Abbreviated Clinical Study Report

An open-label, multicentre, randomised, adaptive platform trial of the safety and efficacy of several therapies, including antiviral therapies, versus control in mild/moderate cases of COVID-19

Short Title	ANTICOV
Name of product(s)	Hydroxychloroquine sulphate; lopinavir/ritonavir ; nitazoxanide/ciclesonide; ivermectin/artesunate-amodiaquine; fluoxetine/budesonide; paracetamol
Indication	Mild/moderate infection in outpatients with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)
Phase	Phase III
Study Design	Multicentre, multiple-country, randomised, open-label, adaptive, platform clinical study in adult patients with confirmed coronavirus disease 2019 (COVID-19) diagnosis and presenting with viral syndrome
Consortium Coordinator	DNDi, 15 chemin Camille-Vidart, 1202 Geneva, Switzerland (until 01 March 2021: 15 chemin Louis-Dunant, 1202 Geneva, Switzerland) Phone: +41 22 906 9230
Consortium Coordinator's Responsible Medical Officer	Dr Nathalie Strub-Wourgaft
Sponsors in each country with at least one participant screened	Burkina Faso, Guinea: Inserm/ANRS (France) Democratic Republic of the Congo, Kenya, and Sudan: DNDi (Switzerland) Ethiopia: Institute of Tropical Medicine (Belgium) Ghana: Bernhard-Nocht-Institut für Tropenmedizin (Germany) Ivory Coast: Centre Suisse de Recherches Scientifiques (Ivory Coast) Mali: Centre for Vaccine Development (Mali) Mozambique: ISGlobal (Spain) Tanzania: Ifakara Health Institute (Tanzania) Brazil: Cardresearch (Sponsor of Together Trial, Brazil)

	Date
Study Initiation	21 September 2020
Study completion	21 December 2022
Study Report Date	28 March 2024

This study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents

2. SYNOPSIS

Name of Coordinating Sponsor: Drugs for Neglected Diseases initiative (DNDi)	**Name of Active Ingredients:** Hydroxychloroquine sulphate; lopinavir/ritonavir; nitazoxanide/ciclesonide; ivermectin/artesunate-amodiaquine; fluoxetine/budesonide; paracetamol (control)
Name of Finished Products: Marketed formulations of the investigational products	
Title of Study: An open-label, multicentre, randomised, adaptive platform trial of the safety and efficacy of several therapies, including antiviral therapies, versus control in mild/moderate cases of COVID-19	
Investigators: 12 Coordinating Principal Investigators in 12 countries	
Study Centre(s): 26 sites (with screened patients) in 12 countries: 11 African countries (Burkina Faso, Democratic Republic of the Congo [DRC], Ethiopia, Ghana, Guinea, Ivory Coast, Kenya, Mali, Mozambique, Sudan, and Tanzania) + Brazil	
Publication (Reference): None	
Studied Period (years): First Patient First Visit: 21 Sep 2020 Last Patient Last Visit: 21 Dec 2022	**Phase of Development:** Phase III

Objectives: The overall objective was to determine the efficacy and safety of various treatment regimens in outpatients with mild/moderate coronavirus disease 2019 (COVID-19) to prevent the need for hospitalisation for specialised care due to severe progression of the disease.

Primary Objective:

- To compare the efficacy of alternative treatment strategies versus (vs) control on the risk of progression to severe respiratory disease.

Secondary Objectives

- To compare the safety of each study arm to control, up to Day 21 of follow-up
- To compare the rate of hospitalisations due to COVID-19 in each study arm vs control
- To compare the time to hospitalisation due to COVID-19 in each study arm vs control
- To compare the rate of hospitalisations for other reason than COVID-19 in each study arm vs control
- To compare the disease-free rate in each study arm vs control
- To compare the death rate in each study arm vs control
- To compare time to worsening of blood oxygen saturation level (SpO2) ≤93% in each study arm vs control
- To compare the capacity to prevent severe progression between study arms
- To identify risk factors for severe progression
- To assess efficacy in sub-groups of participants e.g. with pre-existing conditions/ co-morbidities, by age group, sex, body mass index (BMI), timeframe between onset of symptoms and randomisation.

Methodology:

ANTICOV was designed as a large, multicentre, multiple-country, randomised, open-label, adaptive, platform clinical study. This design offered the flexibility of adding or

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dropping arms (or adjusting the randomisation ratio) as new data emerged, since several repurposed drugs were being tested at the time of designing the study.

A Master Protocol was developed, providing a study design that could be implemented in multiple countries. It included a common appendix providing relevant information on the study treatments available at any given time in the study (rationale for choice, safety profile, justification of the dose, precautions of use, prohibited concomitant therapies), and a country-specific appendix outlining the treatment arms available to the clinical sites within each country.

The study started with balanced randomisation of participants (1:1:1) to a control arm and to two test arms (see figure below). The single control arm, paracetamol alone, was used as the initial reference standard of care. The study treatment arms could be modified during study conduct according to the following rules:

- A treatment arm could be stopped for futility or success, based on the recommendations of the independent Data Safety Monitoring Board (DSMB), after the review of interim analyses.
- New treatment arms could be added if promising new drug candidates or treatment combinations were identified during the study.
- If an active arm was found to be superior to paracetamol during the study, paracetamol was to be dropped and the superior active arm was to become the new control arm.

