NOVARTIS

Novartis Research and Development

CSJ117

Clinical Trial Protocol CCSJ117A12201C / NCT04410523

A 12-week, multicenter, randomized, double-blind, parallel-arm, placebo-controlled study to assess the efficacy and safety of CSJ117, when added to existing asthma therapy in patients ≥18 years of age with severe uncontrolled asthma.

Document type:	Amended Protocol Version
EUDRACT number:	2019-004905-29
Version number:	03 (Track Changes)
Clinical Trial Phase:	IIb
Release date:	21-Jan-2022

Table of contents

List of tables

List of figures

List of abbreviations

ACQ	Asthma Control Questionnaire
ADA	Anti Drug Antibodies
ADSD	Asthma Daytime Symptom Diary
AE	Adverse event
AIC	Allergen inhalation challenge
Alb	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AM	Ante Meridiem (before midday)
ANCOVA	Analysis of covariance
ANSD	Asthma Nighttime Symptom Diary
AQLQ	Asthma Quality of Life Questionnaire
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AV	Atrioventricular block
b.i.d.	Twice a day
BD	Bronchodilator
BEV	Back-extrapolated volume
BfArM	Bundesinstitut fuer Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BMI	Body Mass Index
BP	Blood pressure
BTPS	Body temperature and pressure saturated
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CE	Conformité Européene mark
CFR	Code of Federal Regulation
CMO & PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
COA	Clinical Outcome Assessments
[redacted]	
COVID-19	Corona Virus Disease 2019
CRA	Clinical research associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computed tomography
CTT	Clinical Trial Team
Ctrough	Trough plasma concentration (measured concentration at the end of a dosing interval at steady state)
CV	Coefficient of variation

DBP	Diastolic blood pressure
DDE	Direct data entry
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DMPK	Drug Metabolism & PharmacoKinetics
DNA	Deoxyribonucleic acid
DPI	Dry powder inhaler
DR	Dose response
EBV	Epstein-Barr virus
EC	Ethics committee
ECG	Electrocardiogram
ECLIA	Electrochemiluminescence immunoassay
eCRF	Electronic case report forms
EDC	Electronic Data Capture
EDD	Expected delivery date
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EOFE	End of forced expiration
EOS	Eosinophils
ePEF	Electronic Peak Expiratory Flow
ERS	European Respiratory Society
eSource	Electronic source
EU	Europe
Fab	Fragment antigen binding
FAS	Full analysis set
Fc	Fragment crystallizable region
FDA	Food and Drug Administration
FDC	Fixed dose combination
FeNO	Fractional exhaled Nitric Oxide
FEV1	Forced expiratory volume in 1 second
FIVC	Forced inspiratory vital capacity
FSH	Follicle Stimulating Hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
GCS	Global clinical supplies
GGT	Gamma-glutamyl transferase
GINA	Global Initiative for Asthma guidelines
GLP	Good laboratory practice
HbA1c	hemoglobin A1c
HbcAb	Hepatitis B core antibody
HbsAb	Hepatitis B surface antibody
HbsAg	Hepatitis B surface antigen

HBV	Hepatitis B virus
HBV-DNA	Hepatitis B virus deoxyribonucleic acid
HCV RNA	Hepatitis C virus ribonucleic acid
HCV RNA-PCR	Hepatitis C virus ribonucleic acid polymerase chain reaction
HIV	Human immunodeficiency virus
HIV1/2-Ab	HIV1/2 Antibodies
hr	Hour
HRQOL	Health related quality of Life
HSV	Herpes simplex virus
i.v.	Intravenous
IB	Investigators Brochure
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICS	Inhaled corticosteroid
IEC	Independent Ethics Committee
IG	Immunogenicity
IGRA	Interferon Gamma Release Assay
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IMP	Investigational Medicinal Product
IN	Investigator notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine System
J2R	Jump to reference
L	Liter
LABA	Long acting beta-2 agonist
LAR	Late asthmatic response
LAMA	Long acting muscarinic antagonist
LDH	Lactate dehydrogenase
LFT	Liver function test
LLOQ	Lower Limit of Quantification
LTRA	Leukotriene receptor antagonists
mAb	Monoclonal antibody
MAR	Missing at random
[redacted]	[redacted]
MCP-Mod	Multiple comparison procedures modelling
MDI	Metered dose inhaler
MDRD	Modification of diet in renal disease
MedDRA	Medical dictionary for regulatory activities

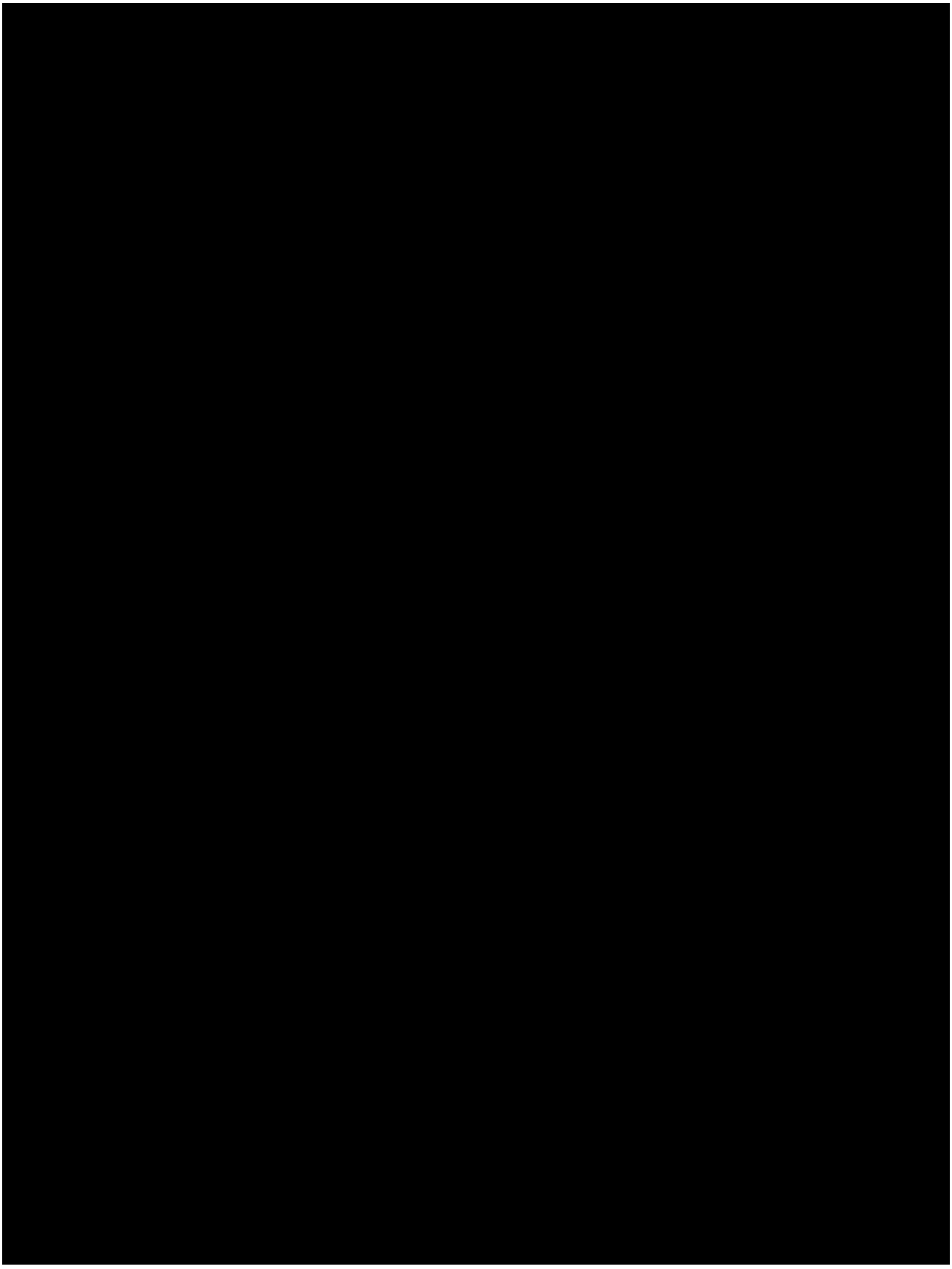
mg	milligram(s)
MI	Myocardial Infarction
MID	Minimally important difference
mL	Milliliter(s)
MMRM	Mixed effects model for repeated measures
NA	Not applicable
ng/mL	Mass per volume units
NO	Nitric oxide
NRS	Numeric rating scale
NYHA	New York Heart Association
o.d.	Once a day
OCS	Oral corticosteroid
OHP	Offsite healthcare professional
p	Probability value
PD	Pharmacodynamic(s)
PEF	Peak expiratory flow
[redacted]	[redacted]
[redacted]	[redacted]
PK	Pharmacokinetic(s)
PM	Post meridiem (after midday)
Pre-BD	Pre-bronchodilator
PRN	Pro re nata (as needed)
PRO	Patient reported outcome
PSW	Premature subject withdrawal
PT/INR	Prothrombin time international normalized ratio
Q4W	Every 4 weeks
QMS	Quality management system
QoL	Quality of Life
RAS	Randomized analysis set
Racc	Accumulation ratio
RTI	Respiratory Tract Infection
RoW	Rest of world
s	Seconds
s.c.	Subcutaneous
SABA	Short acting beta-2 agonist
SAE	serious adverse event
SAMA	Short Acting Muscarinic Antagonists
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SMQ	Standardized MedDRA query
SoC	Standard of Care

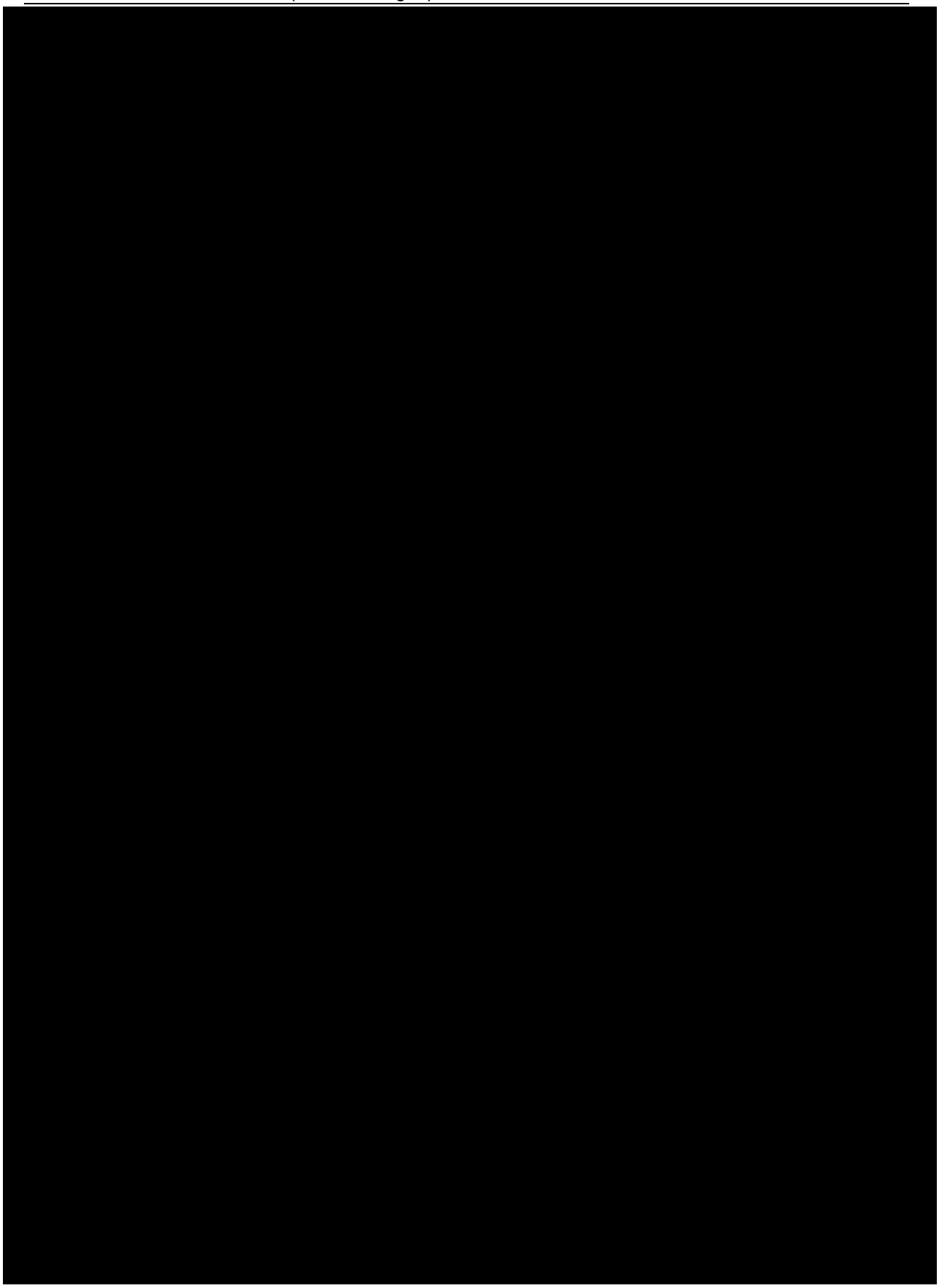
SOP	Standard Operating Procedure
S_{pool}	Standard deviation pooled
SUSAR	Suspected Unexpected Serious Adverse Reactions
[redacted]	[redacted]
TB	Tuberculosis
TBL	Total bilirubin
Th2	T helper type 2
TSLP	Thymic stromal lymphopoietin
ULN	Upper limit of normal
US	United States of America
WHO	World Health Organization
WoC	Withdrawal of Consent
µg	Microgram
µl	Microliters

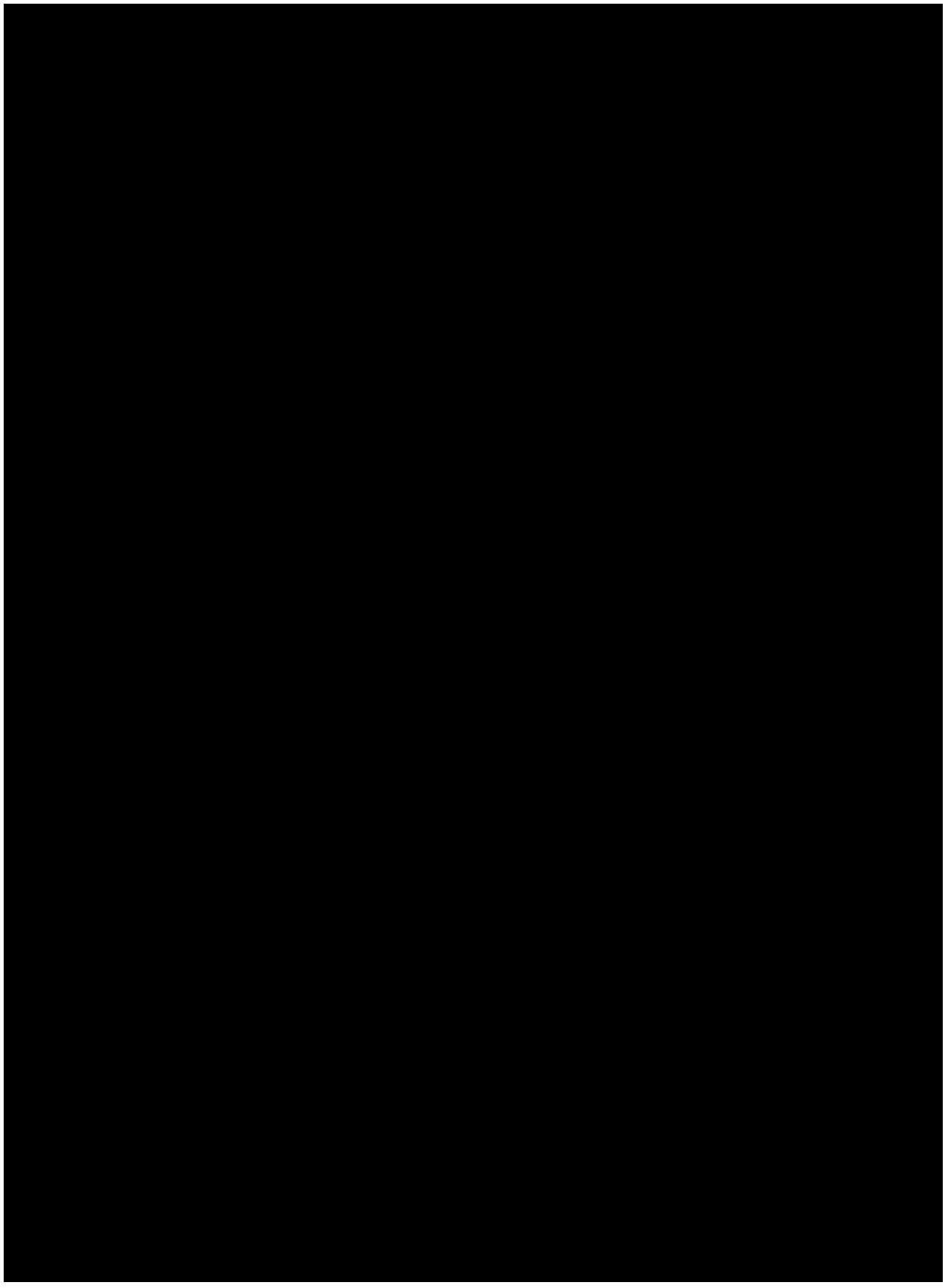
Glossary of terms

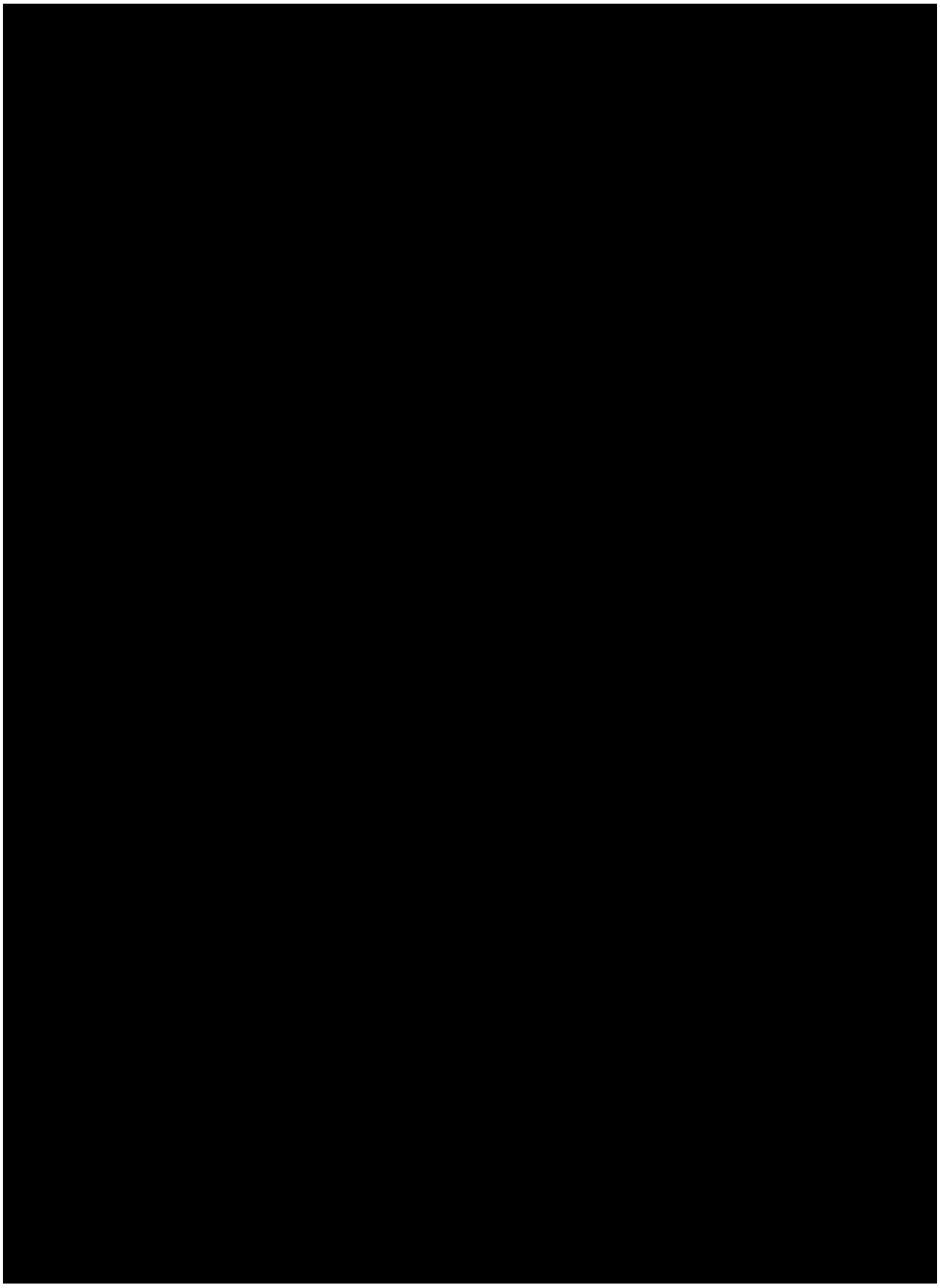
Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biological samples	A biological specimen including for example, blood (plasma, serum), saliva, tissue, urine, stool etc taken from a study subject
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
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)
Electronic Data Capture (EDC)	Electronic data capture is the electronic acquisition of clinical study data using data collection systems such as web-based applications, interactive voice response systems, and clinical laboratory interfaces. EDC includes the use of electronic case report forms which are used to capture data transcribed from paper source forms used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last subject or at a later point in time as defined by the protocol.
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)
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 is synonymous with “investigational new drug” or “investigational medicinal product”.
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Mis-randomized subjects	Mis-randomized subjects are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial subjects, regardless of randomization group, rescue medication, active drug run-ins etc.)
Off-site	Describes trial activities that are performed at a remote location by an off-site healthcare professional, such as procedures performed at the patient’s home.
Off-site healthcare professional	A qualified healthcare professional, such as a Nurse, who performs certain protocol procedures for the participant in an off-site location such as a participant’s home.

