NOVARTIS

Clinical Development

MHV370

CMHV370A12201

A multi-center, randomized, participant- and investigator-blinded, placebo-controlled, parallel group basket study to evaluate the safety, tolerability and efficacy of MHV370 in participants with Sjögren's Syndrome or Mixed Connective Tissue Disease

Statistical Analysis Plan (SAP)

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List of abbreviations

AE	Adverse Event
AUC	Area Under the Curve
b.i.d.	bis in die/twice a day
BMI	Body Mass Index
Cmax	Maximal concentration
CSR	Clinical study report
eCRF	Electronic Case Report/Record Form
ECG	Electrocardiography
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Participant Reported Index
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EULAR	European League against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full Analysis Set
FEV	Forced Expiratory Volume
FVC	Forced Vital Capacity
K-BILD	King's Brief Interstitial Lung Disease
LLOQ	lower limit of quantification
MCTD	Mixed Connective Tissue Disease
MedDRA	Medical dictionary for regulatory activities
MMRM	mixed effect model for repeated measurements
MRI	Magnetic resonance imaging
mRNA	messenger RNA (ribonucleic acid)
PD	Pharmacodynamic(s)
PhGA	Physician global assessment scale
PK	Pharmacokinetic(s)
PRO	Participant Reported Outcomes
PT	Prothrombin time
QTcF	Fridericia QT correction formula
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SjS	Sjögren's Syndrome
SOC	System organ class
Tmax	Time to reach maximum concentration
ULOQ	Upper limit of quantification
WHO	World Health Organization
WoC	Withdrawal of Consent

1 Introduction

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial "**CMHV370A12201**".

The Statistical Analysis Plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

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1.1 Study design

This is a phase 2 randomized, participant- and investigator-blinded, placebo-controlled, multi-center, parallel group basket study to evaluate the safety, tolerability and efficacy of MHV370 in participants with moderate to severe Sjögren's Syndrome (SjS) or participants with diagnosis of Mixed Connective Tissue Disease (MCTD). In case study participants receive concomitant therapy for their underlying disease and still meet entry criteria, they will remain on this therapy provided it remains stable until the end of the study.

A total of approximately 48 participants with SjS will be randomized in a 1:1 ratio to MHV370 (200 mg b.i.d.) or placebo. A total of approximately 12 participants with MCTD will be randomized in a 1:1 ratio to MHV370 (200 mg b.i.d.) or placebo.

As shown in Figure 1-1, participants will first undergo a screening period of up to 6 weeks, followed by a treatment duration of 24 weeks and a follow-up period of 4 weeks. The total duration for each participant in the study will be up to 34 weeks.

Figure 1-1 Study design

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Screening and Baseline

Participants will be assessed for ESSDAI (SjS participants) and RCS, and K-BILD (MCTD participants) as well as completing safety and other assessments to confirm RNP positivity and evaluate eligibility. Eligible participants will return for the Baseline visit on Day 1, to complete baseline assessments prior to dosing on Day 1. Some baseline assessments may be carried out on the day prior to Day 1.

Treatment

As shown from Figure 1-1, treatment period lasts for 24 weeks, from Day 1 to Week 24 (Day 169). On Day 1,

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Follow-up and End of Study visit (EoS)

After the last day of dosing, participants will enter a 4-week follow-up period without study drug treatment. Participants will be asked to return to the site at Week 28 for the End of Study visit. Upon competition of this visit, participants will be discharged from the study.

1.2 Study objectives, endpoints and estimands

Primary Objective(s)	
• **SjS**: To evaluate the efficacy of MHV370 compared to placebo based on change from baseline in ESSDAI at Week 24	• **SjS**: Change from baseline in ESSDAI at Week 24
• **MCTD:** To evaluate the efficacy of MHV370 compared to placebo based on change from baseline in Physician Global Assessment (PhGA) at Week 24	• **MCTD:** Change from baseline in PhGA at Week 24
Secondary Objective(s)	
• **SjS/MCTD**: To evaluate the efficacy of MHV370 compared to placebo based on change from baseline on patient and physician-reported outcomes over time up to Week 24	• **SjS**: Change from baseline in ESSDAI, ESSPRI, FACIT-F and PhGA over time up to Week 24 • **MCTD**: Change from baseline in FACIT-F, PhGA and ESSDAI (articular and pulmonary domains only) over time up to Week 24
• **SjS/MCTD**: To evaluate the safety and tolerability of MHV370	• **SjS/MCTD**: Safety endpoints will include: • Occurrence of treatment emergent adverse events (both serious and non-serious) during the study • Occurrence of treatment emergent abnormal vital signs, laboratory and ECG values during the study
• **SjS/MCTD**: To assess PK parameters of MHV370	• **SjS/MCTD:** PK parameters AUC, Cmax, Tmax and others as needed at steady state.
• **SjS**: To explore the effect of MHV370 on quantitative salivary flow (unstimulated) over 24 weeks	• **SjS**: Changes from baseline to the salivary flow rate over time up to 24 weeks of treatment
• **SjS**: To explore the effect of MHV370 on quantitative tear production over 24 weeks	• **SjS**: Changes from baseline to the Schirmer's test over time up to 24 weeks of treatment

