol, is to evaluate the ability of subjects to self-administer 300 µg abaloparatide-sMTS over a period of 29 days based on pharmacokinetic (PK) and pharmacodynamic (PD) markers.

1.2 Study Design

1.2.1 Synopsis of Study Design

This is an open-label study to evaluate the usability of the abaloparatide-sMTS by subjects with low BMD. The study will consist of a Screening Period (up to 2 months), a Pre-Treatment Period (1 week), a Treatment Period (1 month), and a 1 week Follow-Up after the last dose of study medication. Thus, subjects will be in the study for up to 4 months. Eligible subjects will undergo protocol specified procedures, including BMD (if dual energy x-ray absorptiometry [DXA] was done over 12 months prior to Screening) and bone turnover marker assessment. For the purpose of this study, 1 month is equivalent to 30 days.

All eligible subjects will be provided calcium and vitamin D to ensure that their daily intake is 1,200 mg/day and 800 IU/day, respectively, or a dose determined by the Investigator and agreed by the Sponsor Medical Monitor, according to the subject's need.

The study design is presented in **Figure 1**. All subjects will undergo safety, pharmacokinetic, bone turnover marker (s-PINP), and assessments of User Errors and Subject Preference Outputs according to the Schedule of Assessments (**Table 1**).

Figure 1: Study BA058-05-022 Study Design

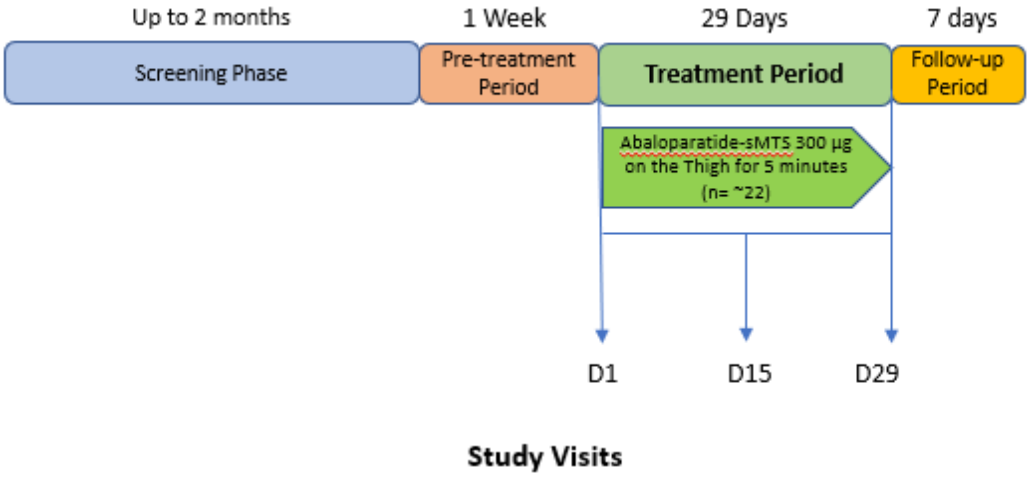

Table 1: Schedule of Assessments

Procedure	*Study Visit*	1	2	Treatment Period 3	4	5	6
	Visit Day	Screening (-67 to -8)	Pre-Treatment (-7 to -1)	Day 1	Day 15	Day 29 / End of Treatment (EOT)	Day 36 (Follow-up)
	Visit Window (Days)	N/A	± 2	± 2	± 2	± 2	± 2
Informed consent		X					
Verification of entry criteria		X					
Physical examination[1]		X					
Review of medical history[2]		X					
Symptom directed physical examination[1]			X	X	X	X	
Vital signs[3]		X		X	X	X	
Weight measurement		X	X	X	X	X	
Height measurement[4]		X					
ECG[5]		X		X	X	X	
Urinalysis (dipstick)[6]		X		X	X	X	
Chemistry blood collection[7]		X		X	X	X	
Serum calcium, albumin, phosphorus[8]				X	X	X	
Cyclic AMP[9]				X	X	X	
24 hour urine collection (for calcium:creatinine and creatinine clearance)[10]			X				
Hematology[7]		X		X	X	X	
Coagulation (PT and PTT) blood collection		X					
PTH (intact)		X					
25-hydroxyvitamin D level		X					
1,25-dihydroxyvitamin D level		X					
Estradiol, FSH		X					
Serum pregnancy		X					
Thyroid stimulating hormone		X					
Urine Drug and Alcohol Test[11]		X		X			

Procedure	*Study Visit*	1	2	Treatment Period 3	4	5	6
	Visit Day	Screening (-67 to -8)	Pre-Treatment (-7 to -1)	Day 1	Day 15	Day 29 / End of Treatment (EOT)	Day 36 (Follow-up)
	Visit Window (Days)	N/A	± 2	± 2	± 2	± 2	± 2
Subject training on study drug administration, completion of subject diary and assessment of symptoms of local skin reactions[12]				X			
Dispensing of calcium and vitamin D supplements			X	X	X		
Study drug administration[13]				Every day between Visit 3 and Visit 5, inclusive			
Collect used abaloparatide-sMTS and swab for residual drug and swab residuals				X	X	X	
BMD of lumbar spine, total hip and femoral neck by DXA [14]		X					
Investigator assessment of signs of local skin reaction[15]				X	X	X	
Subject assessment of symptoms of local skin reaction[16]				Every day between Visit 3 and Visit 5, inclusive			X[23]
Subject assessment of patch adhesion[17]				Every day between Visit 3 and Visit 5, inclusive			
Subject assessment of pain[18]				Every day between Visit 3 and Visit 5, inclusive			
Subject assessment of user errors				Every day between Visit 3 and Visit 5, inclusive			
Assessment of subject preferences for treatment attributes				X	X	X	
Assessment of subject convenience and satisfaction (TSQM9)					X	X	
Assessment of subject acceptability (5-point Likert scale)				X	X	X	
Subject diary review[19]				X	X	X[24]	
Document AEs and concomitant medication[20]		After signing informed consent until follow up visit					
PK draw[21]				X	X	X	
Serum marker of bone metabolism (s-PINP) [22]				X	X	X	
Drug supply / Drug re-supply				X	X		

Procedure	*Study Visit*	1	2	Treatment Period 3	4	5	6
	Visit Day	Screening (-67 to -8)	Pre-Treatment (-7 to -1)	Day 1	Day 15	Day 29 / End of Treatment (EOT)	Day 36 (Follow-up)
	Visit Window (Days)	N/A	± 2	± 2	± 2	± 2	± 2
Drug Accountability					X	X	

1. A complete physical examination includes a review of the following systems: head/neck/thyroid, eyes/ears/nose/throat, respiratory, cardiovascular, lymph nodes, abdomen, skin, musculoskeletal, and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. After screening, any clinically significant abnormal findings from the symptom-directed physical examinations should be reported as AEs.

2. Including alcohol and tobacco use assessment.

3. Blood pressure, pulse rate, body temperature, and respiration rate are to be recorded predose at each study visit. Only blood pressure, pulse rate and respiration rate are to be recorded 1 hour after abaloparatide-sMTS application at each study visit during the treatment period. All blood pressure assessments will be orthostatic. Pulse rate will also be obtained at 15 minutes after abaloparatide-sMTS application at Day 1 (Visit 3), Day 15 (Visit 4) and Day 29 (Visit 5/EOT).

4. Height is to be measured at the screening visit/ Visit 1 in the standing position using a medical stadiometer.

5. During the Treatment Period, ECGs are to be performed predose after 5 minutes of rest and prior to any blood draw, and 1 hour after abaloparatide-sMTS application on Day 1 (Visit 3), Day 15 (Visit 4) and Day 29 (Visit 5/EOT).

6. All routine urinalysis will be performed on a sample freshly voided during the visit and sent to a local laboratory for microscopy if test is positive for micro-organisms via dipstick.

7. Blood draw for serum chemistry and hematology will be done during the Screening (Visit 1) and at predose on Day 1 (Visit 3), Day 15 (Visit 4) and Day 29 (Visit 5/EOT).

8. Blood draw for serum calcium, albumin and phosphorus will be done at predose and at 4 hours after abaloparatide-sMTS application on Day 1 (Visit 3), Day 15 (Visit 4) and Day 29 (Visit 5/EOT).

9. Blood draw for cAMP taken predose and at 30 minutes after abaloparatide-sMTS application on Day 1 (Visit 3), Day 15 (Visit 4) and Day 29 (Visit 5/EOT).

10. A 24 hour urine collection will start on Day -8 and complete on the day of the pre-treatment visit (Day -7).

11. All subjects will have a urine drug screen for drugs of abuse and alcohol performed on the Screening Period (Visit 1), and on Day 1 (Visit 3).

