

# The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with mild COVID-19: a pilot, double-blind, placebo-controlled, randomized clinical trial

**Carlos Chaccour** (✉ [carlos.chaccour@isglobal.org](mailto:carlos.chaccour@isglobal.org))

ISGlobal <https://orcid.org/0000-0001-9812-050X>

**Aina Casellas**

ISGlobal

**Andres Blanco-Di Matteo**

Clinica Universidad de Navarra

**Iñigo Pineda**

Clinica Universidad de Navarra

**Alejandro Fernandez-Montero**

Clinica Universidad de Navarra

**Paula Ruiz Castillo**

ISGlobal

**Mary-Ann Richardson**

ISGlobal

**Mariano Rodriguez Mateos**

Clinica Universidad de Navarra

**Carlota Jordan-Iborra**

Clinica Universidad de Navarra

**Joe Brew**

DataBrew

**Francisco Carmona-Torre**

Clinica Universidad de Navarra

**Miriam Giraldez**

Clinica Universidad de Navarra

**Ester Laso**

Clinica Universidad de Navarra

**Carlota Dobaño**

ISGlobal

**Gemma Moncunill**

ISGlobal

**Jose R Yuste**

Clinica Universidad de Navarra

**Jose L Del Pozo**

Clinica Universidad de Navarra

**Regina Rabinovich**

ISGlobal

**Verena Schoening**

Inselspital

**Felix Hammann**

Inselspital

**Gabriel Reina**

Clinica Universidad de Navarra

**Belen Sadaba**

Clinica Universidad de Navarra

**Miriam Fernandez-Alonso**

Clinica Universidad de Navarra

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## Research Article

**Keywords:** COVID-19, ivermectin, randomized control trial

**DOI:** <https://doi.org/10.21203/rs.3.rs-116547/v1>

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# Abstract

Ivermectin inhibits the replication of SARS-CoV-2 in vitro at concentrations not readily achievable with currently approved doses. There is limited evidence to support its clinical use in COVID-19 patients. We conducted a Pilot, randomized, double-blind, placebo-controlled trial to determine the efficacy of a single dose of ivermectin to reduce the proportion of PCR positives, viral load at day 7 post treatment.

Consecutive patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and mild COVID-19 (no pneumonia) and no risk factors for complicated disease attending the emergency room of the Clínica Universidad de Navarra. Patients were randomized 1:1 to receive ivermectin, 400 mcg/kg, single dose (n = 12) or placebo (n = 12).

The primary outcome measure was the proportion of patients with detectable SARS-CoV-2 RNA by PCR from nasopharyngeal swab at day 7 post-treatment. The primary outcome was supported by determination of the viral load and infectivity of each sample. The differences between ivermectin and placebo were calculated using Fisher's exact test and presented as a relative risk ratio.

All patients recruited completed the trial (median age, 26 [range, 18-54] years; 12 [50%] women; 100% had symptoms at recruitment, 70% reported headache, 62% reported fever, 50% reported general malaise and 25% reported cough). At day 7, there was no difference in the proportion of PCR positive patients (RR 0.92, 95% CI: 0.77-1.09, p = 1.0). The ivermectin group had lower median viral loads at days 4 and 7 post treatment as well as lower median IgG titers at day 21 post treatment. Hyposmia/anosmia (76 vs 158 patient-days) and cough (68 vs 97 patient-days) were less frequent in the ivermectin group.

Among patients with mild COVID-19 and no risk factors for severe disease receiving a single 400 mcg/kg dose of ivermectin within 48 hours of fever or cough onset there was no difference in the proportion of PCR positives. There was however a marked reduction of anosmia/hyposmia, a reduction of cough and a tendency to lower viral loads and lower IgG titers which warrants assessment in larger trials.

**Trial registration** ClinicalTrials.gov Identifier: NCT04390022

<https://clinicaltrials.gov/ct2/show/NCT04390022>

## Introduction

As of November 26, 2020, there have been over 60 million cases and 1.4 million COVID-19 deaths worldwide. Although the threshold is difficult to predict accurately,<sup>1</sup> the spread of SARS-CoV-2 is unlikely to stop before at least 50% of the population has gained immunity, either by vaccination or recovering from a naturally-acquired infection.<sup>2</sup> There are now two promising vaccines candidates advancing to emergency regulatory approval, but there is a projected delay in global access to the level required for population impact on the trajectory of the pandemic. While efforts are ongoing to develop treatment options, relatively less attention has been devoted to evaluating drug-based transmission blocking or transmission reduction strategies. These strategies would consist in administering a drug with the aim of

reducing onward transmission by those infected and could serve to reduce the burden on health system and gain time until a vaccine is fully tested and scaled-up.

Ivermectin is a widely used antiparasitic drug with known partial efficacy against several single-strain RNA viruses.<sup>3-5</sup> Caly et al. reported in vitro inhibition of SARS-CoV-2 replication using non-physiologically relevant concentrations of ivermectin.<sup>6</sup> These findings, together with uncertain data reported in a preprint linked to the Surgisphere scandal in conjunction with case reports and anecdotal or ecological observations, prompted several Latin-American countries to include ivermectin as part of the national policy for COVID-19 treatment.<sup>7</sup>

As of November 17, 2020, there are 42 studies evaluating the efficacy of ivermectin to treat or prevent COVID-19 registered in clinicaltrials.gov, of which 11 are already completed. Some observational and case control studies suggest a potential utility.<sup>8</sup> Yet, there is a dearth of robust, randomized controlled trials.

