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MHV370

Clinical Trial Protocol 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

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANAs	Antinuclear Antibodies
Anti-dsDNA	Anti-double stranded DNA
Anti-HBc	Hepatitis B core antibody
Anti-SSA	Anti-Sjögren's Syndrome A
Anti-SSB	Anti-Sjögren's Syndrome B
Anti-U1-RNP	Anti-Uridylate 1-Ribonucleoprotein
aPTT	activated partial thromboplastin time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
b.i.d.	bis in die/twice a day
BP	Blood Pressure
bpm	Beats per minute
°C	Degree Celsius
CBC	Complete blood count
CD	Cluster of differentiation
CFR	Code of Federal Regulations (United States)
CK	Creatine Kinase
cm	Centimeter(s)
Cmax	Maximal concentration
CMO&PS	Chief Medical Office and Patient Safety
CNS	Central Nervous System
CO	Country Organization
CO	Carbon monoxide
COA	Clinical Outcome Assessment
COVID-19	Corona-virus disease (2019)
CQ	Chloroquine
CRF	Case Report/Record Form (paper or electronic)
CSR	Clinical study report
CT	Computer tomography
CTLA4	cytotoxic T-lymphocyte-associated protein 4
CTT	Clinical Trial Team
CV	Coefficient of variation
CXCL10	C-X-C motif chemokine ligand 10
CYP	Cytochrome P450 (enzyme)
CysC	Cystatin C

DDI	Drug-drug interaction
dL	deciliter(s)
DLCO	Diffusing Capacity of Lungs for Carbon Monoxide
DMARDs	disease-modifying antirheumatic drugs
DNA	Desoxyribonucleic Acid
dsDNA	Double-stranded DNA (desoxyribonucleic acid)
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
e.g.	For example (“exempli gratia”)
EMA	European Medical Agency
EMG	Electromyography
ENA	extractable nuclear antigen
EOS	End of Study
eSource	Electronic Source
ESSDAI	EULAR Sjögren’s Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EULAR	European League against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
Fc	fragment crystallizable region (of an antibody)
FEV	Forced Expiratory Volume
FFPRHC	Faculty of Family Planning and Reproductive Health Care
FIH	First in Human
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
g	gram(s)
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GFR (eGRF/mGFR)	Glomerular Filtration Rate (estimated/measured)
GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
GU	Guanosine-uridine
h	Hour
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HCQ	Hydroxychloroquine
HCV	Hepatitis C Virus
HDPE	High Density Poly Ethylene
HIV	Human immunodeficiency virus

HRCT	High Resolution Computer Tomography
i.e.	that is (“id est”)
Ig	Immunoglobulin
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN	Interferon
IFNAR	Type I interferon receptor
IL	Interleukin
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISG	Interferon Stimulated Genes
IUD	Intrauterine Device
IUS	Intrauterine System
IVIG	Intravenous Immunoglobulin
K-BILD	King’s Brief Interstitial Lung Disease
kg	kilogram(s)
LC-MS/MS	Liquid chromatography mass spectrometry
LDH	lactate dehydrogenase
LFT	Liver function test
LLOQ	lower limit of quantification
LMW	Low molecular weight
mAb	monoclonal antibody
MATE	Multidrug and toxic compound extrusion (transporter enzyme)
MCTD	Mixed Connective Tissue Disease
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
µL	microliter(s)
mm	millimeter(s)
mmol	millimole(s)
MMRM	mixed effect model for repeated measurements
MRI	Magnetic resonance imaging
mRNA	messenger RNA (ribonucleic acid)
ng	nanogram(s)

No.	Number
NOAC	Novel Oral Anti-Coagulant
NSAIDs	nonsteroidal anti-inflammatory drugs
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PhGA	Physician global assessment scale
PK	Pharmacokinetic(s)
PNS	Peripheral Nervous System
PPD	Purified Protein Derivative
PRO	Patient Reported Outcomes
PT	Prothrombin time
PTT	Partial thromboplastin time
QMS	Quality Management System
RCS	Raynaud's Condition Score
RNA	Ribonucleic Acid
RNP	Ribonucleoprotein
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
sCr	Serum creatinine
SD	standard deviation
sec	second
SjS	Sjögren's Syndrome
SOC	System organ class
SOP	Standard operating procedure
SSRI	Selective serotonin re-uptake inhibitor
ssRNA	Single-strand RNA
STAR	Sjögren's Tool for Assessing Response
SUSAR	Suspected, Unexpected, Serious Adverse Reaction
TB	Tuberculosis
TBL	Total bilirubin time
TEARS	Tolerance and Efficacy of Rituximab in Sjögren's Disease (Clinical Study)
TLR	Toll Like Receptor
Tmax	Time to reach maximum concentration
TNF	Tumor necrosis factor
ULN	upper limit of normal
ULOQ	Upper limit of quantification
VAS	Visual Analog Scale
WHO	World Health Organization
WoC	Withdrawal of Consent
WOCBP	Women of child-bearing potential

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.

Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participant allocated to an invalid stratification factor
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study

Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

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Protocol summary

Protocol number	CMHV370A12201
Full Title	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
Brief title	A study to evaluate the safety, tolerability and efficacy of MHV370 in participants with Sjögren's Syndrome (SjS) or Mixed Connective Tissue Disease (MCTD)
Sponsor and Clinical Phase	Novartis. Phase II
Investigation type	Drug
Study type	Interventional
Purpose	This study is designed to establish safety, tolerability and efficacy of MHV370 in Sjögren's Syndrome (SjS) and Mixed Connective Tissue Disease (MCTD).
Primary Objective(s)	**SjS:** • To evaluate the efficacy of MHV370 compared to placebo based on 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.
Secondary Objectives	**SjS and 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. • To evaluate the safety and tolerability of MHV370. • To assess PK parameters of MHV370 (Cmax, AUC, Tmax and others) at steady state. **SjS:** • To explore the effect of MHV370 on quantitative salivary flow (unstimulated) over 24 weeks. • To explore the effect of MHV370 on quantitative tear production over 24 weeks. • To explore the effect of MHV370 on the rate of STAR responders **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. • 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. • To evaluate the efficacy of MHV370 based on change from baseline in the patient reported outcome on lung function.

	• To evaluate the efficacy of MHV370 compared to placebo based on change from baseline in Raynaud's Condition Score (RCS) over time up to Week 24.
Study design	This is a randomized, participant- and investigator-blinded, placebo-controlled, multi center parallel group basket study to evaluate the safety, tolerability and efficacy of 200 mg twice daily (b.i.d) of MHV370 in participants with Sjögren's Syndrome (SjS) or with Mixed Connective Tissue Disease (MCTD) over 24 weeks of treatment, followed by 4 weeks of follow-up. Total study duration for each participant will be up to 34 weeks.
Rationale	Ribonucleoproteins (RNPs), in complex with disease-associated RNP-specific antinuclear autoantibodies (ANAs) are a key driver of TLR7 and TLR8 activation. TLR7 and TLR8 are thought to play a role in several systemic autoimmune diseases, including SjS and MCTD. MHV370 is an orally bioavailable antagonist of human TLR7 and TLR8 and is intended for the treatment of diseases where pathology is thought to be driven by excessive activation of TLR7/8. SjS and MCTD are phenotypically different but in terms of presence of anti-RNP and TLR7/8 signaling, molecularly homogeneous autoimmune diseases, hence we investigate them in one study (i.e. a basket study)
Study population	Female and male participants aged 18 to 75 years with moderate to severe SjS or diagnosis of MCTD; a total of approximately 60 participants will be enrolled in this study: approximately 48 participants with SjS and approximately 12 participants with MCTD.
Key Inclusion criteria	**SjS and MCTD:** • Male or female participants aged 18 to 75 years at screening • Fully vaccinated with any locally approved COVID-19 vaccination, including booster vaccination, if required by local guidelines **SjS:** • Unstimulated whole salivary flow rate of > 0 mL/min at screening • Positive anti-Ro/SSA results at screening • Classification of Sjögren's Syndrome according to the 2016 ACR/EULAR criteria at screening • Screening ESSDAI (based on weighted score) ≥ 5 from 8 defined domains (biologic, hematologic, articular, cutaneous, glandular, lymphadenopathy, renal, constitutional). Participants with involvement of one or more of the remaining 4 domains are eligible but scores of these domains will not contribute to the assessment for eligibility, but will be part of the overall ESSDAI score for that subject **MCTD**: • Diagnosis of MCTD based on modified Kahn's criteria (John et al 2020) o Serological criteria: seropositive for anti-U1-RNP antibodies at central lab o Raynaud's phenomenon o At least two of the four following signs: i) synovitis, ii) myositis, iii) swollen fingers and vi) interstitial lung disease

	• Patients with overlap syndromes, i.e. patients meeting diagnostic criteria for systemic autoimmune disease other than MCTD (e.g. SLE, scleroderma, dermato- or polymyositis, rheumatoid arthritis or Sjögren's syndrome) may be included *unless* they have major organ involvement (e.g. lupus nephritis) as judged by the investigator