12. When necessary, re-training may be done post Day 1 / Visit 3.

13. Study drug is self-administered daily beginning Day 1 (Visit 3) through Day 29 (Visit 5/EOT), inclusive. On Days 1, 15, and 29, subject will self-administer abaloparatide-sMTS at the study site.

14. BMD measured by DXA at Screening visit if most recent DXA was done over 12 months prior to screening.

15. Investigators will perform an assessment of the application site at each clinic visit prior to application of abaloparatide-sMTS, 5 minutes after application (ie, immediately upon removal of the patch), and 1- hour following abaloparatide-sMTS application. Signs of local skin reactions will be assessed using a 4-point scale, as described in Section 6.6.2.1 of the protocol.

16. The subject will maintain a diary to record their assessment of symptoms of local skin reactions for 29 days beginning on Day 1 (Visit 3). The subject will evaluate the application site prior to study drug administration, 5 minutes after application (ie, immediately upon removal of abaloparatide-sMTS), and 1 hour after abaloparatide-sMTS application. Symptoms of local skin reactions will be assessed using a 4-point scale as described in Section 6.6.2.2 of the protocol.

17. Subject assessment of patch adhesion immediately prior to abaloparatide-sMTS removal on each day of the treatment period from Day 1 (Visit 3) to Day 29 (Visit 5/EOT).

18. An assessment of pain (separate from the pain question on the 4-point scale for local tolerance) will be done after sMTS application.

19. The Subject Diary will be reviewed by study personnel at each study visit to ensure subject compliance.

20. AEs and SAEs will be recorded on the case report forms starting from the signing of the informed consent until 7 days after the last dose of study medication. All treatment-related AEs will be followed until resolution or stabilization. Any SAEs that occur at any time after completion of the study, which are considered by the investigator to be related to study treatment, must be reported to the Sponsor or its designee.

21. Blood samples for measurement of plasma concentrations of abaloparatide will be taken at Day 1 (Visit 3), Day 15 (Visit 4) and on Day 29 (Visit 5/EOT). The pharmacokinetic measurements will be assessed predose and at 10 minutes, 20 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 3 hours and 4 hours after abaloparatide-sMTS application.
22. Blood samples for s-PINP taken within 1-hour prior to dosing on Day 1 (Visit 3), Day 15 (Visit 4) and Day 29 (Visit 5/EOT).
23. Assessed only for subjects with signs or symptoms of local skin reactions ongoing as of Day 29.
24. Subject will return diary to study site.

1.2.2 Randomization Methodology

This is a single arm study, and randomization is not used. i.e., not applicable.

1.2.3 Unblinding

This is an open-label study, and there is no blinding of study medication. i.e., not applicable.

1.2.4 Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in **Table 1**.

1.2.5 Study Endpoints

1.2.5.1 Primary Endpoint

The primary endpoint is the systemic exposure of the drug at Day 1, Day 15 and Day 29. Details for the analysis of the primary endpoint are provided in the Pharmacometric Analysis Plan (PAP).

1.2.5.2 Secondary Endpoints

Pharmacodynamic Endpoints

Pharmacodynamic endpoints include:

- Change, percent change from baseline, and ratio from baseline to Day 15 and Day 29 in s-PINP.
- Change and percent change in serum calcium (albumin-corrected) from baseline to each post-dose timepoint.
- Change and percent change in serum phosphorus from baseline to each post-dose timepoint.
- Change and percent change in cAMP from baseline to each post-dose timepoint.

Other Endpoints

Other endpoints include subject/investigator-reported outcomes:

- Investigator assessment of signs of local skin reaction using a 4-point scale at Day 1, Day 15 and Day 29
- Subject assessment of symptoms of local skin reaction using a 4-point scale from Day 1 through Day 29 as recorded in the subject diary
- Subject satisfaction and convenience of treatment as measured by Treatment Satisfaction Questionnaire for Medication (TSQM9) at Day 15 and Day 29
- Subject acceptability measurement (5-point Likert Scale) at Day 1, Day 15 and Day 29
- Subject preference for treatment attributes at Day 1, Day 15 and Day 29
- Daily measurement of patch adhesion as recorded in the subject diary
- Daily measurement of user errors as recorded in the subject diary

1.2.5.3 Safety and Tolerability Endpoints

Safety evaluations will be based on AEs, vital signs (orthostatic blood pressure, pulse rate, body temperature, and respiration rate), ECG, and laboratory tests (serum chemistry, hematology, coagulation, and urinalysis).

2 SUBJECT ANALYSIS POPULATIONS

2.1 Population Definitions

Three subject populations will be considered in the statistical analyses of this study.

Safety Population

The Safety Population is defined as all subjects who received at least 1 dose of study medication.

Pharmacokinetic Analysis Population

The PK Analysis Population will include all subjects in the Safety Population who have sufficient evaluable plasma concentrations to reliably estimate one or more PK parameters. Further details will be provided in the Pharmacometric Analysis Plan (PAP).

Bone Metabolism Population

The Bone Metabolism Population is defined as all subjects in the Safety population who have baseline and at least one post-baseline s-PINP.

The primary population for all safety analyses will be the Safety Population, and the primary population for PK analyses will be the Pharmacokinetic Analysis Population. The primary population for the analysis of the secondary endpoints (i.e., pharmacodynamic and other endpoints) will be the Safety Population, unless otherwise specified. The Bone Metabolism Population will be used for all analyses involving s-PINP.

2.2 Protocol Deviation and Protocol Violation

A protocol deviation is defined as a deviation from the protocol that does not impose added risk to the study data or the study subject.

A protocol violation is defined as a deviation from basic requirements of the study protocol, including inclusion and exclusion criteria, concomitant medication restrictions, or any protocol requirements that result in a significant added risk to the study subject or has an impact on the quality of the data collected or the outcome of the study.

Subjects with protocol deviations and/or protocol violations will be collected by the clinical trial vendor (PRA) using their Clinical Trial Management System (CTMS). The list of protocol deviations and protocol violations will be reviewed by the clinical team on a regular basis throughout the study. At the end of the study, a list of the protocol deviations/violations will be generated from the CTMS and included in the clinical study report (CSR).

3 GENERAL STATISTICAL METHODS

3.1 Sample Size Planned and Specified in the Protocol

This is a hypothesis generating study and the sample size is based on previous clinical trial experience without a formal power calculation.

3.2 General Methods

Analyses of the pharmacokinetic endpoints will be described in a separate Pharmacometric Analysis Plan (PAP).

For all summaries of pharmacodynamic and safety endpoints, continuous variables will be summarized with the following descriptive statistics: number of observations, (arithmetic) mean, standard deviation (SD), median, interquartile range (Q1 and Q3), minimum, and maximum. Categorical data will be summarized with frequencies for each category and corresponding percentages.

All data listings that contain an evaluation date will contain a relative study day. Screening, pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study medication which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc.

In listings, data will be presented with the same precision as the original data. Derived data may be rounded to 1 decimal place greater than the original data for presentation purposes.

Frequency percentages will be presented with 1 decimal.

For all summaries, the mean and median will be presented to 1 decimal place greater than the original data, standard deviation (SD) to 2 greater than the original data, and the minimum and maximum will be presented to the same number of decimal places as the original data.

No statistical tests will be conducted on the pharmacodynamic and safety endpoints.

3.3 Computing Environment

All descriptive and statistical analyses will be performed using SAS statistical software Version 9.4, or later version. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 22.0. Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug Global March 2019 B3).

3.4 Baseline Definitions

Unless otherwise specified, the baseline value is defined as the last value obtained prior to the first dose of study medication.

3.5 Data Pooling

Not applicable since there is only one site involved in this study

3.6 Adjustments for Covariates

No adjustment for covariates will be made in any of the planned analyses for study endpoints.

3.7 Multiple Comparisons

Not applicable.

3.8 Subgroups

Not applicable.

3.9 Withdrawals, Dropouts, Loss to Follow-up

Data from subjects who do not complete the study, or who are lost to follow-up will be included in data listings and in summary tables, as appropriate.

3.10 Missing, Unused, and Spurious Data

Unless otherwise specified, there will be no imputation of pharmacodynamic and safety data.

In the event that incorrect data are discovered after database lock, the impact of such incorrect data will be assessed and a determination will be made as to whether the data need to be corrected in the database (and subsequently in the analysis). In cases where it is decided that the data need to be corrected, the decision will be documented and the documentation will be saved in the Trial Master File.

All available data will be included in data listings.

3.11 Visit Windows

Unless otherwise specified, data will not be analyzed using visit windows; instead, the nominal visit will be used.

3.12 Interim Analyses

There are no interim analyses planned for this study.

4 STUDY ANALYSES

Unless otherwise specified, all summary tables described in this section will be presented for the Safety Population.

