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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Not Applicable

Trial Indication(s)

Systemic Lupus Erythematosus

Protocol Number

CMHS552D12101

Protocol Title

A two-part, randomized, investigator- and participant- blinded, placebo-controlled, multiple ascending dose study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of MHS552 in adult participants with Systemic Lupus Erythematosus (SLE)

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase 1

Study Start/End Dates

Study Start Date: March 15, 2022 (Actual)
Primary Completion Date: June 04, 2023 (Actual)
Study Completion Date: June 04, 2023 (Actual)

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Reason for Termination (If applicable)

Sponsor Decision

Study Design/Methodology

The study was planned as a Phase 1b, randomized, placebo controlled, subject- and investigator-blinded, two-part non-confirmatory multiple ascending dose (MAD) study in adult subjects aged 18-65 (inclusive) with active SLE disease (mild-moderate).

This MAD study was planned to be conducted in two parts, Part A and Part B sequentially. Part A was planned to be a dose ranging study consisting of small cohorts to determine safe and tolerated doses of MHS552 with up to an approximate 4-fold T-regulatory cell (Treg) model predicted median peak expansion from baseline level, the highest targeted biological effect proposed to be studied. At the interim analysis at the end of Part A, proposed dose and regimen for Part B would have been submitted to Health Authorities and Ethic Committees to receive approval to initiate Part B.

In each cohort, four subjects were randomized (in a 3:1 ratio) to receive weekly s.c. doses of MHS552 or placebo for four weeks of treatment. Only doses of 1 mg and 3 mg MHS552 were tested in cohorts A1 and A2a, respectively.

Each patient in cohorts A1 and A2a underwent an approximately 6-week Screening period to assess eligibility, pre-dose assessments (Day -1 or 1), Treatment Period (Day 1 to Day 29), Follow-up period (Day 36 to Day 50 and an end of study (EOS) visit at Day 78). Women of Child-Bearing Potential were to be extended post-study follow-up after the EOS visit.

Due to the early termination, only two cohorts (Cohort A1 and A2a) in Part A were completed and Part B was not initiated. This early termination decision was not associated with any safety reasons and is solely associated with strategic reasons.

Centers

Germany(1)

Objectives:

The primary objective of the trial was to assess the safety and tolerability of multiple doses of MHS552 in adults with mild to moderately active systemic lupus erythematosus (SLE).

The secondary objective of the trial was to assess the pharmacokinetics (PK) of multiple doses of MHS552.

Test Product (s), Dose(s), and Mode(s) of Administration

Participants received 1 mg or 3 mg of MHS552 or matching placebo administered by subcutaneous (s.c.) injection once weekly for 4 weeks.

Statistical Methods

The primary objective of the study was to assess safety and tolerability of multiple doses of MHS552 in adults with mild to moderately active SLE. The primary analysis was conducted when all subjects completed the end of study (EOS) visit or discontinued from the study. All safety data, such as AEs, vital signs, electrocardiogram (ECG) parameters, safety laboratory results, were considered primary endpoints. For all safety analyses, the safety set was used.

The secondary objective was to assess the PK of multiple doses of MHS552. The PK set was used for all PK analyses. Analysis was performed in samples collected from MHS552-treated subjects only. Descriptive summary statistics of MHS552 serum concentrations were provided by treatment and visit/sampling time point. Summary statistics included mean (arithmetic), standard deviation (SD), median, minimum, and maximum. Concentrations below lower limit of quantification (LLOQ) were treated as zero in summary statistics and for PK parameter calculations.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

-Fulfills the 2019 EULAR/American College of Rheumatology (ACR) classification criteria for SLE at least 3 months prior to and at

screening.

- Patients with mild or moderately active SLE (SLEDAI-2K between 3 and 10, inclusive) at screening. Patients with cutaneous lupus are eligible as long as they satisfy the criteria for systemic lupus.
- Patients must be on stable dose(s) of at least one of the following medications, unless the medication has been discontinued due to intolerance, inadequate response, or patient/physician decision:

• steroid at a dose ≥ 5mg but <30 mg of prednisone (or equivalent) per day,
• antimalarial (hydroxychloroquine/chloroquine/quinacrine) or thalidomide,
• disease modifying anti-rheumatic drugs (DMARDs):
• methotrexate (MTX),
• azathioprine (AZA),
• mizoribine,
• mycophenolate derivates.

Steroid dose must be stable for at least 4 weeks prior to the first dosing. The dose of the other medications above must be stable for at least 12 weeks prior to the first dosing. If the patient is not on any medications listed above, they must have been off these medications for at least 12 weeks prior to dosing.