Key Exclusion criteria	**SjS and MCTD:**
	• Prior use of B-cell depleting therapy within 6 months of baseline. For participants who received B-cell depleting therapy within 6 -12 months of baseline visit, B-cell count should be within normal range
	• Prior treatment with any of the following within 3 months of baseline
	  • CTLA4-Fc Ig (abatacept)
	  • Anti-TNF mAb
	  • Intravenous Ig
	  • Plasmapheresis
	  • i.v. or oral cyclophosphamide
	  • i.v. or oral cyclosporine A
	• Screening CBC laboratory values as follows:
	  • Hemoglobin levels < 8 g/dL (< 5 mmol/L)
	  • Total leukocyte count < 2,000/µL (2 x 10^9/L)
	  • Platelets < 50,000/µL (50 x 10^9/L)
	  • Neutrophil count < 1,000/µL (1 x 10^9/L)
	• Cardiovascular disease or ECG abnormalities indicating significant safety risk for the participants
	• Pregnant or nursing (lactating) women
	• Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they use a highly effective method of contraception
	SjS:
	• Sjögren's Syndrome overlap syndromes where another autoimmune disease constitutes the primary illness
	• Required regular use of medications known to cause, as a major side effect, dry mouth / eyes

Study treatment	Two capsules of blinded study medication are to be taken in the morning and two capsules in the evening (see Section 6.1). One capsule of blinded study medication contains 100 mg of MHV370 or placebo.
Treatment of interest	Further details about the investigational treatment are provided in Section 6
Efficacy assessments	**SjS**: • ESSDAI, ESSPRI, FACIT-F, PhGA, salivary flow test, Schirmer's test **MCTD**: • PhGA, ESSDAI (articular and pulmonary domains only), FACIT-F, RCS, K-BILD, FVC, FEV, DLCO

Pharmacokinetic assessments	• Serial blood samples for analysis of MHV370 concentrations and calculation of PK parameters (AUC, Cmax, Tmax and others as defined in Section 12.5.3)
Key safety assessments	• Adverse event monitoring • Physical examinations • Vital Signs • Monitoring of laboratory markers in blood and urine • ECG assessment • Additional liver and renal safety monitoring • Assessment of pregnancy and fertility
Other assessments	Commercially Confidential Information
Data analysis	**SjS** 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 treatment group, visit as category variable and treatment group by visit interaction as fixed effects and baseline ESSDAI as a continuous covariate. An unstructured variance-covariance matrix will be fitted to model the dependency between repeated observations. 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. The following two criteria will be used to assess treatment efficacy • a statistically significant reduction in ESSDAI at Week 24 in 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. **MCTD** A MMRM will be fitted to the changes from baseline in PhGA for all time points until Week 24 with the treatment group, visit as category variable, treatment group by visit interaction CCI as fixed effects and baseline PhGA as a continuous covariate. A random intercepts model will be used. 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.

Key words	Sjögren's Syndrome, Mixed Connective Tissue Disease, ESSDAI, Toll Like Receptor 7/8 inhibitor, MHV370

1 Introduction

1.1 Background

Sjögren's syndrome (SjS) is a systemic autoimmune disease of unknown etiology characterized by lymphoid infiltration and progressive destruction of exocrine glands (Brito-Zerón et al 2016). Although the disease primarily affects the lacrimal and salivary glands, the inflammatory process can target any organ with approximately 15% of patients showing severe extraglandular manifestations (Baldini et al 2014). The clinical presentation is most often characterized by exocrinopathy of salivary and lacrimal glands presenting with dryness of the mouth and eyes. However, symptoms can be systemic and may include musculoskeletal pain and fatigue, affecting nearly all patients, or arthritis, cutaneous vasculitis, peripheral neuropathy, glomerulonephritis, interstitial nephritis, biliary cholangitis, obstructive bronchiolitis and others, involving multiple organ systems and affecting 20-40% of patients (Seror et al 2014). The mechanism underlying the development of SjS is the destruction of the epithelium of the exocrine glands as a consequence of autoreactive B-cells and T-cells (Brito-Zerón et al 2016). The high prevalence of autoantibodies, especially against Ro/SSA, even at an early stage of the disease suggests that autoreactive B-cells participate in the pathomechanism of SjS (Nocturne and Mariette 2018). Sjögren's syndrome is also linked with increased risk for malignancy, with a 10-fold elevation of lifetime-risk for B-cell lymphomas in SjS patients (Baldini et al 2014). SjS is observed in 0.3 to 1 per 1,000 persons, and its prevalence is second only to rheumatoid arthritis among systemic autoimmune disease. The disease affects mainly women with a female/male ratio of 9:1 and can occur at any age (Qin et al 2015). SjS has a severe impact on quality of life and productivity, often caused by disabling fatigue associated with the disease (Mariette and Criswell 2018).

Mixed connective tissue disease (MCTD) was first described in 1972 as a disease syndrome with overlapping features of other systemic autoimmune diseases, associated with antibodies to RNA sensitive extractable nuclear antigen (Sharp et al 1972). Patients with MCTD often have Sjögren's syndrome; notably, 42 % of patients with MCTD are reported to have sicca features (Ramos-Casals et al 2007). Clinical manifestations include a high frequency of Raynaud's syndrome, swollen hands, sclerodactyly, arthritis, polymyositis and interstitial lung disease (Venables 2006). The female to male ratio is around three, and the mean age at diagnosis of adult-onset MCTD is between 35 and 40 years. MCTD is rare, the point prevalence below 4 per 100,000 adults (Gunnarsson et al 2011). There is currently no cure for either SjS or MCTD.

Toll like receptors (TLRs) are part of the innate immune system and recognize conserved microbial structures. TLR7 and TLR8 are expressed intracellularly in endosomes and recognize the same ligand, guanosine-uridine (GU) rich single-strand RNA (ssRNA) (Heil et al 2004). In several autoimmune diseases, including both SjS and MCTD, TLR7/8 are activated by self-RNA after shuttling of ribonucleoprotein (RNP) autoantigens such as Ro60 to endosomes, in the form of immune complexes with autoantibodies (Båve et al 2005; Junt and Barchet 2015). Presence of autoantibodies against another RNP, U1-RNP, is a diagnostic criterion for MCTD (Tani et al 2014), and immune complexes of autoantibodies with U1-RNP lead to activation of TLR7 (Savarese et al 2006), and likely also TLR8.

MHV370 is an orally bioavailable low-molecular weight (LMW) antagonist of human TLR7 and TLR8 and is intended for the treatment of systemic autoimmune diseases, such as SjS or MCTD, where pathology is thought to be driven by excessive activation of TLR7/8 through RNP autoantigen containing immune complexes.

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1.2 Purpose

This study is designed to establish safety, tolerability and efficacy of MHV370 in Sjögren's Syndrome (SjS) and Mixed Connective Tissue Disease (MCTD).

2 Objectives, endpoints and estimands

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for 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)	**Endpoint(s) for 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

Objective(s)	Endpoint(s)
• **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)	**Endpoint(s) for exploratory objective(s)**

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Objective(s)	Endpoint(s)
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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 patients with moderate to severe Sjögren's Syndrome who are receiving a stable dose of 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: Patients with moderate to severe Sjögren's Syndrome receiving a stable dose of certain concomitant medication (systemic corticosteroid treatment, azathioprine, methotrexate, leflunomide, HCQ and CQ). Further details about the population are provided in Section 5.
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 patients with MCTD who are receiving a stable dose of 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: Patients with MCTD receiving a stable dose of certain concomitant medication (systemic corticosteroid treatment, azathioprine, methotrexate, leflunomide, HCQ and CQ). Further details about the population are provided in Section 5.
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.

2.2 Secondary estimands

Not applicable.

3 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 patients with moderate to severe Sjögren's Syndrome (SjS) or patients 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 (for details, see Section 6.2.1).

A total of approximately 48 participants with SjS will be randomized in a 1:1 ratio to MHV370 or placebo. A total of approximately 12 participants with MCTD will be randomized in a 1:1 ratio to MHV370 or placebo.

Figure 3-1 Study design

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Study Conduct

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.

Participants will receive 200 mg b.i.d. (200 mg twice per day) doses of MHV370 or placebo.

Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, biochemistry and urinalysis), pregnancy and fertility assessments, as well as adverse event and serious adverse event monitoring.

Screening

After signing informed consent, 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. For logistical reasons, assessments may be performed on different days during the 6-week screening period if deemed appropriate by the Investigator. Participants that fail screening may be re-screened for one further occasion.

Baseline

Eligible participants will return for the Baseline visit on Day 1. Participants may reside overnight at the site for logistical reasons, although this would not be considered a hospital admission. Eligibility must be confirmed prior to randomization and required baseline assessments must be completed prior to dosing on Day 1. If preferred by the site for scheduling purposes, some baseline assessments may be carried out on the day prior to Day 1.

Treatment

Treatment period lasts for 24 weeks, from Day 1 to Week 24 (Day 169). On Day 1, participants will be randomized to the respective SjS or MCTD treatment arms.

