Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
Funded by the Department of Health

EVIDENCE SUMMARY

Among patients with COVID-19, should artesunate (artemisinin) be used for treatment?

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RECOMMENDATION

We suggest against the use of artesunate, artemisinin or pyronaridine tetraphosphate + artesunate in the treatment of COVID-19. *(Very low certainty of evidence, Weak recommendation)*

Consensus Issues
There may be evidence on the in vitro effect of the drug. Despite being a new drug, we have a similar drug being used for malaria (Artemether-lumefantrine). However, given that the evidences available are very limited and the effect of drug is not yet clear, the panel unanimously suggests against the use of it. We need to wait for ongoing studies and more evidence for its use and effect on COVID 19.

Key Findings

There are three (3) randomized controlled trials (RCTs) that investigate the effect of artesunate (artemisinin) compared to varying standards of care or placebo as treatment for patients with COVID-19. Artesunate showed no significant difference in mortality, clinical deterioration, improvement in chest CT scan or X-ray, time to virologic clearance, and mild and moderate-to-severe adverse effects. Two (2) studies reported shorter time to clinical improvement for artesunate. The overall certainty of evidence was rated very low due to very serious imprecision, serious risk of bias, and in some outcomes, inconsistency and indirectness.

Introduction

Artemisinin and artesunate (one of its chemical derivatives), while known for anti-malarial properties, have demonstrated anti-inflammatory and in-vitro efficacy against viruses, including SARS-CoV-2.[1,2] Artemisinin and its derivative artesunate can inhibit the docking of the SARS-CoV-2 spike protein onto the human ACE2 receptor protein and TGF-β-dependent early steps in the infection process.[1] The combination of pyronaridine-artesunate has demonstrated in-vitro efficacy in inhibiting SARS-CoV-2 viral replication [2,3] (exact molecular mechanisms not elucidated). Consequently, the clinical benefits of this drug are currently being explored in human clinical trials.

Review Methods

A systematic search was done using Medline, Cochrane Library, Google Scholar, and CNKI with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and artemisinin, artesunate, or 青蒿素. The COVID-NMA Living Data was also checked, and ongoing studies in the NIH

clinicaltrials.gov and various trial registries were also searched. Preprints were also searched using MedRxiv, ChinaXiv and BioRxiv. Other sources such as those directly given from the Republic of the Philippines Department of Health were used. Only randomized controlled trials that compared artesunate (artemisinin) against placebo or standard care were included in this review. Outcomes of interest included mortality, clinical deterioration or improvement, development of acute respiratory syndrome, need for mechanical ventilation, need for hospitalization, duration of hospitalization, time to clinical recovery, improvement of radiographic findings, virologic clearance, or adverse events. No limits were placed on age, COVID-19 severity, and dosing strategy.

Results

Three (3) randomized controlled trials (RCTs) with a total of 216 patients are included in this analysis. One RCT is published, one is a preprint, and another is unpublished (data obtained from a pharmaceutical report). All of these RCTs recruited mild-to-moderate RT-PCR confirmed COVID-19 patients.[4-6] Artemisinin was given differently in each RCT as follows: artemisinin [4], artesunate [5], and pyronaridine tetraphosphate / artesunate [6]. The comparator also varied widely across RCTs: standard of care (lopinavir/ritonavir 500mg + α-interferon 500) in one study [5], and placebo in another study [6]. In one RCT, the standard of care varied in three sites with remdesivir, prednisolone, low molecular weight heparin, and doxycycline in one site, azithromycin, dexamethasone in the second site, and ivermectin, doxycycline, and inhaled steroids in the third site.[4] Outcomes measured during the follow-up period of around 21 to 28 days included reducing mortality [6], clinical deterioration [6], time to clinical improvement or recovery [4,5], improvement in chest computed tomography (CT) or radiography (x-ray) [5], virologic clearance by polymerase chain reaction (PCR) test [5], and even mild and moderate-to-severe adverse effects.[4-6] The characteristics of included studies are summarized in Appendix 3.

The overall certainty of evidence was rated very low due to very serious imprecision, serious risk of bias, and in some outcomes, inconsistency and indirectness (from the use of other experimental drugs as control). The serious risk of bias was due issues with performance bias in all 3 studies; selection, detection, attrition bias, and reporting bias in 2 studies. The risk of bias summary is shown in Appendix 4. The GRADE evidence profile is in Appendix 5.