This trial was designed as a pilot to evaluate whether the maximum approved dose of ivermectin in Europe could have an impact on the transmission of SARS-CoV-2 when administered early after disease onset.

## **Methods**

This was a pilot, double-blind, placebo-controlled, single-center, parallel-arm, superiority, randomized clinical trial that compared a single dose of ivermectin with placebo in patients with mild COVID-19 and no risk factors. The trial protocol was published<sup>9</sup>, the last version of the protocol and statistical analysis plan are available as supplementary files. The protocol was approved by the Spanish national ethics committee for drug research (Hospital Puerta de Hierro Majadahonda) and by the Spanish Agency of Medicines and Medical Devices. All procedures were conducted in compliance with the latest revision of the Helsinki Declaration and Good Clinical Practice. All patients provided verbal informed consent at enrollment followed by written consent once their isolation was lifted in accordance to the EMA recommendations: "Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic Version 2 (27/03/2020)".<sup>10</sup>

## ***Patients***

Consecutive outpatients attending the Emergency Room of the Clínica Universidad de Navarra (Pamplona, Spain) with symptoms compatible with COVID-19, no more than 72 hours of fever or cough and a positive PCR for SARS-CoV-2 were enrolled. Patients with positive IgG against SARS-CoV-2, comorbidities considered risk factors for severe disease or COVID-19 pneumonia at baseline were excluded (detailed eligibility criteria are provided in the protocol -Supplementary file-)

## ***Study design and oversight***

The trial was conducted in the Pamplona metropolitan area (Navarra, Spain). Patients were enrolled between July 31, 2020 and September 11, 2020 and randomized in a 1:1 ratio to ivermectin (400 mcg/kg) single oral dose or placebo. The randomization sequence was computer-generated by the trial statistician using blocks of four to ensure balance. Allocation was made by the attending investigator using opaque envelopes. The placebo tablets did not match ivermectin in appearance, therefore, in order for the clinical team to remain blinded, treatment was administered under direct supervision by a nurse not participating in patient's care. There was slow recruitment due to a sharp reduction in local transmission for 10 weeks after the lockdown of March-April 2020, the protocol was amended on September 2<sup>nd</sup> to extend the inclusion criteria from 48 to a maximum of 72 hours of cough or fever.

The main objective was to determine the efficacy of a single dose of ivermectin, administered to low risk, non-severe COVID-19 patients in the first 72 hours after fever or cough onset to reduce onward transmission.

## ***Clinical, laboratory and virological monitoring***

Assessments on enrollment and at days 4, 7, 14, 21 and 28 post treatment included: general symptoms report, physical examination (including respiratory rate, blood oxygen saturation and chest auscultation) and adverse events. All patients were asked to complete a daily online diary of symptoms from day 1 to 28 post treatment. On enrollment, as well as on days 7 and 14 blood samples were obtained to assess full blood count, C reactive protein, procalcitonin, ferritin, creatinine phosphokinase, lactic dehydrogenase, troponin T, D dimer, IL-6, and renal function.

A nasopharyngeal swab for SARS-CoV-2 PCR was taken at enrollment and on days 4, 7, 14 and 21 post treatment. For consistency, these samples were collected by three clinicians using the same technique. All samples were processed by PCR for genes N and E of SARS-CoV-2 (Real Time PCR SARS-CoV-2, Vircell SLU, Granada, Spain). For every sample, the viral load was calculated using standard reference curve (EDX Sars-Cov-2, Exact Diagnostics LLC, Fort Worth Texas). Additionally, all samples from day 4 post treatment were cultured in Vero cells for 7 days, after which the cytopathic effect was assessed and PCR conducted on the harvested cell-free supernatant. If the PCR from the supernatant was positive at day 4, the procedure was repeated on the samples of that patient for day 7. A semi-quantitative serology for IgG against SARS-CoV-2 (COVID-19 VIRCLIA IgG monotest, Vircell SLU, Granada, Spain) was done on samples from all patients on day 21 post-treatment.

## ***Outcome measures***

The primary outcome measure was the proportion of patients with detectable SARS-CoV-2 RNA by PCR from nasopharyngeal swab at day 7 post-treatment.

Relevant pre-specified secondary outcomes included viral load at days 4, 7, 14 and 21 post treatment; proportion of patients with symptoms (particularly fever and cough) at days 4, 7, 14 and 21 post-treatment as well as proportion of patients progressing to severe disease or death during the trial; proportion of patients with seroconversion at day 21 post-treatment and proportion of drug-related adverse events.

## ***Sample size justification***

In COVID-19, viral load peaks right before or at symptom onset<sup>11,12</sup> and most secondary cases occur prior to day five after symptoms. This pilot was designed to assess the use of ivermectin to reduce transmission. With the objective to reduce onward transmission, a robust effect size in the proportion of PCR positives at day seven after treatment would be needed to have a public health impact. A reduction of at least 50% in the proportion of positives was considered of potential value.

