Clinical study protocol

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

Protocol No.: IVM-2021-01; Protocol version: 1.1; Protocol Date: 03 FEB 2021

Sponsor: MEDITOP Pharmaceutical Ltd.

EUDRA CT №: 2021-000166-15

2021

This Protocol contains 78 numbered pages

1 Table of contents

2 Study synopsis

Name of Sponsor:	MEDITOP Pharmaceutical Ltd.
Study code:	Protocol No.: IVM-2021-01; Protocol version: 1.1; Protocol Date: 03 FEB 2021
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***
Study-related main facilities and site(s):	**Sponsor:** MEDITOP Gyógyszeripari Kft. 2097 Pilisborosjenő, Ady Endre utca 1. **CRO (medical writing, regulatory affairs, monitoring, medical monitoring):** CPS Cortex Kft. H-1051 Budapest, József nádor tér 5-6. **Biometry / data management:** Adware Research Kft. H-8230 Balatonfüred, Völgy u. 41. **Clinical study sites:** 3 (three) sites in Hungary
Phase of development:	Phase II
Objectives:	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. Safety Objective: Assessment of safety of per os ivermectin administration in asymptomatic and mild severity SARS-CoV-2 infected patients. For study endpoints, please refer to Synopsis section *"Criteria for evaluation".*
Study design:	This is a randomized, double-blind, placebo-controlled study with per os ivermectin or placebo treatment.
Study and dose rationale:	In December, 2019, Wuhan city, the capital of Hubei province in China, became the centre of an outbreak of pneumonia of unknown cause. By January 2020, Chinese scientists had isolated a novel Coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), from these patients with virus-infected pneumonia, which pathology was later designated as Coronavirus Disease 2019 (COVID-19) in February 2020 by WHO.The COVID-19 pandemic is pushing the limits of hospital care capacities worldwide, including in Hungary. Prolonged hospitalization of patients in severe conditions requiring intensive care followed by invasive ventilation for up to weeks; high mortality rates; possible long-term damage to health - predominantly young / middle-aged patients infected by Sars-CoV-2 showing long-term, persistently debilitating post-COVID-19 symptomatology; individually, but especially in combination, they require drug therapy that can help to avoid hospitalization and reduce health and economic burden of COVID-19. These therapeutic needs clearly cannot be met by the

drugs and treatment regimens currently used for COVID-19 therapy. Thus, there remains an urgent need for effective drugs for prevention and treatment of COVID-19 infections.

SARS-CoV-2 pathogenesis is triggered by viral infection, and amplified by inflammation and dysfunctional immune responses. Antiviral agents or cytokine inhibitors are routinely used to treat the already high viral load and hyperinflammatory syndrome, the "cytokine storm". Both approaches can be strongly criticized: either eliminating high virus levels or overcoming a severe condition are rather challenging, and pose a tangible pharmaceutical and clinical hardship. In addition, effectiveness of cytokine storm-based treatments may be limited ab ovo. Whether cytokine storm plays a role in COVID-19-induced organ dysfunction at all is questionable {Leisman et al, Lancet Respir Med, October 2020, https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30404-5/fulltext#%20}. Functional evaluation of immune system of COVID-patients also supports the hypothesis that severe suppression of host functional adaptive and innate immunity and not a cytokine storm characterizes majority of COVID-infections {Remy et al. JCI insight, July 2020, https://jci.me/140329/pdf}. Accordingly, and not surprisingly, selective cytokine inhibitors may fail to improve symptoms, and immunsuppressive therapy may further worsen the condition of patients.

We have come to the conclusion that it is worth exploring a new therapeutic paradigm. Namely, a multiple targeting drug that has a complex mode of action, including i) a robust antiviral effect, preferably from the host side (to minimize the development of viral resistance), ii) an immunmodulant (not immunsuppressant!) effect together with iii) a finely tuned, complex anti-inflammatory action. Ivermectin (IVM) may be suitable for these purposes. It has been in clinical use for a long time (veterinary: since 1981; human: since 1987) as an orally and topically active agent for treating a range of parasitic infections in both animals and humans. Thus, the pharmacodynamic, ADME and safety profiles of IVM are well studied and characterized. In fact, there are currently almost 50 clinical trials worldwide (www.clinicaltrials.gov) to investigate the possible role of IVM in COVID-19 therapy from prevention to late stage treatments. IVM has a complex mode of action that is fundamentally different from the agents used in COVID to date.

- IVM shows a significant, robust, dose-dependent in vitro antiviral effect against SARS-2 (infected VERO cells), based on its ability to inhibit binding of host importin protein (IMP) to some viral proteins. This action inhibits delivery of viral proteins to nucleus and leads to blockade of the viral infectious cycle.
- IVM is a positive allosteric effector of the alpha7 neuronal nicotinic acetylcholine receptor, which may contribute to both immunmodulant and antiinflammatory effects. In addition, its immunmodulant effect may be mediated via T-helper lymphocytes, whereas its complex antiinflammatory action, providing a wide scope, can also be interpreted by other mechanism components.
- Doses up to 2000 μg/kg are well tolerated in patients with parasitic infections, with analysis of the first 11 years of mass global IVM (Mectizan) administration indicating a cumulative incidence of one serious adverse side effect case per million. Although drug resistance can occur in animals, no resistance in humans has yet been confirmed in over 25 years.
- The risk of mechanism-based central nervous system (CNS) side effects of IVM can be minimized by considering that such effects may originate from the human counterpart of the antiparasitic GABA-receptor based action and can only occur in the case of a damaged blood brain barrier (BBB) (N.B. IVM does not cross intact BBB by passive diffusion).
- Furthermore, adverse events originating from IVM's modulatory effect on several drug transporters and CYP enzymes, can be avoided by excluding concomitant use of certain drugs.

Beyond the usual dose range of up to 200 μg/kg ivermectin, which has a well-documented and

	very favorable safety profile, doses up to 10 times the 200 μg/kg dose were evaluated by Guzzo et al {J Clin Pharmacol, 2002;42:1122-1133} to provide a substantial safety margin over the anticipated dosage range in a double-blind, placebo-controlled, multiple rising dose study in healthy adult men and women. Of the 51 subjects who received ivermectin, 12 subjects (24%) reported at least one clinical adverse experience. This rate was similar to that observed in the placebo group (6 subjects, 35%). In addition, there was no consistent trend in the incidence of adverse experiences indicative of a dose response. All clinical adverse experiences were transient and mild, and no adverse experience recurred with repeated dosing. The most commonly reported adverse experiences were headache, nausea, dizziness, and rash, occurring in both ivermectin- and placebo-treated groups. A fixed and high dose regimen which takes advantage of the wide therapeutic index of IVM is an attractive alternative for improving the distribution and therefore potentially increasing coverage rates of treatment campaigns. A healthy volunteer pharmacokinetic study was designed by Munoz et al {PLoS Negl Trop Dis 12(1): e0006020} to evaluate the safety and pharmacokinetic profile of 3 dosing regimens - 2 experimental treatments using a new 18 mg ivermectin tablet in a fixed-dose strategy of 18 and 36 mg single dose regimens, compared to the standard, weight based 150–200 μg/kg, regimen - of IVM in 54 healthy adult volunteers stratified in 3 weight groups in an open-label, randomized, crossover phase I clinical trial performed under fasting conditions. No abnormal result or significant differences were found between biochemistry at baseline and after the administration of IVM in any of the three study arms. A slight decrease in Haemoglobin (Hb) levels was observed after administration of IVM in the three study arms. The main electrocardiographic parameters were not affected by the administration of IVM. Systemic blood pressure measurements were not affected by treatment administration. A total of 33 treatment emergent adverse events were reported by 22 subjects who received at least one dose of the study medication. No significant association was found between the distribution of adverse events and the three treatments arms. Clinical trials of COVID-19 worldwide employing ivermectin alone or in combination utilize a wide range of regimens, starting from the single dose application, up to a 5-day schedule. Weighing in that IVM favorably accumulates in the respiratory tract tissue, we have decided to employ a daily once 15 mg fixed dose, 4-day regimen to build up steady state conditions, targeting high efficiency of IVM for combatting the COVID-19 infection and providing an early virus clearance.
Benefit-risk assessment:	Since no “gold-standard” therapy exists as yet to treat COVID-19 patients, several therapeutical approaches are being employed both in everyday practice, and also in the domain of clinical research. We chose a novel, multi-targeting approach to the treatment of COVID-19, combining antiviral, immunmodulant and antiinflammatory components in a single molecule with ivermectin, which has a well-established safety profile in parasitic diseases. Together, these may provide a very favorable benefit-to-risk ratio of achieving early virus-elimination in COVID-19 patients. As special safeguards, we exclude individuals from the trial with 1. particular central nervous system interventions and disorders, which may cause breakdown the blood-brain-barrier (BBB) and result in transport of IVM to brain: encephalitis, meningitis, stroke (acute, subacute), lumbal puncture, epidural and spinal anaesthesia within 2 months of randomization; neurodegenerative conditions; 2. concomitant medication which interferes with CYP3A4 or the membrane drug transporters (P-gp, BCRP).

Study duration:	Screening period may last up to 3 days (D-3 … D1). If appropriate (e.g. study entry can be warranted upon positive rapid SARS-CoV-2 antigen test), the screening visit can be considered also as Day 1, start of IMP administration. In this case, activities applicable for both Screening and Day 1 will be conducted only once and results will be captured as data pertaning to Day 1. Treatment with ivermectin or matching placebo will be administered for 4 days as a once-daily dose regimen (D1-D4). Follow-up period (with safety and efficacy assessments) will last 21 days, from treatment initiation (D1-D21).. The visits will be conducted at the domicile (or at the designated quarantine location) of the study subjects, or ambulantory at the study sites while fully adhering to pertinent infection-control quarantine regulations.
Treatment groups:	Total number of randomized patients: 70. Two treatment groups, randomized in a 1:1 ratio to ivermectin or matching placebo. No standard of care COVID-19 therapies are allowed. For symptomatic relief of e.g. fever, sore throat, e.g. antipyretics, analgesics may be used concomitantly.
Study treatment:	***Ivermectin:*** 15 mg (5 x 3 mg tablets), once daily, per os, for 4 (four) consecutive days ***Placebo:*** Placebo dosing schedule will be the same as with the active ingredient, to fulfil double-blind nature of dose administrations: once daily, for 4 (four) days.
Study population:	***Key attributes:*** • 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 ***Inclusion criteria:*** • Males and females 18-75 years of age • 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 • Asymptomatic or mild COVID-19 cases: NO dyspnoe and NO tachypnoe (respiratory rate <22 / min), NO need for oxygen-supplementation; NO radiological findings of pneumonia (NB. No medical imaging will be conducted within the frames of the study. If previous medical imaging report is available, its result will be however utilized.) • Build: $20 \leq BMI \leq 28$ kg/m2 • Subjects who are able to communicate with the Investigator and research staff, who understand the study, are able to comply with all study procedures, and willing to provide written informed consent prior to the screening examinations NB. Women of childbearing potential should agree to use a highly effective method of contraception throughout the study and up to 1 month afterwards. Male subjects shall agree to effective contraception during the study and for 14 days following the last drug administration.

Exclusion criteria:

• Moderate COVID-19 cases: showing dyspnoe and / or tachypnoe, or a need for oxygen-supplementation, or radiological findings of pneumonia. {Definition of moderate COVID-19 as per "Magyar Koronavírus Kézikönyv", "Igazolt COVID-19 fertőzött felnőtt betegek rizikóstratifikációja" fejezet (Hungarian Coronavirus Manual, Section "Risk stratification of confirmed adult COVID-19 patients") } Radiological findings – established either by chest X-ray or native chest (pulmonary) CT scan - include multiplex consolidations and milk-glassy haze, often in a bilateral distribution.

• Severe COVID-19: respiratory distress - respiratory rate ≥ 30/min; or oxygen saturation at rest ≤ 93%; or pulmonary infiltrates occupy > 50% of the lung-fields

• Critical COVID-19: acute respiratory distress; or requiring mechanical ventilation; or radiomorphology of ARDS; or shock, including septic shock; or other organ dysfunction necessitating ICU admission

• High-risk patient for progression of COVID-19, as defined by having a calculated pneumonia PORT-score of > 90

• Concomitant or previous administration of any experimental, non-established COVID-19 therapy, either in off-label indication of a registered medicinal product or as a non-registered drug candidate in a clinical trial setting or compassionate use program (or equivalents thereof)

• NO previous COVID-19 therapies allowed, as per recommendation of the "Magyar Koronavírus Kézikönyv" (Hungarian Coronavirus Manual)

• Concomitant administration of coumarin-derivatives or warfarin

• Concomitant administration of cytochrom-P450 or membrane drug transporter, especially ABCB1/P-gp and ABCG2/BCRP (breast cancer resistance protein) modifiers

• Any clinically significant abnormality identified during screening full physical examination, vital signs, laboratory tests and ECG which is deemed by the investigator to be incompatible / inappropriate for study participation

• A current or recent history of drug or substance abuse, including alcohol (> 14 units per week), within 3 months prior to screening (one unit of alcohol equals ½ pint [285 mL] of beer or lager, one glass [125 mL] of wine, or one shot [25 mL] of spirits)

• Patients who regularly consume more than 4 cups daily of beverage containing caffeine

• Current strong smoker as defined by smoking over 10 cigarettes a day, or its equivalent

• Positive pregnancy test result for women with childbearing potential at screening

• Women who are pregnant or nursing, or who are planning to get pregnant within 3 months after the last dose of study drug

• A history of allergy, intolerance or sensitivity to ivermectin or any component of the study drug formulation

• Exhibiting any pathology, contraindicated with ivermectin administration: e.g. asthma, clinically significant hepatic diseases, human immunodeficiency virus (HIV) infection, immunosuppression, onchodermatitis, Loa loa infection

• Have undergone surgery or have donated blood within 12 weeks prior to the start of the study

• A history of bleeding diathesis or other bleeding disorders

• Investigational drug administration or investigational device application within 1 month preceding study entry, or within 5 terminal half-life of the investigational drug of the previous study, whichever is the longer

• A history of malignancy within 5 years from screening visit, with the exception of resected basal cell carcinoma or squamous cell carcinoma of the skin, or resected cervical intraepithelial neoplasia

• Particular central nervous system interventions and disorders, which may cause breakdown of the blood-brain-barrier (BBB) and result in transport of IVM to brain: encephalitis, meningitis, stroke (acute, subacute), lumbar puncture, epidural and spinal anaesthesia within 2 months of randomization; neurodegenerative conditions (e.g. Alzheimer's disease, Parkinson's

	disease, Huntington disease, amyotrophic lateral sclerosis); multiple sclerosis, HIV-1-associated dementia and chronic traumatic encephalopathy) ***Prohibited concomitant medications:*** • Coumarin-derivatives and warfarin • CYP3A4 modulators (substrates, inhibitors, inducers) according to: "Cytochrome P450 3A4 and 3A5 Known Drug Interaction Chart", https://www.mayocliniclabs.com/it-mmfiles/Cytochrome_P450_3A4_and_3A5_Known_Drug_Interaction_Chart.pdf • Membrane drug transporter P-gp / MDR modulators, according to:"Inhibitors and inducers of P-glycoprotein", https://www.uptodate.com/contents/image/print?imageKey=EM%2F73326&topicKey=RHEUM%2F1666&source=see_link • BCRP modulators (substrates, inhibitors) according to: Table I and Table II of "Role of the Breast Cancer Resistance Protein (BCRP/ABCG2) in Drug Transport—an Update" , AAPS J. 2015 Jan; 17(1): 65–82. doi: 10.1208/s12248-014-9668-6 Please Refer to Appendix 2 for a complete listing of respective prohibited concomitant medication.
Lifestyle regulations:	• Consumption of alcohol, papaverous food, citrus (orange, grapefruit) and their juices will be prohibited 48 hours prior to treatment start until the last follow-up visit • Xanthine-containing beverages and food (e.g. caffeine-containing beverages: coffee, tea, cola, energy drinks; chocolate, cocoa) can be consumed responsibly, not exceeding 4 cups daily of beverage containing caffeine • Consumption of drugs-of-abuse is prohibited, unless with medical intent (e.g. benzodiazepines for anxiety)
Assessments:	***Safety:*** • Demographics and medical history • Body height and weight, calculation of Body Mass Index (BMI) • Physical examination • Vital signs (heart rate, blood pressure) (supine position) • Electrocardiogram • Hemostasis lab panel: Prothrombin time (PT), Partial Thromboplastin Time (PTT), D-dimer • Hematology lab panel: Complete blood cell count, differential blood count, hemoglobin concentration, hematocrit, erythrocyte sedimentation rate • Blood chemistry: Sodium, potassium, chloride, magnesium, calcium, phosphorous, blood urea, creatinine, eGFR, glucose, uric acid, total bilirubin, total protein, albumin, gamma-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, creatinine phosphokinase, C-reactive protein, ferritin • Urine drug test and alcohol breath test • Urine pregnancy test • Urinalysis: specific gravity, pH, glucose, protein, ketones, bacteria / nitrites, bilirubin, urobilinogen, blood, sediment, urinary sodium, urinary creatinine • Adverse events ***Efficacy:*** • SARS-CoV-2 nucleic acid by quantitative RT-PCR • Respiration rate (supine position) • Tympanic temperature (supine position) • Cough burden scale • Dysgeusia-ageusia scale • Anosmia scale

	• Fatigue scale
Criteria for evaluation:	***Objectives:*** 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. 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 (absence of any symptoms mentioned under SEC02B...02E, and physiological body temperature as per SEC02A) • [SEC 02A] Time to resolution from fever (tympanic temperature ≤ 37.5 °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 Safety Endpoint: • [SAF 01] Monitoring Adverse Events, safety laboratory and other safety parameters
Statistical methods:	***Justification of sample size:*** Total number of patients: 70 (35-35 for the ivermectin and placebo treatment arms). This amount has been established empirically – no formal sample size calculation has been conducted. ***Efficacy:*** The statistical analysis will be performed without formal hypothesis testing, resulting p-values will be interpreted in a descriptive manner. Primary analysis: The primary analysis will be performed on the modified-ITT population The primary endpoint of this study is 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)).

	The primary endpoint will be analyzed using ANCOVA model including treatment as fix factor and baseline virus copy number as a covariate. Change from baseline (LSMeans) and 95% confidence intervals will be given by treatment group. If the planned model does not fit well, the empirical mean differences with their 95% confidence intervals between treatment groups will be estimated separately at each time point. Patients with negative PCR results will be imputed with 0. Secondary analysis: The primary analysis will be repeated on the modified-ITT population with missing data imputation and also on the PP population. The analysis of [SEC 01] will be performed on the modified-ITT population and repeated on the PP population. All other secondary analysis will be performed on the ITT population and repeated on the PP population. Results of the statistical tests applied during the secondary efficacy analysis will be interpreted in a descriptive manner. Time to viral clearance and time to recovery will also be characterized using descriptive statistical methods including the calculation of the 95% confidence intervals. Median time to viral clearance and median time to recovery in treatment groups will be compared by log-rank test. Cox regression model will be applied to investigate possible significant factors influencing the time to viral clearance/recovery. Time course of COVID-19 symptoms will be analyzed by MMRM model and descriptive statistical tools. Graphical representation of the scores over time will also be provided. Ratio of hospitalized patients and the 95% confidence interval will be given by treatment group. Ratios will be compared by chi-square test. Absenteeism will be characterized using descriptive statistical methods including the number of cases, mean, standard deviation, median, minimum and maximum values. Absenteeism will be compared by t-test. ***Safety:*** Adverse events that occur during the study will be recorded and coded according to MedDRA. Each AE will 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, will be provided. AEs and SAEs will be summarized by SOC and PT, as well. Frequency of adverse events will be compared between treatment groups by chi-square tests.