There was no significant difference in mortality between patients given artesunate and control (RR 0.35, 95% CI 0.01, 8.44; 1 RCT). Similarly, there was no significant difference in clinical deterioration (RR 0.42, 95% CI 0.09, 2.08; 1 RCT). One study reported significantly shorter time to clinical improvement among patients given artesunate compared to control (mean difference [MD] -1.51 days, 95% CI -2.74, -0.28 days). In another non-peer reviewed (pre-print) study, it also reported shorter time to clinical improvement for artesunate (MD -9 days, confidence interval could not be computed). However, results of the 2 studies could not be pooled due to inadequate data provided.

No significant difference in improvement in chest CT or X-ray (RR 0.67, 95% CI 0.17, 2.64) and time to virologic clearance (MD -5.37 days, 95% CI -11.97, 1.24) was noted between those given artesunate and control.

Adverse Events

There are no significant differences in mild adverse events (RR 0.81, 95%CI 0.62, 1.06; $I^2 = 0\%$) and moderate-to-severe adverse events (RR 0.85, 95% CI 0.37,1.95; $I^2 = 40\%$). Mild adverse events include nausea, muscle aches, fatigue, vomiting, diarrhea, transient mild rash, vertigo, and

loss of appetite. Moderate-to-severe adverse events include AST and ALT elevation, QT interval prolongation, thrombocytopenia, bradycardia, and severe diarrhea.

Recommendations from Other Groups

There are currently no recommendations made by any other group on the use of artesunate for COVID-19, such as the National Institutes of Health, Infectious Disease Society of America, Australian Guidelines, World Health Organization Guidelines.[7-10]

Research Gaps

There are currently fourteen (14) ongoing RCTs (Appendix 7). This review will be updated as soon as full results from these trials become available.

References

[1] Uckun F, Saund S, Windlass H, Trieu V. Repurposing Anti-Malaria Phytomedicine Artemisinin as a COVID-19 Drug. Frontiers in Pharmacology. 2021;12.

[2] Gendrot M, Andreani J, Boxberger M, Jardot P, Fonta I, Le Bideau M et al. Antimalarial drugs inhibit the replication of SARS-CoV-2: An in vitro evaluation. Travel Medicine and Infectious Disease. 2020;37:101873.

[3] Krishna S, Augustin Y, Wang J, Xu C, Staines H, Platteeuw H et al. Repurposing Antimalarials to Tackle the COVID-19 Pandemic. Trends in Parasitology. 2021;37(1):8-11.

[4] Trieu V, Saund S, Rahate P, Barge V, Nalk K, Windlass H et al. Targeting TGF-β pathway with COVID-19 Drug Candidate ARTIVeda/PulmoHeal Accelerates Recovery from Mild-Moderate COVID-19. 2021;.

[5] Lin, Wu, Xie et al. Clinical trial on Artesunate in the treatment of COVID-19. Chinese Critical Care Medicine. 2020;.

[6] Shin Poong Pharm. Co., Ltd. A Multi-center, Randomized, Double-blind, Parallel, Placebo-Controlled, Phase Ⅱ Clinical Trial to Evaluate Efficacy and Safety of Pyramax in Mild to Moderate COVID-19 Patients. South Korea; 2021.

[7] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/

[8] Australian National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical cure of people with COVID-19 v42.0. Available at https://app.magicapp.org/#/guideline/5571

[9] Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2021; Version 5.1.0. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

[10] World Health Organization. Therapeutics and COVID-19 Living Guidelines. 6 July 2021. Available at https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.2

Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 9)