The sample size was calculated to have 80% power at a 5% significance level to detect a 50% reduction (100 vs 50%) in the proportion of participants with positive PCR at day 7 post-treatment. The infectivity outcome was supported by assessing changes in viral load and infectivity in cell cultures.

## ***Statistical analysis***

Descriptive analyses used frequency and percentage (based on the non-missing sample size) for qualitative variables and median, interquartile range and n (non-missing sample size) for quantitative variables.

For the primary objective, the proportion of participants with positive PCR at day seven post treatment was calculated. Proportions were compared between study arms using Fisher's exact test and presented as a relative risk ratio (RR) with their corresponding 95% confidence interval (CI). In the analysis of the symptoms reported by patients (symptom diary), missing data was carried over from the last data available. Significance was set at 0.05. The analysis was carried out using Stata (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). Graphs were produced in R version 4.0.2 (R Core Team, R: A Language and Environment for Statistical Computing, Vienna, Austria: R Foundation for Statistical Computing, 2020) with the package ggplot2 (H. Wickham, ggplot2: Elegant Graphics for Data Analysis, Springer-Verlag New York, 2016.).

Viral load data were synchronized prior to analysis by accounting for days since onset of any symptoms and, since the day of infection was not known, an average incubation time of 5 days was assumed.<sup>13</sup> Peak viral load (Cmax) and time to peak viral load (Tmax) were determined directly from the profiles. Area under the viral load curve was calculated using the trapezoidal rule from assumed time of infection to last sample (AUCobs). Duration of time above a threshold of 35 cycles was derived directly from profiles or linearly extrapolated profiles if the last recorded Ct value was not below the threshold.

## ***Post Hoc analysis***

The effect of study arm on the presence of symptoms was estimated using mixed effect logistic regression models with subject as a random intercept. These models are adjusted by day of follow up (as symptoms are expected to disappear over time) and duration of symptoms before enrolment (as a proxy of disease onset). To assess the potential effect of study arm on symptom progression, the interaction between study arm and day of follow up was also included in the models. Three models were studied for those outcomes for which differences between treatments were observed: any symptom, anosmia or hyposmia, and cough.

Additionally, the observed effect of ivermectin on anosmia/hyposmia was assessed in a sub-analysis by sex.

## **Results**

### ***Patient characteristics***

Of 94 patients assessed, 50 did not meet eligibility criteria, 20 declined to participate and 24 were randomized. All randomized patients received the corresponding study product and completed 28 days of follow-up (Figure 1). The baseline characteristics of patients in both groups are presented in Table 1.

There was a higher proportion of females in the placebo group (58 vs 42%). There was a good balance in terms of other demographics and disease characteristics (Table 1). Overall, 66% of the patients presented with perceived or objective fever, 25% presented with cough, 70% presented with headache and 58% presented with myalgia or general malaise with no remarkable differences between groups. The median earliest start of any symptom before treatment was 24 hours for the ivermectin group (interquartile range, 24-48 hours) and 48 hours for the placebo group (interquartile range, 36-48 hours). At baseline, there were no differences in vital signs, inflammatory markers or full blood count between the groups (Table 1).

### ***Primary Endpoint***

There was no difference in the proportion of PCR positive patients at day 7 post treatment, 12 (100%) patients had a positive PCR for gene N in both groups. For gene E, 11 (91%) in the ivermectin and 12 (100%) in the placebo group had a positive PCR (RR 0.92, 95% CI: 0.77-1.09,  $p = 1.0$ ).

### ***Viral load***

Genes E and N had comparable results at all time points. Patients in both study groups had similar viral load before treatment with median and interquartile range for genes E and N in the same orders of magnitude (Figure 2 and Table S1). Although there was a consistent overlap in interquartile ranges and

full ranges at all points, the median viral load for both genes was lower at days 4 and 7 post treatment in the ivermectin group with differences increasing from 3-fold lower at day 4 to around 18-fold lower at day 7 (Figure 2 and Table S1). A similar trend remained for the viral load at days 14 and 21, with values from patients in the ivermectin group consistently lower for at least one of the genes (Figure 2 and Table S1). The values of cycle thresholds had a very similar behavior (Figure S1). Summary statistics for viral kinetics are provided in Table S2.

## ***Viral culture***

At day 4 post-treatment, 7/12 samples in the ivermectin and 5/12 samples in the placebo group effectively replicated Vero cell culture; by day 7 post treatment only 1/6 in the ivermectin (one previously positive sample was lost) and 1/7 in the placebo group replicated in the cell culture.

## ***Symptoms***

There was good compliance with the daily online questionnaire with 282 patient-days reports (84%) and 295 patient-days reports (88%) in the ivermectin and placebo group respectively (Figure S2).

Patients in the ivermectin group reported fewer patient-days of any symptoms than those in the placebo group (171 vs 255 patient-days). This difference is mostly driven by two symptoms, anosmia/hyposmia and cough. Patients in the ivermectin group reported 50% less anosmia/hyposmia than those in the placebo group (76 vs 158 patient-days of anosmia/hyposmia). The ivermectin group also reported 30% less cough (68 vs 97 patient-days of cough) (Figure 3).

There were no major differences between ivermectin and placebo in the reported patient-days of fever (12 vs 12), general malaise (51 vs 61), headache (34 vs 38), or nasal congestion (91 vs 97). With much lower magnitudes, the ivermectin group reported 3.5-fold more patient-days of gastrointestinal symptoms (21 vs 6) and 5-fold less shortness of breath (3 vs 15) (Figure S3).

