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Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

CACZ885

CACZ885X2206

A multiple-dose, subject- and investigator-blinded, placebo-controlled, parallel design study to assess the efficacy, safety and tolerability of ACZ885 (canakinumab) in pediatric and young adult patients with sickle cell anemia

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CACZ885X2206".***

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

This SAP has been developed using Clinical Trial Protocol version v05 dated 22 March 2018.

1.3 Study objectives

1.3.1 Primary objective

Primary objective	Endpoints related to primary objective
• To determine the effect of ACZ885 versus placebo on daily pain experienced by sickle cell anemia patients	• Reduction of average daily pain VAS over the period of Week 8 to 12 as compared to baseline levels

1.3.2 Secondary objectives

Secondary objectives	Endpoints related to secondary objectives
• To determine the duration of effects of canakinumab versus placebo on daily pain experienced by SCA patients	• Reduction of average daily pain VAS over 4-week intervals up to Week 24 as compared to baseline levels

• To determine the effect of canakinumab versus placebo on laboratory markers of inflammation	• Week 12 versus baseline of:
	  • Serum hs-CRP
	  • WBC count
	  • Absolute counts of blood neutrophils
	  • Absolute counts of blood monocytes

• To determine the effect of canakinumab versus placebo on laboratory and functional markers of hemolysis	• Week 12 versus baseline of:
	  • Hemoglobin concentration
	  • Reticulocyte count
	  • Haptoglobin
	  • LDH
	  • Bilirubin (total, direct and indirect)
	  • Oxygen percent saturation (SaO2)

• To determine the effect of canakinumab versus placebo on SCA-related days missed from school or work	• Number of days absent from school or work due to pain as recorded by daily eDiary
• To determine the effect of canakinumab versus placebo on reducing the need for acute blood transfusion	• The rate of SCA-related acute transfusion
• To assess the safety, including immunogenicity, and tolerability of canakinumab in patients with SCA as measured by adverse events (AEs)	• Adverse events in patients taking ACZ885 compared to placebo up to a total of 56 weeks treatment.
• To determine the PK of ACZ885 in SCA patients	• Serial serum PK determinations in patients with SCA

1.3.3 Exploratory objectives

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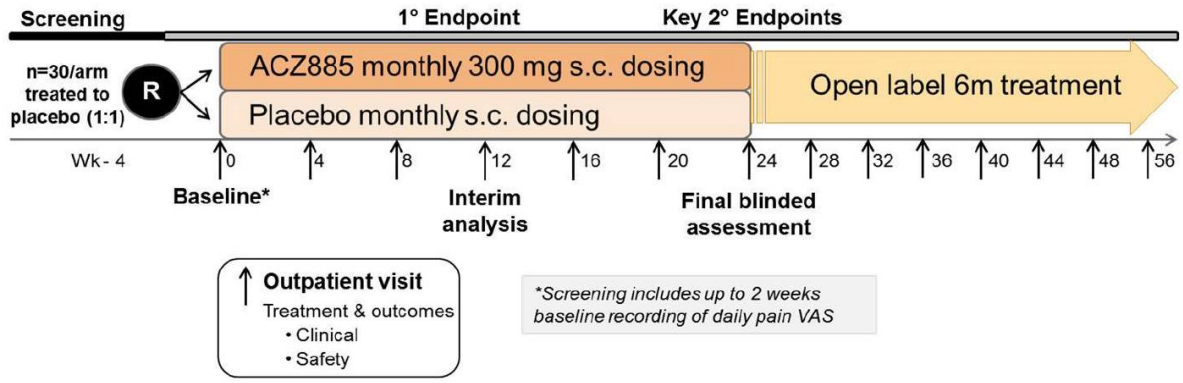
1.4 Study design and treatment

This study (Figure 1-1) is an ambulatory-based study of 24 weeks duration followed by an additional 24-week open label phase and is subject- and investigator-blinded, randomized, placebo-controlled, parallel group, non-confirmatory to assess the clinical efficacy of canakinumab administered s.c. in 6 injections given 28 days apart. This study will randomize approximately 60 pediatric and young adult patients (targeting 48 completers of 8 to 20 years old) diagnosed with SCA who experience chronic or episodic pain, i.e., detectable average daily pain level over a 1-2 week screening period and at least 2 painful episodes in the past year of likely sickle cell etiology requiring analgesia and interfering with the patient's normal daily routine.

