Ivermectin in mild and moderate COVID-19 (RIVET-COV): a randomized, placebo-controlled trial

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Abstract

Introduction: Till date, no drug has shown definite benefit in non-severe COVID-19. Ivermectin is an antiparasitic drug which has in-vitro efficacy in reducing coronavirus-2 (SARS-CoV-2) load in severe disease.

Objectives: To determine if a single oral administration of Ivermectin to patients with mild and moderate COVID-19 is effective in converting SARS-CoV-2 RT-PCR to negative result and in reducing viral load.

Methods: In this double-blind trial, patients were randomized to elixir formulation of Ivermectin in 24 mg, 12 mg or placebo in 1:1:1 ratio. The co-primary outcomes were conversion of RT-PCR to negative result and the decline of viral load at day 5 of enrolment and were assessed in patients with positive RT-PCR at enrolment (modified intention-to-treat population). Safety outcomes included total and serious adverse events and were assessed in all patients who received the trial drug (intention-to-treat population).

Results: Among 157 patients randomized, 125 patients were included in mITT analysis. Forty patients each were assigned to Ivermectin 24 mg and 12 mg, and 45 patients to placebo. The RT-PCR negativity at day 5 was higher in the two Ivermectin arms but failed to attain statistical significance (Ivermectin 24 mg, 47.5%; 12 mg, 35.0%; and placebo, 31.1%; p= 0.30). The decline of viral load at day 5 was similar in the three arms. No serious adverse events were encountered.

Conclusion: In patients with mild and moderate COVID-19, a single administration of Ivermectin elixir (either 24 mg or 12 mg) demonstrated a trend towards higher proportion of RT-PCR negativity at day 5 of enrolment.

The protocol was registered in the Clinical Trial Registry – India (CTRI) vide ref No CTRI/2020/06/026001.

Introduction

The COVID-19 pandemic has become one of the biggest public health challenges of the 21st century by already having affected around 50 million people globally and causing more than a million deaths(1). Although most patients have mild or moderate illness, the high contagiousness of the causative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) contributes to rapid spread of infection.Unfortunately, despite aggressive efforts, no antiviral agent has yet been shown to be conclusively beneficial in non-severe COVID-19.

Several new and repurposed drugs are being trialled in mild and moderate COVID-19 to help suppress viral transmission and prevent disease progression. Ivermectin is one such drug which has an established record of safety with over 2.5 billion doses dispensed over the past three decades(2). Originally introduced as an anti-helminthic agent against tropical parasitic diseases, it has recently been found to

possess additional antiviral, anti-inflammatory and anti-cancer actions(2). A broad-spectrum antiviral effect against single stranded RNA viruses such as HIV-1, dengue, yellow fever, West Nile virus and others has been observed in preclinical studies(3–5). This has been attributed to a host directed action against the importinα/β protein which is used by the viral nucleocapsid to enter the host nucleus(5).

In the urgency to search for effective drugs against COVID-19, ivermectin has also been evaluated. Recently, an in-vitro study by Caly et al demonstrated that micromolar concentrations (2-2.5 µg/mL) of Ivermectin can reduce viral load by 5000-fold at 48 hours in VERO/hSLAM cells (6). Although equivalent plasma concentrations are difficult to achieve with routine antiparasitic doses of Ivermectin (150-400µg/kg), there are inherent differences in the in-vivo and in-vitro responses to drugs. Ivermectin may act through its metabolites, get concentrated three-fold in lung tissue and have additional immunomodulatory actions at routine doses(7,8). Additionally, higher doses of ivermectin (1-2 g/kg), albeit unapproved, have been shown to be well tolerated(9,10). Till date, controlled trials evaluating Ivermectin in COVID-19 are lacking. Hence this exploratory study was designed to determine the efficacy and safety of this drug in COVID-19.

Methodology

We conducted a randomized, placebo-controlled, three-arm, parallel group study of a single oral administration of Ivermectin elixir at two dose strengths (12 mg and 24 mg) in patients with non-severe COVID-19. An independent data and safety monitoring board was constituted to oversee the conduct of the trial. The protocol was approved by the Institutional Ethics Committee vide ref No. IEC-456/22.05.2020)and was registered in the Clinical Trial Registry – India (CTRI) vide ref No CTRI/2020/06/026001.

