CLINICAL STUDY REPORT SYNOPSIS

Protocol Number: NICCAM-001
EudraCT Number: 2020-002233-15

Name of Sponsor: Charité Research Organisation GmbH Charitéplatz 1 10117 Berlin/Germany	
Name of Finished Product: Niclosamide (Yomesan® Bayer Vital GmbH) 500 mg chewing tablets, and camostat (SAWAI Pharmaceutical Co., Ltd.) 100 mg film-coated tablets	
Name of Active Ingredient: Niclosamide and camostat mesilate	
Title of Study: A randomized, single blind, placebo-controlled, multiple dose, parallel-arm study to investigate the safety and preliminary efficacy of the combination of niclosamide and camostat to treat COVID-19 ("NICCAM")	
Study Centre: Charité Research Organisation GmbH Charitéplatz 1 10117 Berlin/Germany	
Publication (Reference): No publications were available at the time of this clinical trial report	
Studied Period 2021*:* First patient in: 12-MAR-2021 Last patient out: 30-JUN-2021	**Phase of Development**: IIa
Objectives: *Primary:* • To assess the safety and tolerability of treatment combination of niclosamide and camostat in mild and moderately affected COVID-19 patients. *Exploratory:* • To assess the preliminary efficacy ('proof of concept') of treatment combination of niclosamide and camostat in mild and moderately affected COVID-19 patients. • To assess the effect of treatment combination of niclosamide and camostat on viral load in mild and moderately affected COVID-19 patients. • To assess the effect of treatment combination of niclosamide and camostat on biomarkers in mild and moderately affected COVID-19 patients.	
Methodology: This was a randomized, single blind, placebo-controlled, multiple dose, parallel-arm study that investigated the safety and tolerability of treatment combination of niclosamide and camostat in mild and moderately affected COVID-19 patients. Patients were randomized in a 1:1 fashion to receive either treatment combination of niclosamide and camostat or placebo, in fasted state, up to a maximum of 7 days. The treatment was discontinued if subject was transferred to ICU on mechanical ventilation (worsening of the clinical condition), or if subject showed negative viral load twice in a row (improvement of the clinical condition).	

Patients received a single dose of 2000 mg of niclosamide in fasted state, in the morning, and 600 mg of camostat 1 h after niclosamide dosing. Patients received three other doses of 600 mg of camostat in fasted state (fasting for at least 1 h after dosing), at midday, evening and night. Breakfast/meals were served at least 1 h after camostat dosing.

Pharmacokinetic samples were collected at Day 1 pre-dose, 30 min, 1 h, 2 h, 4 h, 6 h and 8 h to determine niclosamide concentration, and pre-dose, 30 min, 1 h, 2 h, and 4 h to determine camostat mesilate concentration. For all other days, only 1 pharmacokinetic sample was collected at pre-dose in fasted state, in the morning.

An independent data safety monitoring committee (DSMC) monitored the patients' safety during the whole period of participation. Follow-up visits via phone interviews were conducted 7 and 14 days after the last dose administration to ensure patients' well-being and to gain additional data.

Number of Subjects:

Forty patients were planned in the study: 20 to receive treatment combination of niclosamide and camostat, and 20 to receive placebo. The study was terminated prematurely due to logistics and recruitment issues. The final sample included 4 patients: 2 received treatment combination of niclosamide and Camostat, and 2 received placebo.

Main Criteria for Inclusion:

- Male and female patients who had a recent positive direct test for SARS-CoV-2.
- Had mild to moderate COVID-19 symptoms with no indication for hospitalization due to SARS-CoV-2 infection (WHO clinical ordinal scale 1-2).
- Between 18 and 70 years of age, inclusive at screening.
- Body mass index (BMI) between 18.0 and 30.0 kg/m^2, inclusive at screening.
- Provided written informed consent to participate in the study.

Main Criteria for Exclusion:

- Patients with severe respiratory symptoms related to COVID-19 that required oxygen or intensive care (high flow oxygen or mechanical ventilation or ECMO).
- Patients with pre-existing pulmonary diseases that required oxygen supply.
- Patients with history of hypersensitivity to camostat or niclosamide or to any ingredients of the two drugs.

Medicinal Product, Dose and Mode of Administration, Batch Number:

Investigational Medicinal Product:

Group 1: combination of niclosamide and camostat

Niclosamide chewing tablets: 2000 mg once daily in fasted state.

Camostat tablets: 600 mg 4-times daily in fasted state.