Figure 1-1 Study Design



Acceptable prior established background therapy includes hydroxyurea and supportive antibiotic and analgesic medications. Patients will be randomized to either ACZ885 treatment or placebo treatment in a 1:1 ratio, with treatment stratification based on concurrent hydroxyurea therapy (yes/no).

Subjects who are prematurely withdrawn from the study for reasons other than safety or lack of efficacy will be replaced on a case-by-case basis. Re-screening of subjects may be allowed under the guidance of the Sponsor's medical expert.

For each subject, there will be a maximum 28-day screening period that will include recording of daily pain frequency and intensity by e-diary for at least 1 week.

Subjects who meet the eligibility criteria at screening will undergo evaluation of full baseline clinical and biomarker assessments prior to first dose administration. The screening daily pain results will be used to derive the baseline value for this primary endpoint of average daily pain. All safety evaluations must be available prior to dosing and results must demonstrate all eligibility criteria are met. Enrolled subjects will be randomized at a 1:1 ratio to receive treatment with either canakinumab or placebo with stratification based on concurrent hydroxyurea therapy. On Day 1, monthly s.c. dosing with canakinumab will begin at 4 mg/kg for patients weighing $\leq$ 40 kg and 300 mg for all other patients. Patients in the placebo treatment arm will be injected in a like manner with placebo. All patients will return to the study centers for safety checks on a monthly basis when they will receive treatment with either canakinumab or placebo. Additionally, patients will undergo clinical and laboratory evaluations as outlined in the Assessment Schedule (Section 8.1 within the protocol) every 28 days. The final blinded dosing will take place on Week 20, followed by blinded clinical assessments at Week 24. Patients from both study arms are then offered optional, open label monthly dosing of ACZ885 for an additional 24 weeks (Weeks 24-48), with clinical outcomes again assessed according to the Assessment schedule. Patients return for the end of study (EOS) visit at Week 56. For patients who choose not to participate in the optional, open label portion of the study, or for patients stopping treatment early for any other reason, an EOS visit will occur approximately 8 weeks after last dose received.

The EOS for an individual patient is defined as the EOS visit described above, which will occur approximately 8 weeks after last dose received. The global EOS is defined as the EOS visit of the last patient in the trial performing the EOS.

The mechanism of action of canakinumab is anticipated to effect relatively rapid attenuation of intravascular inflammation and associated daily pain and fatigue. Twelve-week data from the first 24 enrolled patients and the full recruitment will be assessed in two separate interim

analyses for safety and study treatment effects upon clinical markers of pain and intravascular inflammation. To better demonstrate treatment effects upon additional key outcomes such as frequency of vaso-occlusive pain events and reductions in work or school absences, another assessment will occur when all enrolled patients have successfully achieved 24 weeks of treatment.

A follow-up visit or phone call for SAEs must be performed 8 weeks following end-of-treatment visit or early discontinuation, or 8 weeks after last injection of study drug, whichever is later. If anaphylactic reactions occur after injection, two more immunogenicity samples (at the time of the event and 8 weeks later) need to be taken.

2 First interpretable results (FIR)

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3 Interim analyses

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4 Statistical methods: Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The safety analysis set will include all subjects that received any study drug.

The PK analysis set will include all subjects with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

The PD analysis set will include all subjects with available PD data, who received any study drug and no critical protocol deviations with relevant impact on PD data. Subjects missing two consecutive doses or more during the blinded treatment period will be excluded from the primary PD analysis set. All PDs will be captured as such within the database.

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The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from all *(safety)* analysis in case of these PDs:		Exclude subject completely from all ***(safety)*** analysis sets
Subjects are excluded from PK analysis in case of these PDs:		Exclude subject from PK analysis set
INCL02	Written Informed Consent Form not obtained	Yes
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis sets
INCL02	Written Informed Consent Form not obtained	Yes
Subjects are excluded from primary PD analysis in case of these PDs:		Exclude subject from primary PD analysis set
TRT01	Missing two consecutive doses or more during blinded treatment period	To be assessed on a case by case basis

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

The primary efficacy endpoint (average daily pain VAS) and key safety endpoints (AE/SAEs, blood chemistry and hematology) will be reported for pediatric (<18 years old) and adult (>=18 years old) cohorts separately per Novartis internal SOP requirement in the final CSR. Selected tables and figures for these data will therefore be summarized split by pediatric/adult subgroup as well as overall.