No patient from either group progressed to severe disease.

## ***Serology***

All patients in both groups seroconverted by day 21 post treatment. Patients in the ivermectin group had a lower median of IgG titers (Index 4.7, interquartile range [3.5-8.9]) than those in the placebo group (Index 7.5, interquartile range [4.2-9.3]) (Figure 4).

## ***Safety***

All patients completed the follow up period of 28 days. There were 15 adverse events (7 in the ivermectin and 8 in the placebo group) experienced by 10 patients (5 in the ivermectin and 5 in the placebo group). There were no severe adverse events.

The online diary of symptoms included questions about ivermectin-specific adverse events. There were no differences in the reported patient-days between the ivermectin and the placebo group for confusion (1 vs 0), drowsiness (0 vs 0), or pruritus (0 vs 3). Patients in the ivermectin group reported more patient-days of dizziness (7 vs 1) and blurred vision (24 vs 1), with this last value driven by a single patient in the ivermectin group reporting blurred vision on days 2–28, further evaluation suggested previously undiagnosed presbyopia (Figure S4).

There were no major differences in the evolution of vital signs (Table S3), inflammatory markers (C reactive protein, procalcitonin, ferritin and IL-6) and rest of laboratory parameters of patients in each group (Table S4).

## ***Post hoc analyses***

In the logistic regression model, there was no positive nor negative trend in time in the presence of any symptoms for patients in placebo arm (Coeff 0.00 [95% CI: -0.10, 0.03]). However, patients treated with ivermectin showed a significant decrease in the presence of symptoms over time (Coeff: -0.06 [95% CI: -0.08, -0.03]). This difference is driven by an increasing trend in the presence of anosmia/hyposmia in the placebo group (Coeff: 0.07 [95% CI: 0.04, 0.10]) which disappears in the ivermectin group (Coeff: -0.02 [95% CI: -0.05, 0.01]) and a decrease in cough over time in the ivermectin group (Coeff: -0.05 [95% CI: -0.09, -0.02]) which is not seen in the placebo group (Coeff: 0.01 [95% CI: -0.02, 0.04]) (Figure S5).

The overall effect of ivermectin on anosmia/hyposmia was mainly driven by male patients (20 vs 76 patient-days of anosmia/hyposmia in the ivermectin and placebo groups respectively) in sharp contrast with female patients (56 vs 81 patient-days of anosmia/hyposmia in the ivermectin and placebo groups respectively) (Figure S6). A sensitivity analysis to assess if gender had any impact on the logistic regression models was performed. Adding this variable to the models did not change the coefficients presented above.

## **Discussion**

In spite of its partial antiviral properties, ivermectin was discarded early as a potential drug to be repurposed against COVID-19. This was largely based on pharmacokinetic modelling stressing the inability of currently approved oral doses to reach lung tissue levels at the antiviral concentrations described by Caly et al.<sup>14</sup> There are however, several reasons to avoid direct inferences from the results of in vitro experiments or pharmacokinetic models, these include the potential role of ivermectin metabolites, the potential immunomodulatory role of the drug, and questions about the virus/cell ratios and appropriateness of the Vero cellular lines used in the cultures.<sup>15</sup>

This pilot study was designed to assess the question of whether further investments in the potential repurposing of ivermectin were warranted. As such, we aimed at generating evidence on viral kinetics, antibody response and clinical efficacy in a cohort of patients at low risk of severe disease. Without a clearly defined mechanism of action, a sole signal in any of said parameters would not suffice to justify further efforts. This pilot shows a trend to lower viral loads in the ivermectin group, a trend to lower IgG titers that may reflect lesser systemic exposure to the virus and clinical benefit in cardinal symptoms of COVID-19 associated with tissue damage: anosmia/hyposmia and cough. These results are in line with emerging evidence from trials in Bangladesh<sup>16</sup> and Argentina<sup>17</sup>, as well as with recent data from a SARS-CoV-2 hamster model from Institute Pasteur which also showed a marked sex dichotomy in the effect of ivermectin on anosmia/hyposmia.

Pending confirmation of these results, this pilot sheds some light on the potential mechanism of action of ivermectin against COVID-19. Note the trial was not powered to detect modest differences in viral load, yet a small effect is suggested when viral load was ascertained directly by PCR and indirectly using IgG titers as markers of systemic exposure.<sup>18</sup> Also, in this pilot ivermectin has not shortened the duration of symptoms associated with systemic inflammation such as fever or malaise, nor has it had a measurable impact on inflammatory markers. Given these findings, consideration should be given to mechanisms of action different from a direct antiviral or anti-inflammatory effect. One alternative explanation might be a positive allosteric modulation of the nicotinic acetylcholine receptor caused by ivermectin and leading to a downregulation of the ACE-2 receptor and viral entry into the cells of the respiratory epithelium and olfactory bulb.<sup>19</sup>

Albeit requiring confirmation, these results raise several important questions. If the mechanism of action of ivermectin against COVID-19 is related to a nicotinic effect, then inhibitory concentrations for this receptor (which are in the nanomolar range) could be achievable in the lung tissue for a short period of time with oral dosing and for considerable longer periods with nebulized therapy.<sup>20</sup> Before considering higher or multiple dose schemes, there is also need to better understand the potential role of ivermectin's metabolites in any observed effect. Finally, given the tendency to lower IgG titers in the ivermectin group, there is need to evaluate the potential relationship between ivermectin treatment, disease severity, inflammation, viral dynamics and antibody titers;<sup>21,22</sup> particular attention should be paid to the long-term humoral and cellular immune responses against SARS-CoV-2 in ivermectin treated patients.