The randomisation ratio was a global ratio across all countries. In the countries where paracetamol was considered unacceptable, participants were initially randomised with equal probability to one of the available active treatment arms.

The Master Study consisted of 3 periods: a screening period (a single visit at Day 0), an open-label treatment period (up to 14 days depending on treatment arm), and a follow-up period (beginning after final treatment administration and ending 21 or 35 days after treatment start, depending on protocol version).

Study visits at Days 0, 1, 7, 14 and 21 were conducted at the investigational site, whereas the other visits (Days 2 to 6, Days 8 to 13, Days 15 to 20, Day 35) consisted in collecting data using a phone application or phone call.

Efficacy assessments included the measurement of SpO2, the World Health Organization (WHO) clinical progression scale, clinical symptoms of COVID-19, the modified Medical Research Council (mMRC) dyspnoea scale, the recording of all hospitalisations (along with the reasons for hospitalisation), and the self-assessed questionnaire of warning signs for disease progression.

Safety assessments included routine monitoring of adverse events (AEs, also collected via the questionnaire on warning signs for disease progression), physical examination, and vital signs. Optional safety assessments included laboratory safety tests, electrocardiograms (ECGs), chest X-ray, and computed tomography (CT)-scan (to be performed at investigational centres which were equipped to do those tests and performing them as routine measures for outpatients with COVID-19).

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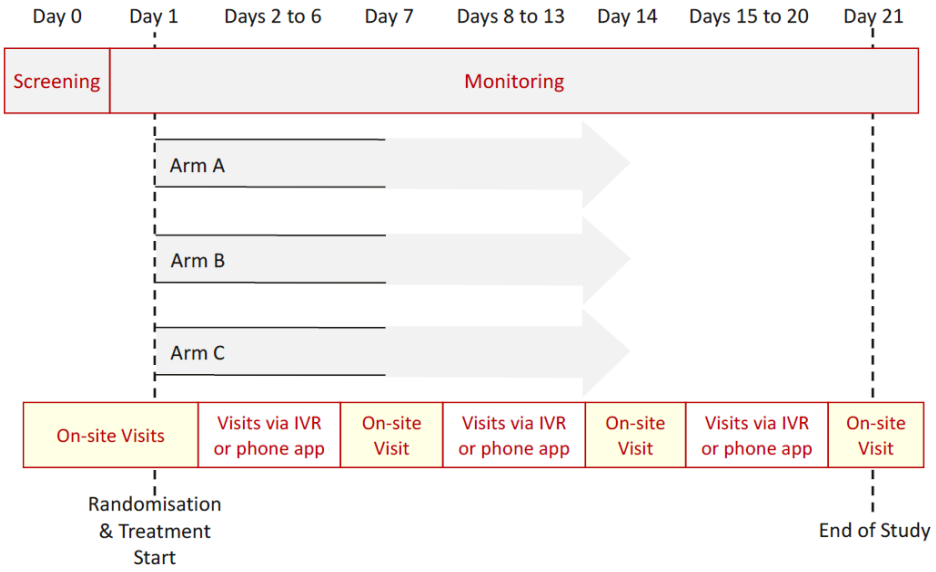
The study design and schedule are presented in the following figure:



IVR = interactive voice response (interview); SAE = serious adverse event.
The figure does not display the telephone call at Day 35 for SAE/pregnancy monitoring (introduced by Protocol Amendment 3).

Number of participants (planned and analysed):

A maximum sample size of 700 per arm was determined by clinical trial simulation. The simulation was carried out for a study evaluating 4 arms, namely one control arm and three active treatment arms (to anticipate the addition of a treatment arm to the 3 starting arms, see figure above) with a sample size of 625 participants per arm for a total of 2500 participants.

Five active treatments were tested during the study, vs paracetamol. A total of 2328 participants were screened and 1942 were randomised to one of the study treatments. Of those randomised, 1893 received at least one dose of study treatment: 83 received hydroxychloroquine (HCQ) sulphate (arm discontinued as per Amendment 1), 77 received lopinavir/ritonavir (arm discontinued as per Amendment 1), 591 received nitazoxanide/ciclesonide (arm introduced by Amendment 1), 182 received ivermectin/artesunate-amodiaquine (ASAQ) (arm introduced by Amendment 2), 143 received fluoxetine/budesonide (arm introduced by Amendment 3), and 817 received paracetamol (reference treatment).

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Diagnosis and main criteria for inclusion:

ANTICOV included adult outpatients with confirmed COVID-19 diagnosis and presenting with viral syndrome (with or without uncomplicated pneumonia).