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Participants will return to the site at approximately 4-weekly intervals. As MHV370 is administered for the first time in patients with SjS and MCTD, an additional visit will be performed at Week 2 (Day 15) for safety and compliance purposes.

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The PK assessments will be performed pre dose and at various time points post dose (until 4 h after dosing) at Week 4, Week 12 and Week 24. At Week 4, an additional PK sample will be taken at 6 hours post dose, at selected sites.

Additionally, as per the Assessment Schedule (Table 8-1), participants with SjS will:

- undergo ESSDAI, salivary flow rate and Schirmer's test assessments
- complete ESSPRI assessments

and participants with MCTD will:

- undergo ESSDAI (articular and pulmonary domains only), local spirometry, DLCO test

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- complete RCS and K-BILD assessments

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On the visit days, participants will be asked to take their morning dose of the study drug at the site. Participants will return their used drug supply packs for compliance and accountability assessment and will receive a new supply of study drug for the next 4-week treatment period.

Each week, participants will be asked to complete diaries to record the administration of treatment.

All study visits will be ambulatory, however, for logistical reasons, it may be necessary for participants to come to the site the evening before their scheduled assessment visit. In these instances, the participants may stay overnight at the site, but this would not be considered a hospital admission.

Participants may be contacted by the Investigator/site staff during the study to ensure compliance/monitor safety by telephone or other means, if it is deemed appropriate or necessary by the Investigator.

The primary endpoint of the study will be assessed after the completion of 24-week treatment (Day 169; Week 24 visit).

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. At this visit, participants will undergo final assessments as indicated in the Assessment schedule (Table 8-1).

Upon completion of this visit, participants will be discharged from the study.

4 Rationale

4.1 Rationale for study design

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Randomization (strata, allocation ratio)	Randomization decreases the chance of imbalance of subject characteristics between groups, thereby facilitating an unbiased assessment of safety, tolerability and efficacy. In addition, randomization prevents selection bias.

Study Design Aspect	Rationale
	Allocation ratio of 1:1 to placebo and MHV370 is used to ensure maximum statistical power given a fixed total sample size.
Blinding	The study is participant- and investigator-blinded until final database lock (except where indicated in Section 6.5) to reduce potential bias in the assessment of subjective readouts.
Duration of study periods	Commercially Confidential Information
Treatment groups	The control group is placebo on top of standard of care because there is no approved systemic treatment for SjS or MCTD. However, all participants can continue with their current immunomodulatory therapy, if on a stable dose and as described in Section 6.2.1.

4.1.1 Rationale for choice of background therapy

There is no approved systemic treatment for SjS and MCTD, though some immunomodulatory treatments, such as antimalarials (i.e. CQ, HCQ) or steroids are often used empirically. All participants can continue with their current immunomodulatory therapy, if on a stable dose, and as described in Section 6.2.1.

4.2 Rationale for dose/regimen and duration of treatment

The dose planned for this study is 200 mg b.i.d. (200 mg twice per day). This dose is expected to be safe and efficacious based on data from the FIH clinical trial:

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

The comparator treatment in the study will be placebo, in order to provide objective control for the evaluation of safety, clinical efficacy and PD during the 24-week treatment with MHV370.

Since there is no approved systemic treatment for SjS and MCTD, the use of placebo as comparator is considered justified. Current standard of care for SjS and MCTD patients is often limited to symptomatic care (e.g. dryness or Raynaud's phenomenon). Steroids and conventional DMARDs are often ineffective. No pharmacologic intervention is effective against the severe, disabling fatigue associated with SjS. Requirements for continuation of concomitant therapy throughout the study are described in Section 6.2.1.

4.4 Purpose and timing of interim analyses/design adaptations

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.

4.5 Risks and benefits

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Please refer to the Investigator's Brochure (Section 7.1) for a full review of potential risks.

4.5.1 Potential benefit

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4.5.2 Potential risks

Potential risks are mitigated by compliance with inclusion/exclusion criteria, study procedures, close clinical monitoring and study drug discontinuation rules. As with investigational drugs in general, not all safety risks are known. Participants and investigators participating in this study will be informed should important new safety information become available.

Please refer to the Investigator's Brochure (Section 7.1) for a full review of potential risks. Below is a summary of risks included in the IB.

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4.5.3 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of 34 weeks, from each participant as part of the study. Additional samples may be required for safety monitoring. Timings of blood sample collection are outlined in the assessment schedule (Table 8-1).

A summary blood log is provided in the laboratory manual. Instructions for sample collection, processing, storage and shipment information are also available in the laboratory manual. See the Section 8.5.2.5 on the potential use of residual samples.

4.6 Rationale for Public Health Emergency mitigation procedures

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

5 Study Population

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria at screening unless specified otherwise below:

All participants

1. Signed informed consent must be obtained prior to participation in the study.
2. Male or female participants aged 18 to 75 years.
3. Fully vaccinated with any locally approved COVID-19 vaccine including booster vaccinations, as required by local guidance, and allowing sufficient time for the vaccine to be protective prior to baseline.
4. Able to communicate well with the Investigator to understand and comply with the requirements of the study.

SjS participants

5. Unstimulated whole salivary flow rate of > 0 mL/min at screening.

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7. Classification of Sjögren's Syndrome according to the 2016 ACR/EULAR Classification Criteria (Shiboski et al 2017).
8. Screening ESSDAI value (based on weighted score) ≥ 5 from 8 defined specific domains (biologic, hematologic, articular, cutaneous, glandular, lymphadenopathy, renal, constitutional). Participants with involvement of one or more of the remaining 4 domains are eligible but scores of these domains will not contribute to the assessment for eligibility, but will be part of the overall ESSDAI score for the efficacy assessment.

MCTD participants

9. Diagnosis of MCTD based on modified Kahn's criteria (John et al 2020)

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10. Patients with overlap syndromes, i.e. patients meeting diagnostic criteria for systemic autoimmune disease other than MCTD (e.g. SLE, scleroderma, dermato- or polymyositis, rheumatoid arthritis or Sjögren’s syndrome) may be included unless they have major organ involvement (e.g. lupus nephritis), as judged by the investigator.

5.2 Exclusion criteria

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

All participants

1. Use of other investigational drugs within 5 half-lives of baseline or within 30 days, whichever is longer; or longer if required by local regulations.
2. Prior use of B-cell depleting therapy (e.g. rituximab or other anti-CD20 mAb, anti-CD22 mAb, anti-CD52 mAb) within 6 months of baseline. For participants who received B-cell depleting therapy within 6-12 months of baseline visit, B-cell count should be within normal range.

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4. Prior treatment with any of the following within 3 months of baseline:
   - CTLA4-Fc Ig (abatacept)
   - Anti-TNF mAb
   - Intravenous Ig
   - Plasmapheresis
   - i.v. or oral cyclophosphamide
   - i.v. or oral cyclosporine A

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14. Screening central laboratory complete blood count values as follows:
    - Hemoglobin levels < 8 g/dL (< 5 mmol/L)
    - Total leukocyte count < 2,000/µL (2 x 10^9/L)
    - Platelets < 50,000/µL (50 x 10^9/L)
    - Neutrophil count < 1,000/µL (1 x 10^9/L)

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19. Pregnant or nursing (lactating) women.
20. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for at least 5 days after stopping of investigational drug. Highly effective contraception methods include:

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SjS participants

22. Sjögren's Syndrome overlap syndromes where another autoimmune rheumatic disease constitutes the primary illness, specifically:

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6 Treatment

6.1 Study treatment

The investigational drug will be provided by Novartis as appropriately blinded labeled HDPE (High Density Poly Ethylene) bottles. The bottles will contain capsules with either 100 mg active substance (MHV370) or matching Placebo.

Each dose (2 capsules) has to be swallowed with water. Between morning and evening doses, a dosing interval of approximately 12 hours (between 10 and 14 hours) should be kept.

Novartis Global Clinical Supply (GCS) will provide IMP supplies as detailed in the table (Table 6-1) below.

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	CCI	Sponsor (global or local)
MHV370 100 mg	Hard Gelatin Capsule	Oral use		Novartis
Placebo	Hard Gelatin Capsule	Oral use		Novartis

6.1.1 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.2 Treatment arms/group

Participants will be assigned at visit Day 1 to one of the following 2 treatment arms/groups in a ratio of 1:1 MHV370:Placebo.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms.

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

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Concomitant treatment may include standard of care for dry eye and dry mouth symptoms, such as the use of artificial tears and artificial saliva/salivary stimulants (e.g. cevimeline, pilocarpine) at the discretion of the treating physician. Amount and frequency of use should be recorded. Please refer to Table 6-2 for guidance on suggested treatment time interval prior to assessment of clinical disease outcome measurements. Artificial tears and artificial saliva are to be provided by the study center or personal physician.

Table 6-2 Treatments against dryness of eyes/mouth

Treatment type	Time interval prior outcome assessment
Artificial tears or other topical ophthalmic medications	4 hrs
Artificial saliva	4 hrs
Pilocarpine	12 hrs
Cevimeline or other salivary stimulants	24 hrs or 5x half-life, whichever is longer

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

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Additionally, herbal treatments should be used with caution.

