Clinical Investigational Plan

A Phase IIb, double blind, placebo-controlled clinical study designed to evaluate the effect of CimetrA in patients diagnosed with COVID-19

Protocol No.: MGC-009

Protocol Version: 02

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Investigational Treatment: CimetrA

Sponsor: MGC Pharma

Protocol Number	MGC-009
Protocol Title	A Phase IIb, double blind, placebo-controlled clinical study designed to evaluate the effect of CimetrA in patients diagnosed with COVID-19
Study Arms	STUDY DRUG – CIMETRA will be administrated as the following: Arm 1: CimetrA-1, with a total dose containing a combination of Curcuma longa rhizome dry extract 28 mg, Boswellia serrata resin dry extract 60 mg in spray administration – divided in 4 separate doses given as an add on therapy, total of 4 doses over 48 hours (day 1 and day 2), twice a day (morning and evening). Arm 2: CimetrA-2, with a total dose containing a combination Curcuma longa rhizome dry extract 19.6 mg, Boswellia serrata resin dry extract 42 mg in spray administration – divided in 4 separate doses given as an add on therapy, total of 4 doses over 48 hours (day 1 and day 2), twice a day (morning and evening). Arm 3: Placebo, composed of the same solvent but without active ingredients, given as an add on therapy in spray administration, total of 4 doses over 48 hours (day 1 and day 2), twice a day (morning and evening). Patients will be randomized in 1:1:1 ratio to one of the three arms.
Overall rationale	A preparation of CimertA (Botanical Drug), comprising Curcuma longa rhizome dry extract and Boswellia serrata resin dry extract in a nanoparticular formulation, is proposed as a treatment for the disease associated with the novel corona virus SARS-CoV-2. This initiative is presented under the urgent circumstances of the fulminant pandemic caused by this lethal disease, which is known as COVID-19 and has spread across the globe causing death and disrupting the normal function of modern society [1]. The grounds for the proposal are rooted in existing knowledge on the components and pharmacological features of this formulation and their relevance to the current understanding of the disease process being addressed. The breakout of a lethal pneumonia in the city of Wuhan, China, towards the end of 2019, has led to the characterization of the new coronavirus related disease COVID-19 [2]. Its

prominent features include a high rate of person-to-person transmission [3], a substantial risk of developing a lethal respiratory syndrome and potential failure of additional organs [4-7]. Risk factors for a life-threatening clinical course have been identified [8, 9], including advanced age [9-11] and assorted comorbidities [9, 12], such as cardiovascular disease [9, 10, 13, 14], diabetes mellitus [9, 15], hypertension [9, 15, 16], cancer [9, 14, 17-20]. However, individuals devoid of any of the recognized risk factors are not immune to the severe manifestation of the disease and once infected carry a certain risk of mortality which has been calculated in Italy at circa 2% [12, 21-23].

CoV is an enveloped, positive-sense single-stranded RNA (ss-RNA) virus belonging to the Coronaviridae family. The severe acute respiratory syndrome associated coronavirus disease 2019 (COVID-19) illness is a syndrome of viral replication in concert with a host inflammatory response. The cytokine storm and viral evasion of cellular immune responses may play an equally important role in the pathogenesis, clinical manifestation, and outcomes of COVID-19. Systemic proinflammatory cytokines and biomarkers are elevated as the disease progresses towards its advanced stages, and correlate with worse chances of survival.

SARS-CoV-2 activates the innate immune system and results in a release of a large number of cytokines, including IL-6, which can increase vascular permeability and cause a migration of fluid and blood cells into the alveoli as well as the consequent symptoms such as dyspnea and respiratory failure. The higher mortality is being linked to the result of ARDS (acute respiratory distress syndrome) aggravation and the tissue damage that can result in organ-failure and/or death.

Serum cytokine levels that are elevated in patients with Covid-19–associated cytokine storm include interleukin-1β, interleukin-6, IP-10, TNF, interferon-γ, macrophage inflammatory protein (MIP) 1α and 1β, and VEGF. Higher interleukin-6 levels are strongly associated with shorter survival. The relative frequencies of circulating activated CD4+ and CD8+ T cells and plasma blasts are increased in Covid-19. In addition to the elevated systemic cytokine levels and activated immune cells, several clinical and laboratory

	abnormalities, such as elevated CRP and d-dimer levels, hypoalbuminemia, renal dysfunction, and effusions, are also observed in Covid-19, as they are in cytokine storm disorders. Laboratory test results reflecting hyperinflammation and tissue damage were found to predict worsening outcomes in Covid-19. CimetrA, comprising Curcuma longa rhizome dry extract and Boswellia serrata resin dry extract in a nanoparticular formulation, was studied on patients with the novel corona virus SARS-CoV-2 in randomized double blind control Phase II study (MGC-006 – under a previous product name - ArtemiC). The study product demonstrated excellent safety and efficacy profiles. In the in vitro clinical trial CimetrA demonstrated the ability to reduce cytokines elevation in PBMC induced cell tissue.
Study Purpose	This study designed to evaluate the efficacy, pharmacokinetic parameters, and safety of CimetrA on patients diagnosed with COVID-19.
Methodology and study procedures	Multi-center multinational-controlled study in Israel, Brazil, South-Africa and the United States. 240 adult patients who suffer from moderate COVID-19 infection. Safety will be assessed through collection and analysis of adverse events, blood and urine laboratory assessments and vital signs. After Screening visit, the study drug will be administrated twice a day morning and evening (every 12 hours) during (day 1 and day 2) The patients will be randomized in 1:1:1 ratio to study drug (CimetrA) in two dosages in addition to Standard of Care - Arm 1, 2 or (Placebo) in addition to Standard of Care- Arm 3.
Study Duration	Study will take place during patient's hospitalization due to COVID-19 infection. The study will last up to 4 weeks, until conclusion on day 28. In case of hospital discharge within the study period, follow up will continue per protocol until day 28 wherever the subject will be located, performed via phone call or in-clinic, depending on the status of the patient and study schedule.
Study Endpoints	**The primary outcomes**:

	Efficacy endpoint: - Change in WHO Ordinal Scale for clinical improvement (measured on days 1, 7, 14, 28) - Change in COVID-19-Related Symptoms score (measured on days 1,7, 14, 28) Safety endpoint: will be assessed through collection and analysis of adverse events, blood and urine laboratory assessments and vital signs. **The secondary outcomes**: • Number of participants with depending on oxygen supplementation through day 28 since onset of symptoms • Change in inflammatory marker levels – IL-6, IL-1β, IL-12, TNF α, IFN-γ, CRP, NLR (Neutrophil / Lymphocyte ratio) at days 1, 2, 4, 7, compared to baseline • Pharmacokinetic profile of the study drug on day 1 through 24 Hrs. • Incidence and duration of mechanical ventilation • Incidence of Intensive Care Unit (ICU) stay during COVID-19 complication • Percentage of participants with definite or probable drug related adverse events • Long term adverse events of COVID-19 on Day 28 • The Impact covid_19 on quality of life of patients on Days 1, 14 and 28. **The exploratory outcomes**: • Course of change in D Dimer levels compared to baseline • Occurrence of secondary infections
Sample size	We expect medium effect (f=0.20) for the differences in Delta between the 3 groups, and standard deviation of 1.5, based on the ordinal scale (0-8). This power analysis is for a one way fixed effects analysis of variance with 3 levels. The study will include 80 patients per group for a total of 240 patients. The criterion for significance (alpha) has been set at 0.05 with Power of at least 80%. The analysis of variance is two-tailed Main effects.

Inclusion/ Exclusion Criteria	**Inclusion Criteria:** 1. Confirmed by PCR test SARS-CoV-2 infection (according to nationally authorized laboratory criteria) 2. Hospitalized patient with COVID-19 of moderate stable or worsening severity not requiring ICU admission (Moderate defined by NIH criteria -as fever, cough, dyspnea, fast breathing, but no signs of severe pneumonia, including SpO2 ≥ 94% on room air). 3. Age: 18 years old and above. 4. Subjects must be hospitalized 5. Ability to receive treatment by spray into the oral cavity **Exclusion Criteria:** 1. Tube feeding or parenteral nutrition. 2. Patients with scores 5 or above per the Ordinal Scale for Clinical Improvement published by the WHO. (i.e., who need oxygen supply beyond use of nozzles or simple mask) 3. Need for admission to ICU during the present hospitalization at any time prior to completion of the recruitment to the study. 4. Any condition which, in the opinion of the Principal Investigator, would prevent full participation in this trial or would interfere with the evaluation of the trial endpoints.

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1. LIST OF ABBREVIATIONS

AE	Adverse Event
ALT/SGPT	Alanine Aminotransferase / Serum Glutamic Pyruvic Transaminase
AST/SGOT	Aspartate Aminotransferase / Serum Glutamic Oxaloacetic Transaminase
CBC	Complete Blood Count
CBD	Cannabidiol
CBT	Cognitive Behavioral Therapy
ConMeds	Concomitant Medicines
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-Reactive Protein
EC	Ethics Committee
ECG	Electrocardiogram
FU	Follow Up
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
GMP	Good Manufacturing Practice
IC/ICF	Informed Consent/Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities

MoH	Israeli Ministry of Health
NA	Not Applicable
PI	Principal Investigator
PP	Per Protocol
PSD	Polysymptomatic Distress Scale
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QA	Quality Assurance
QoL	Quality of Life
RA	Regulatory Authority
RBC	Red Blood Cell
SAE	Serious Adverse Event
SCR	Screening
SD	Standard Deviation
SOC	Standard of Care
SOP	Standard Operation Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBD	To be Determined
THC	9-Tetrahydrocannabinol
ULN	Upper Limit of Normal
WBC	White Blood Cell (Count)
WHO	World Health Organization

2. ETHICS

2.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

i. Approvals will be obtained from the appropriate regulatory authorities. The Investigator must forward a copy of the written approval from the Ethics Committee to MGC-Pharma. The approval should include study identification and the date of review. A list of the Ethics Committee members, their titles or occupation, and their institutional affiliations should also be obtained and filed by MGC-Pharma.

ii. The informed consent form (ICF) and process have been approved by the Helsinki Committee, the Israeli Ministry of Health if needed, and appropriate regulatory authorities.

iii. Inclusion/exclusion criteria have been clearly defined.

iv. Documentation is available that the laboratory(ies) that will perform clinical laboratory tests is (are) qualified for all tests to be performed and are on file at the site.

v. Standard Operating Procedures (SOPs) are on file at the clinical site and all approved laboratories for all analytic procedures and assays that will be performed, and laboratory personnel have been instructed how to maintain Good Laboratory Practices (GLP) when performing these assays.

vi. The approved protocol is on file at the site, and the Principal Investigator and all Co-Investigators have signed the Protocol Compliance Agreement stating that they will adhere to the protocol.

vii. A site initiation meeting will be held at the site, during which the protocol and the responsibilities of the study personnel will be reviewed and any questions answered.

viii. The Study Sponsor has established an effective mechanism for monitoring the study.

ix. The Investigator should file all correspondence with the Ethics Committee/Institutional Review Board. Copies of all correspondence should be forwarded to MGC-Pharma without delay.

2.2. Ethical conduct of the study

This clinical trial will be conducted in compliance with good clinical practices (GCP) as specified in Title 21 of the Code of Federal Regulations of the United States as well as the ICH Guidelines for Good Clinical Practice.

2.3. Subject information and consent

Each candidate subject will be enrolled in the study only after the specific aims, significance, risks and benefits have been explained to him/her by a study physician, and the candidate has read (or been read to), understood and signed the written ICF.

