Study Protocol I-TECH21 (Version 2.0)

Ivermectin Treatment Efficacy in Covid-19 High Risk Patients (I-TECH Study): A Multicenter Open-label Randomized Controlled Trial

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Name and address of Sponsor:
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Study sites:
1. Hospital Raja Permaisuri Bainun, Ipoh
2. Hospital Pulau Pinang
3. Hospital Taiping
4. Hospital Sungai Buloh
5. Hospital Umum Sarawak
6. Hospital Kuala Lumpur
7. Hospital Lahad Datu
8. Hospital Sultanah Bahiyah, Alor Setar
9. Hospital Sultanah Aminah, Johor Bahru
10. Hospital Tuanku Fauziah, Kangar
11. Hospital Sultan Abdul Halim, Sungai Petani
12. Hospital Melaka
13. Hospital Putrajaya
14. Hospital Duchess of Kent, Sandakan
15. Hospital Tumpat
16. Hospital Sultanah Nur Zahirah, Kuala Terengganu
17. Hospital Permai (cluster hospital of Hospital Sultanah Aminah)
18. Hospital Kepala Batas
19. Hospital Sungai Siput (cluster hospital of Hospital Raja Permaisuri Bainun)
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21. Low Risk COVID-19 Quarantine & Treatment Centre – MAEPS 2.0

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List of Abbreviations

COVID-19	Coronavirus disease 2019 (SARS-CoV-2)
CRC	Clinical Research Center
CRF	Case Report Form
CT value	Cycle threshold value
COAD	Chronic obstructive airway disease
DG	Director General of Health, Ministry of Health, Malaysia
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
FDA	Food and Drug Administration
ICU	Intensive Care Unit
ID	Identification
ICF	Informed Consent Form
IEC	Independent Ethnics Committee
MOH	Ministry of Health
MREC	Medical Research Ethnics Committee
NIH	National Institute of Health
PCR	Polymerase Chain Reaction
PDF	Portable Document Format
PI	Principal Investigator
RCT	Randomized controlled trial
RNA	Ribonucleic acid
RT-PCR	Reverse-transcriptase polymerase chain reaction
SOC	Standard of Care
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
WHO	World Health Organization
CDC	Centers for Disease Control and Prevention
REDCap	Research Electronic Data Capture

Research Synopsis

Study title	Ivermectin Treatment Efficacy in Covid-19 High Risk Patients (I-TECH Study): A Multicenter Open-label Randomized Controlled Clinical Trial
Study Population	Symptomatic mild-to-moderate hospitalized COVID-19 patients (clinical stage 2 or 3) who are 50 years old and above, with co-morbidities and within first 7 days of illness.
Study Design	Multicenter Open-label Randomized Controlled Clinical Trial Patients are randomized 1:1 to groups receiving Ivermectin (0.4mg/kg/day for 5 days) with standard-of-care versus standard-of-care alone.
Primary Objective	To assess the effectiveness of ivermectin in preventing progression of Covid-19 to severe disease (clinical stage 4 or 5), which is defined as severe pneumonia requiring oxygen supplement or critically ill requiring ICU care.
Secondary Objectives	a) To assess the efficacy of ivermectin in reducing mortality rate among high risk COVID-19 patients. b) To compare difference in resolution of symptoms, chest x-ray, laboratory investigations, ICU admission, mechanical ventilation and length of hospital stay.
Study endpoints / outcomes	Primary outcome measure: • Number of patients who progressed to severe disease (clinical stage 4 or 5) and time to progression to severe disease after enrollment. Secondary outcome measures: • Number of patients who died in hospital within 28 days of study enrollment (28-day in-hospital all-cause mortality).