FACTORS	JUDGEMENT (N = 9)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)					
Benefits	Large	Moderate (1)	Small (6)	Uncertain (1)			• One study reported significantly shorter time to clinical improvement among patients given artesunate compared to control • Another study also reported shorter time to clinical improvement for artesunate
Harm	Large	Small (7)	Uncertain (2)				• There are no significant differences in mild adverse events and moderate-to-severe adverse events
Certainty of Evidence	High	Moderate	Low (1)	Very low (8)			• The overall quality of evidence was rated very low due to very serious imprecision, serious risk of bias, and in some outcomes, inconsistency and indirectness.
Balance of effects	Favors drug	Does not favor drug (4)	Uncertain (5)				• Artesunate showed no significant difference in mortality, clinical deterioration, improvement in chest CT scan or X-ray, time to virologic clearance, and mild and moderate-to-severe adverse effects.
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (4)	Possibly NO important uncertainty or variability (2)	No important uncertainty or variability			
Resources Required	Uncertain (1)	Large cost	Moderate cost (4)	Negligible cost (2)	Moderate savings (2)	Large savings	• Cost is around 22.78-64 per 100mg capsule or Php 273-768 per patient • Not available in the market
Certainty of evidence of required resources	No included studies (1)	Very low (4)	Low (3)	Moderate (1)	High		• Sources are based on review articles, preliminary searches, and prices vary widely.
Cost effectiveness	No included studies (4)	Favors the comparison (2)	Does not favor either the intervention or the comparison (3)	Favors the intervention			
Equity	Uncertain (4)	Reduced (2)	Probably no impact (2)	Increased (1)			
Acceptability	Uncertain (7)	No	Yes (2)				
Feasibility	Uncertain (4)	No (1)	Yes (4)				

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (Artesunate OR Artemisinin)	September 15, 2021 9:00AM	60	1
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND artemisinin MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND artesunate	September 15, 2021 9:30AM	12	12
COVID-NMA Initiative	Artemisinin, Artesunate, Dihydroartemisinin	September 15, 2021 10:00AM	0	0
Google Scholar	Artemisinin OR Artesunate AND COVID AND randomized trial	September 15, 2021 10:10AM	30	0
ClinicalTrials.gov	Artemisinin and COVID19 Artesunate and COVID19	September 15, 2021 10:15AM	6	0
Chinese Clinical Trial Registry	Artemisinin Artesunate	September 15, 2021 10:20AM	3	0
CNKI	青蒿素, 青蒿素 新冠肺炎治疗	September 15, 2021 10:25AM	1	0
EU Clinical Trials Register	Artemisinin and COVID Artesunate and COVID	September 15, 2021 10:30AM	0	0

Republic of Korea - Clinical Research Information Service	Artemisinin Artesunate	September 15, 2021 10:30AM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Artemisinin Artesunate	September 15, 2021 10:30AM	0	0
CenterWatch	Artemisinin and COVID Artesunate and COVID	September 15, 2021 10:30AM	0	0
chinaxiv.org	Artemisinin Artesunate	September 15, 2021 10:30AM	1	0
Medrxiv.org	Artemisinin Artesunate	September 15, 2021 10:35AM	64	1
Biorxiv.org	Artemisinin and COVID Artesunate and COVID	September 15, 2021 10:50AM	20	0
Files from Republic of the Philippines Department of Health	N/A	N/A	N/A	4

Appendix 3. Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-up	Interventions	Outcomes	Method
Targeting TGF-β pathway with COVID-19 Drug Candidate ARTIVeda/PulmoHeal Accelerates Recovery from Mild-Moderate COVID-19 *Trieu et al., 2021 (India)* [2] *Pre-print*	N = 60 **Patients 21-60 years old with RT-PCR confirmed COVID-19 infection, mild to moderate, without any requirement of oxygen therapy or assisted ventilation** <u>Duration of follow-up:</u> Not defined, but based on results estimated to be at around 28 days	EXPERIMENTAL: Artemisinin 500 mg capsule PO (duration not indicated) + Standard of Care* CONTROL: Standard of Care* *Standard of Care varies: • Site 1: Remdesivir, prednisolone, low molecular weight heparin, and doxycycline • Site 2: Azithromycin, dexamethasone • Site 3: Ivermectin, doxycycline, and inhaled steroids	PRIMARY time to recovery, clinical improvement (WHO score)	Randomized Parallel Open-label
Clinical trial on Artesunate in the treatment of COVID-19 *Lin et al., 2020 (China)* [3]	N = 43 **Patients 25-85 years old with RT-PCR confirmed COVID-19 infection, mild to moderate** <u>Duration of follow-up:</u> Not defined, but based on results estimated to be at least 21 days	EXPERIMENTAL: Artesunate was 60 mg twice a day for 10 days CONTROL: Standard of Care (Lopinavir/Ritonavir 500 mg + α-interferon 500×104 U nebulized inhalation for 10 days)	PRIMARY Time to significant improvement in symptoms; Time of throat swab virus nucleic acid turning negative; Adverse drug reactions; Number of days of hospitalization to evaluate the efficacy	Randomized parallel
A Multi-center, Randomized, Double-blind, Parallel, Placebo-Controlled, Phase II Clinical Trial to Evaluate Efficacy and Safety of Pyramax in Mild to Moderate COVID-19 Patients [4] *Shin Poong Pharm. Co., Ltd. 2021 (South Korea)* [4] *Unpublished*	N = 113 **Patients with RT-PCR confirmed COVID-19 infection, mild to moderate** <u>Duration of follow-up:</u> Not defined, but based on results estimated to be at around 28 days	EXPERIMENTAL: Pyramax (Pyronaridine tetraphosphate 180 mg/Artesunate 60 mg) CONTROL: Placebo	PRIMARY (1) Proportion of patients at a given time with non-viable virus / viral clearance; (2) Clinical deterioration; (3) Drug-related adverse events	Randomized double blind Parallel Double-blind Placebo-controlled