● **SjS**: To explore the effect of MHV370 on the rate of STAR responders	● **SjS**: STAR response over time up to Week 24
● **MCTD**: To evaluate the efficacy of MHV370 based on change from baseline in Forced Vital Capacity (FVC) and Forced Expiratory Volume (FEV1, FEV2, FEV3) over time up to Week 24	● **MCTD**: Change from baseline in FVC, FEV1, FEV2 and FEV3 over time up to Week 24
● **MCTD:** To evaluate the efficacy of MHV370 based on change from baseline in the diffusing capacity of lungs for carbon monoxide (DLCO) over time up to Week 24	● **MCTD**: Change from baseline in the diffusing DLCO over time up to Week 24
● **MCTD:** To evaluate the efficacy of MHV370 based on change from baseline in the patient reported outcome on lung function	● **MCTD**: Change from baseline in King's Brief Interstitial Lung Disease (K-BILD) over time up to Week 24
● **MCTD:** To evaluate the efficacy of MHV370 based on change from baseline in Raynaud's Condition Score (RCS) over time up to Week 24	● **MCTD**: Change from baseline in RCS over time up to Week 24
Exploratory objective(s)	

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1.2.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g. premature discontinuation of treatment).

SjS

The primary clinical question of interest is: What is the effect of MHV370 on change in ESSDAI total score after 24 weeks of treatment in participants with moderate to severe Sjögren's Syndrome who are receiving a stable dose of a certain concomitant medication (systemic corticosteroid treatment, azathioprine, methotrexate, leflunomide,

hydroxychloroquine (HCQ) and chloroquine (CQ)), had treatment continued for the entire 24 week duration, had no dose change in certain allowed concomitant medication occurred and had no prohibited medication been taken?

The justification for the primary estimand is that wish to estimate the effect of the study drug for the full treatment duration when administered without dose changes in certain allowed concomitant medication (systemic corticosteroid treatment, azathioprine, methotrexate, leflunomide, HCQ and CQ) and without intake of prohibited medication.

The primary estimand is described by the following attributes:

1. Population: Participants with moderate to severe Sjögren's Syndrome receiving a stable dose of a certain concomitant medication (systemic corticosteroid treatment, azathioprine, methotrexate, leflunomide, HCQ and CQ).
2. Endpoint: Change from baseline in ESSDAI total score at Week 24.
3. Treatment of interest: the randomized treatment (investigational treatment MHV370 or placebo) with or without the allowed concomitant medication.
4. Handling of remaining intercurrent events:
    - Treatment discontinuations for any reason: had participants taken the assigned treatment for the entire study duration (hypothetical strategy).
    - Unforeseen change in the dose of certain allowed concomitant medication: had no change in the dose of systemic corticosteroid treatment, azathioprine, methotrexate, leflunomide, HCQ and CQ occurred (hypothetical strategy).
    - Intake of prohibited medication: had no prohibited medication been taken (hypothetical strategy).
5. The summary measure: Difference in mean change from baseline in ESSDAI total score at Week 24 between treatments.

MCTD

The primary clinical question of interest is: What is the effect of MHV370 on change in PhGA after 24 weeks of treatment in participants with MCTD who are receiving a stable dose of a certain concomitant medication (systemic corticosteroid treatment, azathioprine, methotrexate, leflunomide, HCQ and CQ), had treatment continued for the entire 24 week duration, had no dose change in certain allowed concomitant medication occurred and had no prohibited medication been taken?

The justification for the primary estimand is that wish to estimate the effect of the study drug for the full treatment duration when administered without dose changes in certain allowed concomitant medication (systemic corticosteroid treatment, azathioprine, methotrexate, leflunomide, HCQ and CQ) and without intake of prohibited medication.

The primary estimand is described by the following attributes:

1. Population: Participants with MCTD receiving a stable dose of certain concomitant medication (systemic corticosteroid treatment, azathioprine, methotrexate, leflunomide, HCQ and CQ).
2. Endpoint: Change from baseline in PhGA at Week 24.

3. Treatment of interest: the randomized treatment (investigational treatment MHV370 or placebo) with or without the allowed concomitant medication.
4. Handling of remaining intercurrent events:
   - Treatment discontinuations for any reason: had participants taken the assigned treatment for the entire study duration (hypothetical strategy).
   - Unforeseen change in the dose of certain allowed concomitant medication: had no change in the dose of systemic corticosteroid treatment, azathioprine, methotrexate, leflunomide, HCQ and CQ occurred (hypothetical strategy).
   - Intake of prohibited medication: had no prohibited medication been taken (hypothetical strategy).
5. The summary measure: Difference in mean change from baseline in PhGA at Week 24 between treatments.