	• Number of patients with complete resolution of symptoms by day 5 of enrollment. • Changes in chest X-ray and laboratory investigations by day 5 of enrollment. • Number of patients admitted to ICU. • Number of patients who required mechanical ventilation. • Length of hospital stay in calendar days.
Sample Size	500 subjects (250 subjects in each arm)
Study Duration	1st May 2021 – 31st December 2021

1. Background and Significance

To date, global Covid-19 cases has surpassed 100 million with over 2 million deaths [1]. Malaysia is currently at 3rd wave of Covid-19, the worst since the pandemic first started. There are more than 2000 daily cases overwhelming our healthcare system. As a result, mortality rises along with increasing severe cases.

The standard of care for Covid-19 patients includes isolation, symptomatic treatment, close monitoring and supportive care. The global search for effective pharmacologic interventions to treat and prevent the consequences of this potentially devastating acute respiratory infection remains a challenge. The only drug which is proven to improve mortality outcome is dexamethasone based on RECOVERY Trial [2]. However, steroids are only found to be beneficial in severe stage of disease when patient requires oxygen supplementation or mechanical ventilation. There are no approved treatments for patients with mild to moderate SARS-CoV-2 infection, either to prevent disease progression or reduce viral transmission.

Based on our previous national data, 80% of Covid-19 patients admitted within the first five days of illness, 95% presented with a mild disease on admission and 3.5% subsequently progressed to severe disease. Older age (≥51 years), underlying chronic kidney disease and chronic pulmonary disease were found to be high risk group to progress to severe disease [3]. Clearly, there is need for an effective pharmacologic therapy for high-risk patients who present to healthcare facility early with mild disease.

As SARS-CoV-2 viral replication causes many of the clinical manifestations of COVID-19, antiviral therapy may have the greatest impact before the illness progresses into the hyperinflammatory state that can characterize the later stages of disease [4-5]. Many antiviral therapies are being repurposed and investigated for the treatment of COVID-19. Unfortunately, the WHO solidarity trial has found remdesivir, hydroxychloroquine, interferon, lopinavir not effective in terms of mortality outcome [6]. Favipiravir, which was not studied in the WHO solidarity trial, remains the only antiviral therapy adopted by our

latest Malaysian consensus guidelines [7]. Favipiravir is only prescribed to high risk Covid-19 patients in Stage 2 or 3 diseases with warning signs, despite the limited evidence of its effectiveness in preventing progression to severe disease or improving mortality outcome [8]. In short, there is still no well proven antivirals for Covid-19.

Ivermectin is a FDA-approved antiparasitic drug that is used to treat several neglected tropical diseases, including onchocerciasis, strongyloidiasis, helminthiases, and scabies. For these indications, it has been widely used and is generally well tolerated. Recently, ivermectin has gained international attention due to some promising results in Covid-19 treatment and prophylaxis.

Reports from SARS-CoV-2 in vitro studies suggested that ivermectin acts by inhibiting the host importin alpha/beta-1 nuclear transport proteins, which are part of a key intracellular transport process that viruses hijack to enhance infection by suppressing the host's antiviral response. Caly et al demonstrated a ≈5000-fold reduction in SARS-CoV-2 viral RNA in ivermectin treated cells compared to control samples by 48 hours [9]. This was followed by some observational cohorts and RCTs which showed positive results in terms of faster viral clearance and clinical recovery, shorter hospitalization and better survival rate [10-15]. Elgazzar et al, in a RCT conducted on 400 Covid-19 patients showed the addition of ivermectin (0.4mg/kg/day for 4 days) to standard care was very effective with significant reduction in mortality compared to hydroxychloroquine plus standard treatment only (0% versus 4% in mild/moderate disease and 2% versus 20% in severe disease, $p<0.001$) [10]. A meta-analysis of 18 RCTs in 2282 patients with Covid-19 showed a 75% improvement in survival, faster time to recovery and signs of a dose dependent effect of viral clearance for patients given ivermectin versus control treatment [22]. Higher dose ivermectin also appeared to be well tolerated in most studies [15, 21].