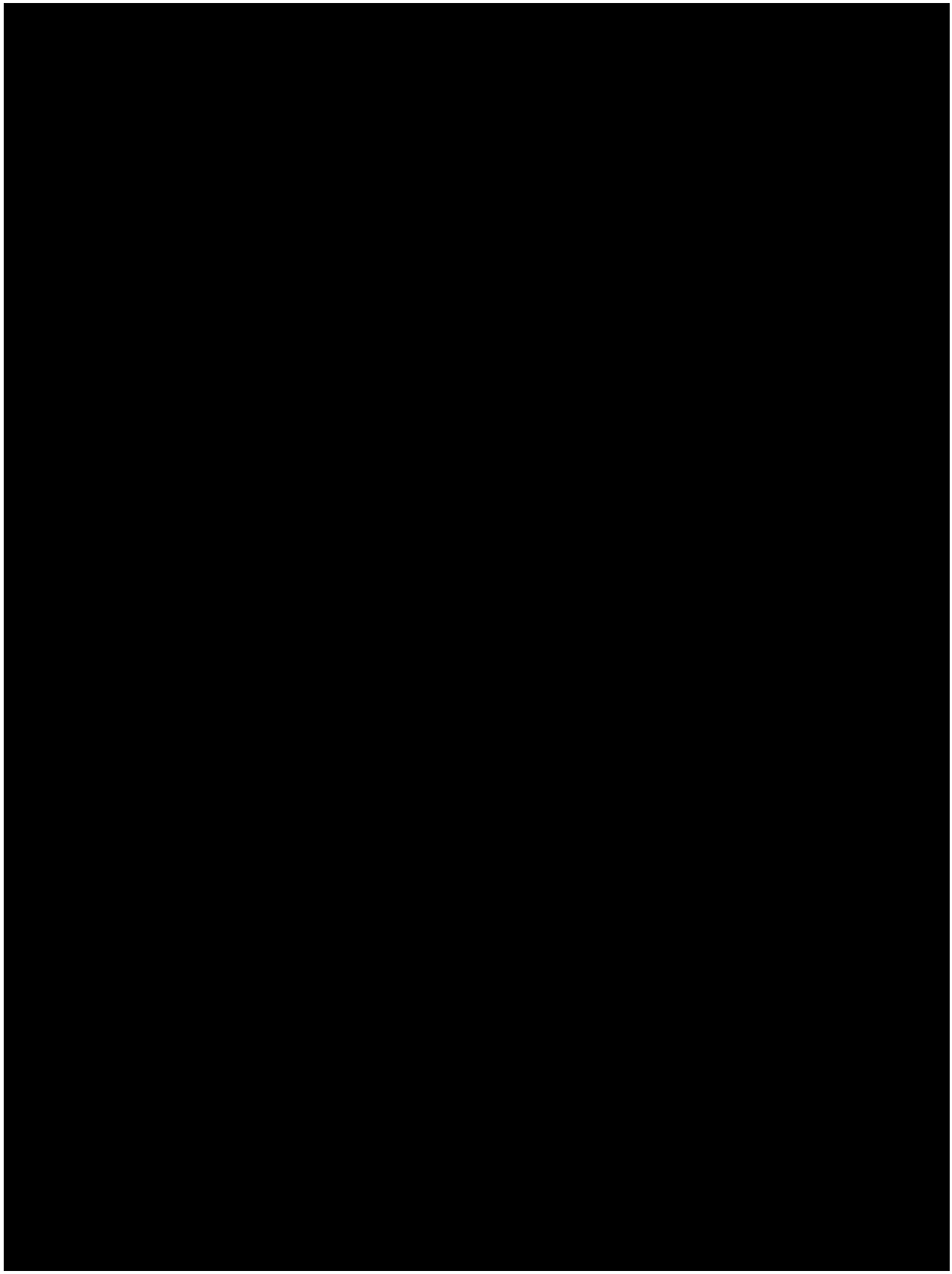
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, 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
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first subject.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study treatment 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 number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the patient is not at the investigative site where the investigator will conduct the trial.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints.
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

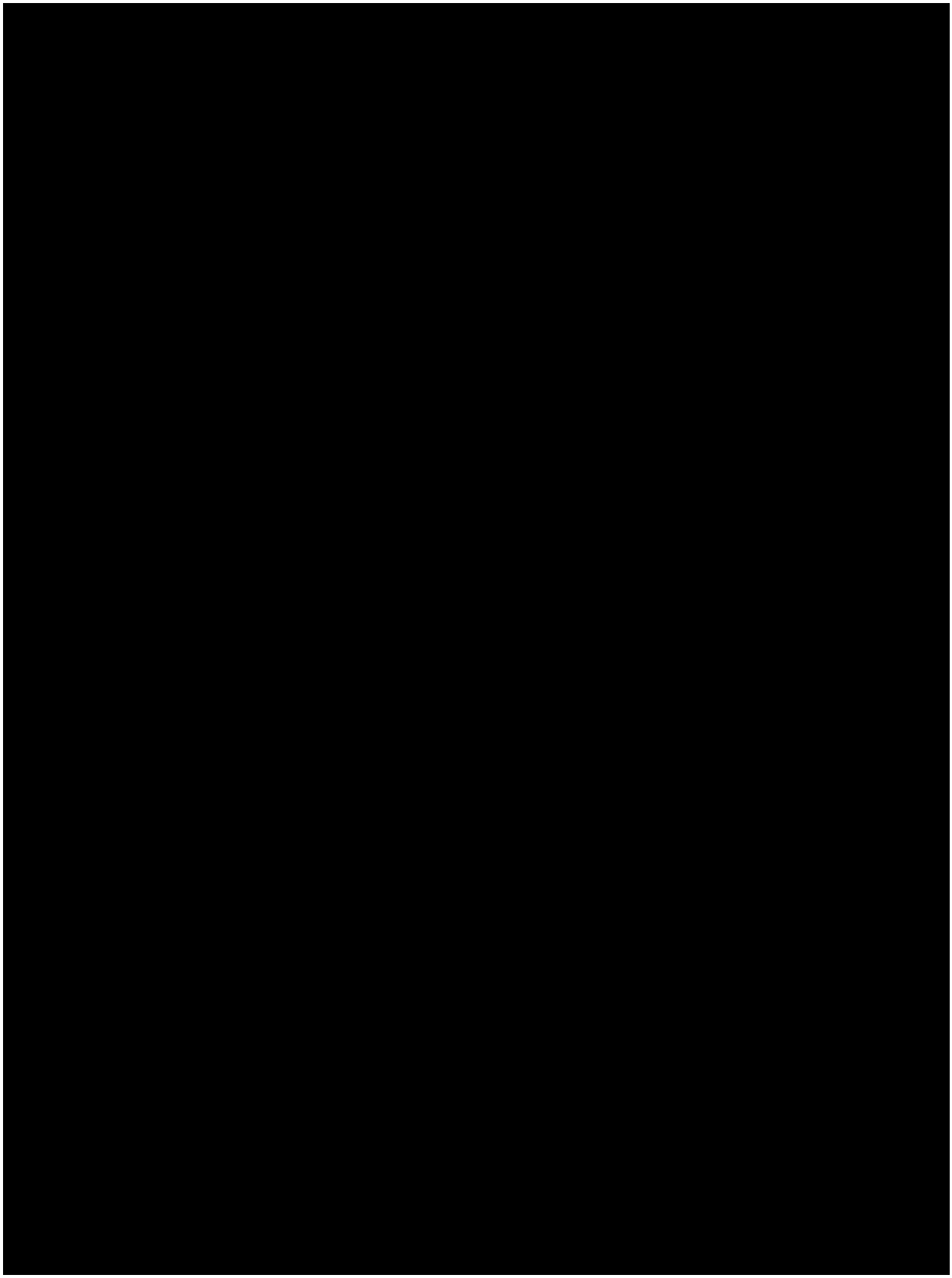


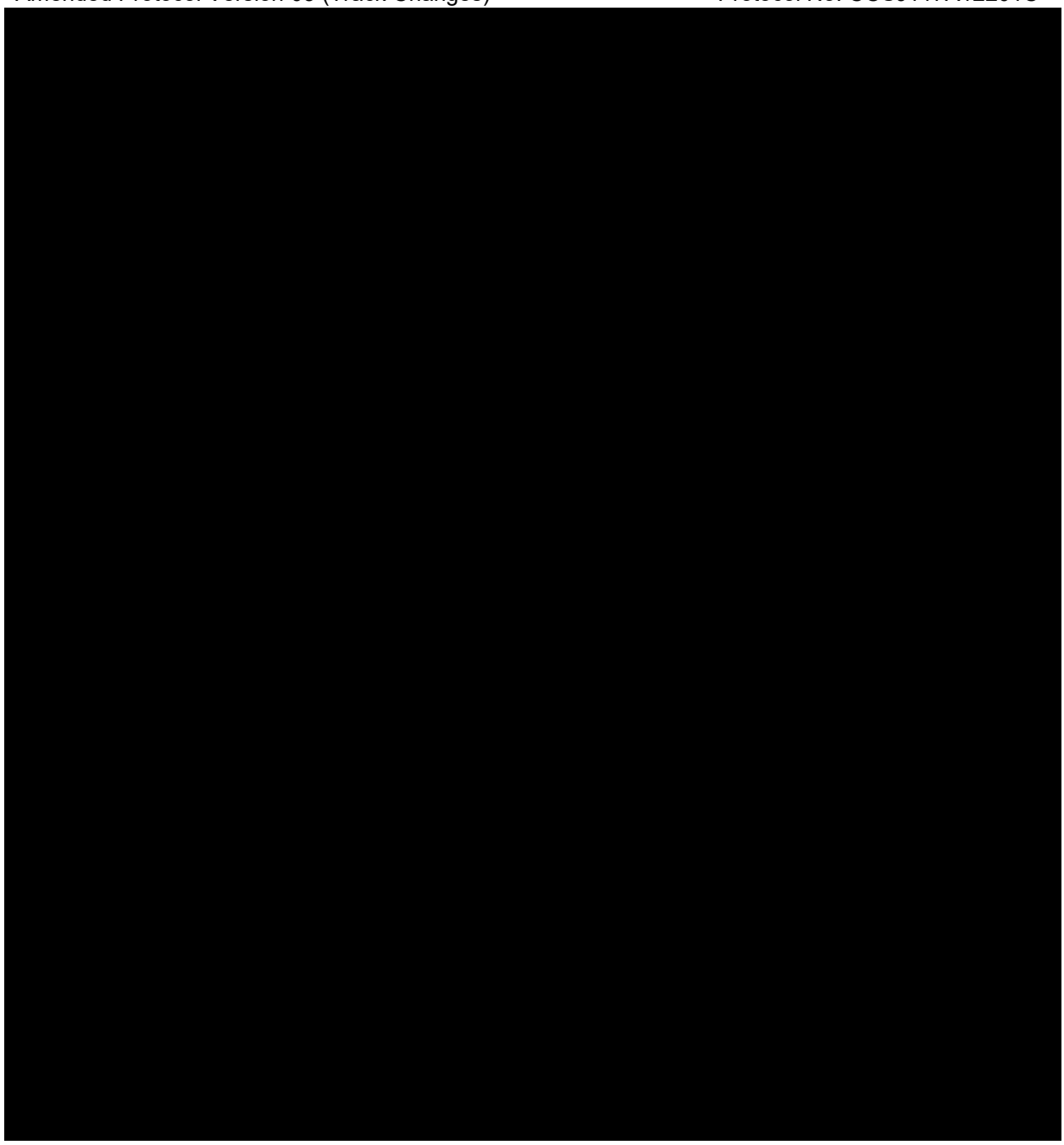












Protocol summary

Protocol number	CCSJ117A12201C
Full Title	A 12-week, multicenter, randomized, double-blind, parallel-arm, placebo-controlled study to assess the efficacy and safety of CSJ117, when added to existing asthma therapy in patients ≥ 18 years of age with severe uncontrolled asthma.
Brief title	Study of efficacy and safety of CSJ117 in patients with severe uncontrolled asthma
Sponsor and Clinical Phase	Novartis Pharma AG Phase IIb
Investigation type	Drug; Biological
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine the efficacy and safety of multiple CSJ117 doses (0.5; 1; 2; 4 and 8 mg) inhaled once daily compared with placebo, when added to standard-of-care (SoC) asthma therapy in adult patients with uncontrolled asthma with respect to change from baseline in FEV1 at the end of 12 weeks of treatment.
Primary Objective(s)	To characterize the dose-response relationship of five doses of CSJ117 inhaled daily on lung function, compared with placebo, at the end of the 12-week active-treatment period.
Secondary Objectives	1. To characterize the dose-response relationship of five doses of CSJ117 inhaled daily on FeNO compared with placebo, during the 12-week active-treatment period 2. To assess immunogenicity of five doses of CSJ117 during the study 3. To characterize the systemic pharmacokinetic (PK) profile of multiple inhaled daily doses of CSJ117 during the 12 week, active treatment period and the 12 week, follow-up period 4. To characterize the efficacy of five doses of CSJ117 once daily, compared with placebo, on peak expiratory flow (PEF; AM and PM), as assessed by mean morning and mean evening PEF over the 12-week active-treatment period 5. To characterize the efficacy of five doses of CSJ117 once daily, compared with placebo, on Asthma Control Questionnaire (ACQ-5) over the 12-week active-treatment period. 6. To characterize the efficacy of five doses of CSJ117 once daily, compared with placebo, on change from baseline in Asthma Quality of Life Questionnaire (AQLQ) score at the end of the 12-week active-treatment period 7. To characterize the efficacy of five doses of CSJ117 once daily, compared with placebo, on daytime and nighttime asthma symptoms over the 12-week active-treatment period 8. To characterize the efficacy of five doses of CSJ117 once daily, compared with placebo, on daily short-acting β-agonist (SABA) use over the 12-week active-treatment period 9. To assess the safety of five doses of CSJ117 once daily, compared with placebo, with respect to adverse events (AE), electrocardiograms (ECGs), vital signs and laboratory tests

Study design	This study uses a randomized, multicenter, double-blind, placebo-controlled, parallel-group study design.
Population	The study population will include: • Males and females aged ≥ 18 and ≤ 75 years. • Asthma patients who are already receiving ICS-LABA combination with up to two asthma controller medications (see Section 5.1, inclusion criterion 4 for allowed ICS doses and combinations) are the target population for this study.

Key Inclusion criteria	• Documented physician-diagnosed asthma (according to GINA 2019) for at least 12 months prior to screening.
	• Patients who have been treated with medium or high dose ICS plus LABA, alone or with up to two additional asthma controllers (allowed only: LTRA, theophylline or its derivatives, and LAMA) in a stable dose for at least 1 month, i.e. 30 days, prior to Screening
	• Subjects must have all morning pre-BD FEV1 values of ≥ 40% and ≤ 85% of the predicted normal after withholding bronchodilators at the start and the end of run-in.
	• Subjects must perform a reversibility test at the run-in visit. Reversibility is demonstrated by a Post-BD reversibility of FEV1 ≥ 12% and ≥ 200 mL within 30 minutes after administration of 400 µg salbutamol/albuterol (or equivalent dose). If reversibility is not demonstrated at the run-in visit and up to two unscheduled visits the following historical information may be used: documented evidence of reversibility that was performed according to American Thoracic Society (ATS)/European Respiratory Society (ERS) Standardization of Spirometry (Graham et al 2019). (ATS/ERS 2019) within the 1 year prior to Screening.
	• Subjects must have an ACQ-5 score of ≥ 1.5 at screening and end of run-in visits.
	•
	• Subjects must meet all of the following criteria at end of run-in visit prior to randomization:
	  • Subjects must demonstrate acceptable inhaler, peak flow meter, and spirometry techniques during the run-in period (from beginning to end of run in).
	  • Subjects must demonstrate ≥ 70% compliance with the asthma controller ICS-LABA during the run-in period based on their inhaler use count.
	  • Subjects must demonstrate ≥ 70% compliance with the CSJ117 placebo/Concept1 during the run-in period based on capsule use count.
	  • Subjects must demonstrate ≥ 70% compliance with required use of the eDiary during the last 2 weeks of the run-in period. 70% compliance is defined as completing the daily eDiary for 70% of the days (either morning or evening, including at least 7 morning and 7 evening eDiaries) in the last 2 weeks of the run in.

Key Exclusion criteria	• Patients, who cannot sustain washout of controllers additional to ICS-LABA before beginning of run-in. • Any oral corticosteroids as a maintenance treatment within 6 weeks, or any use of short-acting, intra-articular, intramuscular, or intravenous

	corticosteroid within 1 month, or any use of long acting, intra-articular or intramuscular corticosteroids within 3 months prior to Screening • Patients who have a cigarette smoking history of greater than 10 pack years or current smokers. • Pregnant or nursing (lactating) women • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using specified methods of contraception during dosing of study drug and until 12 weeks after last study drug treatment (end of follow up) Patients with a history of immunodeficiency disease, or hepatitis B, untreated and not cured hepatitis C or HIV.
Study treatment	CSJ117 (0.5; 1; 2; 4 and 8 mg) inhaled once daily Placebo inhaled once daily
Efficacy assessments	• Lung function (FEV1) • FeNO • Asthma symptoms • ACQ-5 • AQLQ • PEF • SABA use
Pharmacokinetic assessments	• Total CSJ117 serum concentration • Ctrough • Racc • T1/2
Key safety assessments	• Adverse event monitoring • Physical examinations • Vital signs • Laboratory examinations of blood and urine • 12-lead ECG
Other assessments	• ADSD and ANSD [redacted]
Data analysis	Primary objective: The MCP-Mod methodology will be used on the primary endpoint of the average change from baseline in pre-dose FEV1 at Week 8 and Week 12 to address the primary objective. 1. The adjusted mean responses at each individual dose will be estimated by modeling the primary endpoint using a mixed-effect linear model for repeated measures (MMRM). The null hypothesis of flat dose-response (DR) relationship will be tested at a two-sided significance level of 5% against the alternative hypothesis of a non-constant DR curve using a multiple contrast test, taking model uncertainty into account by considering a wide range of possible DR relationships.

	2. Once the DR signal is declared, the final DR curve and the target dose(s) of interest will be estimated by model averaging. Corresponding 95% confidence intervals are obtained using bootstrapping. Secondary objectives: The following secondary endpoints will be analyzed using a MMRM - average change from baseline in FeNO, ACQ-5, AQLQ+12, ADSD, and ANSD at Week 8 and Week 12, weekly mean morning and evening PEF, mean number of puffs of SABA taken per day in each week. Treatment-emergent adverse events will be summarized. Summary statistics will be provided by treatment and visit/time for each lab, vital signs, ECG, and pharmacokinetics variable.
Key words	CSJ117, uncontrolled asthma

1 Introduction

1.1 Background

Asthma is a chronic inflammatory disease of the airways characterized by reversible bronchoconstriction and an exaggerated airways response to bronchoconstrictor stimuli. Asthma presents a major global health burden. Despite existing therapies, there is still significant unmet medical need in asthma, with an estimated 300 million people affected worldwide. The World Health Organization estimates that 15 million disability–adjusted life years are lost annually due to asthma, representing 1% of the total global burden. Annual worldwide deaths have been estimated at 250,000 (Masoli et al 2004). Uncontrolled asthma has a prevalence of greater than 6 million patients worldwide.

In the case of allergic asthma, characterized by eosinophilic inflammation and evidence of atopy, T helper type 2 (Th2) immune pathway elements are crucial in the development and maintenance of airway inflammation and airway hyper responsiveness. A key upstream regulator of the Th2 response is Thymic stromal lymphopoietin (TSLP) (He and Geha 2010).

TSLP is an epithelial-cell derived cytokine produced in response to environmental and pro-inflammatory stimuli. It is upstream and central to the regulation of type-2 immunity through its activity on dendritic, T cells, B cells and innate immune cells. Additionally TSLP stimulates production of cytokines by antigen-specific Th2 cells.

In asthma patients, an increase in TSLP protein levels has been observed in both lung tissue and bronchial alveolar lavage fluid. Moreover TSLP has been shown to correlate with disease severity (Ying et al 2005, Ying et al 2008) and TSLP gene polymorphism is associated with a significant risk of childhood asthma (Biagini Myers et al 2014).

Repression of upstream TSLP is expected to reduce Th2 inflammation through inhibition of multiple pro-inflammatory cytokines simultaneously e.g. IL-5 and IL-13. Thus, reduction of TSLP activity might provide a significant advantage to therapies targeting only individual cytokines, or their receptors, involved in asthma pathogenesis.

CSJ117 is a potent neutralizing antibody fragment (fragment antigen-binding, Fab) directed against human TSLP. CSJ117 is formulated as a PulmoSol™ engineered powder in hard capsules for delivery to the lungs *via* dry powder inhaler (DPI). Compared to a full length antibody, CSJ117 does not have the Fc region and only contains the antigen binding region. Consequently the molecular weight of CSJ117, 46.6 kDa, is smaller than the molecular weight of a full length antibody, ~150 kDa. Once absorbed into the systemic circulation, the Fab molecule is expected to be cleared faster than a full length antibody, due to the smaller size of the Fab and the lack of neonatal Fc receptor binding. In the absence of target-mediated disposition, the systemic terminal elimination half-life (T½) in humans for a Fab typically ranges from 14 to 25 hours (Schaumann et al 1986, Czock et al 2012, Morris et al 2012) versus approximately 23 days for a full length IgG monoclonal antibody (mAb) (Lobo et al 2004).

The use of an anti-TSLP Fab molecule with a DPI formulation is expected to result in improved lung distribution and tissue penetration as compared to a full length systemically delivered antibody, due to the smaller size of the Fab and targeted delivery to the lung. CSJ117, as an inhaled Fab targeting TSLP, offers the potential to be an efficacious therapy for moderate to severe asthma with a favorable safety and tolerability profile.

The aim of the study is to investigate the efficacy and safety of multiple doses of CSJ117, inhaled daily, in uncontrolled asthma patients treated with a medium or high dose of an inhaled corticosteroid (ICS) in combination with a long-acting beta agonist (LABA). Tezepelumab, a human IgG2 monoclonal antibody against TSLP, has demonstrated the validity of targeting TSLP in asthma by showing significant improvements across a wide range of endpoints including asthma exacerbations, lung function, and asthma control (Corren et al 2017). While tezepelumab demonstrated clinical benefits such as decreased rate of exacerbations in patients with low blood eosinophils at baseline, the improvement in lung function (forced expiratory volume in one second; FEV1) was greater in patients with higher blood eosinophil (EOS) counts. Therefore, in this study, at randomization, patients will be stratified based on their blood eosinophil count with approximately 70% of patients recruited to the stratum with higher counts (≥ 300 cells/µl). This overall % of high eosinophil patients may be lower depending on whether sample size is decreased after blinded re-assessment (See Section 12.8.2).

