STATISTICAL ANALYSIS PLAN

A Bioequivalence Study of Injections of Mirikizumab Solution Using an Investigational 1-mL Pre-Filled Syringe and an Investigational 1-mL Autoinjector in Healthy Participants

Statistical Analysis Plan Status: Final
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Study Drug: LY3074828

Sponsor Reference: I6T-MC-AMBW
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Clinical Phase I

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2. ABBREVIATIONS

Abbreviations pertain to the Statistical Analysis Plan (SAP) only (not the tables, figures and listings [TFLs]).

%AUC(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
ADA	Antidrug antibody
ADE	Adverse device effect
AE	Adverse event
AI	Autoinjector
AUC	Area under the concentration versus time curve
AUC(0-∞)	Area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
BQL	Below the lower limit of quantification
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{last}	Last quantifiable drug concertation
C_{max}	Maximum observed drug concentration
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
CV%	Percent coefficient of variation
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
ISR	Injection-site reaction
MedDRA	Medical Dictionary for Regulatory Activities
PFS	Pre-filled syringe
PK	Pharmacokinetic
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation

$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TE ADA	Treatment-emergent antidrug antibody
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
UADE	Unanticipated adverse device effect
ULN	Upper limit of normal
VAS	Visual analog scale
V_{ss}/F	Apparent volume of distribution at steady state after extra-vascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 14 August 2020).

This SAP describes the planned analysis of the safety, tolerability, and pharmacokinetic (PK) data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical and PK analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Eli Lilly and Company. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. This SAP must be signed off prior to first participant visit for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon with Eli Lilly and Company and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

4. STUDY OBJECTIVES AND ENDPOINTS

4.1 Primary Objective and Endpoints

The primary objective of this study is to evaluate the PK of mirikizumab after subcutaneous (SC) administration of 200-mg doses of solution formulation using a 2×1-mL pre-filled syringe (PFS) and a 2×1-mL autoinjector (AI) in healthy participants.

The primary endpoints for this study are:

- Maximum observed drug concentration (C_{max})
- Area under the concentration versus time curve from time zero to infinity (AUC [0-∞])
- Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration (AUC[0-t_{last}])

4.2 Secondary Objective and Endpoints

The secondary objective of this study is to describe the safety and tolerability of mirikizumab in healthy participants.

The secondary endpoints of this study are:

- Treatment emergent adverse events
- Serious adverse events (SAEs)

4.3 Exploratory Objectives and Endpoints

The exploratory objectives and endpoints for this study are:

- To evaluate the effect of mirikizumab delivery device on immunogenicity
    - Treatment-emergent antidrug antibody (TE ADA)
- To evaluate the impact of injection-site location on PK
    - C_{max}
    - AUC (0-∞)
    - AUC(0-t_{last})

5. STUDY DESIGN

Study AMBW is a Phase 1, open-label, 2-arm, randomized, parallel-design, single-dose, multi-site study in healthy participants. At screening, participants will be stratified into 1 of 3 weight categories (less than 70 kg, 70 to 80 kg, and more than 80 kg).

Eligible participants will be admitted to the clinical research unit (CRU) on Day -1.

Within the 3 weight categories, participants will be randomized using a computer-generated allocation code:

- 1:1 to delivery device (either PFS [reference] or AI [test])
- within each delivery-device group 1:1:1 to injection site (abdomen, arm, or thigh)

On Day 1, participants will receive a 2×1 mL (total 200 mg mirikizumab) SC dose delivered via the device and in the location assigned by the randomization.

Participants may be allowed to leave the CRU after completing the 4-hour safety assessments on Day 1, or later at the investigator's discretion, and will return for PK and immunogenicity sampling and safety assessments at predefined times up to 12 weeks postdose. Participants will be monitored for safety between outpatient visits by way of telephone assessment.

Safety and tolerability will be assessed through clinical laboratory tests, vital sign measurements, recording of AEs, physical examination, and immunogenicity.

6. TREATMENTS

The following is a list of the study treatment abbreviations that will be used in the TFLs.