Appendix 4. Study Appraisal

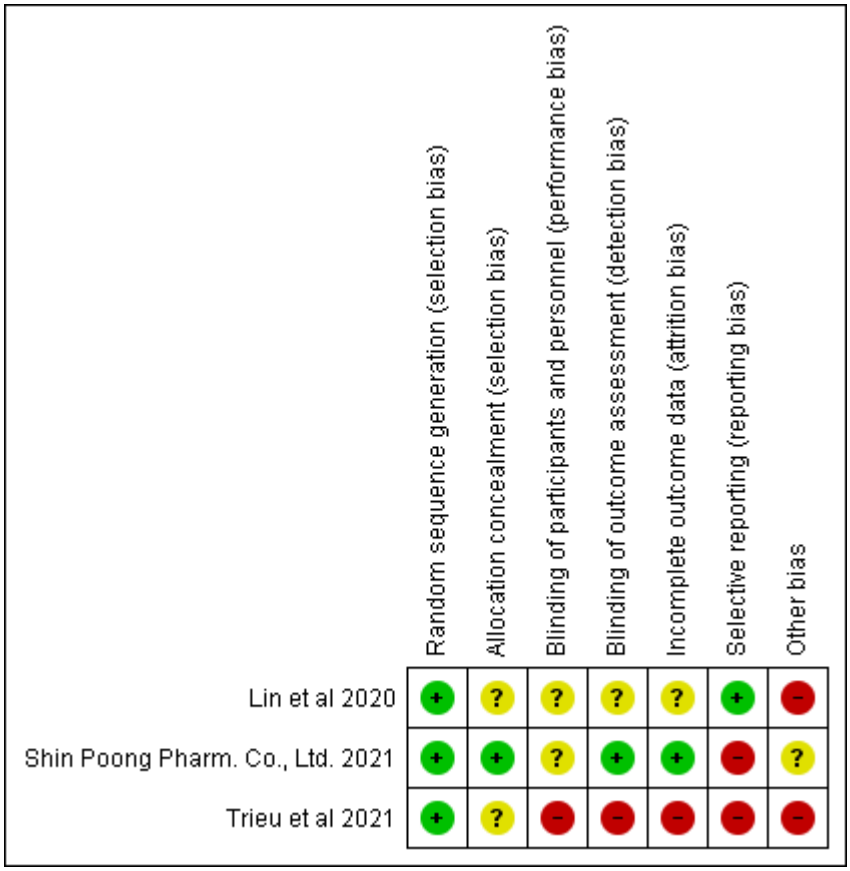

Figure 1. Risk of bias summary table

Appendix 5. GRADE Evidence Profile

Author(s): Dy, Louie
Question: Artemisinin (Artesunate) compared to Placebo or Standard of Care (SOC) for patients with confirmed COVID-19 infection
Setting: Hospital setting
Bibliography: Trieu V, Saund S, Rahate P, Barge V, Nalk K, Windlass H et al. Targeting TGF-β pathway with COVID-19 Drug Candidate ARTIVeda/PulmoHeal Accelerates Recovery from Mild-Moderate COVID-19. 2021;.Lin, Wu, Xie et al. Clinical trial on Artesunate in the treatment of COVID-19. Chinese Critical Care Medicine. 2020;.Shin Poong Pharm. Co., Ltd. A Multi-center, Randomized, Double-blind, Parallel, Placebo-Controlled, Phase Ⅱ Clinical Trial to Evaluate Efficacy and Safety of Pyramax in Mild to Moderate COVID-19 Patients. South Korea; 2021.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Artemisinin (Artesunate)	Placebo or Standard of Care (SOC)	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: 28 days)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/55 (0.0%)	1/58 (1.7%)	**RR 0.35** (0.01 to 8.44)	**11 fewer per 1,000** (from 17 fewer to 128 more)	⨁◯◯◯ VERY LOW	CRITICAL
Clinical Deterioration (follow-up: 28 days)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	2/55 (3.6%)	5/58 (8.6%)	**RR 0.42** (0.09 to 2.08)	**50 fewer per 1,000** (from 78 fewer to 93 more)	⨁◯◯◯ VERY LOW	CRITICAL
Time to Clinical Improvement or Recovery												
2	randomised trials	very serious [c]	serious [d]	serious [e]	very serious [f]	none	One study reported median 1.51 days lower (2.74 lower to 0.28 lower). Another study reported median 9 days lower.				⨁◯◯◯ VERY LOW	CRITICAL
Adverse Effects (Mild) (follow-up: 14-28 days)												