2 Statistical methods

2.1 Data analysis general information

Blinded analyses using dummy treatment codes will be produced by CCI statisticians and programmers according to this SAP, using SAS version 9.4 or later (SAS Institute, Cary NC). Programs and datasets will then be provided to and run by CCI Statistician and Programmer using the true treatment codes to provide the unblinded TLFs in electronic format for discussion.

Interim analyses

One interim analysis is planned for this study, as described in Section 2.13.

Data collected up to the cut-off date will be included in the analysis. The data will include the subjects at various stages of the study. Some subjects may have full data while some may only have partial data available.

Descriptive statistics

Descriptive statistics on continuous data will include mean, standard deviation, median, minimum and maximum, while categorical data will be summarized as frequencies and percentages.

Analyses will be provided *separately* for SjS and MCTD, unless otherwise specified.

In shift tables and tables of abnormal values all unscheduled assessments are included.

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2.1.1 General definitions

Study treatment refers to MHV370 200 mg b.i.d or placebo.

The term ***'date of first administration of study drug/treatment'*** refers to the date on which the study drug/treatment was given for the first time in the CMHV370A12201 study.

The term ***'date of last administration of study drug/treatment'*** refers to the date on which the study drug/treatment was given for the last time in the CMHV370A12201 study.

The term ***'study day'*** refers to the Analysis Relative Day, Relative Start Day or Relative End Day, as applicable. Day 1 is defined as the date of first dose of study drug (MHV370 or placebo). Study day is defined as the number of days since the date of first dose of study treatment (Day 1).

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

- for dates on or after the first administration of study treatment,
  Study day = Assessment date – Date of first dose of study treatment +1
- for dates prior to the date of first administration of study treatment,
  Study day = Assessment date – Date of first dose of study treatment.

The term ***'baseline'*** refers to the last assessment performed prior to administration of the first dose of study treatment. In case the scheduled baseline assessment value is missing, the scheduled screening value if available will be used instead.

The term '***Treatment period***' refers to the 24 weeks period from Day 1 to Week 24 (Day 169).

The term ***'treatment-emergent adverse event'*** refers to any adverse event (AE) started after the first dose of study treatment, or events present prior to the first dose of study treatment but increased in severity (based on preferred term (PT)).

The term '***concomitant medication***' refers to any medication (except study medication) given after the first dose of the randomized study treatment.

2.2 Analysis sets

For all analysis sets, participants will be analyzed according to the study treatment(s) received.

The **safety analysis set** will include all participants that received any study drug.

The **PK analysis set** will include all participants with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations with impact on PK data.

The **PD analysis set** will include all participants who received study drug and have no protocol deviations with relevant impact on PD/efficacy data.

2.2.1 Subgroup of interest

No subgroup analysis is planned.

2.3 Participant disposition, demographics and other baseline characteristics

Safety analysis set will be used for the below analyses.

2.3.1 Participant disposition

The participant disposition will be summarized by treatment group.

The number and percent of participants screened, randomized, completed and discontinued from the study will be summarized with reasons of discontinuation.

2.3.2 Demographics and other baseline characteristics

Demographics (age, sex, race, ethnicity, weight, height, BMI, disease duration) and other baseline data including disease characteristics (ESSDAI and number of participants per ESSDAI stratum, ESSPRI, PhGA, FACIT-F, Salivary flow rate and Schirmer's test for SjS participants and ESSDAI [articular and pulmonary domains only], baseline pulmonary involvement factor, PhGA, FACIT-F, FVC, FEV1, FEV2, FEV3, DLCO, K-BILD and RCS for MCTD participants) will be summarized descriptively by treatment group.

Relevant medical history and current medical conditions at baseline will be summarized combined by SOC, PT and treatment group and listed by treatment group and participant.

Protocol deviations will be summarized by treatment, deviation category and protocol deviation term. A participant with deviations within a protocol deviation coded term is only counted once towards the total.

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

The safety analysis set will be used for the analyses below.

2.4.1 Study treatment / compliance

The duration (in days) of exposure to study treatment will be summarized by means of descriptive statistics for all participants, and by treatment group. The duration of treatment (in days) is defined as the last known date the participant took the study drug – the first day the participant took the study drug + 1, regardless of any temporary treatment interruption.

2.4.2 Prior, concomitant and post therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, and by treatment group.

2.5 Analysis supporting primary objective(s)

All participants within the PD analysis set will be included for the primary analyses.

2.5.1 Primary endpoint(s)

SjS

The primary endpoint is the change from baseline in ESSDAI total score at Week 24, defined as the Week 24 visit ESSDAI total score minus the baseline ESSDAI total score. A negative change indicates an improvement of disease activity. Details for the derivation of ESSDAI total score can be found in Appendix 5.4.1.1.

