STATISTICAL ANALYSIS PLAN

ALK22/ENZ215-DEN1

A randomized, double-blind, three-arm, parallel-group, single-dose study to compare the pharmacokinetics, pharmacodynamics, safety, tolerability, and immunogenicity of Denosumab (ENZ215, EU-sourced Prolia®, and US-sourced Prolia®) in healthy adult male volunteers

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VERSION NUMBER AND DATE: V1.0, 21JUN2024

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 21JUN2024) for Protocol ALK22/ENZ215-DEN1.

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OUTPUT TEMPLATES SIGNATURE PAGE

Output Templates V1.0 (Dated 21JUN2024) for Protocol ALK22/ENZ215-DEN1.

	Name	Signature	Date (DDMmmYYYY)
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	Name	Signature	Date (DDMmmYYYY)
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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	21JUN2024	Ashutosh Ranjan, Piyushkumar Jogani	Not Applicable – First Version

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LIST OF ABBREVIATIONS

ABBREVIATION	TERM
ADAs	Antidrug antibodies
AE	Adverse Event
ANCOVA	Analysis of covariance
$AUC_{0\text{-inf}}$	Area under the drug concentration-time curve from time 0 to infinity
$AUC_{0\text{-t}}$	Area under the drug concentration-time curve from day 0 to day 270
$AUC_{0\text{ - Day 28}}$	Partial area under the drug concentration-time curve from time 0 (pre- dose) to day 28
AUEC	Area under the effect curve from time 0 to day 270
BMI	Body mass index
C_{max}	Maximum observed drug concentration
CI	Confidence Interval
CL/F	Apparent systemic clearance
COVID-19	Coronavirus disease 2019
CTX-1	C-terminal telopeptide type-1
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
EOS	End of Study

EU	European Union
mL	Milliliter
NAB	Neutralizing antibodies
PD	Pharmacodynamic
PK	Pharmacokinetic
SAE	Serious Adverse Event
SARS-CoV- 2	Severe acute respiratory syndrome coronavirus-2
SAP	Statistical Analysis Plan
SC	Subcutaneous
T_{max}	Time to reach C_{max}
$T_{1/2}$	Terminal elimination half-life
ULN	Upper Limit of Normal

1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of safety, pharmacokinetic (PK), pharmacodynamic (PD), and immunogenicity data for Protocol ALK22/ENZ215-DEN1. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This SAP is based on protocol version 4.0, dated 03OCT2022.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to demonstrate bioequivalence between ENZ215 and EU- and US-sourced Prolia® using PK parameters.

2.2. Secondary Objectives

The secondary objectives are:
To compare the serum PK profile of ENZ215 and EU- and US-sourced Prolia®

- To compare the serum CTX-1 profile of ENZ215 and EU- and US-sourced Prolia®
- To compare the immunogenicity profile of ENZ215 and EU- and US-sourced Prolia®
- To compare the safety and tolerability profile of ENZ215 and EU- and US-sourced Prolia®

3. STUDY ENDPOINTS

3.1. Primary Endpoints

The primary endpoints are maximum observed drug concentration (C_{max}), area under the drug concentration-time curve from day 0 to day 270 (AUC_{0-t}) and area under the drug concentration-time curve from time 0 to infinity (AUC_{0-inf}) of ENZ215 and EU- and US-sourced Prolia®.

3.2. Secondary Endpoints

3.2.1. Pharmacokinetics

The secondary PK endpoints are:

- Partial area under the drug concentration-time curve from time 0 (pre-dose) to day 28
- Time to reach C_{max} (t_{max})
- Terminal elimination half-life ($t_{1/2}$)
- Apparent systemic clearance (CL/F)

3.2.2. Pharmacodynamics

The secondary PD endpoint is area under the effect curve (AUEC) from time 0 to Day 270 for serum CTX-1 percent inhibition:

3.2.3. Safety

The secondary safety endpoints are:

- Number of subjects who developed denosumab neutralizing antibodies and antidrug antibodies (Day 1, 28, 90, 180, and 270)
- Incidence of adverse events
- Clinically significant changes in physical examination findings, safety laboratory analyses (serum chemistry, hematology, and urinalysis), vital signs, and 12-lead electrocardiogram (ECG)

