I1F-MC-RHCU Statistical Analysis Plan Final Version 2

Bioequivalence of an Alternate Ixekizumab Formulation Compared to the Commercial Formulation in Healthy Subjects

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STATISTICAL ANALYSIS PLAN

Bioequivalence of an Alternate Ixekizumab Formulation Compared to the Commercial Formulation in Healthy Subjects

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Study Drug: Ixekizumab (LY2439821)

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1. TABLE OF CONTENTS

2. ABBREVIATIONS

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

AE	Adverse event
ADA	Antidrug antibody
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
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
C_{last}	Last observed concentration
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV%	Coefficient of variation
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
HADS	Hospital Anxiety Depression Scale
ICH	International Conference on Harmonisation
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SD	Standard deviation

SC	Subcutaneous
TBL	Total bilirubin
TE ADA	Treatment-emergent antidrug antibody
TFLs	Tables, Figures, and Listings
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
t_{max}	Time of maximum observed drug concentration
t_{last}	Time of last observed drug concentration
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 13 November 2019), Protocol Amendment (a) (final version dated 21 February 2020) and Protocol Amendment (b) (final version dated 29 September 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. 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; where considerations are substantially different, they will be so identified. 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

4.1 Primary Objective

To evaluate the bioequivalence of a single 80-mg subcutaneous (SC) dose of ixekizumab alternate formulation (test) compared to the ixekizumab commercial formulation (reference).

4.2 Secondary Objective

To describe the safety and tolerability of a single 80-mg SC dose of ixekizumab alternate formulation (test) compared to the commercial formulation (reference).

4.3 Exploratory Objective

To evaluate the immunogenicity of ixekizumab in the alternate formulation (test) and the commercial formulation (reference).

5. STUDY DESIGN

Participants should follow local guidance and clinical research unit (CRU) precautions to minimize risk for Coronavirus Disease 2019 infection.

Study RHCU is a Phase 1, subject-blind, 2-arm, randomized, parallel-design study in healthy subjects.

All subjects will be screened within 28 days prior to enrollment. Eligible subjects will be admitted to the CRU on Day -1. At screening, subjects will be stratified into 1 of 3 weight categories (<70.0 kg, 70.0 to 80.0 kg, >80.0 kg). Within the 3 weight categories, subjects will be randomized 1:1 to either 80-mg ixekizumab commercial formulation (reference) or 80-mg ixekizumab alternate formulation (test) and subrandomized 1:1:1 to injection site (arm, thigh, or abdomen) (Table RHCU.1). On Day 1, subjects will receive a single SC dose according to the randomization plan (Table RHCU.1).

Table RHCU.1. Study RHCU Stratification and Randomization Plan

Weight Category (Subjects)	Formulation (80-mg ixekizumab)	Subcutaneous Injection Location[a]	Desired Number of Subjects
Low <70.0 kg (72 subjects)	Commercial (reference)	Arm	12
	Alternate (test)		12
	Commercial (reference)	Abdomen	12
	Alternate (test)		12
	Commercial (reference)	Thigh	12
	Alternate (test)		12
Medium 70.0 kg – 80.0 kg (72 subjects)	Commercial (reference)	Arm	12
	Alternate (test)		12
	Commercial (reference)	Abdomen	12
	Alternate (test)		12
	Commercial (reference)	Thigh	12
	Alternate (test)		12
High >80.0 kg (72 subjects)	Commercial (reference)	Arm	12
	Alternate (test)		12
	Commercial (reference)	Abdomen	12
	Alternate (test)		12
	Commercial (reference)	Thigh	12
	Alternate (test)		12

Abbreviations: RHCU = I1F-MC-RHCU; SC = subcutaneous.

[a] A dose of investigational product will consist of 1 SC injection of 80-mg ixekizumab into the arm, thigh, or abdomen. All doses will be administered by trained site staff.

