NOVARTIS

Clinical Development

QAW039

CQAW039B2201 / NCT03650400

A multicenter, open-label, 8 day treatment study to assess the pharmacokinetics, safety and tolerability of fevipiprant delivered via a once daily chewable tablet in children aged 6 to <12 years with asthma

Statistical Analysis Plan (SAP)

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List of abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under curve
b.i.d	twice a day
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CRF	Case Report/Record Form (paper or electronic)
CT	Chewable tablet
ECG	Electrocardiogram
FDA	Food and Drug Administration
IgE	Immunoglobulin E
ICS	Inhaled Corticosteroid
LABA	Long Acting Beta-2 Agonist
MedDRA	Medical Dictionary for Regulatory Activities
PDS	Programming dataset specification
PT	Preferred term
SoC	System organ class
o.d.	Once a day
PK	Pharmacokinetic
QTc	Corrected QT interval
SAE	Serious Adverse Event
SAF	Safety analysis set
SOC	System Organ Class

1 Introduction

This document contains details of the statistical methods that will be used in the phase II clinical trial CQAW039B2201. This study is designed to evaluate the pharmacokinetics, safety and tolerability of fevipiprant delivered via once daily chewable tablet (CT) in children aged 6 to <12 years with asthma.

The study was terminated by sponsor prematurely on December 16, 2019. Decision was taken to discontinue Study CQAW039B2201 based on evaluation of the QAW039 (fevipiprant) development program in asthma including results from the recently completed LUSTER-1/-2 (CQAW039A2307/A2314) studies. The last Patient Last Visit, LPLV, was on January 22, 2020. All patients from Cohort A completed the study. 5 subjects of Cohort B were treated, none of them completed the trial and none reached scheduled Day 8 visit.
This statistical analysis plan is an abbreviated approach of presenting the limited data collected in the study and does not reflect the full analysis scope described in Section 12 of the study protocol (Version 01, Amendment 1 to original protocol released on 13-Feb-2019). Important information is given in the following sections and details are provided, as applicable, in section 5: Appendix.

1.1 Study design

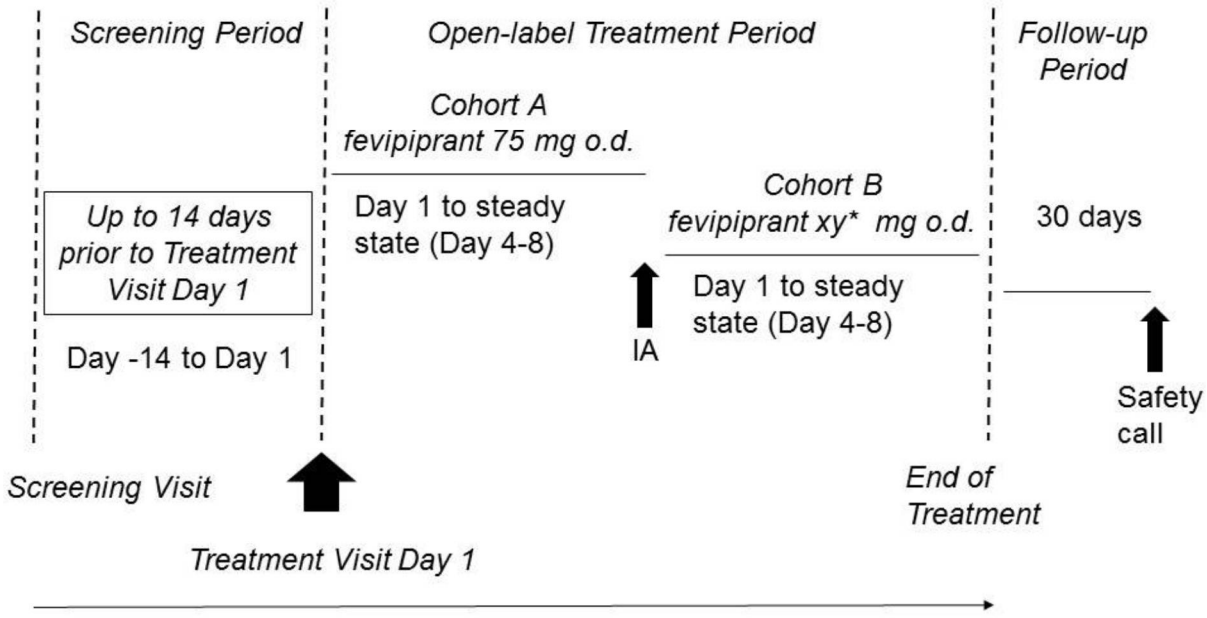
This study uses a multicenter, open-label design to assess the pharmacokinetics, safety, and tolerability of fevipiprant CT in children aged 6 to < 12 years with asthma (figure 1-1). The study includes an 4-8 day, open-label treatment period in which subjects receive fevipiprant CT once daily (o.d.) in addition to their rescue medication (e.g. short-acting β-agonists [SABAs]) and potentially standard-of-care (SoC) asthma therapy (inhaled corticosteroids [ICS] with or without an additional controller therapy).