The subject will be informed that his/her participation in this clinical study is strictly voluntary and that he/she is free to withdraw consent and discontinue participation at any time without jeopardizing any right to receive the conventional treatment or any and all future treatment nor will he/she be denied access to other available treatments. The subject also will be informed that, if the Investigator believes that it is not in the subject's best medical interests to continue in the study, the Investigator may terminate his/her participation without the subject's consent. In addition, the subject will be informed that the Institutional Helsinki Committee or

the appropriate regulatory agencies may terminate the study if continuation is no longer appropriate.

The subject will be reminded that all his/her questions should be willingly answered and that he/she may consult with any additional source (e.g., family doctor, family members, etc.) in order to reach his/her decision to participate in the clinical trial and/or to continue to participate in it.

When the subject's questions have been answered, he/she will sign the ICF, and the study physician will countersign. In case the candidate subject or his/her legal representative is not capable of reading the ICF, an independent witness must be present during the explanation of the clinical trial. After the participant or his/her legal representative expresses consent orally to participate in the trial, the witness will sign the ICF. The candidate subject will be given a copy of the signed ICF to keep.

The approved ICF with a version number and date will be kept on file at the site. Each subject's signed ICF will be checked against the approved and dated consent form to determine that the signed ICF is the correct version. The date of consent will be compared with the date of entry into the study.

If new information becomes available that must be added to the informed consent, a revised version with a revision number will be prepared and submitted to the appropriate regulatory authorities and the Helsinki Committee. All enrolled subjects will be asked to sign the revised formic, and both will be kept on file.

2.4. Subject data protection

In the CRF, subjects will be identified by date of birth, their initials, and screening number and/or enrollment /randomization number in the study. The Investigator should file a subject identification list, which includes sufficient information to link records, i.e., the CRF and clinical records. This list should be preserved for possible

future inspections by Regulatory Authorities but should not be made available to MGC-Pharma except for monitoring or auditing purposes

The subjects should be informed that the data will be stored and analyzed by computer, that all local regulations for the handling of computerized data will be followed, and that identification of individual subject data will only be possible for the Investigator.

Furthermore, the subjects should be informed about the possibility of inspection of relevant parts of the clinical records by representatives of the MGC-Pharma and/or Regulatory Authorities. This information should be included in the written Subject information and in the ICF. Authorization to direct access to the subject's clinical records, as described above, is given by signing the ICF.

The privacy of the subjects and all confidentiality issues will be handled in accordance with applicable law and the guidelines of the institution and the Helsinki Committee, the Israeli Ministry of Health, or other appropriate regulatory authorities.

3. INTRODUCTION

Herbal (Botanical) medicines and purified natural products provide a rich resource for novel antiviral drug development. Identification of the antiviral mechanisms from these natural agents has shed light on where they interact with the viral life cycle, such as viral entry, replication, assembly, and release, as well as on the targeting of virus–host-specific interactions.

3.1. COVID-19

The breakout of a lethal pneumonia in the city of Wuhan, China, towards the end of 2019, has led to the characterization of the new coronavirus related disease COVID-19 [2]. Its prominent features include a high rate of person to person transmission [3], a substantial risk of developing a lethal respiratory syndrome and potential failure of additional organs [4-7]. Risk factors for a life threatening clinical course

have been identified [8, 9], including advanced age [9-11] and assorted comorbidities [9, 12], such as cardiovascular disease [9, 10, 13, 14], diabetes mellitus [9, 15], hypertension [9, 15, 16], cancer [9, 14, 17-20]. However, individuals devoid of any of the recognized risk factors are not immune to the severe manifestation of the disease and once infected carry a certain risk of mortality which has been calculated in Italy at circa 2% [12, 21-23].

The state of emergency associated with the present COVID-19 pandemic has aroused the biomedical community to produce an exceptionally large number of clinical trial proposals [24]. The World Health Organization (WHO) has accordingly addressed the challenge of promoting urgent clinical research on COVID-19 treatment [25]

Selected pathogenetic themes: leading factors driving to the severe manifestations of COVID-19, notably the Severe Acute Respiratory Syndrome (SARS), as well as functional deterioration of additional organs and physiological systems, are the focus of the therapeutic intervention suggested in our proposal:

Perseverance and progression of the viral infection – There is an apparent association between the persistent presence of a high viral load and adverse course of the COVID-19 disease [5, 26]. Thus, any intervention to abort or impede the process of the viral propagation and replication, referred to as antiviral treatment, would appear desirable.

Dysregulation of the immune system, ultimately manifesting as a “cytokine storm” – This phenomenon has long been associated with acute lung injury, notably in its most severe manifestation as an Acute Respiratory Distress Syndrome (ARDS) [27-29]. The data on the COVID-19 from the multitude of clinical reports published so

far, support a central role for immune dysregulation in giving rise to the severe manifestations of COVID-19 [21, 29-31].

Oxidative stress – The damaging effect of this factor has been implicated in the pathogenesis of severe lung injury [32] and specifically proposed play a role in the clinical deterioration in patients with COVID-19 [33].

4. STUDY PRODUCT

CimetrA is a Botanical Drug which is comprised of natural active ingredients and formulated in microscopic structures known as micelles. The elements forming the structure of these micelles are in themselves also of exclusively natural origin. The unique formulation is endowed with highly desirable pharmacological features, providing otherwise unattainable high bioavailability to the active ingredients it is designed to deliver.

4.1. Curcumin

Curcumin – Curcumin has been noted to possess beneficial effects on human health since antiquity [34]. Over decades of research multiple modes of its action have been studied in vitro and in vivo in laboratories as well as in clinical trials in humans [35]. The resulting data provide ample evidence of clinically significant anti-inflammatory [36], immune-modulatory [37], antioxidant [38], anti-aggregant [39] and antimicrobial [40] activities of curcumin.

Of particular interest are the desirable effects curcumin has demonstrated in models of acute lung injury including down regulation of inflammatory cytokines, decreased infiltration and activation of inflammatory cells and accompanying pulmonary edema, and corresponding improvement of survival [41].

4.2. Boswellia

The addition of an extract of Boswellia, also known as Frankincense or Olibanum, to the CimetrA formula is intended to contribute an advantage in the treatment of the marked endothelial injury and related coagulation dysregulation observed in the advanced stages of critical COVID-19 based on inference from observations in other models of pathological endothelial and coagulation activation [42-43]. The restriction by an active ingredient of Boswellia of TNFα induced expression of the adhesion molecules ICAM-1 and VCAM-1 in human microvascular endothelial cells is noteworthy in the present context [44]. This effect, in addition to other consistently observed antioxidant, anti-inflammatory, immuno-modulatory effects [45-46] lends reason to the proposal of its inclusion in a compound formulation intended for use in the complex pathophysiological context of COVID-19 and the surrounding circumstances. Due to the poor bioavailability of active elements in the Boswellia extracts a formulary elaboration, as in the micellar preparation of CimetrA is required as a solution for their pharmacokinetic drawbacks [47].

4.3. Delivery system

With the advent of nano-technology it has become possible to circumvent the barriers to the administration of therapeutic agents with poor solubility in aqueous environments and poor solubility. This progress has made it possible to formulate the active ingredients of CimetrA in the micellar preparation presented in this proposal. Previous studies exploiting the same principles have demonstrated their utility in providing artemisinin with significantly higher bioavailability and pharmacokinetic consistency [42-43]. Notably, it is accepted that micellar structures have improved access to the sites of inflammation associated with increased permeability [44], as expected in conditions of acute lung injury of the nature encountered in COVID-19 pneumonia [45]. The previous study drug ArtemiC was formulated in micelles with an artemisinin concentration of 6mg/ml. Considering

that accepted clinical protocols treated with doses of artemisinin that yield plasma concentrations up to 2000µmg/L [56] dosing with 6mg of nano-encapsulated artemisinin would not be considered to have a potential to attain unacceptably high peak concentrations of the drug in the plasma. This estimate is based on the extreme assumption of 100% entry of the 6mg of nano-capsulated artemisinin into a blood volume of 5 liters. Similar studies have been performed with curcumin [50-51] and Boswellia [47] which also a demonstrated markedly enhanced uptake while the dosing to be used in the present proposal places them securely in a non-toxic range [50, 52-53]. Vitamin C has been repeatedly tested in clinical trials which used intravenous administration with dose up to 200mg/kg/day with demonstrated safety [48].

5. PRECLINICAL EXPERIENCE WITH THE STUDY DRUG

5.1. Acute Tox study - old formulation ArtemiC

Each group 3M+3F rat were treated in splash route of administration of ArtemiC (6 mg/ml of Artemisinin ,10 mg/ml curcumin and 7.5 mg/ml Boswellia) into the oral cavity on day 1 with the experimental substances t according to the group table. Each animal was weighed prior to treatment.

Study groups:

Group 1 (n=3M + n=3F): 50ul saline per rat

Group 2 (n=3M + n=3F): 48ug ArtemiC / per Kg rat

Group 3 (n=3M + n=3F): 96ug ArtemiC / per Kg rat

Group 4 (n=3M + n=3F): 192ug ArtemiC / per Kg rat

During all 7 days of the experiment the animals were monitored for observation and weight to detect the appearance of abnormal clinical signs. No clinical signs were observed in the animals. No blood tests or histopathology abnormalities were observed.

The full Acute Tox Report is be presented in the Investigator Brochure.

5.2. In Vitro Mechanism of Action trial

The study included 2 main stages –

- Viability evaluation of PBMCs
- Examination of anti-inflammatory effect

Conclusions of the study included –

- Treatment of PBMCs with ArtemiC and its components allowed preservation of PBMCs viability and did not lead to cytotoxic effect. The results are presented in Fig. 1-4.

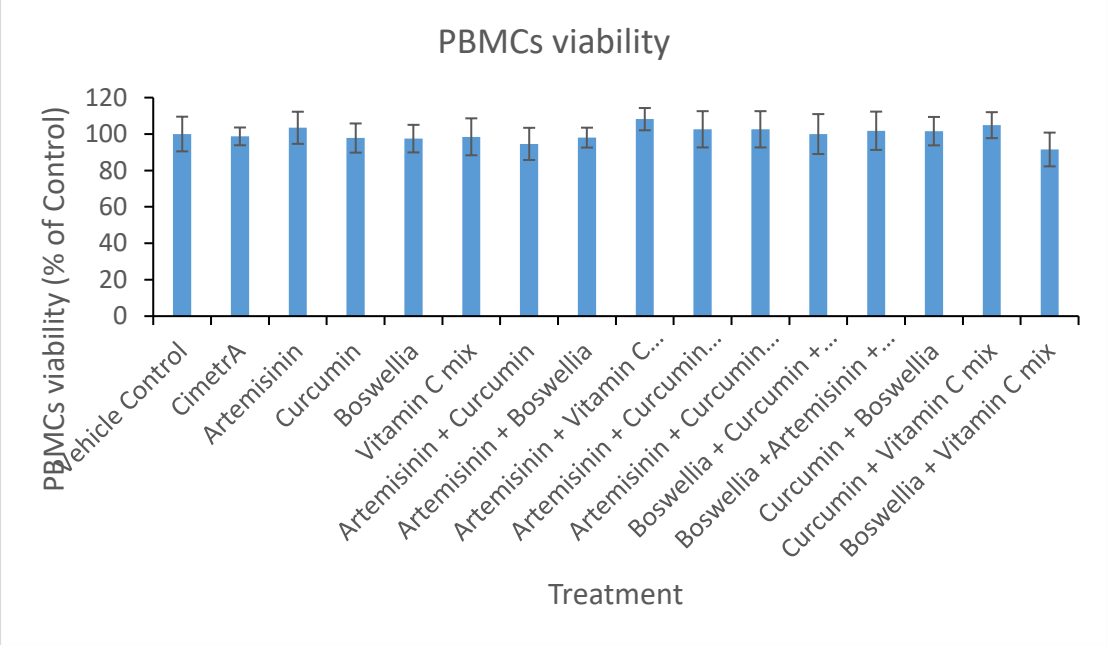

Fig. 1. PBMCs viability after treatment by ArtemiC and its components in different combinations.