The ESSDAI score for SjS participants will be listed by treatment group, participant and visit/time. Descriptive statistics (raw and change from baseline) will be provided by treatment group and visit/time. Graphical methods, such as spaghetti plots up to Week 24, may be employed by treatment and visit/time. In addition, bar plots will be used to visualize (1) the contribution of the individual ESSDAI domains to the estimated change from baseline in the total ESSDAI score by treatment group and visit/time and (2) the difference in the contribution of the individual ESSDAI domains to the estimated change from baseline in the total ESSDAI score between the treatment groups by visit/time.

MCTD

The primary endpoint is the change from baseline in PhGA (ranging from “no disease activity” (0) to “maximal disease activity” (100)) after 24 weeks of treatment. It is defined as the Week 24 visit PhGA value minus the baseline PhGA value. A negative change indicates an improvement in disease activity. The PhGA score for MCTD participants, will be listed by treatment group, participant and visit/time. Descriptive statistics (raw and change from baseline) will be provided by treatment group and visit/time. Graphical methods, such as spaghetti plots up to Week 24, may be employed by treatment and visit/time.

2.5.2 Statistical hypothesis, model, and method of analysis

SjS

The change from baseline in ESSDAI is assumed to be normally distributed. A mixed effect model for repeated measurements (MMRM) will be fitted to the changes from baseline in ESSDAI for all time points until Week 24, with the following fixed effects:

- treatment group
- visit as categorical variable
- treatment group by visit interaction

and baseline ESSDAI as continuous covariate. An unstructured variance-covariance matrix will be fitted to model the dependency between repeated observations. If not possible, other appropriate covariance structures will be explored.

The difference between MHV370 and placebo in change from baseline at each visit will be estimated from the model and presented with 95% confidence intervals and one-sided p-value.

The following two criteria will be used to assess treatment efficacy:

- a statistically significant reduction in ESSDAI at Week 24 in the MHV370 group compared to placebo, at the one-sided 10% significance level, and
- an estimated mean reduction in ESSDAI at Week 24 in the MHV370 group to be at least 2 points greater than in placebo.

A positive sign of efficacy will be considered if both criteria are met.

2.5.3 Handling of intercurrent events

SjS and MCTD

The primary analysis will account for different intercurrent events as explained in the following:

1. Treatment discontinuation: Data from participants who have discontinued treatment early will be regarded as missing after the treatment discontinuation. Data from participants who have temporarily discontinued treatment (defined as missing more than two consecutive doses) will be regarded as missing during the temporary treatment discontinuation.
2. Any change in the dose of certain allowed concomitant mediation (systemic corticosteroid treatment [bethamethasone, prednisone, prednisolone, triamcinolone, methylprednisolone, dexamethasone, hydrocortisone, cortisone, ethamethasoneb], azathioprine, methotrexate, leflunomide, HCQ and CQ). Data after change in the dose of allowed concomitant medication will be regarded as missing (identified with OTH12 protocol deviation code).
3. Intake of prohibited medication: Data after intake of prohibited medication will be regarded as missing (identified with COMD01 protocol deviation code).

2.5.4 Handling of missing values not related to intercurrent event

SjS

Missing baseline value

If the baseline ESSDAI total score is missing, the screening value (if available) will be used to impute the baseline value. If neither the ESSDAI total score at baseline nor the ESSDAI total score at screening can be calculated due to missing domain scores, then the baseline ESSDAI total score is calculated using combination of baseline visit domain scores (where those are not missing) and screening domain scores (where the baseline analogs are missing) if they are available, and otherwise the baseline ESSDAI total score is set to missing.

Other missing data

For post-dose time points with missing data in one of the domains of the ESSDAI, the ESSDAI total score will be set to missing.

SjS

The MMRM utilized for the primary analysis implicitly imputes missing data under a missing at random assumption.

2.5.5 Sensitivity analyses

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2.5.6 Supplementary analyses

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2.6 Analysis supporting secondary objectives

All participants within the PD analysis set will be included for the primary analyses.

2.6.1 Secondary endpoint(s)

SjS

For the analysis of the secondary endpoints ESSPRI, FACIT-F, PhGA, Schirmer's test and salivary flow rate, descriptive summary statistics (raw and change from baseline) will be provided by endpoint, treatment group and visit/time. Graphical methods, such as spaghetti plots, may be employed by endpoint, treatment group and visit/time.

For the secondary endpoint STAR, responder status in STAR will be assessed at Weeks 4, 12 and 24. Descriptive frequency table will be provided by treatment group and visit/time. Missing responses will be treated as non-responders. The percentage of responders together with the 95% confidence interval (Clopper-Pearson method) will be presented along with p-values from Fisher's exact test for the difference between treatment groups will be presented. Graphical methods, such as bar plots, may be employed by treatment group and visit/time.