The 3 key inclusion criteria were the following:

- COVID-19 confirmed by molecular biology [or validated antigenic test available in the country]* for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-Cov-2) according to national guidelines, based on result obtained within 24 hours prior to screening [and 2 days maximum after sampling]**

** Added to facilitate recruitment as some countries used the antigen Rapid Diagnostic Test as an alternative to the Polymerase Chain Reaction testing (Protocol Amendment 1).*

*** It was first specified that the result had to be obtained maximum 48 hours after sampling (Protocol Amendment 2); this was later changed to 2 days after sampling to avoid unnecessary screen failures (Protocol Amendment 3).*

- Viral syndrome with or without uncomplicated pneumonia, defined as SpO2 ≥94%
- Being at risk*, defined as any of the following at screening:
  - Adults aged ≥18 years and having a history of one or more of the following risk factors: diabetes, heart diseases, chronic renal disease, chronic obstructive pulmonary disease (COPD), cerebrovascular diseases, judged to be overweight or underweight with a BMI >25 or ≤16 kg/m^2
  - Adults aged ≥60 years without any co-morbidity
  - Pregnant women**.

** Initially, adults aged ≥18 years regardless of their medical history were eligible, with the option to include children aged ≥12 years if recommended by the DSMB (inclusion criterion 2). After reviewing the first interim analysis results, the DMSB recommended modifying inclusion criterion 2 (as presented above) to include a higher proportion of participants at risk for adverse evolution (Protocol Amendment 3).*

*** Pregnancy was initially an exclusion criterion (see Protocol version 5.0). Inclusion of pregnant women was possible following the removal of the HCQ treatment arm (Protocol Amendment 1). Pregnant or breastfeeding women were randomised only to treatment arms without contraindication for pregnancy and breastfeeding.*

Importantly, participants who had declared feeling unwell for more than 7 days prior to screening were not eligible (exclusion criterion 3), in order to limit enrolment to recently affected participants.

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Test product, dose and mode of administration, batch number:

All the investigational products (IPs) were marketed formulations of medicinal products that were registered for use in indications other than COVID-19. All IPs were administrated by oral/inhaled route, and the doses used were within those for the registered indications of the IPs.

Hydroxychloroquine (HCQ) sulphate: 200-mg tablet

- Day 1: loading dose of 800 mg once a day (QD) (2 daily intakes of 400 mg, 12 h apart)
- Day 2-7: maintenance dose of 400 mg QD (2 daily intakes of 200 mg, 12 h apart)

Lopinavir/ritonavir: 200-mg lopinavir / 50-mg ritonavir tablet

- Day 1: loading dose of lopinavir 1600 mg / ritonavir 400 mg QD (2 daily intakes of lopinavir 800 mg / ritonavir 200 mg, 12 h apart)
- Day 2-14: maintenance dose of lopinavir 800 mg / ritonavir 200 mg QD (2 daily intakes of lopinavir 400 mg / ritonavir 100 mg, 12 h apart)

Nitazoxanide/ciclesonide: 500-mg nitazoxanide tablet / 160-µg ciclesonide per actuation as inhalation aerosol

- Nitazoxanide: 2000 mg nitazoxanide QD (2 daily intakes of 2 tablets of nitazoxanide 500 mg, 12 h apart), for 14 days
- Ciclesonide: 640 µg QD (2 daily inhalations of 320 µg), for 14 days

Ivermectin/artesunate (AS)-amodiaquine (AQ): 9-mg ivermectin tablet / 100-mg AS and 270-mg AQ tablet

- Ivermectin: single dose QD (0.4 mg/kg in fasted condition), for 5 days
- Artesunate-amodiaquine: 200 mg AS and 540 mg AQ QD (2 tablets of 100 mg of AS and 270 mg of AQ) for 3 days

Fluoxetine/budesonide: 20-mg fluoxetine capsule / 400-µg budesonide inhalation rotacaps

- Fluoxetine: 40 mg QD (1 daily intake with 2 capsules of fluoxetine 20 mg) for 7 days
- Budesonide: 800 µg QD (2 inhalations of 400 µg or 4 inhalations of 200 µg) for 7 days

Duration of treatment:

Up to 14 days depending on the treatment arm (see above)

Reference Therapy, Dose and Mode of Administration, Batch Number:

Paracetamol *(initial reference standard of care)*: 500-mg tablet

- 1 to 2 tablets every 4-6 h as required, to a maximum of 6 tablets (3 g) QD in divided doses, for up to 14 days

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Criteria for evaluation:

Efficacy:

Primary Efficacy Endpoint:

- SpO2 ≤93% on repeated measurement within 21 days after randomisation of treatment, which was considered as failure. Death for any reasons occurring within 21 days after randomisation of treatment was considered as failure

Secondary Efficacy Endpoints:

- Mean number and incidence rate of serious AEs (SAEs)
- Mean number and incidence rate of severe AEs
- Mean number of discontinuations or temporary suspensions of IP
- Number of hospitalisations due to severe progression
- Time to hospitalisation
- Number of hospitalisations due to other reason than progression of COVID-19
- Disease-free status: disease-free based on the normalisation of pre-existing symptoms (according to the WHO clinical progression scale) and SpO2 ≥94% at Day 21 and no hospitalisation for COVID-19
- Occurrence of death (up to Day 21)
- Time to worsening of SpO2 ≤93% (or death) within 21 days
- Failure rate for each study arm (see Primary Endpoint)
- Occurrence of SpO2 ≤93% or death or hospitalisation due to COVID-19
- Sub-group analysis of failure rate for each study arm.

Safety:

Safety was assessed through routine monitoring of AEs (also collected via the questionnaire on warning signs), physical examination, vital signs, and optional safety assessments (laboratory safety tests, ECGs, chest X-ray, and CT-scan).