This pilot points towards a potential use of ivermectin in COVID-19 which warrants further exploration under larger trials, with clinical outcomes in patients with risk factors or more severe disease. This is of particular importance for settings with limited resources given ivermectin's low price, broad availability and scalability of manufacturing processes.

## ***Limitations***

This pilot has several key limitations that warrant careful interpretation of the results. Firstly, it was designed to explore a potential signal for the use of ivermectin in COVID-19, not to provide definitive evidence on the subject, hence its small sample size. Second this pilot was restricted to subjects with mild disease and no risk factors in whom the treatment was provided in the first 48 hours of fever or cough, this should be taken into consideration for the design of any confirmatory studies to be conducted. Additionally, the quantification of the viral load presented is intrinsically limited by heterogeneity in the samples, even if all were obtained by the same clinicians, standardization against a human epithelial cell gene would be required to ensure the viral loads are truly comparable.<sup>23</sup>

## **Conclusion**

The positive signal found in this pilot warrants the conduction of larger trials using ivermectin for the early treatment of COVID-19. Such trials should include patients with risk factors for severe disease as well as patients with pneumonia. The potential for a mechanism of action different to direct antiviral effect also opens the door for pre-exposure prophylaxis in high risk groups.

## **Declarations**

### ***Author contributions***

Dr Chaccour had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conceptualization: CCh, NRR, MFA

Data curation: CCh, AC, JB

Formal analysis: AC, CCh, FH, VS

Funding acquisition: CCh, NRR

Investigation: CCh, AB, IP, AFM, PRC, MAR, MRM, CJI, FC, MG, EL, JRY, JLD, GR, BS, MFA

Methodology: CCh, AC, FC, CD, GM, FH, GR, BS, MFA

Supervision: CCh, BS, GR, MFA

Writing - original draft: CCh, AC

Writing - review & editing: all authors contributed, reviewed and approved the last draft.

### ***Conflicts of interest***

No competing interests were disclosed

## ***Funding/Support***

Idipharma SL (Noain, Spain) contributed with in kind placebo tablets. This study was supported by ISGlobal and the University of Navarra. CCh, PRC, MAR, FH and NRR received salary support from Unitaid through the BOHEMIA grant to ISGlobal. ISGlobal acknowledges support from the Spanish Ministry of Science and Innovation through the “Centro de Excelencia Severo Ochoa 2019-2023” Program (CEX2018-000806-S), and support from the Generalitat de Catalunya through the CERCA Program.

## ***Role of funder/sponsor***

The funding source had no role on the design, analysis or decision to publish the results of this study.

## ***Data availability***

Upon publication, all data supporting the results will be archived in a public repository accessible at <http://diposit.ub.edu/dspace/handle/2445/101776>

## ***Additional contributions***

We thank the patients who participated in this study and the nursing staff of the emergency room and technicians of the microbiology lab of the Clínica and the Biobank, Universidad de Navarra for their dedication to this study.

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## Table

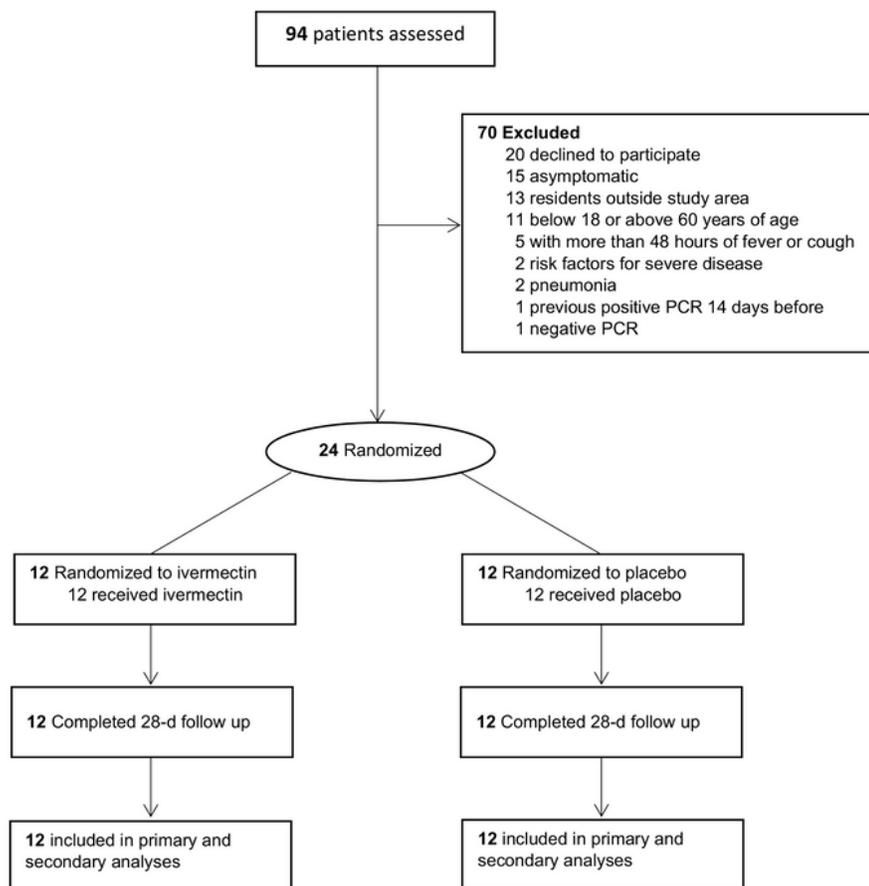
**Table 1. Baseline characteristics of patients by group**