6.2.2 Prohibited medication

Use of treatments displayed in the below table is not allowed in study periods as indicated.

Table 6-3 Prohibited Medication

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Medication	Prohibition period	Action to be taken
anticholinergics, sedatives, antipsychotic drugs, anti-Parkinson agents, diuretics)		
Live attenuated vaccine (locally approved mRNA vaccines, protein subunit vaccines, viral vector vaccines and inactivated vaccines are not "live attenuated" vaccines and are therefore not prohibited) (see also Section 4.5.2)	8 weeks prior to baseline and for at least 7 days after the last dose of MHV370	Study drug discontinuation may be required on a case-by-case basis
Strong and moderate inhibitors of CYP3A (see Table 16-7)	From screening until end of study	Study drug discontinuation may be required on a case-by-case basis
Strong and moderate inducers of CYP3A (see Table 16-8)	From screening until end of study	Study drug discontinuation may be required on a case-by-case basis
Narrow therapeutic index substrates of CYP 2B6, 2C8, 2C9, 2C19 and 3A4 (see Table 16-6)	From screening until end of study	Study drug discontinuation may be required on a case-by-case basis
Substrates of MATE1/2 (see Table 16-9)	From screening until end of study	Study drug discontinuation may be required on a case-by-case basis
Anti-platelet or anticoagulant medication (for example, warfarin, or clopidogrel or Novel Oral Anti-Coagulant - NOAC) other than acetylsalicylic acid (up to 100 mg/d)	From screening until end of study	Study drug discontinuation may be required on a case-by-case basis

6.2.3 Rescue medication

There is no established, approved immunosuppressive treatment for SjS or MCTD, however, in case of acute, severe systemic manifestations, high dose steroid or other systemic immunosuppressant may be administered as rescue. Participants may receive nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, or symptomatic care at the discretion of the treating physician as outlined in Section 6.2.1. Each concomitant drug must be individually assessed against all exclusion criteria and prohibited medication (Table 6-3). When in doubt the investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If any of the medications listed in Table 6-3 is deemed a necessary rescue therapy, the investigator must follow the actions to be taken outlined in this table. Any potential rescue medication is to be provided by the study center or personal physician. Participants should be encouraged to come for the remaining visits and end-of-study visit even when discontinued permanently from study medication.

6.2.4 Restriction for study participants

For the duration of the study, participants should be informed and reminded of the restrictions outlined in this section.

6.2.4.1 Dietary restrictions and smoking

Study participants should not eat or drink for 90 minutes before the assessment of salivary flow. It is recommended that participants do not smoke for 90 minutes before the pre-dose PK assessment and until all the PK study assessments are performed on the study visits of Day 29 (Week 4), Day 85 (Week 12) and Day 169 (Week 24). Study participants should not eat grapefruit or drink grapefruit juice on Day 29 (Week 4), Day 85 (Week 12) and Day 169 (Week 24) due to potential interference with PK assessments. It is also recommended that participants avoid ingestion of cruciferous vegetables (e.g. broccoli, brussel sprouts, cabbage, cauliflower) on these days.

6.2.4.2 Other restrictions

On the study days when PK assessments are performed, any permitted concomitant medication (see Section 6.2.1.1 and Section 6.2.1) should be separated by at least 3 hours of study drug intake. Moreover, on the study days when PK assessments are performed, participants have to avoid strenuous movements for 4 hours after dosing.

6.3 Preparation and dispensation

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

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

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

6.3.1 Handling of study treatment and other treatment

6.3.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the Investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

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

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site or remote monitoring visits, and at the completion of the trial.

If study treatment is administered at home, participants will be asked to return all used and unused study treatment and packaging at every study visit and the end of the study or at the time of discontinuation of study treatment.

The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.3.1.2 Handling of other treatment

Not applicable.

6.3.2 Instructions for prescribing and taking study treatment

Table 6-4 Dose and treatment schedule

Investigational / Control Drug (Name and Strength)	Dose	Frequency and/or Regimen
MHV370 100 mg	200 mg (2 capsules x 100 mg)	b.i.d. (twice daily)
Placebo	2 matching placebo capsules	b.i.d. (twice daily)

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

- Participants should be instructed to take MHV370 twice daily at approximately the same time each day, around 12 hours apart.
- Participants should be instructed not to make up missed doses, i.e. when the full dose is not taken within 4 hours after the time of the usual dosing.
- The first dose of MHV370 should be taken in the morning of Day 1 and the last dose of MHV370 should be taken in the morning of Day 169.
- On study visits, the participant should take their morning dose of MHV370 at the clinic.
- Participants should take MHV370 without regard to food. Each dose may be taken with a glass of water.
- Participants should be instructed to swallow whole capsules and not to chew or open them.
- If vomiting occurs during the course of treatment, participants should not take the study treatment MHV370 again before the next scheduled dose.
- Participants will be provided with individual diaries to record each administration of study treatment. These will be checked regularly by site staff.

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at the subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed.

6.4.2 Treatment assignment, randomization

At Day 1, all eligible participants will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

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

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

6.4.2.1 Replacement policy

Participants will not be replaced on this study.

6.5 Treatment blinding

Participants, investigator staff and the persons performing the assessments will remain blinded to the study treatment from the time of randomization until database lock, except where indicated below.

Site staff

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

Unblinding a single participant at site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site. As a result, the participant should be discontinued from the study treatment.

Sponsor staff

The following unblinded sponsor roles are required for this study:

- Unblinded clinical staff managing drug re-supply to site
- Unblinded sample analysts (PK)

The following methods will be used to maintain the blind:

1. all unblinded personnel will keep randomization list and data or information that could unblind other study team members confidential and secure except as described below
2. the identity of the treatments will be concealed by the use of study drug that are all identical in packaging, labeling, schedule of administration and appearance.

Sponsor clinical staff are required to assist in the management and re-supply of investigational drug product. These individuals are not provided with randomization lists directly, but may be unblinded through communication of drug re-supply needs.

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

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

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

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

Following final database lock all roles may be considered unblinded.

Table 6-5 Blinding and unblinding plan

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6.6 Dose escalation and dose modification

Investigational treatment dose adjustments and/or interruptions are not permitted, with the exception of interruption in case of confirmed SARS-CoV2 infection, as described under Section 4.5.

6.7 Additional treatment guidance

6.7.1 Treatment compliance

The investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts (if applicable) and information provided by the participant in the study medication diary. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all participants treated with MHV370, as detailed in the pharmacokinetics section.

6.7.2 Recommended treatment of adverse events

At present there is insufficient information to provide specific recommendations regarding treatment of adverse events (AEs).

In case of serious adverse events suspected by the investigator to be related to the study medication, a temporary or permanent discontinuation of the study drug needs to be considered.

Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

6.7.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely.

Most often, discontinuation from study treatment and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- participant number

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

After emergency unblinding a permanent discontinuation of the study drug needs to be considered.

7 Informed consent procedures

Eligible participants may only be included in the study after providing IRB/IEC-approved informed consent.

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

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH E6 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

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

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Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

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Declining to participate in these optional assessments will in no way affect the participant's ability to join the main research study.

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

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue from study treatment should continue to attend the remaining study visits and perform the assessments as indicated in the Assessment Schedule.

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The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

Every effort will be made to take the pharmacokinetic samples at the protocol specified time.

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

Table 8-1 Assessment Schedule

Period	Screening	Treatment															Follow up
Visit Name	Screening	Baseline / Day 1	Week 2	Week 4						Week 8	Week 12		Week 16	Week 20	Week 24		EOS
Days	-42	1	15	29						57	85		113	141	169		199
Weeks	-6	0	2	4						8	12		16	20	24		28
Time (post-dose)	-	-	-	0h	0.5h	1h	2h	4h	6h	-	0h	4h	-	-	0h	4h	-
Informed consent	X																
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Inclusion / Exclusion criteria	X																
Demography	X																
Medical history/current medical conditions	X																
Contact IRT / Randomization		S															
Drug dispensation		S		S						S	S		S	S	S		
Dose administration		X		X						X	X		X	X	X		
HIV screen	S																
Hepatitis screen	S																
Hepatitis monitoring (HBsAg)[1]			S	S						S	S		S	S	S		S
TB screen	S																
Physical Examination	S	S	S	S						S	S		S	S	S		S
Vital Signs	X	X	X	X						X	X		X	X	X		X
Body Temperature	X	X	X	X						X	X		X	X	X		X
Body Height	X																

Period	Screening	Treatment														Follow up
Visit Name	Screening	Baseline / Day 1	Week 2	Week 4					Week 8	Week 12		Week 16	Week 20	Week 24		EOS
Days	-42	1	15	29					57	85		113	141	169		199
Weeks	-6	0	2	4					8	12		16	20	24		28
Time (post-dose)	-	-	-	0h	0.5h	1h	2h	4h	6h	-	0h	4h	-	-	0h	4h	-
Body Weight	X	X		X						X	X		X	X	X		X
PhGA - VAS		X		X						X	X			X	X		
FACIT-Fatigue		X		X						X	X			X	X		
Hematology	X	X	X	X						X	X		X	X	X		X
Clinical Chemistry	X	X	X	X						X	X		X	X	X		X
Coagulation Panel	X	X	X	X						X	X		X	X	X		X
Urinalysis	X	X		X						X	X		X	X	X		X
PK blood collection				X[2]	X	X	X	X	X[3]		X[2]	X			X[2]	X	
Electrocardiogram (ECG)	X	X	X	X						X	X		X	X	X		X
Patient diary (paper)		S															