Despite the encouraging trend of existing database demonstrates, there are still insufficient robust data to recommend either for or against the use of ivermectin for the treatment of COVID-19. CDC and WHO only recommend use of ivermectin in clinical

trials [16]. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19.

Our study will compare ivermectin treatment efficacy with standard of care alone. Our target cohort is mild to moderate symptomatic Covid-19 (Stage 2-3), high risk patients aged 50 years and above with comorbidity, who presented to hospitals within first 7 days of illness. The primary endpoint is progression to severe disease (Stage 4-5). Secondary end points are 28-day all-cause mortality, resolution of symptoms, changes in laboratory blood tests and CXR, ICU admission, mechanical ventilation and length of hospital stay.

The study will be conducted in several Malaysian Covid-19 hospitals. The study team principal investigators consist of infectious diseases physicians, a geriatrician and a general physician who are experienced and actively involved in Covid-19 patient management throughout the pandemic.

2. Objectives

Primary Objective:

To assess the effectiveness of ivermectin in preventing progression of Covid-19 to severe disease (clinical stage 4 or 5), which is defined as severe pneumonia requiring oxygen supplement or critically ill requiring ICU care.

Secondary Objectives:

a) To assess the efficacy of ivermectin in reducing mortality rate among high risk COVID-19 patients.

b) To compare difference in resolution of symptoms, chest x-ray, laboratory investigations, ICU admission, mechanical ventilation and length of hospital stay.

3. Methodology

3.1 Study Type and Design

This is a multicenter, open-label, randomized controlled clinical trial involving COVID-19 designated hospitals in Malaysia. Patients are randomized at ratio of 1:1 to groups receiving ivermectin for 5 days plus standard-of-care versus standard-of-care only. Patients will be assigned to stratified randomized treatments based on a central, computer-generated randomization scheme coordinated by an independent third party. Based on national guidelines, all high risk COVID-19 patients will be admitted to hospitals, and allow discharge once criteria met [18].

Summary of treatment and control arm:

1. Treatment group: Ivermectin 0.4mg/kg/day for 5 days + standard-of-care
2. Control group: Standard-of-care only

Rationale of ivermectin dose and duration in this study:

The dose regimens used in various RCT with positive results range from 0.2mg/kg single dose to 0.6mg/kg/day for 5 days [10-15]. PK/PD studies have shown that the antiviral effect of ivermectin is dose dependent [9,15]. As SARS-CoV-2 viral load peaks during the first week of illness and may prolong in severe disease [18], we believe a high dose of ivermectin 0.4mg/kg/day for 5 days would be reasonable and safe to achieve our study objectives.

Standard of care:

Based on our current Malaysian guidelines [18], standard of care for mild to moderate Covid-19 patients includes isolation, infection control, close monitoring (clinical findings, laboratory tests, chest imaging) and symptomatic treatment.

3.2 Study Population

The population for this clinical trial will be comprised of adults with a PCR or antigen test confirmed diagnosis of COVID-19 admitted to any of the participating hospitals.

Participants who fulfil the inclusion criteria and do not meet the exclusion criteria will be enrolled. Identification of eligible participants will be done prospectively at each study site.

3.3 Sample Size

Sample size calculation was performed using ScalexProp Version 1.0.2 (Naing, 2016). The calculation is based on superiority trial design and the primary outcome measure of the need to have supplemental oxygen therapy during the hospital admission. We regard a 9% difference between intervention arm and control arm as a clinically important outcome. Based on local data, 17.5% of COVID-19 aged 50 years and above, with stage 2 and 3 disease and comorbidity, progressed to severe disease [3]. The need of supplemental oxygen therapy is expected to be about 8.8% in intervention arm and 17.5% in control arm. With a margin of superiority set to be 1%, the study requires 231 patients for each arm or in total 462 patients. Considering potential dropouts during the trial, we would require up to 500 patients or 250 patients each arm. The sample size provides a level of significance at 5% with 80% power (2-sided test).