There will be 2 treatment dose cohorts studied (fevipiprant 75 mg o.d. and one higher dose selected based on PK obtained at 75 mg/day, [e.g. 150, 225, 300, or 375 mg once daily]). Within each dose cohort, subjects will be stratified approximately 1:1 ratio into 2 age groups: ages 6 to < 9 years and ages 9 to < 12 years.

Six subjects will be included in Cohort A and 6 to18 subjects in Cohort B. Approximately 20 subjects will need to be screened in order to include 12 subjects into the treatment period (screen failure rate ~40%). After the interim analysis, additional subjects may need to be recruited so that total number of subjects completing treatment is maximum 24, in this case approximately 40 subjects will need to be screened. It is intended that 12 to 24 patients will complete the study. Dropouts, non-completers and patients who are not eligible for PK assessment at End of treatment (e.g. because they did not take study drug for 3 consecutive days prior to EOT visit) will be replaced. Detailed information regarding sample size calculation is provided in section 3.

A planned interim analysis will be conducted to support decision making when 6 subjects (3 subjects from each of the 2 age strata) receiving the 75 mg dose level complete the treatment and provide the planned PK and safety data. At interim analysis, safety, as well as mean and variability of PK data of the 75 mg dose level will be assessed to have the right dose and number of subjects for the higher dose at the second stage. For detailed information, please refer to Section 3.

Figure 1-1 Study design



*Cohort B will be at 225 mg CT o.d. or at a different dose (e.g. 150, 300 or 375 mg)

1.2 Study objectives and endpoints

Section 2 of the study protocol lists the following primary and secondary objectives.

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To determine the key pharmacokinetic parameters of fevipiprant at steady state (ss),	• Area under the curve (AUC0-24h,ss), maximum plasma concentration (Cmax,ss),

Objective(s)	Endpoint(s)
after at least four consecutive days of dosing	and oral clearance (CL/F)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the urinary excretion of fevipiprant and CCN362 at steady state	• CLr, amount and fraction of dose excreted over the PK collection interval
• To evaluate the safety & tolerability of fevipiprant over treatment period	• Safety laboratory values (including peripheral blood eosinophils), vital signs, ECG, adverse events
• To evaluate the pharmacokinetics of CCN362, the major metabolite of fevipiprant at steady state	• Cmax,ss, time of maximum plasma concentration (Tmax,ss), AUC0-24h,ss, minimum plasma concentration (Cmin,ss) of CCN362
• To evaluate additional pharmacokinetic parameters of fevipiprant at steady state	• Tmax,ss, Cmin,ss, (CL/F)/kg of fevipiprant

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed [redacted]. The most recent version of SAS available in the statistical programming environment [redacted] will be used for the analysis.

2.1.1 General definitions

2.1.1.1 Study day

Study day will be defined as the number of days since the date of first dose of study treatment. The date of first dose of study treatment will be defined as Day 1 and the day before the first dose of study treatment will be defined as Day -1.

Therefore, for a particular date, study day will be calculated as follows:

- for dates on or after the first date of study treatment,

  Study day = Assessment date – Date of first dose of study treatment + 1;

- for dates prior to the first date of study treatment,

  Study day = Assessment date – Date of first dose of study treatment.