- Pre-treatment of PBMCs with ArtemiC and its components resulted in attenuation of cytokines related to COVID-19 elevation following LPS stimulation. The results are presented in figures 3-5.

One of the goals of this study was to determine the most effective compounds combination in order to define the final formulation. Based on the results, Artemisinin was taken out of the formulation , the new formulation which was choosen is CimetrA : a combination of curcumin and Bowsellia

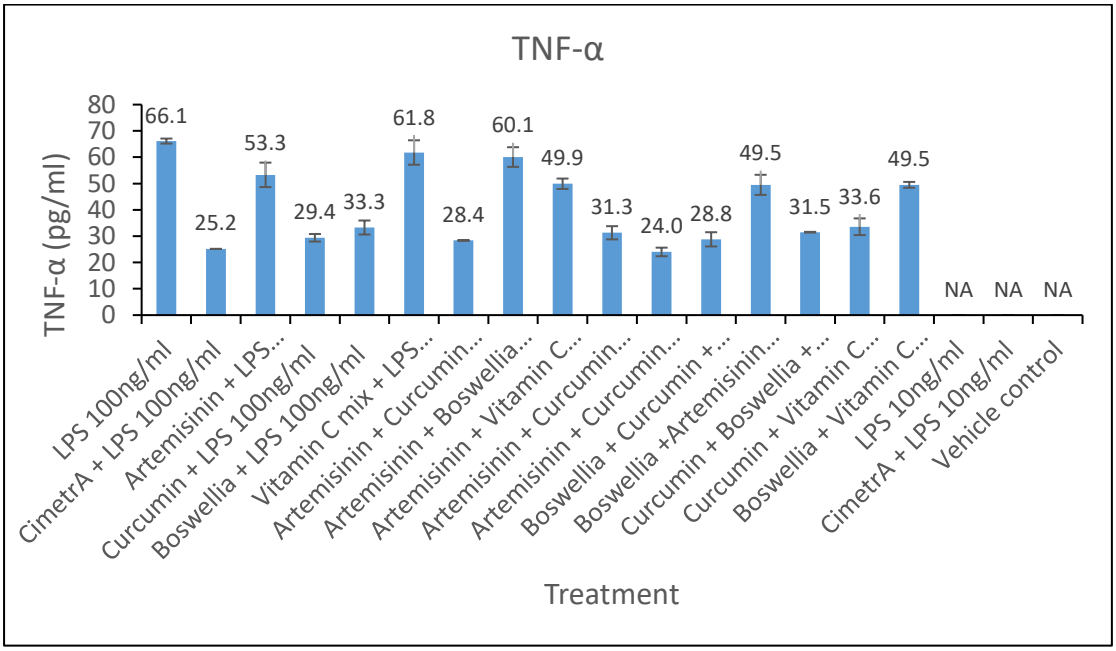

Fig. 2. TNF-α concentration in PBMCs conditioned medium samples after treatment with ArtemiC and its components in different combinations, include the combination of CimetrA .

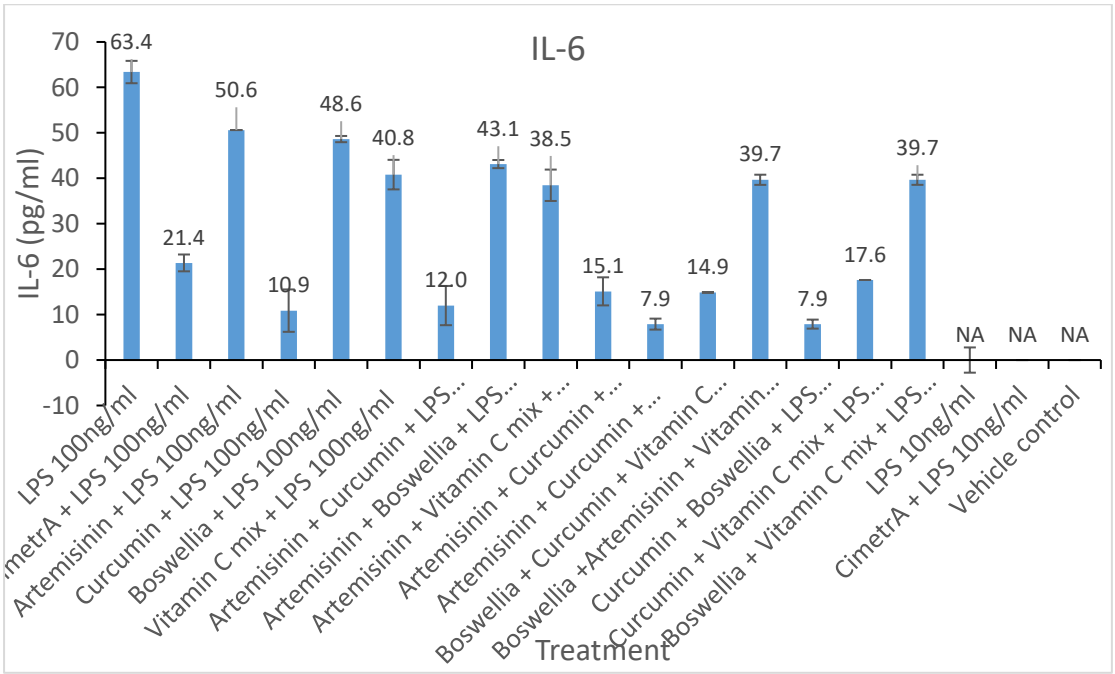

Fig. 3. Il-6 concentration in PBMCs conditioned medium samples after treatment with ArtemiC and its components in different combinations, include the combination of CimetrA .

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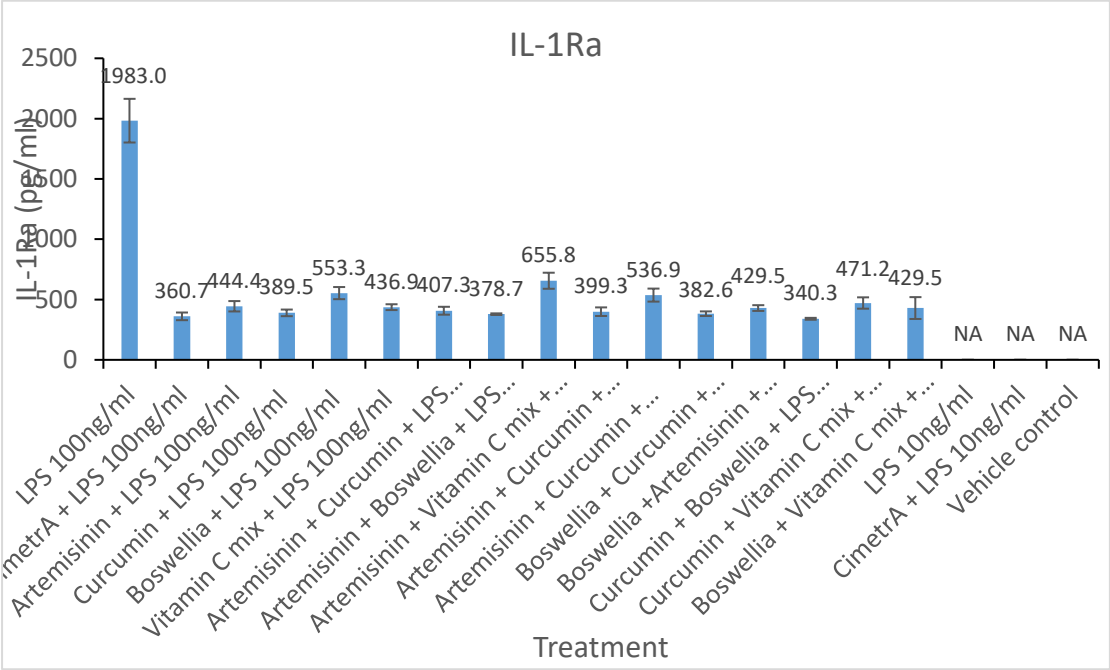

Fig. 4. IL-1Ra concentration in PBMCs conditioned medium samples after treatment with ArtemiC and its components in different combinations, include the combination of CimetrA . Full report is submitted in the Investigator Brochure.

5.3. Efficacy Animal Model Study

Evaluation the efficacy ofArtemiC treatment in ARDS model in mice. The goal of this study is to investigate the efficacy of ArtemiC in the ARDS model in mice by Oral Spray administration in two dosage. Use of animals in ARDS model enabled to test the efficacy of ArtemiC for the inhibition of clinical symptoms, base of the inflammatory response, and will be enable further development of this treatment for

ARDS. The LPS-induced ARDS model is an accepted model for human acute respiratory disease caused by Corona virus infection.

The study investigated the levels of cytokines and chemokines in blood and BALF (bronchoalveolar lavage fluid). Inflammation level of the lung tissue was measured by histopathology.

ArtemiC was found effective in the reduction of elevation of cytokines and chemokines production both in blood and BALF. The histopathological analysis demonstrated the attenuation of the lung injury in the treatment group in comparison with placebo.

The detailed study result information is provided in the Investigator Brochure.

6. CLINICAL EXPERIENCE WITH THE STUDY DRUG -THE OLD FORMULTION- ARTEMIC

Randomized controlled Phase II clinical trial was managed on 50 moderate COVID-19 patients in Israel (40 patients were recruited) and India (10 patients) to measure safety and efficacy of ArtemiC.

Patients were randomized 2:1.

Study drug: ArtemiC was administrated in the dosage of Artemisinin 12 mg, Curcumin 40 mg, Boswellia 30 mg and Vitamin C 120 mg, in spray administration – divided in 4 separate doses given as an add on therapy, 4 doses over 48 hours (day 1 and day 2), twice a day (morning and evening). The study drug dose was defined based on the Acute Tox preclinical study.

Main demographic characteristics are presented in Table 1.

Table 1. Demographic characteristics of patients in Phase II study.

	ArtemiC	*Placebo*	*P*
Age	*52± 14*	*53± 14*	*0.857*
Gender: *Male* *Female*	 *17 (52)* *15 (46)*	 *8 (47)* *9 (53)*	 *0.708*
Race: *Asian* *White*	 *9 (27)* *23 (70)*	 *1 (6)* *16 (94)*	 *0.139*
Smoke: *Current* *In the past* *Never*	 *5 (15)* *1 (3)* *26 (79)*	 *3 (18)* *3 (18)* *11 (65)*	 *0.277*
Alcohol drink: *Occasional* *Weekly* *Never*	 *2 (6)* *0* *30 (91)*	 *0* *1 (6)* *16 (94)*	 *0.321*

The study product demonstrated a full safety profile, no study product AEs were recorded during a trial. The SAEs summary is presented in table 2.

Table 2. Serious Adverse Events in both study groups in Phase II study.