4. STUDY DESIGN

4.1. General Description

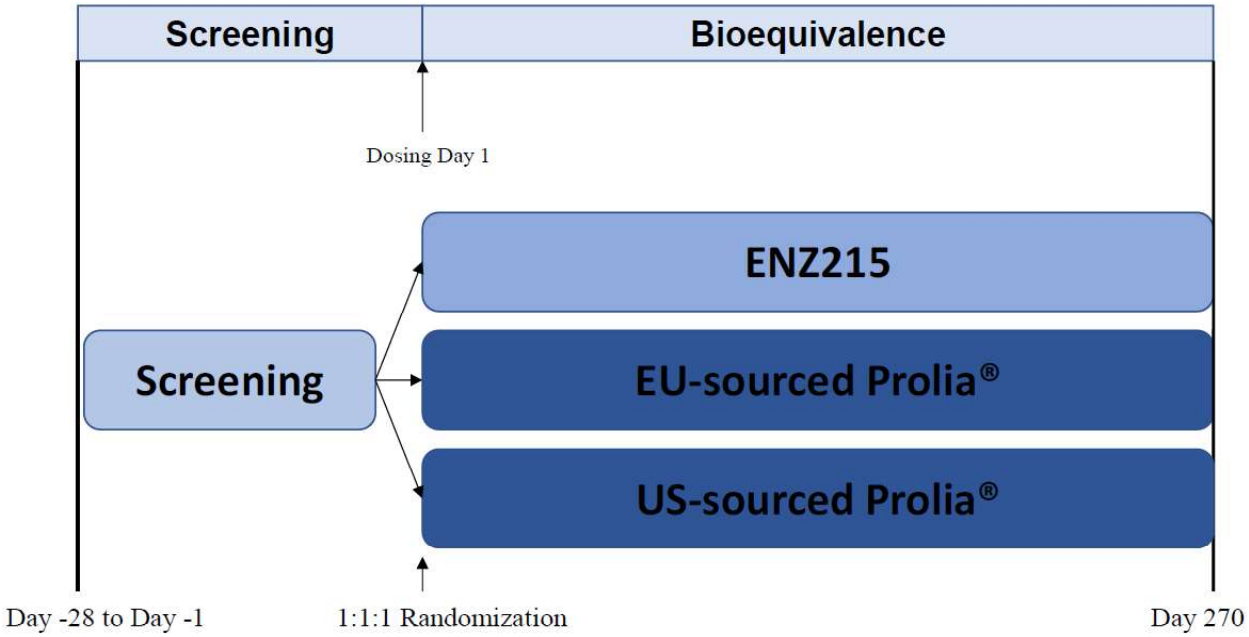
This is a randomized, double-blind, three-arm, parallel-group, single-dose study to demonstrate bioequivalence of ENZ215 and EU- and US-sourced Prolia after a single 60-mg dose administered subcutaneously in healthy adult male volunteers.

Subjects will be screened for enrolment in the study from day -28 to day -1 before randomization. Approximately 207 subjects will be enrolled into 3 groups (69 in each group) in parallel. The subjects may be enrolled in multiple groups at the site. All the eligible subjects will be randomized (1:1:1) to receive a single SC 60-mg dose of either ENZ215 or EU- or US-sourced Prolia on Day 0/1.

Eligible subjects will be admitted/check-in to the phase 1 study site at least 10 hours prior to dosing on day 1 and will be discharged/check out from phase 1 study site on day 2 after PK sample collection (in-subject period).

All screening and on-study blood samples will be processed and sent to local or central laboratory as applicable as defined in the lab manual. Further details on study design are provided in Section 8.1 of study protocol.

Table 1 Study Flow Chart



End of Study (EoS) assessment will be performed on Day 270 (week 39) or at the time of early discontinuation/withdrawal of the subject.

4.2. Schedule of Events

Schedule of events can be found in Section 5.2 of the protocol.

4.3. Changes to Analysis from Protocol

Not applicable.

5. PLANNED ANALYSES

Final analysis following database lock will be performed for this study.

5.1. Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics and Premier Research Group (India) Private Limited following Sponsor Authorization of this Statistical Analysis Plan, identification of major protocol deviations requiring analysis exclusions, Database Lock, determination of analysis sets and Unblinding of Treatment.

6. ANALYSIS SETS

Agreement and authorization of subjects included/excluded from each analysis set will be conducted prior to the unblinding of the study.

6.1. Process for Analysis Set Assignment

Agreement and authorization regarding participants included/excluded from the PK/PD analysis population will be achieved prior to the final database hard lock, once the Premier Research team creates the list of subjects that need to be excluded from the PK/PD population. Before the database lock, the sponsor will review the list of all participants to be excluded from the pertinent analysis populations, along with the reasons for their exclusion from the analysis populations and provide approval/confirmation.

6.2. All Subjects Randomized Set [RAN]

The all subjects randomized (RAN) set will contain all subjects who were randomized to study treatment.

6.3. Safety Analysis Set [SAF]

The safety analysis set (SAF) will contain all subjects who received the single dose of the study drug and subjects will be classified according to treatment received.

6.4. Pharmacokinetic Analysis Set [PKAS]

All subjects who comply sufficiently with the protocol who received the single dose of the study drug and had one pre-dose and at least one post-dose measurement of any of the PK assessment not impacted by any protocol deviations.

6.5. Pharmacodynamic Analysis Set [PDAS]

All subjects who comply sufficiently with the protocol, who received the single dose of the study drug and had one pre-dose and at least one post-dose measurement of any of the PD assessment.

7. GENERAL CONSIDERATIONS

Derivation of the PK and PD parameters for Denosumab in serum will be the responsibility of the clinical pharmacokineticist at Premier Research Group (India) Private Limited. The PK, PD and Immunogenicity summaries (tables and figures) and data listings as well as the datasets including ADaM for PK, PD and Immunogenicity will be the responsibility of the study biostatistician at Premier Research Group (India) Private Limited, whereas the SDTM dataset for PC/PP and IS will be developed by IQVIA. The safety summaries (tables) and data listings will be the responsibility of the study biostatistician at IQVIA.

7.1. Summary Statistics

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will

be summarized using descriptive statistics, including N, n, mean, standard deviation (SD), coefficient of variation (CV%), median, minimum, and maximum values. Coefficient of variation will not be presented for change from baseline results.

Pharmacokinetic concentrations and parameters will be summarized using N, n, mean, SD, coefficient of variation (CV%), median, minimum and maximum. Statistics for PK parameters [except for time to reach C_{max} (t_{max})] will additionally include geometric mean (GM) and geometric CV% (GCV%). The t_{max} will be summarized with N, n, median, minimum, and maximum only.

Pharmacodynamic serum CTX-1 estimation and parameters will be summarized using N, n, mean, SD, coefficient of variation (CV%), median, minimum and maximum. Statistics for PD parameters will additionally include geometric mean (GM) and geometric CV% (GCV%).

Further details of summarization of PK and PD variables are discussed in Section 16 and 17.