1.2 Purpose

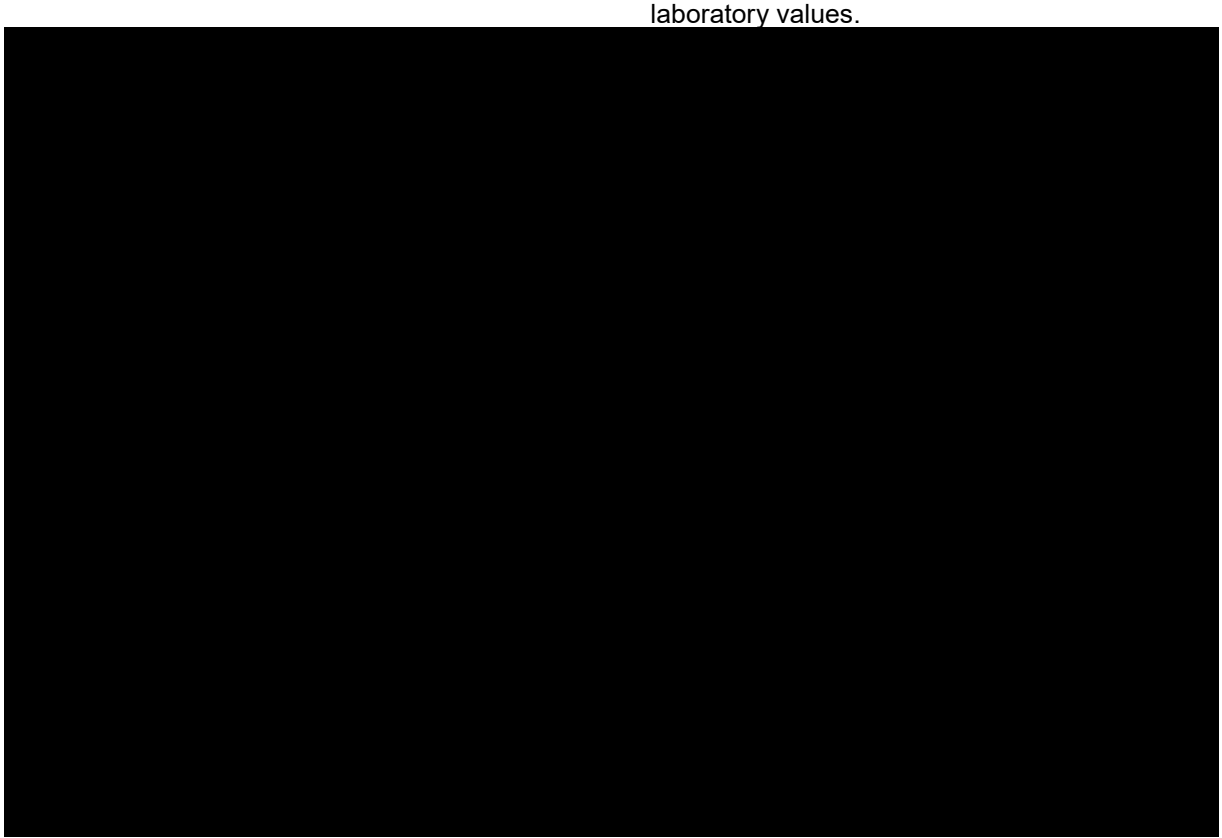
The purpose of this study is to determine the efficacy and safety of multiple CSJ117 doses (0.5; 1; 2; 4 and 8 mg) inhaled once daily compared with placebo, when added to standard-of-care (SoC) asthma therapy in adult patients with uncontrolled asthma with respect to change from baseline in pre-dose, pre-bronchodilator FEV1 at the end of 12 weeks of treatment.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To characterize the dose-response relationship of five doses of CSJ117 inhaled daily on lung function, compared with placebo, at the end of the 12-week active-treatment period.	• Average change from baseline in pre-dose FEV1 (L) at Week 8 and Week 12.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To characterize the dose-response relationship of five doses of CSJ117 inhaled daily on FeNO compared with placebo, during the 12-week active-treatment period	• Average change from baseline in FeNO at Week 8 and Week 12.
• To assess immunogenicity of five doses of CSJ117 during the study	• Measurement of Anti-Drug Antibodies (ADA) titers at baseline and during the study (Week 0 [Day 1] to Week 24)
• To characterize the systemic pharmacokinetic (PK) profile of multiple inhaled daily doses of CSJ117 during the 12 week, active treatment period and the 12 week, follow-up period	• Measurement of total CSJ117 serum concentration during the study (Week 0 [Day 1] to Week 24) and calculation of PK parameters (e.g., Ctrough, Racc, T½).
• To characterize the efficacy of five doses of CSJ117 once daily, compared with	• Change from baseline in peak expiratory flow (PEF; am and pm), as assessed by mean

Objective(s)	Endpoint(s)
placebo, on peak expiratory flow (PEF; AM and PM), as assessed by mean morning and mean evening PEF over the 12-week active-treatment period	morning and mean evening PEF in each week (average over 7 days) during 12 weeks of treatment.
• To characterize the efficacy of five doses of CSJ117 once daily, compared with placebo, on ACQ-5 over the 12-week active-treatment period.	• Average change from baseline in ACQ-5 score at Week 8 and Week 12.
• To characterize the efficacy of five doses of CSJ117 once daily, compared with placebo, on change from baseline in Asthma Quality of Life Questionnaire (AQLQ) score at the end of the 12-week active-treatment period	• Average change from baseline in AQLQ+12 score at Week 8 and Week 12
• To characterize the efficacy of five doses of CSJ117 once daily, compared with placebo, on daytime and nighttime asthma symptoms over the 12-week active-treatment period	• Average change from baseline in ADSD and ANSD score at Week 8 and Week 12.
• To characterize the efficacy of five doses of CSJ117 once daily, compared with placebo, on daily short-acting β-agonist (SABA) use over the 12-week active-treatment period	• Change from baseline in number of puffs of SABA taken per day in each week (average over 7 days) during 12 weeks active-treatment period
• To assess the safety of five doses of CSJ117 once daily, compared with placebo, with respect to adverse events (AE), electrocardiograms (ECGs), vital signs and laboratory tests	• Summaries of treatment-emergent adverse events, systolic and diastolic blood pressure, pulse rate, body weight, ventricular rate, RR interval, PR interval, QRS duration, heart rate, and Fridericia's QTc, laboratory values and change from baseline for continuous laboratory values.



The primary estimand of this trial is defined below.

- **Population**: adult patients with inadequately controlled asthma on medium or high dose ICS/LABA, alone or with up to two additional asthma controllers (LTRA, LAMA or theophylline)
- **Variable**: Average change from baseline in pre-dose FEV1 after 8 and 12 weeks of treatment
- **Treatment**: CSJ117 or placebo
- **Intervention effect of interest**: Effect of interventions initiated at randomization during stable periods (i.e. outside of periods of acute disease worsening requiring additional asthma medications) and that would have been observed had all patients remained on their assigned treatment for 12 weeks, with the following post-randomization events accounted for by assessing:
  - Intake of non-study drug with effect on FEV1: the effect outside of periods of worsening disease that necessitate rescue medication
  - Discontinuation of study treatment due to any reason: hypothetical value of the average between Week 8 and Week 12 pre-dose FEV1 had the patients not stopped the study treatment
  - The case where patient received treatment different from the assigned treatment: hypothetical value of the average between Week 8 and Week 12 pre-dose FEV1 had the patient remained on the assigned treatment for 12 weeks
- **Summary measure**: mean difference between CSJ117 and placebo

This estimand is considered appropriate for a dose finding trial in order to obtain a clear dose response signal and understand the maximum potential effect of the drug.

3 Study design

This study is a phase IIb, multicenter, multi-national, double-blind, randomized, parallel-arm, placebo-controlled study to evaluate the effect of 5 dose levels of CSJ117 in adult subjects with inadequately controlled asthma despite medium to high dose ICS plus LABA. Approximately 625 patients will be randomized into this study. A sample size re-estimation might be performed strictly using the blinded data after approximately 150 high eosinophils subjects completed the week 8 visit.

The study will include:

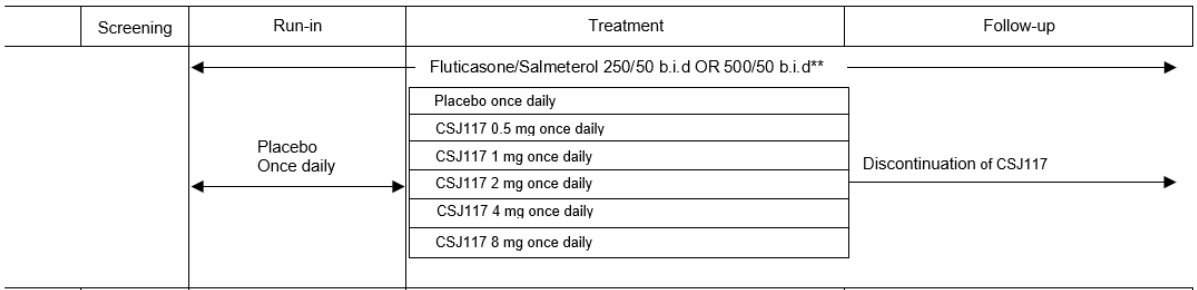
- A screening period of approximately 2 weeks, or shorter, to assess eligibility and baseline EOS count. Screening may optionally be split across 2 days to allow the collection of laboratory samples and the laboratory evaluations including the blood eosinophil (EOS) counts first. Patients will replace their current rescue medication with SABA provided by

Novartis, wash out prohibited medications (see Table 6-3) and practice the electronic peak expiratory flow (ePEF) and eDiary device. Screening must not end before confirmation of EOS count. If the results of EOS count or other laboratory assessments are not available at the end of the 2-week screening period or reversibility was not demonstrated at the run in visit the screening period will be extended.

- A single blinded placebo run-in, i.e. Baseline, period of approximately 4 weeks, to collect baseline data for efficacy variables and compliance with the ePEF and eDiary device as well as to assess adherence with placebo and standardized maintenance medication, fluticasone propionate/salmeterol xinafoate 250/50 µg or 500/50 µg b.i.d.. If a patient experiences an asthma exacerbation or respiratory tract infection (RTI) during the run-in period, the run-in period must be extended to 8 weeks to allow for resolution of the asthma exacerbation or respiratory tract infection before randomization. Eligibility for randomization will be determined at the end of the placebo run-in period. Site staff should not inform patients that during run-in they will receive placebo.
- A double blinded treatment period of 12 weeks.
- A follow-up period of 12 weeks, study drug free, following the last dose of study drug.

At randomization, subjects will be stratified by their blood eosinophil count (EOS) (≥ 300 or < 300 cells/µl), measured at the screening visit. Approximately 70% of the total study population will be enrolled in the high EOS stratum. The proportion of subjects with high eosinophil counts at screening (% of overall population) may vary depending on whether the sample size is decreased after blinded re-assessment. If recruitment for one EOS stratum is completed, only patients with screening visit EOS count allowing randomization to the other stratum will be eligible. Subjects will be randomized in a 2:1:1:1:2:2 ratio to receive placebo or one of 5 doses of CSJ117 (0.5, 1, 2, 4, 8 mg) once daily for 12 weeks. All arms will have the same stratification ratio.

Figure 3-1 Study Design



*it must be extended to 8 weeks for patients experiencing an asthma exacerbation during the run in period

**depending on ICS-LABA entry dose

At the investigator's direction based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option to have certain clinical trial procedures according to Table 8-1 performed at a remote location such as the patient's home, in the event that the patient cannot attend site during a public health emergency as stated in section 4.6. Procedures will be performed remotely under the oversight of the Investigator, who retains accountability for oversight and all efficacy and safety decisions with delegation of tasks to a mobile, offsite healthcare professional (OHP). The remote procedures will be offered in certain countries and sites as determined by Novartis based on national and local regulations. The OHPs will be arranged in agreement with Novartis for example by a third-party vendor. Where a site wishes to use OHPs that are not provided by Novartis this must be agreed with Novartis in advance.

4 Rationale

4.1 Rationale for study design

This randomized, double-blind, parallel-group, placebo-controlled, design supports the assessment of efficacy as well as safety of CSJ117 as add-on treatment for patients with asthma inadequately controlled on medium or high dose ICS plus LABA. According to Global Initiative for Asthma (GINA, 2019) guidelines, the goals of asthma therapy are to attain asthma control and reduce future risk of asthma worsening while maintaining minimal side effects of therapy. By maintaining good asthma control in patients with appropriate use of therapies, potential future risk to patients may be reduced. The endpoints included in this study measure objective and symptomatic parameters of asthma control (objective: lung function [FEV1]; symptomatic parameters: daytime and nighttime asthma symptoms, SABA use, quality of life [QoL], ACQ scores) in patients over 12 weeks of therapy.

4.1.1 Rationale for choice of background therapy

The most common use of biologic medications for asthma are currently in severe asthma patients who remain uncontrolled despite GINA Step 4 and 5 therapy. This trial aims to examine the biological effect of CSJ117 on lung function as assessed by change from baseline in pre-dose, pre-BD FEV1 after 12 weeks of treatment in severe persistent asthmatic population. Preferred step 4 and step 5 treatment of choice in GINA guidelines are medium and high dose ICS-LABA combinations, respectively. Subjects in the study will be severe asthma patients inadequately controlled on medium or high dose ICS-LABA. Subjects who enter the study with medium dose ICS-LABA will receive a fixed dose combination (FDC) of fluticasone propionate/salmeterol 250/50 µg b.i.d., while subjects who enter with high dose ICS-LABA will receive a FDC of fluticasone propionate/salmeterol 500/50 µg b.i.d. from the start of placebo run-in and throughout the study period. If subjects have been using controller medications in addition to ICS-LABA, all additional controllers will be discontinued post the Screening visit with instructions to use SABA as needed and to monitor their symptoms and lung function daily with the eDiary/ePEF device. Other changes to subjects' asthma SoC background treatment will be forbidden during the screening, run-in and active treatment periods. CSJ117 or placebo will be administered as add-on therapy to medium or high dose fluticasone propionate/salmeterol. All patients will be allowed to use SABA as rescue medication when required, throughout the trial.

For patients who do not enter a separate safety extension study (see Section 9.2) after completing the treatment period, investigators will be allowed to modify patients' background asthma therapy after they enter the follow-up period. However, it is forbidden to add during the follow up period any of the following:

- Oral, injectable or systemic corticosteroid (with exception as treatment of asthma exacerbations when necessary)
- Biologic drugs

4.2 Rationale for dose/regimen and duration of treatment

CSJ117 was designed for inhaled delivery. CSJ117 is formulated as a PulmoSol™ engineered powder in hard capsules for delivery to the lungs via dry powder inhaler (DPI; Concept1). Total duration of treatment with CSJ117 is 12 weeks. Total duration of treatment with placebo for all patients is from approximately 4 to 20 weeks, depending on randomization.

This dose range finding study includes 5 active doses of CSJ117 (0.5; 1; 2; 4 and 8 mg) and matching placebo for once daily inhaled delivery via Concept1 device. Based on modelling predictions of the CSJ117 clinical efficacious dose range and PK profile after repeated administration, once daily dosing over 12 weeks is expected to provide adequate pulmonary exposure in order to assess pharmacodynamics (PD) effects (i.e. change in lung function parameters: FEV1, FVC, PEF etc.), change in FeNO, asthma control, and quality of life. The chosen dose range is expected to identify the most appropriate CSJ117 dosing regimen to carry forward to a phase 3 program.

The CSJ117 doses selected for testing are 0.5, 1, 2, 4, and 8 mg o.d and the planned dose range is expected to adequately describe dose-response for CSJ117. The 4 mg o.d. dose is selected because of its demonstrated efficacy after 12 weeks of administration in a bronchoprovocation study (CCSJ117X2201) in mild atopic asthmatics. The efficacy profile of 4 mg o.d. CSJ117 in CCSJ117X2201 was similar to the results published for tezepelumab (700 mg i.v. every 4 weeks (Q4W) for 12 weeks) (Gauvreau et al 2014). The 4 mg inhaled o.d. dose of CSJ117 is also predicted to show similar efficacy as the 210 mg s.c. Q4W dose of tezepelumab, which had a demonstrated efficacy in a Phase 2b study in severe uncontrolled asthmatics. The lowest dose, 0.5 mg o.d., is intended to capture the slope of the dose-response curve (e.g., around the predicted ED50). The top dose of 8 mg o.d. is selected to determine if the 4 mg dose has reached a plateau for efficacy and 1 and 2 mg doses are included to adequately describe the efficacy dose-response.

CSJ117 doses in this trial were selected based on the safety, tolerability and pharmacokinetics of CSJ117 evaluated in a non-clinical good laboratory practice (GLP) toxicity study as well as in three studies mentioned below.

- CSJ117X2101: 49 healthy volunteers, CSJ117 single inhaled dose via the Concept1 device: 1 mg, 3 mg, 9 mg, 32 mg, 64 mg and 160 mg
- CSJ117X1101: 24 adult Japanese male healthy volunteers, CSJ117 single inhaled dose via the Concept1 device: 9 mg, 16 mg and 32 mg
- CSJ117X2201: 28 asthma patients, CSJ117 multiple 4 mg inhaled doses via the Concept1 device.

The final analysis in both studies demonstrated that all doses were well-tolerated with no safety concerns.

The totality of the non-clinical data and clinical data indicates that CSJ117 has a favorable safety profile and supports exposure in humans using inhaled delivery for up to 13 weeks. Please refer to the Investigator Brochure (IB) for additional details on safety margin calculations.

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

Placebo was chosen as the comparator as it will permit the assessment of improvement in terms of pre-dose FEV1 for patients with uncontrolled disease who are treated with CSJ117 plus SoC asthma therapy, in comparison to those solely on SoC asthma therapy. Additionally, the use of placebo will permit a controlled evaluation of the safety of CSJ117 plus SoC asthma therapy, compared with SoC asthma therapy in these patients. As mentioned above, all patients will be treated with SoC as background medication in line with GINA guideline recommendations and all patients will be allowed the use of SABAs as rescue medication when required.

4.4 Purpose and timing of interim analyses/design adaptations

One or more interim analyses may be conducted to support decision-making in relation to the current clinical study, or the future of the sponsor's clinical development plan or in case of any safety concerns from this study or ongoing clinical studies.

4.5 Risks and benefits

CSJ117 is a potent and highly selective inhaled anti-TSLP Fab antibody fragment being developed as a potential therapy treatment for patients with asthma. TSLP is an epithelial-cell derived cytokine produced in response to environmental and pro-inflammatory stimuli. TSLP is a master regulator of the allergic immune response, and inhibition of TSLP has the potential to modulate multiple arms of the allergic immune response simultaneously.

The potential benefits of CSJ117 therapy need to be balanced against its potential risks. The risk to patients in this study will be minimized by compliance with the inclusion/exclusion criteria and close clinical monitoring. Although altering current asthma medication regimens in some patients during the trial carries an inherent risk of a decline in lung function and/or a worsening of symptoms, providing patients with rescue medication (salbutamol/albuterol) and requiring them to take background ICS-LABA (fluticasone propionate/salmeterol b.i.d.) throughout the trial mitigates this risk. Compliance with the background therapy will be monitored at each clinic visit. All patients at screening will receive an eDiary/ePEF for daily monitoring their asthma symptoms and peak expiratory flow. eDiary/ePEF will need to be completed twice daily i.e. in the morning and in the evening. Investigators and their teams will be able to remotely monitor patients' symptoms and lung functions. Additionally eDiary/ePEF device automatically generates alarms when the PEF performance drops down, SABA use increases and when patients wake up due to asthma symptoms. Furthermore, patients will be instructed how to react to worsening of asthma symptoms so patients can be managed appropriately. The Investigators might adjust patient's therapy by adding controllers (allowed:

LAMA, LTRAs, theophylline and its derivatives) during the follow-up period once the active treatment period is completed.

The overall clinical experience with CSJ117 includes 3 studies: 2 completed phase 1 studies in healthy volunteers and one phase 2 proof-of-concept bronchoprovocation trial in mild asthma patients. Overall, the safety profile of CSJ117 has been favorable across studies. As of 31-Dec-2019, 70 subjects have been exposed to CSJ117. CSJ117 has been well tolerated in these subjects, studied at daily doses up to 160 mg.

In two completed phase 1 studies in healthy volunteers (CSJ117X2101 and CSJ117X1101), no patients reported serious adverse events (SAEs), no deaths due to SAEs were reported, and no discontinuations due to SAEs were reported. In the CSJ117X2101 study, CSJ117 treated subjects did not experience a greater number of AEs compared to placebo and all of the AEs were mild except for two moderate AEs: (1) toothache requiring extraction in the 160 mg cohort on day 16, and (2) headache in the placebo group on day 1. In the CSJ117X1101 study, there was only one AE (increased blood triglycerides) reported in one subject in the placebo group. There were no SAEs with a suspected causal relationship to CSJ117. There have been no adverse events of idiopathic drug reactions.

Two Phase 1 studies with healthy volunteers treated with CSJ117 were conducted i.e. Studies CSJ117X2101 and CSJ117X1101. In addition, study CSJ117X2201 in mild asthma patients was completed. Below is a summary of efficacy and safety data from these three completed studies. For detailed information on these studies, please refer to the Investigators Brochure.

Study CSJ117X2101

Study CSJ117X2101 was a first-in-human, randomized, subject-blind, placebo controlled, single ascending dose study to assess the safety, tolerability and pharmacokinetics of CSJ117 in 51 adult healthy subjects. Tested inhaled CSJ117 doses included 1, 3, 9, 32, 64 and 160 mg.

The primary objective of the study was to evaluate the safety and tolerability of single ascending doses of inhaled CSJ117 measured by adverse events, serious adverse events and all other safety assessments, up to and including the study completion visit.

Results showed that CSJ117 was found to be safe and well-tolerated at single inhaled doses of 1 mg, 3 mg, 9 mg, 32 mg, 64 mg, and 160 mg. There were no SAEs, deaths, and discontinuations due to AEs. CSJ117 subjects did not experience a greater number of AEs compared to placebo and the majority of AEs were mild. The most common AE was mild upper respiratory tract infection, which occurred in 8% of CSJ117 subjects and 8% of placebo subjects. Additionally CSJ117 serum exposure increased in a dose-dependent manner in the dose range of 1-160 mg following single inhaled doses of CSJ117 via the Concept1 device. There was no apparent impact of anti-CSJ117 antibodies on CSJ117 PK or safety. Pre-existing anti-CSJ117 antibodies were detected in 11 subjects. The detection of pre-existing anti-CSJ117 antibodies was not expected to increase the risk of clinically significant antidrug antibodies.

Study CSJ117X1101

Study CSJ117X1101 was a randomized, subject-blinded, placebo-controlled, and single ascending dose study to assess the safety, tolerability and pharmacokinetics of a single inhaled CSJ117 dose i.e. 9 or 16 or 32 mg in 24 Japanese healthy male subjects. The primary objective

was to evaluate the safety and tolerability of single ascending doses of inhaled CSJ117 compared with placebo, as measured by all safety endpoints [i.e., physical exam, vital signs, electrocardiogram (ECG) parameters, spirometry parameters, clinical laboratories, and adverse events, including serious AEs (Serious Adverse Event (SAEs)] up to and including the End of Study visit.

Overall, CSJ117 was found to be safe and well-tolerated at single inhaled doses of 9 mg, 16 mg and 32 mg. There were no SAEs, deaths, and discontinuations due to AEs. There was only one AE (blood triglycerides increased) reported in one subject in the placebo group. CSJ117 serum exposure increased in a dose-dependent manner in the dose range of 9-32 mg following single inhaled doses of CSJ117 via the Concept1 device. Pre-existing ADAs were detected in 2 subjects. There was no apparent impact of ADAs on CSJ117 PK or safety. No increase in antibody titers was observed. The detection of pre-existing anti-CSJ117 antibodies is not expected to increase the risk of clinically significant antidrug antibodies.

Study CSJ117X2201

Study CSJ117X2201 was a randomized, double-blinded, placebo-controlled, parallel-design, broncho-provocation study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple doses of inhaled CSJ117 in adult subjects with mild atopic asthma.

The primary objective was to evaluate the safety and tolerability of multiple dose administrations of CSJ117 over 12 weeks in subjects with mild atopic asthma, and to evaluate the late asthmatic response (LAR) after an allergen inhalation challenge (AIC) on Day 84. There was one active dose used in the study, i.e. CSJ117 4 mg.

Overall, CSJ117 was generally safe and well-tolerated. The number, incidence, and severity of treatment-emergent adverse events were comparable between the two treatment groups, although more subjects receiving placebo (92.3%) developed at least one adverse event compared with those receiving CSJ117 (66.7%). No deaths or serious adverse events occurred, and no subject discontinued study drug due to an adverse event. No clinically relevant changes were noted in the hematology, chemistry, urinalysis, and ECG. In the study, no spirometry assessments suggested any untoward effect of CSJ117 on lung function. Although the majority of subjects (13/15) treated with CSJ117 developed CSJ117 anti-drug antibodies, no impact on pharmacodynamics or safety was noted by the last study visit.

Major risks of CSJ117 are listed as follows:

Hypersensitivity reactions

The administration of any foreign protein can cause a hypersensitivity reaction. No hypersensitivity reactions were noted in cynomolgus monkeys administered CSJ117. Patients will be monitored for symptoms and signs consistent with such reactions, including shortness of breath, wheezing, coughing or hypoxemia given the inhaled route of administration. If anaphylaxis or other significant hypersensitivity reactions occur, then dosing must be permanently discontinued and appropriate medications and supportive care provided.

Immunomodulation

Consistent with mechanism of action of TSLP as an upstream regulator of the immune response, blocking TSLP by CSJ117 may indicate a potential for immunomodulation and possible immunosuppression. In the 13-week GLP toxicity study, CSJ117 was not correlated with lymphocyte subset changes or alterations in lymphoid tissue histology. Also, no increased incidence of infections was seen. In the reported bronchoprovocation study with the systemic anti-TSLP mAb, an increase in the incidence of infection was not observed (Gauvreau et al 2014). Given the mild findings in the 13-week toxicity study and the published results with the systemic anti-TSLP mAb, the overall risk for clinically significant immunosuppression is considered low. Clinical monitoring for evidence of infection is included in this study. Patients with evidence of active infection, including bacterial, viral, parasitic or fungal, will be excluded.

Coughing or bronchoconstriction

Because CSJ117 is administered via inhalation, there is a risk that CSJ117 will result in local irritation within the airways, manifested as coughing or bronchospasm, even in the absence of local inflammation or a hypersensitivity reaction. Subjects with a history of reactive airway disease or abnormal pulmonary function tests beyond these observed in asthma will be excluded from the study. In this clinical study, patients will undergo several assessments of pulmonary function, including spirometry and daily PEF. In the event of clinically apparent airway reactivity or irritation, with possible symptoms including coughing, wheezing or shortness of breath, then appropriate medication and supportive care should be provided (i.e. SABA).