	ArtemiC	***Placebo***
Number of patients	*9 patients: (max severity)* *Mild 4* *Moderate 4* *Severe 1*	*7 patients: (max severity)* *Mild 5* *Moderate - 0* *Severe 2*
Number of events	*13 events:* *Mild 6* *Moderate 5* *severe 2*	*16 events:* *Mild 13* *Moderate 1* *Severe 2*
C01-001		*Worsening of abcess (mild)*
C01-002		*Exacerbation of desaturation+ (moderate)* *Acute respiratory..(severe)+* *Melena(mild)+* *Tachycardia(mild)+* *AF (mild)*
C02-005	*Worsening of leuckocytosis(mild)+*	

	Exacerbation of musculoskeletal pain(moderate)+ *Abdominal pain(mild)+* *Worsening of hypokalemia (moderate)*	
C02-013	*Bradycaradia(mild)*	
C02-014	*Elevated BUN(mild)*	
C02-019		*Hypokalemia(mild)+* *Hypophosphatemia(mild)+* *Lymphopenia(mild)+* *Thrombocytopenia(mild)+* *Hypokalemia(mild)+* *Hypophosphatemia(mild)*
C02-023		*Constipation (mild)*
C04-002 *Both files*	*MSSA infection(severe)+* *Septic shok (severe)*	
C04-012		*Constipation (mild)*
C02-002	*Worsening of pannus(mild)*	
C02-003		*(ARDS) (severe)*

C02-004	*Worsening of anemia(moderate)*	
C02-006		*Fall (mild)*
C02-008	*Worsening of cough(moderate)*	
Co2-009	*Pneumonia(moderate)*	
C02-010	*Chest pain (mild)*	

Primary endpoint, NEWS score improvement, was achieved in all patients in the treatment group, the difference with the placebo group was statistically significant.

Table 3. NEWS Score results in Phase II study.

Group Statistics

	groups	N	Mean	Std. Deviation	Std. Error Mean	P
sum_news.1	ArtemiC	33	1.5152	2.00189	.34848	
	Placebo	17	1.8824	2.05798	.49913	0.546
last_news	ArtemiC	33	.5152	.66714	.11613	
	Placebo	17	2.2353	3.19236	.77426	0.042

Daily change in NEWS score is presented in Fig. 5.

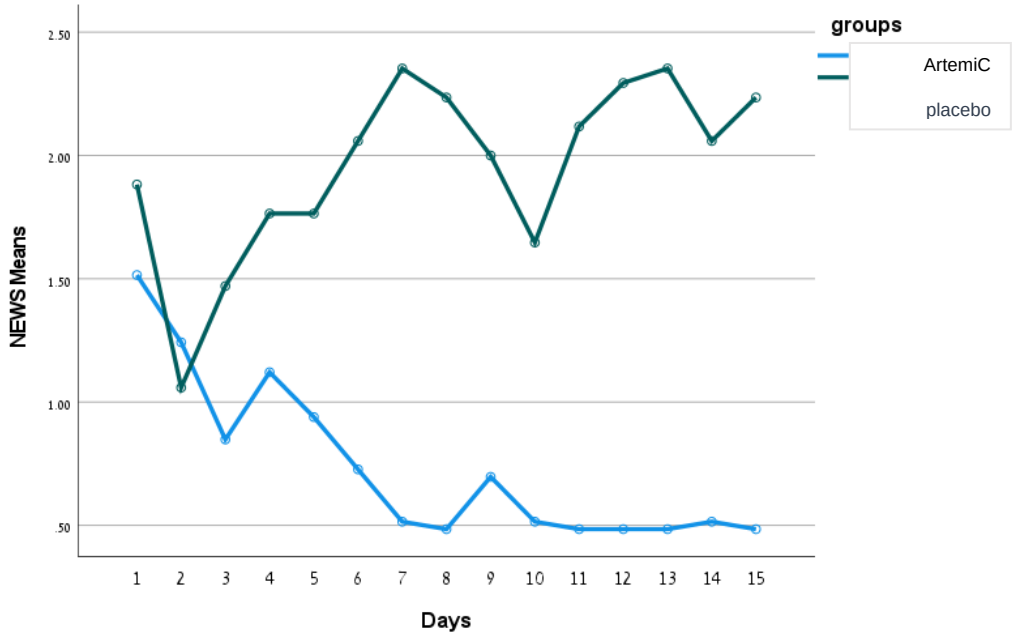

Fig. 5. Daily change of NEWS Score in both study groups in Phase II study.

Room air or supplemental O2 by patients was defined as a secondary endpoint. The results are presented in table 4.

Table 4. Room air or supplemental O2 in study groups in Phase II study.

	Visit 1	*During study*	*Last observed*
ArtemiC *n=33*	*4 patients*	*4 patients*	*0 patients*
Placebo n=17	*3 patients*	*5 patients*	*4 patients*

7. FORMULATION CHANGE

Artemisinin was excluded from the finished product due to insufficient compatibility with other active ingredients. Artemisinin has shown poor stability in low pH water

environment, what is caused by the API boswellic acids and antioxidant vitamin C. This decision is supported by the preclinical data of the in vitro tests of **CimetrA** and its compounds in different combinations, presented in the section of Preclinical experiments of the IB. The analysis of the formulation ultimately clarified that the artemisinin component with which it was formulated was unstable to the extent that neither it, nor its metabolites were present in the preparations used in the phase II trial.

As a part of the development process for the multi APIs medical products, the Sponsor continue the preclinical program and based on the in vivo preclinical study, presented in Section 4.2 of the Investigator Brochure, performed additional preclinical trials in the new formulation, named CimetrA, which does not include Artemisinin.

The in vitro trial aimed to check the anti-inflammatory activity of ArtemiC (Artimisenin,Bowsellia,Vitamin C,Curcumin) versus CimetrA (Bowsellia, Curcumin) in the related to COVID-19 cytokines and chemokines was performed in Science in Action Lab, Ness Ziona, Israel.

The objective of this study was to examine the effect of ArtemiC and CimetrA on human peripheral blood mononuclear cells (PBMCs) viability and their capacity to attenuate inflammatory response upon stimulation with E coli-derived lipopolysaccharide (LPS).

The study demonstrated the superiority of the formulation named CimetrA (based on Curcumin and Boswellia) on ArtemiC (based on Artemisinin, Curcumin ,Boswellia and vitamin C) in the prevention of uncontrolled COVID-19 related cytokines and chemokines production.

The results are presented below.