Details for the derivation of secondary endpoints total scores can be found in Appendix 5.4.1.2, Appendix 5.4.1.3 and Appendix 5.4.1.4.

MCTD

For the secondary endpoints FVC, FEV1, FEV2, FEV3, RCS, FACIT-F, DLCO, K-BILD, PhGA and ESSDAI (articular and pulmonary domains only) descriptive summary statistics (raw

and change from baseline) will be provided by endpoint, treatment group and visit/time. Graphical methods, such as arithmetic mean or spaghetti plots, may be employed for each endpoint.

Details for the derivation of secondary endpoints total scores can be found in Appendix 5.4.1.5.

2.6.2 Statistical hypothesis, model, and method of analysis

SjS

The change from baseline in ESSPRI, FACIT-F total score, PhGA, Schirmer's test and salivary flow rate is assumed to be normally distributed. A mixed effect model for repeated measurements (MMRM) will be fitted to the changes from baseline in each secondary endpoint, for all time points until Week 24, with the following fixed effects:

- treatment group
- visit as categorical variable
- treatment group by visit interaction

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and baseline of corresponding endpoint analyzed as a continuous covariate. An unstructured variance-covariance matrix will be fitted to model the dependency between repeated observations. If not possible, other appropriate covariance structures will be explored.

The difference between MHV370 and placebo in change from baseline at each visit will be estimated from the model and presented with 95% confidence intervals and one-sided p-value.

2.6.3 Handling of intercurrent events

Same as in Section 2.5.3.

2.6.4 Handling of missing values not related to intercurrent event

Same as in Section 2.5.4.

2.7 Safety analyses

All safety endpoints will be summarized by treatment group for all participants in the safety set.

2.7.1 Adverse events (AEs)

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

The number and percentage of participants with treatment emergent adverse events (TEAEs) will be summarized in the following ways:

- by treatment, primary system organ class
- by treatment, preferred term
- by treatment, primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related TEAEs, death, serious TEAEs, other significant TEAEs leading to discontinuation.

A participant with multiple adverse events within a primary SOC or PT, is only counted once towards the total of the primary SOC or PT.

ClinicalTrials.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 5% 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 participant, 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 AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

2.7.2 Deaths

All information obtained on deaths will be listed by treatment group and participant.

2.7.3 Laboratory data

Laboratory data with any abnormal values will be listed by treatment group and participant; in case of any value outside the normal range in a parameter in a participant, all records of this parameter will be presented. Summary statistics will be provided by treatment and visit/time.

Graphical methods for laboratory data, such as spaghetti plots, may be employed over time by treatment group.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

ECG parameters will be obtained from 12-lead ECGs for each participant during the study. ECG values with any abnormal values will be listed by treatment group and participant. Summary statistics will be provided by treatment and visit/time.

2.7.4.2 Vital signs

Vital signs values outside normal range will be listed by treatment group and participant. Summary statistics will be provided by treatment and visit/time.

Graphical methods for vital sings data, such as spaghetti plots, may be employed over time by treatment group.

2.8 Pharmacokinetic endpoints

All participants within the PK analysis set will be included for the PK analyses.

MHV370 PK plasma concentration data will be listed by treatment group, participant and visit/sampling time point. Descriptive summary statistics for PK concentration data will be provided by treatment group and 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), 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.

PK parameters will be listed by treatment group, visit/time and participant. Descriptive summary statistics for pharmacokinetic parameters will be provided by treatment separately and combined for SjS and MCTD subjects. Summary statistics include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented.

Table 2-1 PK Parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (ng x h / mL)
AUC0-t	The AUC from time zero to specified time t (ng x h / mL)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (ng x h / mL)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (ng / mL)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (h)

The PK profile of MHV370 will be characterized but not limited to the PK parameters listed above.

Arithmetic mean (SD) and geometric mean (95% CI) plasma concentration data will be plotted across time, with separate line types for treatment.

2.9 PD and PK/PD analyses

The relationship between PK and PD endpoints may be explored graphically. Modelling of the PK and PD data using a population approach may be performed, as appropriate, and may be reported in a separate, standalone modelling and simulation report.

2.10 Participant-reported outcomes

N/A.

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2.12 Other Exploratory analyses

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2.13 Interim analysis

An interim analysis is planned after approximately 50% of SjS participants have completed 24 weeks of treatment to evaluate the efficacy of MHV370.

Additional interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general or in case of any safety concerns.

3 Sample size calculation

3.1 Primary endpoint(s)

SjS

A total of approximately 48 participants with SjS will be randomized in a 1:1 ratio to MHV370 or placebo, with the aim to have at least 40 participants completing Week 24 assessment.