3 Study flowchart

Study Procedures	**Screening # (Day -3 to Day 1)**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 7 ± 1 day**	**Day 10 ± 1 day**	**Day 14 ± 1 day**	**Day 18 ± 1 day**	**Day 21 ± 1 day**
Informed Consent	X									
Eligibility Review and Confirmation		X								
Randomization		X								
Medical History / Demography	X									
Physical Examination	X	X				X		X		X
Body height, BMI	X									
Body weight	X					X		X		X
Vital Signs *	X	X			X	X	X	X	X	X
ECG	X	X								X
Urine Pregnancy test (WCBP only)		X (pre-dose)								
Drug Screen, Alcohol Breathalyzer		(X) (pre-dose)								
Blood Chemistry & Hematology **	X	(X)				X		X		X
Urinalysis †	X	(X)				X		X		X
AEs / Concomitant medication	X	X	X	X	X	X	X	X	X	X
SARS-CoV-2 nucleic acid by RT-PCR ††	X (N.B. Upon screening only, for study entry: SARS-CoV-2 rapid antigen test can be utilized in parallel with RT-PCR !)	(X)			X	X	X	X	X	X
Cough burden (scale) †††		X			X	X	X	X	X	X
Dysgeusia-ageusia (scale) †††		X			X	X	X	X	X	X
Anosmia (scale) †††		X			X	X	X	X	X	X
Fatigue (scale) †††		X			X	X	X	X	X	X
Study drug administration §		X	X	X	X					

Notes:

If appropriate (e.g. study entry established with positive rapid SARS-CoV-2 antigen test), the screening visit can be considered also as Day 1, start of IMP administration. In this case, activities applicable for both Screening and Day 1 will be conducted only once and results will be captured as data pertaning to Day 1.

* Vital signs: Heart rate, blood pressure, respiration rate, tympanic body temperature, determined in supine position.

** Blood Chemistry & Hematology & Coagulation: Prothrombin time (PT), Partial Thromboplastin Time (PTT); Complete blood cell count, differential blood count, hemoglobin concentration, hematocrit, erythrocyte sedimentation rate; Sodium, potassium, chloride, magnesium, calcium, phosphorous, blood urea, creatinine, eGFR, glucose, uric acid, total bilirubin, total protein, albumin, gamma-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, creatinine phosphokinase, C-reactive protein, ferritin

† Urinalysis: specific gravity, pH, glucose, protein, ketones, bacteria / nitrites, bilirubin, urobilinogen, blood, sediment, urinary sodium, urinary creatinine.

†† SARS-CoV-2 nucleic acid by quantitative RT-PCR: Mandatory for baseline determination either during screening or on Day 1 (if study entry is based upon SARS-CoV-2 rapid antigen test during screening!). If study entry was warranted by rapid antigen test from Screening AND Day 1 RT-PCR test is negative, the RT-PCR test should be repeated as soon as possible, to provide a potentially meaningful baseline virus copy number. If the repeated Day 1 RT-PCR test (captured with its eventual date as Day 1, even if it is later then Day it) is still negative, the patient will still remain on study, randomized and provided with appropriate study medication.
At any other time points, as indicated by the flowchart, sampling for SARS-CoV-2 nucleic acid is mandatory ONLY if viral clearance (i.e. negativity) has not been established upon the PREVIOUS PCR testing.

††† Symptomata-scales (cough burden, dysgeusia-ageusia, anosmia and fatigue): Valid value set is 0..10. A value of 0 (zero) represents absence of the concerned symptom. A value between 1..10 represents manifestation of the symptom, increasing intensity from the minimum (“just a hint of”) 1, up to the maximum (“unbearable”) intensity of 10.

§ Study drug administration: Study drugs will be self-administered. Self-administration will be documented by the patient in the provided Subject Diary.

4 Study approval form

Protocol title:

A randomized, double-blind, placebo-controlled study to assess the safety and efficacy of ivermectin in asymptomatic and mild severity COVID-19 patients
(Protocol No.: IVM-2021-01; Protocol version: 1.1; Protocol Date: 03 FEB 2021)

STATEMENT OF THE SPONSOR

This Study Protocol has been reviewed by the representatives of the Sponsor listed as below. Any modification to the Protocol has to be documented in writing, and agreed upon by the Sponsor and Investigator and should be approved by the competent authority.

_____ *Management Representative* MEDITOP Pharmaceutical Ltd.	**_____ . _____ . _____ (dd.MMM.yyyy)**

Protocol title:

A randomized, double-blind, placebo-controlled study to assess the safety and efficacy of ivermectin in asymptomatic and mild severity COVID-19 patients (Protocol No.: IVM-2021-01; Protocol version: 1.1; Protocol Date: 03 FEB 2021)

STATEMENT OF THE INVESTIGATOR

I have read this protocol, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent. I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, Good Clinical Practice [ICH E6 (R2)], and applicable regional regulatory requirements. I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as an Investigator as provided by the Sponsor. I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

_____ *Principal Investigator* Name: _____ Affiliation: _____ _____	**_____ . _____ . _____ (dd.MMM.yyyy)**

5 Abbreviations and terms

Abbreviation	Definition
#	number
ACE2	Angiotensin-Converting Enzyme 2
ADME	Absroption-Distribution-Metabolism-Excretion
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALI	Acute Lung Injury
ALT	Serum Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ARDS	Acute Respiratory Distress Syndrome
ASA	Acetylsalicylic Acid
AST	Serum Aspartate Aminotransferase
AUC	Area Under the time-concentration Curve
AZT	Azidothymidine
BID	Bis In Die
BMI	Body Mass Index
BCRP	Breast Cancer Resistance Protein
CDC	Centers for Disease Control and Prevention
CK	Creatine Kinase
CNS	Central Nervous System
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organisation
CRP	C-Reactive Protein
CRS	Cytokine Release Syndrome
CT	Computed Tomography
CYP	Cytochrome P450
CXCL	Chemokine (C-X-C motif) Ligand
DENV	Dengue virus
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonucleic Acid
DILI	Drug-Induced Liver Injury
(e)CRF	Electronic Case Report Form
ECG	Electrocardiogram
ER	Endoplasmic Reticulum
ESR	Erythrocyte Sedimentation Rate
FSH	Follicle Stimulating Hormone
GABA	Gamma-Aminobutyric Acid
GGT	Gamma-Glutamyl Transferase
GCP	Good Clinical Practice
GP	General Practitioner (Family Doctor)
HCV	Hepatitis C Virus

Abbreviation	Definition
HIV	Human Immunodeficiency Virus
HLT	High Level Term
HLGT	High Level Group Term
HRT	Hormone Replacement Therapy
ICF	Informed Consent Form
ICH	International Conference of Harmonization
ID	Identification number / code
IFN	Interferon
IL	Interleukin
IMP	Importin
IMP	Investigational Medical Product
IRB	Institutional Review Board
ITT	Intention-to-treat
IVM	Ivermectin
LPS	Lipopolysaccharide
MCP	Monocyte Chemoattractant Protein
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MIP	Macrophage Inflammatory Protein
MMRM	Mixed Model for Repeated Measures
MOI	Multiplicity Of Infection
NF-κB	Nuclear Factor Kappa B
NSAID	Nonsteroidal Anti-Inflammatory Drug
PAI	Plasminogen Activator Inhibitor
Pgp	P-glycoprotein
PP	Per-protocol
PRO	Patient-Reported Outcome
PT	Preferred Term
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RT-PCR	Real-Time Reverse Transcription Polymerase Chain Reaction
SOC	System Organ Class
RA	Regulatory Authority
RNA	Ribonucleic Acid
RR	Risk Ratio
SAE	Serious Adverse Event
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
siRNA	Small Interfering RNA
SOC	System Organ Class
STAT	Signal Transducer and Activator of Transcription
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent Adverse Event
TLR	Toll-like Receptor
TMPRSS2	Transmembrane Protease / Serine Subfamily Member 2
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal
WHO	World Health Organization

6 Facilities related to the clinical study

Sponsor	
Institution	MEDITOP Gyógyszeripari Kft.
Address	2097 Pilisborosjenő, Ady Endre utca 1.
Medical Monitor	Dr. Szabó Krisztina, Pharma Regist Kft.
Email	krisztina.szabo@pharmaregist.hu
Mobile	+36 30 280 5837
CRO	
Institution	CPS Cortex Kft.
Address	H-1051 Budapest, József nádor tér 5-6.
Phone	+36 1 202 4705
Telefax	+36 1 202 4989
Contact person	Dr. István Boglárka
Email	boglarka.istvan@cortexps.hu
Mobile	+36 70 312 7220
Safety Laboratory	Local laboratories of the study sites will be used for safety lab assessments.
PCR Laboratory	
Institution	Corden International (Magyarország) Kft
Address	1117 Budapest, Fehérvári út 84./A.
Phone	+36 30/287-36-56
Contact person	Kócse Ramóna
Email	rkocse@corden.hu
Data Management / Biostatistics	
Institution	Adware Research Kft.
Address	H-8230, Balatonfüred, Völgy u. 41.
Phone	+36 87 789 073
Contact person	Dr. Papp Zsuzsanna
Email	zsuzsa.papp@adwareresearch.com
Mobile	+36 20 942 5628
Pharmacovigilance (SAE) contact	
Institution	MEDITOP Gyógyszeripari Kft.
Address	2097 Pilisborosjenő, Ady Endre utca 1.
Phone	+36 30 235 8994
Telefax	+36 26 336 041
Contact person	Dr Csóka Gabriella
Email	mellekhatas.bejelentes@meditop.hu

7 Background

7.1 Severe Acute Respiratory Syndrome Coronavirus infections – Epidemiology

In December, 2019, Wuhan city, the capital of Hubei province in China, became the centre of an outbreak of pneumonia of unknown cause. By Jan 7, 2020, Chinese scientists had isolated a novel Coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (***SARS-CoV-2***), from these patients with virus-infected pneumonia, which pathology was later designated as Coronavirus Disease 2019 (***COVID-19***) in February, 2020, by WHO. [Zhou]
Since 31 December 2019 and as of 14 December 2020, 71 503 614 cases of COVID-19 (in accordance with the applied case definitions and testing strategies in the affected countries) have been reported, including 1 612 833 deaths. [CDC]
Since the first reports of cases from Wuhan, a city in the Hubei Province of China, at the end of 2019, cases have been reported in all continents, except for Antarctica. The reported case counts underestimate the overall burden of COVID-19, as only a fraction of acute infections are diagnosed and reported. Seroprevalence surveys in the United States and Europe have suggested that after accounting for potential false positives or negatives, the rate of prior exposure to SARS-CoV-2, as reflected by seropositivity, exceeds the incidence of reported cases by approximately 10-fold or more. [McIntosh]

7.2 Pathophysiology – virus lifecycle

Coronaviruses are enveloped positive-stranded RNA viruses. Full-genome sequencing and phylogenic analysis indicated that the coronavirus that causes COVID-19 is a betacoronavirus in the same subgenus as the severe acute respiratory syndrome (SARS) virus (as well as several bat coronaviruses), but in a different clade. The Coronavirus Study Group of the International Committee on Taxonomy of Viruses has proposed that this virus be designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The Middle East respiratory syndrome (MERS-CoV) virus, another betacoronavirus, appears more distantly related. The closest RNA sequence similarity is to two bat coronaviruses, and it appears likely that bats were the primary source; whether COVID-19 virus was transmitted directly from bats or through some other mechanism (e.g. through an intermediate host) is unknown. The coronaviruses are made up of non-structural and structural proteins, which are typically used for replicating itself by different enzymes and transcription factors. Four structural proteins, namely, the spike (S), membrane (M), envelop (E) and nucleocapsid (N) proteins are distinguished. The S protein is seen to be protruding from the viral surface and is the most important one for host attachment and penetration. This protein is composed of two functional subunits (S1 and S2), among which S1 is responsible for binding to the host cell receptor and S2 subunit plays a role in the fusion of viral and host cellular membranes.
The host receptor for SARS-CoV-2 cell entry is the same as for SARS-CoV, the angiotensin-converting enzyme 2 (ACE2). [McIntosh]
The entry process involves the specific binding of virus spike protein to this receptor and a proteolytic activation by host transmembrane protease/serine subfamily member 2 (TMPRSS2).

ACE2 is highly expressed on the pulmonary epithelial cells. It is through this host receptor that the S protein binds initially to start the host cell invasion by the virus. After binding of SARS-CoV-2 to the ACE2, the S protein undergoes activation via a two-step protease cleavage: the first one for priming at the S1/S2 cleavage site and the second cleavage for activation at a position adjacent to a fusion peptide within the S2 subunit. The initial cleavage stabilises the S2 subunit at the attachment site and the subsequent cleavage presumably activates the S protein causing conformational changes leading to viral and host cell membrane fusion.
Post membrane fusion the virus enters the pulmonary alveolar epithelial cells and the viral contents are released inside. Now inside the host cell, the virus undergoes replication and formation of a negative strand RNA by the pre-existing single-strand positive RNA through RNA polymerase activity (transcription). This newly formed negative strand RNA serves to produce new strands of positive RNAs which then go on to

synthesise new proteins in the cell cytoplasm (translation). The viral N protein binds the new genomic RNA and the M protein facilitates integration to the cellular endoplasmic reticulum. These newly formed nucleocapsids are then enclosed in the ER membrane and transported to the lumen, from where they are transported via golgi vesicles to the cell membrane and then via exocytosis to the extracellular space. The new viral particles are now ready to invade the adjacent epithelial cells as well as for providing fresh infective material for community transmission via respiratory droplets. [Parasher] [V'kovski]

7.3 Clinical manifestation of COVID-19

ASYMPTOMATIC PHASE
The SARS-CoV-2 which is received via respiratory aerosols binds to the nasal epithelial cells in the upper respiratory tract. The main host receptor for viral entry into cells is the ACE2, which is seen to be highly expressed in adult nasal epithelial cells. The virus undergoes local replication and propagation, along with the infection of ciliated cells in the conducting airways. This stage lasts a couple of days and the immune response generated during this phase is a limited one. In spite of having a low viral load at this time, the individuals are highly infectious, and the virus can be detected via nasal swab testing.

INVASION AND INFECTION OF THE UPPER RESPIRATORY TRACT
In this stage, there is migration of the virus from the nasal epithelium to the upper respiratory tract via the conducting airways. Due to the involvement of the upper airways, the disease manifests with symptoms of fever, malaise and dry cough. There is a greater immune response during this phase involving the release of C-X-C motif chemokine ligand (CXCL-10) and interferons (IFN-β and IFN-λ) from the virus-infected cells. The majority of patients do not progress beyond this phase as the mounted immune response is sufficient to contain the spread of infection.

INVOLVEMENT OF THE LOWER RESPIRATORY TRACT AND PROGRESSION TO ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)
About one-fifth of all infected patients progress to this stage of disease and develop severe symptoms. The virus invades and enters the type 2 alveolar epithelial cells via the host receptor ACE2 and starts to undergo replication to produce more viral Nucleocapsids. The virus-laden pneumocytes now release many different cytokines and inflammatory markers such as interleukins (IL-1, IL-6, IL-8, IL-120 and IL-12), tumour necrosis factor-α (TNF-α), IFN-λ and IFN-β, CXCL-10, monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1α (MIP-1α). This 'cytokine storm' acts as a chemoattractant for neutrophils, CD4 helper T cells and CD8 cytotoxic T cells, which then begin to get sequestered in the lung tissue. These cells are responsible for fighting off the virus, but in doing so are responsible for the subsequent inflammation and lung injury. The host cell undergoes apoptosis with the release of new viral particles, which then infect the adjacent type 2 alveolar epithelial cells in the same manner. Due to the persistent injury caused by the sequestered inflammatory cells and viral replication leading to loss of both type 1 and type 2 pneumocytes, there is diffuse alveolar damage eventually culminating in an acute respiratory distress syndrome. [Parasher]

7.4 Infectiousness and viral shedding

Viral shedding and period of infectiousness – the precise interval during which an individual with SARS-CoV-2 infection can transmit infection to others -- is uncertain. The potential to transmit SARS-CoV-2 begins prior to the development of symptoms and is highest early in the course of illness; the risk of transmission decreases thereafter. Transmission after 7 to 10 days of illness is unlikely, particularly for otherwise immunocompetent patients with nonsevere infection.
Period of greatest infectiousness – Infected individuals are more likely to be contagious in the earlier stages of illness, when viral RNA levels from upper respiratory specimens are the highest.
Prolonged viral RNA detection does not indicate prolonged infectiousness – The duration of viral RNA shedding is variable and may increase with age and the severity of illness.

Asymptomatic or presymptomatic transmission - transmission of SARS-CoV-2 from individuals with infection but no symptoms (including those who later developed symptoms and thus were considered presymptomatic) – has been well documented. [McIntosh]

7.5 Alcohol consumption and COVID-19

A dose dependent correlation between alcohol consumption and viral infections is well documented, and, furthermore, alcohol consumption has been shown to increase the risk of acquiring community infections. A general increase in the consumption of alcohol has been reported during the SARS- CoV-2 pandemic. It has been hypothesized that patients with alcohol-related disorders are at an increased risk of COVID-19. Lassen et al have found that weekly alcohol consumption was indeed associated with an increased risk of developing ARDS during hospitalization for COVID-19. Prior to the COVID-19 pandemic, Simou et al conducted a review and meta-analysis investigating the association between alcohol consumption and risk of ARDS in hospitalized adults (N=177,674). The authors found that chronic high alcohol consumption significantly increased the risk of ARDS. The increased risk of ARDS in excessive chronic alcohol consumption has been suggested to be caused by alcohol-induced oxidative stress leading to depletion of the critical antioxidant glutathione and ultimately deteriorates alveolar barrier integrity and modulation of the immune response. [Lassen]

7.6 Diagnosis

Molecular tests (RT-PCR and antigen tests)
Samples are collected from the upper respiratory tract via nasopharyngeal and oropharyngeal swabs and from the lower respiratory tract via expectorated sputum and bronchoalveolar lavage (only for mechanically ventilated patients). After being stored at 4°C, the samples are sent to the laboratory where amplification of the viral genetic material is done through a reverse-transcription process.6 This involves the synthesis of a double-stranded DNA molecule from the existing viral RNA by either ***reverse-transcription PCR*** (RT-PCR) or a real- time RT-PCR. Finally, the conserved portions of the SARS-CoV-2 genetic code are identified on the amplified genetic material.
The test is recommended to be repeated for verification in cases of a positive test and again to confirm viral clearance in COVID-19 positive cases. The sensitivity of these tests is not very high, that is, approximately 53.3% of COVID-19-confirmed patients had positive oropharyngeal swabs, and about 71% of patients came out to be RT-PCR positive with sputum samples. The RT-PCR results usually show positivity after 2–8 days. A comprehensive analysis of SARS-CoV-2 respiratory tract, plasma, and urine viral loads of 235 participants who were either hospitalized with COVID-19, evaluated as symptomatic outpatients, or had recovered from COVID-19 disease show a relatively high prevalence of SARS-CoV-2 plasma viremia in hospitalized individuals with severe disease, but plasma viremia was also detected in symptomatic non-hospitalized participants. Levels of SARS-CoV-2 viremia was also associated with markers of inflammation and disease severity, including low lymphocyte counts, and elevated CRP and IL-6 levels. [Fajnzylber]

Antigen tests are commonly used in the diagnosis of respiratory pathogens, including influenza viruses and respiratory syncytial virus. Antigen tests are immunoassays that detect the presence of a specific viral antigen, which implies current viral infection. Antigen tests are currently authorized to be performed on nasopharyngeal or nasal swab specimens placed directly into the assay's extraction buffer or reagent. The currently authorized antigen tests are not restricted to use on persons of a certain age. Antigen tests are relatively inexpensive, and most can be used at the point of care. Most of the currently authorized tests return results in approximately 15 minutes. Antigen tests for SARS-CoV-2 are generally less sensitive than RT-PCR and other nucleic acid amplification tests for detecting the presence of viral nucleic acid. However, RT-PCR can detect levels of viral nucleic acid that cannot be cultured, suggesting that the presence of viral nucleic acid does not always indicate contagiousness. Proper interpretation of both antigen test results and confirmatory testing when indicated is important for accurate clinical management of patients with suspected COVID-19, or for identification of infected persons when used for screening. [CDC2]

Serology
Till date, no effective antibody test has been developed. A Centers for Disease Control and Prevention (CDC) research on a test developed by the US Vaccine Research Centre at the National Institutes of Health is ongoing, which seems to have a specificity higher than 99% with a sensitivity of 96%.