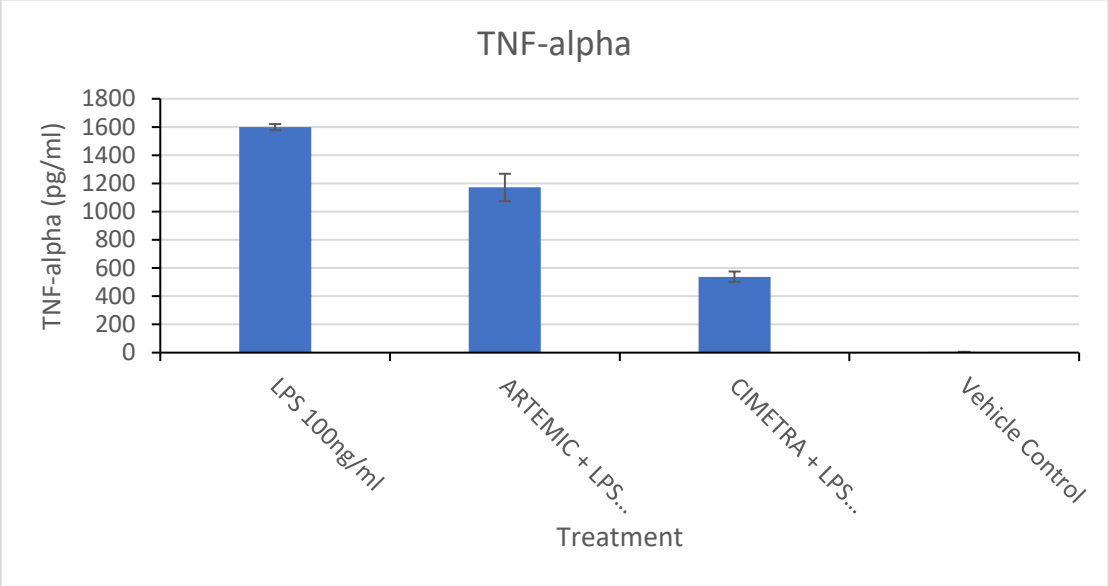

Fig 6. Concentration of TNF-alpha in PBMCs supernatant

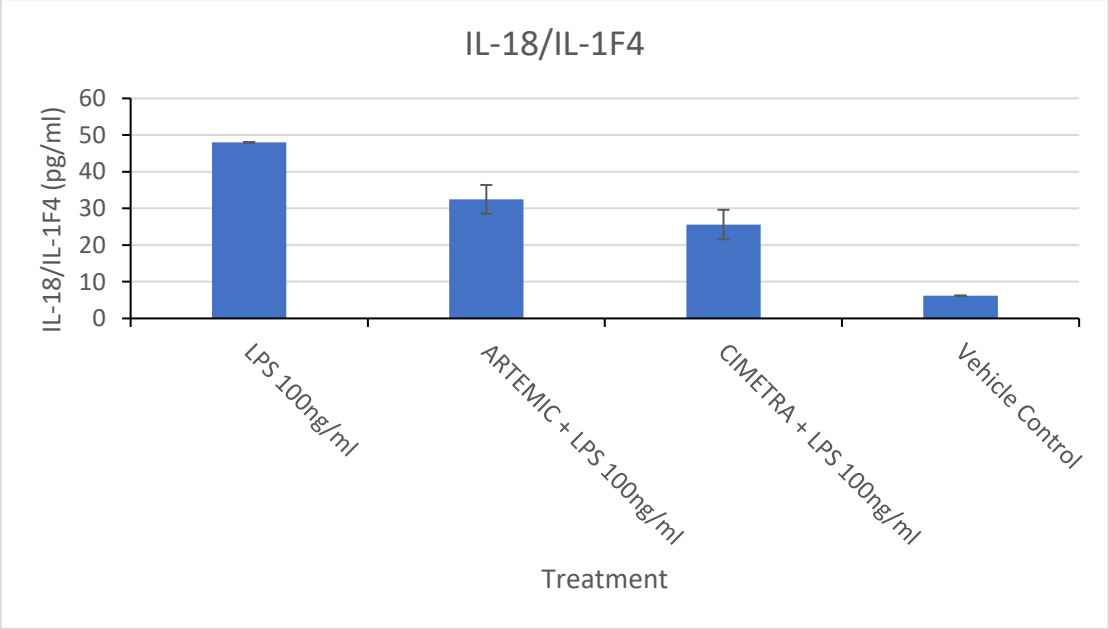

Fig 7. Concentration of IL-18/IL-1F4 in PBMCs supernatant

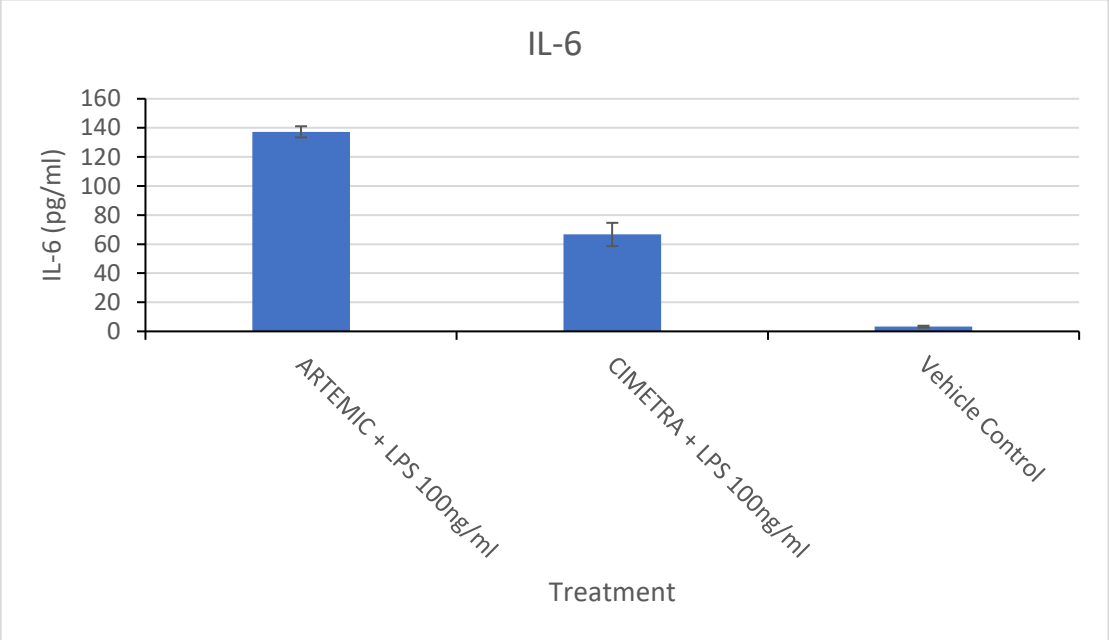

Fig 8. Concentration of IL-6 in PBMCs supernatant

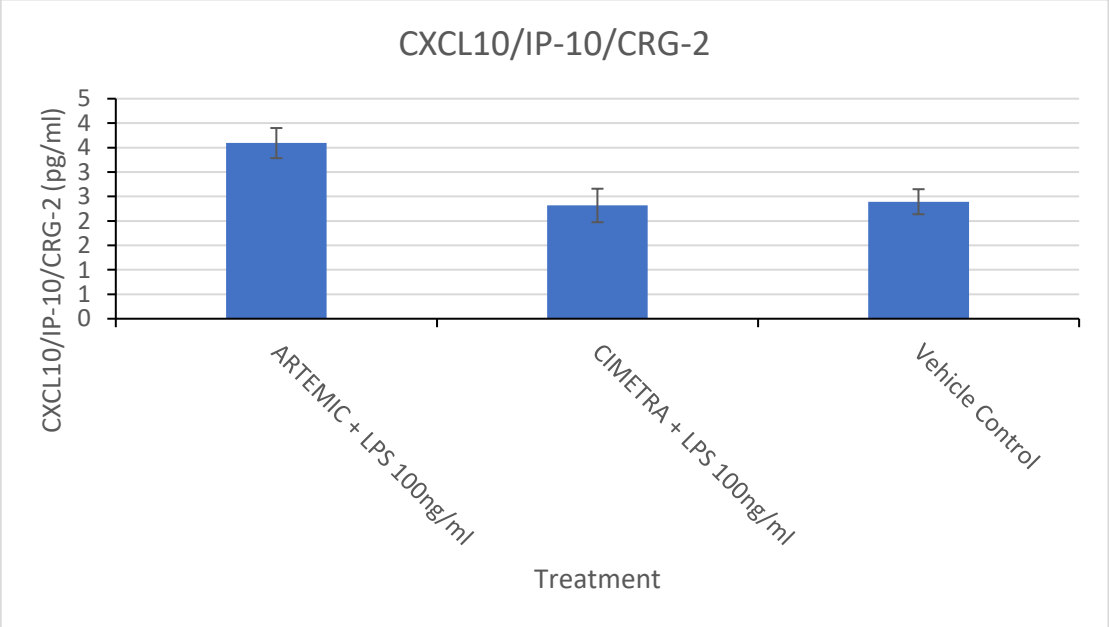

Fig 9. Concentration of CXCL10/IP-10/CRG-2 in PBMCs supernatant

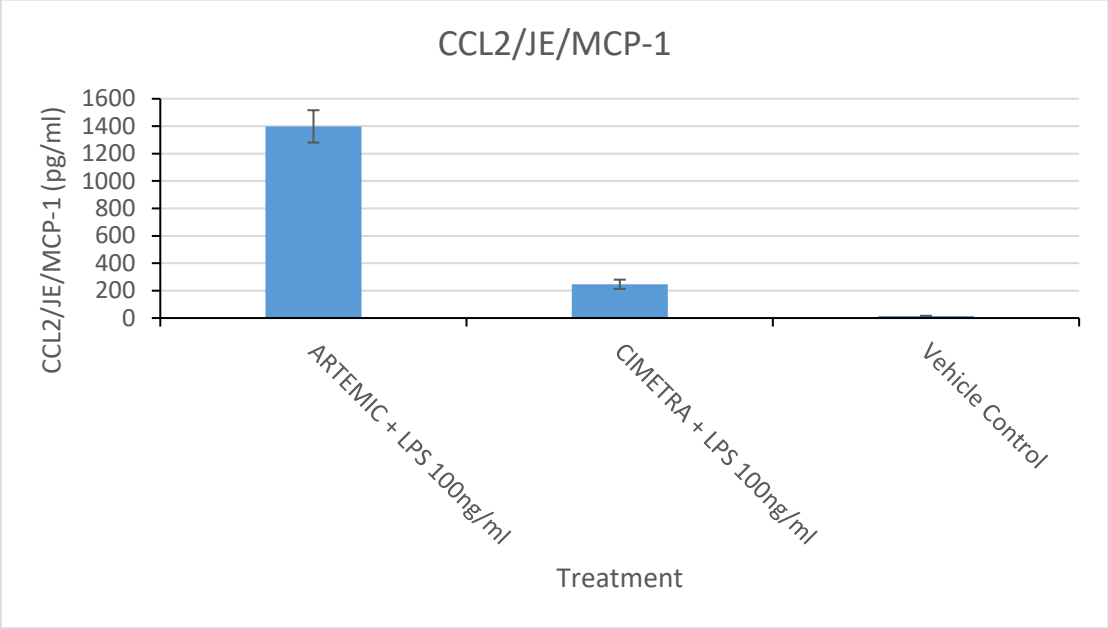

Fig 10. Concentration of CCL2/JE/MCP-1 in PBMCs supernatant

Based on the data presented above, MGC Pharma decided to continue the clinical program (phase IIb) with more active formulation, CimetrA, which answers all the goals of the cytokine storm prevention in COVID-19 patients needs. This formulation is developed and manufactured under EU-GMP conditions and certificates in the EU-certified manufacturing facility of MGC Pharma.

8. STUDY OBJECTIVES

This study designed to evaluate the efficacy, pharmacokinetic parameters and safety of CimetrA on patients diagnosed with COVID-19.

9. STUDY ENDPOINTS

9.1. The primary outcomes:

- **Efficacy endpoint**

  1- Change in WHO Ordinal Scale for clinical improvement (baseline to end of study will be measured on days 1,7,14 and 28).

The World Health Organization (WHO-WHO) has proposed the "Ordinal Scale of Clinical Evaluation of the World Health Organization" presented below as a means of generating a numerical value to assess the health status of the participant to allow comparisons to be made in clinical studies. The scale is shown in the table below and will be used to assess a secondary effectiveness target in this study.

Patient State	**Descriptor**	**Score**
Uninfected	Uninfected; no clinical evidence and viral RNA detected	0
Ambulatory	Symptomatic; independent	1
	Symptomatic; assistance needed	2
Hospitalized:	Hospitalized, no oxygen therapy	3
Moderate diseases	Hospitalized; oxygen by mask or nasal prongs	4

Hospitalized: Severe diseases	Hospitalized; oxygen by NIV or high flow	5
	Hospitalized; mechanical ventilation	6
	Mechanical ventilation and vasopressors, dialysis or ECMO	7
Dead	Dead	8

2- Change in COVID-19-Related Symptoms score (measured on days 1,7, 14, 28)

- **Safety Endpoints**

  Safety will be assessed through collection and analysis of adverse events, blood and urine laboratory assessments and vital signs.

9.2. The secondary outcomes:

- Number of participants with depending on oxygen supplementation through day 28 since onset of symptoms
- Change in inflammatory marker levels - IL-6, IL-1β, IL-12, TNF α, IFN-γ, CRP, NLR (Neutrophil / Lymphocyte ratio) (days 1, 2, 4, 7) compared to baseline
- Pharmacokinetic profile of the study drug on day 1 through 24 Hrs.
- Incidence and duration of mechanical ventilation
- Incidence of Intensive Care Unit (ICU) stay during COVID-19 complication
- Percentage of participants with definite or probable drug related adverse events
- Long term adverse events of COVID-19 on Day 28
- The Impact covid_19 on quality of life of patients on Days 1, 14 and 28

9.3. The exploratory outcomes:

- Course of change in D Dimer levels compared to baseline

- Occurrence of secondary infections

10. STUDY DESIGN AND PROCEDURES

240 adult patients who suffer from COVID-19 infection and do not participate in any other clinical trial. Patient must not agree to participate in any new clinical study during the study duration. Study will take place during patient's hospitalization due to COVID-19 infection. The study will last up to 4 weeks, until conclusion on day 28.
In case of hospital discharge within the study period, follow up will continue per protocol until day 28 wherever the subject will be located, depending on the status of the patient and study schedule.
If patient discharged, visits will be performed via phone call, if he still hospitalized, visits will be performed at corona department.
Only on day 28, all the patients must undergo clinic visit, they will arrive to the research clinic (only patient who will be under quarantine will have a phone call visit).
The study is not designed to include participants from a special population, so that patients with mental and intellectual problems, lack of judgment, children under the age of 18 and pregnant women will not be allowed to participate, or any patient who have a legal guardian.

Standard of care treatment acceptable to be used while patient participates in study:

Treatment will include:

Supportive care - symptomatic

Painkillers

Anticoagulant therapy

Steroids

REMDESIVIR - Compassionate treatment

Antibiotic treatment as needed

Inhalations if necessary

Oxygen

The treatments offered above are given according to the guidelines of the Ministry of Health.

The treatment will be given to the patient according to the clinical judgment of the medical staff and in accordance with the patient's health condition, and therefore the treatment does not have to be the same in each of the medical centers participating in the study.

10.1. Enrollment

Each candidate subject will be reviewed for an inclusion/exclusion criteria. After signing the ICF, the candidate subject will be asked to provide a medical history and undergo a physical examination, including measurement of blood pressure, pulse, temperature (PO), body weight and height, saturation, respiratory rate, vas scale, news score.

Blood will be drawn for a complete blood count (CBC) and other laboratory analyses (Biochemistry, Pk-pharmacokinetics, Inflammatory markers, D-Dimer).

Women of childbearing potential must undergo a urine pregnancy test.

10.2. Trial entry and enrollment: Medication schedule

Study drug will be administrated twice a day during days 1 and 2. Patients will be monitored for adverse events.

10.2.1. *Clinical and laboratory follow up:*

Subjects will be followed through regularly scheduled visits that will include: vital signs, physical examination, ongoing medical history review, and laboratory tests as described in Table 5.

Safety will be assessed by monitoring the subjects for AEs. The subjects will be instructed as to what is an AE and will be requested to fill out a diary detailing any AEs that may occur during the time period between visits.

Evaluation of the effect of oral administration of the study drug will be assessed by determining the clinical and laboratory tests as summarized below.