7.2. Treatment Summarization

In general, data will be presented by treatment. Data for all study subjects combined will also be presented when appropriate.

7.3. Precision

Safety variables (i.e., clinical laboratory values, vital signs, and ECG intervals), including derivations thereof, will be reported to the same precision as the source data.

All PK concentrations and pharmacodynamic results will be reported and analyzed to 3 significant digits. Derived PK and PD parameters will be rounded for reporting purposes in by-subject listings. The un-rounded derived PK and PD data will be considered the source data for the calculation of descriptive statistics and the statistical analysis. For most derived PK (i.e. $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}Day\ 28}$, $T_{1/2}$, CL/F) and PD parameters (i.e. AUEC), 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters directly derived from source data (i.e., C_{max} will be reported and analyzed with the same precision as the source data.

- Parameters derived from actual elapsed sample collection times (eg, t_{max}) will be reported with the same precision as the actual elapsed sampling time value of the source data.

For the reporting of descriptive statistics, the mean, SD, standard error and confidence intervals (CIs) will be presented to one digit more precision than the source data. The minimum, median, and maximum will be presented to the same precision as the source data. Coefficient of variation and GeoCV% will always be reported to 1 decimal place. Ratios of means for PK and PD parameters and their associated CIs will be presented with two decimal places (as a percentage) to meet regulatory requirements. A minimum of n=3 is required for all descriptive statistics to be generated. If n is less than 3, only N, n, minimum and/or maximum will be reported, as appropriate. P-values, if any, shall be reported to four decimal places or as <0.0001.

7.4. Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.
Reference start date is defined as the day of the first study medication administration (Day 1) and Study Day will be determined as:

- If the date of the event is on or after the reference date, then: Study Day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date, then: Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

The PK sample window rule is as follows:

Nominal study Time point	Window Period	Lower	Upper	Target Time (h)
0 hour (pre-dose)	NA	NA	NA	NA
Day 1 (1 hours)	± 10 minutes	50 minutes	70 minutes	1
Day 1 (4 hours)	± 10 minutes	230 minutes	250 minutes	4
Day 1 (8 hours)	± 10 minutes	470 minutes	490 minutes	8
Day 1 (12 hours)	± 10 minutes	710 minutes	730 minutes	12

Nominal study Time point	Window Period	Lower	Upper	Target Time (h)
Day 2 (24 hours)	± 10 minutes	1450 minutes	1430 minutes	24
Day 3 (48 hours)	± 2 hours	46 hours	48 hours	48
Day 4 (72 hours)	± 2 hours	70 hours	74 hours	72
Day 5 (96 hours)	± 2 hours	94 hours	98 hours	96
Day 6 (120 hours)	± 2 hours	118 hours	122 hours	120
Day 8 (168 hours)	± 2 hours	166 hours	170 hours	168
Day 10 (216 hours)	± 2 hours	214 hours	218 hours	216
Day 12 (264 hours)	± 2 hours	262 hours	266 hours	264
Day 16 (360 hours)	± 2 hours	358 hours	362 hours	360
Day 21 (480 hours)	± 2 hours	478 hours	482 hours	480
Day 28 (648 hours) (week 4)	±1 day	27 days	29 days	648
Day 42 (984 hours) (week 6)	±3 days	39 days	45 days	984
Day 63 (1488 hours) (week 9)	±3 days	60 days	66 days	1488
Day 90 (2136 hours) (week 13)	±3 days	87 days	93 days	2136
Day 119 (2832 hours) (week 17)	±3 days	116 days	122 days	2832
Day 147 (3504 hours) (week 21)	±3 days	144 days	150 days	3504
Day 180 (4296 hours) (week 26)	±3 days	177 days	183 days	4296
Day 224 (5352 hours) (week 32)	±5 days	219 days	229 days	5332
Day 270 (6456 hours) (week 39) (EOS)	±5 days	265 days	275 days	6456

If any sample will be collected out of window period it will be considered as deviation and actual sample collection time will be used in the PK analysis.

The PD sample window rule is as follows:

Nominal study Time point	Window Period	Lower	Upper	Target Time (h)
0 hour (pre-dose)	NA	NA	NA	NA
Day 2 (24 hours)	± 10 minutes	1450 minutes	1430 minutes	24
Day 3 (48 hours)	± 2 hours	46 hours	48 hours	48
Day 4 (72 hours)	± 2 hours	70 hours	74 hours	72
Day 5 (96 hours)	± 2 hours	94 hours	98 hours	96
Day 6 (120 hours)	± 2 hours	118 hours	122 hours	120
Day 8 (168 hours)	± 2 hours	166 hours	170 hours	168
Day 10 (216 hours)	± 2 hours	214 hours	218 hours	216
Day 12 (264 hours)	± 2 hours	262 hours	266 hours	264
Day 16 (360 hours)	± 2 hours	358 hours	362 hours	360
Day 21 (480 hours)	± 2 hours	478 hours	482 hours	480

Nominal study Time point	Window Period	Lower	Upper	Target Time (h)
Day 28 (648 hours) (week 4)	±1 days	27 days	29 days	648
Day 63 (1488 hours) (week 9)	±3 days	60 days	66 days	1488
Day 119 (2832 hours) (week 17)	±3 days	116 days	122 days	2832
Day 180 (4296 hours) (week 26)	±3 days	177 days	183 days	4296
Day 270 (6456 hours) (week 39) (EOS)	±5 days	265 days	275 days	6456

If any sample will be collected out of window period it will be considered as deviation and actual sample collection time will be used in the PD analysis.