All tables and figures will be summarized split by concurrent hydroxyurea subgroup (with and without) as well as overall. If the number of subjects without HU use is less than 10% of the total, the summary for this subgroup is not needed; and vice versa.

5 Statistical methods for Pharmacokinetic (PK) parameters

5.1 Variables

PK samples will be collected at the time points defined in the Assessment schedule.

Pharmacokinetic (PK) samples will be obtained and evaluated in all subjects at all dose levels.

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5.2 Descriptive analyses

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5.3 Statistical model, assumptions and hypotheses

No inferential statistical analyses are to be completed on the PK data.

6 Statistical methods for Pharmacodynamic (PD) parameters

6.1 Primary objective

The primary aim of this study is to assess if inhibition of IL-1β by canakinumab will reduce average daily pain in pediatric and young adult patients with sickle cell anemia.

6.1.1 Variables

A numerical pain VAS score between 0 and 10 will be recorded by each patient once daily.

The post-baseline average daily pain VAS will be calculated for each dose from the start of the dose till the day before the next dose, i.e., in an averagely 4-week interval (e.g., Week 0-4, Week 4-8, etc. depending on the actual dosing days).

For double-blind period, the baseline average pain VAS will be calculated as the average of daily pain scores from screening up to pre-dosing over a period of at least 7 days.

For subjects who switched from placebo to ACZ885 treatment in open-label, the average of Week 20-24 will be used as the new baseline to assess the effect of ACZ885 treatment in open-label period. For subjects who continued on ACZ885 treatment, the original baseline will continue to be used.

The reduction from baseline of the 4-week average daily pain VAS for Week 8-12 will be the primary variable for this study.

6.1.2 Descriptive analyses

Summary statistics for PD variables will include sample size (N), mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. A geometric mean will not be reported if the dataset includes zero values.

Summary statistics for the reduction from baseline in the 4-week average daily pain VAS will be provided by treatment, visit/time; and also by hydroxyurea use history.

6.1.3 Statistical model, assumptions and hypotheses

Reduction from baseline in the average daily pain VAS, i.e., baseline minus post-baseline, will be analyzed using a Bayesian model for repeated measures using Proc MCMC in SAS (Chen 2011). The model will include baseline average daily pain score as a continuous covariate; treatment group, time and hydroxyurea use history (Yes/No) as fixed factors. Interactions of time by treatment group and time by baseline covariates will also be included in the model. Non-informative priors will be used for the fixed effects and weakly informative prior, for the covariance. Unstructured covariance structure will be used and other covariance structure will be investigated if there is convergence problem. Posterior mean with 90% credible interval will be presented over time. Interaction of hydroxyurea use and treatment group will be explored graphically, please see section 6.1.3.3; if substantial interaction is suspected it will be further explored by including this interaction term in the whole model.

A comparison of canakinumab 300 mg s.c. versus placebo for the period of Week 8-12 is of primary interest. Data up to Week 24 will be included in the primary model. Bayesian posterior probabilities will be used to assess the following PoC criteria as a guidance for decision making (Fisch et al 2015):

- Prob (the reduction of average pain score over the period of Week 8-12 in canakinumab is greater than Placebo) > 90%, and,
- Prob (the reduction of average pain score over the period of Week 8-12 in canakinumab is greater than Placebo by 1) > 50%.

The target difference of 1 is chosen based on the literature search on the Minimally Clinical Important Difference (MCID) in pain studies.

At the first interim analysis, one futility rule will be assessed. The criterion is defined as:

- Prob (the reduction of average pain score over the period of Week 8-12 in canakinumab is less than Placebo) > 80%.

The dosing regimen of concurrent hydroxyurea remain fixed during the study except for any adjustment according to hematologic parameters or other standard of care clinical monitoring (protocol Section 6.11). The number of patients with hydroxyurea dose adjustment during the study period (especially up to week 12 and up to week 24) will be summarized. Impact on the results for this group may be explored if the proportion of such patients is high.

6.1.3.1 Handling of missing data/censoring/discontinuations

Handling of missing daily pain VAS entries for the calculation of average pain score

At each visit from Day 1, the 4-week average daily pain VAS score will be calculated based on available daily pain data. The proportion of missing data will first be derived at subject level for each time interval and then be summarized at treatment group level to evaluate possible impact on data interpretations. Information about reasons for missing data if available will be included in this consideration.

