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Novartis Research and Development

QAW039

Clinical Trial Protocol 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

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List of abbreviations

AD	atopic dermatitis
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC0-24	area under the drug concentration-time curve from 0 to 24 hours
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CFR	Code of Federal Regulation
CI	confidence interval
CL/F	oral clearance
CLr	renal clearance
Cmax	maximum plasma concentration
Cmin	minimum plasma concentration
CMO&PS	Chief Medical Office and Patient Safety
CO	country organization
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRTh2	Chemoattractant Receptor-homologous molecule expressed on Th2 cells (also called DP2)
CSR	Clinical Study Report
CT	chewable tablet
CTT	Clinical Trial Team
CV	coefficient of variation
DAR	drug administration record
DBP	diastolic blood pressure
DDE	direct data entry
DP2	Prostaglandin D2 receptor 2 (also called CRTh2)
EC	Ethics committee
ECG	Electrocardiogram
eCRFs	Electronic Case Report Forms
EDC	Electronic Data Capture
EOT	end of treatment
EPR-3	Expert Panel Report 3
eSource	electronic source
EU	European Union
FCT	film-coated tablet
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl-transferase
GINA	Global Initiative for Asthma
h	hour
IA	Interim Analysis

IB	Investigator's Brochure
ICF	Inform Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
IL	Interleukin
ILC2	Type 2 innate lymphoid cells
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine System
LABA	Long-acting β-agonists
LAMA	Long-acting muscarinic antagonists
LLOQ	lower limit of quantification
LTRAs	Leukotriene receptor-antagonists
MedDRA	Medical Dictionary for Regulatory Activities
NORA®	Network Oriented Research Assistant
o.d.	once a day
PGD2	Prostaglandin D_2
PIP	pediatric investigation plan
PK	pharmacokinetic(s)
PopPK	A population pharmacokinetics
PT/INR	Prothrombin ratio and international normalized
QMS	Quality Management System
QTc	QT interval
QTcF	Fridericia QT correction formula
RDC	Remote Data Capture
RoW	rest of world
SABAs	Short-acting β-agonists
SAEs	serious adverse event(s)
SAMA	Short-acting-muscarinic-antagonists
SBP	systolic blood pressure
SD	Standard Deviation
SoC	standard-of-care
ss	steady state
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
TD	treatment discontinuation
Th2	Type 2 helper T cells
Tmax	time of maximum plasma concentration
VS	vital signs
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
End of Treatment	A visit that may occur after 3 consecutive days of dosing in subjects where study drug compliance is a concern
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study.
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”.
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

Withdrawal of study consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

Amendment 1

[redacted]

Changes to the protocol

The described changes in the aforementioned amendment rationale are implemented throughout the protocol in the sections noted.

The opportunity was also taken to:

- Updated Section 2 Objectives and endpoints to clarify that steady state could be achieved after four days of consecutive dosing.
- Updated Section 3 Study design to include the addition of a light breakfast about 30 minutes prior to dosing during the clinic/home visit; confirmation light breakfast was given; Figure 3-1 clarified treatment period day 1 to steady state.
- Clarified process on how the chewable tablet should be administered in the following order: banana/yogurt, chewable tablet, followed by banana/yogurt
- Clarified end of treatment visit may occur from Day 4 to 8, after 3 consecutive days of dosing have been confirmed
- Added additional guidance around the time of dosing for the End of Treatment (EOT) Visit
- Updated Section 4.2 Rationale for dose/regimen and duration of treatment based on previous trial data,
- clarified preliminary food effect assessment was conducted using capsules;
- removed reference sentence no major effect of food on fevipiprant pharmacokinetic(s) (PK) is expected, dosing in this study can happen independent of meals;
- added a light breakfast should be provided on all study days
- Updated Section 5 Population to include flexible window in regards to EOT Visit
- Updated Section 5.2 Exclusion criteria to include exclusionary criteria which states "subject is unable to ingest banana and/or yogurt".
- Updated Section 6.1.4 Treatment duration due to the EOT Visit being able to occur on Day 4 to 8.
- Updated Section 6.2.2 , Table 6-3 prohibited medications to include cyclosporine and modified omalizumab language to be consistent with phase 3 clinical trials
- Updated Section 6.3.2Treatment assignment, randomization, added language for remote visit enrollment
- Updated Section 6.7.2 Instructions for prescribing and taking study treatment

- Updated Section 8 Visit schedule and assessments based on changes to treatment duration and steady state occurring after four consecutive days of dosing
- Updated Table 8-1 to include footnote referencing a light breakfast and remote visits
- Updated Section 8.1.1, removed collecting AEs for screen failures; added AEs that are not SAEs will be collected in source data
- Updated Section 12.3 Treatment based on steady state being achieved after four consecutive days of dosing
- Updated Section 12.4.2 Statistical model, hypothesis, and method of analysis due to EOT Visit occurring on Day 4 to 8
- Updated Section 12.5.2 clarified Pharmacokinetics based on steady state
- Updated Section 12.7.1 Primary endpoint(s), updated in terms of exposure i.e. mean AUC0-24h,ss dose lower/higher than 225 mg
- Updated Section 3, Section 6.3.2, Section 8 to allow flexibility for optional remote home visits
- Updated Table 16-3, revised footnotes to define EOT and last dose
- Updated Table 16-4, included footnote referencing treatment timing

IRB Section

A copy of this amended protocol will be sent to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval, a revised Informed Consent that takes into account the changes described in this protocol amendment.

Protocol summary

Protocol number	CQAW039B2201
Full Title	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
Brief title	Pharmacokinetics, safety and tolerability of fevipiprant delivered via a once daily chewable tablet in children aged 6 to < 12 years with asthma
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Fevipiprant Chewable Tablet (CT)
Study type	Interventional
Purpose and rationale	The purpose of this study is to assess the pharmacokinetics (PK) of fevipiprant (QAW039) delivered as a chewable tablet (CT) in pediatric asthma subjects aged 6 to < 12 years. The results of this study will support the identification of a fevipiprant dose for subsequent pediatric efficacy studies aiming to provide an exposure similar to that of the to-be marketed adult/adolescent dose. In addition, the first data on safety and tolerability of fevipiprant in this age group will be obtained.
Primary Objective(s)	To determine the key pharmacokinetic parameters of fevipiprant at steady state (ss), after at least four consecutive days of dosing))
Secondary Objectives	Objective 1: To evaluate additional pharmacokinetic parameters of fevipiprant at steady state Objective 2: To evaluate the pharmacokinetics of CCN362, the major metabolite of fevipiprant at steady state Objective 3: To evaluate the urinary excretion of fevipiprant and CCN362 at steady state Objective 4: To evaluate the safety and tolerability of fevipiprant over treatment period
Study design	This is a multicenter, open-label, study to assess the pharmacokinetics, safety, and tolerability of fevipiprant CT in children aged 6 to < 12 years with asthma. The study includes a 4-8 day, open-label treatment period in which subjects receive fevipiprant CT once daily in addition to their rescue medication (e.g. short-acting β-agonists [SABAs]) and 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 once daily 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.
Population	At least 12 but not more than 24 male or female children. 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.
Key Inclusion criteria	1. Male and female children ≥ 6 years and <12 years 2. Written informed consent by parent(s)/legal guardian(s) for the pediatric patient and assent by the pediatric patient (depending on local requirements) must be obtained before any study-specific assessment is performed. 3. Confirmed/documented diagnosis of asthma, as defined by national or international asthma guidelines for at least 6 months prior to study enrollment. 4. Subjects using asthma rescue medication (e.g. SABA) without asthma controller therapy or subjects receiving daily treatment with a stable dose ICS (with or without additional controller such as long-acting β-agonists [LABA], long-acting muscarinic antagonists [LAMA]) for at least 4 weeks prior to Treatment visit (Day 1). 5. Subjects must be able to attend study visits as per Study Visit Assessment Schedule (Section 8) which includes 8 to 9 hours in the clinic/home on the day of End of Treatment Visit and have blood draws as scheduled in the study.