Exclusion Criteria:

- History of hypersensitivity to drugs of similar biological class, IL-2 protein analogues, or hypersensitivity to any components of the study drug, or history of severe hypersensitivity reaction or anaphylaxis to biological agents, e.g. human monoclonal antibody.
- Patients with central nervous system (CNS) lupus, active Lupus Nephritis, any type of lupus flare requiring pulse steroid or immunosuppressive therapy with cyclophosphamide, rituximab, calcineurin inhibitors, or others except those permitted in the inclusion criteria.

- Systemic autoimmune disease other than lupus, which would interfere with participation in the study according to the Investigator's judgement. Treated, stable Hashimoto’s thyroiditis is not exclusionary.
- Any of the following abnormal laboratory values at Screening or pre-dose Day 1 assessment:
Hemoglobin levels below 8.0 g/dL at screening
Eosinophil count >700 mm3 or >2 X Upper Limit of Normal (ULN), whichever is lower.
- History of capillary leak syndrome (CLS).

Other protocol-defined inclusion/exclusion criteria may apply

Participant Flow Table

Overall Study

	MHS552 1 mg	MHS552 3 mg	Placebo	Total
Arm/Group Description	MHS552 1 mg weekly s.c. dose for 4 weeks	MHS552 3 mg weekly s.c. dose for 4 weeks	Placebo weekly s.c. dose for 4 weeks	
Started	3	3	2	8
Completed	3	3	2	8
Not Completed	0	0	0	0

Baseline Characteristics

	MHS552 1 mg	MHS552 3 mg	Placebo	Total
Arm/Group Description	MHS552 1 mg weekly s.c. dose for 4 weeks	MHS552 3 mg weekly s.c. dose for 4 weeks	Placebo weekly s.c. dose for 4 weeks	

Number of Participants [units: participants]	3	3	2	8
Baseline Analysis Population Description				
Age Continuous (units: years) Analysis Population Type: Mean ± Standard Deviation				
	58.7±5.13	43.0±13.11	34±2.83	46.6±13.08
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
Female	2	3	2	7
Male	1	0	0	1
Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
Asian	0	0	1	1
Black or African American	0	1	0	1
White	3	2	1	6

Primary Outcome Result(s)

Number of participants with treatment emergent adverse events (AEs) and serious adverse events (SAEs)

Description	Number of participants with treatment emergent AEs (any AE regardless of seriousness), AEs led to study treatment discontinuation, SAEs and SAEs led to study treatment discontinuation.
Time Frame	Adverse events were reported from first dose of study treatment until end of study up to a maximum duration of approx. 78 days. For women of child-bearing potential, pregnancies were reported (if occurred) for up to approx. 106 days after first dose.

Analysis Population Description: The safety analysis set included all subjects that received at least one dose of study drug.

	MHS552 1 mg	MHS552 3 mg	Placebo
Arm/Group Description	MHS552 1 mg weekly s.c. dose for 4 weeks	MHS552 3 mg weekly s.c. dose for 4 weeks	Placebo weekly s.c. dose for 4 weeks
Number of Participants Analyzed [units: participants]	3	3	2
Number of participants with treatment emergent adverse events (AEs) and serious adverse events (SAEs) (units: participants)	**Count of Participants**	**Count of Participants**	**Count of Participants**
At least one AE	2 (66.67%)	3 (100%)	2 (100%)
At least one SAE	0 (%)	0 (%)	0 (%)
AE leading to discontinuation of study treatment	0 (%)	1 (33.33%)	1 (50%)
SAE leading to discontinuation of study treatment	0 (%)	0 (%)	0 (%)

Secondary Outcome Result(s)

Area Under serum Concentration-time Curve calculated to the end of a dosing interval (AUCtau) of MHS552

Description: The area under the serum concentration-time curve to the end of a dosing interval at steady-state of MHS552. Due to incomplete PK profiles resulting from concentrations below LLOQ or missed dose due to COVID-19, it was not possible to calculate AUCtau.

Time Frame: Day 1, 2, 5, 8, 15, 22, 23, 26, 29, 36, 50, 78

Analysis Population Description	The PK analysis set included all subjects with at least one available valid PK concentration measurement, who received MHS552 and with no protocol deviations that impact PK data.

	MHS552 1 mg	MHS552 3 mg
Arm/Group Description	MHS552 1 mg weekly s.c. dose for 4 weeks	MHS552 3 mg weekly s.c. dose for 4 weeks
Number of Participants Analyzed [units: participants]	3	3
Area Under serum Concentration-time Curve calculated to the end of a dosing interval (AUCtau) of MHS552 (units: hours*ug/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	NA ± NA[1]	NA ± NA[1]

[1] Due to incomplete PK profiles resulting from concentrations below LLOQ or missed dose due to COVID-19, it was not possible to calculate AUCtau.

Maximum Observed Serum Concentrations (Cmax) of MHS552

Description	Cmax is the maximum (peak) observed serum concentration of MHS552 after dose administration. For MHS552 1mg arm, the majority of MHS552 concentrations were below LLOQ (12.5 ng/mL) making it not possible to calculate Cmax.
Time Frame	Day 1 and Day 22
Analysis Population Description	The PK analysis set included all subjects with at least one available valid PK concentration measurement, who received MHS552 and with no protocol deviations that impact PK data.