3	randomised trials	very serious [a,c]	not serious	serious [e]	very serious [b]	none	49/112 (43.8%)	56/104 (53.8%)	**RR 0.81** (0.62 to 1.06)	**102 fewer per 1,000** (from 205 fewer to 32 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Adverse Effects (Moderate-Severe) (follow-up: 14-28 days)												
3	randomised trials	very serious [a,c]	not serious	serious [e]	very serious [b]	none	9/112 (8.0%)	12/104 (11.5%)	**RR 0.85** (0.37 to 1.95)	**17 fewer per 1,000** (from 73 fewer to 110 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Details on how blinding of participants and outcome assessors was not clearly elaborated; selective reporting
b. Wide confidence interval with a relatively small sample size
c. Serious risk of bias from performance and detection bias (unblinded of participants or outcome assessors) in 2 studies, incomplete outcome data and selective reporting in 1 study
d. Mean difference and median difference of the 2 studies vary widely
e. Control groups include experimental drugs
f. Small sample size

Appendix 6. Forest Plots

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lin et al 2020	12	18	17	25	25.1%	0.98 [0.64, 1.50]
Shin Poong Pharm. Co., Ltd. 2021	19	55	25	58	42.9%	0.80 [0.50, 1.28]
Trieu et al 2021	18	39	14	21	32.1%	0.69 [0.44, 1.09]
Total (95% CI)		**112**		**104**	**100.0%**	**0.81 [0.62, 1.06]**
Total events	49		56			

Heterogeneity: Chi² = 1.24, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.53 (P = 0.13)

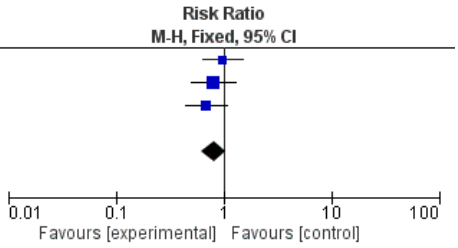

Figure 1. Adverse Effects (Mild)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lin et al 2020	1	18	5	25	38.1%	0.28 [0.04, 2.18]
Shin Poong Pharm. Co., Ltd. 2021	8	55	7	58	61.9%	1.21 [0.47, 3.10]
Trieu et al 2021	0	39	0	21		Not estimable
Total (95% CI)		**112**		**104**	**100.0%**	**0.85 [0.37, 1.95]**
Total events	9		12			

Heterogeneity: Chi² = 1.65, df = 1 (P = 0.20); I² = 40%
Test for overall effect: Z = 0.38 (P = 0.70)

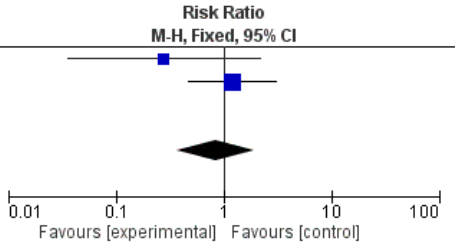

Figure 2. Adverse Effects (Moderate-to-Severe)