	6. Parents/ legal guardian must be willing and able to attend study visits and assist the child with the procedures outlined in the protocol (e.g. compliance with taking study medication and completing the diary).
Key Exclusion criteria	1. Use of other investigational drugs within 5 half-lives of enrollment, or [within 30 days (for small molecules) /until the expected pharmacodynamic effect has returned to baseline (for biologics)], whichever is longer. 2. Subject is unable to ingest banana and/or yogurt. 3. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes. 4. History of chronic lung disease other than asthma such as and not limited to, sarcoidosis interstitial lung disease, cystic fibrosis, mycobacterial or other infection (including active tuberculosis or atypical mycobacterial disease). 5. History of active bacterial, viral or fungal infection within 6 weeks of Treatment Visit (Day 1). 6. Subjects who, in the opinion of the investigator, are not able to be compliant with study treatment or who have any medical or mental disorder, situation, or diagnosis which could interfere with the proper completion of the protocol requirements or risk the subject's safety while participating in the study.
Study treatment	Fevipiprant 75 mg CT Fevipiprant 150, 225, 300 or 375 mg CT or at a different dose
Efficacy assessments	Not applicable
Pharmacokinetic assessments	Blood and urine collection at steady state to determine PK parameters of fevipiprant and its major metabolite CCN362
Key safety assessments	• Medical history and physical examination including oropharyngeal examination • Vital signs • Hematology, blood chemistry, urine dipsticks • Electrocardiogram (ECG) • Adverse events (AEs) including asthma exacerbations, worsening asthma, and serious adverse events (SAEs)
Data analysis	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 PK data. PK parameters will be analyzed by standard non-compartmental analysis and summarized by cohort through descriptive summary statistics (including mean, SD, CV% mean, Geometric mean, CV% geometric mean, median, minimum and maximum). Additionally, CL/F will also be summarized across cohorts.
Key words	Fevipiprant, GINA 2018, Pediatrics

1 Introduction

1.1 Background

Asthma is affecting approximately 300 million people of all ages worldwide. Dramatic increases in the prevalence of asthma have occurred over the past two decades in Westernized countries (Fanta 2009, Wilson et al 2006) and more recently in less-developed nations (Pearce et al 2007, Fanta 2009). Asthma is a common childhood chronic disease (Bastain et al 2011) and its prevalence has increased especially among children over the past 20 years (GINA 2018). Asthma currently affects nearly 6 million or 8.8% of all children less than 15 years of age in the United States (Ward et al 2015), with data showing that the incidence and prevalence of asthma is increasing more rapidly in children than that in adults, particularly in children under 15 years (Masoli et al 2004). Although the exact prevalence of severe asthma in children is unknown, it tends to be rare in the setting of good medication access and compliance and likely affects less than 5% (or approximately 300,000) of all asthmatic children in the US (Coverstone et al 2015).

Although most children with asthma (i.e., up to 95%) derive clinical benefit from daily administration of low-to-medium-dose inhaled corticosteroid (ICS) therapy, (National Asthma Education and Prevention Panel. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007) nearly half of these children experience at least 1 episode of poor asthma control per year despite the prescription of asthma controller therapy (Ward et al 2015).

Consequently, there remains an unmet need for well tolerated, easily administered, cost-effective anti-inflammatory therapies with the capability to improve the asthma control by reducing asthma exacerbations, particularly for those children with severe asthma who appear to be at greatest risk for recurrent asthma exacerbations.

Novartis is developing fevipiprant which is a selective, orally-administered, reversible, competitive antagonist at the prostaglandin D2 receptor 2 (also called CRTh2 or DP_2) with no affinity for the DP receptor, which also blocks prostaglandin (PGD_2)-mediated eosinophil activation in whole blood as well as release of Interleukin (IL)-5 and IL-13 cytokines from type 2 helper T cells (Th2) (Sykes et al 2016). Blockade of the actions of PGD_2 and its DP_2 active metabolites acting at the DP_2 receptor on these cell types, together with type 2 innate lymphoid cells (ILC2) (Xue et al 2014), will enable suppression of the key inflammatory pathways in asthma and is expected to reduce disease progression.

Although there are no published data on DP_2 antagonist's efficacy in pediatric populations below the age of 12, fevipiprant has the potential to be of significant benefit over therapeutic alternatives based on clinical data to date in the adult population.

The pediatric development in children will be initiated by conducting this Phase II study (B2201) investigating the pharmacokinetics (PK), safety and tolerability of fevipiprant in 6 to less the 12 year old children with asthma. The expression of DP_2 across a broad age range was assessed in study [CQAW039B2104] to complement the information about the pharmacokinetics for the dose selection in this age group. Fevipiprant is cleared via glucuronidation by several uridine diphosphate glucuronosyltransferases as well as renal excretion and possibly biliary excretion. Only one major metabolite is formed: the acyl

glucuronide CCN362, which is not pharmacologically active. It is generally assumed that most drug clearance pathways are mature in children 2 years and older (Holford et al 2013). Since a number of enzymes and transporters contribute to the clearance of fevipiprant, a strong sensitivity of PK to any specific slowly maturing clearance pathway in children of 6 years and older is not expected for fevipiprant.

1.2 Purpose

The purpose of this study is to assess the pharmacokinetics (PK) of fevipiprant (QAW039) delivered as a chewable tablet (CT) in pediatric asthma subjects aged 6 to < 12 years. The results of this study will support the identification of a fevipiprant dose for subsequent pediatric efficacy studies aiming to provide an exposure similar to that of the to-be marketed adult/adolescent dose. In addition, the first data on safety and tolerability of fevipiprant in this age group will be obtained.

2 Objectives and endpoints

Table 2-1 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), after at least four consecutive days of dosing))	• Area under the curve (AUC0-24h,ss), maximum plasma concentration (Cmax,ss), and oral clearance (CL/F)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate additional pharmacokinetic parameters of fevipiprant at steady state	• Tmax,ss, Cmin,ss, (CL/F)/kg of fevipiprant
• 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 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, electrocardiogram (ECG), adverse events

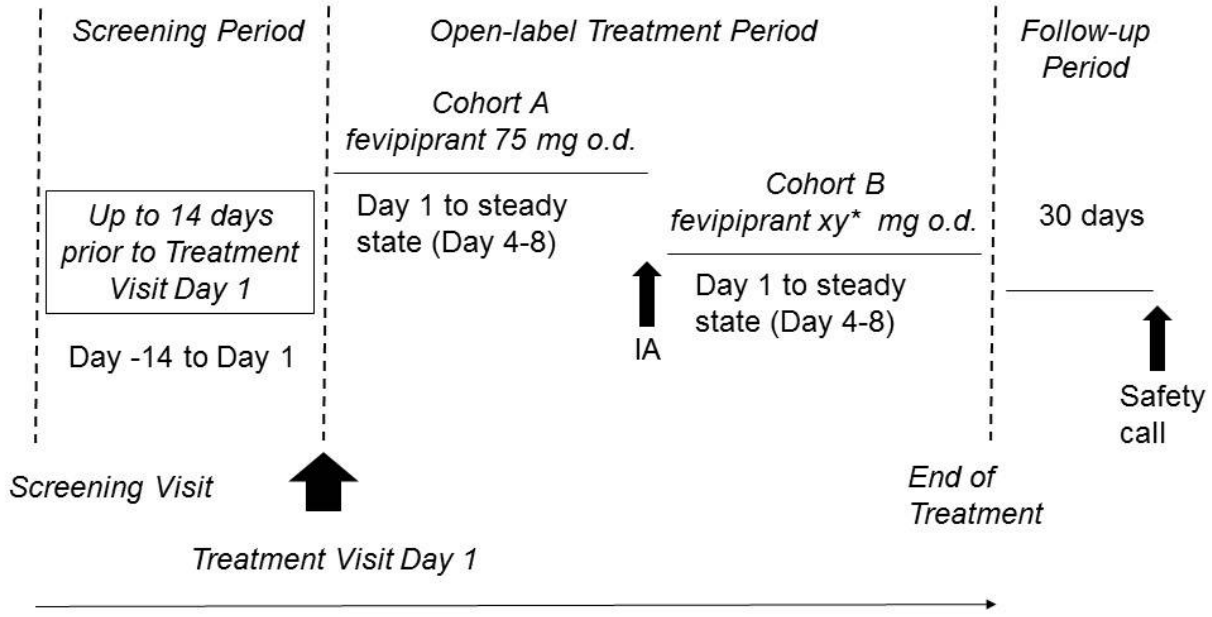
3 Study design

This is a multicenter, open-label, study to assess the pharmacokinetics, safety, and tolerability of fevipiprant CT in children aged 6 to < 12 years with asthma. The study includes a 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.

The study will include the following:

- A Screening period of up to 14 days;
- A Treatment period of 4-8 days for each dose cohort (8 days of treatment is preferred); and
- A Follow-up period of 30 days

Figure 3-1 Study Design



IA-interim analysis, o.d.-once daily

In Cohort (A), 6 subjects (3 subjects from each of the 2 age strata) will be dosed with fevipiprant 75 mg CT o.d. in the morning. After 6 subjects have completed the treatment period, an interim analysis (IA) will be performed. Exposure results and variability of the PK as measured by AUC0-24, steady state (ss) will be used to determine:

- *whether dosing in Cohort B will be at 225 mg CT o.d. or at a different dose (e.g. 150, 300 or 375 mg); and
- the number of subjects for Cohort B.

