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CJM112

Clinical Trial Protocol CCJM112X2204

A randomized, subject- and investigator-blinded, placebo-controlled, multi-center, multiple dose study to assess the efficacy and safety of CJM112 in patients with inadequately controlled moderate to severe asthma

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct. Note: The SOM will not be part of the Clinical Study Report.

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to Section 9.2 of the protocol for SAE criteria and additional requirements. See also page 2 of the Site Operations Manual for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Chief Medical Office and Patient Safety (CMO & PS) **within 24 hours after awareness of the SAE**
- Notify the Novartis Medical Lead
- The fax number(s) and email address(es) are located in the Site Operations Manual.

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List of abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CFR	U.S. Code of Federal Regulation
CO_2	carbon dioxide
COAR	Clinical Operations, Analytics & Regions
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CV	coefficient of variation
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HIV	human immunodeficiency virus
HS	Hidradenitis Suppurativa
i.v.	intravenous
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	lactate dehydrogenase
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)

s.c.	subcutaneous
SAE	serious adverse event
sCR	serum creatinine
SD	standard deviation
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
T2	T helper cell type 2
ULN	upper limit of normal

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Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug(s) (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
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)
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.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
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 Directive 2001/20/EC and is synonymous with "investigational new drug" or "test substance"
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.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
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
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
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/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
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	A trial participant (can be 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 allowany further collection of personal data

Protocol synopsis

Protocol number	CCJM112X2204
Title	A randomized, subject- and investigator-blinded, placebo-controlled, multi-center, multiple dose study to assess the efficacy and safety of CJM112 in patients with inadequately controlled moderate to severe asthma
Brief title	Study of safety and efficacy of CJM112 in moderate to severe asthmatics
Sponsor and Clinical Trial Phase	Novartis Phase II
Intervention type	Biologic
Study type	Interventional
Purpose and rationale	An unmet medical need exists for patients with moderate and severe asthma who continue to demonstrate symptoms despite being on standard of care medications, and are not eligible for other biologic therapies developed or in development for T2-high (allergic/eosinophilic) asthma (such as omalizumab and mepolizumab) because they have low circulating IgE and eosinophil levels at baseline. The purpose of this study is to determine if CJM112, an anti-IL-17A antibody, when added to existing therapy, displays the clinical efficacy and safety profile to support further development in patients with inadequately controlled moderate to severe asthma with low IgE and low circulating eosinophil levels.
Primary Objective(s)	To determine whether treatment with CJM112 in patients with inadequately controlled moderate to severe asthma leads to an improvement in airflow obstruction as reflected by change from baseline in FEV1 in mL.
Secondary Objectives	To determine whether treatment with CJM112 in patients with inadequately controlled moderate to severe asthma: 1. leads to an improvement in FEV1% of predicted. 2. leads to an improvement in asthma control as reflected by change from baseline in ACQ score 3. is safe and well tolerated by evaluating study treatment discontinuations and adverse events
Study design	12 week, non-confirmatory, randomized, subject- and investigator-blinded, placebo-controlled, multi-center, parallel-arm study in which patients will be randomized 3:2 to CJM112:placebo.
Population	The study population will consist of approximately 110 male and female patients between 18 and 75 years old with uncontrolled symptoms of moderate or severe asthma (defined by ACQ score of ≥1.5) who are compliant on standard of care medications.

Key Inclusion criteria	1. Patients with a physician-diagnosed history of moderate to severe asthma for a period of at least one year prior to screening. 2. Patients on a stable therapy regimen of asthma for at least 3 months prior to screening with at least medium dose inhaled glucocorticoid and at least one additional asthma controller medication (such as inhaled long-acting bronchodilator, leukotriene antagonist, theophylline, stable low dose glucocorticoid, etc). 3. Acceptable and reproducible spirometry with FEV1 ≥ 40 and ≤ 90% of predicted at screening and baseline visits (re-testing is allowed once). 4. ACQ score ≥ 1.5 at screening and baseline visits (re-testing is allowed once). 5. Total serum IgE < 150 IU/mL at screening and baseline visits 6. Peripheral blood eosinophils <300/µL at screening and baseline visits
Key Exclusion criteria	1. Previous use of biologics or other concomitant medications within the time periods specified in the SOM/protocol. 2. History of ongoing, chronic, or recurrent moderate or severe infectious disease. 3. Patients who have smoked or inhaled recreational foreign substances such as nicotine, tobacco products, marijuana, e-cigarettes, etc within the 6 month period prior to Visit 1 or who have any smoking history of greater than 10 pack years (Assuming 1 pack = 20 cigarettes or equivalent). 4. Patients who have had an asthma attack/exacerbation requiring systemic corticosteroids for at least 3 continuous days within 4 weeks prior to screening. 5. Patients who have had a respiratory tract infection or asthma worsening within 4 weeks prior to Visit 1 or during the screening period. 6. Women of child-bearing potential unless they are using highly effective methods of contraception during dosing and for 13 weeks after stopping of investigational drug.
Study treatment	• Subcutaneous injections of CJM112 300 mg (2 injections of 150 mg) • Matching placebo
Efficacy/PD assessments	• Spirometry measurements • ACQ score
Key safety assessments	• Physical examination • Vital signs • ECGs • Safety laboratory tests (hematology, blood chemistry, and urinalysis) • Adverse event monitoring
Other assessments	Company Confidential Information

Data analysis	Company Confidential Information
Key words	Phase II, safety, efficacy, CJM112, asthma, T2 low

1 Introduction

1.1 Background

The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the Investigator's Brochure.

