NOVARTIS

Clinical Development

CSJ117

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

Statistical Analysis Plan (SAP)

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List of abbreviations

ACQ	Asthma Control Questionnaire
ADA	Anti-Drug Antibodies
ADSD	Asthma Daytime Symptom Diary
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANSD	Asthma Nighttime Symptom Diary
AQLQ	Asthma Quality of Life Questionnaire
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
[redacted]	
CRF	Case Report Form
CRS	Case Retrieval Strategy
CSR	Clinical Study Report
DMC	Data Monitoring Committee
DMS	Document Management System
DR	Dose Response
ECG	Electrocardiograms
EOS	Eosinophil Count
FAS	Full Analysis Set
FeNO	Fractional exhaled Nitric Oxide
IA	Interim Analyses
J2R	Jump-to-reference
MAR	Missing at Random
[redacted]	[redacted]
MCP-Mod	Multiple Comparison Procedure – Modelling
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMRM	Mixed effects Model for Repeated Measures
PD	Protocol Deviation
PEF	Peak Expiratory Flow
PK	Pharmacokinetics
PRO	Patient-reported Outcomes
PT	Preferred Term
RAS	Randomized Analysis Set
SABA	Short-Acting β-agonist
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	Primary system organ class

[redacted]

1 Introduction

This document contains details of the statistical methods that will be used in the phase IIb clinical trial CCSJ117A12201C. This study is designed to support the dose selection for future studies by evaluating the efficacy and safety of different CSJ117 doses in adult patients with severe uncontrolled asthma. The primary endpoint is the average change from baseline in pre-dose FEV_1 at Week 8 and Week 12.

Data will be analyzed according to Section 12 of the study protocol.

The following document was referred while writing the SAP:

CCSJ117A12201C Clinical Trial Protocol Final version 03 dated 21-Jan-2022.

Important information is given in the following sections and details are provided, as applicable, in Section 5: Appendix.

1.1 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.

The study will include:

- A screening period of approximately 2 weeks
- A single blinded placebo run-in period of 4 weeks (must be extended to 8 weeks for patients experiencing an asthma exacerbation or respiratory tract infection during the run-in period)
- 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. Or a follow-up period of 8 weeks for patients that discontinued the study due to early termination.

Figure 1-1 Study design

	2 weeks	4 weeks*			12 weeks					12 weeks			
Visit	Screening	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
Day	-42	-28	-14	1	1	15	29	57	85	99	113	141	169

*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 randomization, subjects will be stratified by their geographic region and blood eosinophil count (EOS) (≥ 300 or < 300 cells/µl), measured at the screening visit. Approximately 52% of the total study population will be enrolled in the high EOS stratum. If recruitment for one EOS stratum is completed, only patients with baseline 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.

A Safety Extension Study of CSJ117 is planned (CSJ117A12201E1). Patients who successfully complete 12 weeks of treatment or 12 weeks of follow-up 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.

Originally, approximately 625 patients were to be randomized into this study. Subsequent de-prioritzation of the program has led to early termination of this study, resulting in actual enrollment of 335 patients. Detailed information regarding sample size calculation is provided in Section 3.

The primary endpoint will be assessed at the end of the treatment period.

Interim analyses (IA) on safety data are planned for an independent external safety data monitoring committee (DMC) to evaluate the safety data. DMC meetings will occur approximately twice a year. Detailed information regarding DMC analysis will be provided in the DMC charter and a separate DMC SAP.

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.

1.2 Study objectives and endpoints

Section 2 of the study protocol lists the following primary, secondary, [redacted] objectives. All immunogenicity analysis and PK analysis will be conducted and reported separately other than in the CSR. [redacted]

Table 1-1 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 FEV_1 (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	• Average change from baseline in FeNO at Week 8 and Week 12.

Objective(s)	Endpoint(s)
inhaled daily on FeNO compared with placebo, during the 12-week active-treatment period	
• 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 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	• Change from baseline in peak expiratory flow (PEF; am and pm), as assessed by mean 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.
[redacted]	

2 Statistical methods

2.1 Data analysis general information

The statistical analysis will be performed by Novartis. The most recent version of SAS® (SAS Institute Inc., Cary, NC, USA) available in the statistical programming environment of Novartis will be used for the analysis. R version 3.6.1 may also be used as appropriate.

2.1.1 General definitions

The terms ‘double-blind treatment’ will be used in this document and refer to the double-blind CSJ117 doses and placebo.

2.1.1.1 Study day

Study day will be defined as the number of days since the date of first dose of double-blind treatment. The date of first dose of double-blind treatment will be defined as Day 1 and the day prior to first dose of double-blind treatment will be defined as Day -1.

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

for dates on or after the date of first dose of double-blind treatment,

Study day = Assessment date – Day 1 + 1;

for dates prior to the date of first dose of double-blind treatment,

Study day = Assessment date – Day 1.

If a patient never received any double-blind treatment, the date of randomization will be used as Day 1.

2.1.1.2 Baseline definition

In general, baseline is defined as the last measurement taken before the first dose of double-blind treatment. Details on calculation of baseline will be provided in the latter sections.

For patients who never received any double-blind treatment, the baseline is the last measurement taken before randomization.

2.1.1.3 Post-baseline definition

All data collected after the start of double-blind treatment are defined as post-baseline. For patients who are not treated, the post-baseline is any assessments after randomization.

When change from baseline is of interest the following formula will be used for each scheduled visit and time-point where baseline and post-baseline values are both available:

Change from baseline = post-baseline value – baseline value.

