1. Synopsis

Name of Sponsor/Company:	**Name of Active Ingredient:**
MEDITOP Gyógyszeripari Kft.	Ivermectin

Title of Study:

A randomized, double-blind, placebo-controlled study to assess the safety and efficacy of ivermectin in asymptomatic and mild severity COVID-19 patients

Investigators and Study centre(s):

- A/ Dr. Botond Lakatos Dél-pesti Centrumkórház
- B/ Dr. Gabriella Temesi Országos Korányi Pulmonológiai Intézet (Inactive site)
- D/ Dr. István Várkonyi Debreceni Egyetem Kenézy Gyula Egyetemi Kórház
- E/ Dr Eleonóra Harcsa Markhot Ferenc Oktatókórház és Rendelőintézet (Inactive site)
- F/ Dr Judit Simon Családgyógyász Kft. (Inactive site)
- G/ Dr Albert Papp Trial Pharma Kft. Gyula (Inactive site)
- H/ Dr Attila Dombi Trial Pharma Kft. Békéscsaba (Inactive site)
- I/ Dr Erika Unger Trial Pharma Kft. Csorna (Inactive site)
- J/ Dr Enikő Deák Deákpraxis Kft / Trialpharma Kft., Kübekháza Háziorvosi Rendelő (Site was approved but not opened)

Studied period:	**Phase of development:**
First patient first visit: 26/Mar/2021 Last patient last visit: 05/Jul/2021	Phase II

Objectives:

The objective of the study was to evaluate the safety and efficacy of per os ivermectin administration in the treatment of asymptomatic and mild severity SARS-CoV-2 infected patients.

- Primary Objective: To assess the efficacy of per os ivermectin administration in asymptomatic and mild severity SARS-CoV-2 infected patients on reduction of virus load.
- Secondary Efficacy Objective: Assessment of efficacy of per os ivermectin administration in mild severity SARS-CoV-2 infected patients on healing course and post-COVID symptoms.
- Safety Objective: Assessment of safety of per os ivermectin administration in asymptomatic and mild severity SARS-CoV-2 infected patients.

Endpoints:

Primary Endpoint:

- [PRIM] Percentage of SARS-CoV-2 virus copy number at Day 7 compared to baseline (i.e. 100 * (the number of virus copies at Day 7 / number of virus copies at Screening))

Secondary Endpoints:

- [SEC 01] Time to virus clearance, defined as days from randomization (Day 1) to negative SARS-CoV-2 RT-PCR test
- [SEC 02] Time to recovery in patients who have developed symptoms (recovery is defined as absence of any symptoms mentioned under SEC02B...02E by indicating 0 or 1 on each of the relevant scales, and physiological body temperature as per SEC02A)
- [SEC 02A] Time to resolution from fever (oral or tympanic (core body) temperature) ≤ 37.5 °C, axillary, forehead or wrist (surface body) temperature ≤ 37.0 °C for at least 24 hours without antipyretics)
- [SEC 02B] Time course of cough burden - cough remission (reduction on a scale of 0-10, compared to Day 1 baseline)
- [SEC 02C] Time course of dysgeusia-ageusia (reduction on a scale of 0-10, compared to Day 1 baseline)
- [SEC 02D] Time course of anosmia (reduction on a scale of 0-10, compared to Day 1 baseline)
- [SEC 02E] Time course of fatigue (reduction on a scale of 0-10, compared to Day 1 baseline)
- [SEC 03] Percentage of patients with hospitalization due to progression of COVID-19
- [SEC 04] Absenteeism, by self-reporting, expressed in days absent from workplace, due to COVID-19
- [SEC 05] Presence of post-COVID symptoms reported by the patient at D28

Safety Endpoint:

- [SAF 01] Monitoring Adverse Events, safety laboratory and other safety parameters

Number of patients (planned and analysed):

A total of 70 patients were planned to be enrolled to the study. During the course of the study 11 patients were screened, 10 randomised.