Blood tests
- A normal or decreased white blood cell count (and lymphopenia) can be observed in many cases, which is also considered to be indicative of a worse prognosis.
- Increased levels of lactate dehydrogenase, C reactive protein, creatine kinase (CK MB and CK MM), aspartate amino-transferase and alanine amino-transferase can be seen.
- Increased D-dimer levels and an elevated neutrophil-to-lymphocyte ratio are seen in some patients.
- Coagulation abnormalities can be observed in severe cases, as indicated by increase in prothrombin time and international normalised ratio.
- In nonhospitalized patients with COVID-19, there are currently no data to support the measurement of coagulation markers (e.g., D-dimers, prothrombin time, platelet count, fibrinogen). In hospitalized patients with COVID-19, hematologic and coagulation parameters are commonly measured, although there are currently insufficient data to recommend for or against using this data to guide management decisions. [NIH]

Medical imaging
Chest X-ray is usually inconclusive in the early stages of the disease and might not show any significant changes. As the infection progresses, bilateral multifocal alveolar opacities are observed, which may also be associated with pleural effusion.
High-resolution CT (HRCT) is extremely sensitive and the method of choice for diagnosing COVID-19 pneumonia, even in initial stages of the illness. The most commonly seen features are multifocal bilateral "ground-glass" areas associated with consolidation and a patchy peripheral distribution, with greater involvement of the lower lobes. A 'reversed halo sign' is also seen in some patients, which is identified as a focal area of patchy opacities surrounded by a peripheral ring with consolidation. Other findings include pleural effusion, cavitation, calcification, and lymphadenopathy.
[Parasher]

Symptomatology according to the WHO:
- **Frequent: Fever (88%), Dry cough (68%) Fatigue (38%)**
- Less frequent: Productive cough (33%), Dyspnoea (19%), Sore throat (14%), Headache (14%), Muscular pains and arthralgia (15%), Chills (11%)
- Rare symptoms: Emesis (5%), Diarrhoea (4%)

[MKK]

Carillo et al executed a systematic review of studies that compared smell and taste disorders between COVID-19 patients and otherwise healthy subjects; and studies comparing smell and taste disorders between COVID-19 severe and mild/moderate cases. Six studies (n=2 757) reported the proportion of smell and taste disorders among COVID-19 patients. **The frequency of anosmia ranged between 22%-68%. The definition of taste disorders varied greatly, with dysgeusia present in 33% and ageusia in 20%.** People who reported loss of smell and taste had six-fold higher odds of being COVID-19 positive; similarly, anosmia and ageusia were associated with 10-fold higher odds of COVID-19 diagnosis. [Carillo]

Disease severity course according to the WHO:
- Mild or medium severity: 80%
- Severe: 14%
- Critical: 6% (ARDS, shock, multi-organ failure)

[MKK]

7.7 Therapy

With the rapidly escalating situation worldwide, there are multiple approaches to finding potential therapeutic options. The ***first approach*** would be to look into the pool of existing antiviral drugs by using standard assays. This can help to analyze the effects of these drugs on viral replication. Several drugs have been identified using this method, which includes interferon I (interferon alpha, beta, kappa, lambda, epsilon, etc) and interferon II (interferon-gamma). Since the pharmacokinetic and pharmacodynamic properties and also the side effect profile of these drugs are already known, these drugs have a relative advantage. However, their efficacy against coronaviruses remains unknown as yet.
Another approach involves looking through the existing compounds and testing their efficacy for antiviral properties including information about transcription characteristics in different cell lines. These compounds include drugs that alter the neurotransmitter regulation, estrogen receptors, kinase signal transduction, protein processing, and DNA.
A ***third approach*** is to redevelop new drugs to act specifically against individual coronaviruses. This would require a thorough understanding of the genomics and structural characteristics of the virus. This includes small interfering RNA (siRNA) molecules or enzymes that will target specific viral enzymes, inhibition of host cell protease, or host viral endocytosis. Although this seems an effective option because of these drugs' specific anti-coronavirus properties, there is limited data regarding the safety profile as well as the pharmacodynamic and pharmacokinetic properties of these drugs. Hence, it would take a long time to prove the efficacy and reliability of these drugs in patients. [Pujari]

Major drug classes for combating COVID-19 in the everyday clinical practice:

- Anti-viral agents: remdesivir, ribavirin, lopinavir-ritonavir, favipiravir, chloroquine, hydroxychloroquine, oseltamivir, umifenovir
- Immunomodulatory agents: tocilizumab, interferons, convalescent plasma transfusion
- Adjunctive and miscellaneous agents: azithromycin, corticosteroids, camostat mesylate, angiotensin converting enzyme (ACE) inhibitors, angiotensin-2 receptor blockers (ARB)

[Lam]

For nonhospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for the prevention of venous thromboembolism (VTE) or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial. [NIH]

In the ***Hungarian treatment guideline (Hungarian Coronavirus Handbook)*** the following pharmacons are recommended, depending on disease severity: favipiravir, chloroquine / hidroxychloroquine ± azithromycin, remdesivir, lopinavir / ritonavir, dexamethason, tocilizumab, ruxolitinib / baricitinib. [MKK]

Successful and sequelae-free complete resolution of this potential severe viral infection still presents an **unmet medical need**, with therapeutical approaches to various molecular targets and to various patophysiological processes of the infection and consequent bodily processes. In our opinion, current mainstream therapeutic approaches can not be considered optimal. A limitation is that they focus on only one element of the particularly complex pathomechanism of COVID-19, and use selective agents accordingly. Recent data on the pathomechanism suggest that instead of (or, possibly: in addition to) the cytokine storm hypothesis, an overt damage to the immune system – suffered from multiple aetiologies and along several pathways – , plays a central role in the development of the disease. According to our concept, drugs with multiple mode of action that are suitable – in addition to their antiviral effect – for the prevention/treatment of serious consequences of COVID-19 infection are needed for effective therapy.

8 Presentation of the study drug, Ivermectin

8.1 Introduction

Ivermectin is a broad-spectrum anti-parasite medication. It was first marketed under the name Stromectol® and used against worms (except tapeworms), but in 2012 it was approved for the topical treatment of head lice infestations in patients 6 months of age and older, and marketed under the name Sklice™ as well. Ivermectin is mainly used in humans in the treatment of onchocerciasis, but is also effective against other worm infestations (such as strongyloidiasis, ascariasis, trichuriasis and enterobiasis).
[DrugBank]
About 3.7 billion doses of ivermectin have been distributed in mass drug administration campaigns globally over the past 30 years. Presently, ivermectin is approved for use in humans in several countries to treat onchocerciasis, lymphatic filariasis, strongyloidiasis, and scabies. [Cepelowicz]
In Hungary, its topical formulation is utilized in rosacea.

8.2 Pharmaceutical information

Ivermectin is a semisynthetic, anthelminitic agent. It is an avermectin which a group of pentacyclic sixteen-membered lactone (i.e. a macrocyclic lactone disaccharide) derived from the soil bacterium Streptomyces avermitilis. Avermectins are potent anti-parasitic agents. Ivermectin is the most common avermectin. It is a broad spectrum antiparasitic drug for oral administration. It is sometimes used to treat human onchocerciasis (river blindness). It is the mixture of 22,23-dihydro-avermectin B1a (at least 90%) and 22,23-dihydro-avermectin B1b (less than 10%). [DrugBank]

8.3 Indications

Ivermectin is indicated for the treatment of:

- Intestinal strongyloidiasis
- Onchocerciasis

[Merck]

8.4 Contraindications

- Patients who are hypersensitive to ivermectin or to any ingredient in the formulation or component of the container
- Asthma (Patients with a history of severe asthma should receive ivermectin with caution. Occasionally, systemic ivermectin has been reported to worsen bronchial asthma.)
- Hepatic disease (Although not extensively studied, due to its extensive hepatic metabolism, ivermectin should be administered with caution in patients with significant hepatic disease)
- Human immunodeficiency virus (HIV) infection, immunosuppression (In patients with immunosuppression (including those with human immunodeficiency virus (HIV) infection) treated for intestinal strongyloidiasis, repeated ivermectin courses may be necessary.)
- Pregnancy (Data with oral ivermectin use during pregnancy are insufficient to inform a drug-associated risk.)
- Breast-feeding (After oral administration, ivermectin is excreted in human breast milk in low concentrations. Excretion in human breast milk after topical administration has not been evaluated.)
- Loa loa coinfection (Rarely, patients with onchocerciasis and Loa loa coinfection may develop a serious or even fatal encephalopathy either spontaneously or after treatment with an effective microfilaricide.)
- Onchodermatitis (Patients with hyperreactive onchodermatitis (i.e., sowda) may be more likely than

others to experience severe edema and worsening of onchodermatitis after ivermectin use.) [Merck]

8.5 Mechanism of antiparasitic action

Ivermectin blocks synaptic transmission in invertebrates by binding to glutamate-gated chlorine channels in nerve and muscle, leading to hyperpolarization, paralysis and death of the invertebrate, including mosquitoes. These channels are part of the Cys-loop family of ligand-gated ion channels and ivermectin has consequently been shown to have additional effects on other members, for instance the gamma-aminobutyric acid (GABA), histamine, and pH-sensitive chloride channels. In mammals, ivermectin acts as an allosteric agonist of GABA-A receptor, another member of the Cys-loop family of ligand-gated ion channels. These receptors are located on neurons in many central nervous system regions (incl. the cerebral cortex, the limbic system, and thalamus) and increase chloride conductance, resulting in hyperpolarization and less formation of action potentials. In vertebrates, GABA is a major inhibitory transmitter. The net effect of GABA-A receptor stimulation is central nervous depression, which defines the syndrome of ivermectin toxicity in vertebrates. [Chaccour]

8.6 Animal safety studies

Acute oral studies with ivermectin in mice, rats, and monkeys have shown clear species and strain differences in sensitivity, with rodents being relatively sensitive to the CNS toxicity produced by the compound. Doses of 200 μg/kg in mice and slightly higher doses in rats have produced tremors and ataxia, while a 200 μg/kg dose was generally well tolerated in studies in a variety of species. Acute oral studies in rhesus monkeys demonstrated that the minimum toxic dose was 2,000 μg/kg or approximately 10-fold the clinical dose. Doses up to 24 mg/kg in this species (120-fold the clinical dose) produced only slight increases in the observed toxic effects including emesis, mydriasis, and sedation. A repeated dose study of 2 weeks' duration in rhesus monkeys produced no adverse effects at doses up to 1,200 μg/kg/day. Fourteen-week studies in rats and dogs indicated no adverse effects at doses of 400 and 500 μg/kg/day, respectively.
Breeding performance in various species has not been adversely affected by ivermectin.
Ivermectin caused cleft palates in mice and rats at oral doses of 0.4 and 10 mg/kg/day respectively, and cleft palates and clubbed feet in rabbits dosed at 3 mg/kg/day. These development effects were found only at or near doses that were maternotoxic to the pregnant female.
Long-term studies have not been performed to evaluate the carcinogenic potential of ivermectin.
Ivermectin is negative in the Ames microbiological mutation and the mouse lymphoma mutation assays; it did not induce unscheduled DNA synthesis in human fibroblast cell culture.
Significant lethality was observed in mice and rats after single oral doses of 25 to 50 mg/kg and 40 to 50 mg/kg, respectively. No significant lethality was observed in dogs after single oral doses of up to 10 mg/kg. At these doses, the treatment related signs that were observed in these animals include ataxia, bradypnea, tremors, ptosis, decreased activity, emesis, and mydriasis. [Merck]

8.7 Adverse Drug Reactions

8.7.1 Clinical Trial Adverse Reactions

Healthy volunteers
A fixed and high dose regimen which takes advantage of the wide therapeutic index of IVM is an attractive alternative for improving the distribution and therefore potentially increasing coverage rates of treatment campaigns as has been the case for primaquine in the treatment of malaria. A healthy volunteer pharmacokinetic study was designed to evaluate the safety and pharmacokinetic profile of 3 dosing regimens - 2 experimental treatments using a new 18 mg ivermectin tablet in a fixed-dose strategy of 18 and 36 mg single dose regimens, compared to the standard, weight based 150–200 μg/kg, regimen - of IVM in 54

healthy adult volunteers stratified in 3 weight groups in an open-label, randomized, crossover phase I clinical trial performed under fasting conditions. The study was single dose, three-period, comprising 3 experimental phases of treatment with different doses of IVM.
All subjects receiving at least one dose of study drug were included in the safety analysis (n = 57). No abnormal result or significant differences were found between biochemistry at baseline and after the administration of IVM in any of the three study arms. A slight decrease in Haemoglobin (Hb) levels was observed after administration of IVM in the three study arms.
The main electrocardiographic parameters were not affected by the administration of IVM. Systemic blood pressure measurements were not affected by treatment administration.
A total of 33 treatment emergent adverse events were reported by 22 subjects who received at least one dose of the study medication. No significant association was found between the distribution of adverse events and the three treatments arms (p = 0.695). The most frequent adverse event described by study participants was headache (6.02% of the study subjects) (NB. common in participants of phase I trials after deprivation of caffeine and other substances), followed by dysmenorrhea (5.54%), throat pain (1.80%) and diarrhea (1.80%). Of the 33 adverse events reported, 10 were graded as mild and 23 were graded as moderate. [Munoz]

Since the majority of safety and pharmacokinetic data on oral ivermectin are with single doses of 150 to 200 μg/kg, the primary objective of the study conducted by Guzzo et al was to obtain additional information at higher and multiple doses. Doses up to 10 times the 200 μg/kg dose were evaluated to provide a substantial safety margin over the anticipated dosage range in a double-blind, placebo-controlled, multiple rising dose study in healthy adult men and women. Of the 51 subjects who received ivermectin, 12 subjects (24%) reported at least one clinical adverse experience. This rate was similar to that observed in the placebo group (6 subjects, 35%). In addition, there was no consistent trend in the incidence of adverse experiences indicative of a dose response. All clinical adverse experiences were transient and mild, and no adverse experience recurred with repeated dosing. The most commonly reported adverse experiences were headache, nausea, dizziness, and rash, occurring in both ivermectin- and placebo-treated groups. Seven ivermectin-treated subjects (14%) and 3 placebo-treated subjects (18%) had drug-related clinical adverse experiences. None of the subjects discontinued due to clinical adverse experiences. None of the clinical adverse experiences was serious. Two subjects experienced laboratory adverse experiences, both in the 30 mg ivermectin group. A 37-year-old female developed increased alanine transaminase (ALT) to approximately 2.5 times normal on day 14 and elevated gamma-glutamyl transferase (GGT) to approximately 4 times normal on day 18. ALT returned to normal on day 23, but GGT remained mildly elevated (no baseline values obtained). Further hepatic evaluation revealed cholelithiasis. The investigator rated both laboratory adverse experiences as possibly related to study drug. The second subject, a 25-year-old male, developed hematuria that resolved after passing a kidney stone, and the event was evaluated as definitely not related to study drug. [Guzzo]

Parasitic diseases
The main indications for population-level control with ivermectin through mass drug administration are onchocerciasis and lymphatic filariasis; however, there is interest in using higher, fixed-dose regimens for the control of scabies, soil- transmitted helminths and malaria. Safety data for these higher-dose regimens are needed. A systematic literature review and meta-analysis on the safety and doses of ivermectin was conducted. Eligible studies reported patient-level data and, for the meta-analysis, clinical trials reporting data on doses □200 and □400 μg/kg were included. The systematic search identified six studies for inclusion, revealing no differences in the number of individuals experiencing adverse events. A descriptive analysis of these clinical trials for a variety of indications showed no difference in the severity of the adverse events between standard (up to 400 μg/kg) and higher doses of ivermectin. Organ system involvement only showed an increase in ocular events in the higher-dose group in one trial for the treatment of onchocerciasis, all of them transient and mild to moderate in intensity. The findings, although limited by the small number of studies and lack of blinding, add evidence to the safety of ivermectin at doses up to 800 μg/kg, which demonstrated an overall comparable safety to standard doses, which in this meta-analysis was tested in separate analyses using the 200 and 400 μg/kg doses as the highest standard dose since, for W. bancrofti

infections, 400 μg/kg. [Navarro]

Strongyloidiasis
In four clinical studies involving a total of 109 patients given either one or two doses of 170 to 200 μg/kg of ivermectin, the following adverse reactions were reported as possibly, probably, or definitely related to ivermectin:

- Body as a whole: asthenia/fatigue (0.9%), abdominal pain (0.9%)
- Gastrointestinal: anorexia (0.9%), constipation (0.9%), diarrhea (1.8%), nausea (1.8%), vomiting (0.9%)
- Nervous System/Psychiatric: dizziness (2.8%), somnolence (0.9%), vertigo (0.9%), tremor (0.9%)
- Skin: pruritus (2.8%), rash (0.9%), and urticaria (0.9%)

Onchocerciasis
In clinical trials involving 963 adult patients treated with 100 to 200 μg/kg ivermectin, worsening of the following signs and symptoms during the first 4 days post-treatment were reported: arthralgia/synovitis (9.3%), axillary lymph node enlargement and tenderness (11.0% and 4.4%, respectively), cervical lymph node enlargement and tenderness (5.3% and 1.2%, respectively), inguinal lymph node enlargement and tenderness (12.6% and 13.9%, respectively), other lymph node enlargement and tenderness (3.0% and 1.9%, respectively), pruritus (27.5%), skin involvement including edema, papular and pustular or frank urticarial rash (22.7%), and fever (22.6%). These signs and symptoms are considered part of the Mazzotti- type reactions.

In clinical trials, ophthalmological conditions were examined in 963 adult patients before treatment, at day 3, and months 3 and 6 after treatment with 100 to 200 μg/kg ivermectin. Changes observed were primarily deterioration from baseline 3 days post-treatment. Most changes either returned to baseline condition or improved over baseline severity at the month 3 and 6 visits. The percentages of patients with worsening of the following conditions at day 3, month 3 and 6, respectively, were: limbitis: 5.5%, 4.8%, and 3.5% and punctate opacity: 1.8%, 1.8%, and 1.4%. The corresponding percentages for patients treated with placebo were: limbitis: 6.2%, 9.9% and 9.4% and punctate opacity: 2.0%, 6.4% and 7.2%.

In clinical trials involving 963 adult patients who received 100 to 200 μg/kg ivermectin, the following clinical adverse reactions were reported as possibly, probably, or definitely related to the drug in ≥1% of the patients: facial edema (1.2%), peripheral edema (3.2%), orthostatic hypotension (1.1%), and tachycardia (3.5%). Drug-related headache and myalgia occurred in <1% of patients (0.2%, and 0.4%, respectively). However, these were the most common adverse experiences reported overall during these trials regardless of causality (22.3% and 19.7%, respectively).

The following ophthalmological side effects do occur due to the disease itself but have also been reported after treatment with ivermectin: abnormal sensation in the eyes, eyelid edema, anterior uveitis, conjunctivitis, limbitis, keratitis, and chorioretinitis or choroiditis. These have rarely been severe or associated with loss of vision and have generally resolved without corticosteroid treatment.
[Merck]

8.7.2 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Strongyloidiasis
In clinical trials involving 109 patients given either one or two doses of 170 to 200 μg/kg ivermectin, the laboratory adverse experiences, reported irrespective of drug relationship, were leukopenia/anemia in one patient and elevated ALT/alkaline phosphatase in one patient.

Onchocerciasis

In controlled clinical trials, the following laboratory adverse experiences were reported as possibly, probably, or definitely related to the drug in ≥1% of the patients: eosinophilia (3%) and hemoglobin increase (1%).

8.7.3 Post-Market Adverse Reactions

Onchocerciasis

- Conjunctival Haemorrhage

All indications

- Hypotension (mainly orthostatic hypotension), worsening of bronchial asthma, toxic epidermal necrolysis, Stevens-Johnson syndrome, seizures, hepatitis, elevation of liver enzymes, and elevation of bilirubin.