Asthma is a heterogeneous inflammatory disease of the airways that clinically manifests with symptoms and signs of airflow obstruction of varied severity. Although the majority of asthma patients can be effectively treated with currently available medications such as inhaled glucocorticoids and bronchodilators, a substantial subset exists who remain difficult-to-treat and manifest with severe disease. These patients account for a relatively large proportion of resource expenditure Chung et al 2014.

While asthma has been considered to be driven by T helper cell type 2(T2) cells such as IgE activated mast cells, eosinophils and their products, data suggest that a T2-high gene signature is present in the airways of only 50% of asthmatics Woodruff et al 2009. Non-T2-high or non-eosinophilic airway inflammation occurs in approximately 50% of patients with asthma, of which a significant proportion include moderate and severe asthmatics Thomson 2016. Non-eosinophilic inflammation is associated with an impaired therapeutic response to inhaled corticosteroids McGrath et al 2012, and hence asthmatics with non-allergic and non-eosinophilic phenotype are not eligible for available biologic therapies with anti-IgE and anti-IL5 antibodies. Thus, a large unmet medical need exists in moderate and severe non-allergic non-eosinophilic asthmatics who suffer from symptoms of poorly controlled asthma such as cough and shortness of breath, despite being compliant on standard of care therapy. We hypothesize that therapy with anti-IL17 antibodies has the potential to address this unmet medical need in patients with asthma.

Increased levels of IL-17A that correlate with the severity of asthma have been reported in the circulation and airways of individuals with asthma compared to healthy controls. High IL-17A mRNA levels have been found in patients with moderate-to-severe asthma, even if those patients were treated with corticosteroids Bullens et al 2006. Pre-clinical studies in mouse models of allergic pulmonary inflammation have implicated a requirement for IL-17A and its receptor (IL-17RA) in neutrophilic airway inflammation and steroid - resistant airway hyper-responsiveness. Thus, the properties of IL-17A *in vitro*, its presence in increased amounts in asthma, and the pre-clinical models of the disease support a role for IL-17A in neutrophilic and/or T2-low forms of the disease that are poorly responsive to steroids Cosmi et al 2011. Proof of principle that anti-IL17 therapy can lead to clinically relevant beneficial outcomes in a sub-group of asthmatics has been demonstrated Busse et al 2013. Hence, we propose to investigate the efficacy and safety of CJM112, an anti-IL17A antibody, in patients with inadequately controlled, non-T2 driven, moderate to severe asthma in this study protocol.

1.2 Nonclinical data

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1.3 Clinical data

Relevant clinical data are summarized in the sections below. For detailed information, please refer to the Investigators Brochure.

1.3.1 Human safety and tolerability data

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1.3.2 Human pharmacokinetic data

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1.3.3 Human pharmacodynamic data

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1.4 Study purpose

The purpose of this study is to determine whether CJM112, when added to existing therapy, displays the clinical efficacy and safety profile to support further development in patients with inadequately controlled moderate to severe asthma.

2 Study objectives and endpoints

2.1 Primary objective(s)

Primary objective(s)	*Endpoints related to primary objective(s)*
• To determine whether treatment with CJM112 in patients with inadequately controlled moderate to severe asthma leads to an improvement in airflow obstruction	• Change from baseline FEV1 in mL

2.2 Secondary objective(s)

Secondary objective(s)	*Endpoints related to secondary objective(s)*
• To determine whether treatment with CJM112 in patients with inadequately controlled moderate to severe asthma leads to an improvement in FEV1% of predicted	• Change from baseline FEV1 % of predicted
• To determine whether treatment with CJM112 in patients with inadequately controlled moderate to severe asthma leads to an improvement in asthma control	• Change from baseline in ACQ score, % of patients with ≥ 0.5 decrease in ACQ score
• To assess the safety and tolerability of CJM112 in patients with inadequately controlled moderate to severe asthma	• Study treatment discontinuations and adverse events

2.3 Exploratory objective(s)

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3 Investigational plan

3.1 Study design

This is a non-confirmatory, randomized, subject- and investigator-blinded, placebo-controlled, multi-center, parallel-arm study evaluating the efficacy of CJM112 on top of standard of care in patients with inadequately controlled moderate to severe asthma. This study will enroll approximately 110 patients. After an initial screening visit and run-in period of approximately 4 weeks, subjects eligible per inclusion and exclusion criteria at the baseline visit will be randomized (3:2) to receive Company Confidential Information CJM112 or matching placebo subcutaneously over 3 months during visits at the clinical study site. All baseline safety evaluation results must be available prior to the first dose. After the end of the treatment period, subjects will be followed for an additional 13 weeks. Site visits to administer dose and assess safety and efficacy will be scheduled as depicted in the figure below.

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Figure 3-1 Study Design

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Screening and Run-In: Patients will provide informed consent and participate in an initial screening visit consisting of vital signs, physical exam, blood chemistry, ECG, pulmonary function tests, and ACQ. Subjects who meet all eligibility criteria at the screening visit will be dispensed a daily symptom diary and be asked to perform peak flow measurements over the approximately 4 week run-in period until the baseline visit.

Baseline: Subjects who qualify based on screening and run-in assessments will return for a baseline evaluation between Day -5 to Day -2. Subjects who meet all the applicable inclusion/exclusion criteria at screening and baseline will be randomized and will enter the treatment period. All screening and baseline assessments results must be available prior to randomization.

Treatment Period:

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At treatment period visits, safety, Company Confidential Information assessments will be performed. Safety assessments will include physical examinations, open ended health inquiry, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, urinalysis), AEs and SAE monitoring.

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Safety Follow-up: After completing the last dose Company Confidential Information, subjects will enter an additional follow-up period consisting of a visit on Day 92, Day 134 and an End of Study (EOS) visit on Day 176.