See Section 12.6 for the complete details of the IA.

This study may be conducted using the decentralized remote study model, using a telemedicine technology for interactions between the investigator/study staff and study subjects. Network Oriented Research Assistant, or NORA® is the software interface that connects participants to their investigators and study teams. Additionally, mobile study personnel will visit sumjects' homes to complete the designated study procedures, such as the collection of lab samples.

A description of the study by period follows below.

Screening Period (Screening to Treatment Visit)

Within 14 days prior to treatment visit or at Screening Visit, written informed consent from the parent(s)/legal guardian(s), and subject assent (if applicable), will be obtained before any study-related assessments or procedures are performed. The subject's participation in the trial must be documented in the subject's medical record and all study related evaluations performed at each visit must be clearly documented in source documentation and on electronic case report forms (eCRFs).

Study sites should check the interactive response technology (IRT) for subject age cohort availability before Screening Visit begins. If the subject qualifies, Screening Visit can proceed with the documentation of demographic data, the assessment of study inclusion/exclusion criteria, and past/current medical history. The subject can then be entered into the IRT system to continue screening.

Once IRT has confirmed subject participation, physical and laboratory assessments may be performed (Section 8.4). At this visit, subjects will be instructed to withhold any prohibited medication as applicable (Table 6-3) prior to Treatment Visit (Day 1). The window between Screening Visit and Treatment Visit Day 1 (Screening Period) is up to 14 days.

Throughout the study (from Screening Visit through Follow-up period), subjects will continue to receive their rescue medication (e.g. SABA) and potentially SoC asthma therapy which could be ICS with or without additional controller medication. Leukotriene receptor-antagonists (LTRAs) must be stopped at Screening Visit and in that case ICS should be initiated or up-titrated to the next higher dose as per investigator's judgement; this change of treatment should be allowed to stabilize during the 14 days Screening Period. LTRAs treatment can be continued after End of Treatment (EOT) as per investigators decision.

Rescue medication such as SABAs will not be provided in this study, but may be prescribed by the investigator and used as needed.

Treatment period Day 1 to Day 4-8 (Treatment Visit to End of Treatment Visit)

Eligible subjects meeting all inclusion and exclusion criteria will enter the 4-8-day Treatment Period of the respective cohort.

Treatment Visit (Day 1)

On Treatment Visit (Day 1), qualifying subjects should have scheduled visit in the morning. Prior to the performance of Treatment Visit (Day 1) clinical evaluations, the investigator will re-assess inclusion/exclusion criteria, adverse events (AEs) serious adverse events (SAEs), Screening Visit laboratory results and the ECG interpretation. If eligible to continue, subjects will have procedures performed as outlined in Table 8-1 , and entered into the IRT system to obtain treatment pack assignment. For remote visits IRT entry into the system will occur prior to home visit.

Subjects will then receive a witnessed dose of fevipiprant CT. Depending on the assigned cohort, the subjects will receive 1 or more CTs. A light breakfast (e.g. average sized serving of cereal, milk, banana, and/or yogurt) should be provided about 30 minutes prior to dosing during the clinic/remote visit. Subjects will be instructed to chew small piece of banana/yogurt followed immediately by CT(s) and then followed with an additional piece of banana/yogurt. Subjects will be encouraged to drink some water thereafter. Time of dosing and confirmation that a light breakfast was given will be recorded on the patient diary card. Subjects will remain in the clinic/remote visit for at least 2 hours for observation after the witnessed dose of fevipiprant. For remote visits the nurse will remain in the home for 2 hour observation.

At this visit, subjects and parent(s)/guardian(s) will be instructed to:

- Give a light breakfast about 30 minutes prior to administration of study drug at the approximate same time each morning of Treatment Day 2 through 1 day prior to EOT.
- CT(s) administration should be done in the following order: chew small piece of banana/yogurt followed immediately by CT(s) and then followed with an additional piece of banana/yogurt.

  Subjects will be encouraged to drink some water thereafter.
- Record the actual time of dosing and confirmation that a light breakfast was given on the patient diary card each day.
- Dosing 1 day prior to EOT should ideally happen approximately 23 h before the planned arrival at the clinic/remote visit on Day 4 to 8 (End of Treatment Visit).
- Withhold study drug the morning of EOT Visit. Study drug will be administered by study site staff/remote nurse in the clinic/home.

Prior to leaving the clinic/home, parent(s)/legal guardian(s) will be dispensed study drug for home administration during the Treatment Period, a study diary card to record time of dosing, and will make an appointment to return to the clinic on EOT Day.

End of Treatment Visit (Day 4 to 8)

The End of Treatment Visit can only occur after 3 consecutive days of dosing (i.e., as early as Day 4 of dosing).

At the EOT Visit Day, subjects should not take the study drug at home, and arrive at the site or planned remote visit in the morning. Study drug will be taken in the clinic/home, and PK

sampling will occur over 8 hours; the subject and parent/guardian will need to be available to remain in the clinic/home for about 8 to 9 hours.

The scheduling and timing of EOT Visit should ensure dosing of study drug in the clinic/home takes place about 24 ± 2 hours after the last dose of study drug taken at home. On the day prior to EOT, visit study personnel should remind the subject and parent/guardian in a phone call to take study medication at the right time in relation to the scheduled EOT visit. Additionally, PK sampling requires confirmation that study drug was taken for 3 consecutive days prior to EOT Visit. This information must be confirmed by study personnel/remote nurse at EOT Visit by the review of the subject's daily dosing diary. If study personnel/remote nurse cannot confirm that study drug was taken by the subject on 3 consecutive days prior to EOT Visit, the EOT Visit can be rescheduled for +1 to 2 days later. In cases where the subject cannot make the scheduled EOT Visit or has mistakenly taken the study drug at home on the Day of EOT Visit, the Visit can be re-scheduled to the next available clinic/home day.

At the start of the EOT Visit, eligibility to proceed with PK assessments will be confirmed and subjects will receive a light breakfast (e.g. average sized serving of cereal, milk, banana, and/or yogurt) at the study site about 30 minutes prior to dosing. Prior to dosing subjects should be encouraged to empty their bladder in the rest room (not collected for urine PK sampling, but can be used for urine dipstick) in order to get a clear pool of urine post dosing, used for urine PK sampling. Subjects will be administered the final dose of study drug by study staff within approximately 30 minutes after completion of breakfast. Subjects will be instructed to chew small piece of banana/yogurt followed immediately by CT(s) and then followed with an additional piece of banana/yogurt. Subjects will be encouraged to drink some water thereafter. The procedures associated with EOT Visit (including the placement of an indwelling catheter with local anesthetic for blood draws) will be performed in the clinic/home as outlined in Table 8-1 . Section 16.4 outlines the PK and vital sign (VS) timing of assessments noting that at time points where multiple procedures occur; the following order is recommended: VS, e.g. PK sampling, laboratory blood draws.

The time of dosing for witnessed dose of fevipiprant CT will be recorded in the eCRF. Throughout the visit, subjects should be encouraged to drink water in order to allow urine production for urine collection.

Blood for PK sampling may be drawn via intermittent venous punctures with topical anesthetic or via the placement of an indwelling catheter with local anesthetic. PK sampling will be obtained as close as feasible to planned times with the actual times of blood draws recorded in source and on the eCRF.

In addition to breakfast, subjects may have food during their time at the clinic/home, but it is recommended that they wait at least 3 hours after dosing to eat.

To avoid the need for an overnight stay at the clinical site, the pre-dose drug concentration values obtained on EOT Visit will also be used as the 24-hour post-dose drug concentration value to calculate AUC0-24,ss. For this reason it is important to have approximately 24 h between the last at home dose and the witnessed dose in the clinic at the EOT Visit.

Upon completion of all EOT Visit study assessments, at the investigator’s discretion, the subject may go home.

Follow-up Period (Phone call to Parent/Gurdian)

Following the treatment period or discontinuation (last dose of study drug), a follow-up period of 30 days, investigational drug free, will assess any safety-related adverse events.