[Merck]

8.7.4 Neurotoxicology of ivermectin

In vertebrates, the blood brain barrier (BBB) prevents ivermectin (IVM) from disposition to the brain. IVM crosses the BBB weakly by passive diffusion; in addition, P-glycoprotein, of which IVM is a substrate, is able to remove all IVM from the brain. Therefore, no mechanism-based neurotoxicity, due to IVM's action on GABA-receptors, may develop. The risk of mechanism-based CNS side effects of IVM should be considered for any dysfunctioning BBB.

Severe central nervous system side effects seen in various vertebrates following ivermectin (IVM) treatment may be due to an absence of, or functional deficiency of P-glycoprotein (a member of ABC transporters). Changes in IVM disposition observed in the (-/-) mice deficient in MDR1A P-glycoprotein arise through a deficiency in P-glycoprotein rather than any alteration in drug metabolism. [Kwei]

These findings suggest that other P-glycoprotein substrates could compete with ivermectin at this site, resulting in reduced extracellular efflux and enhanced CNS toxicity. Such compounds include cyclosporin and HIV protease inhibitors. It is however questionable whether any of the neurological sequelae associated with administration of ivermectin are directly related to the drug and therefore it seems unlikely that any alterations in the pharmacokinetics of ivermectin for whatever reason would result in a more severe adverse reaction. [Edwards]

In a study of the roles of MRP1-3 transporters in IVM transports, it was shown that P-gp was the main actor for IVM efflux out of brain. [Lespine]

This potentially neurotoxic drug is absorbed in humans only in a very small fraction, and this low level ivermectin absorption is mainly caused by an active extrusion in the intestine by the ABCB1/Pgp transporter. ABCB1, and probably other ABC transporters (especially ABCG2) in the blood-brain barrier (BBB) also have a significant role in protecting the mammalian CNS against toxic ivermectin penetration. In mouse Pgp-knock-out models, in the natural Pgp-knock-out Collie dogs, and also in some humans with low level ABCB1/Pgp expression, ivermectin exerts major neurotoxicity[8,9]. In addition, both ABCB1 and several other multispecific transporters have been shown to be inhibited by micromolar concentrations of ivermectin[10–12], thus ivermectin may influence the pharmacokinetics of several drugs or toxic compounds. [Telbisz: preliminary, non peer-reviewed communication]

Breast cancer resistant protein (Bcrp), another efflux pump in BBB, is not a relevant efflux carrier for IVM. [Geyer]

Decreased Pgp function with increasing age (21-27 vs. 42-50 vs 57-69 y) could account for increased drug

toxicity and increased CNS side effects of drugs that are able to pass the BBB in the elderly. Decreased Pgp function is present in young women compared with young men.

In cases of neurodegenerative diseases there may be a reciprocal causative relationship with dysfunction of P-gp. It has been shown that AD patients have diminished BBB P-gp function compared with healthy elderly aged subjects, further supporting a possible role of P-gp in the aetiology of AD. [van Assema]

Additionally, dysfunction of ABC transporters, at expression and/or activity level, has also been associated with many neurological diseases, including epilepsy, multiple sclerosis, and amyotrophic lateral sclerosis.[Gil-Martins]

In conclusion, the neurotoxic effect of IVM may only develop due to P-gp dysfunction and/or neurological diseases associated with functional changes in permeability of the blood-brain barrier.

8.8 **Pharmacokinetics**

8.8.1 Absorption

In healthy subjects that received 12 mg of ivermectin as oral solution, tablets or capsules, it was shown that the solution had approximately twice the systemic availability as either of the solid forms. The oral solution was given as an ethanolic solution. This may affect bioavailability and could explain why the solution resulted in a twice as high availability as tablets and capsules. Nevertheless, the rate of absorption was similar in the three cases. [Canga]
Following a standard oral dose in healthy humans, IVM reaches peak plasma levels at 3.4 to 5 hours [Munoz].

8.8.2 Distribution

Due to the high lipid solubility of ivermectin, this compound is widely distributed within the body.
In healthy men, the volume of distribution in the central compartment, Vc, was 3.1 and 3.5 l·kg−1, after ingesting 6 and 12 mg of ivermectin, respectively. In onchocerciasis patients, with 6 mg (tablet), the volume of distribution of the area (Vλ) was 9.9 l·kg−1 and the mean residence time (MRT) was 3.7 days..
The tissue distribution of ivermectin was similar in healthy and onchocerciasis volunteers treated orally. Ivermectin binds strongly to plasma proteins in healthy subjects (93.2%). It was also high in onchocerciasis patients (93.1%), with a specific binding for serum albumin.
Ivermectin was not detected in the cerebrospinal fluid of a man with disseminated strongyloidiasis, severe hypoalbuminemia and paralytic ileus, after five subcutaneous doses. [Canga]
Owing to its lipophilicity, ivermectin partitions to adipose tissue, which increases Vd and leads to accumulation with prolonged elimination, as drug distributes back to plasma from fatty tissue. This can explain the different pharmacokinetic pattern seen in women and volunteers with higher body mass index.
Distribution to the brain is hindered by the blood-brain-barrier. Specifically, this is mediated by ivermectin's size, which is not conducive to passive diffusion, and the presence of efflux pumps, for which ivermectin is a substrate. The primary efflux pump is the P-gp (of which ivermectin is also an inhibitor), although BCRP can also transport ivermectin. The blood–brain-barrier therefore restricts ivermectin's access to its toxicity target in mammals, the central nervous GABA-A-receptor and forms the basis for ivermectin's good tolerability. [Chaccour]

8.8.3 Elimination (metabolism, excretion)

Ivermectin is metabolized by CYP3A4 but in vitro studies suggest it does not significantly inhibit its metabolizing activity or that of CYP2D6, CYP2C9, CYP1A2, and CYP2E1, all involved in its metabolism to a lower extent. There is, however, a theoretical possibility of interaction with CYP3A4 inhibitors (such as

protease inhibitors) or inducers such as rifampicin. Ivermectin is both a substrate and a potent inducer of the P-gp. P-gp plays a role in the transportation of ivermectin to the intestinal lumen and in preventing its crossing of the blood-brain barrier. P-gp inhibitors (such as antifungal azoles) can increase ivermectin plasma levels in animals. Post-marketing reports of increased International Normalized Ratio (INR) have been rarely reported when ivermectin was co-administered with warfarin. [Chaccour]

Thirteen different metabolites (M1-M13) were identified after incubation of ivermectin with human liver microsomes. Three (M1, M3, and M6) were the dominant metabolites found in microsomes, hepatocytes, and blood from volunteers after oral ivermectin administration. The chemical structure defined by LC-MS/MS and NMR indicated that M1 is 3″-O -demethyl ivermectin, M3 is 4-hydroxymethyl ivermectin, and M6 is 3″-O -demethyl, 4-hydroxymethyl ivermectin. Metabolic pathway evaluations with characterized cytochrome P450 enzymes showed that M1 was produced by CYP3A4 and CYP3A5, and that M3 and M6 were produced by CYP3A4. Demethylated and hydroxylated ivermectin are thus the main human metabolites in vivo. [Tipthara, non-peer-reviewed]
Since these main three metabolites are more hydrophilic than IVM itself, out of biopharmaceutical reasoning, CNS adverse events can be speculated negligible if any at all.

A significant effect of gender was found in ivermectin pharmacokinetics in healthy volunteers orally treated with 150 μg/kg, with a lower total body Cl/F in males compared to females. [Merck]

The plasma half life is reported as 16 to 28 hours, the volume of distribution is 46.9 L, and clearance is 1.2 L/h after oral administration. [PDR]
Following a standard oral dose of IVM in healthy humans, plasma half-life has been reported to be 12 to 66 hours. [Munoz]
Ivermectin and/or its metabolites are excreted almost exclusively in the feces over an estimated 12 days, with < 1% of the administered dose excreted in the urine. Estimates of plasma half-life have varied from 12 to 56 hours. [Guzzo]

8.9 Interactions

In vitro studies using human liver microsomes and recombinant CYP450 enzymes have shown that ivermectin is primarily metabolized by CYP3A4. Depending on the in vitro method used, CYP2D6 and CYP2E1 were also shown to be involved in the metabolism of ivermectin but to a significantly lower extent compared to CYP3A4. The findings of in vitro studies using human liver microsomes suggest that clinically relevant concentrations of ivermectin do not significantly inhibit the metabolizing activities of CYP3A4, CYP2D6, CYP2C9, CYP1A2, and CYP2E1. [Merck]

- **Aprepitant, Fosaprepitant: (Moderate)** Use caution if ivermectin and aprepitant, fosaprepitant are used concurrently and monitor for an increase in ivermectin-related adverse effects for several days after administration of a multi-day aprepitant regimen. Ivermectin is a CYP3A4 substrate. Aprepitant, when administered as a 3-day oral regimen (125 mg/80 mg/80 mg), is a moderate CYP3A4 inhibitor and inducer and may increase plasma concentrations of ivermectin..
- **Boceprevir: (Moderate)** Close clinical monitoring is advised when administering ivermectin with boceprevir due to an increased potential for ivermectin-related adverse events. If ivermectin dose adjustments are made, re-adjust the dose upon completion of boceprevir treatment. Although this interaction has not been studied, predictions about the interaction can be made based on the metabolic pathway of ivermectin. Ivermectin is partially metabolized by the hepatic isoenzyme CYP3A4; boceprevir inhibits this isoenzyme. Coadministration may result in elevated ivermectin plasma concentrations.
- **Idelalisib: (Major)** Avoid concomitant use of idelalisib, a strong CYP3A inhibitor, with ivermectin, a CYP3A substrate, as ivermectin toxicities may be significantly increased. The AUC of a sensitive CYP3A substrate was increased 5.4-fold when coadministered with idelalisib.

- **Mirabegron: (Moderate)** Mirabegron is a moderate CYP2D6 inhibitor. Exposure of drugs metabolized by CYP2D6 such as ivermectin may be increased when co-administered with mirabegron. Ivermectin has been shown to be a CYP2D6 substrate in vitro. Appropriate monitoring and dose adjustment may be necessary.
- **Mitotane: (Moderate)** Use caution if mitotane and ivermectin are used concomitantly, and monitor for decreased efficacy of ivermectin and a possible change in dosage requirements. Mitotane is a strong CYP3A4 inducer and ivermectin is a CYP3A4 substrate. Coadministration may result in decreased plasma concentrations of ivermectin; however, ivermectin is administered as a single dose, and significant clinical interactions are not expected.
- **Posaconazole: (Moderate)** Posaconazole and ivermectin should be coadministered with caution due to an increased potential for ivermectin-related adverse events. Posaconazole is a potent inhibitor of CYP3A4, an isoenzyme partially responsible for the metabolism of ivermectin. These drugs used in combination may result in elevated ivermectin plasma concentrations, causing an increased risk for ivermectin-related adverse events.
- **Telaprevir: (Moderate)** Close clinical monitoring is advised when administering ivermectin with telaprevir due to an increased potential for ivermectin-related adverse events. If ivermectin dose adjustments are made, re-adjust the dose upon completion of telaprevir treatment. Although this interaction has not been studied, predictions about the interaction can be made based on the metabolic pathway of ivermectin. Ivermectin is partially metabolized by the hepatic isoenzyme CYP3A4; telaprevir inhibits this isoenzyme. Coadministration may result in elevated ivermectin plasma concentrations.
- **Warfarin: (Moderate)** Concurrent administration of warfarin and oral ivermectin has been associated with postmarketing reports of elevated INR. In 1 case report, a patient who was previously stable on warfarin developed supratherapeutic INR concentrations (greater than 20) and subsequent hematoma after receiving two 3 mg oral ivermectin doses. Although data are limited, ivermectin has been shown to antagonize vitamin K-dependent clotting factors II, VII, IX, and X.

[PDR]

Ivermectin interacts with the ABC multidrug transporter P-glycoprotein (P-gp). Lespine et al studied the interactions of ivermectin with the multidrug resistance proteins (MRPs) by combining cellular and subcellular approaches. The inhibition by ivermectin of substrate transport was measured in A549 cells (calcein or 2',7'-bis(2-carboxyethyl)-5(6)-carboxyfluorescein, BCECF) and in HL60-MRP1 (calcein). Ivermectin induced calcein and BCECF retention in A549 cells (IC(50) at 1 and 2.5microM, respectively) and inhibited calcein efflux in HL60-MRP1 (IC(50)=3.8microM). The action of ivermectin on the transporters ATPase activity was followed on membranes from Sf9 cells overexpressing human P-gp, MRP1, 2 or 3. Ivermectin inhibited the P-gp, MRP1, 2 and 3 ATPase activities after stimulation by their respective activators. Ivermectin showed a rather good affinity for MRPs, mainly MRP1, in the micromolar range, although it was lower than that for P-gp. The transport of BODIPY-ivermectin was followed in cells overexpressing selectively P-gp or MRP1. In both cell lines, inhibition of the transporter activity induced intracellular retention of BODIPY-ivermectin. The data revealed the specific interaction of ivermectin with MRP proteins, and its transport by MRP1. Although P-gp has been considered until now as the sole active transporter for this drug, the MRPs should be taken into account for the transport of ivermectin across cell membrane, modulating its disposition in addition to P-gp. [Lespine]

Information about the influence of foods in the pharmacokinetics of ivermectin is scarce. The knowledge of the influence of alcohol in ivermectin kinetic behaviour is scarce; co-ingestion of alcoholic drinks however is not recommended, because of ivermectin association with GABA receptors and the effect of alcohol in the central nervous system. In healthy volunteers administered ivermectin orally (150 μg/kg), plasma levels were significantly higher when coadministered with 750 ml of beer than with 750 ml of water; the plasma concentrations were significantly higher in patients who drank beer (66.3, 109, and 97.2 ng/ml at 1, 3 and 4 h, respectively) vs. those who drank water (44.0, 67.5, and 58.7 ng/ml, respectively, $P < 0.01$ at each time point). Ivermectin (150 μg/kg) was administered to 16 individuals with water or orange juice (750 ml). Orange juice decreased AUC (15.7 ng·d·ml−1) and Cmax (20.7 ng·ml−1) (water: 33.8 ng·ml−1; 24.3

ng·d·ml−1), possibly because fruit juices and constituents are potent inhibitors of certain drug transporters. [Canga]

8.10 Dosage

Dose selection is dependent on the infectious disease concerned, but in general, single or duplicate doses of 150—200 μg/kg per os for relevant indications.

8.11 Ivermectin and COVID-19

8.11.1 Molecular biology and mechanism foundations

Ivermectin, approved for parasitic infections, has received renewed attention in the last eight years due to its apparent exciting potential as an antiviral. Excitingly, cell culture experiments show robust antiviral action towards HIV-1, dengue virus (DENV), Zika virus, West Nile virus, Venezuelan equine encephalitis virus, Chikungunya virus, Pseudorabies virus, adenovirus, and SARS-CoV-2 (COVID-19). Phase III human clinical trials have been completed for DENV, with about 50 trials currently in progress worldwide for SARS-CoV-2. [Jans]
Ivermectin was identified in a high-throughput chemical screen as inhibiting recognition of the nuclear localizing Human Immunodeficiency Virus-1 (HIV-1) integrase protein by the host heterodimeric importin (IMP) α/β1 complex, and has since been shown to bind directly to IMPα to induce conformational changes that prevent its normal function in mediating nuclear import of key viral and host proteins. Host cells contain importin protein which transports viral protein molecules to the nucleus from the cell cytoplasm. It is of two types, namely importin α and importin β. Importin α performs an indispensable role of ferrying proteins from the cytoplasm into the nucleus with a transport carrier, Importin β. In coronavirus replication, nuclear import of viral proteins targeting IMPα is inhibited by IVM. Interestingly, for IVM, molecular modelling studies identified 12 different COVID-19 targets along with IMPα. Of them, the RNA dependent RNA polymerase (RdRp) with RNA and Helicase NCB site show the strongest affinity to IVM, which may contribute to its antiviral activity against SARS-COV-2. [Gupta]

To test the antiviral activity of IVM towards SARS-CoV-2, Caly et al infected Vero/hSLAM cells with SARS-CoV-2 isolate Australia/VIC01/ 2020 at an MOI of 0.1 for 2 h, followed by the addition of 5 μM ivermectin. Supernatant and cell pellets were harvested at days 0–3 and analysed by RT-PCR for the replication of SARS-CoV-2 RNA. At 24 h, there was a 93% reduction in viral RNA present in the supernatant (indicative of released virions) of samples treated with ivermectin compared to the vehicle DMSO. Similarly a 99.8% reduction in cell-associated viral RNA (indicative of unreleased and unpackaged virions) was observed with ivermectin treatment. By 48 h this effect increased to an ~5000-fold reduction of viral RNA in ivermectin- treated compared to control samples, indicating that ivermectin treatment resulted in the effective loss of essentially all viral material by 48 h. Consistent with this idea, no further reduction in viral RNA was observed at 72 h. No toxicity of ivermectin was observed at any of the timepoints tested, in either the sample wells or in parallel tested drug alone samples. [Caly]

Ivermectin also has a remarkable multi-component mediated antiinflammatory effect. LPS-induced murine septic shock model is widely used in the search for drugs and treatment tools for sepsis caused by gram-negative bacterial infections. The authors used a murine endotoxic shock model and studied the effect of ivermectin on survival of mice induced with a lethal dose of LPS. Ivermectin improved the survival rate of mice: Ivermectin inhibited serum TNF-α, IL-1b and IL-6 production. NF-kB has been evidenced to play a major role in LPS-induced expression of inflammatory cytokines including TNF-α, IL-1b and IL-6 in macrophages. NF-kB participates in regulating the expression of cytokines and other mediators that are involved in the inflammatory response. In the presented study, the authors showed that the NF-kB factor p65, which was translocated from the cytoplasm to the nucleus by LPS exposure, was strongly inhibited by ivermectin in a dose-dependent manner. The authors concluded that the inhibition of ivermectin on LPS-

induced inflammatory cytokine production and the improvement of survival in mice with endotoxic shock are at least partially mediated by the suppression of the NF-kB pathway. [Zhang]

Another interesting and relevant mechanistic element of IVM action against SARS-CoV-2 infection, is its **immunomodulant** effect. Ivermectin is a positive allosteric effector of the alpha7 neuronal nicotinic acetylcholine receptor, which may contribute to both immunomodulant and antiinflammatory effects. In addition, its immunomodulant effect may also be mediated via T-helper lymphocytes.