If a patient has not taken study treatment, the date when the study treatment has been assigned, will be used instead of the date of first dose of study treatment. Then, the date when the study treatment has been assigned is defined as Day 1 and the day before is defined as Day -1.

2.1.1.2 Baseline definition

For baseline assessments, checks will be performed to ensure the assessments were indeed taken prior to the first dose of study treatment. If baseline assessment (as mentioned in below

table) is missing or not confirmed to be pre-dose, the last value taken at any scheduled or unscheduled visit before the first administration of study treatment will be used for baseline. Otherwise, the baseline will be set to missing without imputation.

Parameter	Baseline assessment
Laboratory data (hematology, biochemistry)	Screening visit
Vital signs (body temperature, pulse rate, systolic and diastolic blood pressures)	Treatment Day 1 Pre-dose
Height, weight and BMI	Screening visit
ECG	Screening visit

2.1.1.3 Post-baseline measurement

Post-baseline measurements are defined as those assessments after the first dose of study treatment. When change from baseline is of interest the following formula will be used for each scheduled visit and time-point where baseline and post-baseline values are both available: Change from baseline = post-baseline value – baseline value.

2.2 Analysis sets

The following analysis sets are defined:

- The Safety Set will consist of all patients who received at least one dose of study treatment including non-eligible patients who received study treatment in error. Patients will be analyzed according to the treatment they received. The safety set will be used in the analysis of all safety variables.
- 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. Patients will be analyzed according to the treatment they received.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

For treatment epoch, the overall number of patients who entered, completed, and discontinued that phase will be summarized including the reasons for discontinuation.

The number of patients included in each analysis set will be tabulated.
Protocol deviations as well as reason for exclusion from analysis sets will be listed.

2.3.2 Patient demographics and baseline charecteristics

Demographic and baseline characteristics measured including age, age stratum (6 to <9 years and 9 to <12 years), gender, race, ethnicity, height, weight and body mass index (BMI) will be summarized by cohort on safety analysis set.

Continuous variables will be summarized using descriptive statistics (mean, median, standard deviation, minimum, and maximum) and categorical variables will be summarized in terms of the number and percentage of subjects in each category.

Medical history will be coded with the Medical Dictionary for Regulatory Activities terminology (MedDRA) using the most recent version at the time of database lock. Verbatim recorded history/conditions will be listed together with the coded terms, date of diagnosis/surgery and whether the problem was ongoing at start of the study.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Dosage and date of administration at clinic (Treatment Day 1 and End of Treatment (at steady state)) and at home (1 day prior End of Treatment e.g. treatment Day 7) will be listed for all subjects in safety set.

2.4.1.1 Duration of exposure

Duration of exposure to study treatment will be calculated as the number of days starting from the first dose date up to and inclusive the last dose date. The duration of exposure will be summarized by cohort for the safety set as a continuous variable with the standard descriptive statistics.

2.4.2 Prior, concomitant and post therapies

Prior and concomitant medications will be listed on the Safety set.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary objective of the study is to determine the pharmacokinetics of fevipiprant based on AUC0-24h,ss, Cmax,ss and CL/F.

The AUC0-24h,ss, Cmax,ss and CL/F for fevipiprant at steady state after at least four consecutive days will be the primary variables. PK analysis set will be used for analysis of all PK parameters. Due to termination of study no PK data of Cohort B are available, thus all summaries of PK data will be done for Cohort A only.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary variables, AUC0-24h,ss, Cmax,ss and CL/F will be analyzed by standard non-compartmental analysis and summarized for Cohort A, through descriptive summary statistics (including mean, SD, CV% mean, Geometric mean, CV% geometric mean, median, minimum and maximum). .

Plasma concentrations will be assessed at EOT visit (pre-dose, 0.5, 1, 2, 3, 5, 8h) and will be expressed in mass per volume units. All concentrations below the lower limit of quantification (LLOQ) or missing data will be labeled as such in the concentration data listings. Concentrations below the limit of quantification will be treated as zero in summary statistics and for the calculation of parameters and the pre-dose concentration on EOT visit will also be used as 24 h concentrations to derive AUC0-24h,ss.