3.4 Inclusion Criteria

Patients are eligible to be included in the study only if they fulfil ALL the following criteria:

1. RT-PCR or antigen test confirmed COVID-19 cases
2. Aged 50 years and above, with at least one co-morbidities*
3. Within the first 7 days of illness (from symptom onset)
4. Mild to moderate clinical severity (or stage 2 to 3 disease in **Table 1** below)

*Co-morbidities:
Diabetes mellitus, hypertension, chronic kidney disease, chronic cardiac disease, chronic pulmonary disease, chronic liver disease, cerebral vascular disease, chronic neurological disorder, obesity (BMI ≥30kg/m^2), dyslipidemia, autoimmune disease, HIV, thyroid disease, malignancy, immunosuppressive therapy and active smoker.

Table 1. Clinical Severity in relation to Disease Staging from COVID-19 Management Guideline in Malaysia [17]

Clinical Severity	Disease Staging	Description
Asymptomatic	1	Asymptomatic
Mild	2	Symptomatic, No pneumonia
Moderate	3	Symptomatic, Pneumonia
Severe	4	Symptomatic, Pneumonia, Requiring supplemental oxygen
Severe	5	Critically ill

3.5 Exclusion Criteria

1) Asymptomatic stage 1 patients.
2) Patients with SpO2 less than 95% at rest. (unless it is an expected baseline SpO2 due to preexisting disease, eg. COAD or pulmonary fibrosis).
3) Patients who need oxygen supplements.
4) Patients with concomitant bacterial, fungal, parasitic or other viral infections prior to enrollment.
5) Patients with severe hepatic impairment (>Grade 3: ALT >10 times of upper normal limit).
6) Malabsorption syndrome or other clinically significant gastrointestinal disease that may affect absorption of the study drug (non-correctable vomiting, diarrhea, ulcerative colitis, and others).
7) Pregnant or nursing women.
8) Female patients of reproductive age who cannot consent to contraceptive use of oral contraceptives, mechanical contraceptives such as intrauterine devices or barrier devices (pessaries, condoms), or a combination of these devices from the start of ivermectin administration to 7 days after the end of ivermectin administration.
9) Male patient who has female partner of reproductive age and he cannot agree to use contraception from the start of ivermectin treatment till 7 days after treatment.
10) Patients receiving chemotherapy.

11) Patients who received interferon or drugs with reported antiviral activity against COVID-19 (favipiravir, hydroxychloroquine sulfate, chloroquine phosphate, lopinavir-ritonavir combination, remdesivir) in the past 7 days before enrollment.
12) Patients in whom this episode of infection is a recurrence or reinfection of COVID-19.
13) Patients who have previously received ivermectin.
14) Patient receiving warfarin or any medications known to interact with ivermectin.
15) Acute medical or surgical emergency (eg. DKA/MI/stroke).
16) Other patients judged ineligible by the principal investigator or sub-investigator.

3.6 Withdrawal Criteria

Subjects can choose to withdraw at any time. Subjects may be withdrawn if the investigator deems that it is detrimental or risky for the subject to continue. Withdrawn subjects will not be replaced.

3.7 Study Schedules and Procedures

The study schedule is outlined in table below:

Timing of implementation / Item	Study period (Day 1 to maximum Day 28 of enrollment in hospital)			
	Day 1 (Enrollment before treatment initiation) (CRF 1)	Day 5 (Follow-up) (CRF 2)	Day of discharge* or in-hospital death (CRF 3)	Day of study event (clinical deterioration) (CRF 4)
Informed consent	●			
Patient characteristics	●			
Clinical findings	●	●	●	●
Clinical laboratory tests	● (a)	● (c)		● (c)
Chest X-Ray	● (a)	● (c)		● (c)
Urine pregnancy test (b)	○			
Hospitalization	Mandatory hospitalization for at least first 5 days of trial enrollment		(d)	
Adverse event assessment period	●	●	●	●