4 Rationale

4.1 Rationale for study design

This is an open-label study with an 8 day preferred treatment period to assess pharmacokinetics and safety of 2 different doses levels of fevipiprant CT. The 2 dose cohorts (A and B) will be studied consecutively, to allow to assess low dose data before escalating to a higher dose level in this first study in children of 6 to < 12 years. After cohort A an interim analysis will decide the fevipiprant dose and number of subjects tested in cohort B. By this a sufficiently good definition of the primary pharmacokinetic endpoint and an adequate exposure in the high dose group is supported. As the primary objective of the study is a pharmacokinetic assessment, the open-label design is considered appropriate. A population pharmacokinetics (PopPK) modeling approach will be used to integrate data from this study with adult and adolescent PK data to support the pediatric Phase III dose selection. The PK sampling in this study (i.e. from pre-dose to 8 h post dose at steady state) is adequate to inform the PopPK model. This is the first fevipiprant study in this age range and final dose selection requires the data obtained in this study. Therefore, pediatric Phase III dose level may not be identical to one of the dose levels tested in this study. However, the flexility in selecting the high dose based on 75 mg/day data will allow an appropriate range to be covered.

4.1.1 Rationale for choice of background therapy

Subjects will continue to receive their rescue medication (e.g. SABA) and potentially SoC asthma therapy throughout the study (from Screening Visit through Follow-up period). Since the purpose of the study is to assess PK, safety and tolerability of fevipiprant CT there is no need to alter the background medication (with exemption of LTRAs which could potentially interfere with the PK analyses of fevipiprant).

4.2 Rationale for dose/regimen and duration of treatment

The ongoing Phase III program in asthma tests the dose levels of 150 and 450 mg/day once daily in adults and adolescents down to age 12. Dose levels for Phase III studies in subjects < 12 years of age are planned to be selected to provide systemic fevipiprant exposure similar to that of dose level finally selected for treatment of adults and adolescents (either 150 or 450 mg/day).

Since the adult dose of fevipiprant is once daily, a once daily regimen for fevipiprant will also be used in this initial trial to obtain pharmacokinetic exposure of fevipiprant in subjects aged 6 to <12 years. It is known that in adults, steady state exposure is reached within 4 days of once daily dosing with little (~ 1.3 fold) accumulation. Based on adult data a similar duration of dosing to obtain steady state information in subjects 6 to <12 years is also planned.

Pharmacokinetic sampling at steady state in 6 to <12 years old subjects can occur as early as 4 days after dosing as long as study personnel can confirm that study drug was taken by the subject

on 3 consecutive days prior to End of Treatment Visit. In order to introduce flexibility in the protocol a visit window is included, which allows the pharmacokinetic sampling at steady state to occur anywhere from 4-8 days after dosing. In case study personnel cannot confirm that study drug was taken by the subject on 3 consecutive days prior to EOT Visit (which can occur anywhere from Day 4-8), the EOT Visit can be rescheduled for +1 to 2 days later. In addition, this duration will allow the first and last doses of study medication requiring visits at the hospital/clinic to occur during the weekend or on a designated day in the week most convenient to the family.

Based on the current understanding of the dose-effect and dose-safety relationship, it is assumed that children aged 6 to < 12 years can be treated by 1 fixed dose level. The dose levels of 75 mg and potentially 225 mg selected for this study are expected to provide an exposure in children aged 6 to < 12 years which is comparable to the 150 mg and 450 mg dose levels in adults. The dose levels were derived by weight-based allometric scaling, also considering physiologically-based PK modeling results. The bioavailability of the CT used in this study relative to the film-coated tablet (FCT) used in adults and adolescents was assessed in adults and was close to one (~ 1.18). If the exposure at 75 mg/day is relevantly lower or higher than expected, the dose level in the high dose group will be adjusted accordingly considering available dose strength of CTs (e.g. to 150 mg (2*75 mg) or 300 mg (225 + 75 mg)).

In a preliminary food effect assessment with capsules, food had no clinically relevant impact on the PK of fevipiprant: a delay in median Tmax from 2 to 2.5 h was observed with a high fat meal and based on the point estimate Cmax was 7% reduced. Fevipiprant is dosed independent of meals in Phase III studies in asthma. Although no major effect of food on fevipriprant PK is expected, a light breakfast should be provided before dosing on all study days to standardize food effects across the study population and, hence, minimize any potential effect of meal conditions on PK variability as well as to support the well-being of children during blood collection.

Fevipiprant has a good safety profile in populations studied to date at total daily doses up to 500 mg/day given for durations of up to 12 weeks and at doses of 1800 mg/day administered for a duration of up to 1 week; the maximal tolerated dose of fevipiprant in humans has not been identified thus far.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

The study does not include a placebo control as this would not be considered ethical in this population of pediatric asthma subjects and is not required to support the primary pharmacokinetic endpoint.

4.4 Purpose and timing of interim analyses/design adaptations

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 12.7. Once PK data from 6 children are available, an interim analysis will be performed using non-compartmental methods and based on protocol times (e.g. preliminary PK data).

Additional interim analysis may be conducted when at least 6 subjects on high dose will complete the treatment (in case where sample size on high dose is adjusted to be more than 6 after first interim analysis) and the sample size of high dose can be refined based on emerging PK data.

The flexibility to adapt the sample size and dose of the high dose cohort based on mean and variability of PK data at the low dose will ensure that the primary endpoint of this study is met supporting pediatric dose selection for Phase III. The Phase III dose selection will apply population PK methodology and combined analysis with PK data from other age strata. The non-compartmental analysis performed in this study is considered adequate to ensure sufficiently good definition of key PK properties to inform the population PK model.

4.5 Risks and benefits

Fevipiprant is a potent and highly selective oral DP_2 (also referred to as CRTh2) receptor antagonist being developed as a potential therapy treatment for subjects with severe asthma. DP_2 is a receptor for PGD_2 which mediates the activation and migration of Th2 cells and eosinophils, some of the key inflammatory cell types in asthma. Recruitment of these cells into the lung is partly responsible for the intermittent airway obstruction which leads to wheezing and shortness of breath characteristic of asthma.

Fevipiprant is at least 300-fold selective for the DP_2 receptor compared to other available prostanoid receptors and to cyclooxygenase-1 and cyclooxygenase-2, and it has been demonstrated to be a potent *in vitro* inhibitor of human whole blood eosinophil activation and induction of Th2 cytokines. After oral dosing in rats, QAW039 inhibited pulmonary eosinophilia induced by the PGD_2 metabolite DK-PGD_2.

The potential benefits of QAW039 therapy need to be balanced against its potential risks. The risk to subjects in this study will be minimized by compliance with the inclusion/exclusion criteria and close clinical monitoring. All subjects will remain on the background SoC asthma therapy they were taking at screening throughout the study, with exemption of LTRAs (LTRAs have to be stopped but in that case ICS can be initiated or dosed higher in case the subject was already on ICS). Furthermore, subjects will be instructed how to react to worsening of asthma symptoms so subjects can be managed appropriately.

Appropriate eligibility criteria and specific dose-limiting toxicity definitions, as well as specific dose modification and stopping rules, are included in this protocol.

All assessments in this trial are relatively small and part of regular medical assessments in this subject population. Procedural risks are related to blood sampling for safety and PK labratory analyses: puncturing of the veins can cause discomfort, pain, hematoma or in rare cases lead to an infection.

The overall clinical experience with fevipiprant includes 24 studies: 15 (nine in healthy volunteers and six in patients) have completed and nine (five in asthma subjects, 2 in healthy volunteers and 2 in subjects with renal or hepatic impairment) are ongoing. The completed Phase II studies consist of four in subjects with asthma, one in subjects with allergic rhinitis and

one in subjects with atopic dermatitis (AD). Five Phase III studies ([CQAW039A2307], [CQAW039A2314], [CQAW039A2315], [CQAW039A2316] and [CQAW039A2317]) in asthma and four Phase I studies in healthy volunteers ([CQAW039A2114] and [CQAW039A2120] </intref>) and subjects with renal or hepatic impairment ([CQAW039A2107] and [CQAW039A2108]) are ongoing. For detailed information on the 15 completed studies, please refer to Section 5 and Section 5.2.1.2 of the [Investigator's Brochure (IB)].