Study Treatment Name	Injection Site	Abbreviation	Treatment order in TFL
200 mg Mirikizumab 2 x 1-mL (100 mg/mL) PFS (Reference)	Abdomen	Reference (Abdomen)	1
	Arm	Reference (Arm)	2
	Thigh	Reference (Thigh)	3
200 mg Mirikizumab 2 x 1-mL (100 mg/mL) AI (Test)	Abdomen	Reference (Abdomen)	4
	Arm	Reference (Arm)	5
	Thigh	Reference (Thigh)	6

7. SAMPLE SIZE JUSTIFICATION

Up to approximately 240 participants may be enrolled so that approximately 216 participants (108 in the PFS [reference] group and 108 in the AI [test] group) complete the study.

A sample size of 108 participants per treatment group will provide approximately 90% power that the 90% confidence interval (CI) of the geometric mean ratio of C_{max} and AUC between groups will fall within equivalence range of 0.8 to 1.25. This sample size calculation was based on the assumptions that the PK parameters have log-normal distribution, the percent coefficients of variation (CV%) of C_{max} and AUC are approximately 40% (based on previous trials), the expected ratio of geometric means is 1.07, and the CV% are the same for participants from each treatment group.

Participants who are randomized but not administered treatment, and participants who do not complete PK sampling through Day 85, may be replaced to ensure that approximately 216 participants (108 in each group) complete the study.

8. DEFINITION OF ANALYSIS POPULATIONS

The “Enrolled” population will consist of all participants randomly assigned to the study intervention (mirikizumab).

The “Safety” population will consist of all participants randomly assigned and who received study intervention (mirikizumab). Participants will be analyzed according to the intervention they actually received.

The “Pharmacokinetic” population will consist of all enrolled participants who receive a full dose of study intervention (mirikizumab) and have evaluable PK data.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when participants are assigned to analysis populations.

9. STATISTICAL METHODOLOGY

9.1 General

Data listings will be provided for all data that is databased. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, minimum, maximum and N; for log-normal data (e.g. the PK parameters: AUCs and C_{max}) the geometric mean and geometric CV% will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all participants up to the point of withdrawal, with any participants excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for participants included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Mean change from baseline is the mean of all individual participants' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual participant's baseline value from the value at the timepoint. The individual participant's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

Data analysis will be performed using SAS® Version 9.4 or greater.

9.2 Demographics and Participant Disposition

Participant disposition will be summarized and listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, height and body mass index will be summarized by treatment, and listed. All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

Noncompartmental methods applied with a validated software program (WinNonlin Phoenix v8.1 or later) to the serum concentrations of LY3074828 will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	µg*day/mL	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-∞)	µg*day/mL	area under the concentration versus time curve from time zero to infinity
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
C_{max}	µg/mL	maximum observed drug concentration
t_{max}	day	time of maximum observed drug concentration
$t_{1/2}$	day	half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL/F	L/day	apparent total body clearance of drug calculated after extra-vascular administration
V_Z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration
V_{SS}/F	L	apparent volume of distribution at steady state after extra-vascular administration

Additional PK parameters may be calculated, as appropriate. The software and version used for the final analyses will be specified in the CSR. Any exceptions or special handling of data will be clearly documented within the CSR.

Formatting of tables, figures and abbreviations will follow the Eli Lilly Global PK/PD/TS Tool: NON-COMPARTMENTAL PHARMACOKINETIC STYLE GUIDE. The version of the tool effective at the time of PK analysis will be followed.

General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for non-bolus predose sampling times which will be set to zero.

- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification, with at least one of these concentrations following C_{max}. The AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.

- Half-life ($t_{1/2}$) will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each participant will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in plasma

concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{1/2}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{1/2}$ value excluded from summary statistics will be documented in the footnote of the summary table.

- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.

- The parameters based on observed last quantifiable drug concentration (C_{last}) will be reported.

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK parameters except for special handling of certain concentrations reported below the lower limit of quantification (BQL). Plasma concentrations reported as BQL will be set to a value of zero when all the following conditions are met:

    - The compound is non-endogenous.

    - The samples are from the initial dose period for a participant or from a subsequent dose period following a suitable wash-out period.

    - The time points occur before the first quantifiable concentration.

- All other BQL concentrations that do not meet the above criteria will be set to missing.

- Also, where two or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.