4.1 Subject Disposition

Subject disposition will include the number of subjects enrolled, included in the safety population and reasons for exclusion from the safety population, included in the bone metabolism population and reasons for exclusion from the bone metabolism population, completed all doses, not completed all doses with reasons, completed the study, discontinued study with primary reasons for not completing the study.

A by-subject data listing of study completion information, including the primary reasons for study withdrawal as recorded in the eCRF, will be presented.

4.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized. Age will be calculated as of the date of Informed Consent. Age, height, weight, body mass index (BMI), total hip T-score, total hip BMD, femoral neck T-score, femoral neck BMD, lumbar spine T-score, and lumbar spine BMD will be summarized using descriptive statistics (number of subjects, mean, SD, median, interquartile range, minimum and maximum). The number and percentage of subjects in each age, gender, ethnicity, race and total hip/lumbar spine/femoral neck T-score category (> -1.5 to < -1.0; > -2.0 to <= -1.5; > -2.5 to <= -2.0; > -3.0 to <= -2.5; and <= -3.0) will also be presented.

Medical history will be presented by MedDRA system organ class (SOC) and preferred term (PT) summarizing the proportion of subjects who have a condition noted.

All subject data collected for demographics and baseline characteristics will be presented in data listings.

4.3 Extent of Exposure and Compliance

Study drug exposure and compliance will be calculated using the data recorded on the Medication Dosing eCRF as follows:

- Duration of Exposure (days)
  = date of last study medication – date of first study medication + 1
  Note: If date of last dose is missing, the last dose recorded in the subject's diary will be used.
- Number of Doses Received
  = number of successful applications from the subject dosing diary
- Compliance (%)
  = (Number of doses received / Duration of exposure) x 100%

Descriptive statistics (number of subjects, mean, SD, median, interquartile range, minimum and maximum) will be used to summarize study drug exposure and compliance.

4.4 Concomitant Medication

Concomitant medications will be coded using the WHO Drug Dictionary. The number (and percentage) of subjects taking medications will be tabulated by Anatomical Therapeutic Chemical (ATC) class and preferred term (PT).

The tabulations will include concomitant medications taken from the date of the first dose of study medication (Day 1) until 1 week after the last dose of study medication. Medications that did not end prior to the first dose of study medication will be included in the summary.

Prior medications (those with start date prior to the first dose of study medication) will also be summarized by ATC and PT.

All recorded concomitant medications will be presented in a by-subject listing.

4.5 Analyses of the Primary Endpoint

The primary endpoint is the systemic exposure of the drug at Day 1, Day 15 and Day 29. Details are provided in the Pharmacometric Analysis Plan (PAP). Pharmacokinetic (PK) analyses will be conducted by Certara. Details of the planned PK analyses will be described in the PAP and provided as an Appendix to the CSR.

4.6 Analyses of Secondary Endpoints

4.6.1 Percent change of s-PINP from baseline to Day 15 and Day 29

The actual values, change from baseline values, percentage change from baseline values, geometric mean, geometric mean (SE) of ratio (post-baseline value to baseline value) in s-PINP will be summarized descriptively by visit, together with the 90% CI.

4.6.2 Change and percent change in serum calcium (albumin-corrected) from baseline to each post-dose timepoint

The actual values, change from baseline values, and the percentage change from baseline values will be summarized using descriptive statistics by visit and timepoint. A scatter plot will be used to present the relationship between the change from baseline (on y-axis) and total released dose as defined in Section 4.7.7 (on x-axis) for each timepoint.

4.6.3 Change and percent change in serum phosphorus from baseline to each post-dose timepoint

The same analyses described in Section 4.6.2 will be used.

4.6.4 Change and percent change in cAMP from baseline to each post-dose timepoint

The same analyses described in Section 4.6.2 will be used.

4.7 Analyses of Other Endpoints

4.7.1 Subject satisfaction and convenience of treatment as measured by Treatment Satisfaction Questionnaire for Medication (TSQM-9) at Day 15 and Day 29

Subject satisfaction and convenience domain scores will be calculated following the descriptions in section 3.3 of TSQM user manual version 1.1 (October 2018).

Descriptive statistics (number of subjects, mean, standard error [SE], median, interquartile range, minimum and maximum) will be used to summarize TSQM-9 satisfaction and convenience domain scores and will be tabulated for Day 15 and Day 29.

Adherence will be measured by s-PINP. The median percent change from baseline in s-PINP will be obtained at Day 15 and at Day 29.

Descriptive statistics for each of TSQM-9 satisfaction and convenience domain scores will be presented for subject by adherence (i.e., ≥ or < the median percent change from baseline in s-PINP) at Day 15 and Day 29, respectively.

4.7.2 Subject acceptability measurement (5-point Likert Scale) at Day 1, Day 15 and Day 29

Subject acceptability measurement is based upon a 5-point Likert-like scale from 1 (least acceptable/negative experience) to 5 (most acceptable/positive experience). Subject acceptability measurement at each visit and changes from baseline will be summarized with descriptive statistics (number of subjects, mean, standard error [SE], median, interquartile range, minimum and maximum).

Descriptive statistics for the baseline and the change from baseline will be presented for subject with adherence (as defined in Section 4.7.1) vs. without adherence at Day 15 and Day 29, respectively.

4.7.3 Subject preference for treatment attributes at Day 1, Day 15 and Day 29

Since the data is collected as free-text field in eCRF, data will be classified after database lock for summary and further analyses. Association between subject preference for treatment attributes and subsequent acceptability and satisfaction will be evaluated separately for: outcome (effectiveness/safety) and other attributes (duration, frequency of use, mode of intake).

4.7.4 Investigator assessment of signs of local skin reaction using a 4-point scale at Day 1, Day 15 and Day 29

For each sign, the number (%) of subjects in each response category (none, mild, moderate, and severe) will be provided per visit and timepoint. The maximum severity of each sign of local skin reaction will be similarly summarized with the number (%) for each response category by visit and by timepoint, respectively. Aggregate summary of occurrence for each sign of local skin reaction will be similarly summarized with the number (%) for each response category by timepoint.

4.7.5 Subject assessment of symptoms of local skin reaction using a 4-point scale from Day 1 through Day 29 as recorded in the subject diary

For each symptom, descriptive statistics (number of subjects, mean, SD, median, interquartile range, minimum and maximum) will be used to summarize 4-point scale scores (0=None,

1=Mild, 2=Moderate,3=Severe) collected during the treatment period by timepoint. The maximum severity of each symptom of local skin reaction per subject during the treatment period will be summarized with the number (%) for each response category by visit and by timepoint (including any post dose timepoint), respectively.

In addition, for each symptom, the number (%) of subjects in each response category (none, mild, moderate, and severe) at clinic visits (Day 1, Day 15 and Day 29) will be provided per visit and timepoint. The maximum severity of reaction scores at clinic visits will be similarly summarized for each response category by visit and by timepoint, respectively.

For each symptom, the number (%) of subjects in each response category (none, mild, moderate, and severe) at Day 36 follow-up will be provided for each telephone contact, in clinic visit and overall (telephone contact + in clinic visit) group category.

Aggregate summary of occurrence for each symptom of local skin reaction will be similarly summarized with the number (%) of subjects in each response category by timepoint.

All application site local tolerability assessment scores will be presented in a listing.

4.7.6 Daily measurement of patch adhesion as recorded in the subject diary

Frequency counts (and percentages) for the patch adhesion score collected at each clinic visit will be summarized by visit, along with the best adhesion score (i.e., lowest patch adhesion score per subject) and the worst adhesion score (i.e., highest patch adhesion score per subject).

The mean of the patch adhesion scores collected from Day 1 to Day 29 will be calculated for each subject. The mean patch adhesion score will be summarized using descriptive statistics for the entire treatment period. The mean of each subject's best adhesion score and worst adhesion score will also be summarized.

4.7.7 Abaloparatide-sMTS Released Dose

A released dose is defined as "Initial Patch Content – Residual drug amount from Swab and Patch." Descriptive statistics will be provided to summarize the released dose, the percentage of released dose to nominal dose, the percentage of release dose to initial patch content, the residual drug amount from the patch, the residual drug amount from the patch and swab, by visit. Released dose values that are negative will be set to 0 in the summaries, but the recorded values will be presented in the listings.

4.7.8 Daily measurement of user errors as recorded in the subject diary

The following summary statistics will be provided.