Statistical methods:

Efficacy analyses

The final efficacy analyses were conducted in the Intent-to-treat (ITT) Population, which included all randomised participants who received at least one dose of IP (analysis according to the treatment as randomised).

The interim analyses of the primary endpoint were conducted in a modified ITT, including all ITT participants who completed the study with a known Day 21 outcome (progressed or not progressed), or who terminated the study early but had progressed prior to termination.

General approach

Each active arm was compared to the control arm (paracetamol). As a platform study, the total number of IPs that were to be compared to control was unknown, so the study

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was designed to control for type I error/false positive rate on a “per active arm” basis, yielding the same strength of evidence as if a series of separate studies were conducted in which each active arm was compared to the control arm.

Response-adaptive randomisation (RAR) was used to increase the fraction of participants randomised to the better performing IP(s), both to increase the precision of the treatment estimates for those arms and to increase the likely benefit to the individual participants participating in the study.

Interim analyses of the primary endpoint

DSMB interim analyses were conducted after the first 300 participants had been randomised and every 450 participants thereafter, until 1200 participants had been randomised. After the interim analysis on the 1200 randomised participants was performed, the interim analysis plan was changed and analyses were to be conducted every 45 total events, to address the low rate of events seen in the blinded review.

The primary analysis was a test of superiority of an intervention vs the control arm (paracetamol). It was tested using a Bayesian logistic regression model that related the rate of respiratory deterioration to intervention arm effects.

The adaptive platform design pre-specified two statistical triggers within the trial which, if met, would result in public disclosure and declaration of a platform conclusion. The triggers were defined based on the posterior probability that an active arm was super-superior to paracetamol. The posterior probability of super-superiority was determined using a margin of logit(0.10) − logit(0.075) = 0.3151, which was the log-odds difference required for a decrease in respiratory deterioration rate from 10% to 7.5%.

The two statistical triggers were the following:

- Early Futility - posterior probability <0.10: the active failed to demonstrate evidence of clinically meaningful benefit.
- Early Success - posterior probability >0.98: the active arm demonstrated clinically meaningful benefit.

If an active arm met one of the two statistical triggers, enrolment in this active arm stopped at the interim analysis.

The model adjusted for the time period during which a participant was randomised and the baseline risk for progression (defined as high if any of the following risk criteria were met: age >60 years, BMI >30 kg/m^2, ongoing comorbidity of hypertension, coronary artery disease * type 1 diabetes mellitus, or type 2 diabetes mellitus).

Final (supporting) analysis of the primary endpoint

The primary endpoint was analysed using a standard logistic regression model, including the dichotomous outcome variable (Failure Yes or No) as a function of the fixed categorical effect of treatment group. The model provided odds ratios with two-sided 95% confidence interval (CI) of each active treatment group compared with paracetamol (control).

Safety analyses:

Safety data were descriptively summarised in the Safety Population, which included all

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participants who received at least one dose of IP (analysis according to the treatment actually received).

SUMMARY - CONCLUSIONS

Of the 1942 randomised participants, 1893 (97.5%) received at least one dose of IP and 1749 (90.1%) completed study treatment. The main reasons for not completing study treatment were consent withdrawal (54.9%) and occurrence of an AE (29.9%, with a higher frequency in the nitazoxanide/ciclesonide and the ivermectin/ASAQ treatment arms than in the other arms). There were no treatment misallocations, so the ITT and Safety Populations were the same.

Almost all participants in the ITT Population (n=1893) were black (94.0%), with a balanced ratio of male (50.8%) and female (49.2%) participants. Mean age was 42.1 years, with the oldest participant being 89 years old. No children were enrolled. Mean BMI was 26.3 kg/m^2. The countries that contributed the most to study population (>10% each) were DRC, Burkina Faso, Ethiopia, Mali, and Ghana.

No major differences in demographics were noted between treatment arms. The percentage of participants over the age of 60 years (which is a risk factor for COVID-19 progression to severe disease) was similar among all treatment arms (13.8% overall). The percentage of obese participants was higher in the fluoxetine/budesonide treatment arm (15.4%) compared to the other arms (0 to 4.4%).

The objective to recruit recently affected participants with mild/moderate COVID-19 disease was fulfilled. All participants started to have COVID-19 symptoms no more than 7 days prior to the date of informed consent, as per protocol, except 12 participants (4 randomised to nitazoxanide/ciclesonide and 8 randomised to paracetamol). Randomisation occurred, on average, 3.9 days after the onset of COVID-19 symptoms.

SpO2 ranged from 94% to 100% at baseline, as per protocol (except for 1 patient), with a mean value ≥97% in all treatment arms except the HCQ sulphate (96.8%) and ivermectin/ASAQ (96.6%) treatment arms (individual values <94% were considered protocol deviations). Most participants (93.9%) were ambulatory, symptomatic but independent (WHO clinical progression scale score of 2), indicating that the disease was mild. More than 95% of participants only got breathless during strenuous exercise (Grade 0; 72.5%) or moderate exercise (Grade 1; 23.0%).

Considering the comorbidities identified as risk factors of COVID-19 progression to severe disease, hypertension was the most common comorbidity (17.6% of participants overall), with no major differences between treatment arms, while type 1 and type 2 diabetes mellitus were rare (1.7% and 3.9% of participants, respectively) and coronary artery disease was very rare (0.1%).