Subjects who discontinue treatment early (unless they have withdrawn consent) should complete the D92, D134 and End of Study visit D176. All subjects who discontinue the study early (including subjects who withdraw consent) will be required to complete the EOS visit.

3.2 Rationale of study design

This study is an exploratory, multi-center, randomized, subject- and investigator-blinded, placebo-controlled, parallel-group, phase IIa study with a 12-week treatment epoch.

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Rationale for population: An unmet medical need exists for patients with moderate or severe asthma who continue to demonstrate symptoms despite being on standard of care medications and are not eligible for other biologic therapies developed or in development for T2-high (allergic/eosinophilic) asthma (such as omalizumab and mepolizumab) because they have low circulating IgE and eosinophil levels at baseline.

Rationale for study design: In order to optimize the rigor and integrity of the study and minimize bias, a randomized, subject- and investigator-blinded parallel group study design is used. This design is well-established in respiratory clinical trials and enables the study treatment to be given for an appropriate and practical length of time to assess the efficacy and safety of the treatment.

Rationale for placebo control: The placebo arm controls for potential bias in efficacy and safety assessments. The study design includes a placebo control and not an active control because the study treatment will be added on top of standard of care therapy for each patient.

Rationale for run-in period: The run-in period will ensure subject's eligibility for the study at the baseline visit after their standard of care treatment has been adhered to during the run-in period and will minimize the potential for changes in key endpoints as a result of regression to the mean at the end of the study period.

Rationale for follow up period :

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Hence, a follow up period is proposed after the last dose on study Day 85 to ensure patient safety, compliance with contraception requirements, and to assess for loss of efficacy of the investigational treatment .

3.3 Rationale for dose/regimen, route of administration and duration of treatment

The study participants will receive CJM112 300 mg or placebo s.c. injections 9 times during the 12 week treatment period: 5 weekly doses of 300 mg s.c. each (induction/loading) and 4 subsequent doses every 2 weeks (maintenance). This regimen is considered practical and feasible for this severe asthma population. A weekly loading dose regimen of 5 doses of 300 mg has been safe and well-tolerated with early evidence of efficacy in the ongoing clinical study in patients with hidradenitis suppurativa (CCJM112X2202)

Company Confidential Information . The 12 week treatment duration is considered adequate to demonstrate improvements in the key endpoints in patients with severe asthma based on published literature Wenzel et al 2016,

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3.4 Rationale for choice of comparator

Patients with asthma in this study will continue the standard of care medications as prescribed by their primary physicians. Hence the study design includes a placebo control and not an active control because the study treatment will be added on top of standard of care. The placebo arm is expected to control for potential bias in efficacy and safety assessments in the study.

3.5 Rationale for choice of background therapy

Patients eligible to participate in this trial will be required to demonstrate symptoms of un-controlled asthma (as defined by an Asthma Control Questionnaire (ACQ) score of at least 1.5), despite compliance with standard of care therapy for moderate or severe asthma according to local practice. Thus the background therapy will include at least medium dose inhaled glucocorticoid (refer to SOM for glucocorticoid doses) and at least one additional asthma controller medication as required by inclusion criterion 6.

3.6 Purpose and timing of interim analyses/design adaptations

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3.7 Risks and benefits

There is no significant benefit expected for subjects participating in this study. A transient benefit may be observed if CJM112 provides efficacy. A positive outcome from this study may lead to further development of CJM112 for eligible patients with asthma.

The risk to subjects in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, avoidance of prohibited concomitant medications, regular safety reviews, adequate safety follow up and study stopping rules.

Treatment for adverse event should follow general guidelines for standard-of-care and is at the discretion of the investigator or treating physician. There are no specific treatment recommendations for adverse events that may occur in this trial.

Women of child bearing potential should be informed that taking the investigational drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the subject will not reliably comply, they should not be entered in the study.

Because CJM112 is a monoclonal antibody, men participating in the study do not need to use condoms during sexual intercourse.

CJM112 has been well tolerated in clinical trials in other indications to date. Primarily non-serious upper respiratory tract infections have been observed (in particular pharyngitis and nasopharyngitis) more frequently with CJM112 than placebo, and a potential for dose-dependent increase in rates of infection may exist. Most of the events were, however, mild or moderate in severity. Small, incremental risks in Candida infections are reported for IL-17 blocking agents but have not been observed so far for CJM112.

Hypersensitivity reactions have not been observed so far for CJM112, but their future occurrence cannot be excluded. Study subjects should be monitored post-injection for hypersensitivity and anaphylaxis events for an appropriate amount of time, no less than 30 minutes post-dose. Injection site reactions, elevations in liver enzymes, drops in neutrophil counts and ECG abnormalities have been observed sporadically and very rarely in secukinumab trials. These constitute events that may be observed and should be monitored routinely, as with any investigational biologic treatment.

Due to the early stage of development, there may be unknown risks of CJM112 which may be serious and/or unforeseen.

Additional risks to study subjects are related to the procedures of this clinical trial, such as withholding bronchodilators prior to lung function tests and blood sampling. During the collection of blood samples, patients may experience pain and/or bruising at the injection site. In addition, although rare, localized clot formation, infections and nerve injuries may occur. Lightheadedness or fainting may also occur during or after the blood draw.

Certain adverse events, such as shortness of breath, wheezing, cough, chest tightness and asthma flares or exacerbations may occur in study participants. These risks are inherent to the disease process and are unlikely to be caused or worsened by CJM112 or study participation, except when bronchodilators are withheld prior to lung function tests. If a subject is unable to withhold bronchodilators prior to lung function tests, he/she should be treated appropriately and his/her participation in this study should be re-considered.

3.7.1 Blood sample volumes

Approximately 400 mL of blood is planned to be collected over a period of 16 weeks, from each subject as part of the study. Additional samples collected for monitoring of any safety findings would be in addition to this pre-specified volume. This is not considered to be a risk for this population.