4.7.8.1 Summary of patch application by study day

- Frequency counts (and percentages) for the successful first application
- Frequency counts (and percentages) of the application location for the successful application
- Descriptive statistics for the time from removal from refrigerator until application – data from successful application is used
- Descriptive statistics for the time from patch application until removal – data from successful application is used

4.7.8.2 Summary of patch application during the treatment period

- Descriptive statistics for the first application success rate; success rate (%) is defined as number of successful first application / total number of applications for the subject x 100.
- Descriptive statistics for mean time from removal from refrigerator until application; time averaged over the treatment period for the subject; data from successful application is used for the subject mean
- Descriptive statistics for the mean time from patch application until removal; time averaged over the treatment period for the subject; data from successful application is used for the subject mean

4.7.8.3 Summary of patch application difficulties by study day

Frequency counts (and percentages) for items related to patch application difficulty will be provided using the available data collected at the study day

- Steps with difficulty
- Difficulty opening pouch
- Patch falls on floor
- Touch patch before application
- Difficulty caused by pain
- Difficulty caused by other issues

4.7.8.4 Summary of patch application difficulties during the treatment period

Descriptive statistics for the following items per subject will be provided using the available data collected at the study day

- Number of steps with difficulty
- Percentage of with difficulty opening pouch
- Percentage of patch falling on floor
- Percentage of patch touched before application
- Percentage of difficulty caused by pain
- Percentage of difficulty caused by other issues

4.7.8.5 Summary of patch application cleaning by study day

Frequency counts (and percentages) for items related to patch application cleaning will be provided using the available data collected at the study day

- Wash hands before applying
- Clean and inspect application site
- Clean applicator afterwards
- Leg dry before application

4.7.8.6 Summary of patch application cleaning during the treatment period

Descriptive statistics for items related to patch application difficulty will be provided using the available data collected at the study day

- Percentage of washing hands before applying
- Percentage of cleaning and inspecting application site
- Percentage of clean applicator afterwards
- Percentage of leg dry before application

4.7.8.7 Summary of 24-hour skin assessment by study day

Frequency counts (and percentages) of subjects who still identify a clear mark after 24 hours where the patch was applied will be provided.

4.7.8.8 Summary of 24-hour skin assessment during the treatment period

Descriptive statistics for items related to 24-Hour skin assessment will be provided.

- Percentage of applications where a clear mark is identified per subject

  = number of "Yes" for the question (Can you still identify a clear mark where the patch was applied?) / total number of applications for the subject x 100

Frequency (and percentage) of responses where a clear mark is identified across all subjects in the study

Percentage

= Total number of "Yes" for the question across all subjects in the study /

Total number of applications across all subjects in the study x 100

4.8 Safety Analyses

All safety analyses will be conducted using the Safety population. Unless otherwise specified, no formal statistical hypothesis testing will be performed for safety endpoints, and the presentations will be based on descriptive summaries.

4.8.1 Adverse Events

Analyses of AEs will be performed for those events that are considered to be treatment-emergent adverse events (TEAEs). A TEAE is defined as any AE that was absent (i.e., had not occurred) prior to the start of study drug and which occurs on or after the date of the first dose of study drug and within 30 days of the last dose of study drug, or any AE that started during the study period(s) prior to the start of study drug and worsened in severity after the start of study drug within 30 days of the last dose of study drug.

In any tabulation of adverse events, a subject contributes only once to the count for a given SOC or PT. For summaries by severity, a subject with multiple occurrences of an AE will be represented under the most severe occurrence. For summaries by relationship to study drug, a

subject with multiple occurrences of an AE will be represented under the most related occurrence.

The number (%) of subjects with TEAEs will be summarized by SOC and PT. This analysis will also be performed for the following types of AEs: most common (≥5%) TEAEs, severe TEAEs, serious TEAEs (SAEs), TEAEs leading to study withdrawal, drug-related TEAEs (with probable or possible relationship to study drug), and AEs that are not treatment-emergent.

The number (%) of subjects with TEAEs by SOC and PT will also be tabulated by maximum severity (mild, moderate, or severe). Subjects with multiple occurrences of a single AE will be counted using the most severe AE. A similar tabulation will be presented by relationship (related or not related) to study drug.

TEAEs associated with the below AEs of special interest (AESI) will be summarized:

- Skin AESI
- Hypersensitivity AESI

Subject listings will be provided for all AEs by SOC and PT. Listings will also be produced for AEs with outcome of deaths, severe AEs, SAEs, AEs leading to discontinuation of study drug withdrawal, Skin AESI, Hypersensitivity AESI and unanticipated adverse device effects (UADEs).

4.8.2 Laboratory Data

Clinical laboratory values will be provided in standard international (SI) units by the central laboratory.

Summaries of laboratory data using descriptive statistics by study visit will be presented based on the SI units, including absolute results and changes from baseline. This includes serum chemistry, hematology, coagulation, urinalysis, and additional tests. In the event of repeat or unscheduled assessments, the last non-missing value per study day/time will be used in the summary statistics.

Shift analyses of laboratory data from baseline to post-baseline (day 15 and day 29, respectively) will be performed. Results for laboratory data will be presented by category (above normal limit, within normal limit, below normal limit). For shift tables, subjects who are missing either assessment will not be included in the percentage calculation (numerator or denominator).

All laboratory data, including repeated values and results from unscheduled visits, will be presented in data listings, with indication of higher or lower than the associated normal range of each laboratory test.

4.8.3 Vital Signs

Vital signs data will be summarized by visit (and timepoint if applicable). Descriptive statistics will be provided for the observed value and the change from baseline values. If a subject has multiple results on the vital signs at a particular visit, the last non-missing value will be used for the summary.

All vital signs data will be presented for each subject in a data listing.

4.8.3.1 Orthostatic Hypotension

The number (%) of subjects experiencing orthostatic hypotension will be summarized by visit and time point. Orthostatic hypotension will be defined as a decrease in systolic blood pressure (SBP) of ≥ 20 mmHg from seated or supine to standing or in diastolic blood pressure (DBP) of ≥ 10 mmHg from seated or supine to standing.

4.8.3.2 Pulse

Descriptive statistics will be provided for the observed value and the change from pre-dose values by visit. The number (%) of subjects experiencing pulse increase from pre-dose and the occurrence per subject will be summarized with various threshold values (ranging from >5 bpm to >40 bpm).

4.8.4 Electrocardiogram

Descriptive statistics will be provided to summarize ECG parameters and changes from baseline by visit and time point. The ECG parameters include heart rate (bpm), RR interval (msec), PR interval (msec), QRS duration (msec), QT interval (msec), and QTcF (Fridericia) (msec). In the event of repeat or unscheduled assessments for a given time point, the last non-missing value for the time point will be used in the tabulations.

Descriptive statistics will be provided for the observed value and the change from pre-dose values by visit. The number (%) of subjects experiencing heart rate increase from pre-dose and the occurrence per subject will be summarized with various threshold values (ranging from >5 bpm to >40 bpm).

5 CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

The Bone Metabolism Population is not defined in the protocol and has been added in the SAP. It is defined as subjects in the Safety population who have baseline and at least one post-baseline s-PINP.

All other statements in this SAP are enhancements to the statistical considerations described in the protocol.

Signature Page for RAD-CLIN-001231 v1.0

Approval	[redacted] 20-Jun-2019 13:59:04 GMT+0000
Approval	[redacted] 20-Jun-2019 14:02:55 GMT+0000
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PHARMACOMETRIC ANALYSIS PLAN

A PROSPECTIVE, SINGLE ARM STUDY TO EVALUATE THE PK, PD AND USABILITY OF ABALOPARATIDE-sMTS IN POSTMENOPAUSAL WOMEN WITH LOW BONE MINERAL DENSITY

Final
Date: 27-May-2019

Sponsor Protocol No.: BA058-05-022 (Version 1.0)
Investigational Product: Abaloparatide-sMTS

CSC Reference No.: RADI-NCA-ABALOPARATIDE-985

Radius Health, Inc. (Radius)

[redacted]

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SIGNATURE PAGE

Protocol No.: BA058-05-022

Study Title: A Prospective, Single Arm Study to Evaluate the PK, PD and Usability of Abaloparatide-sMTS in Postmenopausal Women with Low Bone Mineral Density

CSC Reference No.: RADI-NCA-ABALOPARATIDE-985

[redacted] _____ 27-may-2019
Date

Certara Strategic Consulting

[redacted] _____ 27 MAY 2019
Date

Certara Strategic Consulting

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Sponsor Review and Approval:

[redacted]

Radius Health, Inc.