The investigator must discontinue study treatment for a given patient and/or withdraw the patient from the study if, he/she believes that continuation would be detrimental to the patient's well-being. Patients are also instructed that they can withdraw from the study at any time, and for any reason.

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 must agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria (see Section 5.2). If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

Safety data will be subjected to Data Monitoring Committee review.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health Emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Population

This study population will consist of male and female adult asthma patients treated with medium or high dose ICS plus LABA alone or with up to two additional asthma controllers (LTRA, LAMA or theophylline). Approximately 70% of the total study population will be enrolled in the high EOS stratum (EOS ≥ 300 cells/µl). The proportion of patients with high eosinophil counts at screening (% of overall population) may vary depending on whether the sample size is decreased after blinded re-assessment. If recruitment for one EOS stratum completes first, only patients with screening visit EOS count applicable to the other stratum will be eligible. It is anticipated that approximately 3125 patients will need to be screened to randomize approximately 625 patients in a 2:1:1:1:2:2 (0 : 0.5 : 1 : 2 : 4 : 8 mg CSJ117) ratio into the study worldwide. The number of screened patients may vary depending on sample size re-estimation. An estimated 15% of patients will discontinue their study drug during the treatment period; these patients will not be replaced.

5.1 Inclusion criteria

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

1. Written informed consent and any locally required authorization obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations
2. Documented physician-diagnosed asthma (according to GINA 2019) for at least 12 months prior to Screening.
3. Male and female patients aged ≥18 and ≤75 years, inclusive at the time of screening.
4. Patients who have been treated with medium or high dose ICS plus LABA*, alone or with up to two additional asthma controllers (allowed only: LTRA, theophylline or its derivatives, and LAMA**) at label approved dosage. The ICS dose and dose of other controllers must be stable for at least 1 month, i.e. 30 days, prior to Screening***.
   - To be classified as being on high-dose ICS, the subjects will be on a **total daily dose (sum of all ICS)** of > 500 µg fluticasone dry powder inhaler (DPI) or metered dose inhaler (MDI) or equivalent.
   - To be classified as being on medium-dose ICS, the subjects will be on a **total daily dose (sum of all ICS)** of 250 to 500 µg fluticasone DPI or MDI or equivalent.

   *ICS-LABA can be a fixed dose combination or separate inhalers

   **LAMA can be a separate to ICS-LABA* inhaler or a single FDC ICS-LABA-LAMA inhaler

   ***If patients use a low dose ICS-Formoterol as a reliever, PRN, on the top of maintenance medium or high dose ICS-LABA combination, the ICS dose of ICS-Formoterol should not be added to the total dose calculation of maintenance ICS. GINA 2019 patients steps 1, 2 and 3 are not eligible for this trial.
5. Subjects must have all morning pre-BD FEV1 values of ≥ 40% and ≤85% of the predicted normal after withholding bronchodilators at the run-in and the end of run-in visits. At the run-in visit all lung function tests must be confirmed acceptable by central spirometry over read. At the end of run-in visit at least one lung function test (-2 hr 45 min and/or -2 hr 15 min) must be confirmed acceptable by central spirometry over read.

6. Subjects must perform a reversibility test at the run-in visit. Reversibility is demonstrated by a Post-BD reversibility of FEV1 ≥ 12% and ≥ 200 mL within 30 minutes after administration of 400 µg salbutamol/albuterol (or equivalent dose). If reversibility is not demonstrated at the run-in visit (FEV1 increase was lower than 12% and 200 mL or pre-BD or post-BD spirometry tests were assessed by the central over reader as unacceptable) reversibility will be attempted at up to two ad hoc, unscheduled separate visits (the second ad hoc visit is allowed only for patients who failed to show positive reversibility during the first ad hoc visit).

   If reversibility is not demonstrated at run-in visit nor the unscheduled separate visits, but both pre and post-BD efforts within the same run-in or permitted unscheduled session are confirmed acceptable by central spirometry overread, the following historical information may be used:

   - Documented evidence of reversibility that was performed according to ATS/ERS guidelines (ATS/ERS 2019) within the 1 year prior to Screening. Where a patient is assessed as eligible based on historical evidence of reversibility, a copy of the original printed spirometry report with relevant spirometry tracings must be available as source documentation.

   Until reversibility is demonstrated patient must continue the screening period or be run in failed, if they do not wish to continue the trial. Use of a spacer device is allowed ONLY for reversibility testing (See section 6.1.2.1).
7. Subjects must have an ACQ-5 score of ≥ 1.5 at screening and end of run-in visits.

9. Subjects must meet all of the following criteria at end of run-in visit (Week 0, Day1) prior to randomization:
   1. Subjects must demonstrate acceptable inhaler, peak flow meter, and spirometry techniques during the run-in period (from beginning to end of run in) as judged by the investigator.
   2. Subjects must demonstrate ≥ 70% compliance with the asthma controller fluticasone propionate/salmeterol during the run-in period based on their inhaler use count. 70% compliance is defined as at least one dose of medication i.e. morning or evening dose, taken in 70% of the days spent in the run-in period.
   3. Subjects must demonstrate ≥ 70% compliance with the CSJ117 placebo/Concept1 during the run-in period based on capsule use count. 70% compliance is defined as medication taken in 70% of the days spent in the run-in period.
   4. Subjects must demonstrate ≥ 70% compliance with required use of the eDiary during the last 2 weeks of the run-in period. 70% compliance is defined as completing the daily eDiary for 70% of the days (either morning or evening, including at least 7 morning and 7 evening eDiaries) in the last 2 weeks.

5.2 Exclusion criteria

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

1. Patients receiving any other asthma treatment that is not stipulated in Inclusion Criterion.

3. Patients who have had an asthma exacerbation requiring systemic corticosteroids, hospitalization, or emergency room visit within 4 weeks prior to Screening. Patients may be re-screened 4 weeks after complete recovery from the exacerbation.
4. Patients who have an asthma exacerbation requiring systemic corticosteroids, hospitalization or emergency room visit during the screening. Patients experiencing an asthma exacerbation during the screening period may be re-screened 4 weeks after complete recovery from the exacerbation.
5. Patients with any chronic condition of the respiratory tract, which in the opinion of the investigator may interfere with study evaluation or optimal participation in the study.
6. Patients, who cannot sustain washout of additional controllers (such as LTRA, theophylline or its derivatives, and LAMA) *

   *If subjects have been using other controllers in addition to ICS-LABA prior to screening, additional to ICS-LABA controllers must be discontinued before run-in. Patients must be instructed to use SABA as needed and to monitor their PEF daily with an eDiary/ePEF device provided by the sponsor. Investigator will have access to patients' daily SABA use, symptoms and daily PEF data.

   If upon discontinuation of the additional controllers (on top of ICS-LABA) patients have excessive SABA use compared to patient's regular rescue medication use, and/or enduring significant daily PEF decrease and/or in the investigator's opinion patients fail to sustain the wash out during the run-in, the additional controllers should be reinstated and patients must not be randomized
7. Patients, who show an absolute difference of 15% in FEV1 predicted value between the beginning and the end of run-in.*

   * In the situation when patients show an absolute >15% difference in FEV1 predicted value at the end of run-in, investigator must investigate the potential cause(s) and a repeat test should be scheduled to the next day or as soon as possible. If the repeated spirometry still shows a difference >15%, the patient must be excluded from the study.
8. Any oral corticosteroids as a maintenance treatment within 4 weeks, or any use of short-acting, intra-articular, intramuscular, or intravenous corticosteroid within 4 weeks, or any use of long acting, intra-articular or intramuscular corticosteroids within 3 months prior to Screening. See Table 6-3.
9. Patients who have a cigarette smoking history of greater than 10 pack years or current smokers or vapers.
10. Use of other investigational drugs within 5 half-lives or 30 days prior to Screening, whichever is longer.
11. History of hypersensitivity to any ingredients of the study drug formulation or to drugs of similar classes to CSJ117.
12. Patients with a history or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study at screening or end of run in.
13. Use of agents known to significantly prolong the QT interval unless it can be permanently discontinued for the duration of the study.
14. Patients with a resting QTcF (Fridericia) ≥450 msec (male) or ≥460 msec (female) at screening or at end of run in, or inability to determine the QTcF interval.
15. Cardiac or cardiac repolarization abnormality, including any of the following:

- History of myocardial infarction (MI), angina pectoris, or coronary artery bypass graft (CABG) within 6 months prior to starting study treatment
- Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)

16. Patients with a history of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
17. Pregnant or nursing (lactating) women
18. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using specified methods of contraception during dosing of study drug and 12 weeks after last study drug treatment (end of follow-up).

    Only the following highly effective contraception methods are permitted:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject) if allowed as effective method of contraception according to local regulations. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Use of oral, injected or implanted hormonal methods of contraception 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 have been stable on the same pill for a minimum of 3 months before randomization/start of treatment period.
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS).

    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) 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.

    If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the Informed Consent Form (ICF).
19. Patients who have had a respiratory tract infection within 4 weeks prior to Screening or during the Screening. Patients may be re-screened 4 weeks after recovery.
20. Patients with a history of chronic lung disease other than asthma, including (but not limited to) chronic obstructive pulmonary disease, bronchiectasis, (non-clinically significant bronchiectasis may be allowed provided recent [within 3 months prior to run-in visit] computed tomography (CT) scan proof is available), sarcoidosis, interstitial lung disease and cystic fibrosis.

21. Patients with a known history of active or latent tuberculosis (TB) or currently experiencing any TB symptom: productive, prolonged cough (> 3 weeks); coughing up blood; fever; night sweats; unexplained appetite loss; unintentional weight loss at screening.

    If requested by local regulations, an Interferon Gamma Release Assay (IGRA) test, e.g. QuantiFERON-TB® Gold test, will be used locally at screening to detect patients with TB.

    - Patients with a positive TB test result must be excluded from the trial prior to randomization.
    - Patients with an indeterminate TB test result may be enrolled if the repeated TB test is negative prior to randomization. Patients with the repeated indeterminate or positive TB test result must be excluded from the trial prior to randomization.

    Addition of TB testing at screening, where applicable, will be included in the ICF.
22. Patients with a history of conditions other than asthma or allergic rhinitis that could result in elevated eosinophils (e.g., hypereosinophilic syndromes, Churg-Strauss Syndrome, eosinophilic esophagitis). Patients with known parasitic infestation within 6 months prior to screening are also excluded.
23. Patients with uncontrolled diabetes having a glycosylated hemoglobin A1c (HbA1c) test result ≥8% at the screening visit laboratory test.
24. Patients who have a clinically significant laboratory abnormality at screening in hematology, clinical chemistry, or urinalysis, which in the opinion of the investigator, may put the subject at risk during the study period. The laboratory test including (but not limited to):
    - Total white blood cell count <2500 cells/μL;
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.0 X upper limit of normal (ULN) or total bilirubin >1.3 X ULN;
    - Estimated Glomerular Filtration Rate (eGFR) by the modification of diet in renal disease study (MDRD) equation.
25. Patients who in the judgment of the investigator have a clinically significant condition such as (but not limited to) unstable ischemic heart disease, New York Heart Association (NYHA) Class III/IV left ventricular failure, arrhythmia, uncontrolled hypertension, cerebrovascular disease, neurodegenerative diseases, or other neurological disease, uncontrolled hypo- and hyperthyroidism and other autoimmune diseases, hypokalemia, hyperadrenergic state, or ophthalmologic disorder or patients with a medical condition that might compromise patient safety or compliance, interfere with evaluation, or preclude completion of the study.
26. Patients with serious co-morbidities including, but not limited to, neurodegenerative diseases, rheumatoid arthritis and other autoimmune diseases.
27. Patients with a history of alcohol or drug abuse within 12 months prior to Screening.
28. Patients with a weight <30 kg at Screening.
29. Patients who started immunotherapy or desensitization for allergies, within 3 months prior to Screening, or where the maintenance dose is expected to change during the study.
30. Patients with a known history of non-compliance to medication or who are unable or unwilling to complete an electronic patient diary or who are unable or unwilling to use the Electronic Peak Expiratory Flow (ePEF) with eDiary device or who are unable to demonstrate good eDiary compliance during the screening period.

31. Patients with any medical or psychological condition that, in the investigator's opinion, renders the patient unable to understand the nature, scope, and possible consequences of the study.
32. Patients who have a history of or current treatment for hepatic disease including but not limited to acute or chronic hepatitis, liver steatosis, cirrhosis or hepatic failure.
33. Patients with a history of immunodeficiency disease or hepatitis B, untreated and not cured hepatitis C or HIV. Patients who have completed hepatitis C treatment at least 12 weeks before, and Hepatitis C virus ribonucleic acid (HCV-RNA) levels at screening are undetectable are considered cured and can be included in the study.
34. No person directly associated with the conductance of the study is allowed to participate as a study subject.
35. No family member of the investigational study staff is allowed to participate in this study.
36. Patients who used other anti-TSLP drugs (investigational or approved).
37. Patients unable to use the Concept1 dry powder inhaler, Discus®/Accuhaler® or a metered dose inhaler. Spacer devices are not permitted for rescue medication with the exception of reversibility testing (See section 6.1.2.1).
38. Patients who are serving a custodial sentence, do not have a permanent residence or who are detained under local mental health legislation/regulations.
39. Patients who discontinued monoclonal antibodies (investigational or approved) for asthma due to lack of efficacy.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

The Investigational treatments are as follows:

- CSJ117 0.5 mg capsules for inhalation, delivered via Concept1
- CSJ117 1.0 mg capsules for inhalation, delivered via Concept1
- CSJ117 2.0 mg capsules for inhalation, delivered via Concept1
- CSJ117 4.0 mg capsules for inhalation, delivered via Concept1
- CSJ117 8.0 mg capsules for inhalation, delivered via Concept1

CSJ117 and matching placebo will be provided as powder filled capsules with a Concept1 inhalation device.

All CSJ117 doses and matching Placebo are prepared for a single inhalation.

Under no circumstances is an alternative inhalation device to be used for the administration of investigational treatment capsules during the treatment period.

All doses of CSJ117 and matching placebo will be supplied by Novartis Global Clinical Supply in blister packs, providing sufficient quantity of medication to last each patient between visits.

Patients will be instructed by study personnel on the correct technique and dosing instructions for the device. Dispensation instructions are provided in Section 6.7.

Instructions for use of the Concept1 device are provided in a separate document.

6.1.2 Additional study treatments

Additional study treatments include:

- Asthma rescue medication i.e. salbutamol or albuterol
- Standardized background ICS-LABA treatment i.e. a fixed dose combination of fluticasone propionate/salmeterol (allowed only Diskus®/Accuhaler®) in one of two doses i.e. either 250/50 µg b.i.d. or 500/50 µg b.i.d.

6.1.2.1 Asthma rescue medication

At Screening all patients will be provided with a SABA (such as salbutamol [100 µg] or albuterol [90 µg], all other regular asthma rescue medication must be discontinued at screening visit) which they will be instructed to use throughout the study as asthma rescue medication on an 'as needed basis'. Patients will be advised that between visits they can take their rescue medication for symptoms of asthma. Rescue medication (i.e. SABAs) will either be supplied to the study sites locally by Novartis or provided by the study site to the patient and reimbursed by Novartis.

Nebulized salbutamol/albuterol is not allowed as rescue medication and will not be supplied.

No other "at home use" asthma rescue treatment PRN is permitted and use of a spacer for rescue medication is not allowed at any time throughout the study, with the exception of reversibility testing.

To standardize measurements, patients will be instructed not to use their rescue medication upon rising in the morning on days requiring spirometric assessments as indicated in Table 6-2, unless absolutely necessary. If rescue medication is taken within 6 hours prior to spirometry at any of the scheduled visits, this information will be recorded by the study site staff using the equipment provided by the central spirometry vendor. Additionally, the spirometry test must be rescheduled to the next possible day.

Daily use of rescue medication (the number of puffs taken in the previous 12 hours) will be recorded (once in the morning and once in the evening) by the patient using ePEF/ eDiary.

6.1.2.2 Standardized background ICS-LABA treatment (fluticasone/salmeterol)

All patients will be supplied with a fluticasone propionate/salmeterol xinafonate inhaler (Diskus®/Accuhaler®) at the run in visit. The fluticasone/salmeterol inhaler will replace patients regular ICS-LABA which they have been using until the run-in visit. Patients who were enrolled to the study with medium dose ICS-LABA at screening will receive a fixed dose combination (FDC) of fluticasone propionate/salmeterol 250/50 µg b.i.d., while patients who were enrolled at screening with high dose ICS-LABA will receive a FDC of fluticasone propionate/salmeterol 500/50 µg b.i.d. from the start of run-in and throughout the study treatment period. This standardized background medication will either be supplied to the study sites locally by Novartis or provided by the study site to the patient and reimbursed by Novartis.

Patients must be instructed not to use their standardized background medication i.e FDC of fluticasone/salmeterol, one day (24 hours) before all visits with spirometry assessments, as indicated in the Table 6-2. If FDC of fluticasone/salmeterol has been taken within 24 hours prior to spirometry at any of the scheduled visits with spirometry assessments, this information will be recorded by the study site staff using the equipment provided by the central spirometry vendor. Additionally, the visit must be rescheduled to the next possible day.

Daily use of FDC of fluticasone/salmeterol will be recorded (once in the morning and once in the evening) by the patient using ePEF/ eDiary. Additionally adherence to the standardized background therapy i.e. FDC of fluticasone/salmeterol will be checked at each visit.

6.1.3 Treatment arms/group

Subjects will be assigned at Randomization visit to one of the following six treatment arms/groups in a ratio of 2:1:1:1:2:2

- Placebo o.d. delivered by Concept1 inhaler (in the morning)
- CSJ117 0.5 mg o.d. delivered by Concept1 inhaler (in the morning)
- CSJ117 1.0 mg o.d. delivered by Concept1 inhaler (in the morning)
- CSJ117 2.0 mg o.d. delivered by Concept1 inhaler (in the morning)
- CSJ117 4.0 mg o.d. delivered by Concept1 inhaler (in the morning)
- CSJ117 8.0 mg o.d. delivered by Concept1 inhaler (in the morning)

6.1.4 Treatment duration

For subjects who in the opinion of the investigator are still deriving clinical benefit from CSJ117, every effort will be made to continue provision of study treatment. The planned duration of treatment is 84 days (12 weeks). Subjects may be discontinued from treatment earlier due to unacceptable toxicity, disease progression and/or at the discretion of the investigator or the subject. Subjects who are discontinued from treatment earlier should remain in the study and finish the study visits as planned.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the patient is enrolled into the study. All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject is enrolled into the study must be recorded on the appropriate Case Report Forms (CRFs).

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

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "prohibited" as listed in Table 6-3. Specifically, subjects should receive full supportive care during the study, including treatment with antibiotics, anti-emetics, anti-diarrheals, analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. In addition to the background asthma medications and rescue medications described in Section 6.1.2, the following concomitant medications related to asthma/allergy treatment are permitted from screening through the follow-up period.

Table 6-1 Medications allowed under certain conditions

Class of medication	Condition
Topical corticosteroids for the treatment of eczema	In recommended doses and dosage regimens
Intra-nasal corticosteroids	Stable dose for at least 1 month prior to Screening. In the case of as needed, provided an established pattern of use has been documented.
Systemic corticosteroids	To treat asthma exacerbations
Topical antihistamines	In recommended doses and dosage regimens
Oral antihistamines	Stable dose for at least 1 month prior to Screening and throughout the trial. In the case of as needed, provided an established pattern of use has been documented
Topical, nasal, and/or ocular formulations of cromones	In recommended doses and dosage regimens
Maintenance immunotherapy for allergies	Stable dose for at least 3 months prior to run-in visit and unchanged throughout study treatment.
COVID-19 vaccination	At least one week before an in-clinic visit

Table 6-2 Medications to be withheld prior to spirometry

Class of medication	Last dose prior to spirometry
Short-acting β_2-agonists (SABA)	≥ 6 hours
Long-acting β_2-agonists (LABAs) given twice daily	≥ 24 hours
ICS-Formoterol given PRN	≥ 24 hours
LABAs given once daily (e.g. vilanterol, indacaterol)	≥ 36 hours
Long-acting muscarinic antagonists (LAMAs e.g. tiotropium)	≥ 7 days
Fixed-dose combinations of LABA and ICS given twice daily	≥ 24 hours
Fixed-dose combinations of LABA and ICS given once daily	≥ 36 hours
Fixed-dose combinations of LABA and LAMA and ICS given once daily or twice daily.	≥ 2 days

The treatment of asthma exacerbations including the initiation of systemic corticosteroids should be done according to investigator's or treating physician's medical judgement and should be in line with their institutional, national and international recommendations. If systemic corticosteroids are required, a patient may return to the study assessments after successfully completing an Oral Corticosteroid (OCS) taper. If patients require treatment with systemic steroids longer than 3 weeks, including taper, or chronic systemic steroid administration, they must be discontinued from treatment.

If indicated for the treatment of an adverse event, including asthma exacerbation, any treatment (including medications in Table 6-3) deemed necessary by treating physician for the safety of the patient is allowed from the start of the event until the event is resolved. If it is transitioning to chronic treatment, the investigator should discuss with Novartis Medical Monitor. Patients may NOT self-medicate (other than administration of rescue medication) or adjust therapy without permission/guidance from treating physician.

6.2.2 Prohibited medication

The specified minimum washout periods prior to the run-in are described in Table 6-3. Use of the treatments displayed in Table 6-3 is NOT allowed after the beginning of run-in (unless for the treatment of adverse events and asthma exacerbations). Each concomitant drug must be individually assessed against all exclusion criteria and the tables below to see if it is allowed. If in doubt, the investigator must contact the Novartis medical monitor or designee before randomizing a patient or allowing a new medication to be started. Medications must be assessed for adherence to the indication and other inclusion/exclusion criteria.

Table 6-3 Prohibited medication

Class of medication	Minimum cessation prior to Run-In[1,2]
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Live attenuated vaccine*	2 days
Inactivated influenza vaccination, pneumococcal vaccination or any other inactivated vaccine*	2 days
Short-acting anticholinergics (SAMA)	6 hours
Long acting muscarinic antagonists (LAMAs)*	7 days
Fixed combinations of short-acting β_2 agonists and short-acting anticholinergics (SABA/SAMA)	12 hours
Xanthines*	7 days
Leucotriene Receptor Antagonists (LTRAs) and leucotriene synthesis inhibitors*	7 days
Systemic mast cell stabilizers (e.g., cromoglycate, nedocromil, ketotifen)*	7 days
Oral corticosteroids	6 weeks
Short-acting, intra-articular, intramuscular, intravenous corticosteroid	6 weeks
Long acting, intra-articular, intramuscular depot corticosteroids	3 months and 2 weeks
Monoclonal antibodies for the treatment of asthma (e.g. omalizumab, mepolizumab, benralizumab etc.) (investigational or approved)	5 half-lives or 6 months, whatever is longer
Other anti-TSLP drugs (investigational or approved)	Not permitted
Methotrexate, gold salts, cyclosporine, troleandomycin, azathioprine, other immunomodulator drugs or immunomodulatory monoclonal antibodies	6 months

[1] This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria
[2] These medications are also prohibited if administered for other indications

*these medications can be used again in the follow up period

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

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

6.3.2 Treatment assignment, randomization

At the end of run-in, prior to the first dosing of the Investigational Medicinal Product (IMP), all patients will have 2 spirometry assessments done i.e. at -2h45min and -2h15min timepoints. Prior to randomization the patient's spirometry assessments will be evaluated by a Central overreader and site staff will be informed if both spirometry assessments are acceptable. Subjects must have an FEV1 value of ≥ 40% and ≤85% of the predicted normal shown in both spirometry assessments in order to be randomized. If both spirometry assessments of a patient are evaluated by the overreader as unacceptable or the average FEV1 predicted value from both spirometry assessments differs >15% (absolute value) from the beginning of run-in FEV1 predicted value, the randomization visit must be stopped and the patient must not be randomized on that day. The patient should return for an ad hoc randomization visit on the following day or as soon as possible and complete all assessments/procedures foreseen for the randomization visit with exception of eCOA assessments. If the difference in FEV1 predicted value between the beginning of Run-in and this ad hoc randomization visit is still > 15%, this patient must be excluded from the study. This patient is not allowed rescreening.