Timings of blood sample collection are outlined in the Assessment schedule, Section 8.1.

A summary blood log is provided in the Site Operations Manual, together with instructions for all sample collection, processing, storage, and shipment information.

See Section 8.9 regarding the potential use of residual samples.

4 Population

The study population will consist of approximately 110 male and female patients with uncontrolled symptoms of moderate or severe asthma (defined by ACQ score of ≥ 1.5) on standard of care medications. Drop-outs after randomization will not be replaced.

The investigator must ensure that all subjects being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible subjects.

Subject selection is to be established by checking through all applicable eligibility criteria at screening and baseline. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from **any** entry criterion excludes a subject from eligibility for the study.

4.1 Inclusion criteria

Population eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed
2. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
3. Male and female adult patients aged ≥ 18 to ≤ 75 years.
4. Patients must weigh between 50 and 120 kg

5. Patients with a physician-diagnosed history of moderate to severe asthma for a period of at least one year prior to screening
6. Patients on a stable therapy regimen for asthma for at least 3 months prior to screening with at least medium dose inhaled glucocorticoid and at least one additional asthma control medication (such as inhaled long-acting bronchodilator, leukotriene antagonist, theophylline, stable low dose glucocorticoid, etc)
7. Acceptable and reproducible spirometry with FEV1 $\geq$ 40 and $\leq$ 90 % of predicted at screening and baseline visits (Re-testing is allowed once)
8. ACQ score $\geq$ 1.5 at screening and baseline visits (Re-testing is allowed once)
9. Total serum IgE < 150 IU/mL at screening and baseline visits (Re-testing is allowed once)
10. Peripheral blood eosinophils < 300/μL at screening and baseline visits (Re-testing is allowed once)

4.2 Exclusion criteria

Population fulfilling any of the following criteria are <u>not</u> eligible for inclusion in this study:

1. Use of investigational drugs at the time of screening, or within 4 weeks or 5 half-lives of screening, or as required by local regulations, whichever is longer.
2. Treatment with IL-17 or IL-17R blocking agents over the previous 12 months, including, but not limited to secukinumab, ixekizumab, bimekizumab and brodalumab.
3. Previous use of biologics or other concomitant medications within time periods specified in the SOM/protocol.
4. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 13 weeks after stopping of investigational drug. ***Highly effective contraception methods include:***
   - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
   - Male sterilization (at least 6 months prior to screening). For female subjects in the study the vasectomized male partner should be the sole partner for that subject.
   - 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 of use of oral contraception, women should be stable on the same pill for a minimum of 3 months before taking investigational drug.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

5. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
6. History of ongoing, chronic or recurrent moderate or severe infectious disease.
7. Patients with chronic lung diseases other than asthma, including (but not limited to) chronic obstructive pulmonary disease, clinically significant bronchiectasis, sarcoidosis, interstitial lung disease, cystic fibrosis, Churg-Strauss syndrome, allergic broncho-pulmonary aspergillosis, or clinically significant chronic lung diseases related to a history of tuberculosis or asbestosis.
8. History of severe systemic Candida infections or evidence of Candidiasis in the 2 weeks prior to baseline visit.
9. Active systemic infections during the 2 weeks prior to baseline.
10. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result at screening.
11. A positive Hepatitis B surface antigen or Hepatitis C test result at screening
12. Any live vaccines (this includes nasal-spray flu vaccine) starting from 6 weeks before baseline
13. Any severe, progressive or uncontrolled, acute or chronic, medical or psychiatric condition, or other factors such as abnormal vital signs, ECG or physical findings, or clinically relevant abnormal laboratory values, that in the judgment of the investigator may increase the risk associated with study participation/treatment or may interfere with interpretation of study results, and thus would make the patient inappropriate for entry into or continuing the study.
14. History of hypersensitivity or allergy to the investigational compound/compound class being used in this study.
15. Donation or loss of 400 ml or more of blood within 8 weeks prior to baseline, or longer if required by local regulation.
16. History of drug or alcohol abuse within the 12 months prior to dosing.
17. At screening, history or symptoms of malignancy of any organ system (except for a history of basal cell carcinoma and/or up to 3 squamous cell carcinomas of the skin, if successful treatment has been performed, with no signs of recurrence; actinic keratosis, if present at screening, should be treated according to standard therapy before randomization), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
18. Patients with known active Crohn’s disease.

19. Patients who have smoked or inhaled recreational foreign substances such as nicotine, tobacco products, marijuana, e-cigarettes, etc within the 6 month period prior to Visit 1, or who have any smoking history of greater than 10 pack years (e.g. 10 pack years = 1 pack/day x 10 years or ½ pack/day x 20 years, etc.) (Assume 1 pack = 20 cigarettes or equivalent).
20. History of life-threatening asthma event in the previous year, such as significant hypercarbia (pCO_2 > 45 mmHg), endotracheal intubation, non-invasive positive pressure ventilation (NIPPV), respiratory arrest, or seizure as a result of asthma.
21. Patients who have had an asthma attack/exacerbation requiring systemic corticosteroids for at least 3 continuous days within 4 weeks prior to screening (re-screening is permitted).
22. Patients who have had a respiratory tract infection or asthma worsening within 4 weeks prior to Visit 1 (Screening) or during the screening period. Patients may be re-screened 4 weeks after recovery from their respiratory tract infection or asthma worsening.

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

5 Restrictions for Study Subjects

During recruitment, screening/informed consent review, and baseline visit, the subjects must be informed and reminded of the restrictions outlined in this section.