If not stated otherwise for efficacy analyses, on-treatment values are defined as values taken post-baseline but no later than 1 day after last dose of double-blind treatment. Off-treatment values are defined as post-baseline values taken more than 1 day after last dose of double-blind treatment.

Details on calculation of post-baseline values are provided in the latter sections.

2.2 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 double-blind treatment has been assigned and who received at least one dose of double-blind 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 double-blind treatment. Subjects will be analyzed according to the treatment they received, where treatment received is defined as the randomized/assigned treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received. The Safety Set will be used for the analysis of all safety variables.

The PK set will include all patients with at least one evaluable drug concentration data sample.

2.2.1 Subgroup of interest

Subgroup analyses are conducted to assess consistency of the treatment effect among the subgroups, without multiplicity adjustments. The following subgroups will be evaluated for the primary endpoint:

- Age group (18 - < 40, 40 - < 65, ≥ 65 years)
- Gender (male, female)
- Race (White, Asian, Black, other)

- Region
- Body mass index (BMI) ($\leq$ 30.0 kg/m^2, > 30.0 kg/m^2)
- Duration of asthma (1 - 5 years, > 5 - 10 years, > 10 - 15 years, > 15 - 20 years, > 20 years)
- Pre-bronchodilator FEV_1 in % of predicted FEV_1 (<40%, 40 - < 50%, 50 - < 60%, 60% - < 80%, 80 - 85%)
- Use of medications at screening in addition to ICS/LABA controllers (Yes, No)
- [redacted]
- Prior asthma treatment (medium or high ICS/LABA)
- Atopic asthma status (Yes, No)
- Baseline FeNO (< 25 ppb, $\geq$ 25 ppb)
- Number of exacerbations in the prior year (1, 2, $\geq$3
- Baseline ACQ-5 (<1.5, 1.5 - < 2, 2 - < 2.5, $\geq$ 2.5)
- [redacted]

2.3 Patient disposition, demographics and other baseline characteristics

No inferential testing on the differences in patient disposition, demographics and other baseline characteristics between treatment arms will be performed.

2.3.1 Patient disposition

The RAS will be used for the summary and listing of patient disposition. The screening disposition and the analysis sets table will be based on all screened patients.

The number of patients in the RAS will be summarized by region, country, center and treatment group. Further, the overall number of patients who entered completed, and discontinued study will be summarized including the reasons for discontinuation for each period: pre-randomization, double-blind treatment and follow-up.

Number of patients with protocol deviations (PDs) and with Covid-19 related PDs will be tabulated by category (e.g., selection criteria not met, subject not withdrawn as per protocol, treatment deviation, prohibited concomitant medication, other) and deviation.

COVID-19 pandemic-related impact to protocol adherence captured as protocol deviations will be tabulated by Pandemic-related PD Relationship to COVID-19 by treatment and category.

The number of patients included in each analysis set will be tabulated. Patients exclusion from analysis sets will be listed for all patients with reasons for exclusion (i.e. including both protocol and non-protocol deviations).

2.3.2 Patient demographics and other baseline characteristics

Demographics and other baseline characteristics will be summarized and listed using the RAS.

Demographic characteristics, including age, gender, race, ethnicity, region, height, weight, and BMI will be summarized by treatment and overall.

Baseline disease characteristics, including duration of asthma, run-in spirometry (FEV_1, FVC, FEV_1/FVC and % of predicted FEV_1 pre- and post-bronchodilator, FEV_1 reversibility), asthma exacerbation history, smoking history, atopic asthma status (Yes/No), baseline ACQ-5, baseline AQLQ+12, blood eosinophils at screening, prior asthma treatment (medium/high ICS/LABA) will be summarized.

Summaries of continuous variables will include mean, standard deviation (SD), first and third quartile, median, minimum and maximum. Summaries of categorical variables will show absolute (n) and relative (%) frequencies including a category for missing data if any.

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

In addition, the following categorizations of continuous variables will be done:

- Age into 18 - < 40, 40 - < 65, and ≥ 65 years;
- BMI into ≤ 30.0 kg/m2 and > 30.0 kg/m2;
- Duration of asthma into < 1 year, 1 - 5 years, > 5 - 10 years, > 10 - 15 years, > 15 – 20 years, and > 20 years;
- Severity of airflow limitation: pre-bronchodilator FEV_1 % predicted values into 40 - < 50%, 50 - < 60%, 60% - < 80%, and 80 - 85%
- ACQ-5 into 1.5 - < 2, 2 - < 2.5, and ≥ 2.5

2.3.3 Medical history/current medical condition

Medical history will be coded with the Medical Dictionary for Regulatory Activities terminology (MedDRA) using the most recent version at the time of database lock. Relevant medical histories and current medical conditions, including pre-specified protocol solicited events, will be summarized for the RAS by primary system organ class and preferred term by treatment group.

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

All summaries of treatments will be performed on the Safety Set.

2.4.1 Study treatment / compliance

The duration of exposure in days to each treatment group (CSJ117 doses or placebo) will be summarized by means of descriptive statistics. In addition, the duration of exposure will be summarized as a categorical variable classified into ≤ 2 weeks, > 2 – 4 weeks, > 4 – 6 weeks, > 6 – 8 weeks, > 8 – 10 weeks, > 10 – 12 weeks, > 12 – 13 weeks, and > 13 weeks.