28 MAY 2019
Date

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4 LIST OF ABBREVIATIONS

Term	Definition
$\%AUC_{extrap}$	Extrapolated portion of $AUC_{0\text{-}inf}$ from t_{last} to infinity
ADaM	Analysis Data Model
ADPC	Analysis dataset containing PK concentrations
ADPP	Analysis dataset containing PK parameters
ADRG	Analysis Data Reviewer's Guide
AUC	Area under the curve
BLQ	Below the limit of quantification
C_{max}	Maximal plasma concentration
CRF	Case report form
CSC	Certara Strategic Consulting
CV%	Coefficient of variation
DTS	Data transfer specification document
EOT	End of treatment
FTP	Secured file transfer protocol
IFU	Instruction for use
LLOQ	Lower limit of quantification
n	Sample size
Max	Maximum
Min	Minimum
NCA	Noncompartmental analysis
PAP	Pharmacometric Analysis Plan
PD	Pharmacodynamics
PK	Pharmacokinetic(s)
QA	Quality Assurance
QC	Quality Control
SD	Standard deviation
SDRG	Submission Data Reviewer's Guide
SDTM	Study Data Tabulation Model
sMTS	Solid microstructure transdermal system
SOP	Standard operating procedure
t_{max}	Time to maximal concentration

5 SCOPE

This Pharmacometric Analysis Plan (PAP) was created using the study protocol BA058-05-022, Version 1.0, dated 18 March 2019. Any further changes to the protocol may require updates to the current analysis plan.

This analysis plan addresses the pharmacokinetic (PK) analysis of abaloparatide-solid Microstructured Transdermal System (sMTS) in plasma in postmenopausal women with low bone mineral density. The intended methods of data analysis and reporting are included in the current analysis plan. This document provides guidance to the extent, scope, and method of analysis. However, due to uncertainty of the nature of the data *a priori*, deviations from this plan may be necessary and will be documented.

The final methods of analysis and results will be reported in the PK Report. Deviations from this plan will be noted.

6 ANALYSIS PLAN OBJECTIVES

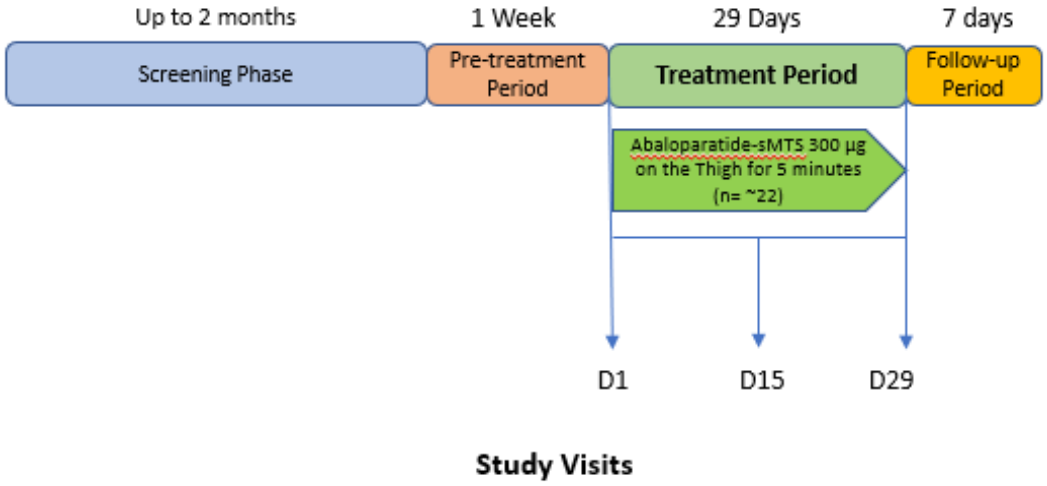
- To characterize the PK profile of abaloparatide-sMTS in postmenopausal women with low bone mineral density following daily self-administrations of 300 μg abaloparatide-sMTS for 5 minutes over a period of 29 days.

7 STUDY DESIGN

7.1 General Study Design

This is an open-label study to evaluate the usability of the abaloparatide-sMTS by subjects with low bone mineral density. The study will consist of a Screening Period (up to 2 months), a Pre-Treatment Period (1 week), a Treatment Period (29 days), and a Follow-Up Period (7 days) after the last dose of study medication. During the Treatment Period, subjects will have clinic visits for study-related protocol procedures at Day 1 (Visit 3), Day 15 (Visit 4) and on Day 29 (Visit 5/End of Treatment (EOT)). The Treatment Period of the study will be considered complete when the last subject completes the last clinic visit. The study design is presented in **Figure 7.1**.

Figure 7.1 Study Design



7.2 Schedule of Drug Administration

The first self-administration is to occur at the study site on Day 1, under observation.

Subjects will be trained by study personnel to self-administer study medication with the abaloparatide-sMTS patch and applicator. Subjects will self-administer a single daily dose of 300 µg of abaloparatide-sMTS to the thigh for 5 minutes during the treatment period, following the Instructions for Use (IFU).

The subject is to remain under observation for a minimum of 60 minutes after the initial abaloparatide-sMTS removal on Day 1.

On the days when blood sampling is required after study medication administration, the subject is to remain at the vicinity of the clinic for the blood collections scheduled up to 4 hours post-administration of the study medication.

7.3 Number of Subjects

Approximately 22 subjects will be enrolled and treated to ensure a minimum of 18 subjects complete the 29-day treatment and study procedures.

7.4 Pharmacokinetic Assessments

Blood samples for measurement of plasma concentrations of abaloparatide will be taken at Day 1, Day 15 and on Day 29. The pharmacokinetic measurements will be assessed predose and at 10 minutes, 20 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 3 hours and 4 hours after abaloparatide-sMTS application.

8 ANALYSIS SETS

8.1 Pharmacokinetic Analysis Population

The Pharmacokinetic Analysis Population will include all subjects who received at least one dose of study medication and have sufficient evaluable plasma concentrations to reliably estimate one or more PK parameters.

9 METHODS

Study data tabulation model (SDTM) and analysis data model (ADaM) clinical datasets (subject identification, dosing times, blood sample collection times, dosing information, etc.) will be transferred from Radius to Certara Strategic Consulting (CSC) via a secured file transfer protocol (FTP), secure file sharing services or password-protected e-mail. Final data will be transferred after the final database lock. It is expected that all final SDTM and ADaM data transferred to Certara from Radius will be validated and quality controlled or quality assured before being sent to Certara. Inconsistencies in the data will be communicated to Radius and may result in a delay in the analysis timelines. For the ADaM datasets, Radius will provide a Specification Document in Excel format to Certara describing each variable in the datasets. For SDTM datasets, any study specific information will be provided to Certara from Radius.

All electronic files that are sent via e-mail to CSC will be addressed to the following CSC designate:

[redacted]
[redacted]
Certara Strategic Consulting
e-mail: [redacted]

Certara will provide to Radius one SDTM dataset containing PK parameters (PP), one analysis dataset containing PK concentration (ADPC) and one analysis dataset containing PK parameter (ADPP) as well as Submission Data Reviewer's Guide (SDRG) and Analysis Data Reviewer's Guide (ADRG) for creating define.xml. Datasets will contain data used for the analysis performed. A test transfer will be made to insure compliance with the data transfer specification document (DTS). Files will be transferred following acceptance of Radius of the results of the test transfer.

9.1 Study Variables

9.1.1 Concentration Data

Concentration values of plasma abaloparatide-sMTS that are reported as below the limit of quantitation (BLQ) will be set to zero for PK parameter calculation and concentration summary statistics.

9.1.2 Pharmacokinetic Parameters of Abaloparatide-sMTS in Plasma

All plasma PK parameter calculations will be performed using actual or nominal times (when actual time is not available) calculated relative to the time of study drug administration in hours. PK parameters will be determined using noncompartmental (NCA) methods[1] based on individual plasma concentration-time data for abaloparatide-sMTS (Table 1).

Table 1: Pharmacokinetic Parameters of Abaloparatide-sMTS in Plasma

Parameters	Description
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (t_{last}) using the linear up-log down trapezoidal rule
AUC_{0-inf}	Area under the plasma concentration-time curve from time zero to infinity calculated using the formula $AUC_{0-t} + (C_{last} / \lambda_z)$, where C_{last} is the last quantifiable concentration and λ_z is the first-order terminal rate constant, calculated by log-linear regression analysis over the terminal log-linear segment of the plasma concentration-time curve. AUC_{0-inf} was calculated using the linear-up log down trapezoid rule.
C_{max}	Maximum observed plasma concentration
t_{max}	Time of maximum observed plasma concentration
$t_{1/2}$	Apparent terminal phase half-life, calculated as $ln(2)/\lambda_z$
λ_z	Elimination rate constant

Assessments of λ_z will include the following key considerations:

- At least 3 time points (in which the first time point must be greater than t_{max}) with measurable plasma concentrations will be required for the calculation of λ_z.
- λ_z must be positive, and calculated from at least three data points in the terminal phase of the concentration-time profile.
- Points prior to t_{max} are not used.
- t_{max} is not included.
- $R^2_{adj} \geq 0.8$ for the log-linear regression analysis of λ_z.