At the end of run-in visit, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the subject.

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

Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Randomization will be stratified by peripheral blood eosinophil counts at the screening visit (< 300 cells/µl or ≥ 300 cells/µl). Treatment randomization will also be stratified at the regional level.

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

6.4 Treatment blinding

This study consists of a single-blind run-in period (i.e., only patients will be blinded to the identity of the treatment) followed by a double-blind randomized treatment period.

Subjects, investigator staff, persons performing the assessments, and CTT will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods:

(1) Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the following exceptions: independent statistician and programmer supporting the DMC and, if deemed necessary by the DMC, the DMC members.

(2) the identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor.

The randomization codes associated with subjects from whom PK samples are taken will be disclosed to PK analysts who will keep PK results confidential until database lock.

Unblinding will occur in the case of subject emergencies, in case of a DMC request as an outcome of their evaluation and at the conclusion of the study.

If sponsor decides to conduct an unblinded interim analysis for internal decision making (Section 4.4), unblinding of predetermined CTT members may occur at the time of interim analyses. The study may then continue under the management of a separate blinded team. In order to maintain the integrity of the study data, separate blinded team members will not have access to any unblinded data. The detailed procedures will be described in a separate charter. The remainder of the members including clinical study team, subjects, investigator staff, persons performing the assessments will also remain blinded.

6.4.1 Independent study-treatment administration site staff member

Owing to a slight difference in capsule powder fill volume between CSJ117 doses and placebo, none of the site staff including the OHP, apart from the independent study-treatment administration site staff member should handle or see the Investigational Medicinal Product (IMP) capsules when assisting patient with administration. An independent study-treatment administration site staff member familiar with the correct inhalation technique will be the only person responsible for assisting patients with removing capsules from their blisters and placing them in the Concept1 inhaler if required and for the onsite IMP administration. The training kit

can be handled by the assigned study site staff for patient training purposes. The OHP must be familiar with the correct inhalation technique, observe the patient inhalation and if necessary retrain the patient on correct inhalation technique but must not directly handle or see the IMP capsules.

Appropriate measures must be taken by the independent study-treatment administration staff to ensure that no information regarding the IMP capsules is discussed with the site staff or OHP and that the site staff do not come into direct contact with the IMP capsules. The independent study-treatment administration staff will not perform any other study related duties (including assessments, procedures, documentation, data collection or record keeping for the study).

Note: the risk of subject unblinding due to the different appearance of capsules is negligible as it is not expected subjects will see other individuals' patient kits. Besides the independent study-treatment administration site staff member, other team members are not allowed to handle or see the IMP capsules directly.

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted.

6.5.1 Dose modifications

Dose adjustments and/or interruptions of a subject's study treatment are not permitted.

The discontinuation of study treatment rules (Section 9.1.1) must be adhered to if a subject cannot complete inhalation of the required capsules per the study protocol.

Any dose interruption must be recorded on the Dosage Administration Record CRF.

6.5.2 Follow-up for toxicities

Not applicable.

6.5.2.1 Follow up on potential drug-induced liver injury (DILI) cases

Subjects with transaminase increase combined with total bilirubin (TBL) increase may be indicative of potential DILI and should be considered as clinically important events.

The threshold for potential DILI may depend on the subject's baseline AST/ALT and TBL value; subjects meeting any of the following criteria will require further follow-up as outlined below:

- For subjects with normal ALT and AST and TBL value at baseline: AST or ALT > 3.0 x ULN combined with TBL > 2.0 x ULN
- For subjects with elevated AST or ALT or TBL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in subjects without bone metastasis, or elevation of ALP liver fraction in subjects with bone metastasis.

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury.

In the absence of cholestasis, these subjects should be immediately discontinued from study treatment, and repeat Liver function test (LFT) testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment, and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR, and alkaline phosphatase.

2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, and history of any pre-existing liver conditions or risk factors, should be collected.

3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.

4. Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.

5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of SAE and should be reported as SAE using the term "potential drug-induced liver injury." All events should be followed up with the outcome clearly documented.

Please refer to Section 16.2 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site. Additional details on actions required in case of liver events are outlined in Table 16-2.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The time of study treatment administration at each dosing visit will be collected on the eCRF as well as any dosing interruptions. For visits where spirometry is performed, time of dose should be taken from the spirometer. While at home administration of study medication and background treatment will be recorded by eDiary during the placebo run-in period and the treatment period. The data from the eDiary will be reviewed at each visit.

Study treatment compliance should be assessed by the investigator and/or center personnel at least for all visits. Where necessary, the Investigator will discuss compliance/documentation issues with the patient. The Investigator or designee, including OHP, will collect the

used/unused study medication and packaging (unused capsules/blister strips DPIs) at all visits. Study treatment compliance will be assessed based on the capsule count from the blisters dispensed at the previous visit.

6.6.2 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 Novartis 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/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- name (if available)
- subject number

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

Study drug must be discontinued after emergency unblinding. Study drug must also be discontinued for any patient whose treatment code has been inadvertently broken or for any other non-emergency reason.

These patients will be not allowed to participate in a separate safety extension study with CSJ117.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section (see Section 6.1.1).

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

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

Before dispensing to the patient, the medication kits are stored in the refrigerator, at 2-8°C. Prior to first dosing from the individual kit (opening of the blisters and use of the device), the medication kit will need to equilibrate to room temperature for a minimum of 1 hour.

As per section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to continue in the study even without performing an on-site visit. Implementation will need to be discussed with Novartis. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be discussed with Novartis and for a maximum of 1 kit supply to last until the next scheduled dispensing visit. In this case, regular phone calls or virtual contacts (every 2 weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from continued participation, drug accountability and discussion of the participant´s health status until the participants can again visit the site.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical deficiencies related to the study treatment e.g. Concept1 inhaler, blisters or capsules are to be reported to the respective Novartis Country Organization Quality Assurance.

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

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

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

6.7.1.2 Handling of additional treatment

The following non-study treatment has to be monitored specifically:

- SABA (such as salbutamol 100 µg or albuterol 90 µg)

- FDC of fluticasone propionate/salmeterol 250/50 µg
- FDC of fluticasone propionate/salmeterol 500/50 µg

The non-study treatment must be handled and stored according to label, kept in a secured location and dispensed only in accordance with the protocol.

If possible, the investigator shall maintain an accurate record of dispensing of the above-mentioned treatment in a drug accountability log / inventory log / source document. Monitoring of drug accountability will be performed by monitors during site visits and at the completion of the study. Patients will be asked to return all unused SABA and FDC of fluticasone/salmeterol treatments and their packaging at least at the end of the study or at the time of discontinuation from the study.

6.7.2 Instruction for prescribing and taking study treatment

The instructions for the investigational drug (CSJ117/placebo) are as follows:

- CSJ117 PulmoSol powder / placebo is provided in a hard capsule to be inhaled via the Concept1 device
- CSJ117/placebo should be taken by patient once a day at approximately the same time each morning together with his/her maintenance ICS/LABA treatment (Fluticasone propionate/salmeterol)

Instructions for fluticasone propionate/salmeterol and rescue medication should be according to the respective product label.

On the run-in visit a medication kit with placebo capsules and a Concept1 inhalation device will be provided for demonstration and training purposes. On this visit, all patients will be fully trained in the correct use of the Concept1 devices used to administer study medication. Patients who are unable to use the device correctly at the end of run-in visit (Day 1) will not be eligible to enter the treatment epoch.

On study visit days, patients should be reminded **not** to take the investigational drug (CSJ117/placebo) prior to the visit to ensure compliance with the pre-dose PK sampling procedure.

On the day prior to and on days of visits, with the study drug administration, patients should be reminded not to take fluticasone/salmeterol in order to ensure compliance with the spirometry pre-dose measurements.

The morning dose of fluticasone/salmeterol on the visit days should be taken after spirometry assessments and the pre-dose PK sampling have been both completed. The evening dose of fluticasone/salmeterol on visit days should be taken as usual.

7 Informed consent procedures

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

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given

his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

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

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

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

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 requirements.

Male subjects must 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.

The study includes optional sub studies/[redacted] component which requires a separate signature if the subject agrees to participate. It is required as part of this protocol that the Investigator presents this option to the subjects, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these optional assessments [redacted]Sub Studies) will in no way affect the subject's ability to participate in the main research study.

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

Where off-site visits are implemented, a separate Home Nursing consent document must be used in addition to the main ICF. The process for obtaining consent should be exactly the same as described above for the main informed consent.

8 Visit schedule and assessments

Assessment schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the protocol schedule designated day/time as possible. Missed or rescheduled

visits should not lead to automatic discontinuation. Subjects who discontinue study treatment should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' Section 9.1.2). **Where possible, they should complete the assessments indicated** in the Assessment Schedule.

Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the Premature Subject Withdrawal (PSW) visit will be performed.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace selected on-site study visits as specified in Table 8-1, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Assessment Schedule

Period	Screening	Baseline			Treatment					Follow up				PSW[1]*
Visit Name	Screening[17]	Run-In	Phone visit	End of Run-In	Day 1	Week 2*	Week 4*	Week 8	Week 12	Week 14*	Week 16*	Week 20*	Week 24	
Days	-42	-28	-14	1	1	15	29	57	85	99	113	141	169	-
Informed consent	X													
Pharmacogenetic Informed Consent[2]	X													
Demography	X													
Inclusion / Exclusion criteria	X	X		X										
Smoking history	X													
Asthma exacerbation history	X													
Prior asthma medication	X													
AEs/SAEs assessment	X	X	X	X	X[3]	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X[3]	X	X	X	X	X	X	X	X	X
Review and record surgeries and procedures	X	X	X	X	X[3]	X	X	X	X	X	X	X	X	X
Medical history/current medical conditions	X													
Body Height	X													
Body Weight	X								X				X	X
Physical Examination	S			S	S[3]				S				S	S
Vital Signs	X	X		X	X[3]				X	X		X	X	X
Abbreviated Physical Examination						S	S	S			S			
Alcohol Test, Drug Screen, and Cotinine Test	X													
Pregnancy test (serum) for women of childbearing potential	X						X	X	X				X	X

Period	Screening	Baseline			Treatment					Follow up				PSW[1]*
Visit Name	Screening[17]	Run-In	Phone visit	End of Run-In	Day 1	Week 2*	Week 4*	Week 8	Week 12	Week 14*	Week 16*	Week 20*	Week 24	
Days	-42	-28	-14	1	1	15	29	57	85	99	113	141	169	-
Pregnancy test (urine) for women of childbearing potential		S		S							S	S		
Dispensation of rescue medication	S	S			S		S	S	S		S	S		
Washout of controllers additional to ICS/LABA	S													
Standardization of background ICS/LABA treatment		X												
Dispensation of background ICS/LABA treatment		S			S		S	S	S		S	S		
Dispensation of eDiary/ePEF	S													
Compliance with eDiary/ePEF		S	S	S		S	S	S	S	S	S	S	S	
Training eDiary/ePEF	S	S[2]		S[2]										
Inhaler devices training		S		S[2]		S[2]	S[2]	S[2]	S[2]					
Dispensation of IMP training kit		S												
Dispensation of Run-In kit		S												
Dispensation of study drug					S		S	S						
Dispense & attach Concept1 add-on sensor[4]					S									
Upload data from the Concept1 add-on sensor/re-attach the sensor[4]							S	S	S					S
IMP administration					X[5]	X	X	X	X					

Period	Screening	Baseline			Treatment					Follow up				PSW[1]*
Visit Name	Screening[17]	Run-In	Phone visit	End of Run-In	Day 1	Week 2*	Week 4*	Week 8	Week 12	Week 14*	Week 16*	Week 20*	Week 24	
Days	-42	-28	-14	1	1	15	29	57	85	99	113	141	169	-
fluticasone/salmeterol administration		X			X	X	X	X	X	X	X	X	X	X
Compliance with Concept1			S	S		S	S	S	S					S
ACQ	X			X			X	X	X				X	X
AQLQ				X			X	X	X				X	X
[redacted]														
FeNO pre-dose at site				X		X	X	X	X	X	X	X	X	X
Peak Inspiratory Flow training		S												
Spirometry training[2,16]	S													
Spirometry Reversibility Test		X[6]												
-2hr45min Pre-dose spirometry				X										
-2hr15min Pre-dose spirometry				X										
-45min Pre-dose spirometry						X	X	X	X		X[7]	X[7]	X[7]	X
-15min Pre-dose spirometry						X	X	X	X		X[7]	X[7]	X[7]	X
Electrocardiogram (ECG) - triplicate				X[8]	X[9]				X					X
Electrocardiogram (ECG) - Single[10]	X						X	X			X		X	
ImmunoCAP test				X										
Hepatitis screen	X													
HIV Screen[11]	X													
Urinalysis	X			X		X	X	X	X		X		X	X
Hematology	X			X[8]		X[8]	X[8]	X[8]	X[8]		X		X	X
Clinical Chemistry	X			X[8]		X[8]	X[8]	X[8]	X[8]		X		X	X

Period	Screening	Baseline			Treatment					Follow up				PSW[1*]
Visit Name	Screening[17]	Run-In	Phone visit	End of Run-In	Day 1	Week 2*	Week 4*	Week 8	Week 12	Week 14*	Week 16*	Week 20*	Week 24	
Days	-42	-28	-14	1	1	15	29	57	85	99	113	141	169	-
Blood collection for ADA				X[8]		X[8]	X[8]	X[8]	X[8]	X	X	X	X	X
[redacted]														
PK Blood collection Pre-Dose				X[8]		X[8]	X[8]	X[8]	X[8]	X	X	X	X	X
PK Blood collection Post-Dose 2hr[14]					X[18]	X[18]	X[18]	X[18]	X[18]					
PK Blood collection Post-Dose 4hr[14]					X[18]				X[18]					
Contact IRT	S	S		S	S		S	S	S					S
CSJ117 Safety Extension Study participation discussion								S[13]						
TB testing[15]	S													

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] Premature Subject Withdrawal, no on site drug administration
[2] Optional, if needed
[3] Only if Day 1 visit was postponed, due to repetition of spirometry or operational issue
[4] Only for participating countries/sites
[5] Patient has to be observed for at least 4 hours post-administration
[6] If not achieved during the Run In visit, up to two additional attempts are allowed at separately scheduled visits before the End of Run in Visit. If reversibility is not demonstrated at Run in Visit and the two additional attempts, historical information may be used (Documented evidence of reversibility that was performed according to ATS/ERS guidelines (ATS/ERS 2019) within the 1 year prior to Screening).
[7] Pre-dose regarding fluticasone/salmeterol
[redacted]
[9] 3 hours post-dose
[10] If ECG results are clinically abnormal, site has to repeat it twice and submit to the central reviewer
[11] To be confirmed by central lab if positive or indeterminate.
[12] Optional, only for consented patients
[13] Latest at day 84. It can be conducted earlier.
[14] In case a patient prematurely discontinued treatment but continued participation in the study, these PK samples will not be collected.

[15] Where applicable by local regulations
[16] Medication washout prior to spirometry training is not required
[17] Screening visit can be optionally conducted across 2 days to collect laboratory samples and allow the laboratory evaluations including the blood eosinophil (EOS) counts first.
*Selected assessments for these visits could be performed off site
[18] Within +/-15 minutes of specified sample collection time.

8.1 Assessments order during randomization

During the end of run-in/Randomization visits (see Table 8-2) suggested order of assessments outlined below should be followed (if possible). The randomization visit should be planned in the morning. This table is not exhaustive, for complete details on recommended timing and ordering of assessments see Section 16.8. Similar assessments order should be followed where these assessments are performed at other visits.

Table 8-2 Assessments at randomization

Order of assessments	Assessment
1	Question on medication withholding for spirometry/check the eDiary entry for the current day and one day before
2	Inclusion/exclusion criteria
3	Patient Reported Outcome instruments to be completed in the following order: ACQ-5, AQLQ
4	Pre-dose ECG triplicate
5	Vital signs
6	Full physical examination
7	Fractional exhaled nitric oxide (FeNO)
8	First pre-dose spirometry assessment: approximately 2hr45 min prior to the dosing of study drug at the clinic visit.
9	Second pre-dose spirometry assessment: approximately 2hr15 min prior to the dosing of study drug at the clinic visit.
10	Confirm acceptable spirometry results with an overread report and FEV1 difference with the run-in visit*
11	Samples for urine/hematology/blood chemistry/ImmunoCAP (including pregnancy test)
12	**In-clinic witnessed dosing of the study drug**
13	Samples for PK at 2 hour post-dose
14	ECG triplicate at 3 hour post-dose
15	In clinic administration of fluticasone/salmeterol background treatment

16	Samples for PK at 4 hour post-dose

*if overread indicates unacceptable spirometry results or an absolute FEV1 difference is >15%, a patient has to inhale a dose of fluticasone/salmeterol and the randomization visit has to be postponed to another ad hoc visit. There must be a minimum withholding time ≥ 24 hr between dosing of fluticasone/salmeterol and the next spirometry. First dosing of the study medication should take place only at the ad hoc scheduled randomization visit.

8.2 Screening and re-screening

Re-screening is allowed once, if a patient fails to meet the eligibility criteria during the screening period or at the run-in visit, before first placebo dosing. This includes:

- Pre-BD FEV1 predicted value at the run-in visit falls within the margin of +/-2.0% allowed for re-screening (i.e. 38 and 87% predicted)
- Asthma exacerbation requiring systemic corticosteroids, hospitalization or emergency. room visit during the screening period or within 4 weeks prior to screening. Patients may be re-screened 4 weeks after complete recovery from the exacerbation.
- When the low EOS strata (blood EOS count at screening ≤300 cells/µL) is closed for recruitment, patients who failed due to low eosinophils may be re-screened once. If these patients have an EOS count >300 cells/µL at screening visit when re-screened, and they meet all other eligibility criteria, they can move to run-in and ultimately be randomized.

Re-screening is NOT allowed in any of the following situations:

- Subject fails to show reversibility in three allowed attempts and has no documented evidence of reversibility that was performed within the 1 year prior to Screening as specified in the inclusion criterion 6 (see Section 5.1) and the assessment schedule (see Table 8-1).

A new patient number will be assigned and the site must record the re-screening information in the corresponding eCRF and in IRT. Rescreened patients must undergo all protocol defined assessment, as for newly screened patients.

Patients who were dosed run-in IMP and were run-in failed are not eligible for re-screening, unless they were run-in failed due to not meeting the spirometry acceptability criteria at the run-in visit and took less than 7 doses of run-in IMP and have met all other eligibility criteria.

8.2.1 Information to be collected on screening failures

Subjects who sign an informed consent form and are subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (see SAE Section 10.1.3 for reporting details). If the subject fails to be randomized, the IRT must be notified within 2 days of the screen fail that the subject was not randomized. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

Subjects who are randomized and fail to start treatment, e.g. subjects randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.3 Subject demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

- Age
- Sex
- Race and ethnicity
- Height
- Weight
- Body mass index (BMI)
- Duration of asthma
- Number of exacerbations in the prior year
- Atopic status (Yes/No) (ImmunoCAP)
- Smoking history
- Baseline Spirometry (FEV1, FVC, FEV1/FVC)
- Reversibility (demonstrated)
- Baseline ADSD/ANSD score
- Baseline ACQ-5
- Baseline AQLQ-12
- [redacted]
- Baseline FeNO
- Baseline PEF
- Baseline ICS dose level
- Peripheral blood eosinophils at screening
- [redacted]
- Relevant medical history/current medical condition present before signing informed consent. Where possible, diagnoses and not symptoms will be recorded.

8.4 Efficacy

The efficacy assessments selected are standard for this indication/subject population.

8.4.1 Spirometry

All visits with spirometry testing (excluding screening visit) must occur in the morning. Please refer to the Table 8-1 for full details of the scheduling of spirometry measurements.

Equipment for spirometry assessments will be provided for all study visits by a Central Spirometry vendor, and overread of spirometry assessments will be performed by trained

spirometry overreaders at the central vendor. The final spirometry assessments will be those provided by the spirometry overreaders of the central spirometry vendor.

Please refer to the Spirometry Guidance, in (section 16.3 Spirometry Guidance), for full details on scheduling and performing spirometry. Reversibility testing must be conducted in the morning.

Variability of FEV1 will be monitored in this study. Any unusual FEV1 difference will require the investigator or delegate to examine potential causes for the difference.

8.4.2 Fractional exhaled Nitric Oxide (FeNO)

To ensure consistency in the measurement of FeNO, all sites participating in this study will be provided with a NIOX FeNO machine. FeNO measurements should be done at all on-site treatment and follow up visits (see Table 8-1).

Several publications reported high fractional concentrations of orally exhaled Nitric Oxide (FeNO) in subjects with asthma as compared with unaffected subjects, and a fall after treatment. The measurement of exhaled nitric oxide is widely accepted as a non-invasive marker of airway inflammation and, amongst other uses, has been proposed to monitor the response to anti-inflammatory medications.

In this study, fractional exhaled nitric oxide will be measured following the published guidelines on standardized techniques (see section 16.6) including calibration of equipment as appropriate for measuring exhaled Nitric Oxide by ATS and ERS (ATS/ERS 2005).

8.4.3 eDiary/ePEF

At screening all patients will be provided with a patient electronic diary (referred to as eDiary or eDiary/ePEF) to record daily asthma symptoms and rescue medication (salbutamol/albuterol) use. The eDiary has automated reminders to remind the patient to inhale the study medication and background therapy i.e. fluticasone propionate/salmeterol. Patients will be instructed to routinely complete the patient diary twice daily – at about the same time each morning and each evening, approximately 12 hours apart. The eDiary/ePEF recordings are to be reviewed at the visits as detailed in Table 8-1 until study completion. Sites and patients will receive appropriate training and guidance on the use of the eDiary device.

8.4.3.1 Asthma Daytime Symptom Diary (ADSD) and Asthma Nighttime Symptom Diary (ANSD)

Asthma Daytime Symptom Diary (ADSD) and Asthma Nighttime Symptom Diary (ANSD) are self-administered patient reported outcome measures of asthma symptom severity designed for use with adolescents and adults with mild to severe persistent asthma. They were developed in accordance with the US Food and Drug Administration's (FDA) PRO guidance.

ADSD and ANSD will be part of the eDiary.

Both diaries are comprised of 6 items assessing breathing symptoms (difficulty breathing, wheezing, and shortness of breath), chest symptoms (chest tightness and chest pain), and cough symptoms (cough). All items are assessed using an 11-point numeric rating scale (NRS) ranging from 0 ('None') to 10 ('As bad as you can imagine')

8.4.3.2 Peak Expiratory Flow (PEF)

PEF will be measured at consistent times for a patient, in the morning and evening each day during the study from the beginning of run-in visit to study completion. The measurements will be performed using an eDiary/ePEF provided to the patients.

Patients should be encouraged to perform morning and evening PEF measurements BEFORE the use of any rescue medication and BEFORE the use of fluticasone/salmeterol medication. Patients will be asked to record if they have taken their rescue medication 6 hours prior to the peak flow assessment.

At each time point, the patient will be instructed to perform 3 consecutive maneuvers within approximately 10 minutes. These PEF values are captured in the eDiary /ePEF.

8.4.3.3 Number of inhalations of Rescue Medication

The total number of inhalations used of rescue medication (number of puffs taken in the previous 12 hours) will be recorded every morning and evening by the patient, in the eDiary/ePEF.

8.4.3.4 Worsening of asthma (and related eDiary alerts)

Asthma worsening criteria will be programmed into the eDiary/ePEF apart from criterion 5 below.