5.1 Contraception requirements

Please refer to exclusion criteria (Section 4.2) for details of contraception requirements for the study.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

Male subjects are not required to wear a condom for the duration of the study. However, he should be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

5.2 Prohibited 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 medical monitor before randomizing a patient or allowing a new medication to be started. The following drugs are excluded to ensure patient safety and prevent confounding of efficacy in this clinical trial.

Table 5-1 Prohibited medication

Medication	Prohibited period	Action to be taken
IL-17 or IL17R blocking agents, including, but not limited to secukinumab, ixekizumab, bimekizumab and brodalumab.	12 months prior to screening through end of study	Exclude until patient re-qualifies for study
Anti-IgE biologic therapy such as omalizumab	3 months prior to screening through end of study	Exclude until patient re-qualifies for study
Anti-IL 4, 5 or 13 biologic therapy such as mepolizumab or dupilumab	3 months prior to screening through end of study	Exclude until patient re-qualifies for study
Other investigational drugs	4 weeks or 5 half-lives, whichever is longer	Exclude until patient re-qualifies for study
Live vaccine	6 weeks prior to baseline visit through end of study	Exclude until patient re-qualifies for study

5.3 Dietary restrictions and smoking

Study participants must refrain from smoking or inhaling nicotine or tobacco products or other recreational inhaled foreign substances such as marijuana, e-cigarettes, etc for the duration of the study.

Participants should refrain from alcohol and caffeine intake 24 hours and 8 hours prior to each study visit respectively.

5.4 Other restrictions

Study participants are expected to refrain from strenuous physical exercise (e.g. weight training, aerobics, football) until after Study Completion evaluation. Restrictions on bronchodilators are described in Section 6.10 and Section 6.11 of the protocol.

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the Site Operations Manual. Refer to Section 5.3 for 'Dietary restrictions and smoking' during study treatment.

6.1.1 Investigational treatment and control drugs

Table 6-1 Overview of study medication

Study drug name	Formulation	Unit dose	Packaging	Provided by
CJM112 150mg/1mL	Liquid in vial	150 mg/mL	Double Blind patient specific kits	Novartis
Placebo to CJM112	Liquid in vial	0 mg/mL	Double Blind patient specific kits	Novartis

6.1.2 Additional study treatment

No additional treatment beyond investigational drug and placebo are included in this trial. The study participant or the investigational site are responsible for sourcing all other treatments such as standard of care inhalers, rescue inhalers, etc.

6.2 Treatment arms

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6.3 Treatment assignment and randomization

At the Day 1 visit, all eligible patients will be randomized and treatment will be assigned via Interactive Response Technology (IRT). Randomization will be stratified by region (US, EU, and Rest of World). Standard of care practice for management of asthma may vary by region due to availability of inhalers; thus, we will stratify randomization by region. The IRT can be contacted via the interactive web response system (IWRS). The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of subjects.

6.4 Treatment blinding

This is a subject and investigator-blinded study. Subjects and investigators will remain blinded to study treatment throughout the study, except where indicated below.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

All site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

Unblinding a single subject at site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see Section 6.7).

Sponsor staff

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

The study statistician will be able to access the randomization list for interim analyses and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in Table 6-2. For example, unblinded summaries and unblinded individual data can be shared with the team for interim analyses.

Study programmers and other personnel involved in study data analysis (e.g. biomarker expert) are allowed to access treatment assignment information for the purpose of conducting interim analyses.

The clinical trial team is allowed to share unblinded results with other sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project at the time of interim analyses while the study is ongoing.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unblinded.

Table 6-2 Blinding levels

Role	Time or Event			
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis
Subjects/Patients	B	B	UI	B
Site staff	B	B	UI	B
Unblinded site staff (see text for details)	B	UI	UI	UI
Drug Supply and Randomization Office	UI	UI	UI	UI
Unblinded sponsor staff (see text for details)	B	UI	UI	UI
Statistician/statistical programmer/data analysts	B	B	UI	UI
Biomarker expert and data manager	B	B	UI	UI
All other sponsor staff not identified above	B	B	UI	UI

B Remains blinded

UI Allowed to be unblinded on individual patient level

6.5 Treating the subject

CJM112 150mg/1mL or placebo will be administered to the subject via the subcutaneous (s.c.) route of administration at the study site. See the Site Operations Manual for further details.

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

6.6 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments and/or interruptions are not permitted unless they are absolutely necessary for subject's safety. Any dose adjustments and/or interruptions will be recorded as protocol deviations. All changes must be recorded on the Dosage Administration Record CRF.

6.7 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the study monitor for the site and the Study Team that the code has been broken.

It is the investigator’s responsibility to ensure that there is a dependable procedure in place to allow access to the IRT system at any time in case of emergency. The investigator will need to provide:

- protocol number
- study drug name (if available)
- subject number.

In addition, the investigator must provide oral and written information to inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable to ensure that un-blinding can be performed at any time.

An assessment will be done by the appropriate site personnel and sponsor after an emergency unblinding to assess whether or not study treatment should be discontinued for a given subject.

6.8 Treatment exposure and compliance

6.9 Recommended treatment of adverse events

AEs should be treated per the judgement of the responsible physician. Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.10 Rescue medication

Use of short-acting rescue inhalers/bronchodilators for asthma, such as albuterol/salbutamol, is permitted. They must be sourced by the investigational site or the subjects themselves. Both short and long acting bronchodilators must be withheld prior to the study visits as described in the SOM. No other specific rescue treatments are planned for this study. Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.11 Concomitant treatment

The investigator must instruct the subject to notify the study site about any new medications he/she takes after the subject was enrolled into the study.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

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

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety, and thereafter no further study treatment will be made available to them.