No value for λ_z and other λ_z-related parameters (e.g., AUC_{0-inf} and $t_{1/2}$) will be reported for concentration profiles that do not exhibit an elimination phase in the concentration versus time profile (i.e., if $R^2_{adj} < 0.8$ for the log-linear regression analysis of λ_z).

For the assessment of λ_z, if the extrapolated portion of AUC_{0-inf} from t_{last} to infinity ($\%AUC_{extrap}$) for a subject is greater than 20%, the λ_z-related PK parameters will be listed for that subject, and the λ_z and λ_z-related PK parameters will be excluded from descriptive statistics with a corresponding footnote to highlight that $\%AUC_{extrap}$ is greater than 20%.

If a dose of abaloparatide-sMTS is missed or if the patch did not adhere correctly to the skin, the complete corresponding concentration-time profile may be excluded from the PK analysis and/or summary statistics after review by CSC and Radius on a case-by-case basis.

9.2 Statistical Methods

9.2.1 Concentrations of Abaloparatide-sMTS

Individual concentration of abaloparatide-sMTS will be listed and summarized in accordance with the grouping factors (i.e., day).

Each data subset will be listed by subject and summarized for each nominal time point with the following descriptive statistics: sample size (n), mean (Mean), standard deviation (SD), coefficient of variation (CV%), median (Median), minimum (Min), maximum (Max), geometric mean (Geo Mean) and coefficient of variation of Geo Mean (Geo Mean CV%).

Individual concentrations of abaloparatide-sMTS will be reported at the level of significance presented in the observed data files. Reporting rules for the concentrations and summary statistics, will be as follows:

- Mean: 1 more level decimal/significant digit than the individual value
- Geo Mean: 1 more decimal/significant digit than the individual value
- SD: 1 more decimal/significant digit than the mean
- CV%: always 1 decimal
- Median, Min, Max: same number of decimals/significant digits reported for the individual value.

Individual concentrations will be plotted vs. actual sampling time on linear-linear and log-linear scales (one plot per subject, as appropriate). Mean concentrations (+SD) will be plotted vs. nominal sampling time on linear-linear and log-linear scales using the appropriate grouping factors (day). Additionally, spaghetti plots of abaloparatide-sMTS plasma concentrations will be prepared for each day.

9.2.2 PK Parameters of Abaloparatide-sMTS

Individual plasma PK parameters of abaloparatide-sMTS will be listed and summarized in accordance with the grouping factors (i.e., day). PK parameters will be summarized with the following descriptive statistics: n, Mean, SD, CV%, Median, Min, Max, Geo Mean and Geo Mean CV%.

Reporting rules for the PK (with the exception of C_{max}) and summary statistics will be as follows:

- Individual values with the number of decimals/significant digits that will allow at least 3 significant figures to be presented for the minimum value of the parameter, except for t_{max} which are parameters of time to be reported with 2 decimals.
- N: integer
- Mean: 1 more decimal/significant digit than the individual value
- Geo Mean: 1 more decimal/significant digit than the individual value
- SD: 1 more decimal/significant digit than the mean
- CV% of Geo Mean CV%: always 1 decimal
- Median, Min, Max: same number of decimals/significant digits as the individual value

Individual and summary statistics for the PK parameter C_{max} will follow the reporting rules described for concentrations of abaloparatide-sMTS (Section 9.2.1).

9.2.3 Statistical Analysis

Comparisons between the abaloparatide PK parameter values on Day 15 and on Day 29 vs Day 1 will be conducted. Variable identifying the day (e.g., PKDAY or VISIT) will be used as fixed effect.

The log transformed AUC0-t, AUC0-inf, and Cmax will be compared among the visits following the methodology of the longitudinal data analysis using a repeated measures model. SAS® Proc MIXED will be used to account for the possibility of having the unbalanced data. Model will have no random effects, however, since the repeated observations for the same subject made on several days will be used in the model, several forms of variance covariance matrices will be explored, e.g., compound symmetry (CS), the first- or nth-order autoregressive covariance matrices, [AR(1) and TOEP respectively], and unstructured (UN) form. The one that produces the minimal corrected Akaike information criterion (AICC) will be used in the final model. Point estimates and 90% CIs for treatment differences on the log scale, obtained from the model, will be exponentiated to obtain estimates on original scale.

9.3 Data Handling

9.3.1 Handling of Missing Plasma Concentrations

For the PK parameter calculations, missing data may be imputed for:

- Missing pre-dose values: for single dose PK profile (i.e., Day 1), the pre-dose concentration will be set to 0. For steady state, the pre-dose will correspond to the minimum concentration observed during the dose interval.

No imputation will be performed for missing post-dose plasma concentrations. Unless otherwise noted, data summaries will be performed only on observed data.

9.3.2 Time Deviation

If the actual time of blood collection post-dose deviates by >20% from the nominal time, those sample concentrations will be reported (flagged with code "/t") and included in the PK analysis. They will be excluded from the summary statistics in concentration tables and mean figures.

9.3.3 Incomplete Dosing Information

Missing dose dates and/or times may be imputed using nominal dosing times. The imputation strategy will be discussed with Radius. All pharmacokinetic samples associated to a missing dosing date and/or time that cannot be imputed will be excluded from the analysis.

Subjects with a documented patch adherence issue will be reviewed by CSC and Radius for inclusion/exclusion from the descriptive statistics on a case-by-case basis.

In the case where subjects were dosed with abaloparatide-sMTS but discontinued from the study (early termination), the concentration data will be reported in the concentration tables and included in all summary statistics and PK analysis if sufficient concentration data are available to usefully contribute to the PK analysis.

9.3.4 Missing Sampling Dates and/or Times

Missing sample dates and/or times may be imputed using nominal collection times. The imputation strategy will be discussed with Radius.

9.3.5 Unexpected Data

After database lock, a visual inspection of concentration-time profiles will be performed to determine dataset integrity and potential outliers. Descriptive statistics of PK parameters may be calculated with and without subjects with potential outlier data. Subjects with potential outlier data will be reviewed by CSC and Radius for inclusion/exclusion from the descriptive statistics on a case-by-case basis.

Single-dose PK profiles (i.e., Day 1) with non-zero pre-dose concentration values will be included in the computation of PK parameters and descriptive statistics on PK parameters and concentrations if the value is not greater than 5% of C_{max}. PK profiles with non-zero pre-dose concentration values greater than 5% of C_{max} will be identified in the PK report and will be reviewed by CSC and Radius for inclusion/exclusion from the PK calculations and descriptive statistics on concentrations and PK parameters.

Multiple observations at the same actual time point will be averaged for the calculation of PK parameters.

Any plasma concentrations that cannot be uniquely and unequivocally attributed to a particular subject, dose, or day and/or time point based on case report form (CRF) records or other observed

data records in the study will be treated as incomplete data. Such data will be compiled, commented, and listed separately in the appendix of the report. Incomplete and/or non-compliant data, if any, will be excluded from analysis datasets; no analyses, summaries or graphs will be produced using these data.

9.4 Software

PK parameters of plasma abaloparatide-sMTS will be calculated using a validated version of Phoenix™ WinNonlin® 7.0 or later. Summary tables and figures of abaloparatide-sMTS in plasma will be generated using a validated version of Phoenix™ WinNonlin® 7.0 or later or R Version 3.3.3 or later.

Statistical analysis for the comparisons between the abaloparatide PK parameter values will be performed using SAS® version 9.3 or later.

9.5 Quality Control and Quality Analysis

Data sets, PK analyses, statistical analyses, tables, figures and listings and the report will be 100% quality-controlled (QC'd) by two scientists at CSC (i.e., by the originator of the work and by a reviewer) as per CSC SOP-104 entitled, "Managing Data in CSC" and CSC SOP-114 entitled, "Analysis Workflow in CSC".

The QC of datasets will involve dataset reconstruction using an appropriate software. This may include the verification of BLQ rules application, management of missing sampling times or concentration data, calculation of actual sampling time points and time deviations, and treatment, cohort and/or dose attribution. Assignments of concentrations to the appropriate dose administration periods (e.g., pre-doses or following dose escalations/de-escalations) will also be reviewed. Datasets and assumptions from the reviewer and authenticator will be compared. The QC of the NCA analysis will include but is not limited to the following items: model settings (use of appropriate post-dose time, PK parameters, units, doses, area under the curve calculation method, etc.), selected time points used for the assessments of λ_z, subject exclusions due to deviation, and the management of missing PK parameters. The QC of the raw outputs (i.e., tables, figures, and listings) will include but is not limited to the following items: the precision of individual values and summary statistics, the comparison of 5 to 10% of values against the raw data, the use of appropriate and consistent abbreviations, axis labels, and footnotes, and the presentation of data in coherence with study design and PAP.