2.5.3 Handling of missing values/censoring/discontinuations

Subjects with no valid PK concentration measurements, will be excluded from the analysis. Under missing completely at random assumption, subjects included in the analysis will be considered as representative of all subjects received treatment. Drop-outs and non-completers will be replaced.

No other methodology is planned to address missing data.

2.5.4 Supportive and Sensitivity analyses

Not applicable

2.6 Analysis of the secondary objectives

The secondary endpoints will be analyzed as described below.

2.6.1 Safety analyses

All safety evaluation will be based on the safety set.

2.6.1.1 Adverse events (AEs)

All adverse events including asthma exacerbations will be coded with MedDRA using the most actual version at the time of database lock. AEs (including asthma exacerbations) starting on or after the time of the first intake of study drug and until the 7 days (30 days for SAEs) after the last intake of study drug will be classified as a treatment-emergent AEs. Any AEs that started during the study after signing informed consent and before the time of the first intake of study drug will be classified as prior AEs and will not be included in tabulations of treatment-emergent AEs.

The number and percentage of patients who reported treatment-emergent adverse events will be summarized by primary system organ class (SOC), preferred term (PT), and cohort forall adverse events by maximum severity

Unless otherwise specified, primary system organ classes will be sorted alphabetically and, within each primary system organ class, the preferred terms will be sorted in descending order of frequency in Cohort A. If a patient reported more than one adverse event with the same preferred term, the adverse event will be counted only once for that preferred term level. If a patient reported more than one adverse event within the same primary system organ class, the patient will be counted only once at the system organ class level.

2.6.1.1.1 AE reporting for CT.gov and EudraCT

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than X% (where X lies between 0-5 %, will be decided later) and on 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.

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.

2.6.1.2 Laboratory data

All laboratory samples will be processed through the central laboratory. Laboratory data consist of hematology and biochemistry including peripheral blood eosinophils.

Laboratory data measured more than 7 days after last dose of study treatment are regarded as post-treatment data and will not be summarized. All data will be included in the analyses regardless of rescue medication use. All data will be listed.

The number and percentage of patients with newly occurring or worsening laboratory abnormalities meeting the clinically notable criteria (see Section 5.4 for definition of notable values) summarized by cohort, laboratory parameter at any time on treatment considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits.

For a patient to meet the criterion of a newly occurring clinically notable value, the patient needs to have a baseline value that is not clinically notable for that parameter. For a patient to meet the criterion of a worsening clinically notable value, the patient needs to have a baseline value that is clinically notable and also have a worse post-baseline value. For patients with missing baseline value, any post-baseline notable value will be considered as newly occurring. A listing of all patients with notable laboratory values will be provided.

For summary tables on laboratory parameters considering values, which are lower or greater than the limit of quantification, the following approach will be taken. For values which are flagged as lower than the lower limit of quantification, the values presented in summary tables should be multiplied by 0.5 and for values which are flagged as greater than upper limit of quantification as 1.5, the values presented in summary tables should be multiplied by 1.5.

Laboratory data, if collected in local LAB CRF page, will be listed only as appropriate.

2.6.1.3 ECG

ECG measurements include ventricular rate, QT interval, RR interval, PR interval, QRS duration, and Fridericia's QTc (calculated as QTcF = QT / 3√ RR(in seconds), where 3√ denotes the cube root).

ECG data measured more than 7 days after last dose of study treatment are regarded as post treatment data and will not be summarized. All data will be included in the analyses regardless of rescue medication use. All data will be listed.

- The number and percentage of patients with newly occurring or worsening notable QTcF values (see Section 5.5 for definition of notable values) summarized by cohort at any time on treatment considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits

The same approach as for notable laboratory values will be used to define a newly occurring notable QTc value and a worsening notable QTc value.

2.6.1.4 Vital signs

Vital signs measurements include body temperature, systolic and diastolic blood pressure (SBP and DBP) and pulse rate.

Vital signs data measured more than 7 days after last dose of study treatment are regarded as post-treatment data and will not be summarized. All data will be included in the analyses regardless of rescue medication use. All data will be listed.