7.5. Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments) and will correspond to Screening value for ECG and safety laboratory assessments, and to Day 1 predose for vital signs, PD and albumin-adjusted calcium.

7.6. Retests, Unscheduled Visits and Early Termination Data

Unscheduled measurements will not be included in summary statistics but will contribute to the assessment of clinical outliers where applicable. Early termination results will be recorded as such and included with the end of study summaries.

In the case of a retest of a scheduled assessment, the earliest available measurement for that scheduled time (i.e., the original assessment) will be used for summaries unless flagged as invalid.

Listings will include all scheduled, unscheduled, retest, and early discontinuation data.

7.7. Statistical Tests

The default significant level will be (5%); confidence intervals will be 90% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

7.8. Common Calculations

For quantitative safety measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value
- Change from baseline (CHG) = Post-baseline Value – Baseline Value

For PK computations, the CV%, GM and GCV% will be computed as below:

- CV% = 100 $*\frac{SD}{mean}$
- GM = $e^{Mean_{Log}}$
- GCV% = $(100) * \sqrt{e^{SD_{Log}^2} - 1}$

For the qualitative immunogenicity data will be described as n(%) for respective visit.

7.9. Software Version

All analyses will be conducted using SAS version 9.4 or higher. All derivations, statistical analyses, summaries and listings will be generated using SAS version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina). Non-compartmental pharmacokinetic and pharmacodynamic parameter calculations will be performed using Phoenix® WinNonlin® 8.3 or higher (Certara, Princeton, New Jersey). Graphics may be prepared using the same versions of SAS.

8. STATISTICAL CONSIDERATIONS

8.1. Missing Data

Missing safety data will not be imputed.
Missing PK and PD data will be handled as described in section 16.2 and 17.2 of this analysis plan.
If any sample data will not be transferred from the bio-analytical lab then it will be considered as missing sample for PK and PD analysis.

9. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs. The mock shells provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by Premier Research Group (India) Private Limited and IQVIA Biostatistics.

The PK, PD and immunogenicity mock shells to be provided by Premier Research Group (India) Private Limited.

Some minor modifications may be necessary to the planned design of tables, figures and listings to accommodate data collected during the actual study conduct.

10. DISPOSITION AND WITHDRAWALS

All subjects who are randomized will be accounted for in this study. Subject disposition will be tabulated for each study treatment and for all subjects combined with the number of subjects who are dosed, complete the study, prematurely discontinue, and the reason for early discontinuation. A listing will present dates of completion or early withdrawal and the reason for early discontinuation, if applicable, for each subject.

Listings of study eligibility, treatment randomization, and study treatment administration will be provided.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Individual subject demographics and baseline characteristics (medical/surgical history and results from drug and alcohol screens, cotinine test, and serology screening) will be presented in listings.

Demographic characteristics such as age, sex, race, ethnicity, height, weight, and body mass index (BMI) will be summarized and tabulated by treatment and for all subjects overall. Descriptive statistics will be presented for age, height, weight, and BMI. Frequency counts and percentages will be presented for sex, race, and ethnicity. No statistical testing will be carried out for demographic or other baseline

characteristics.

12. PROTOCOL DEVIATIONS

12.1. Deviations Related to Study Conduct

A deviation from a protocol occurs when Investigator site staff or a study subject does not adhere to the protocol's stipulated requirements, whether inadvertently or planned. Protocol deviations will be listed and will include a classification of minor or major, as determined by clinical staff.

Protocol deviations will be reviewed by the study pharmacokineticist, sponsor medical monitor, IQVIA medical monitor and biostatistician prior to unblinding to identify deviations which have the potential to affect the pharmacokinetic or pharmacodynamic results.

12.2. Deviations Related to PK and PD Analysis

Based on case-by-case review, Changes to the procedures or events, which may impact the quality of the PK and PD data, will be considered important protocol deviations, and will be described within the clinical study report. These changes or events will include any circumstances that will alter the evaluation of the PK and PD. Examples include, but may not be limited to, inaccurate dosing on the day of PK sampling. Other changes to the procedures or events which do not impact the quality of the PK and PD data will not be considered important protocol deviations. A common example of a non-significant protocol deviation is a missed blood sample or deviations from blood collection times.

13. SURGICAL AND MEDICAL HISTORY

Surgical and medical history, coded using Medical Dictionary for Regulatory Activities (MedDRA), the latest version, will be listed for the safety analysis set.

14. MEDICATIONS

Medication usage, coded using the World Health Organization (WHO) Drug Dictionary, the latest version, will be categorized as Prior or Concomitant and listed for the safety population:

- 'Prior' medications are medications which started and stopped prior to the administration of study medication.
- 'Concomitant' medications are medications which were taken during the treatment period, or specifically:
    - started on or after the administration of study medication
    - started prior to the administration of study medication and were continued after the administration of study medication

See Appendix 2 for handling of partial dates for medications. In the case where it is not possible to define a medication as prior or concomitant, the medication will be classified as concomitant.

15. STUDY MEDICATION EXPOSURE

Exposure to study medication will be listed for the safety analysis set.

16. PHARMACOKINETIC ANALYSIS

16.1. Serum Concentration Data

Subjects with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable estimation of PK parameters. A listing of PK blood sample collection times as well as derived sampling time deviations will be provided.

Serum concentrations of denosumab will be summarized using descriptive statistics for each treatment Concentrations that are below the lower limit of quantification (BLQ) will be treated as zero for the computation of descriptive statistics.