Another important and beneficial mechanism of IVM for SARS-CoV-2 is its interaction with the STAT1/3 – PAI – TLR4 pathway that plays a central role in COVID-19 pathomechanism. Namely, some viral protein components induce STAT1 dysfunction and compensatory hyperactivation of STAT3. It may result in PAI-1 upregulation that leads finally to coagulopathy. Overproduced PAI-1 binds also to TLR4 on macrophages, inducing the secretion of proinflammatory cytokines and chemokines. Severe cases of COVID-19 are commonly dependent on the over-stimulation of the STAT3/PAI-1 signaling network. IVM inhibits STAT3 signaling (and IL-6 production) that, in our opinion, may also contribute to IVM's favorable multi-component therapeutic action. [Matsuyama]

8.11.2 Clinical research

Ivermectin was shown to inhibit severe acute respiratory syndrome coronavirus 2 replication in vitro, which has led to off-label use, but clinical efficacy has not been described previously. In a multihospital retrospective cohort study sequentially consecutive hospitalized patients at four Broward Health-associated hospitals in South Florida with laboratory-confirmed infection with SARS-CoV-2 during their admission, between March 15 and May 11, 2020, treated with or without ivermectin were reviewed.
Two hundred eighty patients, 173 treated with ivermectin and 107 without ivermectin, were reviewed. Most patients in both groups also received hydroxychloroquine, azithromycin, or both. Univariate analysis showed lower mortality in the ivermectin group (15.0% vs 25.2%; OR, 0.52; 95% CI, 0.29-0.96; P = 0.03). Mortality also was lower among ivermectin-treated patients with severe pulmonary involvement (38.8% vs 80.7%; OR, 0.15; 95% CI, 0.05-0.47; P = 0.001). No significant differences were found in extubation rates (36.1% vs 15.4%; OR, 3.11; 95% CI, 0.88-11.00; P = 0.07) or length of stay. After multivariate adjustment for confounders and mortality risks, the mortality difference remained significant (OR, 0.27; 95% CI, 0.09-0.80; P = 0.03). One hundred ninety-six patients were included in the propensity-matched cohort. Mortality was significantly lower in the ivermectin group (13.3% vs 24.5%; OR, 0.47; 95% CI, 0.22-0.99; P < 0.05), an 11.2% (95% CI, 0.38%-22.1%) absolute risk reduction, with a number needed to treat of 8.9 (95% CI, 4.5-263). [Cepelowicz]

Observations showed that SARS-CoV-2 rapidly multiplies in the respiratory tract and evidence from animal models shows 3-fold higher levels of ivermectin in pulmonary tissue than in the plasma one week after oral dosing. To determine the rapidity of viral clearance and safety of ivermectin among adult SARS-CoV-2 patients clinical researchers in Dhaka, Bangladesh, conducted a randomized, double-blind, placebo-controlled trial of oral ivermectin alone (12 mg once daily for 5 days) or in combination with doxycycline (12 mg ivermectin single dose and 200 mg stat doxycycline day-1 followed by 100 mg 12 hourly for next 4 days) compared with placebo among 72 hospitalized patients. Inclusion criteria were: age 18-65 years; admitted to hospital within the last 7 days; with either fever (≥37.5 °C); cough or sore throat; and diagnosed positive for SARS-CoV-2 by rRT-PCR. The primary endpoints were the time required for virological clearance (a negative rRT-PCR result on nasopharyngeal swab); remission of fever (≥37.5 °C) and cough within 7 days. Secondary outcomes included patients failing to maintain an SpO2 > 93% despite oxygenation and days on oxygen support; duration of hospitalization; and all-cause mortality.
A total of 72 (24 per arm) out of 113 patients who consented were enrolled in the trial.
The mean duration of hospitalization after treatment was 9.7 (Confidence interval (CI) = 8.1 - 11.0), 10.1 (CI = 8.5 - 11.8) and 9.6 (CI = 7.7 - 11.7) days in the placebo, ivermectin + doxycycline and ivermectin alone arms respectively (P = 0.93). At enrolment, 82.6% (19/23) of patients in the placebo group, 73.9% (17/23) in the ivermectin + doxycycline arm and 77.3% (17/22) in 5-day ivermectin group were recorded having fever

and among them 84.2% (16/19), 94.1% (16/17) and 100% (17/17) were afebrile at day 7 respectively. Similarly, 65.2% (15/23), 82.6% (19/23) and 81.8 (18/22) had cough on enrolment in the placebo group, the ivermectin + doxycycline arm, and in the 5-day ivermectin group respectively. At day-7 this dropped to 40% (9/15), 63.2% (7/19) and 61.1% (7/18) respectively for cough. Sore throat was present at enrolment in 17.4% (4/23), 13% (3/23) and 18.2% (4/22) of patients in the placebo group, ivermectin + doxycycline group, and 5-day ivermectin group respectively and at day 7, sore throat subsided in 75% (3/4), 33.3% (1/3) and 75% (3/4) patients respectively. It is noteworthy that these changes were not statistically significant for fever ($p = 0.35$ and 0.09), cough ($p = 0.18$ and 0.23) or sore throat ($p = 0.35$ and 0.09) in the ivermectin + doxycycline and the 5-day ivermectin groups when compared with placebo.
The mean duration to viral clearance was 9.7 (CI = 7.8 - 11.8) days, 11.5 (CI = 9.8 - 13.2) and 12.7 days (CI = 11.3 - 14.2) for the 5-day ivermectin arm ($P = 0.02$), ivermectin + doxycycline ($P = 0.27$) arm and the placebo group respectively. Kaplan-Meier survival analysis revealed that the proportion of patients at risk for SARS-CoV-2 was significantly reduced in the 5-day ivermectin group (Figure, below). At day 7 and 14 virological clearance in the 5-day ivermectin group was significantly earlier compared to placebo [Hazard Ratio (HR) = 4.1; Confidence Interval (CI) = 1.1 - 14.7; $p = 0.03$ versus HR = 2.7; CI = 1.2 - 6.0; $p = 0.02$]. This trend was similar with the ivermectin + doxycycline group on day 7 and 14 but not statistically significant (HR = 2.3; CI = 0.6 - 9.0; $p = 0.22$ versus HR = 1.7; CI = 0.8 - 4.0; $p = 0.19$). [Ahmed]

In a very recent (January 2021) meta-analysis of 32 clinical trials, 100% of the 32 studies to date report positive effects. Early treatment is more successful, with an estimated reduction of 85% in the effect measured using a random effects meta-analysis, RR 0.15 (0.06-0.37). Prophylactic use also shows high effectiveness. 100% of the 14 randomized controlled trials report positive effects, with an estimated reduction of 73%, RR 0.27 (0.15-0.51). The probability that an ineffective treatment generated results as positive as the 32 studies to date is estimated to be 1 in 4 billion ($p = 0.00000000023$). [IVMmeta]

9 Study rationale and benefit-risk assessment

9.1 Summary

In December, 2019, Wuhan city, the capital of Hubei province in China, became the centre of an outbreak of pneumonia of unknown cause. By January 2020, Chinese scientists had isolated a novel Coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), from these patients with virus-infected pneumonia, which pathology was later designated as Coronavirus Disease 2019 (COVID-19) in February 2020 by WHO.The COVID-19 pandemic is pushing the limits of hospital care capacities worldwide, including in Hungary. Prolonged hospitalization of patients in severe conditions requiring intensive care followed by invasive ventilation for up to weeks; high mortality rates; possible long-term damage to health - predominantly young / middle-aged patients infected by Sars-CoV-2 showing long-term, persistently debilitating post-COVID-19 symptomatology; individually, but especially in combination, they require drug therapy that can help to avoid hospitalization and reduce health and economic burden of COVID-19. These therapeutic needs clearly cannot be met by the drugs and treatment regimens currently used for COVID-19 therapy. Thus, there remains an urgent need for effective drugs for prevention and treatment of COVID-19 infections.

SARS-CoV-2 pathogenesis is triggered by viral infection, and amplified by inflammation and dysfunctional immune responses. Antiviral agents or cytokine inhibitors are routinely used to treat the already high viral load and hyperinflammatory syndrome, the "cytokine storm". Both approaches can be strongly criticized: either eliminating high virus levels or overcoming a severe condition are rather challenging, and pose a tangible pharmaceutical and clinical hardship. In addition, effectiveness of cytokine storm-based treatments may be limited ab ovo. Whether cytokine storm plays a role in COVID-19-induced organ dysfunction at all is questionable {Leisman et al, Lancet Respir Med, October 2020, https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30404-5/fulltext#%20}. Functional evaluation of immune system of COVID-patients also supports the hypothesis that severe suppression of host functional adaptive and innate immunity and not a cytokine storm characterizes majority of COVID-infections {Remy et al. JCI insight, July 2020, https://jci.me/140329/pdf}. Accordingly, and not surprisingly, selective cytokine inhibitors may fail to improve symptoms, and immunsuppressive therapy may further worsen the condition of patients.

We have come to the conclusion that it is worth exploring a new therapeutic paradigm. Namely, a multiple targeting drug that has a complex mode of action, including i) a robust antiviral effect, preferably from the host side (to minimize the development of viral resistance), ii) an immunmodulant (not immunsuppressant!) effect together with iii) a finely tuned, complex anti-inflammatory action. Ivermectin (IVM) may be suitable for these purposes. It has been in clinical use for a long time (veterinary: since 1981; human: since 1987) as an orally and topically active agent for treating a range of parasitic infections in both animals and humans. Thus, the pharmacodynamic, ADME and safety profiles of IVM are well studied and characterized. In fact, there are currently almost 50 clinical trials worldwide (www.clinicaltrials.gov) to investigate the possible role of IVM in COVID-19 therapy from prevention to late stage treatments. IVM has a complex mode of action that is fundamentally different from the agents used in COVID to date.

- IVM shows a significant, robust, dose-dependent in vitro antiviral effect against SARS-2 (infected VERO cells), based on its ability to inhibit binding of host importin protein (IMP) to some viral proteins. This action inhibits delivery of viral proteins to nucleus and leads to blockade of the viral infectious cycle.
- IVM is a positive allosteric effector of the alpha7 neuronal nicotinic acetylcholine receptor, which may contribute to both immunmodulant and antiinflammatory effects. In addition, its immunmodulant effect may be mediated via T-helper lymphocytes, whereas its complex antiinflammatory action, providing a wide

scope, can also be interpreted by other mechanism components.

• Doses up to 2000 μg/kg are well tolerated in patients with parasitic infections, with analysis of the first 11 years of mass global IVM (Mectizan) administration indicating a cumulative incidence of one serious adverse side effect case per million. Although drug resistance can occur in animals, no resistance in humans has yet been confirmed in over 25 years.

• The risk of mechanism-based central nervous system (CNS) side effects of IVM can be minimized by considering that such effects may originate from the human counterpart of the antiparasitic GABA-receptor based action and can only occur in the case of a damaged blood brain barrier (BBB) (N.B. IVM does not cross intact BBB by passive diffusion).

• Furthermore, adverse events originating from IVM's modulatory effect on several drug transporters and CYP enzymes, can be avoided by excluding concomitant use of certain drugs.

9.2 Study rationale

The evolution of the COVID-19 pandemic to date indicates that drug therapy has failed to achieve breakthroughs in both prevention and treatment. In many countries, hospital capacities have reached or are approaching their limits. Prolonged hospitalization of moderately severe patients and those requiring intensive care followed by long-term invasive ventilation in many cases – high mortality rate, and as an underestimated component so far, long-term health effects even with significant additional load of health care – each of them individually, but especially together, justifies the urgent need for effective drug therapy. Last but not least, high COVID-19 hospitalization rate also limits ultimately fulfilling the care of non-COVID-19 patients.

These therapeutic needs clearly cannot be met by the drugs and therapeutic regimens currently used for COVID-19 therapy.

In the light of all these antecedents, **our approach aims to prevent the development of moderate/severe conditions requiring hospitalization**. **We believe that asymptomatic virus-infected patients or those with mild symptoms need treatment to prevent their condition from progressing.** This strategy is fundamentally different from current medical practice approaches. The pharmacotherapy of COVID-19 has so far primarily, if not exclusively, focused on the treatment of hospitalized patients, whose condition has already – sometimes irreversibly – been worsening. Antiviral agents or cytokine inhibitors are routinely used to treat the already high viral load and hyperinflammatory syndrome, the "cytokine storm". Both approaches can be strongly criticized: either eliminating high virus levels or overcoming a severe condition are rather challenging, and pose a tangible pharmaceutivcal and medical hardship. In addition, anti-cytokine-storm-based treatment is questionable for theoretical reasons. Some studies published in the second half of the year pointed out that a cytokine storm only develops in a small proportion of COVID-19 patients. Thus, Remy et al described that COVID-19 leads to - instead of a cytokine storm - the collapse of immune system, by suppressing host functional adaptive and innate immunity [Remy]. Another excellent study also questioned the role of a cytokine storm in COVID-19-induced organ dysfunction [Leisman]. Accordingly, selective cytokine inhibitors may fail to improve symptoms, while suppression of the immune system can worsen the condition of such patients.

Taking all this into account, we have come to the conclusion that it is worth exploring a new therapeutic paradigm using a multi-targeting drug [Mátyus] that has a complex mode of action, including i) a robust antiviral effect, preferably from the host side (to minimize the development of viral resistance), ii) an immunmodulant (not immunsuppressant!) effect together with iii) a finely tuned, itself complex anti-inflammatory action. These complementary and even synergistic mechanism components provide a reasonable basis for the treatment of non-hospitalized asymptomatic or mildly symptomatic patients to prevent the development of severe conditions requiring hospitalization. Evidently, due to the urgent needs, a drug-repositioning strategy for the development of the drug candidate may be considered, due to its favorable time- and cost-efficiency.

In our opinion, ivermectin (IVM) may be suitable for these purposes. It has been in clinical use for a long time (veterinary: since 1981; human: since 1987) as an orally and topically active agent for treating a range of parasitic infections in both animals and humans. Thus, the pharmacodynamic, ADME and safety profiles of IVM are well studied and characterized. In fact, there are currently almost 50 clinical trials worldwide (www.clinicaltrials.gov) to investigate the possible role of IVM in COVID-19 therapy from prevention to late stage treatments.
The data available for IVM are also in line with our conception and therapeutical expectations. It has a complex mode of action that is fundamentally different from the agents used in COVID-19 to date.

- IVM shows a significant, robust, dose-dependent in vitro antiviral effect against SARS-2 (infected VERO cells), based on its ability to inhibit binding of host importin protein (IMP) to some viral proteins. This action inhibits delivery of viral proteins to nucleus and leads to blockade of the viral infectious cycle. Some researchers dispute that IVM can exert a sufficiently strong inhibitory ability based on the plasma concentration, when used at the usual dose. On the one hand, we are aware that in vitro inhibition concentration and plasma concentration do not necessarily correlate. On the other hand, in line with other opinions, we also consider otherwise much higher tissue (particularly lung) concentrations to be relevant and achievable with IVM in COVID-19 therapy. Therefore, we also consider its antiviral effect to be appropriate. Besides its antiviral effect, IVM contributes to the fight against the infection in two other ways, by helping the immune system, which is in the early stage of infection still helps eliminate the virus, and by inhibiting the inflammatory process initiated by the infection. These effects are based on the following abilities of IVM.
- IVM is a positive allosteric effector of the alpha7 neuronal nicotinic acetylcholine receptor, which may contribute to both immunmodulant and antiinflammatory effects. In addition, its immunmodulant effect may be mediated via T-helper lymphocytes, whereas its complex antiinflammatory action, providing a wide scope, can also be interpreted by other mechanism components [DiNicolantonio].

The safety of therapy is, of course, a basic need. There is a wealth of human and veterinary experience with the acceptable safety profile of IVM. All of this supports the fact that severe side effects have been reported rarely in treatment regimens commonly used in antiparasitic therapy.
Doses up to 2000 μg/kg are well tolerated in patients with parasitic infections, with analysis of the first 11 years of mass global IVM (Mectizan) administration indicating a cumulative incidence of one serious adverse side effect case per million. Although drug resistance can occur in animals, no resistance in humans has yet been confirmed in over 25 years. [Jans]
N.B. More than 2.7 billion 150–200 μg/kg single doses have been distributed by the Mectizan Donation programme, providing ample post-marketing pharmacovigilance experience. Ivermectin is safe in MDA campaigns (Mectizan Donation Programme) at the current dose approved for onchocerciasis and filariasis 150–200 μg/kg administered not more than four times a year. [Chaccour]
The risk of mechanism-based CNS side effects of IVM can be minimized by considering that such effects may originate from the human counterpart of the antiparasitic GABA-receeptor based action and can only occur in the case of a damaged blood brain barrier (IVM does not cross intact BBB by passive diffusion).
N.B. Neuroimaging studies in the living human brain, post-mortem tissue and biomarker studies have demonstrated blood–brain barrier (BBB) breakdown in Alzheimer disease, Parkinson disease, Huntington disease, amyotrophic lateral sclerosis, multiple sclerosis, HIV-1-associated dementia and chronic traumatic encephalopathy [Sweeney], thus such pathologies should be regarded as exclusion criteria in the study population.
Furthermore, adverse events originating from IVM's modulatory effect on several drug transporters (P-gp and BCRP) and CYP enzymes, can be avoided with no concomitant use of certain drugs.

Based on all of the above data and our comprehensive arguments as well as the encouraging interim, in some cases, complete results of clinical studies with IVM in many countries, we recommend and initiate a Phase II clinical study of IVM for the therapy of COVID-19 infected patients.

9.3 **Dose rationale**

Beyond the usual dose range of up to 200 μg/kg ivermectin, which has a well-documented and very favorable safety profile, doses up to 10 times the 200 μg/kg dose were evaluated by Guzzo et al {J Clin Pharmacol, 2002;42:1122-1133} to provide a substantial safety margin over the anticipated dosage range in a double-blind, placebo-controlled, multiple rising dose study in healthy adult men and women. Of the 51 subjects who received ivermectin, 12 subjects (24%) reported at least one clinical adverse experience. This rate was similar to that observed in the placebo group (6 subjects, 35%). In addition, there was no consistent trend in the incidence of adverse experiences indicative of a dose response. All clinical adverse experiences were transient and mild, and no adverse experience recurred with repeated dosing. The most commonly reported adverse experiences were headache, nausea, dizziness, and rash, occurring in both ivermectin- and placebo-treated groups.

A fixed and high dose regimen which takes advantage of the wide therapeutic index of IVM is an attractive alternative for improving the distribution and therefore potentially increasing coverage rates of treatment campaigns. A healthy volunteer pharmacokinetic study was designed by Munoz et al {PLoS Negl Trop Dis 12(1): e0006020} to evaluate the safety and pharmacokinetic profile of 3 dosing regimens - 2 experimental treatments using a new 18 mg ivermectin tablet in a fixed-dose strategy of 18 and 36 mg single dose regimens, compared to the standard, weight based 150–200 μg/kg, regimen - of IVM in 54 healthy adult volunteers stratified in 3 weight groups in an open-label, randomized, crossover phase I clinical trial performed under fasting conditions. No abnormal result or significant differences were found between biochemistry at baseline and after the administration of IVM in any of the three study arms. A slight decrease in Haemoglobin (Hb) levels was observed after administration of IVM in the three study arms.
The main electrocardiographic parameters were not affected by the administration of IVM. Systemic blood pressure measurements were not affected by treatment administration.
A total of 33 treatment emergent adverse events were reported by 22 subjects who received at least one dose of the study medication. No significant association was found between the distribution of adverse events and the three treatments arms.

Clinical trials of COVID-19 worldwide employing ivermectin alone or in combination utilize a wide range of regimens, starting from the single dose application, up to a 5-day schedule. Weighing in that IVM favorably accumulates in the respiratory tract tissue, we have decided to employ a daily once 15 mg fixed dose, 4-day regimen to build up steady state conditions, targeting high efficiency of IVM for combatting the COVID-19 infection and providing an early virus clearance.

9.4 **Benefit-risk assessment**

Since no “gold-standard” therapy exists as yet to treat COVID-19 patients, several therapeutical approaches are being employed both in everyday practice, and also in the domain of clinical research.

We chose a novel, multi-targeting approach to the treatment of COVID-19, combining antiviral, immunmodulant and antiinflammatory components in a single molecule with ivermectin, which has a well-established safety profile in parasitic diseases. Together, these may provide a very favorable benefit-to-risk ratio of achieving early virus-elimination in COVID-19 patients.

As special safeguards, we exclude individuals from the trial with
1. particular central nervous system interventions and disorders, which may cause breakdown the blood-brain-barrier (BBB) and result in transport of IVM to brain: encephalitis, meningitis, stroke (acute, subacute), lumbal puncture, epidural and spinal anaesthesia within 2 months of randomization; neurodegenerative conditions;
2. concomitant medication which interferes with CYP3A4 or the membrane drug transporters (P-gp, BCRP).

10 Study plan

10.1 Study objectives

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.

Safety Objective: Assessment of safety of per os ivermectin administration in asymptomatic and mild severity SARS-CoV-2 infected patients.

For study endpoints, please refer to Section 15.2. Evaluation.

10.2 Structure of the study

This is a randomized, double-blind, placebo-controlled study with per os ivermectin or placebo treatment.

10.3 General time schedule

Screening period may last up to 3 days (D-3 … D1). If appropriate (e.g. study entry can be warranted upon positive rapid SARS-CoV-2 antigen test), the screening visit can be considered also as Day 1, start of IMP administration. In this case, activities applicable for both Screening and Day 1 will be conducted only once and results will be captured as data pertaning to Day 1.

Treatment with ivermectin or matching placebo will be administered for 4 days as a once-daily dose regimen (D1-D4).

Follow-up period (with safety and efficacy assessments) will last 21 days, from treatment initiation (D1-D21).