	Ivermectin (n=12)	Placebo (n=12)
<b>Age, median (IQR)[range]</b>	26 (19-36) [18-54]	26 (21-44) [18-54]
<b>Sex, No. (%)</b>		
Female	5 (42%)	7 (58%)
Male	7 (58%)	5 (42%)
Body mass index, median (IQR) [range] kg/m <sup>2</sup>	23.5 (19.6-27.8) [18.6-29.9]	22.9 (21.0-24.8) [19.3-29.9]
<b>Symptoms</b>		
Any, No. (%)	12 (100%)	12 (100%)
Fever, No. (%)	7 (58%)	9 (75%)
Cough, No. (%)	4 (33%)	2 (17%)
Headache, No. (%)	7 (58%)	10 (83%)
Myalgia/general malaise, No. (%)	8 (67%)	6 (50%)
Earliest start of any symptom <sup>a</sup> , median, (IQR) [range]	24 (24-48) [18-120]	48 (36-48) [24-72]
Earliest start of fever <sup>a*</sup> , No, median. (IQR) [range]	24 (12-24) [12-24], n=7	24 (24-48) [4-48], n=9
Earliest start of cough <sup>a</sup> , No, median. (IQR) [range]	24 (16-36) [8-48], n=4	10 (8 - 12) [8-12], n=2
<b>Vital signs</b>		
Systolic Blood pressure, median. (IQR), mmHg	114 (113 - 117)	129 (116 - 134)
Diastolic blood pressure, median. (IQR), mmHg	76 (72 - 80)	79 (77 - 85)
Heart rate, median (IQR) No., bpm	83 (77-99)	90 (81-100)
Respiratory rate, median (IQR) No., bpm	14 (12 - 17) [11]	14 (12 - 15) [12]
Temperature, median (IQR), °C	36.8 (36.4 - 37.0)	36.9 (36.5 - 37.0)
Oxygen saturation, median (IQR), %	97 (96 - 98)	98 (97 - 100)
<b>Viral load</b>		
Gene E, No. (IQR), copies/ml	1.7·10 <sup>7</sup> (5.9·10 <sup>6</sup> -3.9·10 <sup>8</sup> )	2.7·10 <sup>7</sup> (8.3·10 <sup>5</sup> -4.2·10 <sup>8</sup> )
Gene N, No. (IQR), copies/ml	3.7·10 <sup>8</sup> (1.8·10 <sup>7</sup> -	3.3·10 <sup>8</sup> (5.8·10 <sup>7</sup> -

	9.3·10 <sup>9</sup> )	6.7·10 <sup>9</sup> )
<b>Inflammatory markers</b>		
CRP, median (IQR), mg/dL	0.3 (0.2 - 0.8)	0.3 (0.2-0.6)
Ferritin, median (IQR), mg/dL	165.0 (95.8 - 241.3)	156.1 (103.1-223.0)
IL-6, median (IQR) [No.], pg/mL	6.5 (5.1 - 9.6) [12]	4.5 (3.0-6.5) [11]
D-Dimer, median (IQR), ng/mL	295 (270-420)	280 (270-315)
<b>Full blood count</b>		
Red blood cells, median (IQR), 10 <sup>12</sup> /L	5.05 (4.62 - 5.55)	5.07 (4.67 - 5.45)
Hemoglobin, median (IQR), g/dL	15.3 (13.8-16.0)	15.2 (13.7-15.8)
Platelets, median (IQR), 10 <sup>9</sup> /L	194 (167-216)	205 (179-247)
White blood cells, median (IQR), 10 <sup>9</sup> /L	4.7 (4.3-6.3)	4.4 (3.7-5.9)
Neutrophils, median (IQR), %	52.4 (45.6-65.1)	53.4 (43.9-62.2)
Lymphocytes, median (IQR), %	29.5 (18.5- 7.9)	28.7 (20.8-39.9)