Diagnosis and main criteria for inclusion:

- Ambulatory patients with confirmed SARS-CoV-2 infection by rapid antigen test OR polymerase chain reaction (PCR), regardless whether they show symptoms or are asymptomatic
- Mild cases: NO dyspnoe and NO tachypnoe (respiratory rate <22 / min), NO need for oxygen-supplementation
- Patients at high risk for developing severe COVID-19 case can be enrolled if they are vaccinated and the last dose was given not more than 6 months before screening.

Test product, dose and mode of administration, batch number:

There were two treatment groups, randomized in a 1:1 ratio to receive ivermectin or matching placebo.

- Ivermectin (per os tablets), dose: 5 x 3 mg tablets once daily, batch number: T015953, U009738

Duration of treatment:

4 days

Reference therapy, dose and mode of administration, batch number

- Placebo (per os tablets), dose: 5 x 3 mg tablets once daily; batch number: IP12002A

Statistical methods:

Justification of sample size:

This was an exploratory study, no formal statistical hypothesis was tested.

The planned sample size was calculated to be sufficient to achieve at least 80% power if the effect size is not smaller than 0.34.

Efficacy:

The statistical analysis was performed without formal hypothesis testing, resulting p-values were interpreted in a descriptive manner.

Primary analysis:

The primary analysis was planned to be performed on the modified-ITT population

The primary endpoint of this study was the percentage of virus copy number at Day7 compared to baseline (i.e. 100*(the number of virus copies at Day7/number of virus copies at Screening)).

Secondary analysis:

Results of the statistical tests applied during the secondary efficacy analysis were to be interpreted in a descriptive manner including the calculation of the 95% confidence intervals where applicable. Time course of COVID-19 symptoms were planned to be analyzed by MMRM model and descriptive statistical tools. Graphical representation of the scores over time will also be provided.

Safety:

Adverse events that occur during the study were to be recorded and coded according to MedDRA. Each AE would be counted once only for a given participant. The number and frequency of adverse events (AE), serious adverse events (SAE) and the proportion of patients experiencing an adverse event by treatment group, as well as severity, study drug association, and outcome, would be provided. AEs and SAEs were to be summarized by SOC and PT, as well.

Frequency of adverse events were to be compared between treatment groups by chi-square tests.

Summary – Conclusions

The study was initially authorized on 03rd March 2021.

The first three study sites were opened by 9th March 2021.

The study sites did not start patient recruitment due to the difficult conditions and increased burden of the epidemiological situation. Only 11 patients were screened, 10 were included in the study by Autumn 2021.

In December 2021 the initial 3 study sites were closed and 5 new study sites were selected. During the summer of 2022 COVID case numbers greatly deteriorated, and no patients were enrolled.

In November 2022 the Sponsor suspended enrollment and on 16th January 2023 decided to terminate the study due to lack of enrolment.

The study database contained data on 11 people, 10 of whom were enrolled. The statistical analyses include data only on the patients enrolled.

Due to the high number of major PDs, especially on eligibility criteria, and critical PD about data quality and the low number of patients, patients were excluded from all efficacy analyses, only safety objectives were analysed. Efficacy endpoints that can be considered as safety endpoints were analysed within safety analysis.

Efficacy Results:

No efficacy analysis was performed.

Safety Results:

The number of patients with at least one adverse event was two (33.3%) in the placebo group and one (25.0%) in the ivermectin group

All events were categorized as mild, no events terminated in drug withdrawn or drug interrupted was reported. All of the patients with AE were recovered and causal relationship with study drug was not reported.

The number of patients with at least one serious adverse event was one (16.7%) in the placebo group. It was a progression of COVID-19 infection. The patient recovered.

There was no serious adverse event registered in the ivermectin group.

Conclusion

Due to the low patient number it is impossible to draw any conclusion, no safety concerns were raised by the study.

Date of report

26/Jun/2023