Duration of exposure to double-blind treatment will be calculated as the number of days between the first dose date and the last dose date exposed to that treatment over the specified period (expressed as: Duration of exposure = Date of last known dose of double-blind treatment – Date of first dose of double-blind treatment + 1).

The number of patients who permanently discontinued from double-blind treatment and the reasons will be summarized by treatment group. Patients who permanently discontinued from double-blind treatment will be listed including reason and date of discontinuation.

Compliance will be calculated as the percentage of the number of days where double-blind treatment was administered as per protocol divided by the duration of exposure (i.e., the number of days between first and last dose).

Compliance will be categorized by < 80 % and 80 % - 100 % and summarized by treatment group.

2.4.2 Prior, concomitant and post therapies

Summaries for asthma-related medications will be performed separately for medications prior to the start of double-blind treatment (medications starting prior to Day 1) and for concomitant medications (medications which were taken anytime between the first dose and last dose of double-blind treatment, inclusive). Medications can be considered both prior and concomitant. Asthma-related medications will be summarized by pre-specified drug categories, route of administration, preferred term, and treatment group.

Non-asthma related medication prior to and after the start of double-blind treatment will be summarized by the Anatomical Therapeutic Chemical (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.

Surgical and medical procedures (non-drug therapies) are coded using MedDRA. Presentations will be done by MedDRA primary system organ class and preferred term, separately for prior and concomitant procedures.

2.5 Analysis of the primary objective

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 FEV_1 (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 over placebo based on the estimated DR curve

2.5.1 Primary endpoint

The primary estimand, defined below, quantifies a hypothetical on-treatment effect during stable periods (i.e. outside of periods of acute disease worsening requiring additional asthma medications). This estimand targets the maximum treatment effect for CSJ117 and allows selection of the best dose for those who take it for 12 weeks.

- **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 FEV_1 after 8 and 12 weeks of treatment
- **Treatment**: CSJ117 or placebo

- **Intervention effect of interest**: Effect of interventions initiated at randomization during stable periods 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 FEV_1: the effect outside of periods of worsening disease that necessitate such non-study drug
  - Discontinuation of study treatment due to any reason: hypothetical value of the average between Week 8 and Week 12 pre-dose FEV_1 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 FEV_1 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.

The baseline value is defined as the average of the values taken approximately 2 hours 45 minutes and 2 hours 15 minutes prior to the first dose of double-blind treatment at Day 1. If one of the two values is missing (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.

2.5.2 Statistical hypothesis, model, and method of analysis

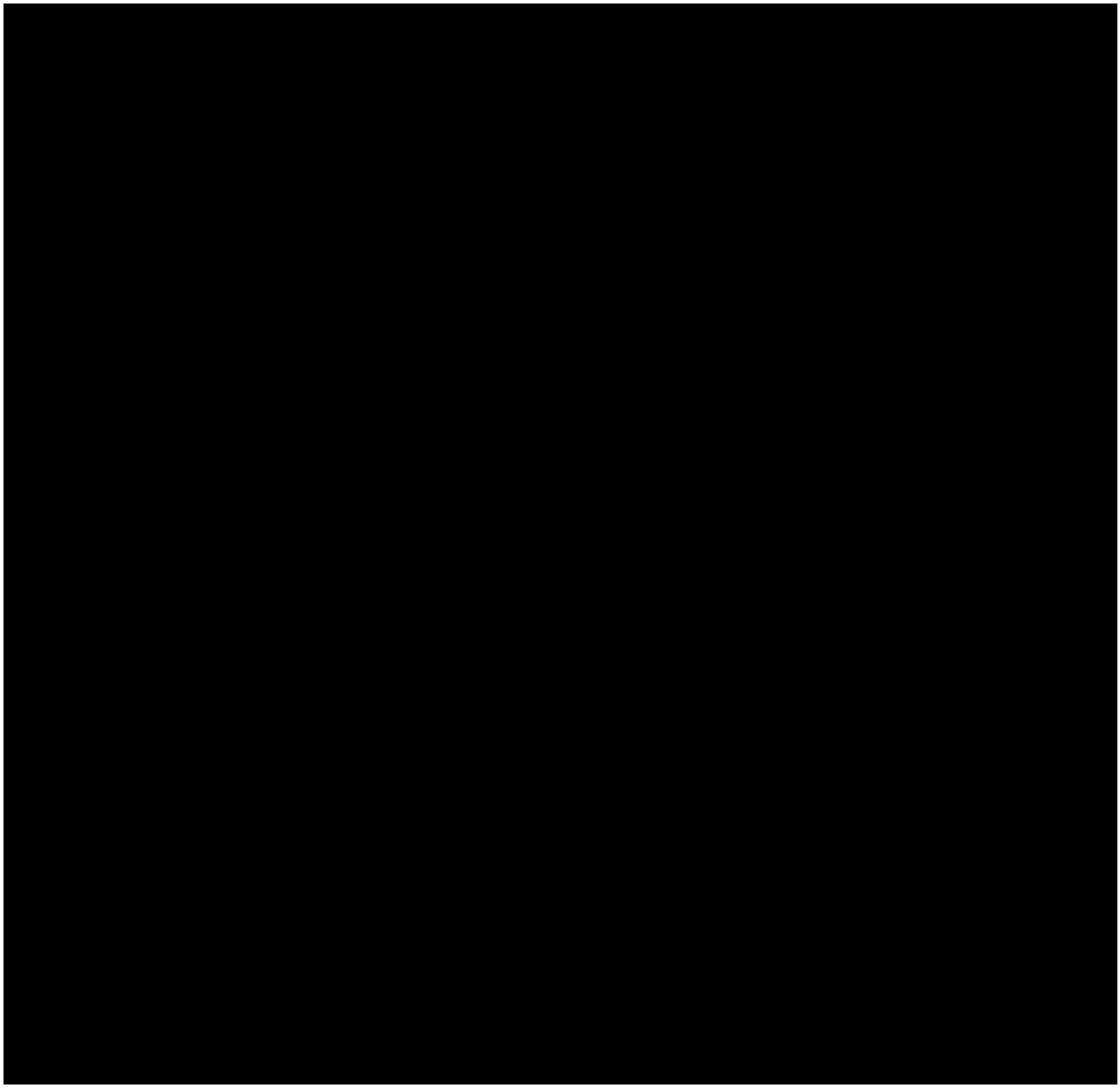
The Multiple Comparison Procedure – Modelling (MCP-Mod) methodology (see Bretz et al 2005 and Pinheiro et al 2014) will be employed to assess the primary objective. An overview of the steps for the MCP-Mod methodology is given below.