- The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times and arithmetic average concentrations.

- The predose average concentration for single-dose data from non-endogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.

- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ± 10%, will be excluded from the average concentration profiles.

- Concentrations excluded from the mean calculation will be documented in the CSR.

- A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ± 10%. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the CSR.

Treatment of Outliers during PK Analysis

Application of this procedure to all PK analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

Data within an Individual Profile

A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For PK profiles during multiple dosing, the concentration of the predose sample exceeds all measured concentrations for that individual in the subsequent post-dose samples.

- For PK profiles during single dosing of non-endogenous compounds, the concentration in a predose sample is quantifiable.

- For any questionable datum that does not satisfy the above criteria, the profile will be evaluated, and results reported with and without the suspected datum.

Data between Individual Profiles

1. If $n<6$, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.

2. If $n\geq6$, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:

    a. Transform all values in the calculation to the logarithmic domain.

    b. Find the most extreme value from the arithmetic mean of the log transformed values and exclude that value from the dataset.

c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.

d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.

e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and $n \geq 6$ following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only one suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

Reporting of Excluded Values

Individual values excluded as outliers will be documented in the CSR. Approval of the CSR will connote approval of the exclusion.

9.3.2 Pharmacokinetic Statistical Methodology

The C_{max}, AUC (0-∞), and AUC(0-t_{last}), will be log-transformed and analyzed using a linear fixed-effects model. The model will include delivery device, injection location, and weight stratification as fixed effects. The dosing regimen differences between AI and PFS administrations will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% CI.

Example SAS Code:

```
proc mixed data=xxx;
by parameter;
class device location strat_weight;
model log_pk = device location strat_weight / residual;
lsmeans device / alpha=0.1 cl pdiff;
ods output lsmeans=lsmeans diffs=diffs;
run;
```

The t_{max} of mirikizumab between the AI (Test) and PFS (Reference) administrations will be analyzed using a Wilcoxon rank sum test. Estimates of the median difference, 90% CIs, and p-values from the Wilcoxon rank sum test will be calculated.

Additional comparisons will be made between:

- The 2 delivery devices (AI [Test] versus PFS [Reference]) separately at each injection location (injection location will be removed from the model above)

- The 3 injection locations (arm [Test] versus abdomen [Reference] and thigh [Test] versus abdomen [Reference]) separately for each device (device will be removed from the model above)

The 2 delivery devices (AI [Test] versus PFS [Reference]) will be considered bioequivalent if the 90% CI of the ratio of geometric least squares means of C_{max}, AUC (0-∞), and AUC(0-t_{last}) fall within 0.8 to 1.25. There would not be power in the model to achieve bioequivalence boundaries for any specific injection location, therefore the bioequivalence for the 3 injection locations will not be determined.

PK parameters may be normalized by body weight for summarizing data. Additional PK analyses may be conducted if deemed appropriate.

9.4 Safety and Tolerability Assessments

9.4.1 Adverse events

Where changes in severity are recorded in the case report form, each separate severity of the AE will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as an AE that starts before the participant has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to dosing. A treatment-emergent AE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. A serious adverse device effect (SADE) is defined as an adverse device effect (ADE) that has resulted in any of the consequences characteristic of an SAE. An unanticipated ADE (UADE) is a SADE which by its nature, incidence, severity, or outcome has not been identified in the current version of the Lilly risk analysis report.

All AEs will be listed. Treatment-emergent AEs will be summarized by treatment, severity and relationship to the study drug. The frequency (the number of AEs, the number of participants experiencing an AE and the percentage of participants experiencing an AE) of treatment-emergent AEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 (or higher if upversioned during the study) system organ class and preferred term. The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug by the investigator. All SAEs, SADEs, and UADEs will be listed.

Discontinuations due to AEs will be listed.

9.4.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary version MAR20B3 (or higher if upversioned during the study). Concomitant medication will be listed.

9.4.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter and treatment, and listed. Urinalysis data will be listed. Changes from baseline (predose) will also be presented. Additionally, clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed and flagged on individual participant data listings.

9.4.4 Vital signs

Vital signs data will be summarized by treatment together with changes from baseline (predose), and values for individual participants will be listed.