The visits will be conducted at the domicile (or at the designated quarantine location) of the study subjects, or ambulantory at the study sites while fully adhering to pertinent infection-control quarantine regulations.

10.4 Test preparations

	Test preparation	Placebo
Name	Ivermectin	Placebo
Manufacturing data	Merck Sharp & Dohme BV Waarderweg 39 2031 BN Haarlem Netherlands Repackaging at MEDITOP Pharmaceutical Ltd. 2097 Pilisborosjenő, Ady Endre utca 1.	MEDITOP Pharmaceutical Ltd. 2097 Pilisborosjenő, Ady Endre utca 1.

The labeling is in accordance with the regulatory specifications and requirements.

10.4.1 Storage conditions

The IMP has to be stored at or below 25 C, and should be accessible for authorized personnel only. The IMP shall be stored in its original package in order to protect it from moisture and light.

The temperature of the storage location shall be controlled, and checked regularly, with any deviations to be recorded. The Sponsor shall decide whether temperature excursions result in a temporary quarantine, and then a release for further use, or the affected package(s) shall be permanently removed from utilization within the frames of the study.

10.4.2 Responsibilities

All IMP shall be dispensed in accordance with this Study Protocol, and it is the responsibility of the Investigator to ensure that an accurate record of IMP issued is duly maintained.

Any quality issue noticed with the receipt or use of an IMP (deficient package in condition, appearance, pertaining documentation, labeling, expiry date, temperature excursions during storage, etc.) should be promptly notified to the Sponsor, and until the Sponsor's decision the concerned package / shipment shall be quarantined separately.

Under no circumstances shall the Investigator supply the IMP to a third party, allow the investigational medicinal product to be used other than as directed by this Clinical Study Protocol, or dispose of the IMP in any other manner.
The Investigator, or its Delegate / Study Pharmacist will confirm the receipt of IMP in writing. The administration of the IMP will be recorded in an appropriate log and afterwards in the Case Report Form. Utilization of each IMP (test preparation and placebo) shall be trackable: the inventory log shall contain an appropriate record of which IMP has been administered, e.g.:

- Package ID and / or Batch number
- Subject ID
- Date of administration (calendar date and designation of study day – i.e. D1… D4)

The study drug inventory shall be thoroughly based on the Subject Diary, which contains the source data about patient self-administration of the IMP.

10.4.3 Retrieval and/or destruction of IMP

10.4.3.1 Partially used or unused IMP

It is the Sponsor's responsibility to ensure the destruction of all partially used or unused IMP. A detailed log of the returned IMP will be established with the Investigator and countersigned by the CRO monitoring team.

The Study Site must not destroy partially used or unused IMP prior to review by and approval of the CRO monitoring team.

10.4.3.2 Potential recall

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

10.5 **Treatment plan**

Distribution of subjects:
Total number of randomized patients: 70.

Two treatment groups, randomized in a 1:1 ratio to ivermectin or matching placebo.

No standard of care COVID-19 therapies are allowed. For symptomatic relief of e.g. fever, sore throat, e.g. antipyretics, analgesics may be used concomitantly.

Please refer to Section 12. Study procedures for a detailed description of study procedures.
Please refer to Section 3. Study flowchart for a detailed description of the timing of study procedures.

10.6 Randomization, emergency unblinding

This will be a double-blind study.
Breaking the blind - unmasking of treatment allocation should only occur in a medical emergency, by the Investigator or its medical delegate (subinvestigator), preferably after consulting this action with the Sponsor.
The Sponsor should be immediately (within 24h of the occurrence) notified about this act.

10.7 Selection of doses

Ivermectin:
15 mg (5 x 3 mg tablets), once daily, per os, for 4 (four) consecutive days

Placebo:
Placebo dosing schedule will be the same as with the active ingredient, to fulfil double-blind nature of dose administrations: once daily, for 4 (four) days.

11 Study population

Key attributes:

• 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

11.1 Inclusion criteria

• Males and females 18-75 years of age

• 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

• Asymptomatic or mild COVID-19 cases: NO dyspnoe and NO tachypnoe (respiratory rate <22 / min), NO need for oxygen-supplementation; NO radiological findings of pneumonia (NB. No medical imaging will be conducted within the frames of the study. If previous medical imaging report is available, its result will be however utilized.)

• Build: $20 \leq BMI \leq 28$ kg/m2

• Subjects who are able to communicate with the Investigator and research staff, who understand the study, are able to comply with all study procedures, and willing to provide written informed consent prior to the screening examinations

NB. Women of childbearing potential should agree to use a highly effective method of contraception throughout the study and up to 1 month afterwards. Male subjects shall agree to effective contraception during the study and for 14 days following the last drug administration.

• For females, adequate birth control methods will be defined as: hormonal contraceptives, intrauterine device or double barrier contraception, i.e., condom + diaphragm, condom or diaphragm + spermicidal gel or foam

• For males adequate birth control methods will be defined as double barrier contraception, i.e., condom + diaphragm, condom or diaphragm + spermicidal gel or foam

11.2 Exclusion criteria

• Moderate COVID-19 cases: showing dyspnoe and / or tachypnoe, or a need for oxygen-supplementation, or radiological findings of pneumonia. {Definition of moderate COVID-19 as per “Magyar Koronavírus Kézikönyv”, “Igazolt COVID-19 fertőzött felnőtt betegek rizikóstratifikációja” fejezet (Hungarian Coronavirus Manual, Section “Risk stratification of confirmed adult COVID-19 patients”) } Radiological findings – established either by chest X-ray or native chest (pulmonary) CT scan - include multiplex consolidations and milk-glassy haze, often in a bilateral distribution.

• Severe COVID-19: respiratory distress - respiratory rate ≥ 30/min; or oxygen saturation at rest ≤ 93%; or pulmonary infiltrates occupy > 50% of the lung-fields

• Critical COVID-19: acute respiratory distress; or requiring mechanical ventilation; or radiomorphology of ARDS; or shock, including septic shock; or other organ dysfunction necessitating ICU admission

• High-risk patient for progression of COVID-19, as defined by having a calculated pneumonia PORT-score of > 90

• Concomitant or previous administration of any experimental, non-established COVID-19 therapy, either in off-label indication of a registered medicinal product or as a non-registered drug candidate in a clinical trial setting or compassionate use program (or equivalents thereof)

• NO previous COVID-19 therapies allowed, as per recommendation of the “Magyar Koronavírus Kézikönyv” (Hungarian Coronavirus Manual)

• Concomitant administration of coumarin-derivatives or warfarin

• Concomitant administration of cytochrom-P450 or membrane drug transporter, especially ABCB1/P-gp and ABCG2/BCRP (breast cancer resistance protein) modifiers
• Any clinically significant abnormality identified during screening full physical examination, vital signs, laboratory tests and ECG which is deemed by the investigator to be incompatible / inappropriate for study participation
• A current or recent history of drug or substance abuse, including alcohol (> 14 units per week), within 3 months prior to screening (one unit of alcohol equals ½ pint [285 mL] of beer or lager, one glass [125 mL] of wine, or one shot [25 mL] of spirits)
• Patients who regularly consume more than 4 cups daily of beverage containing caffeine
• Current strong smoker as defined by smoking over 10 cigarettes a day, or its equivalent
• Positive pregnancy test result for women with childbearing potential at screening
• Women who are pregnant or nursing, or who are planning to get pregnant within 3 months after the last dose of study drug
• A history of allergy, intolerance or sensitivity to ivermectin or any component of the study drug formulation
• Exhibiting any pathology, contraindicated with ivermectin administration: e.g. asthma, clinically significant hepatic diseases, human immunodeficiency virus (HIV) infection, immunosuppression, onchodermatitis, Loa loa infection
• Have undergone surgery or have donated blood within 12 weeks prior to the start of the study
• A history of bleeding diathesis or other bleeding disorders
• Investigational drug administration or investigational device application within 1 month preceding study entry, or within 5 terminal half-life of the investigational drug of the previous study, whichever is the longer
• A history of malignancy within 5 years from screening visit, with the exception of resected basal cell carcinoma or squamous cell carcinoma of the skin, or resected cervical intraepithelial neoplasia
• Particular central nervous system interventions and disorders, which may cause breakdown of the blood-brain-barrier (BBB) and result in transport of IVM to brain: encephalitis, meningitis, stroke (acute, subacute), lumbar puncture, epidural and spinal anaesthesia within 2 months of randomization; neurodegenerative conditions (e.g. Alzheimer's disease, Parkinson's disease, Huntington disease, amyotrophic lateral sclerosis); multiple sclerosis, HIV-1-associated dementia and chronic traumatic encephalopathy.

11.3 **Prohibited concomitant medications**

• Coumarin-derivatives and warfarin
• CYP3A4 modulators (substrates, inhibitors, inducers) according to: "Cytochrome P450 3A4 and 3A5 Known Drug Interaction Chart", https://www.mayocliniclabs.com/it-mmfiles/Cytochrome_P450_3A4_and_3A5_Known_Drug_Interaction_Chart.pdf
• Membrane drug transporter P-gp / MDR modulators, according to:"Inhibitors and inducers of P-glycoprotein", https://www.uptodate.com/contents/image/print?imageKey=EM%2F73326&topicKey=RHEUM%2F1666&source=see_link FDA - Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Table 5-1: Examples of clinical substrates for transporters (for use in clinical DDI studies and/or drug labeling) (12/03/2019) https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-1
• BCRP modulators (substrates, inhibitors) according to: Table I and Table II of "Role of the Breast Cancer Resistance Protein (BCRP/ABCG2) in Drug Transport—an Update" , AAPS J. 2015 Jan; 17(1): 65–82. doi: 10.1208/s12248-014-9668-6

Please Refer to Appendix 2 for a complete listing of respective prohibited concomitant medication.

11.4 Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming post-menopausal, unless permanently sterile. Permanent sterilization methods include: hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with documented hysterectomy or bilateral salpingectomy or bilateral oophorectomy.

Postmenopausal female:
Postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.
Note: Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products
- Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

Women of childbearing potential should agree to use a highly effective method of contraception throughout the study and up to 1 month afterwards. Male subjects shall agree to effective contraception during the study and for 14 days following the last drug administration.

- For females, adequate birth control methods will be defined as: hormonal contraceptives, intrauterine device or double barrier contraception, i.e., condom + diaphragm, condom or diaphragm + spermicidal gel or foam
- For males adequate birth control methods will be defined as double barrier contraception, i.e., condom + diaphragm, condom or diaphragm + spermicidal gel or foam

11.5 Rescreening

Any (failing) parameter of any patient can be re-screened under the discretion of the Investigator, within the predetermined screening period, i.e. within 3 days of providing informed consent.
Outside of this time window, the subject shall be reconsented and assigned a new screening number (please refer to Section 11.7. Identification of the subjects).

11.6 Regulations on lifestyle and nutrition

- Consumption of alcohol, papaverous food, citrus (orange, grapefruit) and their juices will be prohibited 48 hours prior to treatment start until the last follow-up visit
- Xanthines-containing beverages and food (e.g. caffeine-containing beverages: coffee, tea, cola, energy drinks; chocolate, cocoa) can be consumed responsibly, not exceeding 4 cups daily of beverage containing caffeine
- Consumption of drugs-of-abuse is prohibited, unless with medical intent (e.g. benzodiazepines for anxiety)

11.7 Identification of the subjects

Subjects will be identified by a composite string of characters, consisting of two sections: a two-digit number of the study site ("ss") and a running three-digit identification number ("nnn"), upon giving informed consent which will be used throughout the complete study period, i.e. the subject will retain this ID assignment past the screening period after successful randomization, and through the whole treatment period as well.
Study subjects identification number format: ***ss-nnn,*** padded with initial zero(s) per code section, if appropriate.

11.8 Discontinuation of subjects

Subjects have the right to voluntarily withdraw from the study at any time for any reason. In addition, the Investigator has the right to withdraw a subject from the study at any time.

In case of **progression of COVID-19 disease course** appropriate measures should be taken to provide the subject adequate medical care, by e.g. forwarding them to COVID-19 medical inpatient facilities for standard-of-care pharmacotherapy and discontinue study medication and / or withdraw them from the study, as appropriate.

Reasons for withdrawal from the study may include, but are not limited to, the following:

- Subject withdrawal of consent
- Subject non-compliance, defined as failure to comply with protocol requirements as determined by the Investigator or Sponsor
- Study termination or site closure

Every effort should be made to obtain information on subjects who withdraw from the study but have not withdrawn consent. The primary reason for withdrawal from the study should be documented on the (e)CRF. If a subject requests to be withdrawn from the study, this request must be documented in the source documents and signed by the Investigator. Subjects who withdraw from the study may be replaced.

Every effort should be made for withdrawn patients, to conduct an early termination follow-up safety visit at or around the time of the regular, per-protocol last follow-up visit, i.e. on Day 21.

11.9 Replacement of subjects

Any drop-outs shall be replaced at the Sponsor's discretion and at the Sponsor's disbursement of costs.

12 Study procedures

Subject eligibility (i.e. fulfilment of inclusion-exclusion criteria) shall be ultimately checked on Day 1, after finishing screening activities, but still before the first administration of the IMP.

12.1 Study activities

Please refer to Section 3. Study flowchart for a detailed description of the timing of study procedures.
Also, any particularities, details and context of the study activites will be duly explained in the "*Notes"* section of this flowchart.

12.1.1 Safety assessments

• Demographics and medical history
• Body height and weight, calculation of Body Mass Index (BMI)
• Physical examination
• Vital signs (heart rate, blood pressure) (supine position)
• Electrocardiogram
• Hemostasis lab panel: Prothrombin time (PT), Partial Thromboplastin Time (PTT), D-dimer
• Hematology lab panel: Complete blood cell count, differential blood count, hemoglobin concentration, hematocrit, erythrocyte sedimentation rate
• Blood chemistry: Sodium, potassium, chloride, magnesium, calcium, phosphorous, blood urea, creatinine, eGFR, glucose, uric acid, total bilirubin, total protein, albumin, gamma-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, creatinine phosphokinase, C-reactive protein, ferritin
• Urine drug test and alcohol breath test
• Urine pregnancy test
• Urinalysis: specific gravity, pH, glucose, protein, ketones, bacteria / nitrites, bilirubin, urobilinogen, blood, sediment, urinary sodium, urinary creatinine
• Adverse events

12.1.2 Efficacy assessments

• SARS-CoV-2 nucleic acid by quantitative RT-PCR
• Respiration rate (supine position)
• Tympanic temperature (supine position)
• Cough burden scale
• Dysgeusia-ageusia scale
• Anosmia scale
• Fatigue scale

12.2 Precedence order and time window of assessments / interventions and study visits

If at any time-point multiple assessments / interventions are scheduled and interfere with each other, the recommended **precedence** order is the following:

- Medical activities: physical examination, AE and concomitant medication monitoring
- ECG
- Vital signs
- Biological sampling

Applicable time / visit windows:

- Biological sampling should occur in fasting state (a minimum of 8 hours fasting), preferably in the morning hours.
- Other activities, e.g. physical examination, ECG, vital signs are also recommended to be executed in the morning hours, but a fasting state is not required.
- An ± 1 (one) day visit window will be introduced to any visit from Day 7 (inclusive and onward).

13 Practical details

13.1 Study plan deviation, study plan waiver

All study waivers have to be discussed with the Sponsor's representative.
Deviations of the protocol shall be reported as soon as possible to the Sponsor, and their potential ramifications to the study discussed.

13.2 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms (ICFs) for enrolled subjects and for subjects who are not subsequently enrolled will be maintained at the study site.
All screening evaluations must be completed and reviewed to confirm that subjects meet all eligibility criteria before enrolment. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

13.3 Medical history, concomitant medication, and demographics

Medical history, including clinically significant diseases, surgeries, cancer history, reproductive status, and use of alcohol, nicotine, caffeine, and drugs of abuse, will be recorded at screening. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the subject within 30 (thirty) days prior to study drug treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.
Demographic data includes age, sex, and self-reported race/ethnicity.

13.4 Physical examination

- A **complete** physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Gynaecological (incl. breast examination), urological and rectal digital exams can be omitted, unless medically indicated.
- **Symptom-driven partial** physical examinations may be performed any time, at the Investigator's discretion.

Any abnormality identified initially (baseline) should be recorded on the (e)CRF. Changes from baseline abnormalities should also be recorded. New or worsened clinically significant abnormalities should be captured as AEs on the (e)CRF.

13.5 Vital signs

Vital signs comprise measurements of heart rate, blood pressure, respiration rate, and body temperature (tympanic).
These parameters will be assessed in supine position after a bed rest of at least 5 minutes
.

13.6 ECG

ECG recordings must be performed after the subject has been resting in a supine position for at least 5

minutes.
All ECG recordings should be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible.
Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

If the QTcF exceeds 500 ms and/or is at least 60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs.

13.7 Pneumonia Severity Index (PORT Score)

English version: https://qxmd.com/calculate/calculator_248/pneumonia-severity-index-port-score

13.8 Symptom reporting

Symptom-burden will be assessed by ordinal scales, and captured as reported by the patient, i.e. these will be Patient-Reported Outcome (PRO) indicators. The patient shall be asked to evaluate the last 24h symptom experience subjectively:

- Cough burden scale, by weighing in intensity, frequency
- Dysgeusia-ageusia scale
- Anosmia scale
- Fatigue scale

These symptomata-scales (cough burden, dysgeusia-ageusia, anosmia and fatigue) will have a valid value set of 0..10. A value of 0 (zero) represents absence of the concerned symptom. A value between 1..10 represents manifestation of the symptom, increasing intensity from the minimum ("just a hint of") 1, up to the maximum ("unbearable") intensity of 10.

13.9 Pulmonary imaging (optional!)

Medical imaging of radiological manifestation of COVID-19 will be established via native chest (pulmonary) CT (preferably!) or chest X-ray, if this is part of the local standard-of-care.
N.B. This is an optional item for eligibility, to be confirmed only in case of availability of medical imaging, and does not consitute as a study procedure!

13.10 Biological sampling

Blood samples will be taken by direct venipuncture. Procedures of blood sampling and sample processing for safety laboratory follow customary clinical standards. Example sampling and sample storage material and blood volume requirements, per measurement:

- Haematology: K3EDTA 1x2 ml tube
- ESR: 4NC ESR sodium citrate 3.2% 1x 1.6 ml tube
- Chemistry: Z Serum Clot Activator, native 1x 6 ml tube
- Urinalysis: 0.5-1 dl of urine
- Urine drugs-of-abuse: about 3-5 ml of urine

Note: These tube arrangements are shown for demonstration purpose only - local laboratories, rendering service, shall be inquired about their tube preference.

The total amount of blood loss during the study, per subject, will be approximately 56 ml.

Sampling for SARS-CoV-2 nucleic acid determination via RT-PCR will be executed by nasopharyngeal swab. Conduct and sample processing, as per the official guideline of the National Public Health Center (Nemzeti Népegészségügyi Központ)
(https://www.nnk.gov.hu/attachments/article/567/4_sz_melléklet_labor_mintavétel_2020.06.11.pdf)

13.11 Dose administration

- Study drugs will be self-administered. Self-administration will be documented by the patient in the provided Subject Diary.
- The study drugs will be administered in fasting state, in the morning hours, with about 2 dl of non-carbonated water.
- Patient compliance check will be performed during on-site visits.

13.12 Meals during the study

With the exception of the restrictions as described in Section 11.6. Regulations on lifestyle, nutrition and concurrent medication, there are no other special requirements related to food and beverage intake afterwards.

14 Safety monitoring

Continuous questioning for and registration of possible adverse events will be carried out during the whole study. Subjects will be instructed to report any adverse changes occurred in their state of health during the study.
For safety reasons each subject will be kindly requested upon enrolment to inform his/her general practitioner (GP) about her/his participation in this study, unless the subject expressively does not agree to inform her/his GP.
Each subject will be kindly requested to keep a ***Safety Card*** all the time with themselves during the study, containing relevant study data and contact information in case of a medical emergency.

Adverse and serious adverse events shall be captured from the time of informed consent until the final, study close-out visit.