PATIENTS

Consecutive patients admitted at the trial site were screened and were considered eligible for inclusion if aged 18 years or above and diagnosed with non-severe COVID-19, i.e. room air saturation (SpO2) >90%, and with no hypotension or requirement of mechanical ventilation. Diagnosis of COVID-19 was based on a positive result on either SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) or the rapid antigen test. Patients were excluded if they did not give informed consent. Other exclusion criteria included: pregnancy or lactation, known hypersensitivity to ivermectin, chronic kidney disease with creatinine clearance <30 mL/min, elevated transaminase levels (>5 x upper limit of normal), myocardial infarction or heart failure within 90 days prior to enrolment, prolonged corrected QT interval (>450 ms) on electrocardiogram, any other severe comorbidity as per investigator’s assessment, or enrolment in a concomitant clinical trial.

TRIAL PROCEDURES

All subjects fulfilling the trial eligibility criteria underwent a detailed clinical evaluation including history and physical examination. Assessment of comorbidities including diabetes mellitus, systemic

hypertension, coronary artery disease, chronic obstructive pulmonary disease, tuberculosis, and obesity was done. Baseline laboratory investigations including complete blood count, renal function tests, liver function tests, inflammatory markers (including C-reactive protein and serum ferritin) and coagulation profile (prothrombin time, D-dimer and serum fibrinogen) were performed. A baseline chest radiograph was obtained and graded using the Brixia score (11). Patients were managed using standard hospital protocol by the clinical team. The patients were followed up for a minimum of 14 days or till hospital discharge, whichever was later.

INTERVENTIONS AND RANDOMIZATION

Prior to study initiation, our group performed a pharmacokinetic simulation study of the dosing requirements for achieving an Ivermectin lung concentration of 2-2.5 µg/mL (unpublished work). As ivermectin is known to concentrate 2 to 10-fold in tissues(12), it was estimated that a plasma concentration of 150-500 ng/mL would enable sufficient drug concentration in the lungs. Furthermore, plasma Ivermectin concentration may rise 2 to 2.5-fold when administered orally with a high-fat diet or in an alcohol-based formulation(10). Accordingly, we found that an alcohol-based elixir formulation of Ivermectin at a dose of 400 µg/kg administered after a meal may achieve a plasma Ivermectin concentration greater than 150 ng/mL. Accurately weighed Ivermectin was used for formulating Ivermectin elixir formulation. A 20 mL dose of final formulation consisted of ivermectin (12 or 24mg) in ethanol (40% v/v) sweetened with syrup base which was suitability flavoured and coloured. Representative samples were subjected for the quality control to ensure the drug content and batch uniformity. It was compounded and dispensed from the in-house pharmacy by a qualified pharmacist. Similar placebo was also prepared without ivermectin and formulations were coded before delivery to the trial site. After baseline evaluation, eligible patients were randomized in a 1:1:1 ratio to receive Ivermectin 12 mg (equivalent to 200 µg/kg) elixir, Ivermectin 24 mg (equivalent to 400 µg/kg) elixir, or identical placebo. A variable block randomization stratified based on disease severity (mildor moderate illness) was done using a centralized telephone-based system and the patients, investigators, caregivers, and statisticians were blinded to the allocation. The intervention was given two hours after breakfast on the day of randomization as a single dose.

VIROLOGICAL ASSESSMENT

All patients who underwent randomization were evaluated using a baseline oropharyngeal and nasopharyngeal swab for COVID-19 RT-PCR. The sample was collected in a standardized viral transport medium using a nylon-tipped swab. Samples were transported at 2-8 degrees Celsius and were processed within 24 hours. RNA extraction was performed using an automated extraction system (Genolution, South Korea) which is an FDA-approved magnetic bead-based extraction system. For real time RT-PCR, Thermofisher's Quantstudio™ was used. All kits used for COVID-19 assay were pre-approved by the Indian Council of Medical Research (ICMR). To determine sample adequacy and ascertain adequate extraction of RNA, an endogenous control was used for each sample as part of the assay. A reference control was run in 8 serial dilutions to make a standard curve based on cycle threshold (CT) values at each dilution.