Appendix 7. Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
1. A Prospective, Randomized, Multi-center, Open label, Interventional Study to Evaluate the Safety and Efficacy of Artemisinin 500 mg capsule in Treatment of Adult Subjects with COVID-19	Patients with mild to moderate COVID-19 (age 19 to 44 years) + exclusion criteria (refer to link: https://trialsearch.who.int/?TrialID=CTRI/2020/09/028044)	Experimental: Artemisinin + standard of care Control: Standard of care	Clinical improvement, clinical progression, and adverse events	Randomized, open-label trial
2. A Study to Evaluate the Safety and Efficacy of Artemisinin- a Herbal Supplement on COVID-19 Subjects	Patients with confirmed, mild to moderate COVID-19 (≥18 to 60 years of age, + exclusion criteria, please refer to link: https://clinicaltrials.gov/ct2/show/NCT05004753)	Experimental: Artemisinin 500mg and Standard of Care (which includes dexamethasone) Control: Standard of care (which may include cexamethasone)	Clinical improvement, worsening, mortality, duration of supplemental oxygen, duration of ICU stay, duration of hospitalization, ventilator free days, days on ventilation	Open label, prospective, multi-center, comparative, interventional study
3. A Study to Evaluate the Safety and Efficacy of OT-101+Artemisinin in Hospitalized COVID-19 Subjects	Patients with severe COVID-19 (WHO COVID-19 Clinical Improvement Ordinal Scale 5 - non-invasive ventilation or high flow oxygen, or 6 - intubation and mechanical ventilation); more information: https://clinicaltrials.gov/ct2/show/record/NCT04801017	Experimental: OT-101 (TGF β2 specific synthetic 18 mer phosphorothioate antisense oligodeoxynucleotide) plus artemisinin and standard of care Control: Placebo + artemisinin + standard of care	Clinical improvement, worsening, mortality, duration of supplemental oxygen, duration of ICU stay, duration of hospitalization, ventilator free days, days on ventilation	Randomized, double blind, placebo-controlled study
4. A Prospective, Randomized, Multi-center, Open label, Interventional Study to Evaluate the Safety and Efficacy of Artemisinin 500 mg capsule in Treatment of Adult Subjects with COVID-19	Patients with mild to moderate COVID-19 (age 19 to 44 years) + exclusion criteria (refer to link: https://trialsearch.who.int/?TrialID=CTRI/2020/09/028044)	Experimental: Artemisinin + standard of care Control: Standard of Care	Clinical improvement, clinical progression, adverse events	Randomized, open-label trial
5. A Prospective, Randomized, Multi-center, Open label, Interventional Study to Evaluate the Safety and Efficacy of Artemisinin 500 mg capsule in Treatment of Adult Subjects with COVID-19	Patients with mild to moderate COVID-19 (age 19 to 44 years) + exclusion criteria (refer to link: https://trialsearch.who.int/?TrialID=PACTR202012892855610)	Experimental: Artemisinin + standard of care Control: Standard of care	Clinical improvement, clinical progression, adverse events	Randomized, open-label trial
6. Effect of Hesperidin,Artemisinin-Artemisia annua, Noscapine, N-acetylcysteine, Resveratrol supplements and high dose of vitamin C on treatment, clinical symptoms of non-hospitalization and hospitalization patients with symptomatic COVID-19	Patients with confirmed COVID-19 (age 12 years old and above) + exclusion criteria (refer to link: https://trialsearch.who.int/?TrialID=IRCT20181030041504N1)	Experimental: Artemisinin, IV vitamin C, noscapine, hesperidin, N-acetylcysteine Control: Standard of care	CBC, CRP, ESR, LDH< lung involvement, Na, K, Ca, weakness and nausea	Randomized, double-blind, non-placebo-controlled trial
7. Clinical trial of the use of Annual SZ drug in the treatment of patients with Covid-19 disease in Emam Hosein hospital in Tehran.	Patients with confirmed COVID-19 (age 16 to 70 years old); more information: https://trialsearch.who.int/?TrialID=IRCT20181030041504N1	Experimental: Artemisinin + azithromycin Control: Hydroxychloroquine + keltra + lopinavir-ritonavir + azithromycin	Blood oxygen level, coughs, CRP, fever, HRCT score	Randomized, open-label, non-placebo-controlled trial
8. A randomized controlled trial for the efficacy and safety of artemisinin-pipequine tablets in the treatment of the mild and common type novel coronavirus pneumonia	Patients with confirmed COVID-19, mild to moderate (age 2 to 65 years old), excluding pregnant women, liver and kidney disease, blood diseases, ECG with prolonged QT; more information:	Experimental: Artemisinin-Piperaquine Control: Symptomatic treatment with non-antiviral drugs	Tolerance, viral load, routine blood and immunological examination, liver and kidney function tests, myocardial enzymes, ECG, urinalysis, body temperature, pulse,	Randomized controlled trial