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 FEV_1, visit, treatment, randomization strata – eosinophil count (EOS) (≥ 300 or < 300 cells/µl) and region, treatment-by-visit interaction, and baseline FEV_1-by-visit interaction, FEV_1 prior to inhalation, and FEV_1 within 30 min post inhalation of salbutamol/albuterol (components of reversibility test results at the run-in visit) 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 [redacted]



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 by model averaging. 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 [redacted] 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 final DR curve estimate is the median of these predictions while confidence intervals will be calculated from the quantiles. The final DR curve estimate with the model-based two-sided

95% confidence interval will be presented graphically. In addition, the plot will include the mean responses from the MMRM and the associated 95% confidence intervals for each of the studied dose groups. 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).

2.5.3 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 FEV_1 for the whole planned study duration.

The FEV_1 value analyzed at each post-baseline visit is based on the average of the two FEV_1 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 periods of acute disease worsening requiring additional asthma medications, spirometry measurements taken within 6 hours of rescue medication, 7 days of intake of systemic corticosteroid use, 3 months of a single depot corticosteroid injection, 24 hours of background medication use, and/or 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 FEV_1. If both values are missing, then their pre-dose FEV_1 will be regarded as missing at that visit.

For the primary analysis, only on-treatment data (from date of first dose of double-blind treatment up to 1 day after date of last 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 FEV_1 supportive analyses (Section 2.5.4) 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 are provided in Section 5.5.

2.5.4 Supportive analyses

A supplementary analysis will be performed that quantifies the treatment effect in all randomized patients during stable periods (i.e. outside of periods of acute disease worsening requiring additional asthma medications) 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 FEV_1: the effect outside of periods of worsening disease that necessitate such non-study drug.

b. Discontinuation of study treatment due to any reason not covered in bullet c below: 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 early termination of the study by sponsor or any COVID-19 related reason: hypothetical value of the average between Week 8 and Week 12 pre-dose FEV_1 had the patients not stopped the study treatment.

Results will be presented similarly to those of primary analyses. Details are provided in Section 5.5.

The subgroup analyses (subgroups defined in Section 2.2.1) will be explored for the primary estimand and the same MMRM as described for the primary analysis with the additional term of subgroup factor (if not already included in the model), the two-way interaction term of subgroup and treatment, and the three-way interaction term of subgroup, treatment, and visit. In case of analyses on subgroups with extremely imbalanced sample sizes, the subgroup levels can be combined, if appropriate, while fitting the analysis model. The point estimate and 95% CI for treatment differences between CSJ117 doses and placebo for each subgroup will be provided.

2.6 Analysis of the key secondary objective

There is no key secondary objective defined in the protocol.

2.7 Analysis of secondary efficacy objective(s)

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 on-treatment data will be used.

All analysis of secondary efficacy endpoints will be performed on the FAS.

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.

Details on statistical models are provided in Section 5.5.

2.7.1 Secondary endpoints

2.7.1.1 FeNO

The average change from baseline in Fractional exhaled Nitric Oxide (FeNO) at Week 8 and Week 12 will be analyzed using the same MCP-Mod approach described for the primary analysis of the primary endpoint. 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 FEV_1. 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.

2.7.1.2 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 of mean 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 will be reported as well as the average between Week 8 and Week 12 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 inlcude the same terms as for the MMRM analysis of the primary variable with baseline ACQ-5 instead of baseline FEV_1. The estimated adjusted odds ratios at each visit will be displayed along with the associated 95% confidence intervals.

2.7.1.3 Daytime and nighttime asthma symptoms

The baseline of asthma daytime symptom diary (ADSD) and asthma nighttime symptom diary (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.

2.7.1.4 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 at each visit will be displayed along with the associated 95% confidence intervals.

2.7.1.5 Total daily use of SABA

Total daily use of short-acting β-agonist (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 daily use of SABA will be summarized by weekly intervals.

2.7.1.6 Peak Expiratory Flow Rate (PEF)

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 and by weekly intervals. .

2.8 Safety analyses

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.

All safety analysis will be performed on the Safety Set.

2.8.1 Adverse events (AEs)

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. All treatment emergent adverse events (AEs) including asthma exacerbations will be summarized.