As of January 2018, over 2830 subjects have been exposed to fevipiprant in the clinical program. In the completed and ongoing studies of fevipiprant, approximately 2835 subjects (420 healthy volunteers and 2415 subjects with asthma, allergic rhinitis, or atopic dermatitis) received fevipiprant, approximately 1045 subjects received placebo, and approximately 420 received other treatments (rosuvastatin, simvastatin, montelukast, fluticasone, or probenecid). Fevipiprant has been well tolerated in populations studied to date at total daily doses up to 500 mg given for durations of up to 12 weeks and at a total daily dose up to 1800 mg for a duration of up to 1 week. In the four completed studies in the asthma program, 21 subjects reported 21 serious adverse events (SAEs), no deaths due to SAEs were reported, and seven discontinuations due to SAEs were reported. Of the 21 subjects reporting SAEs, 15 subjects reported 15 events, five subjects reported five events, and one subject reported one event in the fevipiprant, placebo, and montelukast treatment groups, respectively. In the one study completed in the atopic dermatitis program, five subjects (one on fevipiprant and four on placebo) experienced a total of 6 SAEs (one in the fevipiprant group in the follow-up period, and 5 in the placebo group with 3 of them occurring during the treatment period). There were no SAEs in either program (including fatal events) with a suspected causal relationship to fevipiprant. There have been no adverse events (AEs) of idiosyncratic drug reactions.

Overall, the safety profile of fevipiprant has been favorable across studies.

5 Population

- At least 12 but not more than 24 male and female children ≥6 years and <12 years diagnosed with asthma.
- Six subjects will be included in Cohort A and 6 to18 subjects in Cohort B.
- It is anticipated that 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 EOT (e.g. because they did not take study drug for 3 consecutive days prior to EOT Visit) will be replaced.

Subjects will be stratified approximately 1:1 ratio into 2 age groups; 6 to < 9 years and 9 to < 12 years to ensure approximately equal allocation of subjects throughout the whole age range being studied.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Male and female children ≥ 6 years and <12 years.
2. Written informed consent by parent(s)/legal guardian(s) for the pediatric patient and assent by the pediatric patient (depending on local requirements) must be obtained before any study-specific assessment is performed.
3. Confirmed/documented diagnosis of asthma, as defined by national or international asthma guidelines for at least 6 months prior to study enrollment.
4. Subjects using asthma rescue medication (e.g. SABA) without asthma controller therapy or patients receiving daily treatment with a stable dose ICS (with or without additional controller such as long-acting β-agonists (LABA), long-acting muscarinic antagonists (LAMA)) for at least 4 weeks prior to Treatment Visit (Day 1).
5. Subjects must be able to attend study visits as per Study Visit Assessment Schedule (Section 8) which includes 8 to 9 hours in the clinic/home on the day of End of Treatment Visit and have blood draws as scheduled in the study.
6. Parents/legal guardian must be willing and able to attend study visits and assist the child with the procedures outlined in the protocol (e.g. compliance with taking study medication and completing the diary).

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

1. Use of other investigational drugs within 5 half-lives of enrollment, or (within 30 days (for small molecules)/until the expected pharmacodynamic effect has returned to baseline (for biologics)), whichever is longer.
2. Subject is unable to ingest banana and/or yogurt
3. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes.
4. History of chronic lung disease other than asthma such as and not limited to, sarcoidosis interstitial lung disease, cystic fibrosis, mycobacterial or other infection (including active tuberculosis or atypical mycobacterial disease).
5. History of active bacterial, viral or fungal infection within 6 weeks of Treatment Visit (Day 1).
6. Subjects who, in the opinion of the investigator, are not able to be compliant with study treatment or who have any medical or mental disorder, situation, or diagnosis, which could interfere with the proper completion of the protocol requirements or risk the subject's safety while participating in the study.
7. Parent/guardian who, in the opinion of the investigator, has a history of psychiatric disease, intellectual deficiency, substance abuse, or other condition (e.g. inability to read, comprehend and write) which will limit the validity of consent for their child to participate in this study.
8. Hemoglobin levels outside normal ranges at screening.
9. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study.

10. Subjects who have a clinically significant ECG abnormality or clinically significant abnormal lab values reported at Screening Visit.
11. Subjects with a history of long QT syndrome or whose corrected QT interval (QTc) measured at Screening Visit (Fridericia method) is prolonged (≥ 450 msec for boys and girls).
12. Subjects receiving any medications in the classes specified in Table 6-3 unless they undergo the required washout period prior to Treatment Visit (Day 1) and follow the adjustment through the treatment period.
13. Subjects receiving medications in the classes listed in Table 6-2 should be excluded unless the medication has been stabilized for the specified period and the stated conditions have been met.
14. History of malignancy of any organ system, treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
15. Subject is an immediate family member of the participating investigator, sub-investigator, study coordinator, or employee of the participating investigator.
16. History or presence of impaired renal function as indicated by clinically significantly abnormal creatinine or blood urea nitrogen (BUN) and/or urea values, or abnormal urinary constituents (e.g. albuminuria) according to investigator's judgement.
17. Pregnant or nursing (lactating) females (Section 8.4.3).

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

All eligible subjects will be assigned to the investigational drug at Treatment (Day 1).

Table 6-1 Fevipiprant (QAW039)

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration		Sponsor (global or local)
Fevipiprant 75/225 mg	Chewable tablet	Oral use	Open-label subject specific supply; bottles	Sponsor global

6.1.2 Additional study treatments

No additional treatment beyond investigational drug is included in this trial.

Subjects may continue to use asthma rescue medication and SoC asthma therapy as outlined in the inclusion criteria.

6.1.3 Treatment arms/group

All eligible subjects will be assigned to the investigational drug (Section 6.1.1) at Treatment (Day 1). Initially, subjects will be assigned fevipiprant 75 mg. Each cohort will be stratified into 2 age groups: ages 6 to < 9 years and ages 9 to < 12 years. Depending on the outcome of the interim analysis (Section 12.6), a second group of subjects may be assigned fevipiprant 225 mg or fevipiprant 300 mg or fevipiprant 150 mg or fevipiprant 375 mg.

6.1.4 Treatment duration

The planned preferred treatment is 8 days, however an early end of treatment visit from Day 4-8 is permitted. Subjects may discontinue from treatment earlier, refer to Section 9.1.1 .

6.2 Other treatment(s)

Not applicable

6.2.1 Concomitant therapy

The medications are only permitted under the circumstances indicated. This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria.

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded in the concomitant medications/significant non-drug therapies or procedures pages.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before enrolling a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Table 6-2 Medications allowed under certain conditions

Class of medication	Condition under which medication is permitted
Topical Corticosteroids for treatment of eczema	Recommended doses and dosage regimens
Maintenance Immunotherapy for allergies	Stable dose for at least 3 months prior to Treatment (Day 1) and must continue unchanged for the duration of the study
Mucolytic agents not containing bronchodilators	If stabilized for at least 4 weeks prior to Treatment (Day 1) and throughout the trial.
Inactivated influenza vaccination, pneumococcal vaccination or any other inactivated vaccine	Not administered within 48 hours prior to a study visit
Nasal corticosteroids Nasal or ocular preparation of antihistamines	Treatment regimen has been stable for at least one month prior to Treatment (Day 1). In the case of as needed use, providing an established pattern of use must be documented prior to Treatment (Day 1).
Systemic mast cell stabilizers (e.g. cromoglycate, nedocromil, ketotifen)	If stabilized for at least 4 weeks prior to Treatment (Day 1) and throughout the trial.

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed after the start of the study treatment. Each concomitant drug must be individually assessed against all exclusion criteria and the table below to see if it is allowed. If in doubt, the investigator should contact the Novartis medical monitor or designee before enrolling a subject or allowing a new medication to be started. This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria.

Table 6-3 Prohibited medications

Class of medication	Minimum cessation period prior to Treatment (Day 1)
Leukotriene receptor-Antagonists (LTRAs)	LTRAs should be stopped at Screening Visit (14 days), and in that case ICS should be up-titrated/initiated as per investigator's judgement and stabilized during the screening period.
Cyclosporine	6 months
Monoclonal antibodies, investigational or approved, for the treatment of asthma (e.g., omalizumab)	5 months
Oral corticosteroids	1 month
Any drug known to prolong QT interval	14 days or 5 half-lives, whichever is longer
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Live attenuated vaccines	30 days
Rifampin, probenecid, ritonavir and valproic acid (i.e. medications blocking several pathways important for the elimination of QAW039 (broad range UGT inhibition and/or inhibition of OAT3, OATP1B3, MXR and P-gp))	7 days

6.2.3 Rescue medication

Rescue medication (SABA, short-acting-muscarinic-antagonists (SAMAs)), will not be provided during this study but can be used as needed.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available.

6.3.2 Treatment assignment, randomization

This study is a single-arm, non-randomized trial. For the purpose of the investigational drug accountability, tracking and age stratification, Interactive Response Technology (IRT) will be

used. All subjects will be stratified into 2 age groups: ages 6 to < 9 years and ages 9 to < 12 years.