●: Required ○: To be performed if necessary

(a) Baseline blood tests is acceptable if done within 48 hours before enrolment. Baseline chest x-ray is acceptable if done within 48 hours before and 24 hours after enrolment

(b) Urine pregnancy test is needed for female who is potentially pregnant

(c) Acceptable if done within 24 hours before and after

(d) Follow discharge criteria based on current national COVID-19 guideline [17]

*Discharge from hospital or from study at Day 28 (if still need to be in hospital)

Study procedure:

1. Eligible patient is counselled and explained about the study
2. Urine pregnancy test is done for female who is potentially pregnant
3. Informed consent is obtained prior to enrolment
4. Randomization is done online (computer generated) via REDCap
5. Management is given according to treatment or control arm. First dose of investigational product (ivermectin) must be given at Day 1 of enrolment.

6. Investigational product (Ivermectin) is directly served to the subjects by the staff nurse in charge at the site. Compliance is monitored daily by checking the medication chart. It is then recorded in CRF.
7. Blood samples for study (CRP, full blood count, renal profile, liver function test) will be taken by Covid team medical officers or physicians as part of routine blood investigations and processed by local hospital laboratory.
8. Chest X-ray will be done in ward by radiographer with mobile X-ray machine in accordance to infection control protocol. X-ray films will be reviewed and reported by treating physician or radiologist if necessary.
9. Documentation is done in patient's hospital record
10. Case report forms are filled up on Day 1 (enrolment), Day 5 (follow-up), Day of study event (clinical deterioration) and Day of discharge (from hospital or from study at day 28) or death.
11. Data is uploaded to a secured online database (REDCap)
12. Follow-up is done until Day of discharge or Day 28 of enrollment.
13. Upon study completion, all CRF and ICF will be sent to principal investigator for storage
14. Online database will be transferred into a password protected computer for further analysis
15. The online database will be deleted after that
16. Source file is kept in each respective site for minimum 3 years
17. All documents (CRF and ICF) will be kept for minimum 3 years in principal investigator's locked office

3.8 Safety Measures and AE/SAE/SUSAR Management

All patients are clinically monitored and managed by Covid team physicians and medical officers throughout the hospitalization in accordance to latest Malaysian Covid-19 management guidelines.

Adverse Event (AE)

When adverse event occurs, for example vomiting, diarrhea or transaminitis, subjects will be managed based on standard clinical practice. They will be monitored closely and given symptomatic treatment if required. If the adverse effect is worsening (moderate to severe), or deemed detrimental or risky to continue by treating physicians or investigators, the study drug shall be discontinued and then reported accordingly. Data on AE will be reviewed weekly by central data monitoring team (electronic CRF). Any signal of increasing AE or safety concern will be discussed with PI for further action.

SAE and SUSAR

In the event of SAE (death, life-threatening, prolongation of existing hospitalization, persistent or significant disability/incapacity, and congenital anomaly/birth defects) and SUSAR, it must be reported immediately to the coordinating team within 24 hours. Action taken including IP discontinuation must be documented. Causality and relatedness are determined. Information about SAE/SUSAR must be recorded in the CRF. All events documented must be notified promptly by the investigator to the MREC within 7 days if it is life-threatening and if not, within 15 days.

Treatment of any AE, SAE or SUSAR in a study participant is at the sole discretion of the study investigators who will follow-up the patient until the event has resolved. Abnormal tests should be repeated and monitored until they return to baseline levels or if alternative explanation of the abnormality has been found.

The focus of SAE events should be on those events that are likely to be related to the study medications. Progression of Covid-19 to severe disease (clinical stage 4 or 5) which involves worsening of Covid-19 related signs and symptoms, increased oxygen

requirement and prolonged hospitalization is a primary study endpoint and should not be reported as a SAE.

Procedures in the Event of Emergency

Any emergency events occurring during the study will be attended to immediately by trained medical personnel who are present at that point of time, performing necessary procedures and treatment required as per standard of care.