The number and percentage of patients with newly occurring or worsening notable vital signs values (see Section 5.5 for definition of notable values) summarized by cohort, parameter at any time on treatment considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits

The same approach as for notable laboratory values will be used to define a newly occurring notable vital sign value and a worsening notable vital sign value.

2.6.2 Pharmacokinetic endpoints

Other pharmacokinetic variables of Fevipiprant at steady state

The pharmacokinetic variables Tmax,ss, Cmin,ss, (CL/F)/kg, CLr, amount and fraction of dose excreted over the PK collection interval of QAW039 at steady state will be secondary variables. All pharmacokinetic variables will be summarized similarly as mentioned for primary variable (Section 2.5).

Summary statistics for plasma and urine concentrations will be provided for cohort A by time point (only 1 time interval for urine). If any concentration value will be set to be zero for any time-point then Geo-mean, CV% geo-mean will not be presented for that time point.

Metabolite CCN362 at steady state

Cmax,ss, Tmax,ss, AUC0-24h,ss, Cmin,ss, CLr, amount of dose excreted over the PK collection interval at steady state of CCN362, the major metabolite of fevipiprant will be summarized similarly as mentioned for primary variable (Section 2.5).

Summary statistics for plasma and urine concentrations of analyte CCN362 will be provided for Cohort A by time point (only 1 time interval for urine). If any concentration value will be set to be zero for any time-point then Geo-mean, CV% geo-mean will not be presented for that time point.

2.7 Interim analysis

A planned interim analysis will be conducted to support decision making when 6 subjects (3 subjects from each of the 2 age strata) receiving 75 mg dose complete the treatment. The interim analysis will be performed based on preliminary PK data e.g. protocol times can be used to calculate PK parameters. At interim analysis, based on PK data from the 75 mg dose level the high dose will be chosen.

For detailed information, please refer to Section 3.

3 Sample size calculation

Sample size is guided by statistical precision and requirements for pharmacokinetic data from pediatric subjects for inclusion in population PK modelling. Based on exploratory optimal design evaluation using modeling and simulation techniques, at least 12 subjects is expected to be sufficient for a pooled population PK analysis which is planned to be used to support dose selection for pediatric phase III studies. Since adult data on fevipiprant does not show a clinically relevant deviation from dose proportionality, data from the low and high dose cohort are equally valuable to inform the population PK model . Drop-outs and non-completers will be replaced.

At first stage it is required to have PK data from 6 subjects receiving 75 mg dose to assess safety, as well as mean and variability of PK data to enable at the second stage to have the right dose and number of subjects. Moreover, data from 6 subjects will provide ~80% probability for acceptable precision in calculating the geometric mean. More specifically, the inclusion of 6 subjects would result in the 95% confidence interval (CI) of the geometric mean of QAW039 AUC0-24h,ss being in the range of (68%U, 147%U). U is the observed geometric mean, assuming a coefficient of variation of 31% based on data from previous study (QAW039A2111 study). This level of precision balances needs for reliable parameter estimation and clinical feasibility and is in agreement with guidance provided by health authorities. (General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, FDA).

An interim analysis will be conducted when 6 subjects (3 subjects from each of two age strata) receiving the 75 mg dose will complete the treatment and provide the planned PK samples. At interim analysis, the following outcomes are foreseen based on AUC0-24h,ss:

In terms of exposure i.e. mean AUC0-24h,ss:

1) If mean AUC0-24h,ss is as expected, i.e. comparable to 150 mg dose in adult/adolescents, then 225 mg dose will be used in high dose cohort. .

2) If mean AUC0-24h,ss is relevantly more than expected while comparing with exposure of 150 mg dose in adult/adolescents, dose lower than 225 mg e.g. 150 mg dose will be used in high dose cohort.

3) If mean AUC0-24h,ss is relevantly less than expected while comparing with exposure of 150 mg dose in adult/adolescents, dose higher than 225 mg e.g. 300 mg or 375 mg dose will be used in high dose cohort.

In terms of variability i.e. coefficient of variation (CV%) of AUC0-24h,ss:

1) If CV% of AUC0-24h,ss is less than or equal to 31% at interim, then 6 subjects will be recruited for the second cohort so that total number of subjects completing treatment is 12.