	MHS552 1 mg	MHS552 3 mg
Arm/Group Description	MHS552 1 mg weekly s.c. dose for 4 weeks	MHS552 3 mg weekly s.c. dose for 4 weeks
Number of Participants Analyzed [units: participants]	3	3
Maximum Observed Serum Concentrations (Cmax) of MHS552 (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**

Day 1	NA ± NA[1]	57.3 ± 19.0
Day 22	NA ± NA[1]	66.9 ± 2.55

[1] For MHS552 1mg arm, the majority of MHS552 concentrations were below LLOQ (12.5 ng/mL) making it not possible to calculate Cmax.

Time to Reach Maximum Serum Concentrations (Tmax) of MHS552

Description	Tmax is the time to reach maximum (peak) observed serum concentration of MHS552 after dose administration. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.
Time Frame	Day 1 and Day 22
Analysis Population Description	The PK analysis set included all subjects with at least one available valid PK concentration measurement, who received MHS552 and with no protocol deviations that impact PK data.

	MHS552 1 mg	**MHS552 3 mg**
Arm/Group Description	MHS552 1 mg weekly s.c. dose for 4 weeks	MHS552 3 mg weekly s.c. dose for 4 weeks
Number of Participants Analyzed [units: participants]	3	3
Time to Reach Maximum Serum Concentrations (Tmax) of MHS552 (units: hours)	**Median (Full Range)**	**Median (Full Range)**
Day 1	NA (NA to NA)[1]	24.2 (22.7 to 24.6)
Day 22 (n= 3,2)	NA (NA to NA)[1]	25.7 (25.6 to 25.8)

[1] For MHS552 1mg arm, the majority of MHS552 concentrations were below LLOQ (12.5 ng/mL) making it not possible to calculate Tmax.

Safety Results

Time Frame	Adverse events were reported from first dose of study treatment until end of study up to a maximum duration of approx. 78 days. For women of child-bearing potential, pregnancies were reported (if occurred) for up to approx. 106 days after first dose.
Source Vocabulary for Table Default	MedDRA (26.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	MHS552 1 mg N = 3	MHS552 3 mg N = 3	Pooled MHS552 N = 6	Placebo N = 2	All patients N = 8
Arm/Group Description	MHS552 1 mg weekly s.c. dose for 4 weeks	MHS552 3 mg weekly s.c. dose for 4 weeks	MHS552 1 mg and 3 mg weekly s.c. dose for 4 weeks	Placebo weekly s.c. dose for 4 weeks	All patients
Total Number Affected	0	0	0	0	0
Total Number At Risk	3	3	6	2	8

Serious Adverse Events

There were no serious adverse events reported

Other (Not Including Serious) Adverse Events

Frequent Event Reporting Threshold	0%

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	MHS552 1 mg N = 3	MHS552 3 mg N = 3	Pooled MHS552 N = 6	Placebo N = 2	All patients N = 8
Arm/Group Description	MHS552 1 mg weekly s.c. dose for 4 weeks	MHS552 3 mg weekly s.c. dose for 4 weeks	MHS552 1 mg and 3 mg weekly s.c. dose for 4 weeks	Placebo weekly s.c. dose for 4 weeks	All patients
Total # Affected by any Other Adverse Event	2	3	5	2	7
Total # at Risk by any Other Adverse Event	3	3	6	2	8
General disorders and administration site conditions					
Injection site erythema	1 (33.33%)	1 (33.33%)	2 (33.33%)	0 (0.00%)	2 (25.00%)
Injection site reaction	2 (66.67%)	1 (33.33%)	3 (50.00%)	0 (0.00%)	3 (37.50%)
Infections and infestations					
COVID-19	1 (33.33%)	1 (33.33%)	2 (33.33%)	0 (0.00%)	2 (25.00%)
Herpes zoster	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (12.50%)
Hordeolum	0 (0.00%)	1 (33.33%)	1 (16.67%)	0 (0.00%)	1 (12.50%)
Injury, poisoning and procedural complications					
Scratch	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (12.50%)
Nervous system disorders					
Headache	1 (33.33%)	1 (33.33%)	2 (33.33%)	1 (50.00%)	3 (37.50%)
Skin and subcutaneous tissue disorders					
Pruritus	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (12.50%)
Rash	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (12.50%)

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Conclusion:

The primary objective of the study was to assess safety and tolerability of multiple s.c. doses of MHS552 in adults with mild to moderately active SLE. MHS552 administered weekly over 4 doses was safe and well tolerated in adult subjects with active mild to moderate SLE disease after multiple dosing at 1 mg and 3 mg.

Date of Clinical Trial Report

6-March-2024