Handling of missing average pain score

Early discontinuations not due to lack of efficacy support the assumption of Missing at Random (MAR). In such scenarios the longitudinal model described earlier remains valid. In the primary analysis for the blinded treatment period, if there were any patients who discontinued early due to lack of efficacy, LOCF (last observation carried forward) approach will be explored. If the reasons of missing are known, other imputation methods such as multiple imputations may be considered.

Handling of acute blood transfusion

Data for those patients who have received interventional acute blood transfusion(s) during the study will be truncated up to the first occurrence of interventional acute blood transfusion, i.e., data since the first interventional blood transfusion will be considered as missing. Data will be truncated at daily level first before the derivation of 4-week average score, i.e. eDiary data from the first date of blood transfusion during the double-blind treatment period will be truncated and then primary endpoint of 4-week average score will be derived using the truncated data. Assuming the occurrence of acute blood transfusion being random to this patient population, such missing data are considered Missing at Random (MAR).

As a supportive analysis, the complete data will be analyzed as if the patients did not receive any blood transfusion.

6.1.3.2 Model checking procedures

In case of convergence issues, the covariance matrix that best fit the data will be chosen.

Diagnostic plots will be provided.

6.1.3.3 Graphical presentation of results

The reduction from baseline in 4-week average pain score will be visualized in Mean (SEM) plots over time by treatment group.

Interaction of hydroxyurea use and treatment will be explored in Mean (SEM) plots in reduction from baseline in 4-week average pain score over time by HU use and group.

Daily pain VAS data for individual patients will be visualized over time using heat map.

6.1.3.4 Supportive analyses

As a supportive analysis, all collected data in the double-blinded period will be analyzed in the same way as described in Section 6.1.3, without truncation of data due to acute blood transfusions. This is to explore the possible impact of such interventional therapy to the treatment effect.

Non-convergence of the primary analysis may occur when there is a great amount of truncated data due to acute blood transfusion. In that scenario the evaluation of efficacy may focus on the analysis of the rate of acute blood transfusion.

6.2 Secondary objectives

For the double-blinded period, the main analysis on secondary efficacy data, including inflammation and hemolysis biomarkers, absence from school/work will also be based on truncated data up to the time of the first acute blood transfusion where applicable. Complete data will also be summarized and visualized.

6.2.1 Reduction from baseline of the 4-week average daily pain up to Week 24

As described in Section 6.1.3, the reduction from baseline of the 4-week average daily pain VAS for Week 12-16, Week 16-20 and Week 20-24 will be evaluated in the same model.

Pain data in the open label period when available will also be summarized, visualized in plots as well as overlaid individual plots over time by treatment group and explored in appropriate statistical models, to evaluate the maintenance of the efficacy in patients randomized to canakinumab group and/or improvements in patients randomized in placebo group.

6.2.2 Novel metrics of pain measurement

In addition to the average daily pain the following additional novel metrics will be calculated and summarized for the period of pre-dosing and every 4-week interval after dosing:

- Mean daily pain (MDP) calculated by obtaining the mean of daily pain scores
- Proportion of pain-free days (PPFD) calculated as the number of days without pain divided by total number of reported days. Pain-free is to be defined as a reported pain intensity score of <1.
- p90 , the 90th percentile of daily pain scores which provides an indication of the upper levels of pain experienced, indicating the point where 10% of pain scores are above the statistic
- Standard Deviation (SD) of daily pain scores
- Coefficient of variation (CV) of daily pain scores (calculated as SD/mean).

6.2.3 Inflammation and hemolysis biomarkers

The inflammation biomarkers, including hs-CRP, WBC count, absolute count of blood neutrophils and absolute count of blood monocytes along with hemolysis biomarkers, including hemoglobin concentration, reticulocyte count, haptoglobin, lactate dehydrogenase, total bilirubin and oxygen percent saturation (SaO2), will be summarized and visualized in Mean (SEM) plots over time by treatment group, visit/time and subgroup (with and without concurrent hydroxyurea). Overlaid individual plots will also be presented.

For each inflammation and hemolysis biomarker (excluding oxygen percent saturation (SaO2)), change from baseline on the log transformed values will be analyzed using an MMRM with the log baseline value as continuous covariate, treatment group, time, hydroxyurea use history (Yes/No) and race as factors.