Furthermore, with each set of samples one reference with high CT value and one with lowest CT value was run, hence a semiquantitative estimate of viral load (expressed as $\log_{10}$ viral copies/mL) was provided.

In patients with positive baseline RT-PCR report, follow up RT-PCR was performed on days 3, 5 and 7 following drug intervention to estimate the change in viral load.

OUTCOMES

The primary outcomes were to evaluate the efficacy of the two different doses of oral ivermectin compared with placebo in reduction of viral load and conversion to negativity of nasopharyngeal/ oropharyngeal RT-PCR on day 5 after intervention. The viral load was estimated using the cycle threshold of the RT-PCR. The secondary outcomes included qualitative and quantitative results of RT-PCR on day 3 and 7 after intervention; time to clinical resolution; frequency of clinical worsening; clinical status of the subject on day 14; and hospital-free days at day 28. The clinical status was expressed using the 8-point World Health Organization (WHO) ordinal scale (13) as follows: 1– not hospitalized, no limitation of activities; 2–not hospitalized, limitation of activities; 3–hospitalized, not requiring supplemental oxygen; 4–hospitalized, requiring supplemental oxygen; 5–hospitalized, on non-invasive ventilation or high-flow oxygen devices; 6–hospitalized, on invasive mechanical ventilation; 7–hospitalized, on vasopressors, renal replacement therapy orextracorporeal membrane oxygenation; and 8–death. The frequency of total and serious adverse events in the study groups was documented.

STATISTICAL ANALYSIS

All consenting patients who were randomized and received a study medication were included in the intention-to-treat (ITT) analysis. Among these, patients with a positive result on nasopharyngeal/oropharyngeal RT-PCR on the day of enrolment were included in the modified intention-to-treat (mITT) analysis. All virological outcomes were assessed in the mITT population as viral load decline and conversion of RT-PCR to negative result was unmeasurable in patients with negative RT-PCR on the day of enrolment. Clinical outcomes were assessed in the mITT population, whereas the adverse effects were evaluated in the ITT population. Statistical analysis was performed using STATA (version 14). Categorical variables were expressed as number and percentage. Continuous variables were presented as mean and standard deviation, or median and interquartile range. Inter-group comparisons of categorical outcome variables were performed using Fisher's exact test. Inter-group comparisons of continuous outcome variables were performed using analysis of variance (ANOVA) or Kruskal-Wallis test. The comparisons of decline of $\log_{10}$ viral copies/mL between different pairings of study groups at various time points were performed using t-test and were expressed as mean difference with 95% confidence intervals (CI). In the presence of a negative RT-PCR test on follow-up sample, the viral load was imputed to 0 on the log scale. A p-value of less than 0.05 was considered statistically significant.

The funder had no role in study design, data collection, data analysis or writing of the report. The corresponding author had full access to the study data and had the final responsibility for the decision to

submit for publication.

Results

Between 28 July, 2020 and 29 September, 2020, a total of 278 patients with mild or moderate COVID-19 were assessed for eligibility**(Figure 1).** Of these, 157 patients were randomized, of whom 5 patients subsequently withdrew consent. The ITT population (n = 152) included 51 patients assigned to ivermectin 24 mg, 49 patients assigned to ivermectin 12 mg, and 52 patients assigned to placebo. Among these, 125 patients had a positive nasopharyngeal/oropharyngeal SARS-CoV-2 RT-PCR result on day of enrolment and were included in the mITT analysis. The mITT population included 40 patients in ivermectin 24 mg arm, 40 patients in ivermectin 12 mg arm, and 45 patients in the placebo arm. In the mITTgroup, 80 patients (64%) had mild illness, while 45 patients (36%) had moderate illness.