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Period	Screening	Treatment															Follow up
Visit Name	Screening	Baseline / Day 1	Week 2	Week 4						Week 8	Week 12		Week 16	Week 20	Week 24		EOS
Days	-42	1	15	29						57	85		113	141	169		199
Weeks	-6	0	2	4						8	12		16	20	24		28
Time (post-dose)	-	-	-	0h	0.5h	1h	2h	4h	6h	-	0h	4h	-	-	0h	4h	-
Pregnancy and assessments of fertility[6,7]	X	S		S						S	S		S	S	S		X
Study completion information																	X
Concomitant medications	X																
Adverse Events	X																
Assessments specific to SjS																	
ESSDAI	X	X		X						X	X			X	X		
ESSPRI		X		X						X	X			X	X		
Anti-Ro/SSA (screening test)	X																
Schirmer's test	X	X		X							X				X		
Salivary flow rate (unstimulated)	X	X		X							X				X		
Assessments specific to MCTD																	
Anti-U1-RNP (screening test)	X																
Local spirometry (FVC/FEV)		X									X				X		
DLCO		X									X				X		

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Period	Screening	Treatment															Follow up
Visit Name	Screening	Baseline / Day 1	Week 2	Week 4						Week 8	Week 12		Week 16	Week 20	Week 24		EOS
Days	-42	1	15	29						57	85		113	141	169		199
Weeks	-6	0	2	4						8	12		16	20	24		28
Time (post-dose)	-	-	-	0h	0.5h	1h	2h	4h	6h	-	0h	4h	-	-	0h	4h	-
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ESSDAI[8]	X	X		X						X	X				X		
Raynaud's Condition score	X	X		X							X				X		
K-BILD questionnaire	X	X		X						X	X				X		

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only

[1] HBsAg and HBV DNA monitoring: only required for anti-HBc positive patients

[2] Pre-dose

[3] Only at selected sites

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[6] Serum pregnancy test will be done at Screening and EOS. For remaining visits urine pregnancy test will be performed.
[7] Assessment of fertility at Screening only
[8] Articular and pulmonary domains only

8.1 Screening

Screening

It is permissible to re-screen a participant if she/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis. Participants can be re-screened only once, and no study-related re-screening procedure should be performed prior to written re-consent by the participant.

- Tests for HIV, Hepatitis B and C do not need to be repeated if they satisfied eligibility criteria in the initial screening and have been conducted within 12 weeks prior to planned date of randomization.
- If tested positive in screening anti-Ro/SSA or anti-U1 RNP, results do not need to be repeated in re-screening.

In case where a safety laboratory assessment at screening is outside of the range specified in the eligibility criteria, the assessment may be repeated once prior to randomization, i.e. without repeating the screening visit. If the repeat value remains outside of the specified ranges, the participant must be excluded from the study.

8.1.1 Eligibility screening

8.1.1.1 Hepatitis screen, HIV screen, TB test

Hepatitis

All participants will be screened for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc). HBV DNA testing will be performed if needed.

- If HBsAg is positive then the participant is not eligible, regardless of other test results, and HBV DNA test is not required.
- If HBsAg and anti-HBc are both negative, then the participant is eligible and HBV DNA test is not required.
- If HBsAg is negative and anti-HBc is positive, then HBV DNA test has to be performed to confirm eligibility: the participant is only eligible if HBV DNA is negative.
    - For such participants, an expert in hepatitis must be consulted and recommendations followed. If enrolled, hepatitis B monitoring must be implemented: HBsAg and HBV DNA tested every 4 weeks until the end of study.
    - In case of sero-conversion (i.e., if either HBsAg or HBV DNA turn positive) during the study, an expert in hepatitis must be consulted and recommendations observed. Immediate initiation of preemptive anti-viral treatment (e.g., lamivudine or entecavir) should be considered.

Table 8-2 Hepatitis screening

HBsAg	Anti-HBc	HBV DNA	Eligible	Comment
-	-	Not required	Yes	
-	+	-	Yes	Monitoring required
-	+	+	No	Consider treatment
+	+ or -	Not required	No	Consider treatment

Screening for hepatitis C will be based on Hepatitis C Virus Antibody (HCV) and Hepatitis C Virus RNA (HCV RNA).

HIV

Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the laboratory site e.g. Western blot. Appropriate counseling will be made available by the Investigator in the event of a positive confirmatory test. Notification of state and federal authorities, as required by law, will be the responsibility of the Investigator.

TB

Tuberculosis (TB) test (i.e. QuantiFERON® TB Gold Plus [QFT Plus] or T-SPOT® TB test [T-Spot], but not PPD test) performed by the local or central lab must be negative within 8 weeks prior to baseline. If a negative test result is not available for any reason or the result is 'indeterminate', then a second negative QuantiFERON® or T-SPOT® TB test (but not PPD) from the local or central lab can be accepted for eligibility if performed within 8 weeks prior to baseline.

If a patient is included based on a negative local QuantiFERON® or T-SPOT® TB test (but not PPD), local test results have to be documented in the patient's source file.

If the QuantiFERON® or T-SPOT® screening test is positive and active TB can be excluded as per the investigator's judgement (i.e. the patient has latent TB), the patient may be eligible if prophylactic treatment according to local guidelines is initiated prior to baseline. The exclusion of active TB has to be documented in the patient's source file.

8.1.1.2 Anti-Ro/SSA and Anti-U1-RNP antibodies

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8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see SAE

section for reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

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

8.2 Participant demographics/other baseline characteristics

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

Participant demographics: year of birth, sex, race/predominant ethnicity (if permitted) and relevant medical history/current medical conditions (until date of signature of informed consent) will be recorded in the eCRF. Where possible, the diagnosis and not symptoms should be recorded. Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics, as well as to assess the diversity of the study population as required by Health Authorities.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See Section 6.2.1 Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF.

8.3 Efficacy

Clinical efficacy measurements related to primary and secondary objectives are outlined below.

Patient reported outcome assessments must be completed before any clinical assessments are performed at any given visit. The resulting scores will be entered in the eCRF.

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

8.3.1 EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) (SjS and MCTD participants)

ESSDAI is a validated disease outcome measure for Sjögren's Syndrome that will be applied to the study participants. 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 subscore from 8 pre-selected domains listed in the inclusion criterion #8 will be calculated to determine participant's eligibility.

For assessments not listed in the protocol as mandatory tests but which may be needed to estimate ESSDAI, including radiography, high resolution computer tomography (HRCT), lung function test (DLCO, FVC), estimated glomerular filtration rate (eGFR), electromyography (EMG), muscle (or any other) biopsy, it is at the investigator's discretion to have these assessed based on the signs and symptoms of the participant so to provide correct ESSDAI readout.

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.

8.3.2 Physician's global assessment scale (PhGA) (SjS and MCTD participants)

The physician's global assessment scale is used for the Investigator to rate the disease activity of their patient using 100 mm VAS (Visual Analog Scale) ranging from "no disease activity" (0) to "maximal disease activity" (100).

To enhance objectivity, the physician must not be aware of the specific patient's patient reported outcome assessments, when performing his own assessment on that patient. Therefore, this assessment must be done prior to viewing the patient's reported outcomes.

8.3.3 FACIT-Fatigue (SjS and MCTD participants)

The Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F v4) is a short, 13-item, easy-to-administer tool that measures an individual's level of fatigue during their usual daily activities over the past week. The level of fatigue is measured on a 5-point Likert scale (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much) (Webster et al 2003).

FACIT-F will be completed by all study participants at the study site as per study assessment schedule (Table 8-1).

8.3.4 EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) (SjS participants only)

ESSPRI is an established disease outcome measure for Sjögren's Syndrome (Seror et al 2011). It consists of three of domains of dryness, pain and fatigue. The participant can assess severity of symptoms they experience on a single 0-10 numerical scale for each of the three domains. The ESSPRI score is defined as mean of scores from the three scales: (dryness + pain + fatigue)/3. ESSPRI will be completed by the study participants at the study site as per study assessment schedule (Table 8-1).

8.3.5 Schirmer's test (SjS participants only)

Schirmer's test is used to measure the quantity of tear secretion especially for those who suffer from dry eye syndrome. Materials required will be provided by the central laboratory. Schirmer testing will be done in an exploratory manner at screening, baseline, and following treatment at time points as specified in the assessment schedule (Table 8-1).

The participant is seated in the examining chair with the room lights dimmed and their head against a headrest for comfort. Both eyes will be assessed simultaneously.