For oxygen percent saturation (SaO2), change from baseline will be analyzed using an MMRM with the baseline value as continuous covariate, treatment group, time, hydroxyurea use history (Yes/No) and race as factors.

For both models, data up to Week 24 will be included and unstructured covariance structure will be used. In case of convergence issues, the covariance matrix that best fit the data will be chosen.

For each of the biomarkers, the difference between canakinumab and placebo groups at Week 12 and 24 will be presented in terms of ratio of geometric mean because of the log transformation.

6.2.4 Absence from school/work

The number of SCA-related days absent from school or work will be derived from eDiary records. The data will be summarized and visualized in Mean (SEM) plots over time (with 4-week interval) by treatment group, visit/time and subgroup. The total number of SCA-related absence days up to Week 24 visit will also be summarized by treatment group. A negative binomial Generalized Linear Model (GLM) will be fitted for the total number of SCA-related days absent from school/work up to Week 24 visit, with treatment group as the factor. The difference between canakinumab and placebo groups will be estimated.

6.2.5 Incidence of acute blood transfusion

Medical review will determine whether the blood transfusion is for disease acute intervention or for prophylactic purpose. The occurrence of acute blood transfusions will be summarized as the proportion of patients who receive at least one acute blood transfusion and the event rate of acute blood transfusions per patient, by study period, group and reason of transfusion.

The proportion of patients who receive at least one acute blood transfusion for disease acute intervention during the double-blinded period will be analyzed in a binomial Bayesian model with non-informative prior for both groups (neutral prior Beta(1/3, 1/3), (Kerman 2011) and the posterior probability of the difference of the two proportions (ACZ885 - placebo) will be presented.

If the data allows, the recurrent event analysis (at least one patient receiving more than one acute blood transfusion), the time to recurrent incidence of acute blood transfusions during the double-blinded period will be analyzed via the Andersen-Gill model (Andersen & Gill 1982), with treatment and hydroxyurea use as independent variables and time to last blood transfusion before study treatment (if available) as a continuous covariate.

The incidence of acute blood transfusions will also be included in the visualizations of all efficacy endpoints where applicable.

6.3 Exploratory objectives

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7 Statistical methods for safety and tolerability data

7.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, as well as subject demographics (including a summary of Genotype), baseline characteristics (including baseline average pain score, baseline hsCRP, hydroxyurea use history, number of VOPE in previous year if available) and treatment information.

7.2 Descriptive analyses

7.2.1 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group. Subject demographics will include age, gender, race, ethnicity, country, height, weight and BMI. Baseline disease characteristics include but are not limited to: baseline average daily pain VAS, baseline hs-CRP, the number of VOPE in the previous year.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject.

7.2.2 Treatment

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment group and subject.

The proportion of patients receiving any rescue medication/therapy post baseline will be summarized by group and study period.

7.2.2.1 Hydroxyurea Use

Hydroxyurea dose may need to be adjusted during the study in consideration of certain blood counts including neutrophils and platelets. The number of patients with a hydroxyurea dose change will be summarized.

7.2.3 Vital signs

All vital signs data will be listed by treatment group, subject, and visit/time, and where ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment, visit/time and subgroup.

7.2.4 ECG evaluations

All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment, visit/time and subgroup.

7.2.5 Clinical laboratory evaluations

All laboratory data (including the exploratory variables, cholesterol subtypes and triglycerides from lipid panel) will be listed by treatment group, subject, and visit/time, and where normal ranges are available, abnormalities will be flagged. Shift tables will be provided by treatment, visit/time and subgroup.

Urine albumin-creatinine ratio (ACR), one renal function parameter, will be analyzed in the same way as for hsCRP.

7.2.6 Adverse events

All information obtained on adverse events will be displayed by treatment group and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on <on-treatment/treatment emergent> adverse events which are not serious adverse events with an incidence greater than X% and on <on-treatment/treatment emergent> serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population. The value of the cutoff value X will be decided with the team when disclosure tables are prepared.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT. Inferential statistical methods may be explored should a reasonable number of incidences/patients with SAEs be reported.

7.2.7 Immunogenicity

All immunogenicity results will be listed by treatment group, subject and visit/time.

7.2.8 Pregnancy test

All pregnancy test results for women will be listed by patient and visit.

7.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be created, including reference lines for lower and upper limits for normal ranges where ranges are present within the data.

8 Statistical methods for Biomarker data

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9 Reference list

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