The mean (SD) age of participants was 35.3 (10.4) years and majority (88.8%) were males. The proportion of patients with moderate illness was 40% in ivermectin 24 mg arm, 32.5% in ivermectin 12 mg arm, and 35.6% in placebo arm**(Table 1).** In contrast, the proportion of asymptomatic patients at enrolment was 22.5% in ivermectin 24 mg arm, 27.5% in ivermectin 12 mg arm, and 17.7% in placebo. Baseline clinical severity by WHO ordinal scale was 3 in the majority (92%) of patients. The median duration of symptoms at the time of enrolment was 5 days (interquartile range, 3 to 7 days) and was similar in the three arms. There were no significant differences in the comorbidities or presenting symptoms in the three arms. Baseline laboratory parameters in the three arms were similar **(Supplementary Table 1).** A minority (10%) of patients received concurrent antiviral therapies including remdesivir, favipiravir or hydroxy-chloroquine as decided by site physicians without any difference in the three arms **(Supplementary Table 2)**

Primary outcomes

The proportion of subjects who became RT-PCR negative on day 5 of enrolment was numerically higher with ivermectin 24 mg arm (47.5%) compared with ivermectin 12 mg arm (35.0%) and placebo arm (31.1%)**(Table2);** however, this difference did not attain statistical significance (p-value =0.30)**(Figure 2).** Subgroup analysis based upon disease severity also demonstrated no significant difference in the negativity of RT-PCR at day 5. In subjects who received intervention early in the course of illness (within 4 days of symptom onset), Ivermectin 24 mg arm had numerically higher negativity of RT-PCR at day 5 compared with placebo (47.0% vs 28.6%, p-value = 0.38).The viral load at enrolment did not impact the efficacy of the therapies to convert to negative RT-PCR at day 5.

There was no significant difference in the viral load (expressed as $\log_{10}$ viral copies/mL) in the three arms, either at baseline or at day 5 of enrolment **(Table 3),** or in the decline of viral load between the ivermectin and placebo arms at day 5 **(Table 4& Figure 3).** Furthermore, no difference was observed in the absolute viral load or the decline of viral load in either the mild or the moderate illness strata at day 5 (Supplementary tables 3, 4, 5 and 6).

Secondary outcomes

Among the secondary virological outcomes, there was no significant difference in the three arms in terms of conversion to negative RT-PCR **(table 2)**, or in the decline of viral load at either day 3 or day 7 of enrolment **(Table 4).**

Secondary clinical outcomes were also similar in the three arms **(Table 5).** There was no difference in the mean (SD) duration of symptom resolution in the three groups or in the duration of hospital-free days at day 28. The proportion of patients with clinical worsening (defined as an increase in the WHO ordinal score during treatment) was similar in the three groups (ivermectin 24 mg, 7.5%; ivermectin 12 mg, 5.0%; and placebo, 11.1%; p-value = 0.65).

Adverse events

There were no serious adverse events reported during the study **(Table 6).** The frequency of all adverse events in the ITT population was similar in the three arms (ivermectin 24 mg, 11.8%; ivermectin 12 mg, 16.3%; and placebo, 11.5%; p-value = 0.76). The most frequent adverse event was epigastric burning sensation, which occurred in 17 (11.2%) patients.

Discussion

In this investigator-initiated, triple-blind, randomized, placebo-controlled trial, we examined the efficacy and safety of Ivermectin at two doses (24 mg and 12 mg) in the management of non-severe COVID-19. Patients in the Ivermectin 24 mg arm demonstrated a numerically higher rate of conversion to negative RT-PCR at day 5 compared to the placebo arm overall and also separately in the mild and moderate subgroups; however, this did not reach statistical significance **(Figure 2).** Further, the decline in viral load at day 5 in all groups was similar.

The interest in Ivermectin in the treatment of COVID-19 was sparked by an in-vitro study by Caly et al, wherein they had demonstrated in Vero/hSLAM cells, that a single application of Ivermectin to achieve concentrations of 2-2.5 µg/mL enable a 5000-fold reduction in the viral load within 48 hours(6). Ivermectin has a plausible broad spectrum anti-viral action by inhibiting the importin α/β protein of the host(3). The inhibition of this protein blocks the entry of the viral nucleocapsid into host nucleus for subsequent replication. Previously, in a phase III clinical trial, Ivermectin increased rate of viral clearance of dengue virus compared with placebo without any demonstrable clinical benefit (14).