14.1 Adverse Events

- ***Clinical adverse events*** are illnesses, signs or symptoms that appear or worsen during the study or the follow-up period.
- ***Laboratory adverse events*** are abnormal values obtained upon laboratory tests during the study and follow-up period. The Investigator shall clearly mark in the (e)CRF all laboratory findings outside the normal range and will indicate which of those deviations are considered as clinically relevant.

The finding of an **elevated ALT or AST** (> 3 * baseline value) in combination with either an elevated total bilirubin (> 2 * ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law) – **Drug-Induced Liver Injury (DILI).** Therefore, Investigators must report the occurrence of either of the following:

- Treatment-emergent ALT or AST > 3 * baseline value in combination with total bilirubin > 2 * ULN (of which > 35% is direct bilirubin)
- Treatment-emergent ALT or AST > 3 * baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the (e)CRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) as a serious AE.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the (e)CRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the (e)CRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

A **pre-existing medical condition** is one that is present at the screening visit for this study. Such conditions should be recorded on the (e)CRF. A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the (e)CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Adverse events, whether believed to be IMP-related or not, should be recorded in the Case Report Forms. For all adverse events concomitant medications should be noted.
To accurately report adverse events, the Investigator shall use the following **definitions**:

- Adverse event (Experience) (AE): any untoward medical occurrence that may present itself during treatment with a pharmaceutical product, but does not necessarily have a causal relationship with the IMP.

- Adverse Drug Reaction (ADR): a response to a pharmaceutical product which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of a physiological function.
- Expected: a response to a pharmaceutical product, which is noxious and unintended which has been observed and recorded in the labeling information.
- Treatment-emergent AEs (TEAEs) are defined as AEs that developed, worsened or became serious during the on-treatment period (from first dose of IMP).

Severity of the experience, regardless of the cause, will be graded by the Investigator using the following terms:
- Severe: incapacitating with inability to work or do usual activity;
- Moderate: enough discomfort to cause interference with usual activity;
- Mild: awareness of sign or symptom, but easily tolerated.

Consistently with regulations and guidelines, adverse events are undesirable experiences whether or not considered causally related to a study preparation.
The assignment of degree of **"relatedness"** to an investigational medicinal product should be made using the following definitions.
- Definite: clear-cut temporal association, with a positive re-challenge test or laboratory confirmation
- Probable: clear-cut temporal association, with improvement upon withdrawal, and not reasonably explained by the subject's known clinical state
- Possible: less clear temporal association; other aetiologies are also possible
- None: no temporal association; related to other aetiologies such as concomitant medications/conditions, or subjects' known clinical state.

14.2 Adverse events of special interest

Not applicable.

14.3 Serious Adverse Event (SAE)

A Serious Adverse Event is any untoward medical occurrence that at any dose:
- Results in death
- Is life-threatening or
- Requires in-patient hospitalisation or prolongation of existing hospitalisation or
- Results in persistent or significant disability/incapacity or
- Is a congenital anomaly/birth defect.

Notes:
- The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Medical and scientific judgement should be exercised in deciding whether other important medical events should be considered serious.
- 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 hospitalisation.

Any serious and unexpected adverse events will be communicated immediately by the subject him/herself or by the observing medical professional to the contact persons of the study site.
The study site (Investigator) in turn informs within 24 hours by telephone or telefax the contact person of the Sponsor following discovery of the event.

The Investigator must inform the appropriate Ethics Committee as soon as possible of any serious and/or unexpected adverse events. The Investigator will be required to provide sufficient information on the event to allow a comprehensive medical evaluation of the adverse experience.

14.4 Pregnancy

Pregnancy should be recorded as an AE. It should be qualified as an SAE only if it fulfils SAE criteria.

14.5 Follow-up of Adverse Events

Any abnormal laboratory values, abnormal clinical findings or adverse events which are of clinical significance in the opinion of the Investigator must be followed up with appropriate medical attention until resolved.
In the event of unexplained or unexpected laboratory value abnormalities encountered during or after the study, the tests have to be repeated as soon as possible and followed up until the results return to normal range and/or adequate explanation for abnormality is found.

If a subject withdraws or is removed from the study because of the occurrence of abnormal laboratory values, the subject will have the tests repeated at suitable intervals (as determined by the Investigator) until they return to normal or until deemed appropriate by the Investigator. If clinically indicated, the subject may be referred to his/her general practitioner or to a specialist for further evaluation. If a subject is withdrawn prior to completion of the study, the reason for this decision will be recorded in the (e)CRF, and included in the analysis.

14.6 Suspected Unexpected Serious Adverse Reactions (SUSARs)

A SAE, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or Summary of Product Characteristics for an approved product) and which has reasonable relationship to IMP administration is called a Suspected Unexpected Serious Adverse Reaction (SUSAR).
The Sponsor or its representative will expediently report the following SUSARs:

- SUSARs that have arisen in the current clinical study
- SUSARs that have arisen in other clinical studies of the same Sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the current clinical study

The Sponsor will expediently report all SUSARs to the Regulatory Authority (RA), as appropriate.

14.7 Immediate reporting by the Investigator to the Sponsor

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event. The following is a list of events that the Investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious AEs
- Pregnancies
- Accidental overdose or medication errors

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative on the clinical course of the event

Investigators must also comply with local requirements for reporting serious AEs to the local health authority and IRB/EC.

15 Evaluation and Statistical analysis

15.1 Statistical analysis plans

Statistical Analysis Plan (SAP) will be prepared for the final analysis in order to describe the statistical analysis processes in details. The SAP will be finalized before the related database lock and the start of any statistical activities of the analysis.

15.2 Analysis datasets

- **Safety Analysis Set:** The Safety Analysis Set (SAS) consists of all patients who were enrolled the study and received at least one dose of study medication.
- **Intention-To-Treat Set:** The Intention-To-Treat Set (ITT) consists of all SAS.
- **modified Intention-To-Treat Set:** The modified Intention-To-Treat Set (modified-ITT) consists of all ITT patients who have positive PCR result at baseline.
- **Per-Protocol Set:** The Per-Protocol Set (PP) consists of compliant ITT patients who have no major protocol deviations. Negative PCR test at baseline is considered as major protocol deviation.

15.3 General approach

Statistical analysis will be performed using SAS 9.4 or higher.

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

Patients will not be substituted in any form.

15.4 Adherence and retention analysis

Patient disposition will be analysed at the end of the study. Withdrawals, discontinuation and lost-to-follow-up patients will be listed together with the reason for withdrawal/discontinuation, if possible.
If a patient is withdrawn from the study, no further data are collected from this patient. Data collected so far will be included in the safety and efficacy analyses up to the time point of the withdrawal.

15.5 Compliance

Treatment compliance will be documented during the study by recording the package codes of study medications at each study visit. Study medication accountability will be performed on an on-going basis by the study personnel and checked by the field monitor during site visit and at the completion of the study.
Patients should receive all treatment doses as prescribed in the protocol.
If a patient receives less than 80% of the prescribed doses then he/she is considered as non-compliant. These patients will then be included in the ITT dataset and excluded from the PP dataset.

15.6 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 (absence of any symptoms mentioned under SEC02B...02E, and physiological body temperature as per SEC02A)
• [SEC 02A] Time to resolution from fever (tympanic temperature ≤ 37.5 °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

Safety Endpoint:
• [SAF 01] Monitoring Adverse Events, safety laboratory and other safety parameters

15.7 Analysis variables

15.7.1 Efficacy variables

Efficacy data comprise parameters of the following assessments:

- SARS-CoV-2 nucleic acid by quantitative RT-PCR
- Respiration rate
- Body temperature
- Cough burden score measured on a 0-10 points scale
- Dysgeusia-ageusia score measured on a 0-10 points scale
- Anosmia score measured on a 0-10 points scale
- Fatigue score measured on a 0-10 points scale
- Recovery status (yes/no) as defined in [SEC 02]
- Time to viral clearance (days)
- Time to recovery (days)
- Number of hospitalized days
- Absenteeism (days)

15.7.2 Safety variables

Safety variables comprise of relevant parameters of the following observations:

- Body weight, calculation of Body Mass Index (BMI)
- Physical examination data
- Vital signs (heart rate, blood pressure)
- Electrocardiogram
- Hemostasis lab panel: Prothrombin time (PT), Partial Thromboplastin Time (PTT), D-dimer
- Hematology lab panel: Complete blood cell count, differential blood count, hemoglobin concentration, hematocrit, erythrocyte sedimentation rate
- Blood chemistry: Sodium, potassium, chloride, magnesium, calcium, phosphorous, blood urea, creatinine, eGFR, glucose, uric acid, total bilirubin, total protein, albumin, gamma-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, creatinine phosphokinase, C-reactive protein, ferritin

- Urine drug test and alcohol breath test
- Urine pregnancy test
- Urinalysis: specific gravity, pH, glucose, protein, ketones, bacteria / nitrites, bilirubin, urobilinogen, blood, sediment, urinary sodium, urinary creatinine
- Adverse events

15.8 Statistical methodology

15.8.1 Primary analysis

Primary analysis will be performed on the modified-ITT population.
The primary endpoint of this study is the percentage of virus copy number at Day7 compared to baseline (i.e. 100 * (the number of virus copies at Day 7 / number of virus copies at Screening)).
The primary endpoint will be analyzed using ANCOVA model including treatment as fix factor and baseline virus copy number as a covariate. Change from baseline (LSMeans) and 95% confidence intervals will be given by treatment group. If the planned model does not fit well, the empirical mean differences with their 95% confidence intervals between treatment groups will be estimated separately at each time point. Patients with negative PCR results will be imputed with 0.
No other missing data imputation will be applied in the primary analysis.

15.8.2 Secondary analysis

Sensitivity analysis of the primary analysis:

- The primary analysis will be repeated on the PP population.
- The primary analysis will be repeated on the modified-ITT population with missing data imputation (not only for negative PCR results but also for missing values). Multiple imputation will be used, each missing value will be imputed ten times to generate ten imputed complete data sets based on the fully conditional specification (FCS) method with the regression option with gender, and age entered into the model. Proc MIANALYZE will be used to combine the imputed datasets to render an analysis of covariance. Patients with negative PCR result at baseline will be excluded from this analysis as well.

The analysis of [SEC 01] will be performed on the modified-ITT population and repeated on the PP population.
All other secondary analyses will be performed on the ITT population and repeated on the PP population.

<u>[SEC 01] Time to virus clearance: number of days from treatment start to virus elimination</u>

Time to viral clearance will be characterized using descriptive statistical methods including the calculation of the 95% confidence intervals. Median time to viral clearance in treatment groups will be compared by log-rank test.
Cox regression model will be applied to investigate possible significant factors influencing the time to viral clearance.
Patients with negative PCR result at baseline will be excluded from the [SEC 01] analysis.

<u>[SEC 02] Time to recovery in patients who have developed symptoms</u>

Time to recovery will be characterized using descriptive statistical methods including the calculation of the 95% confidence intervals. Median time to recovery in treatment groups will be compared by log-rank test.
Cox regression model will be applied to investigate possible significant factors influencing the time to recovery.
Only patients with at least one Covid-19 symptom (from [Sec 02A] – [SEC 02E]) will be included in the analysis.

[SEC 02A]

Number and proportion of patients with normal/abnormal body temperature will be provided. Ratios will be given with the 95% confidence intervals at each time point. Only patients who had abnormal temperature at least at 1 time point will be included in the analysis of [SEC 02A].

[SEC 02B] – [SEC 02E]

Time course of these scoring variables will be characterized using descriptive statistical methods. The number of cases, mean, standard deviation, median, minimum and maximum values will be given by treatment group at each time point. The time course of the symptom will be analyzed using an MMRM method including treatment, time point and treatment*time point interaction as fixed effects and baseline score value as a covariate. Graphical representation of the score values by treatment group over time will also be provided. Only patients who had at least 1 non-zero value of the analyzed score over the examined interval will be included in the analysis.

[SEC 03] Percentage of patients with hospitalization due to progression of COVID-19

Ratio of hospitalized patients and the 95% confidence interval will be given by treatment group. Ratios will be compared by chi-square test.

[SEC 04] Absenteeism, by self-reporting, expressed in days absent from workplace, due to COVID-19

Absenteeism will be characterized using descriptive statistical methods including the number of cases, mean, standard deviation, median, minimum and maximum values. Absenteeism will be compared by t-test.

15.8.3 Safety analysis

Adverse events [SAF 01]

Adverse events that occur during the study will be recorded and coded according to MedDRA. Each AE will be counted once only for a given participant.

The number and frequency of treatment-emergent adverse events (TEAE), serious TEAEs and the proportion of patients experiencing at least one TEAE by treatment group, will be provided by SOC and PT. TEAEs and serious TEAEs will also be summarized by severity, study drug association, and outcome.

TEAEs leading to death or permanent treatment discontinuation will be presented by SOC and PT.

Non-treatment emergent adverse events will only be listed.

An individual list of adverse events will be presented.

Laboratory parameters

Laboratory parameters will be categorized as normal, abnormal – clinically not significant and abnormal – clinically significant by the investigator. The categorized laboratory values will be summarized by time point and treatment group using frequency tables. Frequency of abnormal (both clinically significant and non-significant) values will be compared by chi-square tests between treatment groups at each time point. Shift tables will be presented at each time point by treatment group. Individual listing of the original and the derived category variables will be presented.

Vital signs

Descriptive summary statistics will be presented for vital signs data. Both measured values and changes from baseline will be summarized. The number of cases, mean, standard deviation, minimum, median and maximum values will be given by treatment group at each time point.

Other safety variables

Physical examination and ECG results will be categorized as normal, abnormal – clinically not significant and abnormal – clinically significant by the investigator. The categorized values will be

summarized by time point and treatment group using frequency tables. Frequency of abnormal (both clinically significant and non-significant) values will be compared by chi-square tests between treatment groups at each time point. Shift tables (number and frequency of patients switching from one category to another) will be presented at each time point by treatment group. Individual listing of the original and the derived category variables will be presented.

Descriptive summary statistics for alcohol breath test will be provided. Results will be presented by time point and treatment group. The number of cases and the frequency of each category will be calculated.

Pregnancies will be individually listed with all available information.

15.8.4 Baseline descriptive statistics

Descriptive summary statistics will be presented for demography and baseline characteristics data. For continuous data (e.g., age, weight, height, and body mass index) the number of cases, mean, standard deviation, minimum, median and maximum will be given. For categorical data (e.g., gender) the number of cases and the frequency will be calculated.

15.9 Sample size

This is an exploratory study. The number of enrolled patients was determined by empirical and feasibility considerations. No formal statistical sample size estimation was performed.

16 Ethical and regulatory standards

16.1 Ethical principles

This clinical study will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the Good Clinical Practice (ICH GCP E6 (R2)).

16.2 Laws and regulations

This clinical study will be conducted in compliance with applicable international (EU) laws and regulations, and national laws and regulations of the country where the clinical study is performed, as well as any applicable guidelines.

16.3 Patient Information Sheet and Informed Consent

Informed Consent Forms and Patient Information Sheets can be used to confirm the subjects' informed consent to participate in the trial. After the subject has read the Information Sheet and received verbal information about the trial, participation in the study will be confirmed by signing and dating the Informed Consent Form.
The Investigator (according to applicable regulatory requirements), or a medically qualified person designated by the Investigator, and under the Investigator's responsibility, should fully inform the subject of all pertinent aspects of the clinical study, including the written information giving approval/favorable opinion by the Regulatory Authority / Ethics Committee, as appropriate. All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a subject's participation in the clinical study, the written Informed Consent Form and any other local applicable documents in accordance with local laws and regulations, should be signed, the name completed and personally dated by the subject, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form and Information Sheet must be provided to the subject.

The Informed Consent Form used by the Investigator for obtaining the subject's informed consent must be reviewed and approved by the Sponsor prior to submission to the Regulatory Authority / Ethics Committee, as appropriate, for approval / favorable opinion.
The Investigator is responsible for archiving of the Informed Consent Forms, and shall allow inspection of these documents by authorized personnel, upon request.

16.4 Regulatory matters

The Sponsor or the Sponsor's delegate Contract Research Organisation must submit this clinical study protocol and other appropriate documents (e.g. Informed Consent Form, Patient Information Sheet), to the Regulatory Authority, and is required to forward to the Investigator a copy of the written and signed, dated approval / favorable opinion thereof. The IMP shall not be released at the study site and the clinical study shall not start until a copy of this written and dated approval/ favorable opinion has been received by the Sponsor / CRO.

During the clinical study, any substantial amendment or modification to the study protocol should be submitted to the Regulatory Authority for approval. The Regulatory Authority and Central Ethics Committee should also be informed of any event likely to affect the safety of subjects or the continued conduct of the clinical study, in particular any change in safety.

Minor changes that do not affect the conduct of the study or do not have a significant effect on the safety of the subject's or do not significantly reduce the scientific value of the trial, do not need a re-submission for formal review. These amendments will only be sent on an "information only" (notification) basis.

It is the responsibility of the study site to inform the Institutional Review Board (hereinafter IRB) about the start and close-out of the study.

If requested or appropriate, a progress report is sent to the Institutional Review Board, to the Ethics Committee and to Regulatory Authority periodically (usually annually), and a summary of the clinical study's outcome at the end of the clinical study.

17 Responsibilities

17.1 Responsibilities of the Investigator

The Investigator undertakes to perform the clinical study in accordance with this clinical study protocol, Good Clinical Practice, and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the clinical study protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical study protocol (with the help of the Case Report Form (CRF), or other appropriate instrument) in an accurate and legible manner according to the instructions provided, and to ensure direct access to source documents by Sponsor representatives.

The Investigator may appoint such other individuals as he/she may deem appropriate as sub-investigators to assist in the conduct of the clinical study in accordance with the clinical study protocol. All Sub-Investigators shall be appointed and listed in a timely manner. The Sub-Investigators should be supervised by and act under the responsibility of the Principal Investigator. The Principal Investigator should provide them with a copy of the clinical study protocol and all necessary information.

17.2 Responsibilities of the Sponsor

The Sponsor of this clinical study is responsible to Regulatory Authorities for taking all reasonable steps to ensure the proper conduct of the clinical study with regards to ethics, clinical study protocol compliance, and integrity and validity of the data recorded on the Case Report Forms.
Thus, the main duty of the monitoring team is to support the Investigator and the Sponsor maintaining a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical study.

The Sponsor is entitled to delegate its duties to a Contract Research Organisation with properly documented transfer agreements, but the ultimate responsibility of the clinical study remains at the Sponsor.

At regular intervals during the clinical study, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and subject compliance with clinical study protocol requirements and any emergent problems. During these monitoring visits, the following but not exhaustive list of points should be scrutinized with the Investigator: patient informed consent, subject eligibility, subject recruitment and follow-up, Serious Adverse Event documentation and reporting, investigational medicinal product allocation, subject compliance with the clinical study protocol and treatment regimen, investigational medicinal product accountability, concomitant therapy use and quality of data.

17.3 Source document requirements

According to the Good Clinical Practice, the monitoring team must check the Case Report Form entries against the source documents. The Informed Consent Form will include a statement by which the subject allows the Sponsor's duly authorized personnel, the ethics committee(s), and the competent authorities to have direct access to source data which support the data on the Case Report Forms (e.g., medical and analytical laboratory notes, original laboratory records, ECG recordings etc.). Such personnel, bound by professional secrecy, must keep confidential all personal identity or personal medical information (according to confidentiality rules).

17.4 Use and completion of Case Report Forms (CRFs) and additional request

It is the responsibility of the Investigator to maintain adequate and accurate eCRFs to record (according to Sponsor instructions) all observations and other data pertinent to the clinical study.eCRF data access shall be trackable, containing non-modifiable logs of who, when and under what circumstances has entered or modified the data.
The computerized handling of the data by the data management after receipt of the CRFs may generate additional requests (queries) to which the Investigator is obliged to respond by confirming or modifying the data questioned.

17.5 Use of computerized systems

Computerized systems will be used in data entry (eCRF), data management and data analysis.

18 Administrative and legal matters

18.1 Curriculum Vitae

An updated copy of the curriculum vitae demonstrating the experience, qualification and training for each Investigator and Sub-Investigator should be provided to the Sponsor prior to the beginning of the clinical study.