The data captured in the eDiary/ePEF will be used to alert the patient and/or investigator to possible signs of worsening asthma.

The investigator should instruct the patient to contact the investigator if the patient develops one or more of the following asthma worsening criteria at any time during the trial from the screening onwards. Patients may also receive an alert via their eDiary requesting them to contact their investigator:

- >50% increase in SABA use on 2 out of any 3 consecutive days compared to baseline and/or >8 puffs on 2 out of any 3 consecutive days *. For screening phase only: >8 puffs on 2 out of any 3 consecutive days
- ≥20% decrease in AM or PM PEF from baseline on 2 out of any 3 consecutive days compared to baseline*.
- <60% of PEF compared to baseline*,
- Night time awakenings requiring SABA use on at least 2 out of any 3 consecutive nights; or
- Urgent unscheduled clinic visit due to asthma-related deterioration.

*Note:

- The baseline for the run-in period is set at the run-in visit.
- The baseline during the treatment is set at the beginning of treatment (end of run-in visit, Day 1).
- Automated eDiary/ePEF PEF alerts will be implemented from the run-in visit until the study completion visit. During screening patients will be informed to monitor their PEF daily. At each morning and evening sessions they will be reminded to contact the PI in case of PEF decrease.

If a patient develops any of the above criteria while he or she is in the screening (apart from >50% change in SABA use and PEF related criteria), run-in or treatment period, the investigator should assess the patient condition. If this occurs during screening, and it is considered a clinically significant worsening in the investigator's opinion, the patient must be treated as appropriate and discontinued prior to run-in. Once the condition is resolved, if eligibility criteria are met, the patient may be reconsidered for rescreening.

The alerts which are triggered by above criteria are in place to detect early onset of asthma worsening at any time during the study to help direct early intervention. Therefore, the investigator should do the following when alerts are received:

- Review alert trends over time, in particular PEF decreases
- Call the patient promptly when any one specific alert type (e.g. PEF<60%) is received on consecutive days to further assess the clinical status. This may include urgent clinic visits as appropriate and/or immediate treatment.
- Implement prompt treatment as necessary
- Report all types of events in the CRF

If patients believe their symptoms are worsening and/or receive alerts as outlined above, the patient should also notify the investigator and be evaluated by the investigator and treated as clinically appropriate.

Investigator and the site study team must check and encourage patients' compliance with study medications and the eDiary/ePEF device. Should there be any compliance issue on study drug or e-diary completion potentially putting the patient's safety at risk, Investigator must consider temporary or permanent discontinuation of study drug.

Worsening of asthma symptoms may require unscheduled evaluation between visits. Study site personnel must be available to monitor and document the patient's progress until the asthma worsening has resolved.

8.4.4 Appropriateness of efficacy assessments

The efficacy assessments selected are standard for this indication/patient population.

8.5 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

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

Spirometry will be used to monitor the safety of patients during the study. Patients will also be provided with an eDiary/ePEF. The data captured in the eDiary/ePEF will be used to alert the patient and/or investigator to possible signs of worsening asthma.

A central laboratory will be used to analyze and report blood chemistry/hematology/urinalysis.

Where required by local regulations TB testing will be done at screening. A local laboratory will be used to analyze and report TB testing.

A central ECG vendor will be used to collect, assess and report ECGs.

A Data Monitoring Committee will be set up to overview safety. See Section 10.2.2 for details.

Physical assessments are defined in below table.

Table 8-3 Assessments & Specifications

Assessment	Specification
Physical	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. An abbreviated physical examination will include the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include BP and pulse measurements. After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in Table 8-1.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls will occur aligned with the visit schedule for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

If participants cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result

to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

8.5.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens detailed in this section with the exception of urine pregnancy test and TB test. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, or in the event of other conditions, that delays or prevents laboratory samples reaching the analysis laboratory within sample stability or acceptable timeframe, exceptionally local laboratory analysis may be implemented. Prior to implementation, this mitigation must be discussed and agreed with Novartis and permitted/approved by local or regional Health Authorities and Ethics Committees as appropriate.

Table 8-4 Laboratory Evaluations

Test Category	Test Name
Hematology	Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Other) , HbA1C
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, GGT, Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Indirect Bilirubin, Direct Bilirubin, Total Bilirubin, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose
Urinalysis	Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells), Macroscopic Panel (pH, specific gravity, blood, protein).
Hepatitis markers	HBV-DNA, HbsAg, HbsAb, HbcAb, HCV RNA-PCR, Hepatitis C Virus Antibody
Screening for HIV	HIV1/2-Ab
Pregnancy Test	Serum pregnancy test, urine pregnancy test
Atopic status	ImmunoCAP test
Tuberculosis test	IGRA test

8.5.2 Electrocardiogram (ECG)

Timing and type of electrocardiograms (ECGs) is indicated in the Table 8-1. ECG must be recorded after 10 minutes rest in the supine position to ensure a stable baseline according to the ECG investigator manual. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, blood sampling and spirometry. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Triplicate 12 lead ECGs are to be collected at visits specified in the Table 8-1 with ECG machines supplied by the central laboratory. Full details of all procedures relating to the ECG collection and reporting will be contained in an investigator manual to be provided to each investigator site.

Single 12 lead ECGs are collected at visits specified in the Table 8-1 with ECG machines supplied by the central laboratory.

For any single ECGs with subject safety concerns, two additional ECGs must be performed to confirm the safety finding and copies forwarded to the central ECG laboratory for assessment. A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially at baseline before administration of study treatment.

Any identifier details must be redacted e.g. subject initials, date of birth.

In the event that a clinically significant ECG abnormality is identified (e.g. severe arrhythmia, conduction abnormality of QTcF > 500 ms), a copy of the assessment is sent to the central

laboratory for expedited review if applicable, and the ECG is repeated to confirm the diagnosis. If the subject is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

The original ECGs appropriately signed, must be collected and archived at the study site.

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

8.5.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have serum pregnancy or urine pregnancy testing at visits specified in the assessment schedule Table 8.1. Additional serum pregnancy testing might be performed if requested by local requirements or if urine pregnancy test is positive.

A positive serum pregnancy test requires immediate discontinuation from study drug.

A positive urine test requires interruption of study treatment until serum test is done. If the serum test is negative, study treatment should continue.

The patient must be followed to understand the outcome of the pregnancy.

If the result of urine pregnancy test at the end of run-in visit is positive, the patient must not be randomized until the results is confirmed by a serum pregnancy test.

Assessments of Fertility

Medical documentation of oophorectomy, hysterectomy, or bilateral tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

- Surgical bilateral oophorectomy without a hysterectomy
- Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH (Follicle Stimulating Hormone) testing is required of any female subject regardless of reported reproductive/menopausal status at screening/baseline.

8.5.4 Hepatitis and HIV screen

All subjects will be screened for Hepatitis B markers, i.e. HBsAg, HbsAb and HbcAb. Patients with a positive HBsAg and/or positive HbcAb are excluded. Patients who are vaccinated for Hepatitis B (HbsAb positive, both HBsAg and HbcAb negative) can participate in the study.

Screening for Hepatitis C will be based on HCV antibodies and if positive, or indeterminate, HCV RNA levels must be determined. Patients who have completed Hepatitis C treatment at least 12 weeks before, and HCV-RNA levels at screening are undetectable are considered cured and can be included in the study.

Evaluation for HIV seropositivity will be performed, and, if positive, or indeterminate, confirmation by a second technique e.g. Western blot.

Appropriate counseling will be made available by the site Investigator in the event of a positive finding.

Notification of state and federal authorities, as required by local law, will be the responsibility of the site Investigator.

8.5.5 Tuberculosis testing

Per exclusion criteria all patients with history of active or latent tuberculosis or experiencing any TB symptom, defined in the exclusion criteria, at screening must be excluded from the trial.

In addition if required by local regulations laboratory TB testing will be done at the screening visit. Recommended IGRA test is the QuantiFERON-TB® Gold test. Patients with a positive TB test result will be excluded from the trial prior to randomization. Patients with an indeterminate TB test result may be enrolled if the repeated TB test is negative prior to randomization. Patients with the repeated indeterminate or positive TB test result will be excluded from the trial prior to randomization.

8.6 Additional assessments

No additional tests will be performed on subjects entered into this study.

8.6.1 Clinical Outcome Assessments (COAs)

Patient reported outcomes (PRO)

The impact of CSJ117 on various aspects of patient's health status will be assessed by the following measures:

- Asthma Control Questionnaire-5 (ACQ-5) to assess improvement in asthma symptom control;
- Asthma Quality of Life Questionnaire+12 (AQLQ+12) to measure health-related quality of life (HRQOL);
- [redacted]

All patients will complete the PRO questions via a handheld electronic device or an electronic tablet as specified in the assessment schedule in clinic visits (Table 8-1). Available training materials related to the administrative procedures of the questionnaires will be provided to the sites.

The subject should be given the PRO measure(s) to be completed at the scheduled visit before any clinical assessments are conducted. Subject's refusal to complete all or any part of a PRO measure should be documented in the study data capture system and should not be captured as a protocol deviation.

Subject questionnaires should be completed in the language most familiar to the subject. The subject should be given sufficient space and time to complete the PRO measure(s). The site

personnel or OHP should check PRO measure(s) for completeness and ask the subject to complete any missing responses. The responses stored electronically on the database will be considered the source file.

Completed measure(s) and any unsolicited comments written by the subject should be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the subject to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 10.1.1 of the study protocol.

As per section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, COA data may be collected remotely depending on local regulations, technical capabilities, and following any applicable training in the required process.

8.6.1.1 Asthma Control Questionnaire-5 (ACQ-5)

In this study, the ACQ-5 will be used to assess improvements in asthma symptom control. The ACQ-5 will be collected in an electronic format.

The original ACQ consists of 7 items: 5 items on symptom assessment, 1 item on rescue bronchodilator use, and 1 item on airway caliber (% FEV1 predicted). The rescue bronchodilator use and % FEV1 predicted items are not included in the ACQ-5. The ACQ is validated in patients with asthma over 17 years (Juniper et al. 1999, Juniper et al. 2006), and is one of several asthma control measures recommended by the GINA Guidelines. The ACQ has been fully validated, including patients aged from 6 to 16 years (Juniper et al. 2010) and including a minimal important difference (MID) or smallest change that can be considered clinically important (0.5).

The ACQ-5 (see Section 16.5) only takes a few minutes to complete. Patients will be asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment, 6=maximum impairment). The questions are equally weighted and the ACQ-5 score is the mean of the 5 questions: therefore, between 0 (totally controlled) and 6 (severely uncontrolled) (Juniper et al. 1999; Juniper et al. 2005; Juniper et al. 2006).

The ACQ will be completed by patients at the visits specified in the table of assessments (See Table 8-1). The questionnaire should be completed before the AQLQ and before any other assessments (see Section 8) [redacted]. The appropriate language version(s) of the questionnaire will be used in each participating country. The same language version of the questionnaire should be used by a particular patient throughout the study.

The study coordinator or OHP should be familiar with the instrument and the associated user guides and training materials provided. Patients should complete the questionnaire in a quiet area and are allowed to ask questions; however the site staff/OHP should take care not to influence the patient's response. In response to a question, patients should be instructed to provide the truest or best response for them.

Missing data should be avoided; therefore, the study coordinator/OHP will check the questionnaire for completeness before the patient's next assessment in the clinic, and if necessary, encourage the patient to complete any missing responses. At later visits patients are not allowed to review their previous responses.

Completed questionnaires will be reviewed by the investigator for responses which may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaire but also for any unsolicited comments written by the patient. If AEs or SAEs are confirmed then the physician must record the events as per instructions given in Section 10.1.1 and Section 10.1.2 of the protocol. Investigators should not encourage the patients to change the responses reported in the completed questionnaires.

8.6.1.2 Asthma Quality of Life Questionnaire (AQLQ)

In this study, the disease-specific AQLQ+12 will be used to measure health-related quality of life in patients. The measure was originally validated for use in patients with asthma aged “12 to 80 years" (Juniper, et al. 2005). The AQLQ+12 will be collected in an electronic format.

The AQLQ+12 comprises a total of 32 individual questions that span a total of four domains: symptoms, activity limitation, emotional function, and environmental stimuli. Test-retest reliability, construct validity (cross-sectional and longitudinal), and responsiveness have been demonstrated (See Section 16.7).

The AQLQ+12 takes about 4 to 5 minutes to complete. Patients are asked to recall their experiences during the previous 2 weeks and to score each item on a 7-point scale (7 = not at all impaired to 1 = severely impaired). The AQLQ+12 yields individual domain scores, which is the mean of all items in each domain, and an overall score, which is the mean of all 32 individual responses. Higher scores indicate less impairment in Health Related Quality of Life (HRQOL).

The questionnaire will be completed by patients at the visits specified in the table of assessments (See Table 8-1).

The appropriate language version(s) of the questionnaire will be used in each participating country. The same language version of the questionnaire should be used by a particular patient throughout the study.

The study coordinator/OHP should be familiar with the instrument and the associated user guides and training materials provided. The patient should complete the questionnaire in a quiet area and be allowed to ask questions; however site staff/OHP should not influence patient’s responses. The patient will be instructed to provide the truest and best response for them.

Missing data should be avoided, therefore, the study coordinator/OHP will check the questionnaire for completeness before the patient's next in clinic assessment, and if necessary, encourage the patient to complete any missing responses. At later visits patients are not allowed to review their previous responses.

Completed questionnaires will be reviewed by the investigator for responses which may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaire but also for any unsolicited comments written by the patient. If AEs or SAEs are confirmed then the physician must record the events as per instructions given

in Section 10.1.1 and Section 10.1.2 of the protocol. Investigators should not encourage the patients to change the responses reported in the completed questionnaires.

[redacted]

8.6.2 Pharmacokinetics

PK samples will be collected at the visits defined in the assessment schedule (Table 8-1). Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing, and shipment. [redacted]

The number of samples/blood draws collected will not exceed those stated in the protocol.

Pharmacokinetic (PK) samples will be obtained but only evaluated in all subjects at all dose levels except the placebo group.

Total CSJ117 will be determined by a validated immunoassay method; the anticipated Lower Limit of Quantification (LLOQ) is 3 ng/mL. [redacted]

Concentrations will be expressed in mass per volume units (ng/mL)

Concentrations below the LLOQ will be reported as “zero” and missing data will be labeled as such in the Bioanalytical Data Report.

The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher): Ctrough, Racc, and T1/2 from the serum concentration-time data. Additional pharmacokinetic parameters may be calculated as necessary.

8.6.3 Biomarkers

[redacted]

[redacted] **Pharmacogenetics**

The study includes an optional genetic research component which requires a separate informed consent signature if the subject agrees to participate. As permitted by local governing regulations and by IRB/EC, it is required as part of this protocol that the Investigator presents these options to the subject.

The purpose of genetic research may be to better understand the safety and efficacy of CSJ117, or to learn more about human diseases, or to help develop ways to detect, monitor and treat diseases.

[redacted]

Laboratory manuals will be provided with detailed information on sample collection, handling, and shipment.

[redacted]

8.6.4 Asthma exacerbations

The following definitions of exacerbations are used in this study.

A **moderate asthma** exacerbation is defined as treatment with 'rescue' systemic corticosteroids for at least 3 days either as an outpatient or in emergency department visits (Emergency department visit less ≤ 24 hours).

A **severe asthma** exacerbation is defined as treatment with 'rescue' systemic corticosteroids for at least 3 days and hospitalization; or

- treatment with 'rescue' systemic corticosteroids for at least 3 days and emergency department visit (> 24 hours*); or
- death due to asthma.

*An emergency room visit greater than 24 hours is considered to be a hospitalization

A single depo-injectable dose of corticosteroid will be considered the equivalent to a 3-day course of systemic steroids (Reddel, et al 2009).

Scheduled spirometry should not be performed during an exacerbation until it has completely resolved.

The first day of treatment with systemic corticosteroid will determine the onset date of the exacerbation while the last day of treatment will define the stop date. If the second exacerbation episode starts within the 7 days after the end of the first exacerbation episode, it should be counted as a single exacerbation.

If a patient experiences an asthma exacerbation during the screening period, the patient may be re-screened 4 weeks after complete recovery from the exacerbation. If a patient experiences an asthma exacerbation during the run-in period, the run-in period must be extended to 8 weeks in order to allow for resolution of the asthma exacerbation before randomization. An additional run-in medication kit should be dispensed in this case.

8.6.5 Other Assessments

8.6.5.1 Immunogenicity

Immunogenicity (IG) blood samples for ADA will be obtained and evaluated in all subjects at all dose levels, including the placebo group, at the timepoints defined in the Assessment schedule (Table 8-1). In case of positive immunogenicity, backup of previous pre-dose PK samples could be used to better characterize the onset of immunogenicity response.

[redacted]

Immunogenicity analytical method(s)

A validated bridging electrochemiluminescence immunoassay (ECLIA) will be used for the detection of potential anti-CSJ117 antibodies in serum, including 3 tiers of screening, confirmation and titration. [redacted]

8.6.5.2 Concept1 add on sensor (only in selected countries)

The add on sensor detects and records the Concept1 inhaler use from randomization. Recorded use of the inhaler is transferred through Bluetooth wireless technology to a vendor provided tablet at the clinical site. Data is then uploaded to the propeller server.

The sensor stores and transfers inhaler use data i.e. Date / Time and Sensor Technical events.

The sensor does not interfere with the use or drug delivery of the inhaler and the patient is never prevented from taking a dose due to the add-on sensor.

[redacted]

[redacted]

8.6.5.5 Peak Inspiratory Flow training

At selected visits (see Table 8-1) patients will be trained on generating optimal inspiration flow for their inhalers i.e. Concept1 and Diskus®/Accuhaler® inhalers using In-Check device. This training should assure proper drug delivery into lungs during the trial.

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

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

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances:

- Subject/guardian decision
- Pregnancy
- Permanent use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the subject
- Female patients non-compliant with the chosen effective method of contraception during the study. The investigator must provide appropriate advice on the continued use of

effective contraception for at least 12 weeks (at least 5 half-lives of CSJ117) after study drug discontinuation and follow up with the subject as appropriate at least to the end of this period

- Following emergency or accidental unblinding
- 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

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information.

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 'Withdrawal of Informed Consent' section 9.1.2). **Where possible, they should complete the assessments indicated** in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

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

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

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section (see Section 6.6.2).

9.1.2 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use of data/ and/or biological samples occurs when a subject:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be in writing (depending on local regulations (e.g. in writing) and recorded in the source documentation.

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 their consent/opposition to use data/biological samples and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the subject therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

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.

If the subject agrees, a final evaluation at the time of the subject's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8).

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.1.3 Lost to follow-up

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

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision. For patients not entering a safety extension study after treatment period the Study Completion Visit is the last follow up visit i.e. Week 24 visit. For patients who enter the safety extension study after treatment period the Study Completion Visit is the Week 12 visit.

Patients will be allowed to continue study participation if eligible, if they have already entered run-in period when enrolment target for a particular EOS stratum, or for the entire study, have been met.

At sites participating in the Safety Extension Study (CSJ117A12201E1), patients who successfully complete 12 weeks of treatment in this study (Study CCSJ117A12201C) may be offered participation in the Safety Extension Study; patient participation in the Safety Extension Study will be optional. Patients not entering the safety extension study directly after the treatment period will complete the 12 week follow-up period. Patients not entering the extension study will not be given further access to study drug because the risk/benefit ratio will not yet have been substantiated and there are already other marketed therapeutic alternatives available to treat these patients. At the time of study completion or early termination, all patients will be placed on the appropriate asthma treatment as prescribed by the investigator.

The investigator must provide appropriate advice on the continued use of effective contraception for at least 12 weeks after the last study drug treatment and follow up with the subject as appropriate at least to the end of this period.

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

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

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

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

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by

the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

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

1. The severity grade:
- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities
2. its relationship to the study treatment and other investigational treatment (if any). If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. whether it constitutes a serious adverse event (SAE) (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding study treatment
6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving; recovered/resolved with sequelae; fatal; or unknown)

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

- Investigational treatment interrupted/withdrawn
- Concomitant medication or non-drug therapy given
- Patient hospitalized/hospitalization prolonged
- No action taken (i.e. further observation only)

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

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

To ensure patient safety, every adverse event, occurring after the patient has provided informed consent and until end of the trial for each patient must be reported.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions that are already known for the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the patient

informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the investigational product 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 has then to be discussed with the patient.

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 16.2.

10.1.2 Serious adverse events

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

- is fatal or life-threatening. Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires 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 (specify what this includes)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the subject's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be

considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

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

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred (see Section 10.1.5).

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until end of the trial for each individual patient, must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

For patients NOT participating in the separate CSJ117A12201E1 safety extension study:

Any SAEs experienced after the 30 day period after end of the trial for each patient should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

For patients participating in the separate CSJ117A12201E1 safety extension study:

Any SAEs experienced after the patient's last visit in the CSJ117A12201C study should ONLY be assigned to safety extension study and be reported to Novartis regardless of suspected causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information. (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

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

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

10.1.4 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 should be recorded on a Pharmacovigilance Pregnancy Form, and reported by the investigator to CMO&PS. 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 pregnancy must be reported.

Tracking of pregnancy cases occurs until after Expected Delivery Date (EDD) for all prospective pregnancy cases received from clinical studies

- EDD +1 month (mandatory for all cases). Requesting the pregnancy outcome and other clinically relevant pregnancy data or changes in data
- EDD+2 month (mandatory if no answer is obtained after request at EDD+1 month). A reminder letter for the outcome
- The follow up at EDD+3 and EDD+12 months is mandatory for all cases of live birth and unknown outcome. Information on the status of the baby 3 months after delivery and information on any development issue or abnormality that would not be seen at birth must be collected.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

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

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

For more information on AE and SAE definition and reporting requirements, please see the respective Section 10.

10.1.6 Concept1 related adverse events reporting

Any Concept1 device related adverse events must be reported to Novartis within 24 hours of learning of its occurrence. Concept1 device related adverse events must be recorded on the relevant device-related pages of the CRF. Country regulations have to be followed for the Concept1 device related adverse events reporting to Health Authorities and/or Ethics Committees.

The investigator has the responsibility for managing the safety of individual subjects.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

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

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

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

Please refer to Section 16.2 for complete definitions of liver laboratory triggers and liver events.

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

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment Section 9.1.1), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include investigations (can include based on investigator's discretion): serology tests, imaging and pathology assessments,

hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

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

10.2.2 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of the clinical trial, safety data and recommend to the sponsor whether to continue, modify, or terminate a trial.

Specific details regarding composition, responsibilities, data monitoring, meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

11 Data Collection and Database management

11.1 Data collection

Data not requiring a separate written record will be defined in the protocol and the Assessment Schedule (Table 8-1) 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.

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

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

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

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 the vendor working on behalf of Novartis.

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

11.2 Database management and quality control

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

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (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.

ECG, spirometry and Concept1 add on sensor readings will be processed centrally and the results will be sent electronically to Novartis.

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

Randomization codes and data about all study treatment (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 data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

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.

Once all the necessary 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 after written agreement by Novartis development management.

11.3 Site monitoring

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

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

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

12 Data analysis and statistical methods

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

12.1 Analysis sets

The Randomized Analysis Set (RAS) consists of all randomized subjects. Subjects will be analyzed according to the treatment they were assigned to at randomization. Demographics and baseline characteristics will be summarized using the RAS.

The Full Analysis Set (FAS) comprises all subjects to whom study treatment has been assigned and who received at least one dose of study treatment. Subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure. The FAS will be used for the analysis of all efficacy variables.

The Safety Set includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received. The Safety Set will be used for the analysis of all safety variables.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data, including disease characteristics will be summarized descriptively by treatment group for the RAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term by treatment group.

12.3 Treatments

The duration of exposure in days to each treatment group (CSJ117 dose or placebo) will be summarized by means of descriptive statistics.