However, the micromolar doses described in the in-vitro study by Caly et al are difficult to achieve in vivo with the FDA-approved dose (200 µg/kg) of Ivermectin(15). Although Ivermectin is usually administered in tablet form, its bioavailability may increase upto 2.5-fold when given alongwith a fat-rich meal or in an alcohol-based formulation(10,16). Furthermore, Ivermectin may preferentially distribute into the tissues, including the lung(12). Hence, we included a higher dose (400 µg/kg) of Ivermectin in an alcohol-based elixir given after breakfast. Nonetheless, even higher doses may be required to achieve optimal

therapeutic doses against SARS-CoV-2. Indeed, doses up to 1-2 g/kg have been found to be safe and may be explored further(9,10). Furthermore, Ivermectin may have immunomodulatory actions at nanomolar doses by inhibiting the nicotinic acetylcholine receptor (nAChR). The nAChR may act as a receptor for SARS-CoV-2 and drive dysregulated cytokine release (IL1, IL6, TNF and IL18) from macrophages(17,18).

In our study subjects, Ivermectin did not improve the time to symptom recovery, clinical status at day 14, or hospital-free days at day 28 after drug administration. Similar results were observed in the only other randomized-trial of Ivermectin (12 µg/kg) in predominantly mild COVID-19 patients (n=62) in Bangladesh, wherein Podder et al(19) found that Ivermectin failed to hasten the resolution of symptoms compared to usual care. The same investigators repeated RT-PCR only once on day 10 and found that most patients had attained a negative result(19). In contrast, we performed RT-PCR at days 3, 5 and 7 to serially evaluate decline in viral load with Ivermectin. Our rationale was that faster viral load decline may enable the non-severe COVID-19 patient to become non-infectious sooner, thereby limiting the contagion. Indeed, it has been shown that at a lower viral load (CT > 24), infectivity declines with lower viral culture positivity(20). Hence the trend towards increased viral negativity at day 5 with ivermectin 24 mg in our trial, particularly among mildly ill patients, encourages further exploration in this regard.

In a retrospective study of hospitalized patients in Florida(21), patients who received Ivermectin were found to have a significantly lower mortality that those who did not (15% versus 25%). The mortality benefit remained significant after propensity-matched analysis and adjusting for confounders. However, they included patients with greater illness severity than our study population, illustrated by lack of mortality in our trial. Furthermore, the greater use of concurrent therapies and retrospective design preclude drawing definitive conclusions from their data. Nonetheless, we did find a 56.2-61.5% RT-PCR negativity among moderately ill patients who received Ivermectin at day 5 of enrolment. The immunomodulatory rather than antiviral effect of Ivermectin may be hypothetically more important in moderate and severe COVID-19(22).

There were no serious adverse events in our trial. Since we have used a novel elixir-based formulation with an aim to maximize plasma bioavailability of Ivermectin, this reassures us regarding its safety for further study. The frequency of mild adverse events was similar with ivermectin at either dose or placebo. Other studies of Ivermectin in COVID-19 have also found a low rate of adverse events(19,23). The predominant adverse event in our study was transient burning sensation in the epigastrium which could be attributed to the alcohol-based elixir preparation.

The major limitation of our study was that it was conducted at a single centre with a relatively small sample size. Most of our patient population was male and relatively young (mean age, 35.3 years) with few comorbidities which reflects the demographics of the catchment area of our centre. Such a patient population is likely to have an uncomplicated disease course(24,25). Furthermore, in the absence of previous clinical trials and considering the urgency of the research question, our sample size was exploratory. Hence, we cannot exclude the possibility that a similarly conducted study in a larger and more diverse population could have uncovered clinical efficacy of Ivermectin, if such benefit indeed

exists. Furthermore, the favourable safety profile is encouraging for the conduct of larger trials to further clarify the role of ivermectin in COVID-19.

Secondly, the elixir formulation of ivermectin used by us is not yet commercially available. Although our Ivermectin formulation and dosing strategy was determined by a simulation study to attain an adequate drug concentration in the lung, further pharmacokinetic studies are necessary to define the optimal therapeutic dosing of Ivermectin in COVID-19. Furthermore, Ivermectin has a plasma half-life of 18 hours and does not accumulate on repeat dosing(10). Whether multiple doses of Ivermectin in this disease may be superior to a single dose strategy is currently unknown. Hence, the translation of our findings to the use of Ivermectin tablet at various dosing strengths and frequencies in clinical practice requires caution.