The first 6 subjects enrolled will be stratified into 2 age groups; 6 to < 9 years and 9 to < 12 years. Safety data and available PK data from these subjects will be assessed prior to extending enrollment to Cohort B.

At Treatment (Day 1), the investigator or his/her delegate will contact the IRT after confirming that subject fulfills all the inclusion/exclusion criteria. For remote visits, study personnel will contact IRT prior to the remote home visit to have medication dispensed and administration of medication will not occur until after subject fulfills inclusion/exclusion criteria. The IRT will assign a unique medication number for the package(s) of study drug to be dispensed to the subject.

6.4 Treatment blinding

Treatment will be open to subjects, investigator staff, persons performing the assessments, and the Clinical Trial Team (CTT).

6.5 Dose escalation and dose modification

Not applicable

6.5.1 Dose modifications

Not applicable

6.5.2 Follow-up for toxicities

Not applicable

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Each subject will obtain a patient diary to record the time of dose intake during the Treatment period at home. Compliance will be assessed by the investigator and/or study personnel at EOT Visit using tablet counts, patient diary and information provided by the subject/legal guardian. This information should be captured in the source document at EOT Visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log. Pharmacokinetic parameters (measure of treatment exposure) will be determined in all subjects, as detailed in pharmacokintetis section.

6.6.2 Emergency breaking of assigned treatment code

Not applicable

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis country organization (CO) Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the subject except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

Not applicable

6.7.2 Instruction for prescribing and taking study treatment

Table 6-4 Dose and treatment schedule

QAW039 (Fevipiprant)	Dose	Frequency
QAW039 75 mg	75 mg	Daily (4-8 days)

QAW039 (Fevipiprant)	Dose	Frequency
QAW039 225 mg (or different dose 150, 300, 375 mg)	225 mg	Daily (4-8 days)

Initially, subjects will be assigned fevipiprant 75 mg (one 75 mg CT daily). Depending on the outcome of the interim analysis (Section 12.6), a second group of subjects may be assigned fevipiprant 150 mg (two 75 mg CTs every day) or fevipiprant 225 mg (one 225 mg CT daily) or fevipiprant 300 mg (one 225 mg CT and one 75 mg CT every day) or fevipiprant 375 mg (two 75 mg and one 225 mg CTs every day).

Subjects will be instructed to chew the dose as described in Section 3.

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent/assent.

Since this study includes 6 to < 12 year old children, the subject's representative(s) gives consent , and the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

8 Visit schedule and assessments

The study will consist of up to 14 days screening period, a 4-8 day treatment period for each dose cohort and a follow-up period of 30 days after the last investigational treatment.

Subjects must be seen for all visits on the designated day. End of Treatment Visit must occur in the morning, prior to study drug dosing. At this visit, all dispensed investigational product will be reconciled by study staff and AEs and concomitant medications recorded on the CRF.

At End of Treatment Visit, PK blood samples will be taken pre-dose, 0.5, 1, 2, 3, 5 and 8 hours post dose. Urine samples post dose will be collected from dosing to 8 h post dose and pooled. All blood samples will be taken by either direct venipuncture or indwelling catheter inserted in the arm or vein at time points specified in Section 16.4 . Local or Topical anesthetic may be used per investigator's decision. Based on exploratory optimal design evaluation using modeling and simulation techniques, this schedule in at least 12 subjects are 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.

Subjects who prematurely discontinue from the study for any reason should be scheduled for a visit as soon as possible, at which time all of the indicated assessments for discontinued subjects will be performed (Table 8-1). PK assessment will not be done for subjects who discontinue from the study before the completion of 3 consecutive days of dosing. For subjects who have interrupted study drug compliance during the treatment period, the EOT Visit can be rescheduled for +1 to 2 days later to ensure study drug compliance of at least 3 consecutive days prior to the EOT Visit. In cases where the subject cannot make the scheduled EOT Visit or has mistakenly taken the study drug at home on the EOT Day, the Visit can be re-scheduled to the next available clinic/home day. It has to be confirmed by study personnel that study drug was taken by the subject on 3 consecutive days prior to the EOT Visit.

After the EOT Visit, there will be a 30 day Follow-up period. In case the study treatment was discontinued, the subject/parent/legal guardian will still be contacted for the safety evaluation 30 days after the last study drug intake. SAEs/AEs occurred during 30 day Follow-up period will be captured in the eCRF.

Assessment schedule, Table 8-1 lists all of the assessments and indicates with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the subject’s source documentation.

Table 8-1 Assessment Schedule

Period	**Screening**	**Treatment**[1]							**Safety Follow-up**
Visit Name	**Screening**	**Treatment**	**End of Treatment**						**Follow-up**[2]
Days	**up to -14**	**1**	**4 to 8**						**34 to 38**
Time (post-dose)	**-**	**-**	**0h**[3]	**0.5h**	**1h**	**2h**	**3h**	**5h**	**8h**	**-**
Informed consent	X									
Demography	X									
Inclusion / Exclusion criteria	X	X								
Medical history/current medical conditions	X									
Concomitant medications (including Asthma)	X[4]									
Prior and concomitant non-drug therapies-procedures	X[4]									
Current medication review/adjust	S									
Physical Examination	S	S	S[4]							
Body Height	X									
Body Weight	X									
Vital Signs	X	X	X[4]			X				
Clinical Chemistry	X		X[4]							
Hematology	X		X[4]							
Urine dipstick	S		S[4]						S[5]	
PK blood collection			X	X	X	X	X	X	X	

Period	**Screening**	**Treatment**[1]							**Safety Follow-up**
Visit Name	**Screening**	**Treatment**	**End of Treatment**						**Follow-up**[2]
Days	**up to -14**	**1**	**4 to 8**						**34 to 38**
Time (post-dose)	**-**	**-**	**0h**[3]	**0.5h**	**1h**	**2h**	**3h**	**5h**	**8h**	**-**
PK urine collection[5]				X						
Pregnancy and assessments of fertility	S	S	S[4]							
Electrocardiogram (ECG)	X		X[4]			X				
Dispense patient diary card		S								
Drug dispensation		S								
Adverse Events	X[4]									
Asthma Exacerbation Episodes	X[4]									
Serious Adverse Events	X[4]									
Study drug administration at visit		X	X							
Record/interruption changes in study drug administrations to assess compliance		X	X[4]							
Record time of study drug taken one day prior to end of treatment			X							

Period	**Screening**	**Treatment**[1]							**Safety Follow-up**
Visit Name	**Screening**	**Treatment**	**End of Treatment**						**Follow-up**[2]
Days	**up to -14**	**1**	**4 to 8**						**34 to 38**
Time (post-dose)	**-**	**-**	**0h**[3]	**0.5h**	**1h**	**2h**	**3h**	**5h**	**8h**	**-**
Disposition (Treatment/Study disposition)	X									
Reconcile study medication			S[4]							
Collect unused study medication			S[4]							
Collect patient diary card			S[4]							

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Treatment visits may be conducted at the clinic or remotely at the subject's home. Ensure light breakfast is provided about 30 minutes prior to all doses from treatment day 1 to end of treatment (0h).
[2] Not a visit to site. Call Patient to collect the information on AE/SAE occurred within 30 days after last dosage
[3] 0h refers to pre-dose
[4] These assessments should be conducted for patients who discontinue.
[5] Urine samples: Pre-dose, child should empty their bladder. This sample can be used for urine dipstick and then discarded. All urine from dosing to 8 h after dosing will be pooled. Children should be encouraged to empty their bladder directly before or after the 8 h blood collection and this urine should be part of the pool. After mixing, capturing the volume of the pool, and taking aliquots for PK, the urine should be used for a urine dipstick and the rest discarded.

8.1 Screening

Re-screening for subjects who screen-failed is permissible on a case-by-case basis. Please contact Novartis for guidance to get information on how to process screen failures.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (see SAE section for reporting details). Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

Subjects who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition Case Report Form.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data to be collected on all subjects include: age, sex, race, ethnicity, source of subject referral, relevant medical history/current medical condition present before signing informed consent where possible, diagnoses and not symptoms will be recorded.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

8.3 Efficacy

Not applicable

8.3.1 Appropriateness of efficacy assessments

Not applicable

8.4 Safety

Safety assessments are specified below.

For details on AE collection and reporting, refer to AE section.

Table 8-2 Physical assessments

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological or any other evaluations the investigator considers appropriate based on the subjects clinical status at the clinic at the time of the visit. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after first administration of investigational drug which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the CRF.
Vital sign	Vital signs include body temperature, blood pressure (BP) and pulse measurements. After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Clinically notable vital signs are defined in Appendix 1 (Section 16.1).
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

All subjects with laboratory tests containing clinically significant abnormalities should be followed regularly until the values return to within the normal ranges or until a valid reason other than drug-related adverse experiences is identified, even after the medication has discontinued.