9.4.5 Body Temperature

Body temperature data will be summarized by parameter and treatment, and listed. Changes from baseline (predose) will also be presented. Figures of mean body temperature will be presented by treatment, over all timepoints.

9.4.6 Electrocardiogram (ECG)

ECGs will be performed for safety monitoring purposes only and will not be presented. Any clinically significant findings from ECGs will be reported as an AE.

9.4.7 Hepatic Monitoring

If a participant experiences elevated alanine aminotransferase ≥3× upper limit of normal (ULN), alkaline phosphatase ≥2× ULN, or elevated total bilirubin ≥2× ULN, liver tests will be performed to confirm the abnormality. Additional safety data may be collected if required, as defined in the protocol. Where applicable, the following will be presented.

The participants' liver disease history and associated person liver disease history data will be listed. Any concomitant medications that have potential for hepatotoxicity, including acetaminophen will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography scan, and biopsy assessments will be listed, if performed.

Hepatic risk factor assessment data will be listed. Liver related signs and symptoms data will be summarized by treatment and listed. Alcohol and recreational drug use data will also be listed.

All hepatic chemistry, hematology, coagulation, and serology data will be listed. Values outside the reference ranges will be flagged on the individual participant data listings.

9.4.8 Immunogenicity Assessments

The frequency and percentage of participants with pre-existing antidrug antibody (ADA) and with TE ADAs to mirikizumab will be tabulated and listed.

For participants who are ADA negative at baseline, TE ADAs are defined as those with a titer 2-fold (1 dilution) or greater than the minimum required dilution of the assay (1:10). For

participants who are ADA positive at baseline, TE ADAs are defined as those with a 4-fold (2 dilution) or greater increase in titer compared to baseline. The frequency and percentage of participants with neutralizing antibodies, if measured, may also be tabulated for participants with TE ADA.

The relationship between the presence of antibodies and PK and safety parameters of mirikizumab may be assessed.

9.4.9 Hypersensitivity reactions

For all drug hypersensitivity reactions that occur, additional follow-up data will be collected to assess the patient's medical history, alternative causes, and symptoms.

These data will be listed.

9.4.10 Injection-Site Reactions

Although there will be no prospective collection of injection-site reaction (ISR) information, any spontaneously reported ISR by the participant will be reported as AEs.

Any ISR data (including erythema, induration, pain, pruritus, and edema) will be summarized by treatment, and listed.

9.4.11 Visual Analog Scale (VAS) Pain

If injection-site pain is reported at any time during the study, the intensity of pain will be quantified using the 100-mm validated pain visual analog scale (VAS). The VAS is a well validated tool (Williamson and Hoggart 2005) to assess injection-site pain; it is presented as a 100-mm line anchored by verbal descriptors, usually "no pain" and" worst imaginable pain." The pain categories of VAS for presentation in the TFLs will be no pain (VAS pain score = 0), mild pain (VAS pain score > 0 and ≤ 30), moderate pain (VAS pain score > 30 and ≤ 70), and severe pain (VAS pain score > 70). The participant will be asked to rate any pain at the injection site on a scale of 0 to 100 on the line as soon as is practical following reporting of the event.

If available, this data will be summarized by treatment and timepoint, and listed.

9.4.12 Bleeding/Bruising Assessment

The presence of visible bleeding/bruising at the injection site will be recorded as an AE if judged to be more severe than expected with a typical SC administration.

If available, any bruising or bleeding data will be listed.

9.4.13 Other assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed.

10. INTERIM ANALYSES

No interim statistical analyses are planned.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

12. REFERENCES

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

3. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs. 2005;14(7):798-804.

13. DATA PRESENTATION

13.1 Derived Parameters

Individual derived parameters (e.g. PK parameters) and appropriate summary statistics will be reported to three significant figures. Observed concentration data, e.g. C_{max}, should be reported as received. Observed time data, e.g. t_{max}, should be reported as received. N and percentage values should be reported as whole numbers. Median values should be treated as an observed parameter and reported to the same number of decimal places as minimum and maximum values.

13.2 Missing Data

Unless otherwise stated, there are no plans to impute missing data. Any missing data will not be displayed in listings.

13.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of participants or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

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