Finally, in our study we have recruited patients irrespective of the duration of illness prior to enrolment. The median duration of symptoms at randomization was 5 days in the three arms. Hence, a significant number of patients had a negative RT-PCR result at baseline and were excluded from the modified intention-to-treat analysis. The recruitment of mild patients at a later stage of illness could also have contributed to high rates of RT-PCR negativity in the placebo arm at day 5 of enrolment (31.1%). In a previous study, over 90% of patients with mild COVID-19 have been found to have negative RT-PCR at day 10 of onset of illness(26). Furthermore, antiviral benefits of Ivermectin are postulated to be maximal early in disease course, while hypothetical immunomodulatory benefits may occur later in the illness. Hence, a better understanding of the cellular actions of ivermectin is necessary to define target populations precisely for future trials.

Conclusion

In conclusion, in this exploratory randomized placebo-controlled trial of a single oral administration of Ivermectin elixir at two different dosage strengths (12 mg and 24 mg) in patients with mild and moderate COVID-19, a trend towards higher negativity of RT-PCR at day 5 was observed with the use of Ivermectin 24 mg, while the decline in viral load was similar in all three arms. Reassuringly, there were no safety concerns with the use of Ivermectin at either dose. Larger studies employing different dosing regimens of Ivermectin are required to further elucidate its potential role in treatment of COVID-19.

Declarations

Authorship Statement:

This is to state that all co-authors have contributed substantially to the conduct of this trial.

Disclosure Statement:

This is to state that none of the co-authors have any potential conflicts of interest to declare pertaining to this manuscript or work.

Declaration of interests

We declare no competing interests.

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Tables

Table 1: Demographic details and baseline clinical characteristics of patients included in modified intention-to-treat (mITT) analysis.

Variable	Ivermectin 24mg (n = 40)	Ivermectin 12mg (n = 40)	Placebo (n = 45)	p value
Age (years), mean (SD)	34.3 (10.45)	36.3 (10.54)	35.3 (10.52)	0.64
Sex, n (%)				0.77
- Male	37 (92.5)	35 (87.5)	39 (86.7)	
- Female	3 (7.5)	5 (12.5)	6 (13.3)	
BMI (kg/m^2), mean (SD)	24.9 (3.50)	25.354 (3.53)	25.5 (3.51)	0.77
Severity, n (%)				0.80
- Mild	24 (60.0)	27 (67.5)	29 (64.4)	
- Moderate	16 (40.0)	13 (32.5)	16 (35.6)	
Comorbidities, n (%)				
- Hypertension	3 (7.5)	6 (15.0)	5 (11.1)	0.60
- Diabetes mellitus	2 (5.0)	4 (10.0)	5 (11.1)	0.63
- Post-TB sequelae	3 (7.5)	0 (0.0)	1 (2.2)	0.21
- Coronary artery disease	0 (0.0)	0 (0.0)	1 (2.2)	1.00
Smoking history, n (%)				0.68
- Active	1 (2.5)	4 (10.0)	4 (8.9)	
- Former	3 (7.5)	2 (5.0)	2 (4.4)	
Symptoms, n (%)				
- Fever	23 (57.5)	20 (50.0)	23 (51.1)	0.81
- Cough	14 (35.0)	21 (52.5)	24 (53.3)	0.19
- Breathlessness	14 (35.0)	12 (30.0)	16 (35.6)	0.89
- Sore throat	10 (25.0)	10 (25.0)	12 (26.7)	1.00
- Fatigue	8 (20.0)	7 (17.5)	6 (13.4)	0.76
- Headache	2 (5.0)	2 (5.0)	3 (6.7)	1.00
- Myalgia	12 (30.0)	7 (17.5)		0.39
- Nausea/vomiting	1 (2.5)	3 (7.5)		0.52

- Loss of taste/smell	4 (10.0)	3 (7.5)	13 (28.9)	0.92
- Chest pain	0 (0.0)	2 (5.0)	1 (2.2)	0.55
			3 (6.7)	
			2 (4.4)	
Asymptomatic at the time of enrolment, n (%)	9 (22.5)	11 (27.5)	8 (17.7)	0.53
Duration of symptoms prior to enrolment (days), median (IQR)	4 (3-7)	5 (3-7)	4 (3-6)	0.88
Early presentation (symptoms < 4 days), n (%)	17 (51.5)	16 (48.5)	21 (51.2)	1.00
WHO Ordinal Scale at baseline, n (%)				
- 3				0.50
- 4	38 (95.0)	35 (87.5)	42 (93.3)	
	2 (5.0)	5 (12.5)	3 (6.7)	
Baseline chest radiograph severity score, n (%)[#]				1.00
- <2	36 (90.0)	35 (89.7)	41 (91.1)	
- >2	4 (10.0)	4 (10.3)	4 (8.9)	
High viral load at baseline (CT < 24), n (%)	18 (45.0)	18 (45.0)	21 (46.7)	1.00