Clinically notable laboratory findings are defined in Section 16.1 .

Table 8-3 Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Mean corpuscular volume (MCV), Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Other).
Chemistry	Albumin, Alkaline phosphatase (ALP), ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Direct Bilirubin, Total Bilirubin (TBL), Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid Amylase, Lipase, Glucose (non-fasting)
Urinalysis	Macroscopic Panel (Dipstick, performed locally): Bilirubin, Blood, Glucose, Ketones, Leukocytes, Nitrite, pH, Protein, Specific Gravity, Urobilinogen
Coagulation	International normalized ratio (INR), Activated partial thromboplastin time (APTT)
Pregnancy Test	Serum/Urine pregnancy test (refer to Pregnancy and assessments of fertility section)

HDL-High-density lipoprotein, LDL-Low-density lipoprotein

8.4.2 Electrocardiogram (ECG)

Local ECGs must be recorded after the subject rests (5-10 minutes if possible) in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12 lead ECGs are collected. The original ECGs on non-heat-sensitive paper, appropriately signed, must be collected and archived at the study site.For any ECGs with subject safety concerns, two additional ECGs must be performed to confirm the safety finding. Clinically significant ECG findings throughout the study and especially at baseline before administration of study treatment must be discussed with the Novartis responsible person or designee. Any identifier details must be redacted e.g subject initials, date of birth.

In the event that a clinically significant ECG abnormality is identified at the site (e.g. severe arrhythmia, conduction abnormality of QTcF > 500 ms), the ECG is repeated to confirm the diagnosis. If the subject is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

8.4.3 Pregnancy and assessments of fertility

Given the age of this subject population, there may be female subjects who have reached menarche (and therefore of child-bearing potential). Female subjects who fall in this category will have routine urine pregnancy tests as noted in the assessment schedule.

If there is evidence of sexual activity in female subjects of child-bearing potential, appropriate moral and legal actions for reporting should be taken by the investigator to ensure the safety of the child and minimize the risk of becoming pregnant.

Abstinence from sexual activity while participating in a clinical trial should be encouraged in this category of subjects. Otherwise, contraceptive methods should be discussed and may be provided as appropriate to sexually active pediatric subjects after careful consideration of any medical conditions, the individual situation, and cultural and legal aspects.

The basic contraception methods are (if allowed by local regulations):

- Barrier method: Condom or Occlusive cap (diaphragm or cervical/vault caps).
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

In case local regulations deviate from the methods listed, local regulations apply and will be described in the Inform Consent Form (ICF).

8.4.4 Asthma Exacerbation

Asthma exacerbations will be recorded as Adverse Events.

- A **severe asthma exacerbation** is defined as treatment with 'rescue' systemic corticosteroids for ≥ 3 days and hospitalization; or treatment with 'rescue' systemic corticosteroids for ≥ 3 days and emergency department visit (> 24 hours); or death due to asthma.
- A **moderate asthma exacerbation** is defined as treatment with 'rescue' systemic corticosteroids for ≥ 3 days either as an outsubject or in emergency department visits (emergency department visit ≤ 24 hours).

8.5 Additional assessments

8.5.1 Pharmacokinetics

PK samples for plasma and urine fevipiprant and CCN362 concentrations will be collected at the time points defined in the Assessment schedule (Section 16.4). Follow instructions outlined in the Laboratory Manual regarding sample collection, numbering, processing and shipment.

Plasma and urine PK samples will be obtained and evaluated in all subjects at all dose levels. Concentrations in acidified plasma and urine of fevipiprant and CCN362 will be determined by a validated LC-MS/MS method. Concentrations below the lower limit of quantification (LLOQ) will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report.

[redacted]

Concentrations will be expressed in mass per volume units.

The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher):

AUC0-24h,ss, Cmax,ss, Tmax,ss, Cmin,ss, CL/F (fevipiprant only), renal clearance (CLr), amount and fraction of dose excreted over the PK collection interval.

The linear trapezoidal rule will be used for AUC calculation.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by the subject, subject's parent/legal guardian, or the investigator.

The investigator must discontinue study treatment for a given subject if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- subject`s or parent/legal guardian's wish
- Administration of a prohibited medication
- ECGs:
  - If the absolute QTcF ≥ 450 msec or an increase from baseline of > 60 msec on 2 adequate ECGs at least a minute apart
  - 2nd or 3rd degree AV block
  - Atrial or ventricular arrhythmias (as judged clinically significant by the investigator)
- Any severe AE or SAE considered possibly related to the study medication
- Adverse events for which continuation of the study drug would be detrimental
- If a subject develops a medical condition that requires use of prohibited treatment as per Section 6.2.2 , or if subject exhibits a behavior of non-compliance regarding prohibited medications.
- Pregnancy (see Section 10.1.4)
- Any situation in which study participation might result in a safety risk to the subject
- Clinically significant abnormal laboratory value(s) for children 6 to < 12 years, as per the discretion of the physician
- Any other protocol deviation that results in a significant risk to the subject's safety

If discontinuation of study treatment occurs, the subject should NOT be considered withdrawn from the study. The subject should return to the clinic as soon as possible, after discontinuation of study drug, for a study treatment discontinuation visit (End of Treatment will act as an early discontinuation visit in this case) and directly move into the 30 day follow-up period. Treatment discontinuation visit assessments detailed in the Table 8-1 should be completed and recorded in the eCRF. The investigator must determine the primary reason for the subject's premature discontinuation of study treatment and record this in the Study Disposition eCRF.

The investigator must contact the IRT to register the subject's discontinuation from study treatment.

The data which must continue to be collected for all discontinued subjects are adverse event and serious adverse events for up to 30 days after drug discontinuation until the end of the study follow-up visit. Documentation of attempts to contact the subject must be recorded in the source documentation.

If the subject fails to return for an end of study visit for unknown reasons, every effort should be made to contact them.

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Dose not want any further visits or assessments and
- Does not want any further study related contacts

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For European Union (EU) and Rest of World (RoW): All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up

appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

Subjects that completed the study or prematurely discontinued will not be given further access to the investigational treatment.

The investigator must provide follow-up medical care for all subjects who completed or prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

All treated subjects should have a safety follow-up call conducted 30 days after last administration of study treatment. The information to be collected at this follow-up visit includes concomitant medications, adverse events and asthma exacerbation episodes. All SAEs reported during this time period must be reported as described in Section 10.1.3 . Documentation of attempts to contact the subject should be recorded in the source documentation.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade.

- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be ‘Not suspected’. The rationale for this guidance is that the symptoms of a

lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject

3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Information about adverse drug reactions for the investigational drug can be found in the IB.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 16.1 .

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires insubject hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
  - treatment on an emergency outsubject basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Consider the following 2 categories to determine SAE reporting timeframes:

1. Screen Failures: SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.
2. Enrolled and/or Treated Subjects: SAEs collected between time subject signs ICF until 30 days after the subject has discontinued or stopped study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Novartis Chief Medical Office and Patient Safety (CMO&PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period after the last study visit following the last administration of study treatment should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the drug administration record (DAR) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be

collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Drug Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the, respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities/adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on appropriate CRFs

Please refer to Table 16-1 in Section 16.2 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2 . Repeat liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and GGT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on appropriate CRF
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event

- These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.

11 Data Collection and Database management

11.1 Data collection

Data not requiring a separate written record will be defined in the protocol and the assessment schedule and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the Electronic Data Capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

Novartis personnel (or designated Contract Research Organization (CRO)) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Data about all study treatment (s) dispensed to the subject and all dosage administrated will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a

vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/delegated CRO representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture/data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO/Clinical Research Associate (CRA) organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 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.

12.2 Subject demographics and other baseline characteristics

Demographic and baseline characteristics measured including age, age stratum (6 to <9 years and 9 to <12 years), gender, race, ethnicity, height, weight, body mass index (BMI), relevant medical history, prior medication (taken before first dose of study drug) and concomitant medications, vital signs (body temperature, systolic and diastolic BP, radial pulse rate) and QTc using Fridericia's correction 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.

Baseline is defined as the last measurement before first dose of study drug.

No statistical analyses will be provided for baseline comparability among the cohort.

12.3 Treatments

Dosage and date of administration at the 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.

Subjects taking prohibited concomitant medications will be noted in the summary of protocol deviations. Treatment compliance with study medication over the study period will be summarized by cohort.