2) If CV% of AUC0-24h,ss is more than 31% at interim analysis, more than 6 subjects will be recruited at the high dose level to provide ~80% probability for acceptable precision in calculating the geometric mean, more specifically to have the 95% confidence intervals (CI) of geometric means of QAW039 AUC0-24h,ss approximately within the range of (68%U, 147%U), where U is the observed geometric mean. The number of subjects on higher dose will be based on observed CV% at interim analysis.

The following table provides the range in which 95% CIs will fall with 80% probability in terms of percentage of observed geometric-mean, at different sample and different observed CV% at interim:

N (sample size)	Observed CV % at interim									
	35%	**40%**	**45%**	**50%**	**55%**	**60%**	**65%**	**70%**	**75%**	**80%**
7	**69%-146%**	65%-153%	62%-161%	59%-168%	57%-176%	54%-185%	52%-193%	50%-201%	48%-209%	46%-217%
8	71%-140%	**68%-146%**	65%-153%	63%-160%	60%-166%	58%-173%	56%-180%	54%-187%	52%-194%	50%-201%
9	74%-136%	71%-142%	**68%-147%**	65%-153%	63%-159%	61%-165%	59%-171%	57%-177%	55%-183%	53%-189%
10	75%-133%	73%-138%	70%-143%	67%-148%	65%-154%	63%-159%	61%-164%	59%-169%	57%-175%	56%-180%
11	77%-130%	74%-135%	72%-140%	**69%-144%**	67%-149%	65%-154%	63%-159%	61%-163%	59%-168%	58%-173%
12	78%-128%	75%-133%	73%-137%	71%-141%	**69%-146%**	67%-150%	65%-154%	63%-159%	61%-163%	60%-167%
13	79%-127%	77%-131%	74%-135%	72%-139%	70%-143%	**68%-147%**	66%-151%	65%-155%	63%-159%	61%-163%
14	80%-125%	78%-129%	75%-133%	73%-137%	71%-140%	69%-144%	68%-148%	66%-152%	64%-155%	63%-159%
15	81%-124%	78%-128%	76%-131%	74%-135%	72%-138%	70%-142%	**69%-145%**	67%-149%	66%-152%	64%-156%
16	81%-123%	79%-126%	77%-130%	75%-133%	73%-136%	71%-140%	70%-143%	**68%-147%**	67%-150%	65%-153%
17	82%-122%	80%-125%	78%-128%	76%-132%	74%-135%	72%-138%	71%-141%	69%-144%	**68%-147%**	66%-151%
18	83%-121%	81%-124%	79%-127%	77%-130%	75%-133%	73%-136%	72%-140%	70%-142%	69%-145%	**67%-148%**

For example, if we observe a CV% of 55% in the interim data, then 12 subjects are required to complete treatment with the high dose and to provide the planned PK samples to give ~80% probability for the 95% confidence intervals (CI) of geometric means of QAW039 AUC0-

24h,ss to fall approximately within the range of (68%U, 147%U). The sample size for the high dose can vary from 6 to 18 subjects, so that total number of subjects completing treatment (75 mg or high dose) and providing planned PK samples is maximum of 24. For example, if we observe a CV% of 80% in the interim data, then 18 subjects will be recruited at the high dose to provide the planned PK samples, though the 95% CI of geometric means of QAW039 AUC0-24h,ss will fall outside the range of (68%U, 147%U).

4 Change to protocol specified analyses

This statistical analysis plan is an abbreviated approach of presenting the limited data collected in the study and does not reflect the full analysis scope described in Section 12 of the study protocol (Version 01, Amendment 1 to original protocol released on 13-Feb-2019).
The following changes to the protocol specified analyses will be done:

- Definition of treatment emergent for safety adjusted: treatment end + 1 day will be replaced by treatment end date + 7 days for laboratory, vital signs, ECG and AEs, and to + 30 days for SAEs, to follow standard of QAW program.

5 Appendix

This appendix gives details about statistical methods in addition to the report text. All analyses will be performed by the most recent version of SAS available in the statistical programming environment.

5.1 Imputation rules

5.1.1 Study treatment

Missing/partial start date or end date of study treatment will not be imputed.