[#] - Brixia score; data available for 124 out of 125 patients

SD – standard deviation, BMI – body mass index, TB – tuberculosis, CAD – coronary artery disease, IQR – interquartile range, WHO – World Health Organization, CT – cycle threshold

Table 2: Virological outcomes in the patients included in modified intention-to-treat (mITT) analysis

Variable	Ivermectin 24mg (n=40)	Ivermectin 12mg(n=40)	Placebo (n=45)	p value
Negative RT-PCR in mITT population, n/N (%)				
- Day 3 RT-PCR	3/40 (7.5)	7/40 (17.5)	7/45 (15.6)	0.42
- Day 5 RT-PCR	19/40 (47.5)	14/40 (35.0)	14/45 (31.1)	0.30
- Day 7 RT-PCR[#]	16/36 (44.4)	13/36 (36.1)	16/42 (38.1)	0.79
Negative RT-PCR in mild disease, n/N (%)				
- Day 3 RT-PCR	0/24 (0.0)	3/27 (11.1)	4/29 (13.8)	0.18
- Day 5 RT-PCR	8/24 (33.3)	6/27 (22.2)	7/29 (24.1)	0.66
- Day 7 RT-PCR	10/23 (43.5)	7/25 (28.0)	9/29 (31.0)	0.52
Negative RT-PCR in moderate disease, n/N (%)				
- Day 3 RT-PCR	3/16 (18.8)	4/13 (30.8)	3/16 (18.8)	0.74
- Day 5 RT-PCR	9/16 (56.2)	8/13 (61.5)	7/16 (43.8)	0.66
- Day 7 RT-PCR	6/13 (46.2)	6/11 (54.5)	7/13 (53.8)	1.00
Negative RT-PCR at day 5 by duration of clinical symptoms, n/N (%)[##]				
- Early presenters (<4 days)	8/17 (47.0)	4/16 (25.0)	6/21 (28.6)	0.38
- Late presenters (>4 days)	9/16 (56.2)	8/17 (47.0)	7/20 (35.0)	0.45
Negative RT-PCR at day 5 by viral load at baseline, n/N (%)				
- High viral load (CT < 24)				

-	Low viral load (CT > 24)	4/18 (22.2)	5/18 (27.8)	2/21 (9.5)	0.33
		15/22 (68.2)	9/22 (40.9)	12/24 (50.0)	0.19

[#] - RT-PCR results on day 7 available for 114 out of 125 patients included in mITT analysis.

[##] - This analysis was performed only in patients who were symptomatic at time of enrolment.

RT-PCR – reverse transcriptase-polymerase chain reaction, CT – cycle threshold

Table 3: Viral load (expressed as log_{10} viral copies/mL) by RT-PCR at various time points in all patients included in the modified intention-to-treat analysis

Variable	Ivermectin 24mg (n = 40)	Ivermectin 12mg (n = 40)	Placebo (n = 45)	p value
Viral load at enrolment (log_{10} viral copies), mean (SD)	5.54 (2.02)	5.79 (1.82)	6.12 (1.73)	0.35
Viral load at day 3 (log_{10} viral copies/mL), mean (SD)				
- Absolute	3.89 (1.88)	3.85 (2.17)	3.96 (2.00)	0.97
- Decrease (day 0 to day 3)	1.65 (1.63)	1.94 (1.86)	2.16 (1.74)	0.40
Viral load at day 5 (log_{10} viral copies/mL), mean (SD)				
- Absolute	2.49 (2.50)	2.75 (2.30)	3.04 (2.44)	0.58
- Decrease (day 0 to day 5)	3.05 (2.29)	3.04 (2.05)	3.08 (1.98)	0.99
Viral load at day 7 (log_{10} viral copies/mL), mean (SD)[#]				
- Absolute	1.95 (1.84)	2.30 (1.99)	2.37 (2.20)	0.62
- Decrease (day 0 to day 7)	3.56 (2.51)	3.56 (1.83)	3.88 (2.19)	0.76

[#] - RT-PCR viral load results on day 7 available for 113 out of 125 patients included in mITT analysis.