EFFICACY RESULTS

The primary endpoint, e.g. the occurrence of respiratory deterioration (SpO2 ≤93% within 21 days, including death for any reason), was analysed in successive planned interim analyses using Bayesian statistics.

The primary analysis was conducted during the third interim analysis, scheduled after 1200 participants had been randomised. This third interim analysis demonstrated early

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futility of the nitazoxanide/ciclesonide treatment arm, vs paracetamol control arm. This treatment arm was immediately discontinued, as per protocol. The statistical comparison of failure rate within 21 days vs the concurrently randomised control arm (paracetamol) could not be performed for the other treatment active arms as the required sample size was not reached and the number of events (i.e. failures) was insufficient.

In the primary analysis, deterioration rate was 3.25% in the nitazoxanide/ciclesonide active treatment arm (15 of 462 participants analysed) vs 1.13% in the paracetamol control arm (5 of 443 participants analysed). The median of the model-estimated odds ratio was 2.58 (95% credible interval 1.05 – 7.05). The model of this primary analysis was structured such that an odds ratio less than one implied benefit.

The posterior probability of super-superiority for nitazoxanide/ciclesonide (vs paracetamol) was 0.0026, which was lower than the statistical trigger for early futility (<0.10).

At the time of the primary analysis, a number of participants were still ongoing in their follow-up period (33 assigned to nitazoxanide/ciclesonide and 36 assigned to paracetamol). The primary result was confirmed by the supporting analysis conducted with all follow-up data for all participants in the paracetamol and nitazoxanide/ciclesonide arms. In this analysis, the posterior probability of super-superiority for nitazoxanide/ciclesonide was 0.0065.

In the final analysis including all study data, the deterioration rate within 21 days was 2.7% in the nitazoxanide/ciclesonide arm and 1.1% in the paracetamol arm.

SAFETY RESULTS

A total of 1893 participants were exposed to study treatments during this study): 83 to HCQ sulphate (4.4%), 77 to lopinavir/ritonavir (4.1%), 591 to nitazoxanide/ciclesonide (31.2%), 182 to ivermectin/ASAQ (9.6%), 143 to fluoxetine/budesonide (7.6%), and 817 to paracetamol (43.2%; control arm).

The incidence of treatment-emergent AEs was heterogeneous between treatment arms, going from 32.8% in the nitazoxanide/ciclesonide treatment arm down to 6.0% in the HCQ sulphate treatment arm.

Most AEs (95.9% of events) were mild or moderate in severity.

The most common AEs (reported in ≥1% of participants overall) were:

- Diarrhoea (3.5% overall), with a higher incidence in the lopinavir/ritonavir (11.7%) and nitazoxanide/ciclesonide (8.0%) treatment arms (compared to other arms)
- Dyspepsia (2.0%), with a higher incidence in the nitazoxanide/ciclesonide (4.7%) and ivermectin/ASAQ (2.7%) treatment arms
- Headache (1.6%), with a higher incidence in the nitazoxanide/ciclesonide (2.9%) treatment arm
- Abdominal pain (1.5%), with a higher incidence in the nitazoxanide/ciclesonide (3.0%) treatment arm

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- Abdominal pain upper (1.1%), with a higher incidence in the lopinavir/ritonavir (5.2%) and nitazoxanide/ciclesonide (2.0%) treatment arms
- Chromaturia (1.3%), with a higher incidence in the nitazoxanide/ciclesonide (4.1%) treatment arm.

The incidence of treatment-related AEs was heterogeneous between treatment arms, going from 22.8% in the nitazoxanide/ciclesonide treatment arm, 16.9% in the lopinavir/ritonavir treatment arm, down to 0.7% in the fluoxetine/budesonide treatment arm.

The most common treatment related AEs (reported in ≥1% of participants) were:

- Diarrhoea (2.9% overall), with a higher incidence in the lopinavir/ritonavir (10.4%) and nitazoxanide/ciclesonide (7.4%) treatment arms than the other arms (0 to 1.1%)
- Dyspepsia (1.6%), with a higher incidence in the nitazoxanide/ciclesonide (4.4%) treatment arm than the other arms (0 to 1.1%)
- Chromaturia (1.3%), with a higher incidence in the nitazoxanide/ciclesonide (4.1%) treatment arm than the other arms (0 to 0.1%)
- Abdominal pain (1.0%), only reported in the nitazoxanide/ciclesonide (2.5%) and ivermectin/ASAQ (1.6%) treatment arms.

Permanent discontinuation of study treatment due to an AE was reported in 2.3% of participants overall, with an incidence of 5.8% in the nitazoxanide/ciclesonide treatment arm and <3% in the other arms.

A total of 34 SAEs were reported in 28 participants (1.5%) overall, with heterogeneous incidence between treatment arms (from 2.6% in the lopinavir/ritonavir treatment arm, 2.4% in the nitazoxanide/ciclesonide treatment arm, down to 0% in the HCQ sulphate treatment arm).