Summaries will be provided by MedDRA primary system organ class, preferred term, and treatment group showing the number and percentage of patients with events for the on-treatment and off-treatment periods, respectively, as defined below:

on-treatment period (Safety Set): AE started or worsened in [Day 1, last treatment day];

off-treatment period (Only include patients in the Safety Set who had at least one day in the off-treatment period): AE started or worsened in [last treatment day + 1 day, last treatment day + 30 days].

The rationale to summarise AE by on- and off- treatment periods is that for patients who complete the 12-week treatment and enter the extension study immediately, they will not have any AEs reported in the off-treatment period. For other patients, they would potentially have data from both the on- and off-treatment period (either in the follow up epoch or discontinue the treatment but remained on study). Therefore, to avoid the mixture of these patients, we split AEs into on- and off-treatment summaries.

Note that in the off-treatment AE summary, only patients who had at least one day in the off-treatment period will be included. Since there could be imbalance in such patient population across different treatment arms, there is no causal interpretation for the comparison. To aid the

interpretation, the total sum of off-treatment days will also be reported in each arm in the off-treatment AE summary tables.

Summaries will be presented in the following ways:

- by treatment and preferred term (PT).
- by treatment, primary system organ class (SOC) and PT.
- by treatment, SOC, PT and maximum severity.

Separate summaries by SOC and PT will be provided for :

- serious adverse events (SAEs)

Further SAEs will be summarized by PT separately for on-treatmnet and off-treatment periods.

Unless otherwise specified, SOCs will be sorted alphabetically and, within each SOC, the PTs will be sorted in descending order of frequency in the highest CSJ117 dose. A subject with multiple adverse events within a SOC or PT is only counted once towards the total of the SOC or PT.

Listings will be provided for all AEs, SAEs and fatal AEs.

2.8.1.1 Adverse events of special interest / grouping of AEs

The number and percentage of patients who reported treatment-emergent adverse events of special interest (AESI) will be summarized by risk name, PT and treatment group separately on-treatment and off-treatment periods.

Risk names will be sorted alphabetically and, within each risk name, the PTs will be sorted in descending order of frequency in the highest CSJ117 dose. If a patient reported more than one adverse event with the same PT, the AE will be counted only once. If a patient reported more than one AE within the same risk, the patient will be counted only once at that risk.

The Compound Case Retrieval Strategy (CRS) will be used to determine the MedDRA search criteria to be used to identify AESI. The most recent list of adverse events of special interest at the time of database lock will be used.

A listing for all AESI will be provided.

2.8.1.2 AE reporting for CT.gov and EudraCT

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 2% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

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

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

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

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

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.2 Deaths

Fatal AEs will be summarized and listed as specified in Section 2.8.1.

2.8.3 Laboratory data

Summaries of laboratory data will include on-treatment measurements, which are defined as measurements taken post-baseline but no later than 30 days after last dose of double-blind treatment for patients not entering the safety extension study (as described in Section 1.1) directly after the treatment period or not participating in the safety extension study. For patients entering the safety extension study directly after the treatment period, the on-treatment period lasts from the date of first administration of double-blind treatment to the date of the last actual administration of double-blind treatment.

For selected laboratory tests, the number and percentage of patients with newly occurring or worsening laboratory abnormalities meeting the clinically notable criteria at any time on-treatment, considering all on-treatment data from scheduled, unscheduled and premature discontinuation visits, will be summarized by laboratory parameter. Notable criteria are defined in Section 5.3.

Furthermore, the number and percentage of patients with newly occurring or worsening abnormalities in liver function tests (LFT) will be summarized by treatment and at any time on-treatment considering all on-treatment data from scheduled, unscheduled and premature discontinuation visit. LFT criteria are defined in Section 5.3.

The baseline value is the last value prior to first dose of double-blind treatment.

Laboratory data of patients with notable values will be listed.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Summaries of ECG data will include on-treatment measurements, which are defined as measurements taken post-baseline but no later than 30 days after last dose of double-blind treatment for patients not entering the safety extension study (as described in Section 1.1) directly after the treatment period or not participating in the safety extension study. For patients entering the safety extension study directly after the treatment period, the on-treatment period lasts from the date of first administration of double-blind treatment to the date of the last actual administration of double-blind treatment. Triplicate ECGs and single ECGs will be performed at different visits specified in the assessment schedule table in the protocol. For the analysis of

continuous ECG parameter involving triplicate ECGs, the mean value of the 3 ECG measurements will be used; for ECG interpretation, all findings of the 3 ECGs will be considered.

The number and percentage of patients with newly occurring or worsening notable Fridericia's QTc values will be summarized at any time on-treatment, considering all on-treatment data from scheduled, unscheduled and premature discontinuation visits. For derivation of notable values for the triplicate ECGs, the mean of the three ECGs will be used. Notable criteria are defined in Section 5.4.

The number and percentage of patients with ECG abnormalities will be summarized by evaluation type, abnormality finding, visit and time point.The baseline value is the last value prior to first dose of double-blind treatment.

ECG data of patients with notable Fridericia's QTc values will be listed.

2.8.4.2 Vital signs

Summaries of vital signs data will include on-treatment measurements, which are defined as measurements taken post-baseline but no later than 30 days after last dose of double-blind treatment for patients not entering the safety extension study (as described in Section 1.1) directly after the treatment period or not participating in the safety extension study. For patients entering the safety extension study directly after the treatment period, the on-treatment period lasts from the date of first administration of double-blind treatment to the date of the last actual administration of double-blind treatment.

The number and percentage of patients with newly occurring or worsening notable vital sign values will be summarized at any time on-treatment, considering all on-treatment data from scheduled, unscheduled and premature discontinuation visits. Notable criteria are defined in Section 5.4.