Figures of arithmetic mean concentration-time data (±SD, as appropriate) will be presented for each treatment on linear and semi-logarithmic scales. Individual subject concentration-time data will be graphically presented on linear and semi-logarithmic scales for each treatment. Individual concentrations which are BLQ will be displayed as zero in the graphic presentations on linear scale; but will not be plotted on semi-logarithmic scale. Mean values BLQ will be displayed as 0 in the graphic presentations on linear scale but will not be plotted on semi-logarithmic scale.

16.2. Pharmacokinetic Parameters

For PK parameter calculations, predose samples that are BLQ will be assigned a numerical value of zero. Any anomalous (quantifiable) concentration values observed at predose will be identified in the study report and used for the computation of PK parameters. The parameters resulting from such an anomalous concentration value will be determined on a case-by-case basis as to whether they will be included in descriptive analyses as well as in Primary endpoint analysis.

Actual elapsed time from dosing will be used if a sample is collected outside the time-window period otherwise scheduled time will be used for the final serum PK parameter calculations.

Any other BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile. A BLQ value that occurs between quantifiable data points, especially prior to C_{max}, will be assigned a concentration of zero. Following $C_{max,}$ BLQ values embedded between 2 quantifiable data points will be set to missing when calculating PK parameters. If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration), it will be set to zero.

Pharmacokinetic exclusion criteria:

- No value for $AUC_{0\text{-}inf,}$ CL/F or $T_{½}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration-time profile.
- Criteria for exclusion of pharmacokinetic parameters of a particular subject will be as below:
    - Three consecutive missing (M) / Non-Reportable (NR) samples in elimination phase may significantly influence the $AUC_{0\text{-}t,}$ $AUC_{0\text{ -Day }28}$ and elimination phase dependent parameters ($AUC_{0\text{-}inf}$ and $T_{1/2,}$ CL/F). Inclusion of such parameters in the statistical analysis may mislead the final outcome. Hence, $AUC_{0\text{-}t,}$ $AUC_{0\text{-Day }28}$ and elimination phase dependent parameters ($AUC_{0\text{-}inf}$ and $T_{1/2}$) will be excluded.
    - Additionally, any subject with at least 3 consecutive Missing (M) / Non-reportable (NR) samples during the absorption phase such subject will be excluded from the pharmacokinetic and statistical analysis. In such a scenario, only plasma concentration versus time data of that subject will be tabulated and reported in the study report.
    - Subjects without measurable concentrations or who have only very low serum concentrations from the reference medicinal product will be excluded from the pharmacokinetic and statistical analyses for the assessment of bioequivalence. A

subject is considered to have very low serum concentrations if his/her AUC is less than 5% of reference medicinal product geometric mean AUC, calculated without inclusion of data from the outlying subject.

- AUC_{0-t}/AUC_{0-inf} is found to be <0.80 with R^2 adjusted < 0.80 for Kel estimation: In such case elimination phase dependent parameters will not be reliably characterized. Hence, elimination phase dependent parameter (AUC_{0-inf}) will be excluded from statistical analysis.

- Handling of Subjects with Non-Zero Pre-dose Concentrations:

If non-zero pre-dose concentrations occur, the following procedure will be used:
If the pre-dose concentration is less than or equal to 5% of the corresponding C_{max} value for that subject, the subject's data will be included in all PK measurements and calculations without any adjustment.
If the pre-dose value is greater than 5% of the corresponding C_{max} value for that subject, the subject's data for the period in question will be excluded from the statistical evaluations (descriptive statistics for that period and ANOVA).

The following pharmacokinetic parameters for ENZ215 and EU- and US-sourced Prolia® will be computed using non-compartmental model using linear trapezoidal method:
Primary Pharmacokinetic Parameters:

C_{max}	:	Maximum observed drug concentration
AUC_{0-t}	:	Area under the drug concentration-time curve from time day 0 to day 270, as calculated by linear up/log down trapezoidal summation
AUC_{0-inf}	:	Area under the drug concentration-time curve from time 0 to time infinity.

Secondary Pharmacokinetic Parameters:

$AUC_{0-\text{Day 28}}$	:	Partial area under the drug concentration-time curve from time 0 (Pre-dose) to day 28 as calculated by linear up/log down trapezoidal summation.
T_{max}	:	Time to reach C_{max}. If the maximum value occurs at more than one time point, t_{max} is defined as the first time point with this value.
$T_{1/2}$	:	The terminal elimination half-life as calculated by $0.693/\lambda_{z}$.

CL/F : Apparent systemic clearance will be calculated using the formula: [Dose/$AUC_{0\text{-}inf}$]

Analysis of Primary Pharmacokinetic Endpoints:

To demonstrate bioequivalence between ENZ215 and EU - and US-sourced Prolia® of the ln-transformed pharmacokinetic parameters C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$, Analysis of Variance (ANOVA) will be performed on the natural log (ln)-transformed PK parameters ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}) using Type III sum of squares, with the fixed effect of treatment using General Linear Model (PROC GLM) of SAS software.
Each analysis of variance will include calculation of least square mean (LSM). Two one-sided tests procedure at 5% level of significance will be used to compare the geometric LSM values of PK parameters determined after administration of test (Treatment A) and reference products (Treatment B i.e., US Source Prolia & Treatment C i.e., EU Source Prolia).
Bioequivalence testing hypothesis as follows:

H0: 90% confidence interval (CI): lower limit < 80.00% or upper limit > 125.00% (ie, both treatments are bio-inequivalent).
H1: 90% CI: lower limit ≥ 80.00% and upper limit ≤ 125.00% (i.e., both treatments are bioequivalent).