Of the 34 SAEs reported during the study, 7 were fatal. Five fatal SAEs started during study treatment and led to treatment discontinuation. Death was due to COVID-19 pneumonia (2 participants who received paracetamol and 1 who received lopinavir/ritonavir), acute respiratory distress syndrome (1 participant who received nitazoxanide/ciclesonide), sepsis (1 participant who received ivermectin/ASAQ), septicaemia (1 participant who received paracetamol), and unexplained malaise and cardiac arrest (1 participant who received nitazoxanide/ciclesonide). Of the 7 participants (0.4%) who died, 3 were older than 70 years with a normal BMI, and 4 were younger than 70 years but with a high BMI (3 of whom had other comorbidities such as arterial hypertension and/or diabetes). None of the fatal AEs were considered related to treatment.

Most non-fatal SAEs started during the treatment period, and only 4 events in 3 participants were considered by the investigator as possibly related to study treatment: transaminases increased in a participant treated with lopinavir/ritonavir, as well as syncope and dehydration (same participant) and vomiting in 2 participants treated with nitazoxanide/ciclesonide.

All non-fatal SAEs resolved by the end of the study, except the SAE of transaminases

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increased (outcome unknown, but the participant indicated he was doing well when contacted more than 1 year after the first dose).

The child of a participant exposed to nitazoxanide/ciclesonide during pregnancy had an SAE of hypospadias, which was considered unrelated to study treatment. The child was otherwise healthy, and repair surgery was planned for when the child is 2 years old.

Concerning the 5 cases of exposure to study treatment during pregnancy (2 randomised to paracetamol, 1 to nitazoxanide/ciclesonide, 1 to fluoxetine/budesonide, and 1 to ivermectin/ASAQ), 3 had newborns who were healthy and developing normally (including 1 who had a low birthweight), 1 had a newborn diagnosed with hypospadias at birth (see above), and 1 had to have an abortion. The SAE of abortion was considered unrelated to study treatment by the investigator and the sponsor.

A total of 17 participants were exposed to study treatment while breastfeeding.

There were no major changes in vital signs over the 21 days of follow-up. Physical examinations and ECGs did not raise any specific safety concerns.

CONCLUSION

In a large population of recently affected outpatients with mild/moderate COVID-19 disease across Africa and Brazil, the trial did not allow to identify an alternative treatment to paracetamol to better prevent the progression of COVID-19 to severe respiratory disease. The large majority of patients were enrolled during the Omicron wave of COVID-19, which may partly explain why the number of severe progressions was lower than expected.

Early futility (vs paracetamol) could however be demonstrated for one treatment arm (nitazoxanide/ciclesonide), and the number of failures in the other arms (HCQ sulphate, lopinavir/ritonavir, ivermectin/ASAQ, and fluoxetine/budesonide) was insufficient to allow a statistical comparison.

No new safety signals were identified in this trial on repurposed medications and safety results were consistent with the known safety profiles of the tested drugs.

Date of the report: 28 March 2024

3. TABLE OF CONTENTS

3.1 LIST OF IN-TEXT TABLES (SECTIONS 1-13)

3.2 LIST OF IN-TEXT FIGURES (SECTIONS 1-13)

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase (also abbreviated as SGPT in CIOMS form)
AQ	Amodiaquine
AS	Artesunate
ASAQ	Artesunate-amodiaquine
AST	Aspartate aminotransferase (also abbreviated as SGOT in CIOMS form)
AVAREF	African Vaccine Regulatory Forum
BID	Twice a day
BMI	Body mass index
bpm	Beats per minute
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRO	Contract Research Organization
CT	Computed tomography
DBP	Diastolic blood pressure
DNDi	Drugs for Neglected Diseases initiative
DRC	Democratic Republic of the Congo
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
IEC	Independent Ethics Committee
EMA	European Medicines Agency
FAS	Full analysis set
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCQ	Hydroxychloroquine
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	Inhaled corticosteroid
INN	International Non-proprietary Name
IP	Investigational product
IRT	Interactive response technology
ITT	Intent-to-treat
IVR	Interactive voice response (interview)
JSC	Joint Steering Committee
LMP	Last menstruation period
MedDRA	Medical Dictionary for Regulatory Activities
mMRC	modified Medical Research Council
NA	Not applicable
OCD	Obsessive-compulsive disorder

PP	Per protocol
PT	Preferred term
QD	Once a day
q.s.	Quantum satis (as much as needed)
RAR	Response-adaptive randomisation
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System organ class
SpO2	Blood oxygen saturation level
SSRI	Selective serotonin reuptake inhibitor
Swiss TPH	Swiss Tropical and Public Health Institute
TID	Three times per day
vs	Versus
WHO	World Health Organization
WHO / AFRO	World Health Organization / Regional Office for Africa
WHO-ERC	World Health Organization-Ethics Review Committee

9. INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN - DESCRIPTION

9.1.1 Study Rationale and Overall Aim

Coronavirus disease 2019 (COVID-19) is the disease caused by a new human coronavirus with respiratory tropism, the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which emerged in China in December 2019, rapidly spreading to other parts of the world.

At the time of designing the study, the management of COVID-19 was essentially symptomatic, as no antiviral treatment had demonstrated a clinical benefit in the outpatient setting.