Table 5: Schedule of events

Day	**1**	**2**	**3-6**	**7**	**8-13**	**14**	**Day 21(phone visit)**	**Day 28 Clinic visit**
Confirmed SARS-CoV-2 infection	X					X		X
Treatment administration (twice a day)	X	X						
Inclusion/Exclusion criteria evaluation	X							
Informed Consent	X							
Medical History	X							
Concomitant Medications	X	X	X	X	X	X	X	X
AE Assessment		X	X	X	X	X	X	X
Randomization	X							
Physical Examination	X	X	X	X	X	X		X
Vital Signs	X	X	X	X	X	X		X
Hematology blood test (local)	X	X	X**	X	X**	X		X
Biochemistry blood test (local)	X	X	X**	X	X**	X		X
WHO Ordinal Score	X			X		X	X	X
COVID-19-Related Symptoms assessment	X			X		X	X	X
PK test*	X							
Blood test for inflammatory markers (IL-6, IL-1β, IL-12, TNF α, IFN-γ) (local)	X	X	X	X		X		X

D-Dimer test (local)	X	X		X		X		X
VAS scale	X	X	X	X	X	X	X	X
Urine pregnancy test for women of childbearing potential	X							X
ECG	X							x
COVID-19–Impact on Quality of Life Questionnaire	X			X		X	X	X
POST- COVID-19 Functional Status Scale								X

Biochemistry blood test: Sodium (Na), Potassium (K), Chloride (Cl), Creatinine, Glucose, Urea, Albumin, Calcium total, Alkaline Phosphatase (ALP), ALT, AST, Total Bilirubin, Direct Bilirubin, LDH, Total Protein, Uric Acid, CRP, and Lipid Profile (including Total Cholesterol, HDL, LDL, Triglycerides).

Hematology blood test: complete CBC.

D-Dimer test (coagulation): one tube for coagulation test

Inflammatory markers: the blood will be centrifuged and frozen according to the Lab manual, Local Lab.

Vital signs: blood pressure, pulse, weight, weight, body temperature (PO), saturation, respiratory rate.

VAS scale: will be performed by study staff member.

WHO Ordinal Score: will be completed by the study staff member based on patient status.

COVID-19-Related Symptoms assessment: will be completed by the study staff member based on patient status and answers.

COVID-19–Impact on Quality-of-Life Questionnaire: will be completed by the study staff member based on patient answers.

POST- COVID-19 Functional Status Scale: will be completed by the study staff member based on patient answers.

Pregnancy test: women of childbearing potential must undergo a urine pregnancy test.

Physical examination: full examination by doctor.

** Measurements will be performed per institutional schedule by the hospital staff, not necessarily by the principal investigator or the sub-investigators.

PK parameters*: will be performed only on 14 patients that will agree to participate in the PK analysis (only for Brazil andSouth Africa).

The PK will be performed only for the first dose of drug, after patient received the first dose (5 puffs) the study staff need to follow the table below.

For each test, approximately 5 ml of blood will be drawn (equivalent to one teaspoon) total of 55 ml of blood will be drawn.

Table 6: List of time points for pharmacokinetic assessments

Study Visit Number 1	
Time point 0	**Dosing (before the first dose of the drug)**
Time Point 1	15 minutes post dose
Time Point 2	30 minutes post dose
Time point 3	45 minutes post dose
Time point 4	1 h post dose
Time point 5	1.5 h post dose
Time point 6	2 h post dose
Time point 7	4 h post dose
Time point 8	6 h post dose
Time point 9	8 h post dose
Time point 10	10 h post dose

Time point 11	12 h post dose

Day 1

Prior to engaging in any study procedures, the subject must meet the inclusion/exclusion criteria by history (which includes a signed declination), and review and sign an ICF.
Following procedures will be performed during the visit –

- Inclusion/Exclusion criteria evaluation
- Informed Consent
- Medical History
- Concomitant Medications
- Physical Examination
- Vital Signs
- Hematology blood test (local, mandatory even if there are available results from the day before)
- Biochemistry blood test (local, mandatory even if there are available results from the day before)
- PCR test for detection COVID-19 (within 5 days from admission to hospital)
- COVID-19-Related Symptoms Assessment
- WHO Ordinal scale
- Blood test for inflammatory markers (IL-6, IL-1β, IL-12, TNF α, IFN-γ) (local)
- D-Dimer test (local)
- VAS scale
- Urine pregnancy test for women of childbearing potential
- ECG
- COVID-19–Impact on Quality of Life Questionnaire

- Randomization in 1:1:1 ratio to study drug (CimetrA-1) (Arm 1) or study drug (CimetrA-2) or to Placebo (Arm 3)
- Treatment administration (twice a day, morning, and evening)
- **PK test (only for Brazil and South Africa)** for first dose of the drug (5 puffs) as the table on page 36, PK must be done **before** receiving standard of care.

Day 2

- Concomitant Medications
- AE Assessment
- Physical Examination
- Vital Signs
- Hematology blood test (local, mandatory even if there are available results from the day before)
- Biochemistry blood test (local, mandatory even if there are available results from the day before)
- Blood test for inflammatory markers (IL-6, IL-1β, IL-12, TNF α, IFN-γ) (local)
- D-Dimer test (local)
- VAS scale
- Treatment administration (twice a day, morning and evening)

Days 3-6

- Concomitant Medications
- AE assessment
- Physical Examination
- Vital Signs
- Hematology blood test **

- Biochemistry blood test **
- Blood test for inflammatory markers (IL-6, IL-1β, IL-12, TNF α, IFN-γ) (local)
- VAS scale

Day 7

- Concomitant Medications
- AE assessment
- Physical Examination
- Vital Signs
- Hematology blood test (local, mandatory even if there are available results from the day before)
- Biochemistry blood test (local, mandatory even if there are available results from the day before)
- WHO Ordinal Score
- COVID-19-Related Symptoms assessment
- Blood test for inflammatory markers (IL-6, IL-1β, IL-12, TNF α, IFN-γ) (local)
- D-Dimer test (local)
- VAS scale
- COVID-19–Impact on Quality of Life Questionnaire

Days 8-13

- Concomitant Medications
- AE assessment
- Physical Examination
- Vital Signs

- Hematology blood test **
- Biochemistry blood test **
- VAS scale

Day 14

- Concomitant Medications
- AE assessment
- Physical Examination
- Vital Signs
- Hematology blood test (local, mandatory even if there are available results from the day before)
- Biochemistry blood test (local, mandatory even if there are available results from the day before)
- WHO Ordinal Score
- COVID-19-Related Symptoms assessment
- Blood test for inflammatory markers (IL-6, IL-1β, IL-12, TNF α, IFN-γ) (local)
- D-Dimer test (local)
- VAS scale
- PCR test for detection COVID-19
- COVID-19–Impact on Quality of Life Questionnaire

Day 21 (phone visit)

- Concomitant Medications
- AE assessment
- VAS scale
- COVID-19–Impact on Quality of Life Questionnaire WHO Ordinal Score

- COVID-19-Related Symptoms assessment

Day 28 – Follow Up (clinic visit)

- Concomitant Medications
- AE assessment
- Physical Examination
- Vital Signs
- Hematology blood test (local, mandatory even if there are available results from the day before)
- Biochemistry blood test (local, mandatory even if there are available results from the day before)
- WHO Ordinal Score
- COVID-19-Related Symptoms assessment
- Blood test for inflammatory markers (IL-6, IL-1β, IL-12, TNF α, IFN-γ) (local)
- D-Dimer test (local)
- VAS scale
- PCR test for detection COVID-19
- Urine pregnancy test for women of childbearing potential
- ECG
- COVID-19–Impact on Quality of Life Questionnaire
- POST- COVID-19 Functional Status Scale

In case of **hospital discharge** within the study period, follow up will continue per protocol until day 28 wherever the subject will be located, depending on the status of the patient and study schedule.

If patient discharged, visits will be performed via phone call, if he still hospitalized, visits will be performed at corona department.

Only on day 28, all the patients must undergo clinic visit , they will arrive to the research clinic.(only patient who will be under quarantine will have a phone call visit.)

11. STUDY POPULATION

11.1. Inclusion Criteria:

1. Confirmed by PCR test SARS-CoV-2 infection (according to nationally authorized laboratory criteria).
2. Hospitalized patient with COVID-19 of moderate stable or worsening severity not requiring ICU admission (defined by NIH criteria - fever, cough, dyspnea, fast breathing, but no signs of severe pneumonia, including SpO2 ≥ 94% on room air).
3. Age: 18 years old and above.
4. Subjects must be hospitalized
5. Ability to receive treatment by spray into the oral cavity

11.2. Exclusion Criteria:

1. Tube feeding or parenteral nutrition.

2. Patients with scores 5 or above per the Ordinal Scale for Clinical Improvement published by the WHO. (i.e., who need oxygen supply beyond use of nozzles or simple mask)

3. Need for admission to ICU while of the present hospitalization at any time prior to completion of the recruitment to the study.

4. Any condition which, in the opinion of the Principal Investigator, would prevent full participation in this trial or would interfere with the evaluation of the trial endpoints.

11.3. Removal of subjects from therapy or assessment

a. If any of the inclusion criteria fails to be met, or any of the exclusion criteria is met during the period in which the interim history, physical examination and laboratory tests are performed, the subject will be ineligible to continue in the study. These subjects will be classified as screened but not enrolled.
b. If the subject begins a regimen of medication at any time during the study that includes any of the medications listed in the exclusion criteria or begins an increase in dose of an existing regimen of medication at any time during the study, the subject will be terminated from the study. These subjects will not be used in the primary analyses.
c. If continuing in the study does not appear to be in the best medical interest of the subject, his/her participation may be terminated by either the Principal

Investigator or the study director. Removal of an individual by the Principal Investigator will be reported to the Institutional Helsinki Committee and the appropriate regulatory agencies according to the guidelines of these groups. These subjects will not be used in the primary analyses unless the reason for removal was due to reasons of safety in which case data would be used in the primary analyses.

d. In addition to a participant being able to voluntarily withdraw from the study at any time, the Investigator may withdraw participants from the study under the conditions noted below, and such subjects will not used in the primary analyses.

e. Participants will be withdrawn from the treatment protocol if participants are unwilling or unable to comply with the schedule of treatment, follow-up or safety monitoring, and will not be used in the primary analyses.

f. Subjects considered treatment failures will be removed from the study and will be offered alternative standard therapy by their treating physician and will not be used in the primary analyses.

11.4. Screening and Enrollment logs

A screening log of subjects who are screened but not enrolled will be kept by the site. The reason(s) for not enrolling a subject should be stated in each case. An enrollment log of subjects who did not meet eligibility criteria at Randomization will also be kept by the clinic. The reason(s) for not including a subject should be stated in each case.

12. STUDY TREATMENT

12.1. STUDY DRUG DOSAGE AND ADMINISTRATION

The study drug dosage groups are defined based on the preclinical and clinical experience with CimetrA.

Arms 1 and 2 doses were defined based on the preclinical data, presented in the Investigator Brochure, when CimetrA formulation demonstrated an anti-inflammatory activity in lower dosages. The rationale of additional dosage is based on the potential ability of CimetrA to be active in different ways in prevention of deterioration of COVID-19 patients. As per FDA's requirement for the dose finding, additional study arm dosage was defined based on the preclinical studies described above.

Minor dose adjustment was performed according to the CMC limitation as a result of the nano-particles characteristics.

Arm 1: CimetrA-1, with a total dose containing a combination of Curcuma longa rhizome dry extract 28 mg, Boswellia serrata resin dry extract 60 mg in spray administration – divided in 4 separate doses given as an add on therapy, total of 4 doses over 48 hours (day 1 and day 2), twice a day (morning and evening).

Single dose: 1ml of dose contain Curcuma longa rhizome dry extract 7 mg/ml, Boswellia serrata resin dry extract 15 mg/ml in spray administration , for one dose are required 5 puffs from the study drug spray.

Daily dosage is 2 ml which equal to 10 puffs from the study drug spray.