With 40 participants in the analysis of the primary efficacy variable (20 in MHV370 and 20 in placebo), the study would have approximately 80% chance of meeting both efficacy criteria, when the true difference between MHV370 and placebo is 3.5 points. In case the difference between MHV370 and placebo is zero points, the study would have approximately 10 % chance of meeting both efficacy criteria.

These calculations are based on assumed standard deviation of 5.1 in change from baseline in ESSDAI, based on data from TEARS study with rituximab (Devauchelle-Pensec et al 2014).

MCTD

A total of approximately 12 participants with MCTD will be randomized in a 1:1 ratio to MHV370 or placebo. The sample size was chosen for logistical reasons and no sample size calculations were made.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

No imputation will be made to the start date and end date of study treatment.

5.1.2 AE date imputation

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	**Month**	**Year**
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

As per Novartis standard AE date imputation rules, the following matrix explains the logic behind the imputation.

	MON MISSING	**MON < TRTM**	**MON = TRTM**	**MON > TRTM**
YYYY MISSING	**(1)** No convention	**(1)** No convention	**(1)** No convention	**(1)** No convention
YYYY < TRTY	**(a)** Before Treatment Start	**(b)** Before Treatment Start	**(b)** Before Treatment Start	**(b)** Before Treatment Start
YYYY = TRTY	**(a)** Uncertain	**(b)** Before Treatment Start	**(c)** Uncertain	**(c)** After Treatment Start
YYYY > TRTY	**(a)** After Treatment Start	**(b)** After Treatment Start	**(b)** After Treatment Start	**(b)** After Treatment Start

Before imputing AE start date, find the AE start reference date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min(informed consent date, earliest visit date).
2. Else AE start reference date = treatment start date

Rules for imputing the AE start date:

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
   a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
   b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
   a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
   b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

4. If the AE start date year value is equal to the treatment start date year value:
   a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
   b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
   c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

Rules for imputing the AE end date:

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, 31DECYYYY, date of death).
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, last day of the month, date of death).
3. If AE year is missing or AE is ongoing, the end date will not be imputed

5.1.3 Concomitant medication date imputation

The following table explains the notation used in the logic matrix. Please note that missing start dates will not be imputed.

	Day	Month	Year
Partial CMD Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	**MON < TRTM**	**MON = TRTM**	**MON > TRTM**
YYYY MISSING	**(1)** Uncertain	**(1)** Uncertain	**(1)** Uncertain	**(1)** Uncertain
YYYY < TRTY	**(a)** Before Treatment Start	**(b)** Before Treatment Start	**(b)** Before Treatment Start	**(b)** Before Treatment Start
YYYY = TRTY	**(a)** Uncertain	**(b)** Before Treatment Start	**(a)** Uncertain	**(c)** After Treatment Start
YYYY > TRTY	**(a)** After Treatment Start	**(b)** After Treatment Start	**(b)** After Treatment Start	**(b)** After Treatment Start

Rules for imputing the CM start date:

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.

2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
   a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
   b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
   a. If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).
   b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the treatment start date year value:
   a. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date.
   b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
   c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

Rules for imputing the CM end date:

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of treatment end date and the last day of the month.
2. If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of treatment end date and the end of the year (31DECYYYY).
3. If CM day/month/year is missing then use the treatment end date + 1 day as the imputed CM end date.
4. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

The above imputation rules apply to both prior therapies and post therapies.

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology. AEs will be categorized as mild, moderate, or severe.

5.3 Laboratory parameters derivations

Central laboratory assessments:

The central laboratory will flag on the central laboratory report all values falling outside of the central laboratory normal ranges

Vital and ECG signs:

Clinically notable values for vital signs are defined as:

- heart rate of < 50 and > 100 bpm
- systolic blood pressure of < 90 and ≥ 140 mmHg
- diastolic blood pressure of < 60 and ≥ 90 mmHg
- history of long QT syndrome or resting QTcF (Fridericia) prolonged (>450 ms for males or >460 ms for females)
- QT increase from baseline ≥ 60msec

5.4 Statistical models

The mean responses at treatment group will be obtained through covariate-adjusted treatment effects by using a MMRM as specified in Section 2.5.2 and Section 2.6.2. The model will be fitted using the SAS procedure "PROC MIXED". For SjS MMRM related model, the unstructured covariance matrix will be used (TYPE = UN), thus allowing adjustment for correlations between time points within participants. In order to get the variance covariance matrix of treatment effects to be full rank matrix, no intercept option will be used (NOINT option in MODEL statement).

Adjusted means and the corresponding variance covariance matrix will be estimated. The estimated treatment differences for treatment comparisons will be tabulated along with the associated 95% confidence intervals (two-sided ALPHA = 0.05) and one-sided p-value. No adjustment for multiplicity will be made. For calculation of denominator degrees of freedom Kenwood-Rogers method would be used (DDFM=KR).