The baseline value is the last value prior to first dose of double-blind treatment.

Vital sign data of patients with notable values will be listed.

2.8.5 Immunogenicity

All immunogenicity analysis will be conducted for each safety set and reported separately other than in the CSR.

2.8.5.1 Immunogenicity (IG) analysis sets

The Immunogenicity prevalence set includes all subjects in the Safety set with a non-missing baseline ADA sample **or** at least one non-missing post-baseline ADA sample. The Immunogenicity incidence set includes all subjects in the Immunogenicity prevalence set with a non-missing baseline ADA sample **and** at least one non-missing post-baseline ADA sample.

Any ADA sample collected beyond 150 days of the last dose of CSJ117 will not be used for summaries or derivations and will only be included in the listing

The following definitions apply only to non-missing samples:

- *ADA-negative sample*: Sample where assay result is 'NEGATIVE' and CSJ117 concentration at the time of ADA sample collection is ≤ the drug tolerance level (10 microgram/mL)
- *ADA-positive sample*: Sample where assay result is 'POSITIVE'
- *ADA-inconclusive sample:* Sample where assay is ADA negative and CSJ117 PK concentration at the time of ADA sample collection is > the drug tolerance level (10 microgram/mL) or missing

The following definitions apply only to post-baseline ADA-positive samples with a corresponding non-missing baseline sample. To be classified as *treatment-boosted* or *treatment-unaffected*, both the post-baseline and baseline titer must be non-missing.

- *treatment-induced ADA-positive sample:* ADA-positive sample post-baseline with ADA-negative sample at baseline
- *treatment-boosted ADA-positive sample:* ADA-positive sample post-baseline with titer that is at least 3 fold change greater than the ADA-positive baseline titer
- *treatment-unaffected ADA-positive sample*: ADA-positive sample post-baseline with titer that is less than 3 fold change greater than the ADA-positive baseline titer

The following summaries of ADA sample status (n and %) will be provided using the *Immunogenicity prevalence set*: ADA-positive samples (i.e. ADA prevalence) both overall, by treatment and by time point (including baseline). For summaries by time point, the denominator is the number of subjects at that time point with a non-missing sample.

2.8.5.2 Subject ADA status

Any ADA sample collected beyond 150 days of the last dose of CSJ117 will not be used for summaries or derivations and will only be included in the listing.

Subject ADA status is defined as follows:

- *Treatment-induced ADA-positive subject*: subject with ADA-negative sample at baseline and at least one treatment-induced ADA-positive sample
- *Treatment-boosted ADA-positive subject*: subject with ADA-positive sample at baseline and at least one treatment-boosted ADA-positive sample
- *Treatment-unaffected ADA-positive subject*: subject with ADA-positive sample at baseline, no treatment-boosted ADA-positive samples, and at least one treatment-unaffected ADA-positive sample
- *Treatment-reduced ADA-positive subject*: subject with ADA-positive sample at baseline and at least one non-missing post baseline sample, all of which are ADA-negative samples
- *ADA-negative subject*: subject with ADA-negative sample at baseline and at least one non-missing post baseline sample, all of which are ADA-negative samples
- *Inconclusive subject*: subject who does not qualify for any of the above definitions or a subject for which the baseline sample is missing and CSJ117 PK concentration at the

time of ADA sample collection is > the drug tolerance level (10 microgram/mL) or missing

Following data with number and percentage of subjects will be reported/tabulated by treatment group and during overall study duration. The following summaries of ADA subject status (n and %) will be provided using the *Immunogenicity incidence set* (for % the denominator is the number of subjects in the *Immunogenicity incidence set* unless otherwise specified). :

- ADA negative
- ADA positive (prevalence set)
    - Total ADA positive with no boost
- ADA inconclusive (exposure above drug tolerance according to validated method)
- Missing ADA data at pre-dose
- Missing ADA data at post-dose (Number of patients with atleast 1 missing sample)

Following data with number and percentage of subjects will be reported/tabulated by treatment group for the whole study period:

Pre-dose ADA positive

- boosted: boosted is defined as ADA positive at pre-dose, and post dose titer values increase from pre-dose by more than 3-fold at any time point (Treatment-boosted ADA-positive subjects; for % the denominator is the number of subjects with ADA-positive sample at baseline)

Pre-dose ADA negative

- induced: ADA-positive sample post-baseline with ADA-negative sample at baseline (Treatment-induced ADA-positive subjects; for % the denominator is the number of subjects with ADA-negative sample at baseline)
    - Transient
    - Persistent

Overall ADA incidence (combined results of treatment-boosted and induced)

For induced ADA positive , summaries will also be provided based on the persistent or transient ADA status. The definition of persistent and transient is as follows.

Persistent ADA: a) Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer or b) Treatment-induced ADA incidence only in the last sampling time point of the treatment or follow up observation period or at a sampling time point within less than 16 weeks before an ADA-negative last sample.

Transient ADA: a) Treatment-induced ADA detected only at one sampling time point during the treatment or follow-up observation period (excluding the last sampling time point) and that

sampling point is 16 weeks or more before an ADA negative last sample or b) Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the subject's last sampling time is ADA Negative.

ADA titer kinetics will be summarized by treatment group with data reported as boxplot (titer range, Q1, Median (Q2), Q3, and outliers) of ADA titer at each time point for each treatment group up to Week 24. The plot will include total subjects, number of subjects with positive ADA, and % of subjects with positive ADA at each time point. Please see example below from Shankar et al.