3.9 Study Duration

The study duration is planned for 8 months, from 1st May 2021 till 31st December 2021.

The participation for each subject starts from day of enrolment until day of discharge (from hospital or from study at day 28 of enrolment) or death. Patients will require at least 5 days of hospitalization during the study.

3.10 Study Timeline

Literature review, protocol development: 2 months
Ethical review and research approval: 1 month
Study enrolment: 5 months
Compilation of data, analysis and interpretation: 1 month
Presentation and publication: 1 month

3.11 Statistical Analysis Plan

The study will be analyzed based on intention-to-treat protocol, whereby once a subject is given ivermectin ≥ 1 dose, subject will be follow-up and analyzed for safety and efficacy. Descriptive date will be expressed as mean ± standard deviation (SD) unless otherwise stated. Categorical data will be analyzed using Chi-square or Fisher's exact test. Non-categorical variables were tested using student t-test or Mann-Whitney U test. Multivariate analysis is performed for variables with $P < 0.1$ in univariate analysis. Independent variables are evaluated using logistic regression. P value < 0.05 is considered statistically

significant. Statistical analysis is done using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

One efficacy interim-analysis is planned when 50% of target sample were recruited. The overall level of significance is maintained at P value of 0.05 calculated according to the O'Brien-Fleming stopping boundaries. Early stopping will be considered at the interim analysis if P value for efficacy data is less than 0.003. And for final analysis, a P value of the less than 0.049 is considered as statistically significant. Statistical analysis is done using R version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria.

3.12 Ethics of Study

Study will be conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline. Ethical approval will be obtained from MREC and other relevant approvals prior to the start of any study related activities. Patient's privacy and confidentiality is strictly maintained.

3.13 Informed Consent/Assent Process

Eligible patients will be identified and explained thoroughly by investigator in language they understand. Information sheet will be provided. If patient is willing to participate, the consent form will be signed and dated. If patient is not fit to give consent, the patient will be excluded from the study. Informed consent is obtained prior to enrolment. Please refer to the attachment for the consent. No reimbursement or compensation will be given to study subjects.

3.14 Privacy and Confidentiality

Patient's privacy and confidentiality are strictly maintained. Subject's names will be kept on a password-protected database in each study site. They will be linked only with a study identification number for this research. The identification number instead of patient identifiers will be used on subject data sheets. All data will be entered into a computer that is password protected. On completion of study, data in the computer will be copied to CDs and the data in the computer erased. CDs and any hardcopy data will be stored

in a locked office of the investigators and maintained for a minimum of three years after the completion of the study. The CDs and data will be destroyed after that period of storage. Source file will be kept for at least 3 years. Subjects will not be allowed to view their personal study data, as the data will be consolidated into a database.

3.15 Conflict of Interest

The investigators declare they have no conflict of interest.

3.16 Publication Policy

Permission from the Director General of Health, Malaysia will be obtained prior to publication. No personal information will be disclosed, and subjects will not be identified when the findings of the survey are published.

3.17 Termination of Study

Study maybe suspended or terminated earlier upon recommendation from the DSMB based on interim analysis or any safety concerns during the conduct of the study. The investigator may decide to terminate the study at any time. Subjects will be informed if the study is suspended or terminated.

4.0 Study Drug

4.1 Dosage and Regimen

Ivermectin 0.4mg/kg/day × 5 days

4.2 Duration of Therapy

The treatment period is 5 days in principle.

However, this does not apply to cases where the investigator or treating physician judges that treatment must be discontinued because of adverse events, etc.