Study completion is defined as when the last subject completes their End of Study 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.
All subjects should complete the follow up visits 201, 202 and an End of Study visit 299. Additionally, in case the treatment is prematurely interrupted due to AE or any other reason and not resumed, site should conduct visit 201 approximately 7 days after the last treatment visit, visit 202 approximately 6 weeks after visit 201, and visit 299 approximately 6 weeks after visit 202. Thus, the patient will complete all 3 follow up visits, which will enable patient safety assessment for 13 weeks after the last dose. Additional unscheduled safety visits may be conducted per the judgement of the PI if required to ensure patient safety.

All SAEs reported during the entire study duration must be reported as described in Section 9.2 and the Site Operations Manual. If a subject is lost to follow-up, documentation of attempts to contact the subject should be recorded in the source documentation. Subjects are expected to continue their standard of care treatment during and after the study.

7.2 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration. Discontinuation of study treatment can be decided by either the subject or the investigator.

Study treatment must be discontinued under the following circumstances:

- Subject decision - subjects may choose to discontinue study treatment for any reason at any time.
- The investigator believes that continuation would negatively impact the safety of the subject or the risk/benefit ratio of trial participation.
- Any protocol deviation that results in a significant risk to the subject's safety.
- Pregnancy (see Section 8.6 (Safety) and Section 9.6 (Pregnancy reporting)*)*
- Adverse events, abnormal laboratory values or abnormal test result that indicate a safety risk to the subject.
- Patients who experience an asthma exacerbation during the treatment epoch that requires treatment with systemic corticosteroids.
- Patients with > 50% decrease in FEV_1 confirmed by a repeat measurement during the study period.
- Emergence of the following severe adverse events :
  - Severe, grade 3 or higher allergic or hypersensitivity reaction
  - Severe, acute, grade 3 or higher infection as judged by the investigator
  - Severe neutropenia grade 3 or higher
- If a liver or renal event occurs, follow guidelines outlined in Appendix 1 and Appendix 2 regarding discontinuation of study treatment.
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study.

Treatment for patients experiencing an asthma exacerbation with systemic steroids is considered standard of care. The dose and duration for such treatment will be left at the discretion of the clinical site study investigator, so that appropriate treatment can be tailored to the severity of the patient's clinical condition. Treatment discontinuations due to asthma exacerbations will be considered "treatment failures".

Use of prohibited treatment as per Table 5-1 might result in treatment discontinuation (decision will be taken on case by case basis after consultation with Sponsor).

The appropriate personnel from the site and Novartis will assess whether investigational drug treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

If discontinuation of study treatment occurs, investigator must determine the primary reason for the subject's premature discontinuation of study treatment and record this information on the Dosage Administration CRF.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 7.3, Withdraw of Informed Consent). Where possible, they should return for visits 201, 202 and 299. If they fail to return for these visits for unknown reasons, every efforts (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in Section 7.4 (Lost to follow-up).

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

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- new / concomitant treatments
- adverse events/Serious Adverse Events

7.3 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
- Does not allow further collection of personal data

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 EU and Rest of the World: 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.

7.4 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 should 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 cannot be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.5 Study Stopping rules

The study may be put on hold pending full safety data review if one or more of the following criteria are met:

- Two or more similar investigational drug (CJM112)-related SAEs are reported
- Other clinically significant events that in the opinion of the investigator or sponsor preclude to continue dosing (especially events that are suspected to be drug related, such as severe infections, anaphylaxis)

In these cases, ad hoc internal experts along with representative site investigators will carefully evaluate the safety data of the entire study. The experts and investigators will recommend whether the study can be continued, should be stopped or if other safety measures need to be taken. The findings and recommendations of the internal experts and investigators will be documented and will be made available to all investigators, their respective Institutional Review Board/Independent Ethics Committee (IRB/IEC) and health authorities, as appropriate.

7.6 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. Should this be necessary, subjects must be seen as soon as possible 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 subjects' interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

8.1 Assessment schedule

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8.2 Informed consent procedures

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

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. The date of signing of informed consent (and withdrawal, if later withdrawn) should be documented in the CRF.

Novartis will provide to investigators a proposed informed consent form that complies with the ICHE6 GCP guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the subject agrees to future research. Any changes to the proposed consent form suggested by the investigator must be agreed to 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.

Ensure subjects are informed of the contraception requirements outlined in the Section 4.2 (Exclusion criteria) and in Section 5.1 (Contraception requirements).

Pregnancy outcomes must be collected for any females who become pregnant during the study and from the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

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

8.3 Subject screening

Re-screening once per subject is allowed if deemed feasible or necessary by the study site investigator. Information on what data should be collected for screening failures is outlined in the Site Operations Manual.

8.4 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. This will include detailed information on their asthma and allergy history, such as age of onset of asthma, duration since first diagnosis of asthma, environmental and drug allergies (including allergy to aspirin), asthma exacerbations, failed therapy, family history of asthma and allergies, smoking history, and so on. Details are outlined in the Site Operations Manual.

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

8.4.1 Demography

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Details are outlined in the Site Operations Manual.

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

8.4.2 Medical history/current medical conditions

Relevant medical history and current medical conditions will be recorded on the CRF until signature of the informed consent.

Where possible, diagnoses and not symptoms will be recorded.

Any event or change in the subject's condition or health status occurring *prior to* informed consent will be reported in the Relevant medical history / Current medical conditions section of the CRF.

8.5 Efficacy / Pharmacodynamics

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Lung function test reports will be subject to central reading and adjudication. Kindly refer to the SOM for further details.

8.5.1 Clinical Outcome Assessments (COAs)

Clinically relevant questionnaires that will be administered during the course of the study include two validated questionnaires (the Asthma Control Questionnaire or ACQ,). These will be administered at various timepoints during the study as depicted in the Assessment schedule. Additionally, daily symptoms, and rescue inhaler use will be captured on an electronic device which will be dispensed to each subject by the study site. Further details will be described in the SOM.