Table 4: Mean difference in decrease of viral load (expressed as log_{10} viral copies/mL) from baseline value at enrolment between subjects enrolled in different trial arms at various time points in the entire modified intention-to-treat (mITT) population

	Ivermectin 24mg vs Placebo	Ivermectin 12mg vs Placebo	Ivermectin 24mg vs Ivermectin 12mg
	(p value)	*(p value)*	*(p value)*
Day 3,	-0.51 (-1.23 – 0.22)	-0.22 (-1.00 – 0.55)	-0.29 (-1.07 – 0.49)
mean difference (95% CI)	*0.17*	*0.57*	*0.46*
Day 5,	-0.03 (-0.95 – 0.89)	-0.04 (-0.92 – 0.82)	0.01 (-0.95 – 0.98)
Mean difference (95% CI)	*0.95*	*0.92*	*0.98*
Day 7[#],	-0.32 (-1.39 – 0.75)	-0.32 (-1.24 – 0.60)	0.00 (-1.03 – 1.03)
Mean difference (95% CI)	*0.56*	*0.49*	*1.00*

[#] - RT-PCR viral load results on day 7 available for 113 out of 125 patients included in mITT analysis.

Table 5: Clinical outcomes in patients in the modified intention-to-treat (mITT) population

Variable	Ivermectin 24mg (n = 40)	Ivermectin 12mg (n = 40)	Placebo (n = 45)	p value
Days to symptom resolution[#], mean (SD)	4.26 (2.65)	4.76 (2.44)	4.58 (2.94)	0.77
WHO Ordinal Scale (day 14), n(%)				
- 1				0.40
- 2	37 (92.5)	37 (92.5)	39 (86.7)	
- 3	1 (2.5)	0 (0.0)	0 (0.0)	
	2 (5.0)	3 (7.5)	6 (13.3)	
Change in WHO Ordinal Scale score between daily 0-14, n(%)				0.67
- No change	2 (5.0)	3 (7.5)	5 (11.1)	
- Decrease by 1	1 (2.5)	0 (0.0)	1 (2.2)	
- Decrease by 2	35 (87.5)	32 (80.0)	37 (82.2)	
- Decrease by 3	2 (5.0)	5 (12.5)	2 (4.4)	
Discharge by day 14, n(%)	38 (95.0)	37 (92.5)	39 (86.7)	0.42
Hospital-free days at day 28, mean (SD)	17.0 (2.3)	16.7 (2.0)	17.0 (2.0)	0.79
Any clinical worsening[##], n (%)	3 (7.5)	2 (5.0)	5 (11.1)	0.65

[#] - data available for patients who were symptomatic at the time of drug administration (n = 97)

[##] - defined as progression in WHO ordinal scale during course of treatment, or need for escalation of care (e.g. new oxygen requirement)

SD – standard deviation, WHO – World Health Organization

Table 6: Adverse effects in all patients who received Ivermectin (intention-to-treat population)

Variable	Ivermectin 24mg (n = 51)	Ivermectin 12mg (n = 49)	Placebo (n = 52)	p value
Patients with any adverse event, n (%)				
- All	6 (11.8)	8 (16.3)	6 (11.5)	0.76
- Serious	0 (0.0)	0 (0.0)	0 (0.0)	–
Specific adverse events, n (%)				
- Epigastric burning	6 (11.8)	5 (10.2)	6 (11.5)	1.00
- Oral ulcers	0 (0.0)	1 (2.0)	0 (0.0)	0.32
- Pain abdomen	0 (0.0)	0 (0.0)	2 (3.8)	0.33
- Diarrhea	0 (0.0)	1 (2.0)	0 (0.0)	0.32
- Dizziness	1 (2.0)	1 (2.0)	0 (0.0)	0.55
- Palpitations	0 (0.0)	0 (0.0)	1 (1.9)	1.00
Need for invasive mechanical ventilation, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	–
Death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	–