All data sets, PK parameters and the PK report will be audited by CSC Quality Assurance (QA) for compliance with this Pharmacometric Analysis Plan, as well as internal CSC SOPs. A QA release statement will be provided with the report.

10 ARCHIVING

The project documentation (documents, records, and data) will be retained in hardcopy for a period of three years following project completion at CSC (Montreal, Quebec, Canada). During these retention periods, electronic versions of project documentation will be retained on CSC's servers, with access limited to personnel assigned to the project.

11 REFERENCES

1. Gabrielsson, J., Weiner, D. (2016). Pharmacokinetic & Pharmacodynamic Data Analysis: Concepts and Applications (5th Edition). Swedish Pharmaceutical Society, Stockholm, Sweden.

12 LISTINGS, TABLES, AND FIGURES

The following list of tables and figures, and their associated shells, are provided in order to provide a framework for the display of data from this study. The list of tables and figures and their shells may change based on the data collected following completion of the conduct of study.

LIST OF PLANNED IN-TEXT TABLES

Geometric Mean (CV%) Plasma Pharmacokinetic Parameters of Abaloparatide-sMTS Following Single Application of 300 µg Abaloparatide-sMTS –Day 1

Geometric Mean (CV%) Plasma Pharmacokinetic Parameters of Abaloparatide-sMTS Following Multiple Daily Applications of 300 µg Abaloparatide-sMTS - Day 15

Geometric Mean (CV%) Plasma Pharmacokinetic Parameters of Abaloparatide-sMTS Following Multiple Daily Applications of 300 µg Abaloparatide-sMTS - Day 29

Geometric LS Means Ratios and 90% Confidence Intervals of Abaloparatide Following Multiple Daily Applications Versus Single Application of 300 µg Abaloparatide-sMTS – Day 15

Geometric LS Means Ratios and 90% Confidence Intervals of Abaloparatide Following Multiple Daily Applications Versus Single Application of 300 µg Abaloparatide-sMTS – Day 29

LIST OF PLANNED IN-TEXT FIGURES

Mean (+SD) Plasma Concentrations of Abaloparatide-sMTS vs. Time Following Single or Multiple Daily Applications of 300 µg Abaloparatide-sMTS (Linear and Semi-Log Scales)

LIST OF PLANNED PHARMACOKINETIC TABLES AND FIGURES

8. TABLES AND FIGURES

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Table 8.1.1.2 Plasma Concentrations of Abaloparatide-sMTS Following Multiple Daily Applications of 300 µg Abaloparatide-sMTS – Day 15

Table 8.1.1.3 Plasma Concentrations of Abaloparatide-sMTS Following Multiple Daily Applications of 300 µg Abaloparatide-sMTS – Day 29

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Table 8.1.3.2 Terminal Phase Characterization of Abaloparatide-sMTS Following Multiple Daily Applications of 300 µg Abaloparatide-sMTS – Day 15

Table 8.1.3.3 Terminal Phase Characterization of Abaloparatide-sMTS Following Multiple Daily Applications of 300 µg Abaloparatide-sMTS – Day 29

8.2. FIGURES

8.2.1. Mean Plasma Abaloparatide-sMTS Concentration-Time Profiles

Figure 8.2.1.1 Mean (+SD) Plasma Concentrations of Abaloparatide-sMTS vs. Time Following Single or Multiple Daily Applications of 300 µg Abaloparatide-sMTS (Linear and Semi-Log Scales)

8.2.2. Individual Concentration-Time Profiles (Spaghetti Plots)

Figure 8.2.2.1 Spaghetti Plots of Individual Plasma Concentrations of Abaloparatide-sMTS vs. Time Following Single Applications of 300 µg Abaloparatide-sMTS – Day 1 (Linear and Semi-Log Scales)

Figure 8.2.2.1 Spaghetti Plots of Individual Plasma Concentrations of Abaloparatide-sMTS vs. Time Following Multiple Daily Applications of 300 µg Abaloparatide-sMTS – Day 15 (Linear and Semi-Log Scales)

Figure 8.2.2.3 Spaghetti Plots of Individual Plasma Concentrations of Abaloparatide-sMTS vs. Time Following Multiple Daily Applications of 300 µg Abaloparatide-sMTS – Day 29 (Linear and Semi-Log Scales)

8.2.3. Individual Concentration-Time Profiles (One Plot Per Subject)

Figure 8.2.3.1 Individual Plasma Concentrations of Abaloparatide-sMTS vs. Time Following Application of 300 µg Abaloparatide-sMTS (Linear and Semi-Log Scales)

APPENDIX

Appendix 1 - List of Subjects Excluded From the Pharmacokinetic Analyses

13 TABLE AND FIGURE SHELLS

In-Text PK Tables

Plasma PK Parameters	Day 1 N=X	Day 15 N=X	Day 29 N=X
$AUC_{0\text{-last}}$ (h*xg/mL)	9999 (99.9); N	9999 (99.9); N	9999 (99.9); N
AUC_{inf} (h*xg/mL)	9999 (99.9); N	9999 (99.9); N	9999 (99.9); N
C_{max} (xg/mL)	9999 (99.9); N	9999 (99.9); N	9999 (99.9); N
t_{max}[a] (h)	9.99 (9.99– 9.99); N	9.99 (9.99– 9.99); N	9.99 (9.99– 9.99); N
$t_{1/2}$ (h)	99.99 (99.9); N	99.99 (99.9); N	99.99 (99.9); N

[a]Median (Min, Max)

<The concentration-time profile did not exhibit a terminal log-linear phase, therefore, the PK parameters V_z/F and $t_{1/2}$ were not calculated for some subjects.> NC= Not calculated

Source: Table X.X.X.X to Table X.X.X.X

Individual and Summary Concentration-Time Tables

		Nominal Time (units)									
		0.00	XX	XX	XX	XX	XX	XX	XX	XX	XX
Day	**Subject**	**<Matrix> <Analyte> Concentrations (Units)**									
X	X	BLQ	0.00	NS	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	X	BLQ	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	X	BLQ	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	X	BLQ	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	N	0	0	0	0	0	0	0	0	0	0
	Mean	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	SD	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Min	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Max	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
	CV%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Geometric Mean	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	CV% Geometric Mean	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

BLQ = Below limit of quantification (x.xx pg/mL), were set to zero.

</t = Blood draw time deviation >20% of nominal time; excluded from summary statistics>

NS = No sample
NC= Not Calculated

Note: No cell will be left as blank.

Missing concentration values will be presented at "NS'' for no sample and missing summary statistics will be presented as "NC" for not calculated

Font size will be no smaller than 9.

Note: Similar tables will be presented for each day.

Individual and Summary Plasma PK Tables

Day	Subject	AUC_{0-t} (units)	AUC_{0-inf} (units)	C_{max} (units)	t_{max} (units)	$t_{1/2}$ (units)
X	X	0000	0000	0000	000	0.00
	X	0000	0000	NR	00.0	NR
	X	0000	0000	0000*	000	0.00*
	X	0000	0000	0000	00.0	00.0
	X	0000	0000	NR	000	NR
	X	0000	0000	0000	000	000
	N	0	0	0	0	0
	Mean	0.000	0.000	0.000	0.000	0.000
	SD	0.0000	0.0000	0.0000	0.0000	0.0000
	Min	0.00	0.00	0.00	0.00	0.00
	Median	0.00	0.00	0.00	0.00	0.00
	Max	NC	NC	NC	NC	NC
	CV%	0.0	0.0	0.0	0.0	0.0
	Geometric Mean	0.000	0.000	0.000	0.000	0.000
	CV% Geometric Mean	0.0	0.0	0.0	0.0	0.0

NC = Not Calculated
<* = $\%AUC_{extrap}$ is greater than 20%; excluded from the summary statistics>

Note: No cell will be left as blank.

Missing PK parameter values will be presented as “NR” for “not reported” and missing summary statistics will be presented as “NC” for “not calculated” or “NA” for “not applicable”.

Font size will be no smaller than 9.

Note: Similar tables will be presented for each day.