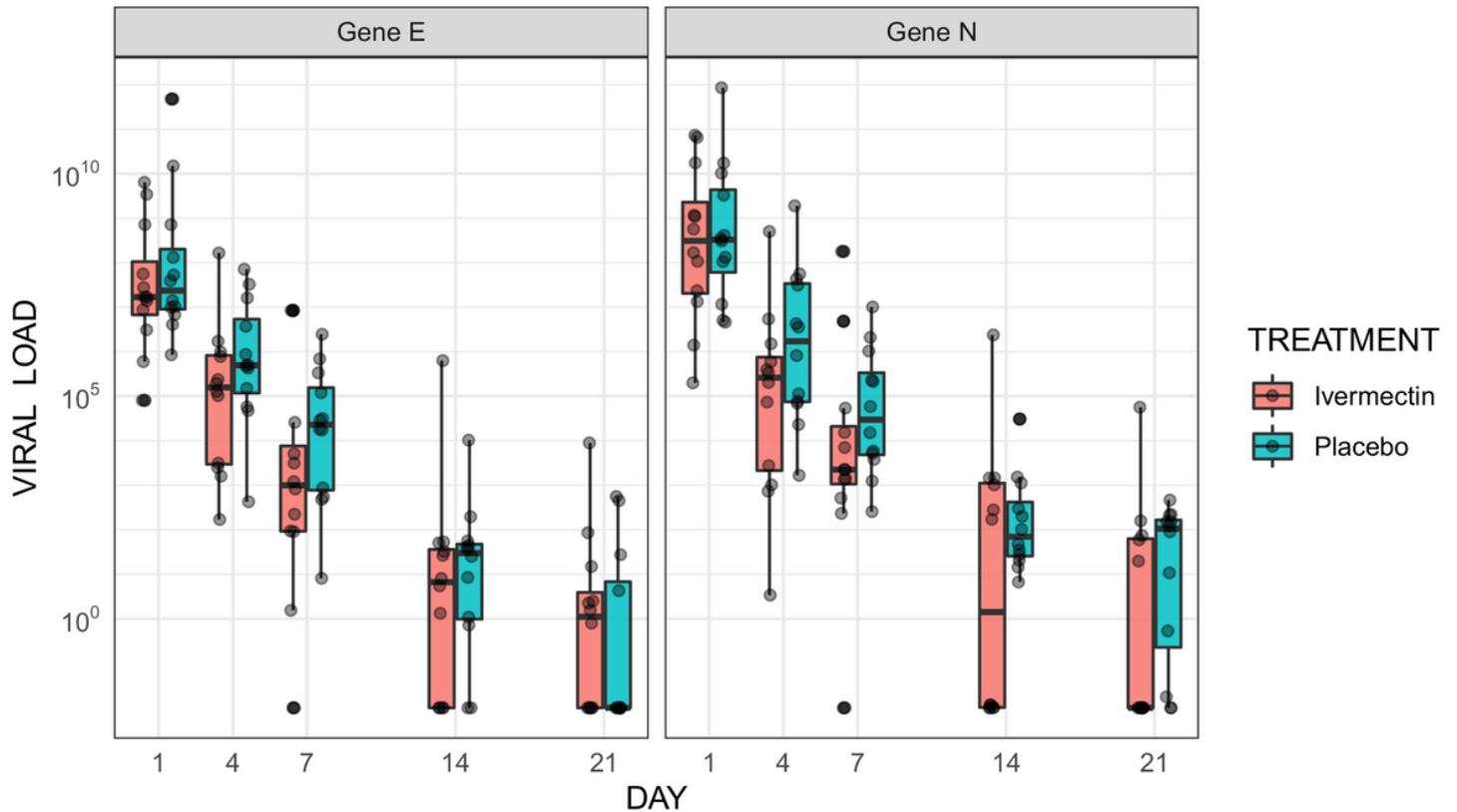
<sup>a</sup>Hours before dosing, \*Reported or measured fever. IQR: interquartile range

## Figures



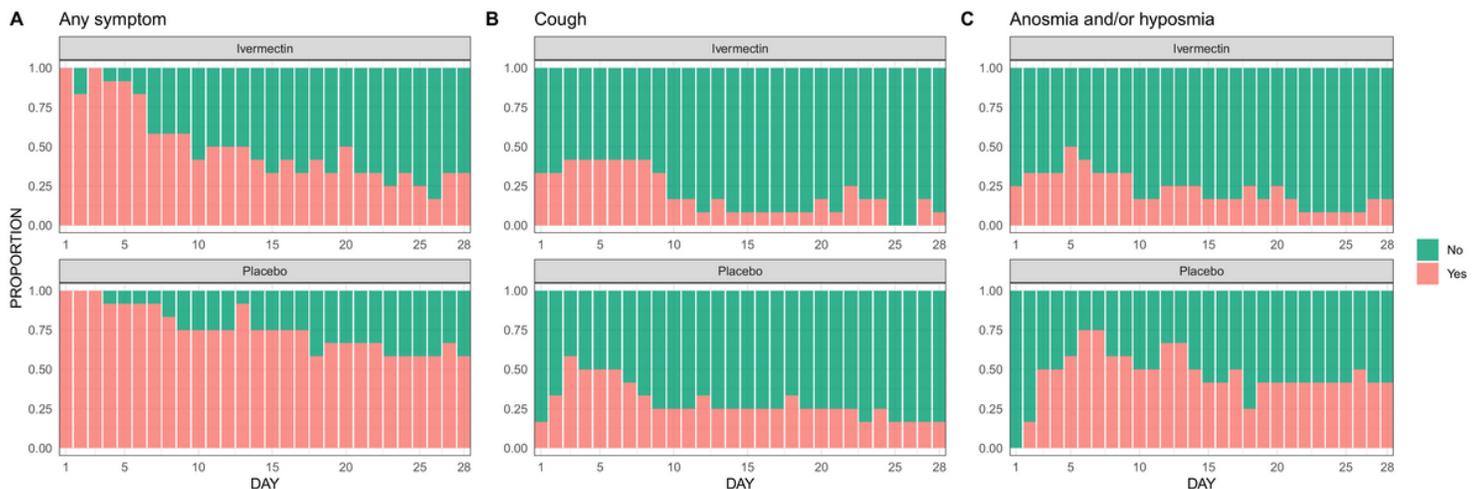
**Figure 1**

Enrollment and patient flow. a One presented with pneumonia in the ER and one had a compatible X-ray during screening. b Formally screened based on epidemiological and clinical suspicion but had a negative PCR.