Arm 2: CimetrA-2, with a total dose containing a combination of Curcuma longa rhizome dry extract 19.6 mg, Boswellia serrata resin dry extract 42 mg in spray administration – divided in 4 separate doses given as an add on therapy, total of 4 doses over 48 hours (day 1 and day 2), twice a day (morning and evening).

Single dose: 0.7 ml of dose contain Curcuma longa rhizome dry extract 4.9 mg/ml, Boswellia serrata resin dry extract 10.5 mg/ml in spray administration, for one dose are required 5 puffs from the study drug spray.

Daily dosage is 1.4 ml which equal to 10 puffs from the study drug spray.

Arm 3: Placebo, composed of the same solvent but without active ingredients, given as an add on therapy in spray administration, total of 4 doses over 48 hours (day 1 and day 2), twice a day (morning and evening).

Patients will be randomized in 1:1:1 ratio to one of the three arms.

12.2. Packaging and Labelling of Study Products

CimetrA-1, CimetrA-2 and Placebo is supplied in a bottle containing 5 ml.

The Product is packed in a bottles with a spray pump. It is administered by spraying into the oral cavity.

bottles are closed with a validated spray delivery system , Spray pump on product bottle enables dosing 0.2 ml of CimetrA-1 /0.14 ml of CimetrA-2 in each press and will be packaged and labelled in compliance with the GMP, and EU regulation regarding drugs used in clinical trials.

The lot number and date of manufacture for the clinical lot used in the study will be provided to the clinical site and will be reported in the Clinical Study Report. The documentation supplied by the Sponsor for the study medication (i.e. Certificate of

Analysis for the test product) will make it possible to retrace the composition and pharmaceutical profiles of the test product .

Study Product will be labeled with :

- Product name
- Dose
- Lot number
- Date of manufacture
- Protocol number
- Sponsor's name
- Instructions for use and storage
- "Investigational Use Only" statement

Placebo will be administrated in the same way, and will be identical in its characteristics to the study drug in order to prevent bias.

12.3. Storage, Dispensing and Return of the Investigational product

Bottles containing the study product should be stored at room temperature. Records should also be kept by the Investigator or pharmacist as to how much study drug was used by each subject. The study monitors must check during each visit the study drug supplied to ensure expiry date and sufficient amount of study drug. All investigational products must be kept in a locked area with access to the study drug limited to designated study personnel. Only personnel under the supervision of either the Investigator or the local pharmacist are authorized to dispense study drug. During storage at the pharmacy, the temperature will be monitored and recorded by a pharmacist or a temperature log. The Sponsor will be notified for any deviation from the storage conditions.

12.4. Accountability and Compliance

Each delivery must be acknowledged by the pharmacist (or authorized study team member responsible for the investigational medicinal product) by filling in the receipt record form. The study staff will confirm the receipt of clinical supply and will return signed drug accountability logs to the study monitor.

The pharmacist (or authorized study team member responsible for the investigational medicinal product) are responsible for ensuring the supervision of the storage and allocation of these supplies, which will be forwarded to the Investigator at the appropriate time before administration. The Investigator or pharmacist may dispense investigational drug only to subjects enrolled in the study.

Treatment compliance will be assessed at all visits during the Treatment Period. It will be based on drug accountability (volume measure), and subject's diary review. Study drug compliance may be enhanced with regular telephone and other reminders. Drug accountability records must be maintained by the clinical investigation site at all times. At the last study visit, all used and unused investigational drug will be assessed for accountability by the study monitor.

The subject identification number, the date, batch number/pack number, and quantity of study drug used by the subject will be checked for correctness and recorded on the appropriate accountability forms. Unused drug supplies will be returned to the Sponsor. At the end of the study, all the clinical supply and the corresponding accountability forms must be returned by the study monitor for reconciliation and destruction. A copy of these records must be kept at the clinical investigation site.

The inventory will be made available to the study monitor who will verify accountability and verify dose during the course of the study. Study drug orders, records of study drug receipts, dispensing records, and inventory forms located at

the site will be examined and reconciled by the study monitor periodically during and at the end of the study.

13. CONCOMITANT MEDICATIONS DURING THE STUDY

13.1. General guidelines

All prior treatments received by the subject within 60 days of the initial screening visit will be recorded on the subject's CRF including the treatment's name, indication and the start and stop dates.

All concomitant medications taken by the subject (including prescription, over-the-counter, herbal supplements and health store products) must be recorded on the CRF, along with the indication and start and stop dates as well as daily dose.

13.2. Allowed Concomitant Medications/Therapies during Study

Concomitant medications allowed to be used in this study are those used at screening to control existing medical condition and/or those taken during the study to treat possible adverse events. All concomitant medications used to treat adverse events will be recorded in the subject's medical file and on the appropriate CRF page.

If intake of a drug should become necessary for any reason during the course of the study, the subject is required to inform the Investigator immediately, who will record the drug, the dose and the time of administration in the subject's CRF.

<u>Standard of care treatment acceptable to be used while patient participates in study :</u>

Treatment will include:

Supportive care - symptomatic

Painkillers

Anticoagulant therapy

Steroids

REMDESIVIR - Compassionate treatment

Antibiotic treatment as needed

Inhalations if necessary

Oxygen

The treatments offered above are given according to the guidelines of the Ministry of Health.

The treatment will be given to the patient according to the clinical judgment of the medical staff and in accordance with the patient's health condition, and therefore the treatment does not have to be the same in each of the medical centers participating in the study.

13.3. Potential Adverse Events and risks for the patient in the study

During Phase II study on 50 COVID-19 patients no drug related adverse events were reported. The full safety profile is presented above .

It is important to say that both active ingredients of the study drug is defined as GRAS and found to be safe with no adverse events in clinical studies. Based on the literature, the following data regarding the potential risks of the Curcumin and Boswellia is available –

1. Madhu K at al., Rahmani et al. and Selvi et al. reported gastrointestinal adverse events related to diarrhea, nausea and abdominal pain
2. Chuengsamarn et al. reported hot flashes and constipation that were observed in the clinical trial in type 2 diabetes patients .

14. ADVERSE EVENT

14.1. Definition of adverse event

Adverse event means any untoward medical occurrence associated with the use of a drug in

humans, whether or not considered drug related.

An Adverse Event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product, whether it is related to the pharmaceutical product in question or not. This includes a change in a subject's condition or laboratory results, which has or could have a deleterious effect on the subject's health or well-being.'

In this study, local reactions due to study treatment will be captured in the diary, and this information will not be duplicated in the CRFs.

AEs to be recorded in the CRFs are systemic reactions that also are captured in the diary and other AEs occurring that are not due to study treatment.

14.2. Methods for eliciting AEs

All subjects should be carefully monitored for occurrence of AEs during the study and for a reasonable time period thereafter. No distinction should be made between the investigational treatment and the placebo treatment for the purpose of AE reporting.

All directly observed and spontaneously reported AEs should be recorded in the CRF. If no AE has occurred during the study period, this should also be recorded in the CRF. In addition, each study subject will be asked an open question about possible AEs at each clinic visit following initiation of treatment.

The following evaluations are to be done by the Investigator in connection with the AE:

- type of event
- seriousness
- degree of severity
- duration (start - end)
- action taken

- likelihood of causality with study product
- outcome of the adverse event

14.3. Follow-up period after an AE

After an occurrence of an AE, the subject has to be followed up until either the AE has ceased or until the subject is under professional medical care and a potential causality between the study drug and the AE has been penetrated. The post-treatment safety observation period will under AE's resolution or stabilization.

14.4. Definition of Serious Adverse Events

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that at any dose fulfills at least one of the following criteria:

- is life-threatening
- results in death
- requires hospitalization, initial or prolonged
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect or
- is regarded as medically important without meeting the above-mentioned criteria

14.5. Reporting of Serious Adverse Events

SAEs must be reported by the Investigator within one working day by cell phone and Email to the Clinical Monitor or, if unreachable, other members of the staff at Sponsor or CRO, regardless of the time that may have elapsed from the time the event occurred to when the Investigator first learns of it. The Initial Report should contain at a minimum the following information:

- subject identification
- treatment date

- adverse event symptoms/ diagnosis
- time specification for the medical event
- name of the original reporter

An SAE Report must also be completed, signed and sent to the Clinical Monitor within five working days via fax or regular mail after a direct voice contact. Apart from the information above, the Follow-up Report should also contain the following information based on WHO-UMC system:

- assessment of severity
- assessment of causality

15. MONITORING AND AUDITING PROCEDURES

The study site will be visited by the Clinical Monitor periodically, as agreed upon by the Investigator and MGC-Pharma. It is a function of the Clinical Monitor to ascertain that all aspects of the protocol are complied with and that the conduct of the study conforms to established rules for Good Clinical Practice (GCP).
At the time of each monitoring visit, the Clinical Monitor will review the CRF of the subjects in the study to ascertain that all items have been completed and that the data provided are accurate and obtained in the manner specified in the protocol.
The subject's clinical records will be reviewed to confirm that the protocol has been adhered to with respect to the randomization procedures, subject's information and informed consent, and inclusion/exclusion criteria.
The Clinical Monitor will also check that the data in the CRF are consistent with the clinical records (Source Data Verification) and that study results are recorded completely and correctly. The Monitor will check the reporting of SAEs and the procedures for product accountability and record keeping. For this purpose the

Clinical Monitor must be given direct access to clinical records, original laboratory data, etc., as far as these relate to the study and without jeopardizing subject integrity. CRFs for all included subjects must be made available to the Monitor for review.

The study site may also be subject to Quality Assurance audit by MGC-Pharma. A Regulatory Authority may request to make an inspection of the study site. The procedures of such a visit would be similar to those of a monitoring visit, and data already checked by the Monitor may be checked again. The Investigator is required to inform MGC-Pharma immediately of an inspection requested by a Regulatory Authority.

15.1. Case Report Forms (CRFs)

eCRFs of a design mutually agreed upon by the Investigator and MGC-Pharma will be supplied by the contracted CRO. The CRF must be completed and signed for each included subject.

The completed CRFs should be made available for checking of accuracy by the Clinical Monitor as agreed in advance. The original CRFs are the sole property of the MGC-Pharma and should not be copied or made available in any form to a third party, with the exception of authorized representatives of local Regulatory Authorities, without written permission from MGC-Pharma.

15.2. Source Data

The printouts from the laboratory analysis will be considered as source and must be labeled with the subject number and measurement period. The printouts must be dated and signed by the Investigator. Results from the blood pressure, heart rate, weight and height measurements are to be recorded directly into the CRF. The subject diary is part of the CRF. Copies of the clinical laboratory and hematology data will be stored in the subject records.

Signed Informed Consent Forms, the existence of medical notes, inclusion/exclusion criteria and AE/SAE will be checked in 100% of the CRFs.

Source data verification

On site subject charts, outside laboratory reports and outside notes, including MD notes, letters and follow-up to subjects/families, are used to verify CRF data. At least 30% of source documents will be verified during the study as follows:

- 100% of the source documents for the first two visits of the first eight study subjects.
- 30% source verification for all visits of all subjects.
- 100% source verification for inclusion/exclusion criteria for all subjects.
- 100% source verification for adverse event assessment for all subjects.
- 100% source verification for medication history.

16. STUDY STAFF INFORMATION

It is the responsibility of the Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, and have detailed knowledge of and training in the procedures that are to be executed by them. This should be documented in writing stating the time at which training was performed, what was trained, by whom, and who attended.

17. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

A prospective, randomized (1:1:1), double-blind, multi-center, placebo-controlled clinical study.

Statistical Hypothesis

The hypothesis of this study is that treating with CimetraA and CimetraA2 will be more effective, while maintaining a favorable safety profile. This will be demonstrated by a significant difference between the two active and the control groups.