In case the MMRM model does not converge the following sequential steps will be used:

1. change ddfm=kr to ddfm=bw. If still no convergence, perform step 2.
2. change type=un to type=cs. If still no convergence, perform step 3. This is for SjS analysis
3. remove covariates in the following order until convergence: stratification factor, treatment group by visit interaction.

5.4.1 Analysis supporting primary objective(s)

5.4.1.1 ESSDAI

The instrument contains 12 organ-specific domains contributing to disease activity. For each domain, features of disease activity are scored in 3 or 4 levels according to their severity. These scores are then summed across the 12 domains in a weighted manner to provide the total score. The domains (weights) are as follows: constitutional (3), lymphadenopathy (4), glandular (2), articular (2), cutaneous (3), pulmonary (5), renal (5), muscular (6), PNS (5), CNS (5), hematological (2), and biological (1). The maximum possible score is 123.

To calculate ESSDAI, all 12 organ domains must be individually assessed at every scheduled timepoint (from screening visit till end of study). Domain assessments will be entered by the site in the eCRF. At screening, the ESSDAI sub-score from 8 pre-selected domains listed in the inclusion criterion #8 will be calculated to determine participant's eligibility.

Participants with MCTD will complete the articular (from 0 “no activity” to 3 “high activity”) and pulmonary (from 0 “no activity to 3 “high activity”) domains of the ESSDAI only. These domains will be assessed separately over the treatment period.

5.4.1.2 ESSPRI

The total score of ESSPRI is defined as the mean of the three domains (pain, fatigue and dryness). If at least one of the domains is missing, then the total score of ESSPRI will not be derived for the corresponding participant.

5.4.1.3 Sjögren Tool for Assessing Response (STAR)

STAR is a composite responder index, including in a single tool all main disease feature. In this study lacrimal gland function will be assessed using the Schirmer’s test, while ocular staining score will not be used to calculate STAR response. Further, the biological domain will be assessed using IgG, while rheumatoid factor (RF) will not be used to assess STAR response.

Domain	Point	Definition of response
Systemic activity	3	Decrease from baseline of ≥3 in clinESSDAI.
Patient-reported outcome	3	Decrease from baseline of ≥1 point or ≥15% in ESSPRI.
Lachrymal gland function (assessed by Schirmer's test*)	1	Schirmer's test: If abnormal score at baseline: increase ≥5 mm from baseline. If normal score at baseline: no change to abnormal.
Salivary gland function (assessed by unstimulated whole salivary flow)	1	Unstimulated whole salivary flow: If score is >0 at baseline: increase of ≥25% from baseline. If score is 0 at baseline: any increase from baseline.
Biological (assessed by serum IgG)	1	Serum IgG level: decrease from baseline of ≥10%.

Star responder ≥ 5 points.

*For ocular tests, Schirmer’s test should be performed without anaesthesia and is considered abnormal if <5 mm. The mean of both eyes was used for calculation.

5.4.1.4 FACIT-F

The total score of FACIT-F will be used to assess the impact on fatigue. The FACIT-F contains 13 questions, where each has a scale from 0 to 4, where 0 is for “Not at all”, 1 is for “A little bit”, 2 is for “Somewhat”, 3 is for “Quite a bit” and 4 is for “Very much”.

The total score is derived as the sum of all item scores. Theoretical values of the total score range from 0 to 52. A high (low) total score corresponds to a high (low) quality of life.

Table 5-1 FACIT-F questions

Question no	Question
1	I feel fatigued
2	I feel weak all over
3	I feel listless (“washed out”)
4	I feel tired
5	I have trouble starting things because I am tired
6	I have trouble finishing things because I am tired
7	I have energy
8	I am able to do my usual activities
9	I need to sleep during the day
10	I am too tired to eat
11	I need help to do my usual activities
12	I am frustrated by being too tried to do the things I want to do
13	I have to limit my social activity because I am tired

Each item score, except for questions 7 and 8, is calculated as 4 minus the corresponding item response, since questions have negative directions, and it is necessary to reverse the responses for all questions except 7 and 8. The item score for questions 7 and 8 is calculated as 0 plus the corresponding item response.

When there are missing item scores, the total score will be computed by summing the non-missing item scores, multiplying by 13 (the total number of items) and dividing by the number of non-missing items (i.e. normalizing the result). The latter rule is applied only when at least half of the items (seven or more) are non-missing.

5.4.1.5 FVC and FEV

Forced expiratory volume (FEV) measures how much air a person can exhale during a forced breath. The amount of air exhaled may be measured during the first (FEV1), second (FEV2), and/or third seconds (FEV3) of the forced breath. Forced vital capacity (FVC) is the total amount of air exhaled during the FEV test. Forced expiratory volume and forced vital capacity are lung function tests that are measured during spirometry and are important measures of lung function.