Yomesan® 500 mg chewing tablets, Batch number: 507574

Camostat® 100 mg film-coated tablets, Batch number 519X03

Duration of Treatment:

Patients received multiple doses of treatment combination of niclosamide and camostat in fasted state up to a maximum of 7 days. The treatment could be discontinued if patient was transferred to the ICU on mechanical ventilation (worsening of the clinical condition), or if patient showed negative viral load twice in a row (improvement of the clinical condition).

Reference Therapy, Dose and Mode of Administration, Batch Number:

Group 2: Placebo tablets 7mm, white, Batch number: 192054 and 192064

Criteria for Evaluation:

Primary endpoints:

Safety of the study was evaluated according to the following parameters:

- Adverse event monitoring – AEs and SAEs.
- Physical examination.
- Vital sign monitoring (systolic and diastolic blood pressure, pulse rate, body temperature, respiratory rate, and oxygen saturation).
- ECG.
- Safety laboratory parameters (hematology, clinical chemistry, coagulation, serology and urinalysis).

Exploratory endpoints:

Efficacy of the study was evaluated as preliminary proof of concept according to the following parameters:

- Time-weighted viral load (SARS-CoV-2) via RT-PCR from throat/nasal swabs.
- WHO ordinal scale for clinical improvement (0 – 8).

Inflammatory biomarker endpoints:

- hs-CRP.
- Ferritin.
- LDH.

Pharmacokinetics endpoints:

Pharmacokinetics samples to determine niclosamide concentration at Day 1 were evaluated according to the following parameters:

- AUC_{0to8}
- C_8
- C_{max}
- T_{max}

Statistical Methods:

Due to the small sample size (N = 4), no statistical analyses were performed on the data. All medical terms reported as adverse events (AE) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Baseline characteristics, safety, efficacy, pharmacodynamics and pharmacokinetics outcomes were summarized for each patient.

Summary - Conclusions:

Due to logistics and subject recruitment issues, the study was terminated prematurely. The final sample included 4 patients, of whom 2 patients received treatment combination of niclosamide chewing tablets and camostat in fasted state, and 2 patients received placebo in fasted state.

Safety results:

In total, 7 TEAEs were reported in 3 patients, of which 4 TEAEs were judged to be related to study medication. All the reported TEAEs were of mild intensity. Two patients who received combination of niclosamide and camostat reported gastrointestinal symptoms which were judged to be related to study medication. No AE led to death or discontinuation of the study.

There were no apparent trend or treatment related changes in haematology, clinical chemistry, physical examination, vital signs and ECG intervals.

Key pharmacokinetic results of niclosamide:

Systemic exposure of niclosamide reached nearly 790 h*ng/mL (i.e. AUC_{0to8}) after 8 h of niclosamide dosing. Absorption was delayed and reached a maximum concentration of approximately 120 ng/mL (i.e. C_{max}) after 7 h (i.e. T_{max}) of niclosamide dosing. Niclosamide concentration was detected after 8 h of niclosamide dosing, and no niclosamide concentration was detected in the plasma after 24 h of niclosamide dosing.

PK parameters	T_{max}	C_{max}	AUC_{0to8}	C_8
Unit	h	ng/mL	h*ng/mL	ng/mL
Patient ID				
10003	6.00	120.10	804.09	94.74
10004	8.00	119.89	774.93	119.89
Mean	7.00	120.00	789.51	107.31
S.D.	1.41	0.15	20.6	17.8
CV%	20.2	0.1	2.6	16.6

Key pharmacodynamic results:

Patients who received treatment combination of niclosamide and camostat showed normal inflammatory levels and slight improvements in inflammatory levels before vs. after treatment. One patient who received placebo showed a gradual decrease in hs-CRP levels during the 7 days of treatment, but not much improvements in other inflammatory levels before vs. after 7 days. Although it is hard to conclude with such a small sample size, treatment combination of niclosamide and camostat did not seem to have an effect on the fluctuations of the inflammatory levels during the 7 days of treatment.

Key preliminary efficacy results:

Regardless of treatment group, all patients showed a significant decrease of viral load after 2-3 days of treatment but PCR status remained positive during the 7 days of treatment. Clinical outcome as measured via WHO ordinal scale for clinical improvement, indicated very mild symptoms that did not impede daily activities throughout the treatment, and there were no fluctuations relating to the treatment.

Conclusions:

The treatment combination of niclosamide and camostat resulted in mild gastrointestinal adverse reactions that stopped as soon as drug administration was stopped, thus providing support that the treatment was safe and well tolerated by COVID-19 patients. However, PK data showed relatively low bioavailability in these patients that did not have an impact on the viral load since all patients, irrespective of treatment group, showed viral load decrement across time.

Date of the Report: 10 MAY 2022