The procedure is briefly outlined below:

- The eye is gently dried of excess tears
- The Schirmer strip is folded 5 mm from one end and kept in the lower fornix at the junction of lateral 1/3 and medial 2/3 (do not touch cornea or lashes)
- The participant is asked to close the eyes
- Tears in the conjunctival sac will cause progressive wetting of the paper strip
- After 5 minutes, the filter paper is removed and the distance between the leading edge of wetness and the initial fold is measured, using a millimeter ruler

8.3.6 Salivary flow rate (unstimulated) (SjS participants only)

Unstimulated whole salivary fluid is obtained from participants at Screening, Baseline, Week 4, Week 12 and Week 24.

Unstimulated salivary secretions are collected over 5 minutes. All assessments are to be performed at a fixed time of the day to minimize fluctuations related to the circadian rhythm of salivary flow and composition. Participants are instructed not to eat, drink or smoke for 90 minutes before the assessment. The start time and end time of saliva collection will be recorded to calculate the salivary flow rate per minute.

8.3.7 Forced Vital Capacity (FVC) and Forced Expiratory Volume (FEV) (MCTD participants only)

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.

8.3.8 Diffusing capacity of the lungs for carbon monoxide (DLCO) (MCTD participants only)

DLCO is a measurement to assess the ability of the lungs to transfer gas from inspired air to the bloodstream. Inhaled carbon monoxide (CO) is used for this test due to its high affinity for hemoglobin. In brief, during a ten-second breath-hold, DLCO measures uptake of CO per time per CO pressure (cc of CO/sec/mm of Hg; (Ogilvie et al 1957; Cotes et al 1993; Modi et al 2020).

8.3.9 Raynaud's Condition Score (RCS) (MCTD participants only)

The Raynaud's Condition score (RCS) is participant's rating of difficulty considering number of attacks, duration, amount of pain, numbness, or other symptoms caused in the fingers (including painful sores) due to the Raynaud's phenomenon and impact of Raynaud's alone on use of hands every day. An 11 point Likert scale is used to rate the difficulty caused by the condition with 0 = no difficulty and 10 = extreme difficulty. Participants are asked to select the number that best describes their difficulty, with higher score indicating worse condition.

RCS will be completed by the study participants with MCTD at the study site as per study assessment schedule (Table 8-1).

8.3.10 King's Brief Interstitial Lung Disease (K-BILD) (MCTD participants only)

The K-BILD questionnaire is a self-administered health-status questionnaire that has been developed in patients with interstitial lung diseases. It consists of 15 items in three domains: i) breathlessness and activities, ii) psychological factors, and iii) chest symptoms. Domain and total scores range from 0 to 100, with higher scores representing better health status (Patel et al 2013; Sinha et al 2019; Nolan et al 2019; Flaherty et al 2019).

K-BILD will be completed by the study participants with MCTD at the study site as per study assessment schedule (Table 8-1).

8.3.11 Sjögren's Tool for Assessing Response (STAR)

STAR is a composite responder index, including in a single tool all main disease features, and designed for use as a key efficacy endpoint in SjS randomized clinical trials (Seror et al 2022).

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.

Table 8-3 STAR response criteria used in the study

Domain	Point	Definition of response
Systemic activity	3	Decrease in clin ESSDAI ≥ 3 points
Patient reported outcome	3	Decrease in ESSPRI ≥ 1 point or 15%
Lacrimal gland function (assessed by Schirmer's test)	1	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 salivary flow)	1	increase ≥ 25% from baseline
Biological (assessed by serum IgG levels)	1	Decrease ≥ 10%
STAR responder ≥ 5 points		

8.3.12 Appropriateness of efficacy assessments

Efficacy measures in this study are primarily based on ESSDAI measuring organ-specific disease criteria, and on ESSPRI measuring the patient's subjective disease impact. Both instruments are widely accepted and validated, gold-standard measures of systemic and symptomatic manifestations of SjS, respectively.

ESSDAI is a systemic disease activity index that classifies disease activity in 3-4 levels, over each of 12 differentially weighted domains (biologic, hematologic, articular, glandular, cutaneous, constitutional, lymphadenopathy, renal, pulmonary, PNS, CNS and muscular). A composite weighted score provides an accurate assessment of disease activity, with a good sensitivity to change, as validated in multiple cohort studies (Seror et al 2015a). The ESSPRI tool, on the other hand, is a patient reported composite score of symptoms of dryness, limb pain and fatigue evaluated on 0-10 visual analog scale, during the preceding 2 weeks (Seror et al 2011). Patient reported scores have poor sensitivity to change in disease activity, but among available tools, ESSPRI has been reported to have significantly better sensitivity. A recent prospective study reported poor correlation between systemic and patient scores, suggesting that the two indices evaluate complementary components of disease activity, therefore underscoring the importance of evaluation of both parameters to arrive at an accurate assessment of disease activity and change thereof (Seror et al 2015b).

8.4 Safety

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

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

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant's health status until it is safe for the participant to visit the site again.

Table 8-4 Assessments & Specifications

Assessment	Specification
Physical	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed. The investigator should ask the participant for and pay attention to presence of signs and symptoms of infection. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.

Assessment	Specification
Vital signs	Vital signs will include the collection of otic or oral body temperature (recorded in °C), blood pressure (BP) and pulse measurements. After the participant has been sitting for 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic BP will be measured using an automated validated device, e.g. OMRON with an appropriately sized cuff. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. In case of repeated vital assessments, the eCRF should contain all the results. Clinically notable vital signs are defined in Section 16.1.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

8.4.1 Laboratory evaluations

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

Urinalysis

A midstream urine sample (approx. 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and to allow proper assessments.

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Clinically notable laboratory findings are defined in Section 16.1.

Table 8-5 Laboratory evaluations

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Ery. Mean Corpuscular Hemoglobin, Ery. Mean Corpuscular HGB Concentration, Ery. Mean Corpuscular Volume, Platelets, Erythrocytes, Leukocytes, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands), Immunoglobulins quantitative (IgG, IgA, IgM, IgE), Ccomplement (C3, C4, CH50)

Test Category	Test Name
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Chloride, Sodium, Potassium, Creatinine, eGFR, Cystatin C, Creatine kinase, Total Bilirubin (if elevated above 1.5x, Direct Bilirubin and Indirect Bilirubin will be differentiated), Total Cholesterol, Total Protein, Triglycerides, Urea Nitrogen or Urea, Uric Acid, Amylase, Lipase, Glucose (non-fasting), CRP,
Urinalysis	Microscopic Panel (Erythrocytes, Leukocytes, Casts, Crystals, Bacteria, Epithelial cells) Macroscopic Panel (Dipstick) (Color, Bilirubin, Macroscopic Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
Coagulation	Prothrombin time (PT), International normalized ratio [INR]), Activated partial thromboplastin time (APTT)
Serology (Hepatitis and HIV)	Hepatitis B Virus Surface Antigen (HBsAg), Hepatitis B Virus core antibody (Anti-HBcAb), Hepatitis B Virus DNA (HBV DNA), Hepatitis C Virus Antibody (HCV), Hepatitis C Virus RNA (HCV RNA), HIV Ab
Pregnancy Test	Serum / Urine pregnancy test

8.4.2 Electrocardiogram (ECG)

ECGs will be collected at the site and evaluated centrally.

Single 12-lead ECGs will be recorded at each study visit.

Full details of all procedures relating to the ECG collection and reporting are contained in the technical manual provided by the core laboratory.

Electrocardiograms (ECGs) must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The Fridericia QT correction formula (QTcF) will be used for clinical decisions.

All ECGs, including unscheduled safety ECGs with clinically relevant findings collected during the study need to be transmitted to the central ECG laboratory for review.

Additional, unscheduled safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings before administration of study treatment and during the study.

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

8.4.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements. Serum pregnancy testing is required at screening and the follow up visit. During the study, urine pregnancy testing should be done at monthly intervals. The positive urine test needs to be confirmed with serum test. If positive, the participant must be discontinued from study treatment.

Local pregnancy test and associated results will not be collected on CRF.

If participants cannot visit the site to have serum pregnancy tests during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

Assessments of fertility

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

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

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

8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population.

8.5 Additional assessments

8.5.1 Pharmacokinetics

PK blood samples will be collected at the visits and time points defined in the assessment schedule (Table 8-1). Instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment should be followed.

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PK samples will be obtained in all participants. They will be evaluated in all participants, except the placebo group. From those blood samples, plasma will be prepared and plasma concentrations over time of MHV370 will be determined by a validated LC-MS/MS method with an anticipated Lower Limit of Quantification (LLOQ) of 1.0 ng/mL. Concentrations will be expressed in mass per volume units (ng/mL) and will refer to the free base. Concentrations below the LLOQ will be reported as “zero” and missing data will be labeled as such in the Bioanalytical Data Report.

In the optional case of further exploratory assessment (e.g. investigation of metabolites), a non-validated method will be used and results will be provided in a separate standalone report.

For standard PK abbreviations and definitions see the list provided in Section 12.5.3.