6. TREATMENTS

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

Study Treatment Name	Abbreviation	Treatment order in TFL
80-mg ixekizumab commercial formulation	Reference	1

80-mg ixekizumab alternate formulation	Test	2

7. SAMPLE SIZE JUSTIFICATION

Up to approximately 240 subjects may be enrolled so that approximately 216 subjects (108 in the 80-mg ixekizumab commercial formulation [reference] group and 108 in the 80-mg ixekizumab alternate formulation [test] group) complete the study.

A sample size of 108 subjects per treatment group will provide approximately 90% power that the 90% confidence interval (CI) of the geometric mean ratio of maximum observed drug concentration (C_{max}) and area under the concentration versus time curve (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 less or equal to 48% (from study RHCT), the expected ratio of geometric means is between 0.997 to 1.04, and the CV% are the same for subjects from each treatment group.

Subjects who are randomized but not administered treatment and subjects who do not complete PK sampling (including Day 85) may be replaced so that approximately 216 subjects (108 for each treatment) complete the study.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all enrolled subjects, whether or not they completed all protocol requirements.

The "Pharmacokinetic" population will consist of all subjects who received at least one complete dose of ixekizumab and have evaluable PK data. Only subjects who had all PK samples collected up to Day 85 or subjects who had one missing PK sample after Day 15 but with at least 3 data points and Rsq adj>0.7 to calculate half-life parameter could be included in the statistical analysis of the PK parameters.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when subjects 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, min, max 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 subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. Summary

statistics and statistical analyses will generally only be performed for subjects 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 subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject'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 Subject Disposition

Subject disposition will be listed. The demographic variables age, sex, race, ethnicity, body weight, height and body mass index will be summarized and listed. All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

Non-compartmental methods applied with a validated software program (Phoenix WinNonlin Version 8.1 or later) to the serum concentrations of ixekizumab 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
C_{max}	µg/mL	maximum observed drug concentration
t_{max}	day	time of maximum observed drug concentration
t_{last}	day	time of last observed drug concentration
$t_{1/2}$	h	half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL/F	L/h	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 final study report.

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 time point, 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 serum concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.

- 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. If AUC(0-∞) cannot be determined for all subjects an alternative AUC measure, such as AUC to a fixed time point, may be used in the assessment exposure between dose groups.

- Half-life ($t_{½}$) 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 subject 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 serum 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 $t_{½}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ 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 last observed concentration (C_{last}) will be reported.

Individual PK Parameter Rules

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

    - The compound is non-endogenous.

    - The samples are from the initial dose period for a subject.

    - 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.

- The average concentration profiles will be graphed using 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 final study report.

- 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 final study report.

Treatment of Outliers during Pharmacokinetic 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 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 may be 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 final report. Approval of the final report will connote approval of the exclusion.

9.3.2 Pharmacokinetic Statistical Methodology

PK parameters will be evaluated to determine the bioequivalence of ixekizumab alternate formulation (test) compared to the ixekizumab commercial formulation (reference). Log-transformed C_{max}, AUC(0-∞) and AUC(0-t_{last}) will be evaluated in a linear mixed-effects model with fixed effects for formulation and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% CI.

Example SAS code:

```
proc mixed data=pk;
   by parameter;
   class formulation subject;
   model log_pk= formulation / residual ddfm=kr;
   random intercept / subject=subject;
   estimate 'Test - Ref' trtmnt -1 1 / cl alpha=0.1;
run;
```

The t_{max} will be analyzed using a Wilcoxon rank sum test. Estimates of the median difference based on the observed medians, 90% CIs and p-values from the Wilcoxon rank sum test will be calculated.

Bioequivalence will be concluded if the 90% CI is completely contained within the interval (0.80, 1.25).

PK parameters may be normalized by body weight for summarizing the data and may be summarized by site of injection location using descriptive statistics. Additional comparisons may also be conducted as necessary.

A sensitivity analysis will be performed to complete the statistical comparison above using the subjects who completed the PK sampling schedule to Day 85 only (subjects with no missing PK samples).