5.1.2 AE date imputation

Rules for imputing AE end date or start date will be provided in Programming Dataset Specification (PDS) document in details.

5.1.3 Concomitant medication date imputation

Rules for imputing the CM end date or start date will be provided in Programming Dataset Specification (PDS) document in details.

5.2 AEs coding/grading

The MedDRA version which will be available at the time of database lock, will be used for the coding purpose of the adverse events.

5.3 Data pooling and assessment windows

Data from unplanned or unscheduled visits or the early treatment/study discontinuation visits will be listed, as appropriate. For patients who do not complete the study treatment, the treatment discontinuation visit will be an unscheduled visit.

Clinical laboratory measurements, vital signs and ECG data from unplanned or unscheduled visits will only be included in the summaries of the notable values. All efficacy data from these visits will not be used for missing data imputation unless specified otherwise.

Laboratory, vital signs, and ECG values that have complete date and time values will be slotted into pre- or post-dose assessment based on the actual date/time. For values with missing date/time, scheduled visit date and time will be used. This rule will be applied to data from scheduled visits only. If a measurement scheduled as pre-dose is actually performed post-dose, or vice versa, the data will not be used for by time point assessments.

5.4 Laboratory parameters – definition of clinically notable values

The following table shows the criteria for clinically notable laboratory values. Not all parameters have notable criteria defined.

Laboratory parameter (unit)	Bound for notably low values	Bound for notably high values
Hematology		
Hematocrit (v/v) Male 6-12 Female 6-12	 0.31 0.31	
Hemoglobin (g/L) Male 6-12 Female 6-12	 97 92	
Thrombocytes (x10E9/L)	75	500
WBC's (x10E9/L)	2.8	16.0
Chemistry		
Alkaline Phosphatase (IU/L)	-	3xULN
Total Bilirubin (µmol/L)	-	34.2
Creatinine (µmol/L)		105
Potassium (mmol/L)	3	6
Glucose (mmol/L)	2.78	9.99
ALT/SGPT (U/L)	-	3 x ULN
AST/SGOT (U/L)	-	3 x ULN
BUN/ Urea (mmol/L)		9.99
Sodium (mmol/L)	125	160
Gamma GT (U/L)		3 x ULN
v = volume, ULN = upper limit of normal		

5.5 Vital signs and ECG – definition of clinically notable values

The following table shows the clinical notable criteria for vital signs.

Vital sign parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range
Notable value considering newly occurring or worsening cases		
Systolic blood pressure (mmHg)	< 80 (all)	> 150 (all)
Diastolic blood pressure (mmHg)	< 45 (all)	> 105 (all)
Pulse rate (bpm)	< 50 (all)	> 150 (6-8), >130 (9-12)
Notable change from baseline		
Systolic blood pressure (mmHg)	≤ 90 and decrease from baseline by ≥ 15	≥ 140 and increase from baseline by ≥ 15
Diastolic blood pressure (mmHg)	≤ 55 and decrease from baseline by ≥ 15	≥ 95 and increase from baseline by ≥ 15
Pulse rate (bpm)	≤ 60 and decrease from baseline by ≥ 15	≥ 140 and increase from baseline by ≥ 15 (6-8) ≥ 120 and increase from baseline by ≥ 15 (9-12)

The following table shows the clinical notable criteria for QTcF.

ECG parameter (unit)	Clinically notable range
Notable value criterion for newly occurring or worsening cases	
QTc (msec)	> 450 msec for males and females
QTc (msec)	> 500 msec for males and females
Notable change from baseline	
QTc	30 – 60 msec
QTc	> 60 msec

5.6 Statistical methodology and assumptions

Not applicable as no inferential analyses will be conducted.

5.7 Rule of exclusion criteria of analysis sets

The following table provides the protocol deviations (PD) and other criteria leading to partial or complete exclusion from analyses sets

Deviation ID	Description of Deviation
Deviations leading to exclusion from all analyses sets	
INCL02A	Subject entered the study without the parent/legal guardian signing the informed consent
INCL02B	Subject entered the study without signing the assent where local law requires assent
Deviations leading to exclusion from PK analysis set	
TRT01	Subject did not receive a total of at least four consecutive, daily doses of study drug

6 Reference

General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, FDA