(COVID-19) patients whose nCoV Nucleic acid did not turn negative after treated by hydroxychloroquine and Abidor	https://trialsearch.who.int/?TrialID=ChiCTR2000032915		respiratory rate, blood pressure, CT examination of the lungs	
9. A Phase II, Open label controlled clinical study designed to evaluate the effect of ArtemiC in patients diagnosed with COVID-19.	Patients with confirmed COVID-19, admitted to controlled facility or hospital (age 18 years old and above) + exclusion criteria (pregnancy, critically ill, autoimmune disease, uncontrolled diabetes; refer to link: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=52515)	Experimental: ArtemiC medical nasal spray (artemisinin, curcumin, frankincense, vitamin C) Control: Standard of care	Time to clinical improvement, adverse drug events, time until negative PCR, proportion of participants with normalization of fever, COVID-19 related survival, incidence and duration of mechanical ventilation, incidence of ICU stay, duration of ICU stay, duration of time on supplemental oxygen	Randomized, placebo-controlled trial
11. A Phase II, Controlled Clinical Study Designed to Evaluate the Effect of ArtemiC in Patients Diagnosed With COVID-19	Patients with confirmed COVID-19, admitted to controlled facility or hospital (age 18 years old and above) + exclusion criteria (pregnancy, critically ill, autoimmune disease, uncontrolled diabetes; refer to link: https://clinicaltrials.gov/ct2/show/NCT04382040)	Experimental: ArtemiC medical nasal spray (artemisinin, curcumin, frankincense, vitamin C) Control: Placebo (oromucosal medical spray)	Time to clinical improvement, adverse drug events, time until negative PCR, proportion of participants with normalization of fever, COVID-19 related survival, incidence and duration of mechanical ventilation, incidence of ICU stay, duration of ICU stay, duration of time on supplemental oxygen	Randomized, placebo-controlled trial
12. Evaluating the Efficacy of Artesunate in Adults with Mild Symptoms of COVID-19	Patients with mild to moderate COVID-19, no risk factors, not on other medications (age 18 to 60 years) + exclusion criteria (refer to link: https://clinicaltrials.gov/ct2/show/record/NCT04387240)	Experimental: Artemisinin Control: Placebo	Clinical improvement, worsening, mortality, duration of supplemental oxygen, duration of ICU stay, duration of hospitalization, ventilator free days, days on ventilation	Randomized, double blind, placebo-controlled study
13. No title yet; study by Shin Poong Pharma Co. Ltd. In South Africa	Symptomatic COVID-19 outpatients self-reported symptoms of COVID-19 of up to 72 hours duration who tests positive for SARS-CoV-2	Experimental: SOC + artesunate-amodiaquine; SOC + pyronaridine-artesunate; SOC + favipiravir + nitazoxanide; SOC + sofosbuvir / daclatasvir Control: Standard of care (SOC)	Virologic clearance on Day 7, clinical improvement, adverse events, mortality	Randomized, single center, open-label Placebo-controlled
14. No title yet; study by Shin Poong Pharma Co. Ltd. In the Philippines	Mild to severe COVID-19 patients (can be modified depending on stage 1 results)	[Stage 1: open-label] - Pyramax only (20 patients) [Stage 2: randomized, double-blinded, placebocontrolled] - Experimental: Pyramax - Control: Placebo	Clinical improvement, virologic clearance on Day 7, adverse events, mortality	Randomized, multicenter, 2 stages (stage 1: open-label/ stage 2: double-blinded)