The following PK parameters at steady-state after 4 weeks of b.i.d. treatment will be determined from the plasma concentration time data using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher): Cmax, Tmax, AUClast. Additional PK parameters may be added to further characterize the dose/exposure relationship or refine PK/PD analysis. In addition, concentrations of MHV370 at selected time points will be characterized at Week 12 and Week 24.

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8.5.3 Other Assessments

8.5.3.1 Patient Diary

Participants will receive a medication diary where they have to record the intake of study medication daily.

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9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration, if any) and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being. Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section (see Table 6-3)
- Any situation in which continued study participation might result in a safety risk to the participant
- Emergency unblinding
- Emergence of the following adverse events:
  a. Laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study (see also Section 16.1)
  b. ECG abnormalities, if the investigator considers that continued study participation might result in a safety risk to the participant
  c. Severe treatment related hypersensitivity reaction requiring treatment
  d. Severe systemic infection or severe opportunistic infection requiring treatment
  e. Severe, treatment related and persisting changes in heart rate or blood pressure (see Section 16.1 for clinically notable vital sign values)
  f. Pancreatitis, as confirmed by clinical symptoms, elevated levels of pancreatic enzymes and/or imaging techniques (CT, MRI, ultrasound)
  g. Myofiber toxicity, as attested by acute muscle weakness, myalgia, muscle swelling, dark (tea/cola) colored urine, creatine kinase (CK) elevation (> x 5 ULN) and/or myoglobinuria, in the absence of exercise (Stahl et al 2020).
- For liver events, please see Section 10.2.1 and consult the Hepatotoxicity Clinical Safety Standard Guideline. For renal events, please see Section 10.2.2 and consult the Drug Induced Nephrotoxicity Guidelines at the Renal Safety Group site, [http://go/rsg or CSSG].
- If a liver- or renal event occurs, follow guidelines outlined in Section 16.2 and Section 16.3 regarding discontinuation of study treatment.

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

Participants who discontinue from study treatment agree to return for the end of treatment and follow-up visits indicated in the Assessment Schedule (refer to Section 8).

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

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

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

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

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Lost to follow-up

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

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

Withdrawal of consent/opposition to use data/biological samples occurs when a participant:

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

and

- No longer wishes to receive study treatment

and

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

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

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/opposition to use data/biological samples and record this information.

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

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

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

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

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

9.3 Study stopping rules

The study will be placed on hold if any of the following occurs, unless clearly unrelated to treatment:

- One patient with treatment related death
- Two or more treatment related SAEs within one system organ class (SOC)
- Two or more participants presenting with the following AEs
  a. severe treatment related hypersensitivity reaction requiring treatment
  b. severe systemic infection or severe opportunistic infection requiring treatment
  c. severe, treatment related and persisting changes in heart rate or blood pressure (see Section 16.1 for clinically notable vital sign values)

d. pancreatitis, as confirmed by clinical symptoms, elevated levels of pancreatic enzymes and/or imaging techniques (CT, MRI, ultrasound)
e. myofiber toxicity, as attested by acute muscle weakness, myalgia, muscle swelling, dark (tea/cola) colored urine, creatine kinase (CK) elevation (> x 5 ULN) and/or myoglobinuria, in the absence of exercise (Stahl et al 2020).

- The Sponsor and Investigator considers that based on available safety data (including number and/or severity of AEs, laboratory tests, vital signs, etc.) putting the study on hold is justified.

The study may resume following the safety review, if the Investigator and Sponsor agree it is safe to proceed. Any restart of the study following a full safety review will require notification to health authorities or submission and approval of a substantial amendment, whichever is appropriate based on local requirements.

9.4 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision. Each participant will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them. All randomized and/or treated participants should have a safety follow-up call conducted 4 weeks after last administration of study treatment (in case of early study termination and EOS visit not performed). The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the participant should be recorded in the source documentation.

9.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination

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

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

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

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

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

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments (such as e.g. Patient-Reported Outcomes).

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

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

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

- Dose not changed
- Drug interrupted/permanently discontinued

6. Its outcome i.e., its recovery status or whether it was fatal

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

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

Adverse event monitoring should be continued for at least 4 weeks following the last dose of study treatment.

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

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

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

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

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

10.1.2 Serious adverse events

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

- fatal
- life-threatening

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

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent

  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

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

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

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

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 4 weeks following the last administration of study treatment must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

No pre-specified study endpoints are considered to be exempted from SAE reporting.

SAE reporting timeframes:

- Screen Failures (e.g. a participant who is screened but is not treated or randomized): SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis within 24 hours of learning of its occurrence.
- Randomized OR Treated Participants: SAEs collected between time participant signs ICF until 4 weeks after the participant has discontinued from study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, and under no circumstances later than within 24 hours of

the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

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

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

Any SAEs experienced after the 4 weeks period *following the last study visit* should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO & PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship of MHV370 to any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

If a female partner of a male trial participant who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

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

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

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

For more information on AE and SAE definition and reporting requirements, please see the respective sections (Section 10.1).

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

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

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

Once a participant is exposed to study treatment, every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Section 16.2.

- Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation. These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment, Section 9.1.1), if appropriate
- Hospitalization of the participant if appropriate

- Causality assessment of the liver event
- Thorough follow-up of the liver event. These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Exclusion of underlying liver disease
- Imaging such as abdominal US, CT or MRI, as appropriate
- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

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

10.2.2 Renal safety monitoring

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events should be monitored and followed up by the investigator or designated trial staff as summarized in Section 16.3.

10.3 Committees

There are no Committees applicable for this trial.

11 Data Collection and Database management

11.1 Data collection

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

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

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

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

11.2 Database management and quality control

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

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

Laboratory samples will be processed centrally, and the results will be sent electronically to Novartis.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

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

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked, **and the treatment codes will be unblinded** and made available for data analysis/ moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

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

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical

information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

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

12 Data analysis and statistical methods

The analyses will be provided separately for SjS and MCTD unless otherwise specified.

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

12.1 Analysis sets

For all analysis sets, 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 MHV370 and with no protocol deviations with impact on PK data.

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

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data will be summarized descriptively by treatment group for the safety set.

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

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

12.3 Treatments

The safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

The duration of exposure in weeks to MHV370 and placebo will be summarized by means of descriptive statistics using the safety set.

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, by treatment group.

12.4 Analysis supporting primary objectives

The PD analysis set will be used.

SjS

The primary objective is to assess the efficacy of MHV370 based on change from baseline in ESSDAI at Week 24. The statistical analysis model will include data on the ESSDAI from all time points at which it was recorded (Baseline, Week 4, Week 8, Week 12, Week 20, Week 24) but the primary comparison is made for Week 24.

MCTD

The primary objective is to assess the efficacy of MHV370 based on change from baseline in Physician Global Assessment (PhGA) at Week 24. The statistical analysis model will include data on the PhGA from all time points at which it was recorded (baseline, Week 4, Week 8, Week 12, Week 20, Week 24) but the primary comparison is made for Week 24.

12.4.1 Definition of 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.

MCTD

The primary endpoint is the change from baseline in PhGA 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.

12.4.2 Statistical model, hypothesis, 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 a continuous covariate. An unstructured variance-covariance matrix will be fitted to model the dependency between repeated observations.

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.

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.

MCTD

The change from baseline in PhGA is assumed to be normally distributed.

A MMRM will be fitted to the changes from baseline in PhGA for all time points until Week 24 with the following fixed effects

- treatment group
- visit as categorical variable
- treatment group by visit interaction
- stratification factor pulmonary involvement at baseline (yes/no)

and baseline PhGA as a continuous covariate. A random intercepts model will be used.

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.

12.4.3 Handling of intercurrent events of primary estimand

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 will be regarded as missing during the temporary treatment discontinuation.
2. Change in the dose of certain allowed concomitant mediation (systemic corticosteroid treatment, azathioprine, methotrexate, leflunomide, HCQ and CQ): Data after change in the dose of allowed concomitant medication will be regarded as missing.
3. Intake of prohibited medication: Data after intake of prohibited medication will be regarded as missing.

12.4.4 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 and MCTD

The MMRM utilized for the primary analysis implicitly imputes missing data under a missing at random assumption. The reasonableness of this assumption will be checked and, if necessary, further methods may be applied.

12.4.5 Sensitivity analyses

Other models that the one specified in Section 12.4.2 may be considered. For SjS, simpler covariance structures than the unstructured one may also be considered.

12.4.6 Supplementary analyses

SjS

The target population, the primary variable and the summary measure of the supplementary estimand are the same as for the primary estimand. Differently from the primary estimand, the intercurrent events will be ignored. Data from participants who have discontinued treatment early (permanently or temporarily), had a dose change in the concomitant medications or had prohibited medication during the study will be included in the analyses.

12.5 Analysis supporting secondary objectives

SjS

For the analysis of the secondary endpoints of change from baseline in ESSPRI, FACIT-F and PhGA, the same population and a similar estimand framework as for the primary endpoint (Section 12.4.1) will be adopted. Descriptive summary statistics will include all participants in the PD analysis set.

Responder status in STAR will be assessed at weeks 4, 12 and 24. Missing responses will be treated as non-responders. The percentage of responders together with the 95% confidence interval (Clopper-Pearson method) will be presented by treatment.