From a public health perspective, the primary objective of disease management was to limit the number of COVID-19-related hospitalisations for oxygen therapy and/or intensive care to a number that was practicable, i.e. to treat patients before they became critically ill and required intensive care, especially in low- and middle-income countries. It was also likely that early treatment in the most at-risk individuals was the best way to reduce mortality.

ANTICOV was designed as a large, multicentre, multiple-country, randomised, open-label, adaptive, platform clinical study, aiming to determine the efficacy and safety of various treatment regimens in outpatients with mild/moderate COVID-19 to prevent the need for hospitalisation for specialised care due to severe progression of the disease.

9.1.2 Study Objectives and Endpoints

Table 1: Study objectives and endpoints

Objectives	Endpoints
Primary	
• To compare the efficacy of alternative treatment strategies vs control on the risk of progression to severe respiratory disease	• SpO2 ≤93% on repeated measurement within 21 days after randomisation of treatment, which was considered as failure. Death for any reasons occurring within 21 days after randomisation of treatment was considered as failure.
Secondary	
• To compare the safety of each study arm to control, up to Day 21 of follow-up	• Mean number and incidence rate of SAEs • Mean number and incidence rate of severe AEs • Mean number of discontinuations or temporary suspensions of IP
• To compare the rate of hospitalisations[1] due to COVID-19 in each study arm vs control	• Number of hospitalisations due to severe progression
• To compare the time to hospitalisation[1] due to COVID-19 in each study arm vs control	• Time to hospitalisation
• To compare the rate of hospitalisations for other reason than COVID-19 in each study arm vs control[2]	• Number of hospitalisations due to other reason than progression of COVID-19[2]
• To compare the disease-free rate in each study arm vs control	• Disease-free status: disease-free based on the normalisation of pre-existing symptoms[3] (according to the WHO clinical progression scale) and SpO2 ≥94% at Day 21 and no hospitalisation for COVID-19
• To compare the death rate in each study arm vs control	• Occurrence of death (up to Day 21)
• To compare time to worsening of SpO2 ≤93% in each study arm vs control	• Time to worsening of SpO2 ≤93% (or death) within 21 days
• To compare the capacity to prevent severe progression between study arms	• Failure rate for each study arm (see Primary Endpoint)
• To identify risk factors for severe progression	• Occurrence of SpO2 ≤93% or death or hospitalisation due to COVID-19
• To assess efficacy in sub-groups of participants e.g. with pre-existing conditions/ co-morbidities, by age group, sex, BMI, timeframe between onset of symptoms and randomisation	• Sub-group analysis of failure rate for each study arm

AE = adverse event; BMI = body mass index; COVID-19 = coronavirus disease 2019; IP = investigational product; mMRC = modified Medical Research Council; SAE = serious adverse event; SAP = statistical analysis plan; SpO2 = blood oxygen saturation level; vs = versus; WHO = World Health Organization.
[1] 'Hospitalisation due to COVID-19' was defined as a hospitalisation due to the worsening of COVID-19 symptoms and not due to the isolation/quarantine of COVID-19 patients at hospitals.
[2] Objective and endpoint not included in Protocol version 5.0; added Protocol version 6.0 (see Table 5).
[3] The assessment of disease-free status was modified from the protocol to the SAP (see Section 9.8.2.1).

9.1.3 Overall Study Design

At the time of designing the study (from March until June 2020), several repurposed drugs were being tested in severe cases or as prophylaxis, and several other drug candidates were being evaluated for *in vitro* efficacy or in small proof-of-concept studies. In view of the rapidly evolving landscape in Africa, it was decided to select an adaptive platform design to offer the flexibility of adding or dropping arms (or adjusting the randomisation ratio) as new data emerged during the study.

The study started with balanced randomisation of participants (1:1:1) to a control arm and to two test arms (Figure 1). The single control arm, paracetamol alone, was used as the initial reference standard of care.

The study treatment arms could be modified during study conduct according to the following rules:

- A treatment arm could be stopped for futility or success, based on the recommendations of the independent Data Safety Monitoring Board (DSMB, see Section 9.1.4.2), after the review of interim analyses (see Section 9.1.8.3).
- New treatment arms could be added if promising new drug candidates or treatment combinations were identified during the study.
- If an active arm was found to be superior to paracetamol during the study, paracetamol was to be dropped and the superior active arm was to become the new control arm.

The randomisation ratio could be adjusted depending on the results of the interim analyses. If differential trends were shown between arms, the ratio was adapted to favour randomisation in the most promising arms (see Section 9.1.8.1).

The study treatments at study start are described in Section 9.1.6.1, and those introduced by the protocol amendments are described in Section 9.1.6.2.

A Master Protocol was developed, providing a study design that could be implemented in multiple countries. It included a common appendix providing relevant information on the study treatments available at any given time in the study (rationale for choice, safety profile, justification of the dose, precautions of use, prohibited concomitant therapies), and a country-specific appendix outlining the treatment arms available to the clinical sites within each country.

The Master Protocol included similar inclusion and non-inclusion criteria, the same primary and secondary endpoints, common data entry procedures, a common Joint Steering Committee (JSC, see Section 9.1.4.1), a common DSMB (see Section 9.1.4.2), a shared database, and a single statistical methodology for analysis of the primary endpoint.

