2 Synopsis

Name of product: MHS552

Protocol identification number: Protocol no. CMHS552A12101, EudraCT no. 2018-004233-33

Title of study: A first-in-human, randomized, subject-blinded, placebo-controlled, single ascending dose study to investigate the safety, tolerability and pharmacokinetics of MHS552 in healthy volunteers

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Study center(s): The Netherlands (1)

Publication (reference): None

Study period

Study initiation date: 08-Oct-2019 (first subject first visit)

Early termination date: 19-Jul-2021

Phase of development (phase of this clinical study): I

Objectives:

Primary Objective	**Endpoint Related to Primary Objective**
To assess the safety and tolerability of MHS552 of single i.v./s.c. doses	All safety endpoints (including physical examination findings, vital signs, ECG parameters, safety laboratory, adverse events)
Secondary Objectives	**Endpoints Related to Secondary Objectives**
To assess the pharmacokinetics (PK) of MHS552 of single i.v./s.c. doses in healthy subjects.	PK parameters of MHS552 after i.v. and s.c. single doses such as Cmax, Tmax, AUClast, AUCinf, T1/2, Vz, CL and other PK parameters as appropriate.
To assess immunogenicity (IG) of MHS552	Anti-drug antibodies against MHS552
Exploratory Objectives	**Endpoints Related to Exploratory Objectives**
To explore the effect of MHS552 on proximal and distal pharmacodynamic (PD) and target engagement markers.	pSTAT5 and IL-2R on different cell types such as Tregs, CD4 non-Treg, CD8, natural killer cells Treg count Soluble CD25 concentrations
To explore the mechanism of action of MHS552.	Endpoints include but are not limited to: Results from immune cell phenotyping including Tregs, Teff, natural killer cells Results from Treg functional assay Results from characterization of the total Treg pool by epigenetic and gene expression analyses Measures of lymphocyte activation
To assess the effects of MHS552 on cytokines and acute phase responses	The endpoints include but are not limited to changes in serum concentrations of IFN-gamma, CXCL10, IL-10, IL-1beta, IL-6, TNF-alpha, IL-5, IL-2
To perform genetic research to investigate drug-related response mechanisms, to better understand the safety and efficacy of MHS552*	Due to the exploratory nature of this objective, endpoints are not predefined.

*No genetic research has been done.

Methodology: This was a single-center, randomized, placebo-controlled, subject-blinded, single-ascending dose study conducted in healthy subjects, in the Netherlands. A total of 60 healthy subjects were enrolled. This study evaluated five single ascending doses of MHS552 (cohorts A1 to A5) administered as an i.v. infusion to healthy subjects. Additionally, three single s.c. doses of MHS552 (cohorts B1 to B3) in healthy subjects were evaluated after the i.v. doses had been tested and established as safe. Based on emerging data, the study also included the option to add up to two additional cohorts (one for each route of administration, A6 and B4) intermediate doses or repeat doses but the maximum dose of MHS552 was not to exceed 90 µg/kg for i.v. dose and 15 mg for s.c. dose.

Number of subjects (planned and analyzed): The study consisted of 8 cohorts: 5 i.v. dose-escalating cohorts (A1 to A5) and 3 s.c. cohorts (B1 to B3). The targeted enrollment in each cohort was 8 subjects randomized in 3:1 (MHS552: placebo) ratio.

5.1.1.c

Diagnosis and main criteria for inclusion:

- Healthy female and male subjects 18 to 45 years of age inclusive, and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram and laboratory tests at screening.
- Subjects must have weighed at least 50 kgs and must have a body mass index (BMI) of 18 - 30 kg/m^2 (inclusive). Subjects in the first cohort A1 must have weighed at least 60 kg.
- At screening, and baseline, vital signs were to be within the following ranges:
  - oral body temperature between 35.0-37.5 °C
  - systolic blood pressure, 90-139 mmHg
  - diastolic blood pressure, 50-89 mmHg
  - pulse rate, 40-90 bpm

Duration of treatment: The investigational drug MHS552, and a matching placebo were administered as a single dose i.v. or s.c. route on Day 1. Within each cohort, subjects were assigned to one of the following two treatment arms in a ratio of 3:1.

- Single i.v. or s.c. dose of MHS552 (dose varied by cohort)
- Single i.v. or s.c. dose of matching placebo

The infusion was administered over a period of 120 minutes.

Test and reference therapies, dose and mode of administration, batch number: The investigational drug, MHS552 vials were packed by Novartis and supplied to the Investigator.

Study drug name	Formulation	Appearance	Unit dose	Packaging	Batch Number
MHS552	5.1.1.c	5.1.1.c	5.1.1.c	5.1.1.c	5.1.1.c
	5.1.1.c				
Placebo	5.1.1.c	5.1.1.c	5.1.1.c	5.1.1.c	5.1.1.c

Criteria for evaluation

Pharmacokinetics: 5.1.1.c

Immunogenicity: 5.1.1.c

Biomarkers: 5.1.1.c

5.1.1.c

Safety: 5.1.1.c

Statistical methods: 5.1.1.c

5.1.1.c

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Summary - Results

Demographic and background characteristics:

5.1.1.c

5.1.1.c

5.1.1.c

5.1.1.c

Pharmacokinetic results:

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Immunogenicity results:

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Biomarker results:

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Safety results:

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Conclusion: The purpose of this FIH study was to assess the safety and tolerability of MHS552 in healthy subjects. In this study, MHS552 up to 90 µg/kg i.v. route and up to 3 mg s.c. route showed good safety and tolerability. Two subjects in the last two s.c. cohorts (one in B2/8 mg and one in B3/15 mg) developed CTCAE Grade 2 hypersensitivity-like reactions, i.e., skin rash, thereby meeting one of the study's pre-specified stopping rules. After a safety review, it was determined that sufficient information on MHS552 including reaching maximal tolerated dose (MTD) was achieved (8 mg) and therefore it would not be necessary to request approval to reopen the study to test additional subjects. The study was then terminated early.

The pharmacokinetic exposure and Treg responses increased with increasing doses and a subcutaneous bioavailability of 27% was calculated across the cohorts. A data review of the grade, time of onset and duration of AEs and the titer, time of onset and duration of anti-MHS552 antibodies, has not shown any clear correlation between development of ADA and safety.

Overall, all the single i.v. doses up to 90 µg/kg of MHS552 and s.c. doses up to 3 mg were safe and well tolerated, with 8 mg s.c. identified as the MTD supporting further development.

History of changes to the synopsis			
Version	**Date (content final)**	**Summary of Changes**	**Change to overall conclusion**
1.0	18-Mar-2022	Original version	