**Figure 2**

Viral load evolution by study arm. Viral load values were log-transformed. The boxes show the interquartile range. Dots represent each individual value.



**Figure 3**

Daily proportion of any symptoms, cough and anosmia/hyposmia by study arm. Each graph represents the daily proportion of individuals (n/N) who suffered from each symptom in the corresponding study arm for a 28 day follow up. Missing answers were replaced by the value in the immediately preceding day.

# IgG

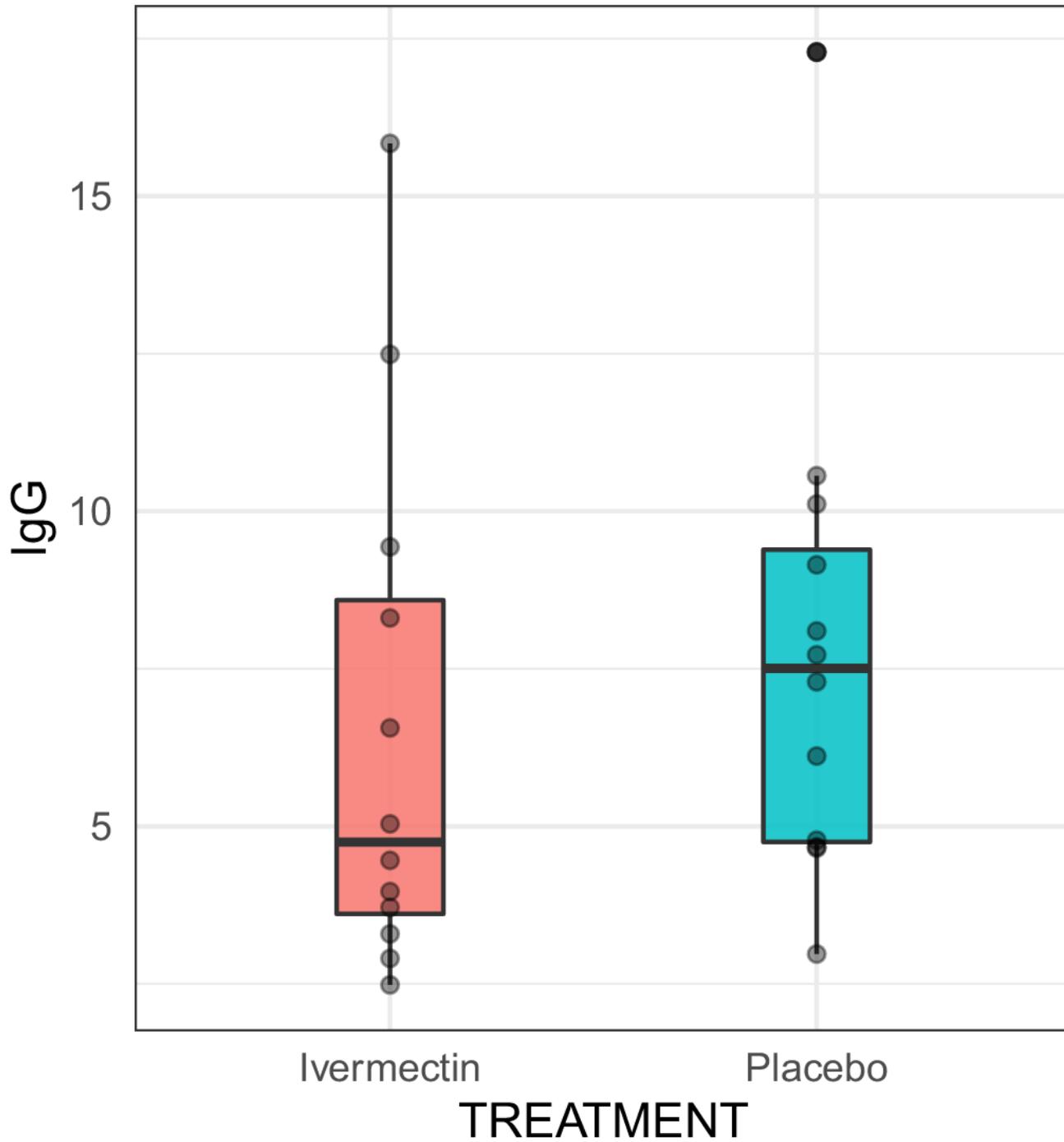


Figure 4

IgG titers by study arm. The boxes show the interquartile range. Dots represent each individual value.

## Supplementary Files

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- [20201126Supplementarymaterial.docx](#)
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- [SAINTprotocolv2.0Clean.pdf](#)