Point estimates of the ratio of geometric least squares means of ENZ215(test)/EU sourced Prolia (Reference B), ENZ215(test)/ US sourced Prolia (Reference A), EU sourced Prolia /US sourced Prolia treatments will be calculated and reported for ln-transformed PK parameters C_{max} $AUC_{0\text{-}t}$ and $AU_{C0\text{-}\infty}$.
The inter subject variability will be calculated and reported for ln-transformed pharmacokinetic parameters C_{max} $AUC_{0\text{-}t}$ and $AU_{C0\text{-}\infty}$.

The following treatment comparisons will be made to assess the bioequivalence between the test and each of the 2 reference treatments.

ENZ215 versus EU sourced Prolia
ENZ215 versus US sourced Prolia

The 90% CI of the geometric least squares mean ratios (ENZ215(test)/EU sourced Prolia and ENZ215/ US sourced Prolia) for log-transformed primary PK parameters ($AUC_{0\text{-}\infty}$, $AUC_{0\text{-}t}$, and C_{max}) will be determined exponentiation of the CIs obtained for the difference between treatment least-squares means (LSM) resulting from the analyses on the ln-transformed primary PK parameters for ENZ215 versus EU

sourced Prolia and ENZ215 versus EU sourced Prolia.

The respective treatment product (ENZ215) will be concluded bioequivalent to the reference product (EU sourced Prolia and US sourced Prolia), if the 90% CI for geometric LSM ratios of ln-transformed parameters $C_{max,}$ AUC_{0-t} and $AUC_{0-\infty}$ and falls within the acceptance range of 80.00% to 125.00%.

Analysis of Secondary Pharmacokinetic Endpoints:

The time to maximum observed serum concentration (t_{max}), partial Area under curve from time 0 to 28 days ($pAUC_{0-28days}$), apparent terminal half-life ($t_{½}$), terminal rate constant (λ_z), and systemic clearance (CL) as a secondary parameter will be summarized as described below.

The above PK parameters will be summarized by-treatment using n, mean, SD, %CV, minimum, median, maximum, geometric mean, and geometric %CV except that t_{max} will be reported with n, minimum, median, and maximum only.
The ln-transformed pharmacokinetic parameter of partial Area under curve from time 0 to 28 days ($pAUC_{0-28days}$) will be compared between ENZ215 and Prolia using PROC TTEST of SAS software.

The non-parametric analysis (Wilcoxon-rank sum test) will be used for the comparison of t_{max} between ENZ215 and Prolia.
All Pharmacokinetic data analysis, summaries, Figures and listings will be based on the Pharmacokinetic Analysis Set.

17. PHARMACODYNAMIC ANALYSIS

17.1. Pharmacodynamic Concentrations

Subjects with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable estimation of PD parameter. A listing of PD blood sample collection times as well as derived sampling time deviations will be provided.

Serum concentrations of CTX-1 will be summarized using descriptive statistics for each treatment Concentrations that are below the lower limit of quantification (BLQ) will be treated as zero for the

computation of descriptive statistics.

Figures of arithmetic mean concentration-time data (±SD, as appropriate) will be presented for each treatment on linear and semi-logarithmic scales. Individual subject concentration-time data will be graphically presented on linear and semi-logarithmic scales for each treatment.

Individual concentrations which are BLQ will be displayed as zero in the graphic presentations on linear scale; but will not be plotted on semi-logarithmic scale. Mean values BLQ will be displayed as 0 in the graphic presentations on linear scale but will not be plotted on semi-logarithmic scale.

17.2. Pharmacodynamic Parameters

For PD parameter calculations, predose samples that are BLQ will be assigned a numerical value of zero. The BLQ value may be observed during the reduction of the profile then it will be set to zero. Following BLQ values embedded between 2 quantifiable data points will be set to missing when calculating PD parameters.. Actual elapsed time from dosing will be used if a sample is collected outside the time-window period otherwise scheduled time will be used for the final serum PD parameter calculations.

The following pharmacodynamic parameter for ENZ215 and EU- and US-sourced Prolia® will be computed using non-compartmental model using linear trapezoidal method:

Pharmacodynamic exclusion criteria:

- Criteria for exclusion of pharmacodynamics parameter of a particular subject will be as below:
    - Three consecutive missing(m) samples in the late phase may significantly influence AUEC, such subjects will not be considered for the AUEC comparison.
    - Subjects having any major protocol deviations or other clinical observations that can impact the PD.

Pharmacodynamic Parameters:

AUEC : Area under the effect curve (AUEC) from time 0 to day 270 for serum CTX-1 percent inhibition

Pharmacodynamic effect for serum CTX-1will be assessed as % reduction from baseline.

Note: % reduction from baseline serum of CTX-1 will be calculated using following formula:
% reduction from baseline serum CTX-1 =[(CTX-1 (0) – CTX-1 (Ti))/CTX-1 (0)]*100
Where CTX-1 (Ti) is the measured CTX-1 at the time Ti and CTX-1 (0) is the measured CTX-1 prior to administration of Denosumab. Here Ti (i=24, 48, 72, …., 6456 hrs.) denotes the post dose time points at which sample has been taken. If the predose concentration is zero, then the % change cannot be calculated, and it will be considered as missing for the statistical analysis.

Analysis of Secondary Pharmacodynamic Endpoints:
The AUEC will be calculated as the area under the effect curve from baseline until CTX-1 values return to baseline for the first time.

An ANCOVA will be performed on the log-transformed AUEC, including treatment as a fixed effect and baseline CTX-1 value as covariate. The assessment of serum CTX-1 similarity as a secondary endpoint will be based upon the 95% confidence intervals for the ratio of the geometric means (ENZ215 and Prolia) for AUEC of baseline-corrected serum CTX-1 (i.e. % change from baseline), which have to be contained entirely within the pre-specified limits of 0.80-1.25.