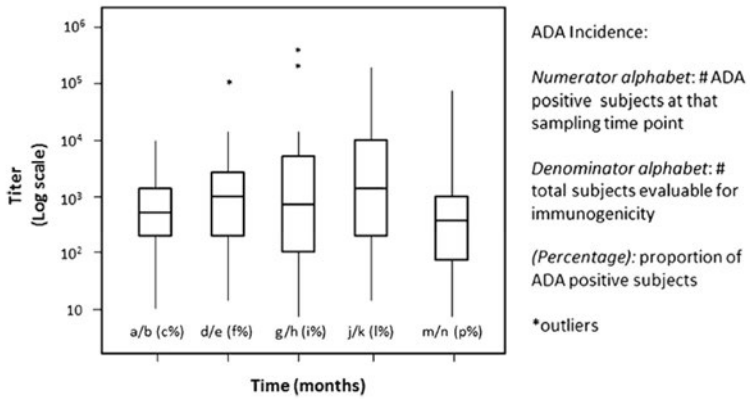


Fig. 3. ADA titer kinetics. This plot of titers over time in a study is useful in determining whether the ADA levels tend to change over time during the treatment. Each *box plot* represents the titer range, Q1, Median (Q2), Q3, excluding outliers (*asterisks*)

Listings of all ADA titer values will be presented for all subjects by treatment group, subject, and visit/time and by study period. Samples collected at unscheduled visits will not part of the analysis. ADA titer values will be summarized as a table by treatment arm for ADA titer at each time point for each arm up to Week 24.

Systemic exposure of CSJ117 will be measured concomitantly with ADA levels for interpretation purposes. Systemic exposure data will be summarized and listed. No correlative analysis will be conducted.

Additional analyses might be performed to assess immunogenicity and may depend on emergent data from the study.

2.9 Pharmacokinetic endpoints

Pharmacokinetic analysis will be conducted and reported separately other than in the CSR.

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 lower limit of quantification (LLOQ) and reported as zero. Summary statistics will include mean (arithmetic and geometric), standard deviation, coefficient of variation (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.

Summary serum concentrations would be plotted by visit. Dose proportionality of serum concentrations will be assessed. .

[redacted]

2.11 Patient-reported outcomes

Patient-reported outcomes in this study include ACQ-5, and AQLQ+12, which are discussed respectively in Section 2.7.1.2, Section 2.7.1.3, and Section 2.7.1.4.

[redacted]

2.13 Interim analysis

2.13.1 Safety

IAs are planned for the monitoring of safety data and do not inflate the type I error for the primary efficacy hypothesis testing. Thus no adjustment for multiplicity is required. These analyses will be performed by an external Independent Statistician and an Independent Programmer for an independent external safety DMC. Persons directly involved in the conduct of the clinical trial will not be involved in performing the IA or reviewing the results. The DMC will be provided with reports which are semi-blinded. If necessary, the study treatment can be unblinded by the chair of the DMC. The DMC will review safety data and make recommendations regarding the conduct of the trial and/or alteration of the current protocol, including termination of a treatment arm.

The DMC meetings will occur approximately twice a year.

More details will be outlined in the DMC charter and a separate DMC SAP.

2.13.2 Efficacy

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.

3 Sample size calculation

For the primary endpoint pre-dose FEV_1, 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.

4 Change to protocol specified analyses

Due to depriorization of the program, this study will be terminated early and will have abbreviated CSR instead. The following protocol specified analyses will be removed:

- The mean daily scores of ADSD and ANSD will be 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.
- 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.
- The mean daily use of SABA will be 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.
- 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.

- The mean morning/evening PEF will be 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.
- Summary statistics will be provided by treatment and visit/time for each vital signs variable.
- Summary statistics and change from baseline will be provided by treatment and visit/time by each lab variable.
- [redacted]
- The impact of ADA on the efficacy/safety endpoints
- [redacted]

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Missing/partial start date or end date of double-blind treatment will not be imputed.

5.1.2 AE date imputation

Partial AE start and end dates will be imputed. If there is uncertainty whether an AE occurred on-treatment or not, imputation will be performed, such that AE will be considered as on-treatment. Rules for imputing AE end date or start date will be provided in Programming Dataset Specification (PDS) document in details.

5.1.3 Concomitant medication date imputation

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

5.2 AEs coding/grading

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

5.3 Laboratory parameters derivations

The following table shows the direction of interest when analyzing worst case values in form of maximum and/or minimum post-baseline values. If the direction of interest is given as "High" the maximum value will be calculated and used as worst value, if the direction is given as "Low" the minimum value will be taken, and if it is given as "Low and high", both the minimum value and the maximum value will be calculated and presented in summary tables.