8.5.2 Spirometry

Spirometry testing will be performed according to the American Thoracic Society guidelines at screening to assess patients' eligibility for the study and at repeated intervals as detailed in the Assessment schedule. Details regarding equipment, study site personnel training and certification, spirometric values captured in the database and quality control will be included in the SOM.

8.6 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the Assessment schedule (Section 8.1) detailing when each assessment is to be performed.

Study inclusion and exclusion criteria will be reviewed at screening and baseline. Review of medical history and concomitant medications and any changes therein must be reviewed at

each study visit. Alcohol test, drug screen, cotinine test, hepatitis and HIV screen will be conducted at screening and baseline. Review of EKG, vital signs and physical exam will be conducted during the study as per the Assessment schedule. Clinical chemistry, hematology and urinalysis samples will be collected and results reviewed by eligible study site personnel at regular intervals. Hypersensitivity reactions have not been observed so far for CJM112, but their future occurrence cannot be excluded. Study subjects should be monitored post-injection for hypersensitivity and anaphylaxis events for an appropriate amount of time, no less than 30 minutes post-dose. Women of child-bearing potential will be subject to pregnancy test as per the Assessment schedule. Patient diary will be reviewed at each visit. Adverse events will be reviewed and documented at each visit.

8.6.1 Clinical Chemistry

Sodium, potassium, creatinine, BUN/urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, bicarbonate/HCO_3, LDH, GGT, AST, ALT, amylase, lipase, hs-CRP, CK, glucose, total cholesterol, triglycerides. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

8.6.2 Electrocardiogram (ECG)

Full details of all procedures relating to the ECG collection and reporting are contained in the core laboratory technical manual or in the Site Operations Manual.

In the event that a clinically significant ECG abnormality is identified at the site (e.g. severe arrhythmia, conduction abnormality of QTcF > 500 ms, significant T wave changes) the ECG is repeated to confirm the diagnosis.

Clinically significant abnormalities must be reported in the AE CRF.

If the subject is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

The following parameters will be entered into the eCRF: PR interval, QRS duration, heart rate, RR, QT, QTc, QTcF.

The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

8.6.3 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differentials, ESR, and platelet count will be measured.

8.6.4 Immunogenicity

8.6.5 Physical Examination

See Site Operations Manual for details.

8.6.6 Vital Signs

- Body temperature
- Blood pressure (BP)
- Pulse
- Respiratory Rate
- Oxygen saturation by pulse oximetry

8.7 Pharmacokinetics

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8.7.1 PK blood collection

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8.8 Other assessments

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8.9 Use of residual biological samples

Residual blood and urine samples may be used for another protocol specified endpoint.

9 Safety monitoring

9.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., 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 until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an adverse event irrespective if a clinical event has occurred. See Section 9.5 for an overview of the reporting requirements.

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 finding, laboratory test finding, or other assessments.

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 should 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 patients with underlying disease. Investigators have the responsibility for managing the safety of individual

subject and identifying adverse events. Alert ranges for liver and kidney related events are included in Appendix 1 and Appendix 2, respectively.

Adverse events must be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

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
   - Yes or
   - No
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 9.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding investigational treatment.
   All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - no action taken (e.g. further observation only)
   - investigational treatment dosage increased/reduced
   - investigational treatment interrupted/withdrawn
   - concomitant medication or non-drug therapy given
   - hospitalization/prolonged hospitalization (see Section 9.2 for definition of SAE)
6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

The investigator must also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject’s personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator’s source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

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:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient 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 the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

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

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 (see Annex IV, ICH-E2D Guideline).

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. 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 (see Annex IV, ICH-E2D Guideline).

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

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis Drug Safety & Epidemiology (DS&E) as per Section 9.2.2.

9.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the end of the study [must be reported to Novartis **within 24 hours of learning of its occurrence** as described below. Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Note: SAEs reported by subjects deemed to be screen failures must be reported to Novartis as outlined here with appropriate information also captured in the CRFs as specified in the Site Operations Manual.

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.

Follow- up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

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 Drug Safety and Epidemiology 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.

Follow the detailed instructions outlined in the Site Operations Manual regarding the submission process for reporting SAEs to Novartis. Note: **SAEs must be reported to Novartis within 24 hours** of the investigator learning of its occurrence/receiving follow-up information.

9.3 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.

Please refer to Table 15-1 in Appendix 1 for complete definitions of liver events.

Follow-up of liver events

Every liver event defined in Table 15-1 of Appendix 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 15-2 of Appendix 1.

- Repeating liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and γGT) to confirm elevation within 48-72 hours.

  These liver chemistry repeats should always be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, 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 the unscheduled local laboratory 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 Section 7.2 (Discontinuation of study treatment), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include:
  - Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and gGT. If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. Retesting should be continued up to resolution.
  - Obtaining a more detailed history of symptoms and prior or concurrent diseases.
  - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
  - Exclusion of underlying liver disease, as specified in Table 15-3.
  - Imaging such as abdominal US, CT or MRI, as appropriate
  - Obtaining a history of exposure to environmental chemical agents.
  - Considering gastroenterology or hepatology consultations.

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

9.4 Renal safety monitoring

Every renal laboratory trigger or renal event must be followed up by the investigator or designated personnel at the trial site. Recommended follow-up assessments are listed in Section 16 (Appendix 2).

9.5 Reporting Medication 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, patient/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.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Novartis Drug Safety and Epidemiology department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Drug Safety and Epidemiology. As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 9-1 summarizes the reporting requirements.