9.4 Safety and Tolerability Assessments

9.4.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the adverse event (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 subject 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.

If the investigator determines an injection-site reaction (ISR) is clinically significant or it is an unsolicited reporting, the event will be recorded as an AE and findings of the ISR (including induration, pain, edema, pruritus, and erythema) will be captured on the ISR AE form. Any ISRs that are present (besides induration, pain, edema, pruritus, and erythema) will be recorded as AEs at the discretion of the investigator only.

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 subjects experiencing an AE and the percentage of subjects experiencing an AE) of treatment-emergent AEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 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. Any serious AEs will be listed.

Discontinuations due to AEs will be listed.

9.4.2 Concomitant medication

Concomitant medication will be coded using the World Health Organization (WHO) drug dictionary (Version September 2019 B3). Concomitant medication will be listed.

9.4.3 Clinical laboratory parameters

All clinical chemistry and hematology data, with changes from baseline, will be summarized by parameter and treatment, and listed. Urinalysis data will be listed. Additionally clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed and flagged on individual subject data listings.

9.4.4 Vital signs

Vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as the Day 1 predose assessment. Figures of mean vital signs and mean changes from baseline profiles will be presented by treatment.

Values for individual subjects will be listed.

9.4.5 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.

9.4.6 Hepatic Monitoring

If a subject experiences elevated alanine aminotransferase (ALT) ≥3× upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2× ULN, or elevated total bilirubin (TBL) ≥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 subjects' liver disease history and associated person liver disease history data will be listed. Any concomitant that have potential for hepatotoxicity, including acetaminophen will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography (MRE) 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 subject data listings.

9.4.7 Immunogenicity Assessments

The frequency and percentage of subjects with pre-existing antidrug antibody (ADA) and with treatment-emergent ADAs (TE ADA) to ixekizumab will be tabulated.

For subjects who are ADA negative at baseline, TE ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution of the assay (1:5). For subjects who are ADA positive at baseline, TE ADAs are defined as those with a 4-fold (2 dilution) increase in titer compared to baseline. The frequency and percentage of subjects with cross-reactive and neutralizing antibodies, if measured, may also be tabulated for subjects with TE ADA.

9.4.8 Hypersensitivity reactions

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

These data will be listed.

9.4.9 Injection-Site Assessments

Injection sites will be assessed for reactions including bleeding, induration, pain, edema, pruritus, and erythema. Any available injection-site assessment data will be listed.

9.4.10 Visual analog scale (VAS) pain

Intensity of pain data will be quantified using a 100-mm validated visual analog scale (VAS) for any subject that answers "Yes" to the question "How much pain have you had at the injection site?". The data will be listed and summarized by treatment and time point.

In addition, the severity of pain will be categorized by VAS pain score as no pain (0), mild pain (> 0 and ≤ 30), moderate pain (> 30 and ≤ 70), and severe pain (> 70). The number and percentage of subjects in each pain severity category will be summarized by treatment and time point. The percentage of subjects in each pain severity category will also be presented in a frequency figure. Figures of the continuous injection-site pain VAS score will also be presented, by treatment and measuring time point.

9.4.11 Columbia-Suicide Severity Rating Scale (C-SSRS), Self-Harm Supplement and Hospital Anxiety Depression Scale (HADS)

Given that few or no suicidal ideation or behaviors are anticipated, a listing of C-SSRS data will be produced by subject and visit. Only subjects that show suicidal ideation/behavior or self-injurious behavior without suicidal intent will be included in the listing (i.e., if a subject's answers are all 'no' for the C-SSRS, then that subject will not be displayed). However, if a subject reported any suicidal ideation/behavior or self-injurious behavior without suicidal intent at any time point then all their ideation and behavior will be included, even if not positive.

HADS item scores will be listed for subjects with HADS depression subscale ≥ 11 at any time.

9.4.12 Other assessments

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

9.4.13 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

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.

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

Missing data will not be displayed in listings.

13.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of subjects 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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