Table 5-1 Directions of interest for worst case value for laboratory parameters

Laboratory Parameter	Direction of interest for worst case value
A. Hematology	
Hemoglobin	Low
Hematocrit	Low
Erythrocytes	Low
WBC	Low and high
Basophils	High
Eosinophils	High
Lymphocytes	Low and high
Monocytes	High
Neutrophils	Low and high
Platelets	Low and high
B. Chemistry	
Albumin	Low
Alkaline Phosphatase	High
ALT/SGPT	High
AST/SGOT	High
Bilirubin Total	High
Blood Urea Nitrogen (BUN)	High
Creatinine	High
Gamma GT	High
Potassium	Low and high
Magnesium	Low and high
Calcium	Low and high
LDH	High
Phosphorus	Low and high
Sodium	Low and high
CRP	High
Fibrinogen	High
HbA1c	Low and high

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

Table 5-2 Clinical notable criteria for selected laboratory tests

Laboratory parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range
Hematology		
Hematocrit (v/v)		
Male	0.37	
Female	0.32	
Hemoglobin (g/L)		
Male	115	
Female	95	
Platelets (x10E9/L)	75	700
WBC (x109/L)	2.8	16.0
Chemistry		
Albumin (g/L)	25	-
Alkaline Phosphatase (U/L)	-	3xULN
ALT/SGPT (U/L)	-	3xULN
AST/SGOT (U/L)	-	3xULN
Bilirubin Total (mcmol/L)	-	34.2
BUN (mmol/L)	-	9.99
Creatinine (mcmol/L)	-	176.8
Gamma GT (U/L)	-	3 x ULN
Potassium (mmol/L)	3	6
Magnesium (mmol/L)	0.51	1.07
Sodium (mmol/L)	125	160

v = volume, ULN = upper limit of normal

Table 5-3 Notable liver function test values

Criterion
ALT > 3 x the upper limit of normal range (ULN) ALT > 5 x ULN ALT > 8 x ULN ALT > 10 x ULN ALT > 20 x ULN
ALT or AST > 3 x ULN ALT or AST > 5 x ULN ALT or AST > 8 x ULN ALT or AST > 10 x ULN ALT or AST > 20 x ULN
Total bilirubin > 1 x ULN Total bilirubin > 1.5 x ULN Total bilirubin > 2 x ULN Total bilirubin > 3 x ULN
ALP > 1.5 x ULN ALP > 2 x ULN ALP > 3 x ULN ALP > 5 x ULN
ALT or AST > 3 x ULN and total bilirubin > 1.5 x ULN ALT or AST > 3 x ULN and total bilirubin > 2 x ULN ALT or AST > 5 x ULN and total bilirubin > 2 x ULN ALT or AST > 8 x ULN and total bilirubin > 2 x ULN ALT or AST > 10 x ULN and total bilirubin > 2 x ULN ALT or AST > 20 x ULN and total bilirubin > 2 x ULN
ALP > 3 x ULN and total bilirubin > 2 x ULN ALP > 5 x ULN and total bilirubin > 2 x ULN
ALT or AST > 3 x ULN and Total Bilirubin > 2 x ULN and ALP < 2 x ULN (Hy's law)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP = alkaline phosphatase

When a criterion contains multiple laboratory parameters, the criterion will only be considered to have been met when all conditions occur within a 3-day window. A case where all criteria are met at a post-baseline time point will be considered as newly occurring if the criteria are not met at baseline and will be considered as worsening if the criteria are met at baseline and at least one component is worsening from baseline irrespective of whether the other(s) are better.

5.4 Vital signs and ECG – definition of clinically notable values

The following two tables show the clinical notable criteria for vital signs and QTcF respectively.

Table 5-4 Clinical notable criteria for vital signs

Vital sign parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range
Notable value considering newly occurring or worsening cases		
Systolic blood pressure (mmHg)	< 75	> 200
Diastolic blood pressure (mmHg)	< 40	> 115
Pulse rate (bpm)	< 40	> 130
Notable change from baseline		
Systolic blood pressure (mmHg)	≤ 90 and decrease from baseline by ≥ 20	≥ 180 and increase from baseline by ≥ 20
Diastolic blood pressure (mmHg)	≤ 50 and decrease from baseline by ≥ 15	≥ 105 and increase from baseline by ≥ 15
Pulse rate (bpm)	≤ 50 and decrease from baseline by ≥ 15	≥ 120 and increase from baseline by ≥ 15
Weight (kg)	Decrease > 7% from baseline	Increase > 7% from baseline

Table 5-5 Clinical notable criteria for QTcF (Fridericia's formula)

ECG parameter (unit)	Clinically notable range
Notable value considering newly occurring or worsening cases (Males)	
QTc (msec)	> 450
QTc (msec)	> 480
QTc (msec)	> 500
Notable value considering newly occurring or worsening cases (Females)	
QTc (msec)	> 460
QTc (msec)	> 480
QTc (msec)	> 500
Notable change from baseline	
QTc (msec)	30 – 60
QTc (msec)	> 60
Combined criterion	
QTc (msec)	> 500 & increase > 60

5.5 Statistical models

Primary analysis

The following MMRM will be used for pre-dose FEV_1:

Dependent variable = intercept + treatment + region + baseline FEV_1 + eosinophils count at screening (≥ 300 or < 300 cells/μl) + FEV_1 prior to inhalation + FEV_1 within 30 min post inhalation of salbutamol/albuterol + visit + treatment*visit + baseline value*visit + error.

The within-patient correlation will be modeled using an unstructured covariance matrix in the mixed model. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (Kenward and Roger, 1997).

If the model fails to converge with unstructured covariance matrix, either a compound symmetry (first choice) or first order autoregressive (AR1) (second choice) covariance structure will be used.

[redacted]

Rule of exclusion criteria of analysis sets

The following table provides the PDs and other criteria leading to partial or complete exclusion from the analyses sets.

Table 5-6 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses
INCL01	Informed consent not obtained	RAS, FAS, Safety Set
TRT01	Patient received study drug but not randomized	RAS, FAS
TRT02	Randomized but no study drug given	Safety Set, FAS

6 Reference

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