12.4 Analysis of the primary endpoint(s)

The primary objective of the study is to determine the pharmacokinetics of fevipiprant at steady state after at least four consecutive days of dosing based on AUC0-24h,ss, Cmax,ss and CL/F.

12.4.1 Definition of primary endpoint(s)

The AUC0-24h,ss, Cmax,ss and CL/F for fevipiprant at steady state will be the primary variables. PK analysis set will be used for analysis of all PK parameters.

12.4.2 Statistical model, hypothesis, 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 by cohort through descriptive summary statistics (including mean, SD, CV% mean, Geometric mean, CV% geometric mean, median, minimum and maximum). Additionally, CL/F will also be summarized across cohort.

Plasma concentrations will be assessed at the 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 the EOT Visit will also be used as 24 h concentrations to derive AUC0-24h,ss.

PK data from this study will be analyzed together with PK data from other studies in adult subjects using a population pharmacokinetic modeling approach with the aim to support dose selection for pediatric phase III studies. The modeling approach will be specified in a separate analysis plan and results will be reported separately from the CSR.

12.4.3 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.

No other methodology is planned to address missing data.

12.4.4 Sensitivity and Supportive analyses

Not applicable

12.5 Analysis of secondary endpoints

The secondary endpoints will be analyzed as described below.

12.5.1 Safety endpoints

For all safety analyses, the safety set will be used.

Adverse events

AEs (including asthma exacerbations) starting on or after the time of the first intake of study drug and until the day 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 a prior AEs and will not be included in tabulations of treatment-emergent AEs.

Treatment-emergent AEs will be summarized, by system organ class and preferred term, overall by system organ class, preferred term and maximum severity, suspected drug-related AEs by system organ class and preferred term. Treatment-emergent SAEs will be summarized, by system organ class and preferred term. The summarization will be provided by cohort.

If a subject reported more than one AE with the same preferred term, the AE will be counted only once. If a subject reported more than one AE within the same primary system organ class, the subject will be counted only once at the system organ class level.

Vital signs

Vital signs measurements include body temperature, systolic and diastolic blood pressure (SBP and DBP) and pulse rate. Summary statistics will be provided by cohort and visit/time-point.

ECG evaluations

ECG measurements include ventricular rate, QT interval, RR interval, PR interval, QRS duration, and Friderica's QTc (calculated as QTcF = QT / 3√ RR (in seconds), where 3√ denotes the cube root). Summary statistics will be provided by cohort and visit/time-point.

Clinical laboratory evaluations

Laboratory data consist of hematology and biochemistry including peripheral blood eosinophils.

Summary statistics for continuous laboratory parameters will be provided by cohort and visit/time-point. Frequency tables of results for categorical laboratory parameters will be provided by visit/time point.

12.5.2 Pharmacokinetics

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 12.4).

Summary statistics for plasma and urine concentrations will be provided by cohort and 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. Mean and individual concentration-time profile will be displayed graphically by cohort.

Metabolite CCN362 at steady state

Cmax,ss, Tmax,ss, AUC0-24h,ss, Cmin,ss, CLr, amount and fraction 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 12.4).

Summary statistics for plasma and urine concentrations of analyte CCN362 will be provided by cohort and 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. Mean and individual concentration-time profile will be displayed graphically by cohort.

12.6 Interim analyses

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 12.7.

Additional interim analyses may be conducted in case of any safety concerns or when at least 6 subjects on high dose have completed the treatment (in case where sample size on high dose is

adjusted to be more than 6 after 1st interim analysis) and the sample size of high dose can be refined based on emerging PK data.

12.7 Sample size calculation

12.7.1 Primary endpoint(s)

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 2 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%-141%	**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).

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable

local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last subject last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal standard operating procedures, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any

additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

14.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

There are no specific notable range criteria for this study; however, the Central Laboratory will flag laboratory values falling outside of the normal range on the Central Laboratory Report (which the investigator should sign off) and the investigator will report any values considered clinically significant in the eCRF.

16.2 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 16-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	3 x ULN < ALT / AST ≤ 5 x ULN 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	ALT or AST > 5 × ULN ALP > 2 × ULN (in the absence of known bone pathology) TBL > 2 × ULN (in the absence of known Gilbert syndrome) ALT or AST > 3 × ULN and INR > 1.5 Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) Any clinical event of jaundice (or equivalent term) ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia Any adverse event potentially indicative of a liver toxicity*
*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal	

LFT-Liver function test, ULN-upper limit of normal

Table 16-2 Follow-Up Requirements for Liver Events and Laboratory Triggers

Criteria	**Actions required**	**Follow-up monitoring**
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the subject • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN [b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia [c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

16.3 Appendix 3: Blood Volume Table

Table 16-3 Blood volume

Study phase	Time (h)[2]	Safety	PK		
			Dose Reference ID	Sample no.	mL
Screening (days -14 to -1)		5			
Treatment Day 1 (Baseline)					
End of Treatment	0 (pre-dose)	5	10[1]/11	101	1
	0.5		11	102	1
	1		11	103	1
	2		11	104	1
	3		11	105	1
	5		11	106	1
	8		11	107	1
Sub-total blood volume		10			7
TOTAL Blood volume (mL)					17

[1]only one PK sample is collected at pre-dose, but the time difference to the doses on day prior to EOT and EOT day will be derived, requiring 2 dose reference IDs.

[2]Times are relative to the last dose on Day 4-8.

Table 16-4 PK urine sample

	Time (h)[2]		PK urine Samples[3]		
Study Visits					
	Start	End	Dose Reference ID	Sample No.	Volume (ml)
End of Treatment (Day 4-8)	0	8	11	201	2 x 1.5 mL

[2]Times are relative to the last dose on Day 4- 8.

[3]Urine samples: Pre-dose, child should empty their bladder. This sample can be used for urine dipstick and then discarded. All urine from post-dose up to 8h will be pooled for analysis including urine dipstick.

16.4 Appendix 4: Pharmacokinetic/Vital signs/ECG/Lab assessment timed schedule (End of treatment)

Table 16-5 PK/VS/ECG/Lab assessment schedule (EOT)

Time point vs. 0 (dose time, hours)*	Vital Signs (Systolic/ diastolic BP /radial pulse)	ECG	PK	Hematology/ chemistry
Pre-dose	x	x	X*	x
0.5			X	
1			X	
2	x	x	X	
3			X	
5			X	
8			X	

Note: For Time points where multiple procedures occur, the following order is recommended: e.g. vital signs, PK, and lab. The PK blood draw should be as close as possible to the scheduled time.

*In case a local anesthetic is used for placing the indwelling catheter, the time for it to take effect has to be accounted for prior to any assessment.

16.5 Appendix 5: Definition of pharmacokinetic parameters

Table 16-6 Pharmacokinetic parameters

Parameter	Definition
AUC0-24h,ss	The AUC calculated to the end of a dosing interval (24 h) at steady-state (amount x time x volume-1)
Cmax,ss	The maximum (peak) observed plasma concentration at steady state (mass x volume-1)
Tmax,ss	The time to reach maximum (peak) plasma concentration at steady state (time)
Cmin,ss	The minimum observed plasma concentration at steady state (mass x volume-1)
Ae	The amount of drug excreted into urine (mass); can be used to derive a fraction of the dose excreted into urine (%)
CL/F	The total body clearance of drug from the plasma following extravascular administration (volume x time-1)
CLr	The renal clearance of drug from the plasma (volume x time-1)
(CL/F)/kg	The total body clearance of drug from the plasma following extravascular administration normalized to body weight ((volume x time-1)/kg)

16.6 Appendix 6: List of idiosyncratic drug reactions (IDRs) for investigators

Table 16-7 Definition of potential idiosyncratic drug reactions

Reaction	Possible events diagnoses and signs/symptoms
Anaphylaxis	Anaphylactic/anaphylactoid reactions
Angioedema: diagnosis and/or signs and symptoms	Angioedema, site specific angioedema urticaria, anisarca/generalized edema urticaria
Severe skin reactions	Acute generalised exanthematous pustulosis, Cutaneous vasculitis, Drug reaction with eosinophilia and systemic symptoms (DRESS), Epidermal necrosis, Toxic skin eruption , Oculomucocutaneous syndrome, Skin necrosis, Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TENS)
Agranulocytosis and other cytopenic events	Agranulocytosis, aplastic anemia, pancytopenia
Other hypersensitivity reactions	Other suspected hypersensitivity to suspected drug
Liver reactions	Any event that qualifies as a liver laboratory trigger or event as defined in Appendix 2
While this list is intended as a guide to the investigator, other potential IDRs may arise.	