In this study, we will test the following hypothesis:

- H0: Delta1=Delta2=Delta3
- H1: at least one is different.

Where Delta is the difference between baseline and end of study in WHO Ordinal Scale for clinical trial.

If the null hypothesis is rejected in favor of the alternative hypothesis the study will be deemed successful.

Safety will be assessed by adverse events, blood and urine laboratory assessments and vital signs.

Planned Sample Size

For this phase IIb, 3-armed clinical trial, we use the ANOVA test to estimate the expected improvement in the primary outcome; the WHO ordinal scale for clinical improvement.

We expect medium effect (f=0.20) for the differences in Delta between the 3 groups, and standard deviation of 1.5, based on the ordinal scale (0-8). This power analysis is for a one-way fixed effects analysis of variance with 3 levels. The study will include 80 patients per group for a total of 240 patients.

The criterion for significance (alpha) has been set at 0.05 with Power of at least 80%. The analysis of variance is two-tailed Main effects.
For immunogenicity assessment, larger sample size will reduce mean variability in the observed outcomes and will increase the opportunity to detect real changes.
For 80 participants per group we ensure the desired precision for phase 3 trial to assess safety and effectiveness. Total sample 240 ptients.

Computer Software

Sample size and Power were calculated with the Power and Precision statistic program ver 4.1 and all statistical analyses and data presentations, including tabulations and listings, will be performed using the SPSS statistic program version 27.0 (or higher) software.

Randomization

Randomization tend to produce study groups comparable with respect to known and unknown risk factors, removed investigator bias in the allocation of participants and guarantees that statistical tests will have valid false positive error rates.

After a participant will meet the eligibility criteria, he/she will be randomly allocated (with a 1:1:1 ratio) to one of the following treatment groups based on a randomization scheme stratified by center.

The randomization scheme will be prepared by an independent statistician using statistic program for random number generator. The block size is set in ahead and study personnel will be blinded to the randomization block size.

Blinding

This is a double-blind study: neither the participants nor the investigators will be aware of arm allocation of each study participant.

Blindness is important to avoid bias. Monitoring and reporting of the success of blindness are important for the reader's confidence of the trial results. Groups should be marked by capital letter and blindness should maintain throughout the study.

Missing Data

Safety data should be collected from non-adherent/withdrawal participants to avoid possible bias.

Prior to analyzing the data, extreme laboratory values should be checked. Missing values will be treated as ITT.

Multiple imputation for binary data will be used as the primary imputation method in the case of missing data for the primary efficacy endpoint.

Dropout/AE Imputation: A participant with no post baseline measurement or a participant withdrawn due to an adverse event or treatment intolerability will use last observation carried forward imputation methods.

Baseline Data

Baseline participant characteristics will be collected at screening. The specific baseline ("start of treatment") endpoints and other symptoms will be collected prior to each treatment.

Significance Levels and Handling of Type I Error

The overall significance level for this study is 5% using two-tailed tests, except for treatment by center/region interaction that will be tested at a significance level of 10%.

When multiple comparisons between the groups are made, the chance of finding a significant difference in one of the comparisons is greater than the stated significance level, therefore we will use pot-hoc analysis.

Efficacy endpoints:

Time to sustained clinical improvement (as defined earlier).

Safety Endpoints

The safety endpoints of adverse events and tolerability will be assessed by review of all safety parameters, including adverse events.

The incidence of adverse events will be assessed as a function of severity and association to the device. The time of resolution of the adverse events and need for treatment will also be analyzed.

Analysis Sets
The ITT analysis set will serve as the main set for safety assessments.

The primary and secondary performance efficacy assessments will also be performed on the PP and the ITT analysis sets.

Statistical Analysis

Demographic and Baseline

Demographic and baseline condition related characteristics will be tabulated and compared between the study arms by data type. Continuous variables will be summarized by a mean, standard deviation, minimum, median and maximum and categorical variables by a count and percentage.

Primary Efficacy Analysis

The primary efficacy endpoint of the study is the mean change in the WHO Ordinal Scale. It will be evaluated using a General Linear Model ANOVA test.

Subset Analyses

The primary endpoint will also be evaluated stratified by center using a General Linear Model ANOVA test.

A sensitivity analysis of the primary endpoint will be performed to assess the impact of missing data on the study outcome.

Adjustment for other covariates such as demographics or other baseline participant characteristics may be performed by adding these variables into a multivariate linear regression.

Secondary Efficacy Analysis

The 3 groups will be compared with the ANOVA test or Kruskal Wallis non-parametric test, following by post-hoc analysis for pairs differences.

Additional Efficacy Parameters of Interest

A count and percentage of participants responding to each of the exploratory efficacy endpoints will be presented. The groups will be compared with a chi-squared test or a Fisher's exact test.

Safety Analysis

The primary safety variable, the cumulative incidence (and 95% CI) of device related adverse events (AEs) throughout the study, will be presented in tabular format and will include incidence tables by severity.

Serious adverse events, device-related SAEs, adverse events (by type and overall), device-related AE, adverse device reactions and device malfunction rates will be compared between the study arms with a Fisher's exact test.

Serious adverse events will be listed and discussed individually.

PK test

Actual times of dosing and blood collection at various time points will be recorded in source documents as well as CRF's. Objectives of PK sampling are to measure values of CimetrA active ingredients in plasma at different time point after first administration of study medications and at different time point after multiple administrations during steady state.

PK samples will be processed and frozen on site. Labels have been prepared for the site again containing patient No., visit No., type of test (PK) and time point. Upon completion of the study, samples will be sent to selected analytical laboratory with dedicated courier service. The PK parameters will be obtained from plasma concentration data for curcumin and boswellia.

Analyses of PK data will be based on the PK Set, which will include all subjects who received at least one treatment and for whom concentration data is available.

Plasma concentration data will be tabulated and plotted for each subject for whom concentrations are quantifiable and for each treatment group. Actual times of sample collection will be used. PK analysis will be performed using appropriate non-compartmental techniques to obtain estimates of the following standard PK parameters if deemed possible:

- Maximum observed serum drug concentration (C_{max})
- Time to C_{max} (t_{max})
- Lag time to start of absorption (Tlag)
- Area under the plasma drug concentration-time curve (AUC) from time 0 to the last quantifiable concentration (AUC_{0-t})
- AUC from time 0 to infinity ($AUC_{0-\infty}$)
- Percentage of $AUC_{0-\infty}$ extrapolated (AUC_{ext})
- Apparent total volume of distribution at the terminal phase (V_z/F)
- Apparent total body clearance (CL/F)
- Terminal elimination rate constant (λz)
- Apparent terminal elimination half-life ($t_{½, z}$)
- Dose normalized C_{max}, $AUC_{0-\infty}$, AUC_{0-t}

Details of storage, handling and shipping of blood samples will be described in a Laboratory Manual.

<u>Randomization and stratification</u>.

Subjects would be assigned in sets of four as one per each of the four study groups – this would assure that we maintain exact balance among groups in terms of n / group.

Stratification will be performed according to the medical history and risks factors, based on the data will be received in the study.

18. DATA MANAGEMENT

Data management based on GCP refers to the activities defined to achieve safe routines to enter subject information into a database efficiently and with avoiding of errors.

The data management routines include procedures for handling of CRFs, database and data entry screens set-up, validation of the database and data entry screens, data entry and verification, and documentation of the performed activities including information of discrepancies in the process. The database, data entry screens and programs will be designed in accordance with the study protocol and the CRF.

The Clinical Monitor will check entries in the CRF data from the site. The data are exported to a clinical database. Logical checks programs will systematically check the clinical database and obvious errors will be corrected.

Findings from visual and automated logical checks will be compiled on Data Clarification Forms (DCF) per each Subject. The DCF will be sent to the site for resolution. The signed DCF will be returned to MGC-Pharma. The error resolutions/data clarifications (query resolution process during the study) will be entered into the clinical database. When a clean file has been accomplished, the database will be locked after a formal clean file procedure.

The computerized data processing will be the responsibility of MGC-Pharma using standard software. The statistical analysis will be performed by MGC-Pharma or a

consultant approved by MGC-Pharma. Data will be processed in agreement with local legislation and accepted practice.

19. CHANGES IN THE APPROVED STUDY PROTOCOL

Any proposed protocol change must be discussed with and approved by MGC-Pharma and the Investigator before submitted to IEC/IRB and Regulatory Authority, for approval or notification according to applicable national regulations. Substantial protocol changes should be documented in a written and numbered Protocol Amendment, which must be signed and dated by the same parties who signed the Final Study Protocol.

20. CURRICULUM VITAE

A Curriculum Vitae (CV) must be obtained from all Investigators and staff members carrying out observations of primary or other important variables involved in the study. It should include name, title, occupation, education, and research experience, present and former positions and should be signed and dated.

21. PROCEDURES IN CASE OF MEDICAL EMERGENCY

The Investigator is responsible for ensuring that there are procedures and expertise available to cope with medical emergencies during the study.

21.1. Emergency contact between Investigator/Monitor/MGC-PHARMA

If a need for emergency contact arises, Principal Investigator or, if unavailable, MGC-Pharma's Clinical Monitor should be contacted. Although a message may be left with a voice mailbox, the search must nevertheless continue until direct contact is established and the emergency message has been communicated to the appropriate person. The Investigator should provide the study subjects with an emergency contact hospital telephone number.

22. DISCONTINUATION OF THE STUDY

MGC-Pharma reserves the right to discontinue the study at any time, but intends only to exercise this right for valid scientific or administrative reasons.

In the case of overdose, treatment with antiviral therapy will have to be discontinued and the participant should be carefully monitored for potential adverse events and receive appropriate medical treatment according to their clinical condition.

23. FINAL STUDY REPORT AND PUBLICATION OF STUDY RESULTS

After completion of the study, Statistician will perform the statistical analysis. The results will be presented to and discussed with the Investigators as soon as possible. Based on these discussions, MGC-Pharma will prepare a Clinical Study Report. It is agreed between the Investigators and MGC-Pharma that data from the study will be used in connection with the development of the study product. Information about the study may therefore be disclosed by MGC-Pharma to MGC-Pharma's scientific advisers, Board of Directors, the public, Regulatory Authorities, and others.

The final report will be submitted to Regulatory Authorities and could also form the basis for a manuscript intended for publication in a medical journal, as separately agreed between MGC-Pharma and the Investigators and subject to approval by mutual consent.

Record retention

The Investigator must arrange for retention at the investigational site of a list of the subjects and their identifying codes, subject files and other study documents as hard-copy and electronic files as applicable according to applicable regulatory requirements for:

1. at least two years after the last approval of a marketing application in the EU and US and until there are no pending or contemplated marketing applications in the EU and US; or
2. at least two years have elapsed since the formal discontinuation of clinical development of the investigational product.

The study documents include IEC approvals, the study protocol and all its amendments, all source documents and laboratory records, copies of Case Report Forms, subject informed consent forms, and any other pertinent study document.

It is the responsibility of MGC-Pharma to inform the Investigator/institution as to when these documents no longer need to be retained.

Alternatively, the source documents may be stored at a safe place outside the study site after agreement between the Investigator and MGC-Pharma.

Disclosure and confidentiality

All unpublished information concerning the study product and research carried out by MGC-Pharma, including patent applications, manufacturing processes, basic scientific data, etc., is considered confidential and the sole property of MGC-Pharma, and will be disclosed by MGC-Pharma at its sole discretion.

Protocol Signature Page

Date……	Date……
……	……
Name:	Name:
Study Sponsor	Principal Investigator

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