Table 9-1 Summary of reporting requirements for medication errors

Treatment error type	Document in Dose Administration (DAR) CRF	Document in AE CRF	Complete SAE form/CRF
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 Section 9.1 and Section 9.2, respectively.

9.6 Pregnancy reporting

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 must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

9.7 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs 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 monitor will visit the site to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

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 CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety 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.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to ClinBAY. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and 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.

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

10.3 Database management and quality control

Novartis staff or CRO working on behalf of Novartis review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff or CRO working on behalf of Novartis who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant 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.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Diary data will be entered into an electronic diary by the subject. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the COAR Analytics NIBR Franchise Head and the relevant NIBR TA Head.

10.4 Data Monitoring Committee

Not required.

10.5 Adjudication Committee

Not required.

11 Data analysis

The analyses will be conducted on all subject data at the time the trial ends.

11.1 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.

11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

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

All data for background and demographic variables will be listed by treatment and subject. Summary statistics will be provided for all subjects, as well as for each treatment sequence.

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

11.3 Treatments

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

11.4 Analysis of the primary variable(s)

Company Confidential Information

11.4.1 Variable(s)

Company Confidential Information

11.4.2 Statistical model, hypothesis, and method of analysis

Company Confidential Information

11.4.3 Handling of missing values/censoring/discontinuations

Company Confidential Information

The repeated measures regression model can accommodate subjects with missing follow-up FEV1 and will produce valid estimates of mean and covariance parameters if the data are missing at random.

11.5 Analysis of secondary variable(s)

11.5.1 Efficacy / Pharmacodynamics

Company Confidential Information

11.5.2 Safety

Vital signs

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

ECG evaluations

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

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

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

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

Other safety evaluations

Pregnancy test results will be listed by treatment group, subject and visit/time.

11.5.3 Pharmacokinetics

Company Confidential Information

11.5.4 Other assessments

Company Confidential Information

11.6 Analysis of exploratory variables

Company Confidential Information

Company Confidential Information

11.7 Sample size calculation

Company Confidential Information

11.8 Interim analyses

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12 Ethical considerations

12.1 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 Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 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.

For multi-center trials, a Coordinating Investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

13 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 is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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.

13.1 Protocol Amendments

Any change 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.

Amendments that are intended to eliminate an apparent immediate hazard to subjects 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, the reporting requirements identified in Section 9 (Safety Monitoring) must be followed and the Study Lead informed.

14 References

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15 Appendix 1: Liver Event Definitions and Follow-up Requirements

Table 15-1 Liver Event Definitions

Definition	Thresholds
Potential Hy's law cases	• ALT or AST > 3 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT or AST elevation with coagulopathy	• ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
ALT or AST elevation accompanied by symptoms	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	• ALT or AST > 8 × ULN • 5 x ULN < ALT/AST ≤ 8 x ULN • 3 x ULN < ALT/AST ≤ 5 x ULN
Isolated ALP elevation	• ALP > 2 × ULN (in the absence of known bone pathology)
Others	• Any clinical event of jaundice (or equivalent term) • Any adverse event potentially indicative of liver toxicity

Table 15-2 Actions required for Liver Events

Criteria	Actions required
Potential Hy's Law case ALT or AST elevation with coagulopathy ALT or AST elevation accompanied by symptoms Isolated ALT or AST elevation > 8 × ULN Jaundice	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete CRFs per liver event guidance
Isolated ALT or AST elevation > 5 to ≤ 8 × ULN	• If confirmed, consider interruption or discontinuation of study drug • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete CRFs per liver event guidance
Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	• Monitor liver chemistry tests two or three times weekly
Isolated ALP elevation	• Repeat liver chemistry tests within 48-72 hours • If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality • Complete CRFs per liver event guidance
Any AE potentially indicative of liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalize if clinically appropriate • Complete CRFs per liver event guidance

Table 15-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, gGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

16 Appendix 2: Specific Renal Alert Criteria and Actions

Table 16-1 Specific Renal Alert Criteria and Actions

Criteria	Action required
Serum creatinine (sCr) increase 25 – 49% compared to baseline	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50%	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider hospitalization and specialized treatment
Protein-creatinine or albumin-creatinine ratio increase ≥ 2-fold or new onset dipstick proteinuria ≥ 1+ or Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; or Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol	• Consider causes and possible interventions • Assess serum albumin & serum protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset glucosuria on urine dipstick (unless related to concomitant treatment, diabetes)	Assess & document: • Blood glucose (fasting) • Serum creatinine • Urine albumin-creatinine ratio
New hematuria on dipstick	Assess & document: • Urine sediment microscopy • Assess sCr and urine albumin-creatinine ratio • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

Additional specialized assessments are available to assess renal function or renal pathology. (Note: In exceptional cases when a nephrologist considers a renal biopsy, it is strongly recommended to make specimen slides available for evaluation by Novartis to potentially identify project-wide patterns of nephrotoxicity.)

Whenever a renal event is identified, a detailed subject history and examination are indicated to identify, document and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size)
- Signs and symptoms such as fever, headache, shortness of breath, back or abdominal pain, dysuria, hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other potential causes of renal dysfunction, e.g., dehydration, hemorrhage, tumor lysis

Table 16-2 Follow-up of renal events

Action	Follow up
Assess*, document and record in the Case Report Form (CRF) or via electronic data load. Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc) in the CRF.	• Urine dipstick and sediment microscopy • Blood pressure and body weight • Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Monitor subject regularly (frequency at investigator's discretion) until:	• Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) • or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

* Urine osmolality: in the absence of diuretics or chronic kidney disease this can be a very sensitive metric for integrated kidney function that requires excellent tubular function. A high urinary osmolality in the setting of an increase in sCr will point toward a "pre-renal" cause rather than tubular toxicity.