Individual Terminal Phase Characterization Tables

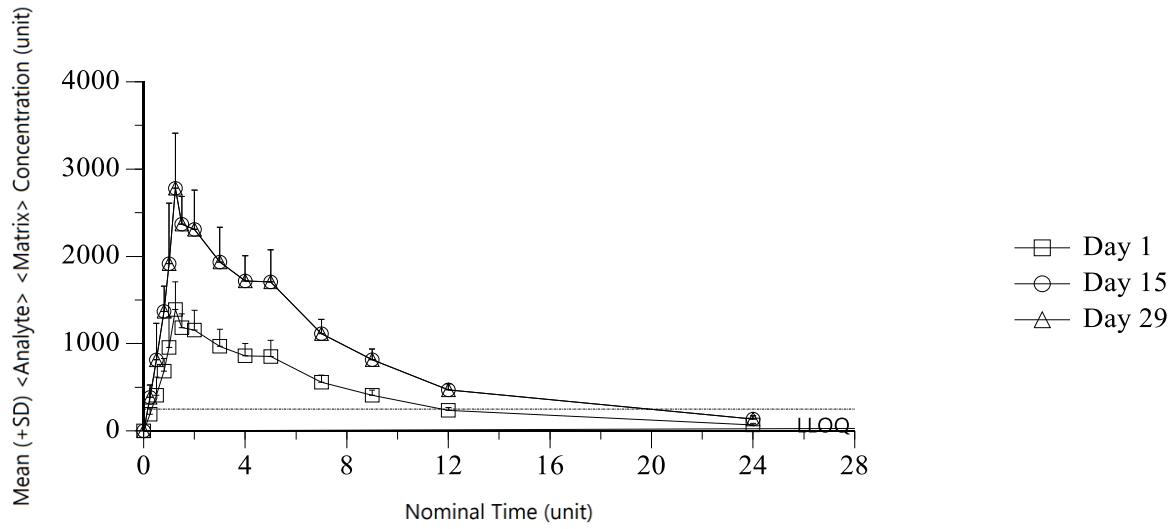
Day	Subject	R^2Adj	Number of Points	λ_z (1/h)	$\lambda_{z\ Lower}$ (h)	$\lambda_{z\ Upper}$ (h)	$\%AUC_{extrap}$ (%)	t_{last} (h)
X	X	0.000	0	0.0000	0.00	0.00	0.00	0.00
	X	0.000	0	0.0000	0.00	0.00	0.00	0.00
	X	0.000	0	0.0000	0.00	0.00	0.00	0.00
	X	0.000	0	0.0000	0.00	0.00	0.00	0.00
	X	0.000	0	0.0000	0.00	0.00	0.00	0.00
	X	0.000	0	0.0000	0.00	0.00	0.00	0.00

Note: No cell will be left as blank.
Missing parameter value will be presented as "NR" for not reported.
Font size will be no smaller than 9.

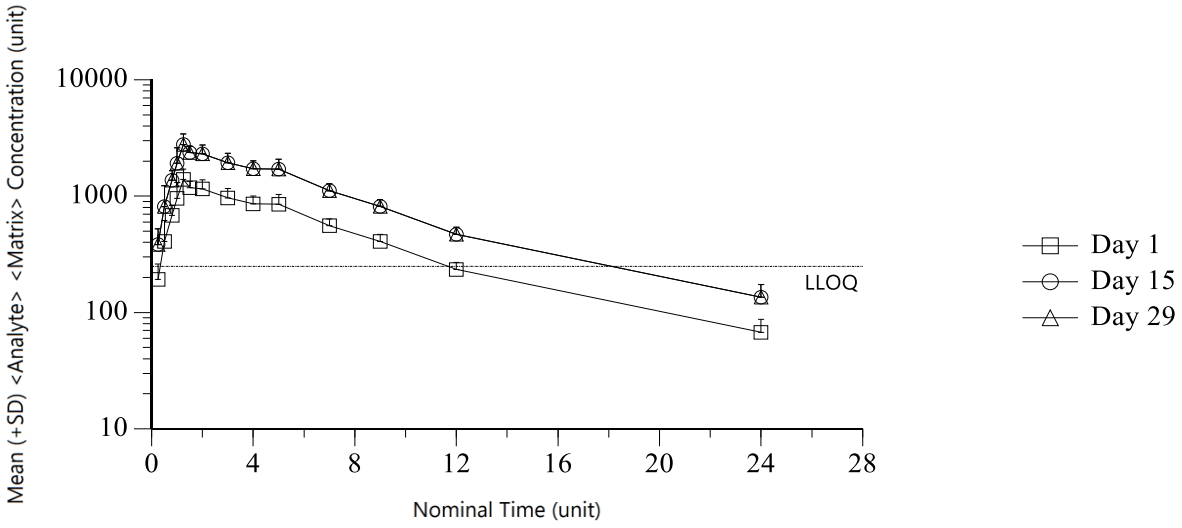
Note: Similar tables will be presented for each day.

Mean Concentration-Time Profiles

Linear Scale



Semi-Log Scale

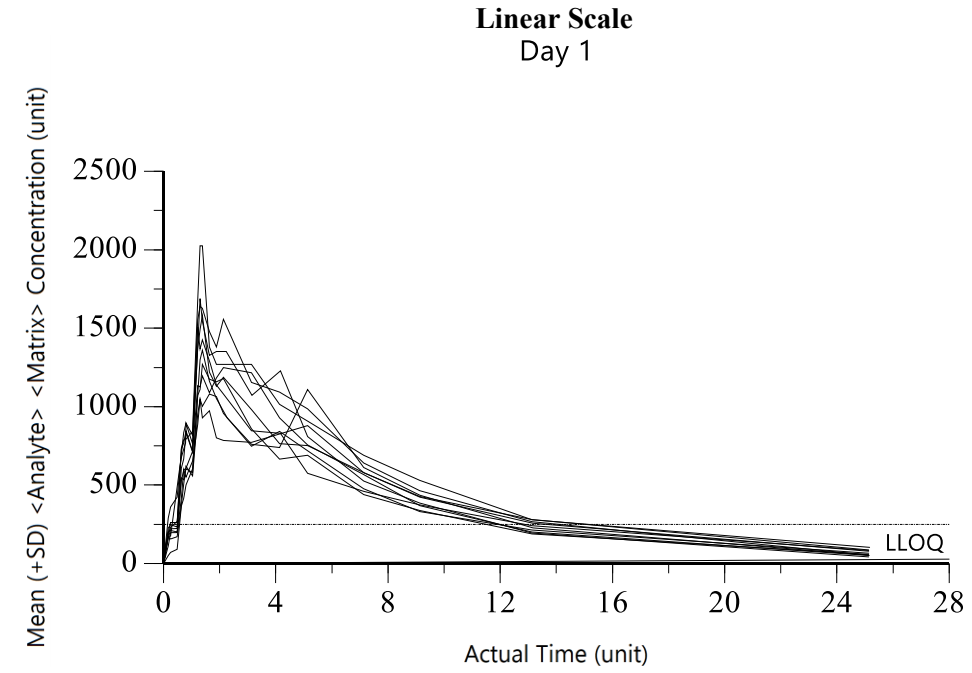


LLOQ = Lower limit of quantification

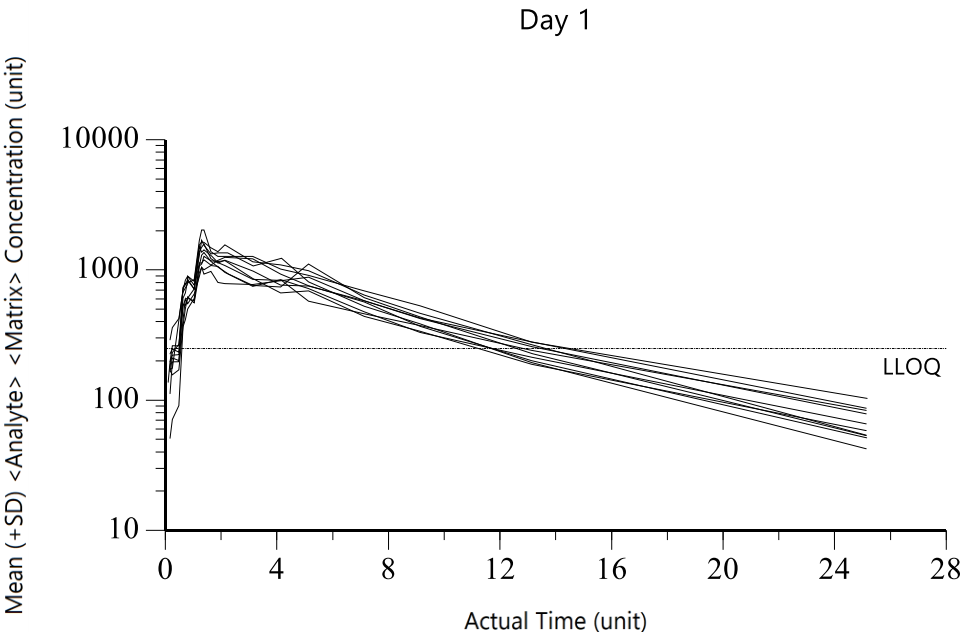
Note: Figures do not represent the actual data of the study. Similar figures will be provided for the individual subject profiles.

Spaghetti Plots

Linear Scale



Semi-Log Scale



LLOQ = Lower limit of quantification

Note: Figures do not represent the actual data of the study. Similar figures will be provided for day 15 and Day 29.

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