For the Schirmer's test and salivary flow data descriptive summary statistics will be provided for all participants in the PD analysis set.

MCTD

For the secondary endpoints change from baseline in FVC, FEV1, FEV2, FEV3, RCS, FACIT-F, DLCO, K-BILD, RCS, PhGA and ESSDAI (articular and pulmonary domains only) descriptive summary statistics will be provided for all participants in the PD analysis set.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

SjS

The change from baseline over time for secondary efficacy endpoints (ESSPRI, FACIT-F and PhGA) will be presented by treatment group and visit. Summary statistics will be presented for original results and mean change from baseline, together with adjusted mean change from baseline and 95% confidence interval estimated from similar MMRM as the one used for the primary efficacy variable. Differences in change from baseline between MHV370 treatment group and placebo, along with associated 95% confidence intervals, will be presented by visit.

For the Schirmer's test and salivary flow data descriptive summary statistics will be presented by treatment group and visit.

MCTD

The change from baseline over time for secondary efficacy endpoints FVC, FEV1, FEV2, FEV3, RCS, FACIT-F, DLCO, K-BILD, RCS, PhGA and ESSDAI (articular and pulmonary domains only) will be presented by treatment group and visit.

12.5.2 Safety endpoints

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

Adverse events

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 (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term) 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 adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

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

Vital signs

Summary statistics will be provided by treatment group and visit/time.

12-lead ECG

Summary statistics will be provided by treatment group and visit/time.

Clinical laboratory evaluations

Summary statistics will be provided by treatment group and visit/time.

12.5.3 Pharmacokinetics

Descriptive summary statistics for MHV370 PK plasma concentration data will be provided by visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations.

Descriptive summary statistics for pharmacokinetic parameters will be provided. Summary statistics include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is *Tmax* where only median, minimum, and maximum will be presented.

Table 12-1 Non-compartmental pharmacokinetic 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.

12.5.4 PK/PD relationships

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.

12.6 Analysis of exploratory endpoints

Details of the statistical analyses of exploratory endpoints will be described in the Statistical Analysis Plan (SAP).

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12.7 Interim analyses

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12.8 Sample size calculation

12.8.1 Primary endpoint(s)

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13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

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

13.3 Publication of study protocol and results

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

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

13.4 Quality Control and Quality Assurance

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

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

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

13.5 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the timepoints indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter
- Plain language trial summary - after CSR publication
- Treatment Sharing Information

14 Protocol adherence

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

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

14.1 Protocol amendments

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

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

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

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

Central laboratory assessments:

The central laboratory will flag on the central laboratory report

i) all values falling outside of the central laboratory normal ranges

ii) all values falling in the below alert range:
   a. Hemoglobin levels < 8 g/dL (< 5 mmol/L)
   b. Total leukocyte count < 2,000/µL (2 x 10^9/L)
   c. Platelets < 50,000/µL (50 x 10^9/L)
   d. Neutrophil count < 1,000/ µL (1 x 10^9/L)

Vital 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

The investigator will report an adverse event for clinically significant vital-sign or laboratory abnormalities.

16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity
If ALT or AST abnormal at baseline:	• ALT or AST > 3x baseline or > 300 U/L (whichever occurs first)

Table 16-2 Follow up requirements for liver laboratory triggers - ALT, AST, TBL

	ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **No change to study treatment** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms.
	If normal at baseline: ALT > 5 x ULN for more than two weeks **If elevated at baseline:** ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **Interrupt study drug** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours.
	If normal at baseline: ALT > 8 x ULN	Normal	None	• Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
ALT increase with bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:**	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	

	ALT	TBL	Liver Symptoms	Action
	ALT > 2 x baseline or > 300 U/L (whichever occurs first)			

Table 16-3 Follow up requirements for liver laboratory triggers - Isolated Hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	• Maintain treatment • Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	• Interrupt treatment • Repeat LFT within 48-72 hours • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	• Discontinue the study treatment immediately • Hospitalize the participant • Establish causality • Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors(e.g., conmeds, med hx, lab) in the appropriate CRF	Investigator's discretion

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

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-4 Specific Renal Alert Criteria and Actions

Criteria	Action required
Serum cystatin C increase 25 – 49% compared to baseline	• Consider causes and possible interventions • Follow up within 2-5 days
Serum cystatin C increase ≥ 50%	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation • Consider hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 1+	• Consider causes and possible interventions • Assess serum albumin & serum protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset glycosuria on urine dipstick (unless related to treatment, diabetes)	Assess & document: • Blood glucose (fasting) • Serum cystatin C
New hematuria on dipstick concomitant	Assess & document: • Urine sediment microscopy • Assess serum cystatin C • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

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

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

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

Table 16-5 Follow up of renal events

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

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

16.4 Appendix 4: Prohibited Co-Medication

Table 16-6 Narrow therapeutic index CYP substrates

Category	Drug Names
Narrow therapeutic index substrates of CYP2B6	None reported to date
Narrow therapeutic index substrates of CYP2C8	paclitaxel
Narrow therapeutic index substrates of CYP2C9	phenytoin, (S)-warfarin (also sensitive)
Narrow therapeutic index substrates of CYP2C19	(S)-mephenytoin (also sensitive)
Narrow therapeutic index substrates of CYP3A	abemaciclib, acalabrutinib, astemizole, cyclosporine, dihydroergotamine, entrectinib, ergotamine, pimozide, quinidine, sirolimus, tacrolimus, zanubrutinib

Table 16-7 Strong and moderate inhibitors of CYP3A

Category	Drug Names
Strong inhibitors of CYP3A	boceprevir, ceritinib, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir, indinavir/ritonavir, itraconazole, josamycin, ketoconazole, lopinavir/ritonavir, mibefradil, mifepristone, nefazodone, nelfinavir, ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak), posaconazole, ribociclib, ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, tucatinib, voriconazole
Moderate inhibitors of CYP3A	ACT-178882, ACT-539313, aprepitant, amprenavir, atazanavir, atazanavir/ritonavir, casopitant, cimetidine, ciprofloxacin, crizotinib, darunavir, darunavir/ritonavir, diltiazem, dronedarone, duvelisib, erythromycin, faldaprevir, fedratinib, FK1706, fluconazole, grapefruit juice, GSK2647544, imatinib, isavuconazole, istradefylline, lefamulin, letermovir, Magnolia vine (*Schisandra sphenanthera*), netupitant, nilotinib, ravuconazole, tofisopam, verapamil, voxelotor

Table 16-8 Strong and moderate inducers of CYP3A

Category	Drug Names
Strong inducers of CYP3A	apalutamide, avasimibe, carbamazepine, enzalutamide, ivosidenib, lumacaftor, mitotane, phenobarbital, phenytoin, rifampicin, rifapentine, St. John's wort (*Hypericum perforatum*)
Moderate inducers of CYP3A	asunaprevir / beclabuvir / daclatasvir, bosentan, cenobamate, dabrafenib, elagolix, efavirenz, etravirine, lesinurad, lersivirine, lopinavir, nafcillin, PF-06282999, phenobarbital, primidone, rifabutin, talviraline, telotristat ethyl, thioridazine, tipranavir/ritonavir

Table 16-9 Substrates of MATE1/2

Category	Drug Names
Substrates of MATE 1/2	acyclovir, cephalexin, cimetidine, ganciclovir, fexofenadine, glycopyrronium, metformin, pindolol, pilsicainide, procainamide, ranitidine, topotecan, varenicline

16.5 Appendix 5: Permitted concomitant therapy requiring caution and/or action

Table 16-10 Sensitive CYP substrates

Category	Drug Names
Sensitive substrates of CYP2B6	bupropion
Sensitive substrates of CYP2C8	daprodustat, repaglinide
Sensitive substrates of CYP2C9	benzbromarone, celecoxib, glimepiride, glipizide, ibuprofen, lornoxicam, meloxicam, piroxicam, tolbutamide
Sensitive substrates of CYP2C19	(R)-(-)-hexobarbital, clobazam, (R)-lansoprazole (dexlansoprazole), diazepam, gliclazide, (S)-lansoprazole, (R)-mephobarbital, (R)-omeprazole, omeprazole, pantoprazole, proguanil, rabeprazole, tilidine
Sensitive substrates of CYP3A	alisporivir, almorexant, alfentanil, alpha-dihydroergocryptine, aplaviroc, atorvastatin, avanafil, avapritinib, blonanserin, bosutinib, brecanavir, brigatinib, brotizolam, budesonide, buspirone, cabazitaxel, capravirine, cobimetinib, darifenacin, dasatinib, ebastine, eletriptan, eliglustat, eplerenone, everolimus, felodipine, fluticasone, grazoprevir, ibrutinib, itacitinib, ivabradine, ivacaftor, levomethadyl (LAAM), lomitapide, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, morphothiadin, naloxegol, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, sildenafil, simeprevir, simvastatin, ticagrelor, tilidine, tolvaptan, triazolam, ubrogepant, ulipristal, vardenafil, venetoclax, vicriviroc, vilaprisan, voclosporin