Asthma-related medications will be summarized separately for medications prior to the start of randomized treatment and for concomitant medications (medications which were taken anytime between the first dose and last dose of randomized treatment, inclusive) by pre-defined categories, route of administration, preferred term, and treatment group. Non-asthma related medication prior to and after the start of randomized treatment will also be summarized by ATC classification system, preferred term, and treatment group. More than one ATC class per medication is possible and the medication will be reported under all applicable classes.

The number of patients who permanently discontinued from double blind treatment and the reasons will be summarized by treatment group.

Treatment compliance with study medication over the entire study will be summarized by treatment group.

12.4 Analysis of the primary endpoint(s)

The primary objective of this study is to characterize the DR (dose response) efficacy relationship among CSJ117 doses (0.5, 1, 2, 4, and 8 mg daily) and placebo with regards to the average change from baseline in pre-dose FEV1 (L) at Week 8 and Week 12. The goals associated with this objective are below.

- To confirm an overall drug response signal
- To estimate the dose(s) that corresponds to the target effect (e.g., 120 mL) over placebo based on the estimated DR curve

12.4.1 Definition of primary endpoint(s)

The primary endpoint for this study is the average change from baseline in pre-dose FEV1 (L) at Week 8 and Week 12.

The baseline value is defined as the average of the values taken approximately 2 hours 45 minutes and 2 hours 15 minutes prior to first dose of randomized drug at Day 1. If one of the two values is missing or unacceptable per the central spirometry overreader (or is not confirmed to be pre-dose) then the remaining non-missing value will be taken as the baseline. If both values are missing (or are not confirmed to be pre-dose), then the measurements taken at the run-in visit will be used as the baseline.

12.4.2 Statistical model, hypothesis, and method of analysis

The Multiple Comparison Procedure – Modelling (MCP-Mod) methodology (see Bretz et al 2005 and Pinheiro et al 2014) will be employed to assess the primary objective. An overview of the steps for the MCP-Mod methodology is given below. Further details will be provided in the Statistical Analysis Plan (SAP).

Step 1 (Testing an overall dose-response signal - MCP part):

The covariate adjusted least-squares means averaged across Week 8 and Week 12 visits for each individual dose group and the corresponding variance-covariance matrix will be obtained from a linear mixed effects model for repeated measures (MMRM) with terms for baseline FEV1, visit, treatment, randomization strata – eosinophil count (EOS) (≥ 300 or < 300 cells/µl) and region, treatment-by-visit interaction, and baseline FEV1-by-visit interaction, FEV1 prior

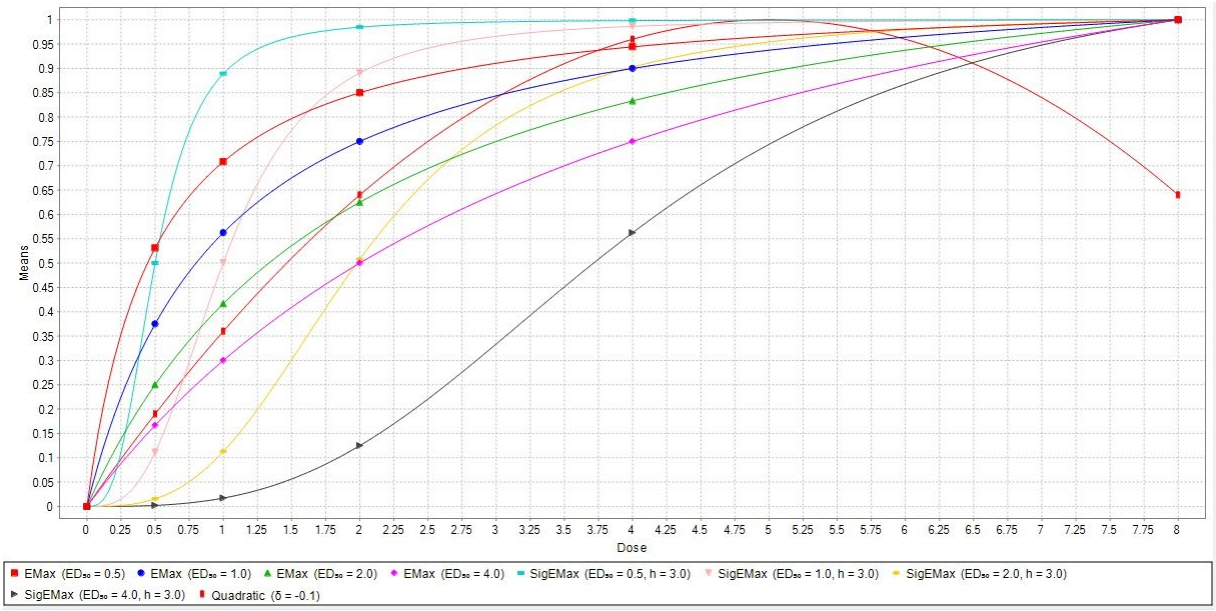
to inhalation, and FEV1 within 30 min post inhalation of salbutamol/albuterol (components of SABA reversibility) as fixed effects. To allow adjustment for correlations between time points within patients, an unstructured variance-covariance structure will be used.

The adjusted treatment means from the MMRM will be used to test the null hypothesis of a flat DR relationship for the primary efficacy endpoint at a two-sided significance level of 5% against the alternative hypothesis of a non-constant DR curve. Two one-sided tests will be performed to obtain the two-sided test. The testing will be performed with a multiple contrast test described in the MCP-Mod methodology.

A wide range of possible dose response relationship will be considered to take model uncertainty into account (Figure 12-1). Based on inputs from Drug Metabolism & PharmacoKinetics (DMPK) and Clinical, nine candidate DR curves (4 Emax, 4 Sigmoid Emax, and 1 Quadratic) will be used to derive the optimal model contrasts for the multiple contrast tests. The ED50 (the dose at which half of the maximum effect is reached) values for the Emax models will be 0.5, 1, 2 and 4. The parameters of the sigmoidal Emax models (ED50, h) will be (0.5, 3), (1, 3), (2, 3) and (4, 3) where h is the Hill parameter that determines the steepness of the dose-response shape. A quadratic model is considered to capture a possible non-monotonic DR curve. The discriminant parameter of the Quadratic model will be -0.1.

For each of the 9 candidate DR curves, a contrast test statistic will be derived that maximizes the power assuming the true mean response is the one assumed by the candidate DR curve. The detection of a significant DR signal is based on the maximum of the 9 contrast test statistics. The overall null hypothesis of no DR relationship is rejected if the multiplicity adjusted p-value for at least one contrast test is less than 0.05 (two sided).

Figure 12-1 Candidate Dose Response Curves



Step 2 (Estimation of the dose-response curve and target dose – Mod part):

Once the DR signal is tested, the DR curve and the target dose(s) of interest will be estimated.

A large number of bootstrap samples from the multivariate normal distribution will be drawn with adjusted means from the MMRM and corresponding covariance matrix. For each sample:

- DR models from the candidate families (Emax, Sigmoid Emax, Quadratic) will be fitted to the data and the best model according to the generalized Akaike information criterion will be chosen.
- The predictions for dose response will be obtained from the best model.

The median of the predicted differences to placebo for each dose based on the selected model for each sample will be used as the estimated dose response curve. Bootstrap pointwise 95% confidence intervals will also be provided. This bootstrap model averaging approach reflects model uncertainty in the inference and typically leads to more reliable confidence intervals as well as more precise estimates of the dose-response curve compared to selection of a single model (Bornkamp 2015; Schorning et al 2016).

The target dose(s) that corresponds to a clinically relevant effect over placebo can be estimated using inverse regression techniques (Bretz et al 2005).

12.4.3 Handling of missing values/censoring/discontinuations

Despite all attempts to ensure complete follow-up for all patients, some patients may not be followed for pre-dose FEV1 for the whole planned study duration.

The FEV1 value analyzed at each post-baseline visit is based on the average of the two FEV1 assessments taken at approximately 45 minutes and approximately 15 minutes prior to the dosing of study drug at clinic visits. Since the estimand is related to an effect outside of rescue med intake, spirometry measurements within 6 hours of rescue medication, within 7 days of intake of systemic corticosteroid use, or within 3 months of a single depot corticosteroid injection, or within 24 hours of background medication use, or within 48 hours of LAMA use will be set to missing. In cases where one of the two values is missing, the remaining non-missing value will be taken as pre-dose FEV1. If both values are missing, then their pre-dose FEV1 will be regarded as missing at that visit.

For the primary analysis, only on-treatment data (from date of first randomized dose up to 1 day after date of last randomized dose) will be used as the estimand specifies a hypothetical on-treatment effect. Missing on-treatment data will not be explicitly imputed as the MMRM implicitly imputes missing data assuming the missing at random (MAR) mechanism.

The imputation procedures related to the pre-dose FEV1 supportive analyses (Section 12.4.4) are "jump-to-reference" (J2R) and MAR (Carpenter et al 2013). The imputations will be based on all available data (i.e. from all scheduled timepoints) using all covariates as specified in the MMRM. For J2R, only placebo (reference) data will be used. For MAR, data from the same treatment arm will be used for building the imputation model. Imputation of intermittent missing observations before treatment discontinuation will be carried out following a MAR mechanism for all treatment arms. Additional details will be available in the SAP.

12.4.4 Sensitivity and Supportive analyses

Sensitivity analyses

Sensitivity analysis will be outlined in the SAP as appropriate.

Supportive analyses

A single supplementary analysis will be performed that quantifies the treatment effect in all randomized patients during stable periods (i.e. outside episodes of asthma worsening that require rescue medication) with an adherence to treatment like we would see in clinical practice in a world without COVID-19, with the following post-randomization events accounted for by assessing:

a. Intake of non-study drug with effect on FEV1: the effect outside of periods of worsening disease that necessitate rescue medication.

b. Discontinuation of study treatment due to any non-COVID-19 related reason: actual off-treatment value. If no data was retrieved after study treatment discontinuation, missing data will be multiply imputed based on placebo arm data: J2R assumption for the CSJ117 arms and MAR assumption for placebo arm.

c. Discontinuation of study treatment due to any COVID-19 related reason: hypothetical value of the average between Week 8 and Week 12 pre-dose FEV1 had the patients not stopped the study treatment

Any additional supportive analysis will be outlined in the SAP.

12.5 Analysis of secondary endpoints

No multiplicity adjustment will be carried out for secondary analyses described below. In addition, the treatment effect of CSJ117 compared to placebo that would have been observed had all patients remained on their assigned treatment will be estimated. Only data obtained while patient is on-treatment (from date of first randomized dose up to 1 day after date of last randomized dose) will be used. Missing data for any reason will not be explicitly imputed and will be handled by the respective mixed effects model which implicitly imputes missing data assuming MAR.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

12.5.1.1 FeNO

Fractional exhaled Nitric Oxide (FeNO) is a non-invasive marker for airway inflammation and is used to monitor the response to anti-inflammatory medications. Several publications reported high fractional concentrations of orally exhaled NO (FeNO) in subjects with asthma as compared with unaffected subjects, and a fall after treatment. It will be measured following the recently published guidelines (ATS/ERS) on standardized techniques.

Repeated, reproducible exhalations should be performed to obtain two FeNO measurements within 10% of each other. Exhaled NO is the mean of these two values.

The average change from baseline in FeNO at Week 8 and Week 12 will be analyzed using the same MCP-Mod approach described for the primary analysis of the primary variable. The change from baseline in FeNO will be analyzed using a similar MMRM (including all scheduled post-baseline visits with FeNO data) on the FAS as used for the primary analysis but will include baseline FeNO instead of baseline FEV1. The estimated treatment difference (CSJ117

– placebo) at each visit will be reported as well as the average between Week 8 and Week 12 along with the associated 95% confidence interval.

12.5.1.2 ACQ-5

The ACQ-5 measures asthma symptom control and consists of 5 items (questions) on symptom assessment. Patient recall is one week.

All 5 questions of the ACQ-5 are equally weighted. Items are scored along a 7-point response scale, where 0 = totally controlled and 6 = severely uncontrolled.

The total score is calculated as the mean of all five questions.

The average change from baseline in ACQ-5 at Week 8 and Week 12 will be analyzed using the same MMRM (including all scheduled visits with ACQ data) on the FAS as used for the primary analysis but will include baseline ACQ-5 instead of baseline FEV1. The estimated treatment difference (CSJ117 – placebo) at each visit as well as the average between Week 8 and Week 12 will be reported along with the associated 95% confidence interval.

The proportion of patients who achieve an improvement of at least 0.5 in ACQ-5 (i.e. decrease of ACQ-5 score of at least 0.5 from baseline) at post-baseline visits will be analyzed using a repeated measurements logistic regression. The model will include the same terms as for the MMRM analysis of the primary variable with baseline ACQ-5 instead of baseline FEV1. The estimated adjusted odds ratios will be displayed along with the associated 95% (two-sided) confidence intervals.

12.5.1.3 Daytime and nighttime asthma symptoms

The baseline of ADSD and ANSD will be defined as the average of the respective scores during the run-in period.

The mean daily scores of ADSD and ANSD will be summarized by weekly intervals and analyzed using a similar MMRM as specified for the primary analysis but including the appropriate weeks and baseline as a covariate. The estimated treatment difference (CSJ117 – placebo) at each week as well as the average between Week 8 and Week 12 will be reported along with the associated 95% confidence interval.

12.5.1.4 AQLQ+12

AQLQ (Asthma Quality of Life Questionnaire) is a 32-item disease specific questionnaire designed to measure functional impairments that are most important to patients with asthma, with 7-point scale (1-totally limited/problems all the time, 7-not at all limited/no problems). It consists of 4 domains: symptoms, emotions, exposure to environmental stimuli and activity limitation. Mean score will be calculated for the four domains, as well as the overall quality-of-life score defined as the mean score of all 32 items.

The average change from baseline in AQLQ+12 (overall and by domain) at Week 8 and Week 12 will be analyzed using the same MMRM model as specified for the primary efficacy variable with baseline AQLQ as covariate. The estimated adjusted treatment difference at each visit as well as the average between Week 8 and Week 12 will be reported along with the associated 95% confidence interval.

The proportion of patients who achieve an improvement of at least 0.5 in the change from baseline in AQLQ (i.e. increase of AQLQ score of at least 0.5 from baseline) at post-baseline visits will be analyzed using the same repeated measurements logistic regression model for the ACQ-5 analysis except that baseline AQLQ will be used instead of the baseline ACQ-5. The estimated adjusted odds ratios will be displayed along with the associated 95% (two-sided) confidence intervals.

12.5.1.5 Total daily use of SABA

Total daily use of SABA (the number of puffs taken in the previous 24 hours) by the patient will be analyzed using ePEF/ eDiary data. The baseline of SABA use will be defined as the average of total daily SABA use during the run-in period.

The mean of change from baseline in the total daily use of SABA over the 12 weeks of treatment will be analyzed using an ANCOVA model with factors for treatment group, randomization strata (eosinophil count ≥ 300 or < 300 cells/µl, region), as well as baseline total daily SABA use, and baseline pre-dose FEV1 as continuous linear covariates. The estimated treatment difference (CSJ117 – placebo) will be reported along with the associated 95% confidence interval.

In addition, the mean daily use of SABA will be summarized by weekly intervals and analyzed using a similar MMRM as specified for the primary analysis but including the appropriate visits and baseline as a covariate. The estimated treatment difference (CSJ117 – placebo) at each week will be reported along with the associated 95% confidence interval.

12.5.1.6 Peak Expiratory Flow Rate (PEF)

All the patients are instructed to record PEF twice daily using a mini Peak Flow Meter device, once in the morning (before taking the morning dose of asthma medications) and once approximately 12 hr later in the evening (before taking the evening dose of asthma medications), from the beginning of screening period to study completion.

The morning/evening PEF (liters/min) will be averaged over the whole 12 weeks. E-diary data recorded during the run-in period will be used to calculate the baseline value.

Mean morning/evening PEF will be summarized by treatment. Between-treatment differences of the change from baseline in mean morning/evening PEF will be performed using the same ANCOVA models as specified for rescue medication data except that baseline rescue medication use will be replaced with baseline morning/evening PEF as the covariate. LS mean and associated 95% confidence intervals will be presented for treatments and treatment differences.

In addition, the mean morning/evening PEF will be summarized by weekly intervals and analyzed using a similar MMRM model as specified for the primary analysis with baseline FEV1 value replaced with the appropriate baseline PEF. The estimated treatment difference (CSJ117 – placebo) at each week will be reported along with the associated 95% confidence interval.

12.5.2 Safety endpoints

Safety summaries include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided.

Adverse events

For patients not entering the safety extension study directly after the treatment period or not participating in the safety extension study, the on-treatment period for adverse events (AEs) lasts from the time of first administration of double-blind study treatment to 30 days after the time of the last administration of randomized study treatment. For patients entering the safety extension study directly after the treatment period, the on-treatment period lasts from the time of first administration of double-blind study treatment to the time of the last actual administration of randomized study treatment. Summary tables for AEs will summarize only on-treatment events (also known as treatment-emergent AEs).

All information obtained on adverse events will be summarized by treatment group.

The number (and percentage) of subjects with treatment emergent adverse events will be summarized separately for the treatment period and the follow-up period (30 days after the last time of the last administration of randomized study treatment) in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation separately for the treatment period and the follow-up period (30 days after the last time of the last actual administration of randomized study treatment).

A subject with multiple adverse events within a primary system organ class or preferred term is only counted once towards the total of the primary system organ class or preferred term.

Vital signs

Summary statistics will be provided by treatment and visit/time for each vital signs variable. Notable values (to be defined in the SAP) and change from baseline will also be summarized. The baseline value is the last value prior to first dose of double-blind treatment.

12-lead ECG

Summary statistics will be provided by treatment and visit/time for each ECG variable. Categorical analysis of QTc interval data based on the number of subjects meeting or exceeding predefined limits (to be defined in the SAP) in terms of absolute QTc intervals or changes from baseline will be presented. The baseline value is the last value prior to first dose of double-blind treatment.

Clinical laboratory evaluations

Summary statistics will be provided by treatment and visit/time by each lab variable.

For selected laboratory tests, the number and percentage of patients with newly occurring or worsening laboratory abnormalities meeting the clinically notable criteria (to be defined in the SAP) will be summarized by laboratory parameter. Change from baseline will also be summarized. The baseline value is the last value prior to first dose of double-blind treatment.

Immunogenicity

Results of the anti-CSJ117 antibodies (anti-drug antibodies, ADA) will be listed by treatment group, subject and visit/time.

12.5.3 Pharmacokinetics

CSJ117 plasma concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n%) of concentrations below the LLOQ and reported as zero. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. If at a single time point a substantial number of concentrations are below LLOQ, they may be substituted with a pre-defined value, such as ½ LLOQ for calculation of PK parameters.

[redacted]

[redacted]

12.7 Interim analyses

DMC analyses are planned for the monitoring of safety data, and details will be provided in the DMC charter. Such safety analyses do not inflate the type I error for the primary efficacy hypothesis testing and thus no adjustment for multiplicity is required.

A blinded sample size re-estimation might be performed when approximately 150 high eosinophil subjects completed week 8 visit (see Section 12.8.2).

One or more interim analyses may be conducted to support decision-making in relation to the current clinical study, or the future of the sponsor's clinical development plan or in case of any safety concerns from this study or ongoing clinical studies.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

For the primary endpoint pre-dose FEV1, we assume a variance of 0.1461 L at week 8, 0.1456 L at week 12, and a covariance of 0.1163 between the week 8 and 12 assessments (based on a recent asthma dose ranging study (Bateman et al 2017) and literature data (Corren et al 2017). On this basis, the average of the week 8 and 12 assessments has a standard deviation of 0.3622 L.

We assume 2:1:1:1:2:2 randomization to placebo, CSJ117 0.5 mg o.d., CSJ117 1 mg o.d., CSJ117 2 mg o.d., CSJ117 4 mg o.d. and CSJ117 8 mg o.d..

With these assumptions 531 patients result in above 80% power (on average across dose response shapes) to have a significant contrast test at the one-sided 2.5% significance level for a maximum treatment effect over placebo of 0.120 L in the absence of missing data. If we assume that 15% of patients will have missing data and if we conservatively assume that these patients will not contribute any information to the primary analysis, 625 patients are needed for the dose response part of the trial. These calculations were performed using ADDPLAN DF 4.0.9.

The precision of the DR curve estimation were obtained from simulations. Specifically, the average half-length of 95% confidence interval of the estimated DR curve is 57.61 mL, and that of the estimated placebo-adjusted DR curve is 76.93 mL.

12.8.2 Sample size re-estimation

A sample size re-estimation might be performed strictly using the blinded data when approximately 150 high eosinophil subjects completed week 8 visit. No treatment information would be used for sample size re-estimation, thus there would be no inflation of type I error rate.

Let S_{pool} be the pooled standard deviation of the primary endpoint. The decision on the final sample size will be based on the decision guidance specified in the following Table 12-1.

Table 12-1 Decision guidance on approximate sample size to ensure at least 80% power to detect a dose-response signal

Estimated S_{pool}	Approximate final sample size
$S_{pool} \leq 315$ ml	466
315 ml < $S_{pool} \leq 320$ ml	480
320 ml < $S_{pool} \leq 325$ ml	495
325 ml < $S_{pool} \leq 330$ ml	509
330 ml < $S_{pool} \leq 335$ ml	523
335 ml < $S_{pool} \leq 340$ ml	540
340 ml < $S_{pool} \leq 345$ ml	555
$S_{pool} > 345$ ml	Keep original sample size

When 315 ml < $S_{pool} \leq 345$ ml, the proposed total sample size will assure at least 80% power (on average across dose response shapes) to have a significant contrast test at the one-sided 2.5% significance level for a maximum treatment effect over placebo of 0.120 L assuming 15% drop-out rate.

Based on findings from sample size re-estimation, the overall sample size for the study may be reduced accordingly.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

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

13.3 Publication of study protocol and results

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

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

13.4 Quality Control and Quality Assurance

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

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

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal Standard Operating Procedures (SOPs), and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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

14.1 Protocol amendments

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

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

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

15 References

References are available upon request

ATS/ERS (2005) Recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am. J. Respir. Crit. Care Med; p. 912-30.

Bateman ED, Guerreros AG, Brockhaus F, et al (2017) Fevipiprant, an oral prostaglandin DP2 receptor (CRTh2) antagonist, in allergic asthma uncontrolled on low-dose inhaled corticosteroids. Eur. Respir. J.;50(2).

Biagini Myers JM, Martin LJ, Kovacic MB, et al (2014) Epistasis between serine protease inhibitor Kazal-type 5 (SPINK5) and thymic stromal lymphopoietin (TSLP) genes contributes to childhood asthma. J. Allergy Clin. Immunol; 134(4):891-9.

Bornkamp B (2015) Viewpoint: model selection uncertainty, pre-specification, and model averaging. Pharm Stat; 14(2):79-81.

Bretz F, Pinheiro JC, Branson M (2005) Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics; 61:738-48.

Carpenter JR, Roger JH, Kenward MG (2013) Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat; 23(6):1352-71.

Corren J, Lemanske R, Hanania N, et al (2011) Lebrikizumab Treatment in adults with Asthma. N. Engl. J. Med; 365 (12):1088-98.

Corren J, Parnes JR, Wang L, et al (2017) Tezepelumab in Adults with Uncontrolled Asthma. N. Engl. J. Med; 377:936-46.

Czock D, Keller F, Seidling HM (2012) Pharmacokinetic predictions for patients with renal impairment: focus on peptides and protein drugs. Br J Clin Pharmacol; 74(1):66-74.

Gauvreau GM, O'Byrne PM, Boulet LP, et al (2014) Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. N. Engl. J. Med;370(22):2102-10.

Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2019. Available from http://www.ginasthma.org/

Graham BL, Steenbruggen I, Miller MR, et al (2019) Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am. J. Respir. Crit. Care Med;200(8):e70-e88.

He R, Geha RS (2010) Thymic stromal lymphopoietin. Ann. N. Y. Acad. Sci; 1183:13-24.