18.2 Record retention in study site(s)

The Investigator must maintain confidentially all study documentation, and take measures to prevent accidental or premature destruction of these documents.
According to the governing law and regulation, study related documents, case report forms and source documents (e.g. laboratory findings, case history, other source data) should be archived to assure a possible subsequent scrutiny (audit or inspection) of the clinical study.
The Investigator must notify the Sponsor prior to destroying any essential documents following the clinical study completion or discontinuation.
If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

18.3 Clinical study protocol amendments

All appendices attached hereto and referred to herein are made part of this clinical study protocol.
The Investigator should not implement any deviation from, or changes of the clinical study protocol without agreement by the Sponsor and prior review and written approval/ favorable opinion from the ethics committee(s) of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Any change agreed upon shall be recorded in writing, the written amendment must be signed by the Investigator and by the Sponsor and the signed amendment be filed with this clinical study protocol.
Any amendment to the clinical study protocol requires written approval/ favorable opinion by the ethics committee(s) prior to its implementation, unless there are overriding safety reasons.
In some instances, an amendment may require a change to the Informed Consent Form. The Investigator must receive an ethics committee approval concerning the revised Informed Consent Form prior to implementation of the change.

18.4 Premature discontinuation of the study or premature close-out of the site

18.4.1 Decided by the Sponsor

- If the information on the product leads to doubt as to the benefit/ risk ratio
- If the Investigator has received from the Sponsor all means and information necessary to perform the clinical study and has not included any subject after a reasonable period of time mutually agreed upon
- In the event the results of the clinical study do not appear to be scientifically convincing to the Sponsor
- If the aim of the clinical study has become outdated or is no longer of interest
- In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the clinical study protocol, breach of the applicable laws and regulations or breach of the Good Clinical Practice

In any case the Sponsor will notify the Investigator of its decision by written notice.

18.4.2 Decided by the Investigator

If, in the opinion of the Investigator, continuation of the study could not be justified for medical reason he or she may terminate the study at a given study site, after consultation with the Sponsor.
In all cases (decided by the Sponsor or by the Investigator), the appropriate ethics committee(s) and competent authorities should be informed.
In case of premature termination of the study a complete follow-up procedure has to be performed.

18.5 Insurance

The Sponsor certifies that it has taken out a liability insurance policy covering this clinical study. This insurance policy is in accordance with local laws and requirements. The insurance obtained by the Sponsor does not relieve the Investigator and his/ her collaborators from maintaining their own liability insurance policy. A copy of the insurance certificate will be provided to the ethic committees and competent authorities in countries requiring such documentation.

18.6 Sponsor audits and inspections by regulatory agencies

For the purpose of ensuring compliance with the clinical study protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by applicable regulatory authorities.
The Investigator agrees to allow the auditors/ inspectors to have direct access to his/ her study records for review, being understood that this personnel is bound by professional secrecy, and as such should not disclose any personal identity or personal medical information.
The Investigator should make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.
As soon as the Investigator is notified of an upcoming inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to attend to the inspection.
The confidentiality of the data verified and the protection of the subjects should be respected during these audits / inspections.
Any result and information arising from the inspections by the regulatory authorities should be immediately communicated by the Investigator to the Sponsor.
The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

18.7 Confidentiality

All information disclosed or provided by the Sponsor (or any company/ institution acting on their behalf), or produced during the clinical study, including, but not limited to, the clinical study protocol, the (e)CRFs, and the results obtained during the course of the clinical study, are confidential. The Investigator Responsible Person and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical study protocol and other necessary documentation to the ethics committee(s) is expressly permitted, with the ethics committee(s) members having the same obligation of confidentiality.
The Sub-Investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-Investigators of the confidential nature of the clinical study.
The Investigator and Sub-Investigators shall use the information solely for the purposes of the clinical study, to the exclusion of any use for their own or for a third party's account.

18.8 Property rights

All information, documents and investigational medicinal product provided by the Sponsor or its designee are and remain the sole property of the Sponsor.
The Investigator shall not mention any information or the investigational medicinal product in any application for a patent or for any other intellectual property rights.
All the results, documents and inventions, which arise directly or indirectly from the clinical study in any form, shall be the exclusive property of the Sponsor.
The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical study.

18.9 Data protection

The subject's personal data, and Investigator's personal data which may be included in the Sponsor database shall be treated in compliance with all applicable laws and regulations.
When archiving or processing personal data pertaining to the Investigator and/or to the subjects, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

18.10 Publications and communications

The Investigator shall send to the Sponsor a copy of the manuscript for review and possible comments at least thirty (30) calendar days in advance of the date of submission to the journal and at least fifteen (15) days in advance for abstracts. The publication shall be delayed until a written response is received by the Sponsor, but not to exceed thirty (30) days. The Sponsor can delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein, it being understood that the Sponsor cannot refuse its consent without reasonable cause. The Investigator agrees to include the modifications requested by the Sponsor, provided they do not jeopardize the accuracy and/or the scientific value of the publication.
The Sponsor recognizes the Investigator's right to utilize data derived from the clinical study for teaching purposes, communication at congresses and scientific publications. Nevertheless, in order to ensure the accuracy and scientific value of the information, while preserving the independence and accountability of the Investigator, and the confidentiality of the information, only checked and validated data will be used. To that effect, it is essential that the parties exchange and discuss, prior to any publication or communication, any draft publication or communication made by the Investigator.
If no publication has occurred within twenty four (24) months of the termination of the clinical study, the Investigator shall have the right to publish independently the results of this clinical study, subject to the review procedure set forth herein. No other publication is allowed before the primary publication. Any subsequent presentation or publication by a study participant (including for substudies) must be approved by the Sponsor and make reference to the study and the primary publication.
The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/ or their prior written consent(s).
The Sponsor has the right at any time to publish the results of the clinical study.

19 References

- [Ahmed] Ahmed S et al: A five day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. International Journal of Infectious Diseases. Published:December 02, 2020. DOI:https://doi.org/10.1016/j.ijid.2020.11.191
- [Caly] Caly L et al: The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in T vitro. Antiviral Research 178 (2020) 104787. Available online 03 April 2020. https://doi.org/10.1016/j.antiviral.2020.104787
- [Canga] Canga AL et al: The Pharmacokinetics and Interactions of Ivermectin in Humans—A Mini-review. The AAPS Journal, Vol. 10, No. 1, March 2008 (# 2007). DOI: 10.1208/s12248-007-9000-9
- [Carillo] Carillo R et al: Anosmia and dysgeusia in COVID-19: A systematic review. May 2020Wellcome Open Research 5:94. DOI: 10.12688/wellcomeopenres.15917.1
- [CDC] COVID-19 situation update worldwide, as of 14 December 2020. https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases
- [CDC2] CDC - Interim Guidance for Antigen Testing for SARS-CoV-2. Updated Dec. 16, 2020. https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html
- [Cepelowicz] Cepelowicz RJ et al: Use of Ivermectin Is Associated With Lower Mortality in Hospitalized Patients With Coronavirus Disease 2019 64 The ICON Study. Chest, Published:October 12, 2020. DOI:https://doi.org/10.1016/j.chest.2020.10.009
- [Chaccour] Chaccour C et al: Ivermectin to reduce malaria transmission I. Pharmacokinetic and pharmacodynamic considerations regarding efficacy and safety. Malar J (2017) 16:161 DOI 10.1186/s12936-017-1801-4
- [DiNicolantonio] DiNicolantonio JJ et al: Ivermectin may be a clinically useful anti-inflammatory agent for late-stage COVID-19. Open Heart 2020;7:e001350. doi:10.1136/ openhrt-2020-001350.
- [DrugBank] Drugbank – Ivermectin pharmaceutical information page. https://go.drugbank.com/drugs/DB00602.
- [Edwards] Edwards G: Ivermectin: does P-glycoprotein play a role in neurotoxicity? Filaria J. 2003 Oct 24;2 Suppl 1(Suppl 1):S8. doi: 10.1186/1475-2883-2-S1-S8
- [Fajnzylber] Fajnzylber J et al: SARS-CoV-2 viral load is associated with increased disease severity and mortality. Nature Communications (2020)11:5493. https://doi.org/10.1038/s41467-020-19057-5.
- [FLCC] Kory P et al: Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19. Updated Dec. 7, 2020. FLCCC Alliance. https://covid19criticalcare.com/wp-content/uploads/2020/11/FLCCC-Ivermectin-in-the-prophylaxis-and-treatment-of-COVID-19.pdf
- [Geyer] Geyer J et al: Brain penetration of ivermectin and selamectin in mdr1a, b P-glycoprotein- and bcrp-deficient knockout mice. J. vet. Pharmacol. Therap. 2007, 32, 87–96
- [Gil-Martins] Gil-Martins E et al: Dysfunction of ABC transporters at the blood-brain barrier: Role in neurological disorders. Pharmacol. Therap. 213 (2020) 107554
- [Guzzo] Guzzo CA et al: Safety, Tolerability, and Pharmacokinetics of Escalating High Doses of Ivermectin in Healthy Adult Subjects. J Clin Pharmacol, 2002;42:1122-1133. doi: 10.1177/009127002401382731
- [IVMmeta] Ivermectin is effective for COVID-19: real-time meta analysis of 32 studies. Covid Analysis, Nov 26, 2020 (Version 18, Jan 13, 2021). https://ivmmeta.com

- [Jans] Jans DA et al: Ivermectin as a Broad-Spectrum Host-Directed Antiviral: The Real Deal? Cells 2020, 9(9), 2100; https://doi.org/10.3390/cells9092100
- [Kwei] Kwei GY et a:. Disposition of ivermectin and cyclosporin A in CF-1 mice deficient in MDR1A p-glycoprotein. Drug Metab Dispos 1999, 27, 581–587
- [Lassen] Lassen MCH et al: Alcohol Consumption and the Risk of Acute Respiratory Distress Syndrome in COVID-19. Annals of the American Thoracic Society. Received: August 17, 2020 Accepted: December 11, 2020. https://doi.org/10.1513/AnnalsATS.202008-988RL
- [Leisman] Leisman DE et al: Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. Lancet Respir Med 2020; 8: 1233–44. https://doi.org/10.1016/ S2213-2600(20)30404-5.
- [Lespine] Lespine A: Interaction of ivermectin with multidrug resistance proteins (MRP1, 2 and 3). Chemico-Biological Interactions Volume 159, Issue 3, 25 February 2006, Pages 169-179. https://doi.org/10.1016/j.cbi.2005.11.002
- [Mao] Mao Q et al: Role of the breast cancer resistance protein (BCRP/ABCG2) in drug transport--an update. AAPS J. 2015 Jan; 17(1): 65–82. doi: 10.1208/s12248-014-9668-6
- [Matsuyama] Matsuyama T et al: An aberrant STAT pathway is central to COVID-19. Cell Death & Differentiation 27(2020), 3209–3225
- [Mátyus] Mátyus P: Több támadáspontú gyógyszerek: múlt, jelen és jövő. Orv Hetil. 2020; 161(14): 523–531.
- [McIntosh] McIntosh K: Coronavirus disease 2019 (COVID-19): Epidemiology, virology, and prevention. Literature review current through: Nov 2020. | This topic last updated: Dec 03, 2020. https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-epidemiology-virology-and-prevention
- [Merck] STROMECTOL® (ivermectin) - PRODUCT MONOGRAPH. Merck Canada Inc., Last Revised March 13, 2020. https://www.merck.ca/static/pdf/STROMECTOL-PM_E.pdf; STROMECTOL® (ivermectin) - PRODUCT MONOGRAPH. Merck Sharp & Dohme BV, Netherlands. Revised 02/2018. https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf
- [MKK] Magyar Koronavírus Kézikönyv - A 2020. évben azonosított új koronavírus (SARS-CoV-2) okozta fertőzések (COVID-19) megelőzésének és terápiájának kézikönyve. 2020. június 25. http://bpok.hu/wp-content/uploads/2020/07/Magyar-Koronav%C3%ADrus-Kézikönyv_0625_emmi.pdf
- [Munoz] Muñoz J et al: Safety and pharmacokinetic profile of fixed- dose ivermectin with an innovative 18mg tablet in healthy adult volunteers. PLoS Negl Trop Dis 12(1): e0006020. https://doi.org/10.1371/journal. pntd.0006020
- [Navarro] Navarro M et al: Safety of high-dose ivermectin: a systematic review and meta-analysis. J Antimicrob Chemother 2020; 75: 827–834. doi:10.1093/jac/dkz524
- [NIH] NIH: Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Antithrombotic Therapy in Patients with COVID-19. Last Updated: December 17, 2020. https://www.covid19treatmentguidelines.nih.gov/adjunctive-therapy/antithrombotic-therapy/
- [Parasher] Parasher A: COVID-19: Current understanding of its pathophysiology, clinical presentation and treatment. Postgrad Med J 2020;0:1–9. doi:10.1136/postgradmedj-2020-138577
- [PDR] Prescriber's Digital Reference: Ivermectin – Drug Summary. https://www.pdr.net/drug-summary/Stromectol-ivermectin-391
- [Pujari] Pujari R et al: Therapeutic Options for COVID-19: A Review. Cureus. 2020 Sep; 12(9): e10480. Published online 2020 Sep 16. doi: 10.7759/cureus.10480

- [Remy] Remy KE et al: Severe immunosuppression and not a cytokine storm characterizes COVID-19 infections. JCI Insight. 2020;5(17):e140329. https://doi.org/10.1172/jci.insight.140329.
- [Sweeney] Sweeney MD et al: Blood–brain barrier breakdown in Alzheimer's disease and other neurodegenerative disorders. Nat Rev Neurol. 2018 March; 14(3): 133–150. doi:10.1038/nrneurol.2017.188
- [Telbisz] Telbisz Á et al: Interactions of anti-COVID-19 drug candidates with multispecific ABC and OATP drug transporters. BioRxiv 23 Nov 2020. doi: https://doi.org/10.1101/2020.11.21.392555
- [Tipthara] Tipthara P et al: Identification of the metabolites of ivermectin in humans. https://www.authorea.com/users/347810/articles/473347-identification-of-the-metabolites-of-ivermectin-in-humans?commit=e2b57a7ccef5c74385df5721d5b708aab6656303
- [V'kovski] V'kovski P et al: Coronavirus biology and replication: implications for SARS-CoV-2. Nat Rev Microbiol (2020). https://doi.org/10.1038/s41579-020-00468-6
- [van Assema] van Assema DME et al: P-Glycoprotein Function at the Blood–Brain Barrier: Effects of Age and Gender. Mol Imaging Biol. 2012 Dec; 14(6): 771–776
- [van den Brand] van den Brand JMA t al: The Pathology and Pathogenesis of Experimental Severe Acute Respiratory Syndrome and Influenza in Animal Models. J. Comp. Path. 2014, Vol. 151, 83-112. http://dx.doi.org/10.1016/j.jcpa.2014.01.004
- [Zhou] Zhou F et al: Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. www.thelancet.com. Published online March 9, 2020. https://doi.org/10.1016/S0140-6736(20)30566-3

20 Appendices

Appendix 1 **The World Medical Association Declaration of Helsinki**

Appendix 2 **Prohibited concomitant medication**

Appendix 1 The World Medical Association Declaration of Helsinki

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy subjects requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.
Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation. Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed. When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, Sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.
In clinical studys, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the Sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.
The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.
After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.
Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the

best proven intervention(s), except in the following circumstances:
Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical study, Sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, Sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 2 Prohibited concomitant medication

Coumarin-derivatives and warfarin

CYP3A4 modulators
Substrates:
Antihistamines: Astemizole, Chlorpheniramine,
Antimetric: Aprepitant, Ondansetron
Anesthesia/Pain: Cafergot, Codeine-N-Demethylation, Fentanyl, Levolevomethadyl Acetate (LAAM), Lidocaine, Methadone
Antibiotic/Antiviral: Alfentanil, Boceprevir, Clarithromycin, Efavirenz, Erythromycin, Indinavir, Nelfinavir, Nevirapine, Quinine, Ritonavir, Saquinavir, Telaprevir, Telithromycin.
Cardiovascular: Amlodipine, Cilostazol, Diltiazem, Eplerenone, Lercanidipine, Nifedipine, Nisoldipine, Nitrendipine, Propranolol, Quinidine, Verapamil
HMG COA Reductase Inhibitors: Atorvastatin, Lovastatin, Simvastatin
Immune Modulators: Cyclosporine, Sirolimus, Tacrolimus
Neuropsychiatric: Alprazolam, Diazepam, Midazolam, Triazolam, Haloperidol, Aripiprazole, Buspirone, Carbamazepine, Pimozide, Quetiapine, Risperidone, Trazodone, Zaleplon, Ziprasidone, Zolpidem
Oncology: Docetaxel, Gleevec, Irinotecan, Paclitaxel, Romidepsin, Sorafenib, Sunitinib, Torisel, Vemurafenib, Vincristine
Pulmonary: Salmeterol, Sildenafil
Steroid: Dexamethasone, Estradiol, Hydrocortisone, Progesterone, Testosterone
Other: Cocaine, Dapsone, Dextromethorphan, Finasteride, Nateglinide
CYP3A4 Inhibitors
Strong Inhibitors: Clarithromycin, Indinavir, Itraconazole, Ketoconazole, Nefazodone, Ritonavir, Saquinavir, Suboxone, Telithromycin
Intermediate Strength Inhibitors: Aprepitant, Erythromycin, Fluconazole, Grapefruit Juice, Verapamil, Diltiazem
Weak Inhibitors: Cimetidine
Other Possible Inhibitors: Amiodarone, Boceprevir, Chloramphenicol, Ciprofloxacin, Delaviridine, Diethyl-Dithiocarbamate, Fluvoxamine, Gestodene, Imatinib, Mibefradil, Mifepristone, Norfloxacin, Norfluoxetine, Starfruit, Telaprevir, Voriconazole
CYP3A4 Inducers: Barbiturates, Carbamazepine, Efavirenz, Glucocorticoids, Modafinil, Nevirapine, Oxcarbazepine, Phenobarbital, Phenytoin, Pioglitazone, Rifabutin, Rifabutin, St. John's Wort, Troglitazone

Selected Drugs That Are Substrates of Pgp:
Dabigatran etexilate, digoxin, fexofenadine

{FDA - Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Table 5-1: Examples of clinical substrates for transporters (for use in clinical DDI studies and/or drug labeling) (12/03/2019)
https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-1 }

Selected Drugs That Are Substrates of wild-type BCRP:
Anthracenes: Mitoxantrone, Bisantrene, Aza-anthrapyrazole (BBR3390)
Camptothecin derivates: Topotecan, SN-38, Irinotecan, Diflomotecan
Polyglutamates: Methotrexate, Methotrexate-Glu2, Methotrexate-Glu3
Nucleoside analogs: AZT, AZT 5'-monophosphate, Lamivudine (3TC)
Other drugs: Prazosin, Indolocarbazole, Flavopiridol, Canertinib (CI1033), Imatinib mesylate (STI571), Gefitinib (ZD1839), Nilotinib, Glyburide, Cimetidine, Sulfasalazine, Nitrofurantoin, Rosuvastatin Pantoprazole

Selected Drugs That Are Inhibitors of BCRP:
Tyrosine kinase inhibitors: Gefitinib, Imatinib mesylate, Erlotinib, Nilotinib, Lapatinib
HIV protease inhibitors: Ritonavir, Saquinavir, Nelfinavir, Lopinavir

HCV protease inhibitors: Boceprevir, Telaprevir
Calcium channel blockers: Dipyridamole, Nicardipine, Nimodipine, Nitrendipine
Antifungal azoles: Ketoconazole, Itraconazole, Fluoconazole
Immunosuppressants: Cyclosporin A, Tacrolimus, Sirolimus
Other drugs: Novobiocin, Tamoxifen, Reserpine, Omeprazole, Pantoprazole

{"Role of the Breast Cancer Resistance Protein (BCRP/ABCG2) in Drug Transport—an Update" , AAPS J. 2015 Jan; 17(1): 65–82. doi: 10.1208/s12248-014-9668-6}