All Pharmacodynamic data analysis, summaries, figures and listings will be based on the Pharmacodynamic Analysis Set.

18. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set.
There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

18.1. Adverse Events

Adverse Events (AEs) will be coded using MedDRA, the latest version.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or

after the administration of study medication. Pretreatment AEs are defined as AEs occurring prior to dosing. These events will be presented in the listing only and are not included in the tabular summary of TEAEs.

Multiple occurrences of the same TEAE in one subject during the study will be counted as multiple events in the frequency counts for adverse events. If a subject experiences more than one occurrence of the same TEAE during the trial, the subject will only be counted once using the worst severity.

See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case, i.e. treatment emergent.

18.1.1. All TEAEs

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and broken down further by maximum severity and relationship to study medication.

18.1.1.1. SEVERITY

Severity is classed as mild/ moderate/ severe/ life threatening/ death. TEAEs starting after the first dose of study medication with a missing severity will be classified as severe. If a subject reports a TEAE more than once within that SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

18.1.1.2. RELATIONSHIP TO STUDY MEDICATION

Relationship, as indicated by the Investigator, is classed as “unrelated” and “related”. TEAEs with a missing relationship to study medication will be regarded as “related” to study medication. If a subject reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study medication will be used in the corresponding relationship summaries.

All AE tabulations will be performed by treatment. Incidence of TEAEs will be tabulated by the following:

- An overall summary across all SOC and PT, any TEAE, any related TEAE, severe, serious, leading to study discontinuation, leading to death, and TEAEs by maximum severity
- By SOC and PT

- By SOC and PT for related TEAEs
- By SOC, PT and Severity
- By SOC, PT and Outcome
- By SOC, PT and Seriousness (Serious = Yes or No)
- By SOC, PT and Severity for related TEAEs

18.1.2. TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to permanent discontinuation of study medication will be identified by using the field "Action taken with study treatment = Drug withdrawal" on the AE page of the (e)CRF, and listed.

18.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the (e)CRF and will be listed and summarized

18.1.4. Injection Site Reaction Assessment

Injection site reaction assessment will be listed including intensity grade.

18.2. Deaths

If any subjects die during the study as recorded on the AE page of the eCRF, the information will be presented in a data listing.

18.3. Laboratory Evaluations

Results from the central laboratory will be included in the reporting of this study for Hematology, Serum Chemistry and Urinalysis. A list of laboratory assessments to be included in the outputs is included in the protocol, Section 11.2.

Presentations will use units as per Celerion lab units with the conversion factor provided in Appendix 3. Quantitative laboratory measurements reported as "< X", i.e., below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the

purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements)
- Listing of laboratory results outside the normal range

18.3.1. Laboratory Reference Ranges

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

18.4. ECG Evaluations

The following ECG parameters will be reported for this study: PR, QRS, QTcB, QTcF, RR and heart rate.

- Overall assessment of ECG (Investigator's judgment):
    - Normal
    - Abnormal, Not Clinically Significant (ANCS)
    - Abnormal, Clinically Significant (ACS)

The following summaries will be provided for ECG data:

- Actual and change from baseline by visit (for quantitative measurements)
- Incidence of clinically noteworthy criteria
- Listing of subjects meeting clinically noteworthy criteria

18.4.1. Clinically Noteworthy ECG Criteria

Clinically noteworthy quantitative ECG measurements will be identified in accordance with the following predefined criteria:

- Absolute values for QTcF will be classified as:
  - > 450 msec and <=480 msec
  - > 480 msec and <=500 msec
  - > 500 msec
- Change from Baseline for QTcF will be classified as:
  - Increase from baseline >30 msec and <=60 msec
  - Increase from baseline >60 msec

18.5. Vital Signs

The following Vital Signs measurements will be reported for this study:

- Supine Systolic Blood Pressure (mmHg)
- Supine Diastolic Blood Pressure (mmHg)
- Supine Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Body temperature (^{0} C)

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit

18.6. Physical Examination

Physical examination results will be listed including specification of any abnormalities observed.

18.7. Oral Examination

Oral examination results will be listed including specification of any abnormalities observed.

18.8. COVID-19 Assessment

Results from COVID-19 testing and assessment of COVID-19 signs and symptoms will be listed.

18.9. Immunogenecity Assessment

All immunogenicity data summaries will be based on the safety analysis population. Immunogenicity (ADA) including NAb data will be presented for all subjects' samples collected in data listing.

The frequency and percentage of positive ADA or NAb result will be provided. The proportion of positive ADA or NAb in each treatment group will be compared using chi-square or Fisher's exact tests. The p-value, relative risk and corresponding 95% CI will be presented.

19. DATA NOT SUMMARIZED OR PRESENTED

Comments will not be summarized or presented but will be available in clinical study database.

20. REFERENCES

There are no references.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA Output Conventions

Outputs will be presented according to the IQVIA Global Biostatistics Standard Output Conventions, which is available upon request.

Dates & Times

Depending on data availability, if not otherwise specified, dates will take the format DDMMMYYYY; times will take the format hh:mm; combined dates and time will take the format DMMMYYYY/hh:mm.

Spelling Format

English US.

Presentation of Treatment Groups

For outputs, treatment groups will be represented as follows, as appropriate:
ENZ215, US-Prolia, EU-Prolia, All Subjects (where applicable).

Presentation of Visits

For outputs, visits will be represented as collected on eCRF, as appropriate.