Hurst H, Bolton J (2004) Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther; 27(1):26-35.

Juniper EF, Bousquet J, Abetz L, et al. (2006) Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med; 100(4):616-21.

Juniper EF, Gruffydd-Jones K, Ward S, et al (2010) Asthma Control Questionnaire in children: validation, measurement properties, interpretation. Eur. Respir. J; 36:1410-6.

Juniper EF, O'Byrne PM, Guyatt GH et al. (1999) Development and validation of a questionnaire to measure asthma control. Eur. Respir. J; 14(4):902-7.

Juniper EF, Svensson K, Mörk AC, et al (2005) Modification of the asthma quality of life questionnaire (standardised) for patients 12 years and older. Health Qual Life Outcomes; 3:58.

Kubota M, Kobayashi H, Quanjer PH, et al (2014) Reference values for spirometry, including vital capacity, in Japanese adults calculated with the LMS method and compared with previous values. Respir Investig p. 242-50.

Lobo ED, Hansen RJ, Balthasar JP (2004) Antibody pharmacokinetics and pharmacodynamics. J Pharm Sci; 93(11):2645-68.

Masoli M, Fabian D, Holt S, et al (2004) The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy; 59(5):469-78.

Morris PE, Zeno B, Bernard AC, et al (2012) A placebo-controlled, double-blind, dose-escalation study to assess the safety, tolerability and pharmacokinetics/pharmacodynamics of single and multiple intravenous infusions of AZD9773 in patients with severe sepsis and septic shock. Crit Care; 16(1):R31.

Pinheiro J, Bornkamp B, Glimm E, et al (2014) Model-based dose finding under model uncertainty using general parametric models. Stat Med; 33(10):1646-61.

Reddel HK, Taylor DR, Bateman ED et al. (2009) An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med; 180: 59-99.

Quanjer PH, Stanojevic S, Cole TJ, et al (2012) Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur. Respir J;40(6):1324-43.

Schaumann W, Kaufmann B, Neubert P, et al (1986) Kinetics of the Fab fragments of digoxin antibodies and of bound digoxin in patients with severe digoxin intoxication. Eur. J. Clin. Pharmacol; 30(5):527-33.

Schorning K, Bornkamp B, Bretz F, et al (2016) Model selection versus model averaging in dose finding studies. Stat Med; 35(22):4021-40.

Ying S, O'Connor B, Ratoff J, et al (2005) Thymic stromal lymphopoietin expression is increased in asthmatic airways and correlates with expression of Th2-attracting chemokines and disease severity. J. Immunol; 174(12):8183-90.

Ying S, O'Connor B, Ratoff J, et al (2008) Expression and cellular provenance of thymic stromal lymphopoietin and chemokines in patients with severe asthma and chronic obstructive pulmonary disease. J. Immunol; 181(4):2790-8.

16 Appendices

16.1 Clinically notable laboratory values and vital signs

The central laboratory will flag laboratory values falling outside of the normal ranges on the central laboratory reports. Investigators are responsible for reviewing these abnormal values for clinical significance, signing the laboratory reports to indicate their review, and reporting values considered clinically significant in the appropriate electronic case report form (eCRF).

Any clinically significant abnormal laboratory value should be evaluated and followed-up by the investigator until normal or a cause for the abnormality is determined.

See Section 16.2 for specific liver event and laboratory test trigger definitions and follow-up requirements.

16.2 Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal

Table 16-2 Follow up requirements for liver events and laboratory triggers

Criteria	**Actions required**	**Follow-up monitoring**
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
	• Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

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

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

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.3 Spirometry Guidance

Equipment

Spirometers must meet the accuracy specifications according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) Standardization of Spirometry (Graham et al 2019). Spirometers must have the capacity to print forced vital capacity (FVC) tracings. All spirometry values should be reported at body temperature and pressure saturated (BTPS) by the method established by the manufacturer.

Calibration

The spirometer should be calibrated every morning before any spirometric measurements for the study are performed. Calibration reports should be printed and stored as source data at the site.

Preparing the test subject

On study days when spirometry will be performed, patients should refrain from the following:

- Coffee, tea, chocolate, cola and other caffeine-containing beverages and foods and ice-cold beverages for 4 hours prior to spirometry
- Alcohol for 8 hours prior to spirometry
- Strenuous activity for 1 hour prior to spirometry
- Exposure to environmental smoke, dust or areas with strong odors
- Wearing clothing that substantially restricts full chest and abdominal expansion

Every effort should be made to assure consistent testing conditions throughout the study. A seated position with nose clips is recommended to reduce risks related to dizziness or syncope. When possible, spirometry should be conducted by the same technician using the same spirometer. To minimize the effects of diurnal variation on lung function, spirometry visits should start at approximately the same time of day at each visit.

Performing Spirometry

For full details on performing spirometry see Graham et al 2019.

In summary the subject's age, height and gender will be entered into the spirometer. It is important that the height is measured accurately at the study site. Spirometry, an effort-dependent test, requires careful instruction and cooperation of the subject. The technician should ensure a good seal around the mouthpiece, and confirm that the subject's posture is correct. The results of spirometry should meet the ATS/ERS criteria for acceptability and FEV1 repeatability. Acceptability criteria should be applied before repeatability is determined.

FEV1 and FVC Maneuver

The subject should be instructed to perform:

1) Maximal inspiration
2) A "blast" of expiration
3) Continued complete expiration for a maximum of 15 seconds
4) Inspiration at maximal flow back to maximum lung volume

Number of trials

A minimum of 3 maneuvers should be performed. If a subject is unable to perform a single acceptable maneuver after 8 attempts, testing should be discontinued.

Acceptability

- Must have BEV <5% of FVC or 0.100 L, whichever is greater
- Must have no evidence of a faulty zero-flow setting
- Must have no cough in the first second of expiration
- Must have no glottic closure in the first second of expiration
- Must have no glottic closure after 1 second (s) of expiration
- Must achieve one of these three end of forced expiration (EOFE) indicators:
    1. Expiratory plateau (<0.025 L in the last 1 s of expiration)
    2. Expiratory time $\geq$15 s
- Must have no evidence of obstructed mouthpiece or spirometer
- Must have no evidence of a leak

Overall acceptability will be determined by expert over-read by spirometry vendor.

All spirometry assessments at the run in visit must be confirmed as acceptable by the central over read. At least one spirometry assessment, i.e. -2 hr 45 min or/and -2 hr 15 min, at the end of run in visit must be confirmed as acceptable by the central over read before randomization takes place.

Repeatability

For acceptable spirometry the difference between the two largest FEV1 values must be $\leq$0.150 L.

Recording of data

The greatest FEV1 and FVC from any of the acceptable curves are recorded. (The greatest FEV1 and FVC may not necessarily result from the same acceptable curve).

Predicted normal

For all patients, this study will utilize the global lung function 2012 equations (GLI2012) published by Quanjer et al 2012 or Japanese Respiratory Society (Kubota et al 2014).

Reversibility

All reversibility evaluations should follow the recommendations of the ATS/ERS Task force: Standardization of Lung Function Testing (Graham et al 2019). A pre-bronchodilator spirometry assessment should be performed after withholding of specified medications as specified in Table 6-2 "Medications to be withheld prior to spirometry".

Administer 400µg of salbutamol/albuterol (or equivalent) following the completion of the pre-bronchodilator assessment. Spacers will be allowed for the administration of salbutamol/albuterol (or equivalent) for reversibility testing. Post-bronchodilator spirometry assessment is then performed within 30 minutes after administration of the salbumatol/albuterol.

Reversibility is calculated as:

$$\frac{100 \times \text{FEV1 (post-bronchodilator)} - \text{FEV1 (pre-bronchodilator)}}{\text{FEV1 (pre-bronchodilator)}}$$

Patients will be considered reversible if an increase of at least 12% and 200 mL is demonstrated after administration of the salbutamol/albuterol.

16.4 Repeat of the run in or end of run in visits

16.4.1 Run in visit

The run in visit, with initiated spirometry, can be repeated twice.

The visit must be repeated when:

1. Central over read assessed pre- or post-SABA spirometry data as unacceptable
2. FEV1 repeatability was not demonstrated at pre- or post-SABA spirometry
3. Reversibility was not demonstrated

If pre- or post-SABA spirometry test at the run in visit is assessed, by the central over read, as unacceptable, the visit must be repeated so that pre- AND post-SABA spirometry assessments at the repeated visit are assessed, by the central over read, as acceptable.

Until all criteria for the run in visit are satisfied at a single visit i.e. both pre- and post-SABA spirometry are acceptable with FEV1 repeatability and reversibility met, site staff MUST NOT initiate the run in period, i.e. the site staff is NOT ALLOWED to:

- Dispense to patients fluticasone-Salmeterol (SoC)
- Dispense to patients the run in kit
- Reprogram eDiary

16.4.2 End of run in visit

The visit must be repeated when:

1. Central over read assessed both -2hr45min AND -2hr15min spirometry tests as unacceptable
2. FEV1 repeatability was not demonstrated at both -2hr45min AND -2hr15min spirometry
3. Absolute difference in FEV1 predicted value between the beginning and the end of run in is >15%

If both -2hr45min AND -2hr15min spirometry test at the end run in visit are assessed, by the central over read, as unacceptable, the visit must be repeated so that at least one spirometry assessment at the repeated visit is assessed, by the central over read, as acceptable.

Repetition of the visit is possible only if FEV1 measured on a previous visit were in range of 40-85% predicted FEV1 for both -2hr45min and -2hr15min spirometry tests.

16.5 Asthma Control Questionnaire (ACQ-5)

A **SAMPLE** of the Asthma Control Questionnaire – 5 is included below. The format of the administered test may vary.

ASTHMA CONTROL QUESTIONNAIRE
(SYMPTOMS ONLY)

For further information:

Elizabeth Juniper, MCSP, MSc
Professor
20 Marcuse Fields,
Bosham,
West Sussex,
PO18 8NA. UK
Telephone: + 44 (0) 1243 572124
Fax: + 44 (0) 1243 573680
E-mail: juniper@qoltech.co.uk
Web: www.qoltech.co.uk

December 2002

SYMPTOMS ONLY MODIFIED 30 JAN 04 NORTH AMERICAN ENGLISH

ASTHMA CONTROL QUESTIONNAIRE© Page 1 of 1

Please answer questions 1 - 5

Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you **woken by your asthma** during the night?
   - 0 Never
   - 1 Hardly ever
   - 2 A few times
   - 3 Several times
   - 4 Many times
   - 5 A great many times
   - 6 Unable to sleep because of asthma

2. On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?
   - 0 No symptoms
   - 1 Very mild symptoms
   - 2 Mild symptoms
   - 3 Moderate symptoms
   - 4 Quite severe symptoms
   - 5 Severe symptoms
   - 6 Very severe symptoms

3. In general, during the past week, how **limited were you in your activities** because of your asthma?
   - 0 Not limited at all
   - 1 Very slightly limited
   - 2 Slightly limited
   - 3 Moderately limited
   - 4 Very limited
   - 5 Extremely limited
   - 6 Totally limited

4. In general, during the past week, how much **shortness of breath** did you experience because of your asthma?
   - 0 None
   - 1 A very little
   - 2 A little
   - 3 A moderate amount
   - 4 Quite a lot
   - 5 A great deal
   - 6 A very great deal

5. In general, during the past week, how much of the time did you **wheeze**?
   - 0 Not at all
   - 1 Hardly any of the time
   - 2 A little of the time
   - 3 A moderate amount of the time
   - 4 A lot of the time
   - 5 Most of the time
   - 6 All the time

SYMPTOMS ONLY MODIFIED 30 JAN 04 NORTH AMERICAN ENGLISH

16.6 Recommendation for FeNO Measurements

FeNO measurements should be performed PRIOR to spirometry assessments, as spirometric maneuvers have been shown to transiently reduce exhaled NO levels. FeNO measurements have to be performed within 4 hours of getting up from bed.

Where possible, serial NO measurements should be performed in the same period of the day and the time should always be recorded.

Repeated, reproducible exhalations should be performed to obtain two measurements within 10% of each other. Exhaled NO is the mean of these two values. The duration of exhalation must be sufficient (up to 10 seconds) to achieve a stable NO plateau. Allow subjects at least 30 seconds of relaxed tidal breathing to rest between repeated exhalations in order not to exhaust the patient.

The patient should be seated comfortably with the equipment at the proper height and position.

Patients should refrain from eating and drinking at least 2 hours before measurements.

Patients should avoid strenuous exercise for 1 hour before measurements.

The time of last bronchodilator should be noted, as FeNO levels may vary with the degree of airway obstruction or after bronchodilation.

Respiratory tract infections may lead to increased levels of exhaled NO in asthma, therefore the measurements should be re-scheduled until recovery if possible, or the infection should be recorded in the patient's medical file (and as an AE in the CRF).

Holding breath results in NO accumulation which causes NO peaks in the exhalations profiles of NO versus time and should therefore be discouraged.

16.7 Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12)

A **SAMPLE** of the Asthma Quality of Life Questionnaire for 12 years and older is included below. The format of the administered test may vary.

ASTHMA QUALITY OF LIFE QUESTIONNAIRE WITH STANDARDISED ACTIVITIES (AQLQ(S))

SELF-ADMINISTERED

(≥12 years)

For further information:

Elizabeth Juniper, MCSP, MSc
Professor
20 Marcuse Fields
Bosham, West Sussex
PO18 8NA, England
Telephone: +44 1243 572124
Fax: +44 1243 573680
E-mail: juniper@qoltech.co.uk
Web: http://www.qoltech.co.uk

APRIL 2008

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

Please complete **all** questions by circling the number that best describes how you have been during the **last 2 weeks as a result of your asthma.**

HOW **LIMITED** HAVE YOU BEEN **DURING THE LAST 2 WEEKS** IN THESE ACTIVITIES **AS A RESULT OF YOUR ASTHMA**?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
1. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
2. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
3. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
4. WORK/SCHOOL-RELATED ACTIVITIES* (tasks you have to do at work/in school)	1	2	3	4	5	6	7
5. SLEEPING	1	2	3	4	5	6	7

*If you are not employed or self-employed, these should be tasks you have to do most days.

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS**?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
6. How much discomfort or distress have you felt over the last 2 weeks as a result of CHEST TIGHTNESS?	1	2	3	4	5	6	7

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
7. Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7
8. Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
9. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO CIGARETTE SMOKE?	1	2	3	4	5	6	7
10. Experience a WHEEZE in your chest?	1	2	3	4	5	6	7
11. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF CIGARETTE SMOKE?	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS**?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
12. How much discomfort or distress have you felt over the last 2 weeks as a result of COUGHING?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
13. Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
14. Experience a feeling of CHEST HEAVINESS?	1	2	3	4	5	6	7

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
15. Feel CONCERNED ABOUT THE NEED TO USE MEDICATION for your asthma?	1	2	3	4	5	6	7
16. Feel the need to CLEAR YOUR THROAT?	1	2	3	4	5	6	7
17. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO DUST?	1	2	3	4	5	6	7
18. Experience DIFFICULTY BREATHING OUT as a result of your asthma?	1	2	3	4	5	6	7
19. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF DUST?	1	2	3	4	5	6	7
20. WAKE UP IN THE MORNING WITH ASTHMA SYMPTOMS?	1	2	3	4	5	6	7
21. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
22. Feel bothered by HEAVY BREATHING?	1	2	3	4	5	6	7
23. Experience asthma symptoms as a RESULT OF THE WEATHER OR AIR POLLUTION OUTSIDE?	1	2	3	4	5	6	7
24. Were you WOKEN AT NIGHT by your asthma?	1	2	3	4	5	6	7
25. AVOID OR LIMIT GOING OUTSIDE BECAUSE OF THE WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
26. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
27. Feel AFRAID OF GETTING OUT OF BREATH?	1	2	3	4	5	6	7
28. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
29. Has your asthma INTERFERED WITH GETTING A GOOD NIGHT'S SLEEP?	1	2	3	4	5	6	7
30. Have a feeling of FIGHTING FOR AIR?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS**?

	Severely Limited Most Not Done	Very Limited	Moderately Limited Several Not Done	Slightly Limited	Very Slightly Limited Very Few Not Done	Hardly Limited At All	Not Limited Have Done All Activities
31. Think of the OVERALL RANGE OF ACTIVITIES that you would have liked to have done during the last 2 weeks. How much has your range of activities been limited by your asthma?	1	2	3	4	5	6	7

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID _____

SELF-ADMINISTERED DATE_____

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS?**

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
32. Overall, among ALL THE ACTIVITIES that you have done during the last 2 weeks, how limited have you been by your asthma?	1	2	3	4	5	6	7

DOMAIN CODE:

Symptoms: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
Activity Limitation: 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
Emotional Function: 7, 13, 15, 21, 27
Environmental Stimuli: 9, 17, 23, 26

16.8 Timed assessment schedule

16.8.1 Randomization visit: End of Run-In/Day 1

Table 16-3 Timed assessments for the randomization visit

Visit Name	**End of Run In**					**Day 1**			
Timepoint	**-3hr50min**	**-2hr45min**	**-2hr15min**	**-1hr15min**	**-1hr**	**0**	**2hr**	**3hr**	**4hr**
Review: 1.Incl./Excl. Criteria	✓								
Review: 1.AEs/SAEs assessment, 2.Concomitant medications, 3. Surgeries and procedures	✓								
1.ACQ 2.AQLQ	✓								
ECG	triplicate							triplicate	
1.Vital signs 2.Physical Examination (S)	✓								
FeNO pre-dose at site	✓								
-2hr45min Pre-dose spirometry		✓							
Urinalysis		✓							
Pregnancy test (Urine)		S							
-2hr15min Pre-dose spirometry		-	✓						
Contact IRT upon feedback received from overreader				S					
Equilibrate IMP					S				
Dispensation of study drug					S				

Visit Name	**End of Run In**					**Day 1**			
Timepoint	**-3hr50min**	**-2hr45min**	**-2hr15min**	**-1hr15min**	**-1hr**	**0**	**2hr**	**3hr**	**4hr**
Inhaler Devices training**					S				
Attach the add on sensor to the Concept1 inhaler					S				
Blood sampling: 1. Hematology 2. Chemistry 3. ADA [redacted] 6.ImmunoCAP [redacted]					✓				
PK Blood collection Pre-Dose					✓				
On site IMP administration						✓			
Compliance with Concept1						S			
PK Blood collection Post-Dose 2hr							✓		
eDiary/ ePEF training**							S		
PK Blood collection Post-Dose 4hr									✓
Dispensation of: 1.Fluticasone/salmeterol 2.SABA rescue									S
Inhale Fluticasone/salmeterol									S

*only for consented patients
**optional if needed
S source only

16.8.2 Weeks 2-24

Table 16-4 Timed assessments for visits week 2-12

Visit Name	Week 2					Week 4					Week 8					Week 12					
Timepoint	-1hr15min	-45min	-15min	0	2hr	-1hr30min	-45min	-15min	0	2hr	-1hr30min	-45min	-15min	0	2hr	-1hr30min	-45min	-15min	0	2hr	4hr
Before patient comes in: 1.Contact IRT 2.Equilibrate IMP						S					S					S					
Review: 1.AEs/SAEs assessment, 2.Concomitant medications, 3. Surgeries and procedures	✓					✓					✓					✓					
[redacted]																					
1.ACQ 2.AQLQ						✓					✓					✓					
ECG						Single					Single					Triplicate					
Vital Signs																✓					
1.Physical Examination (S) 2.Body weight																✓					
Abbreviated Physical Examination	S					S					S										
FeNO pre-dose at site**	✓					✓					✓					✓					
-45min Pre-dose spirometry		✓					✓					✓					✓				
Urinalysis		✓					✓					✓					✓				

Visit Name	**Week 2**					**Week 4**					**Week 8**					**Week 12**					
Timepoint	**-1hr15min**	**-45min**	**-15min**	**0**	**2hr**	**-1hr30min**	**-45min**	**-15min**	**0**	**2hr**	**-1hr30min**	**-45min**	**-15min**	**0**	**2hr**	**-1hr30min**	**-45min**	**-15min**	**0**	**2hr**	**4hr**
Pregnancy test (urine)																					
Blood sampling: 1.Hematology 2.Chemistry		✓					✓					✓					✓				
Blood sampling: 1.ADA [redacted]		✓					✓					✓					✓				
PK Blood collection Pre-Dose		✓					✓					✓					✓				
[redacted]																					
Pregnancy test (serum)							✓					✓					✓				
[redacted]																					
-15min Pre-dose spirometry			✓					✓					✓					✓			
Dispensation of study drug								S					S								
Inhaler Devices Training***				S				S					S					S			
Upload data from the Concept1 add-on sensor/re-attach the sensor								S					S					S			
Inhale IMP				✓					✓					✓					✓		
Compliance with Concept1				S					S					S					S		

Visit Name	Week 2					Week 4					Week 8					Week 12					
Timepoint	-1hr15min	-45min	-15min	0	2hr	-1hr30min	-45min	-15min	0	2hr	-1hr30min	-45min	-15min	0	2hr	-1hr30min	-45min	-15min	0	2hr	4hr
Compliance with eDiary/ePEF				S					S					S					S		
PK Blood collection Post-Dose 2hr					✓					✓					✓					✓	
Inhale Fluticasone/salmeterol					S					S					S					S	
Dispensation of: 1.Flutisacone/salmeterol 2.SABA rescue										S					S					S	
PK Blood collection Post-Dose 4hr																					✓
CSJ117 Safety Extension Study participation discussion															S						

*only for consented patients

***optional if needed

**only for onsite visits

S source only

Table 16-5 Timed assessments for visits week 14-24

Visit Name	Week 14	Week 16					Week 20					Week 24				
Timepoint	**-1hr**	**-1hr**	**-45 min**	**-30 min**	**-15 min**	**0**	**-1hr**	**-45 min**	**-30min**	**-15 min**	**0**	**-1hr20min**	**-45 min**	**-30min**	**-15 min**	**0**
Before patient comes in: 1.Contact IRT 2.Equilibrate IMP																

Visit Name	**Week 14**	**Week 16**					**Week 20**					**Week 24**				
Timepoint	**-1hr**	**-1hr**	**-45 min**	**-30 min**	**-15 min**	**0**	**-1hr**	**-45 min**	**-30min**	**-15 min**	**0**	**-1hr20min**	**-45 min**	**-30min**	**-15 min**	**0**
Review: 1.AEs/SAEs assessment, 2.Concomitant medications, 3. Surgeries and procedures	✓	✓					✓					✓				
[redacted]																
1.ACQ 2.AQLQ												✓				
ECG		Single										Single				
Vital Signs	✓						✓					✓				
1.Physical Examination (S) 2.Body weight												✓				
Abbreviated Physical Examination		S														
FeNO pre-dose at site**	✓	✓					✓					✓				
-45min Pre-dose spirometry			✓					✓					✓			
Urinalysis				✓										✓		
Pregnancy test (urine)				✓					✓							
Blood sampling: 1.Hematology 2.Chemistry				✓										✓		
Blood sampling: 1.ADA [redacted]	✓			✓					✓					✓		
PK Blood collection Pre-Dose	✓			✓					✓					✓		
[redacted]																
Pregnancy test (serum)														✓		

Visit Name	**Week 14**	**Week 16**					**Week 20**					**Week 24**				
Timepoint	**-1hr**	**-1hr**	**-45 min**	**-30 min**	**-15 min**	**0**	**-1hr**	**-45 min**	**-30min**	**-15 min**	**0**	**-1hr20min**	**-45 min**	**-30min**	**-15 min**	**0**
[redacted]																
-15min Pre-dose spirometry					✓					✓					✓	
Dispensation of study drug																
Upload data from the Concept1 add-on sensor/re-attach the sensor																
Compliance with Concept1																
Compliance with eDiary/ePEF	S			S					S							S
Inhale Fluticasone/salmeterol	S					S					S					S
Dispensation of: 1.Flutisacone/salmeterol 2.SABA rescue				S					S							

*only for consented patients

**only for onsite visits

S source only