4.3 Concomitant Medications

4.3.1 Concomitant treatment based on national treatment guideline [18] is permitted in both ivermectin and control group. This includes:

1. Immunomodulatory drugs: Dexamethasone, methylprednisolone, tocilizumab
2. Convalescent plasma
3. Thromboembolism prophylaxis or treatment: Enoxaparin, Fondaparinux

4.3.2 The use of the following drugs is prohibited during the study period because they may affect the efficacy evaluation:

1. Favipiravir
2. Interferon alpha or beta
3. Hydroxychloroquine sulfate, chloroquine phosphate
4. Lopinavir and ritonavir combination
5. Remdesivir

4.4 Benefit, Risk and Adverse Effects

To our knowledge, there are no approved treatments for individuals with mild to moderate SARS-CoV-2 infection to prevent progression to severe disease. Ivermectin may be beneficial in this setting and potentially leads to lower morbidity and mortality in high-risk patients. A meta-analysis of 18 RCTs in 2282 patients with Covid-19 showed a 75%

improvement in survival, faster time to recovery and signs of a dose dependent effect of viral clearance for patients given ivermectin versus control treatment [22].

Ivermectin is a well-established anti-parasitic drug used worldwide. At standard doses of 0.2-0.4mg/kg for 1-2 days, ivermectin has a good safety profile and has been distributed to billions of patients worldwide in mass drug administration programs for various parasitic infections. A recent meta-analysis found no significant difference in adverse events in those given higher doses of ivermectin, of up to 2mg/kg, and those receiving longer courses, of up to 4 days, compared to those receiving standard doses [21].

Side effects of ivermectin reported include pruritus (2.8%), urticaria (0.9%), dizziness (2.8%) and Mazzotti reaction [19]. Neurological adverse effects have been reported with the use of ivermectin for the treatment of onchocerciasis and other parasitic diseases, but it is not clear whether these adverse effects were caused by ivermectin or the underlying conditions [20].

Adverse events occurred in this study will be managed by treating physicians and investigators and study medications may be stopped if deemed necessary.

4.5 Drug-drug interaction

Concurrent use of ivermectin and warfarin may result in elevated INR values [19]. Otherwise, there is no other significant drug-drug interaction involving ivermectin.

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IVERMECTIN

Available as 6 mg & 12 mg tablet

(FOR I-TECH STUDY SITES USE ONLY)

Dose: 0.4mg/kg/day X 5 days*

(To be given within first 7 days of illness)

*Refer to next page for detailed dosing & supply

Administration: To be taken with meal (high-fat preferably)

Enteral administration (e.g. Ryle's tube):

Tablet can be crushed.

Patient Criteria:

- Confirmed COVID-19
- Age ≥ 50 years
- At least one co-morbidity
- Symptomatic mild to moderate disease (Cat 2 or 3)
- Did not receive Favipiravir or any other antivirals against COVID-19

Pregnancy & Lactation: Avoid use (Excluded from study)

Precautions:

- **Female patients:** Contraception during and for 7 days after the end of treatment.
- **Male patients:** Avoid sexual intercourse with pregnant women/use effective contraception during treatment and for 7 days after treatment ended.

Renal impairment: No dosing adjustment

Liver impairment: Not recommended when elevated liver enzymes > 10x ULN / > Grade 3

Monitoring: LFT, Bilirubin, Eosinophil

Adverse effect: Pruritus, urticaria, dizziness, hypotension, Steven-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)

Drug interaction:

Warfarin - Elevated INR

Diethyl carbamazepine (DEC) – Increase risk of severe side effects

Storage: Store at or below 25°C. Protect from light, heat and moisture.

IVERMECTIN

Available as 6mg & 12mg tablet

(FOR I-TECH STUDY SITES USE ONLY)

Ivermectin 0.4mg/kg/day x 5 days

Body weight (kg)	Ivermectin dose (mg)	12mg tab	6mg tab	5-day course per patient	
				12mg tab	6mg tab
38-52	18	1	1	5	5
53-67	24	2		10	
68-82	30	2	1	10	5
83-97	36	3		15	
98-112	42	3	1	15	5
113-127	48	4		20	
128-142	54	4	1	20	5
143-157	60	5		25	
158-172	66	5	1	25	5
173-187	72	6		30	
188-202	78	6	1	30	5