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

- Treatment
- Subject number
- Date and Time (where applicable)
- For listings where non-randomized subjects are included (e.g. screen failures, if applicable), these will appear in a category after the randomized treatment groups labeled 'Not Randomized'

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

Algorithm for Treatment Emergence of Adverse Events:

START DATE/TIME	STOP DATE/TIME	ACTION
Known	Known/Partial/ Missing	If start date/time < study med start date/time, then not TEAE If start date/time >= study med start date/time, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study med start date OR Missing	Known	If stop date/time < study med start date/time, then not TEAE If stop date/time >= study med start date/time, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date/time < study med start date/time, then not TEAE If stop date/time >= study med start date/time, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior / Concomitant Medications:

START DATE/TIME	STOP DATE/TIME	ACTION
Known	Known	If stop date/time < study med start date/time, assign as prior If stop date/time >= study med start date/time, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date/time < study med start date/time, assign as prior If stop date/time >= study med start date/time, assign as concomitant
	Missing	If stop date is missing could never be assumed a prior medication assign as concomitant
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date/time < study med start date/time, assign as prior If stop date/time >= study med start date/time, assign as concomitant
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date/time < study med start date/time, assign as prior If stop date/time >= study med start date/time, assign as concomitant

START DATE/TIME	STOP DATE/TIME	ACTION
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication , assign as concomitant
Missing	Known	If stop date/time < study med start date/time, assign as prior If stop date/time >= study med start date/time, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date/time < study med start date/time, assign as prior If stop date/time >= study med start date/time, assign as concomitant
	Missing	Assign as concomitant

APPENDIX 3. SAFETY LABORATORY CONVERSION FACTOR AND UNITS

	MTZ	COMAC	Celerion	Conversion factor	Conversion units
Lab tests	**Units**	**Units**	**Units**		
Alanine Aminotransferase	U/L	U/L	U/L		
Albumin	g/dL	g/L	g/L	10.0	Conventional unit to SI unit
Alkaline phosphatase	U/L	U/L	U/L		
Aspartate Aminotransferase	U/L	U/L	U/L		
Bilirubin, total	mg/dL	umol/L	umol/L	17.1	Conventional unit to SI unit
Chloride	mmol/L	mmol/L	mmol/L		
Creatinine	mg/dL	umol/L	umol/L	88.4	Conventional unit to SI unit
Magnesium	mg/dL	mmol/L	mmol/L	0.411	Conventional unit to SI unit
Phosphate (Phosphorus)	mg/dL	mmol/L	mmol/L	0.323	Conventional unit to SI unit
Potassium	mmol/L	mmol/L	mmol/L		
Protein, Total	g/dL	g/L	g/L	10.0	Conventional unit to SI unit
Sodium	mmol/L	mmol/L	mmol/L		
Blood Urea Nitrogen	mg/dL	mmol/L	mmol/L	0.357	Conventional unit to SI unit
	mmol/L				
Glucose	mg/dL	mmol/L	mmol/L	0.0555	Conventional unit to SI unit
	mmol/L				
Calcium	mg/dL	mmol/L	mmol/L	0.25	Conventional unit to SI unit
Albumin adjusted calcium	mg/dL	mmol/L	mmol/L	1 mg/dl= 0.2495 mmol/L	Conventional unit to SI unit

	MTZ	COMAC	Celerion	Conversion factor	Conversion units
Lab tests	**Units**	**Units**	**Units**		
Red Blood Cell Count (Total)	10**12/L	T/L	X 10^{12}/L		
Hemoglobin	g/dL	g/L	g/dL	10.0	SI unit to Conventional unit
White Blood Cell Count (Total)	10**9/L	G/L	X 10^{9}/L		
Platelets	10**9/L	G/L	X 10^{9}/L		
Neutrophils, Absolute Count	10**9/L	G/L	X 10^{9}/L		
Lymphocytes, Absolute Count	10**9/L	G/L	X 10^{9}/L		
Monocytes, Absolute Count	10**9/L	G/L	X 10^{9}/L		
Eosinophils, Absolute Count	10**9/L	G/L	X 10^{9}/L		
Basophils, Absolute Count	10**9/L	G/L	X 10^{9}/L		
Neutrophils (Rel, %)	%	%	%		
Lymphocytes (Rel, %)	%	%	%		
Monocytes (Rel, %)	%	%	%		
Eosinophils (Rel, %)	%	%	%		
Basophils (Rel, %)	%	%	%		

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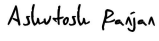
Ashutosh Ranjan ashutosh.ranjan@quintiles.com Statistical Scientist IQVIA Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 55DBAAC8-8C76-431C-8552-29B736B6AF8D Using IP Address: 162.44.245.32 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document I am the author of this document	Sent: 21-Jun-2024 | 21:12 Viewed: 24-Jun-2024 | 14:35 Signed: 24-Jun-2024 | 14:36
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Envelope Sent	Hashed/Encrypted	21-Jun-2024 | 21:12
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Operating Systems:	Windows® 2000, Windows® XP, Windows Vista®; Mac OS® X
Browsers:	• Internet Explorer (Windows Only) 8.0 or above – compatibility mode is supported only for 9.0 and above. • Windows Edge Current Version • Mozilla Firefox Current Version • Safari (Mac OS only) 6.2 or above • Google Chrome Current Version
PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	1024 x 768 Recommended
Enabled Security Settings:	Allow per session cookies
Mobile Signing:	• Apple iOS 7.0 or above • Android 4.0 or above

** These minimum requirements are subject to change. If these requirements change, we will provide you with an e-mail message at the e-mail address we have on file for you at the time the hardware and software requirements are revised.

Pre-release (e.g. beta) versions of operating systems and browsers are not supported.

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