5.4.1.6 K-BILD

The K-BILD is comprised of 15 items in three distinct health status domains, including:

- breathlessness and activities (items 1,4,11 and 13)
- chest symptoms (items 2,7 and 9)
- psychological (items 3,5,6,8,10,12 and 14) domains

A final item (15) is used to assess the impact of the respondent’s lung condition on their financial state.

The 15 items could be combined into a total score (12). The domain and total scores each range from 0-100 and higher scores indicate a better health status. Response options for all 15 items are on a 7-point Likert scale, ranging from 1 to 7. For each of the items, the response options

vary, including: item 1 (1='Every time', 7='Never'); items 2-4 and 6-14 (1='All of the time', 7='None of the time'); item 5 (1='None of the time', 7='all of the time') and item 15 (1='A significant amount', 7='Not at all').

To score the K-BILD, the Likert response scale weightings for individual items are combined, to ensure they detect progressive change in health status. Table 5-2 shows the recoded scale weightings associated with each raw, item-level score value. Raw domain and total scores are then calculated by summing the recoded scale values provided in that table.

Table 5-2 K-BILD Response Option Weightings

Item	Response						
	1	2	3	4	5	6	7
1	0	1	2	3	4	5	6
2	0	0	1	1	2	2	3
3	0	1	2	3	4	5	6
4	0	0	1	1	2	2	3
5	0	0	1	1	1	2	2
6	0	1	2	3	4	5	6
7	0	0	1	1	2	2	3
8	0	0	1	1	2	2	3
9	0	0	1	1	1	2	2
10	0	1	2	3	4	5	6
11	0	1	2	3	4	5	6
12	0	1	2	3	4	5	6
13	0	1	2	3	4	5	6
14	0	1	2	3	4	4	5
15	0	0	1	1	1	2	2

1. Domain scores should be generated first.
   - If there is more than 50% of missing items per domain, then the domain score is set to missing.
   - In case of missing data in each domain, missing item scale scores will be imputed based on the average of the non-missing item scores within that domain, rounded to the nearest integer (up or down as appropriated).
2. Then re-score all individual items by transforming each 1-7 score to the new scoring system as per scoring in Table 5-2.
3. Calculate the sum of all the transformed scores in the domain and then total score.
4. The raw domain and total scores will be transformed to a range of 0-100 by using logit values as provided by the transformation tables for each domain below.
5. If item 15 is missing, it will be replaced by the average of all available items 1-14. If any of the domain scores are missing, the total score is set to missing.

Breathlessness and Activities

Scale 0-21 Breathlessness and Activities domain score	Scale 0-100 score
0	0
1	10
2	18
3	23
4	27
5	30
6	33
7	36
8	38
9	40
10	42
11	44
12	46
13	48
14	50
15	53
16	55
17	58
18	63
19	69
20	80
21	100

Chest symptoms

Scale 0-8 Chest symptoms domain score	Scale 0-100 score
0	0
1	17
2	32
3	44
4	54
5	64
6	73
7	85
8	100

Psychological

Scale 0-34 Psychological domain score	Scale 0-100 score
0	0
1	11

Scale 0-34 Psychological domain score	Scale 0-100 score
2	17
3	22
4	25
5	28
6	30
7	32
8	34
9	36
10	37
11	38
12	40
13	41
14	42
15	44
16	45
17	46
18	48
19	49
20	51
21	52
22	54
23	55
24	57
25	59
26	61
27	63
28	65
29	68
30	72
31	76
32	81
33	89
34	100

Total Score

Scale 0-65 Total score	Scale 0-100 score
0	0
1	9
2	15
3	19

Scale 0-65 Total score	Scale 0-100 score
4	23
5	25
6	27
7	29
8	31
9	32
10	33
11	34
12	36
13	37
14	38
15	38
16	39
17	40
18	41
19	42
20	42
21	43
22	44
23	45
24	45
25	46
26	47
27	47
28	48
29	48
30	49
31	50
32	50
33	51
34	52
35	52
36	53
37	53
38	54
39	55
40	55
41	56
42	57

Scale 0-65 Total score	Scale 0-100 score
43	57
44	58
45	59
46	59
47	60
48	61
49	62
50	63
51	63
52	64
53	65
54	66
55	67
56	69
57	70
58	71
59	73
60	75
61	78
62	81
63	85
64	91
65	100

5.4.2 Analysis supporting secondary objective(s)

N/A.

5.5 Considerations due to COVID-19

Due to the COVID-19 pandemic, it might not be possible to perform some procedures as per protocol. All deviations due to COVID-19 may be listed separately to other deviations and may be also tabulated.

5.6 Rule of exclusion criteria of analysis sets

Table 5-3 Criteria leading to exclusion

Analysis Set	Criteria that cause participants to be excluded

6 Reference

Devauchelle-Pensec V, Mariette X, Jousse-Joulin S, et al (2014) Treatment of primary Sjögren syndrome with rituximab: a randomized trial. Ann. Intern. Med. p. 233-42.