Data from across all countries were compiled in order to conduct the analyses outlined in the Master Protocol and statistical analysis plan (SAP).

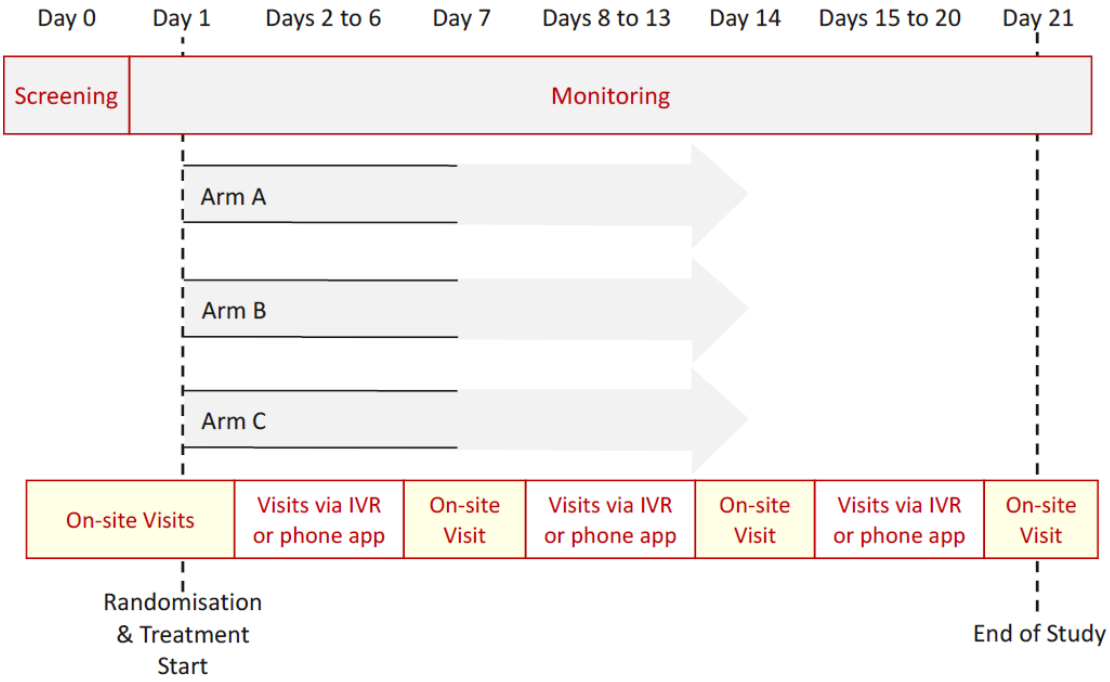
The Master Study consisted of 3 periods:

- Screening period (a single visit at Day 0)
- Open-label treatment period (up to 14 days depending on treatment arm)
- Follow-up period (beginning after final treatment administration and ending

21 or 35 days after treatment start, depending on protocol version*).

Study visits at Days 0, 1, 7, 14 and 21 were conducted at the investigational site, whereas the other visits (Days 2 to 6, Days 8 to 13, Days 15 to 20, and Day 35) consisted in collecting data using a phone application or phone call (Figure 1).
*An additional phone call at Day 35 was implemented in Protocol Amendment 3 (see Section 9.8.1.1). Due to this change, the total duration of the Master Study for each participant was 22 days for those enrolled before version 13.0 of the Master Protocol and 36 days for those enrolled under version 13.0 (Table 4).

Figure 1: Study design at study start



IVR = interactive voice response (interview); SAE = serious adverse event.
Figure 1 does not display the telephone call at Day 35 for SAE/pregnancy monitoring (introduced by Protocol Amendment 3).

In addition to the Master Study, ancillary studies (Immunology, Epidemiology and Coverage Africa) were conducted in some countries, which could extend the participant follow-up. When applicable, these studies are described in Appendices 2, 3, and 6 (or country-specific format) of the protocol. The results of the ancillary studies are not presented in the report.

9.1.4 Study Coordination

The ANTICOV study involved 9 sponsors in 12 countries, a shared database, a common JSC and a common DSMB, as further described below.

The Drugs for Neglected Diseases initiative (DNDi) coordinated the activities of the Master Study.

The study was conducted by the various sponsors in 12 countries: 11 African countries (Burkina Faso, Democratic Republic of the Congo (DRC), Ethiopia, Ghana, Guinea, Ivory Coast, Kenya, Mali, Mozambique, Sudan, and Tanzania),

and Brazil (see Section 9.8.1.2).

ANTICOV governance is fully described in Section 13 of the Master Protocol (see Appendix 16.1.1).

No audits were performed during this study. However, a remote monitoring of the sites was performed by the Swiss Tropical and Public Health (TPH) Institute (completed almost once in all participating countries).

The list of Investigators with their affiliations, a description of their role in the study, and their qualifications, is provided in Appendix 16.1.4. Signed approval of the report is provided in Appendix 16.1.5.

9.1.4.1 ANTICOV Consortium Joint Steering Committee (JSC)

The management teams of all sponsors as well as implementing partners of the study, and partners involved in the operational part of the study conduct (e.g. training, diagnosis) were part of the ANTICOV Consortium JSC.

The JSC, which was a committee by itself, was a decision-making body. It included 3 subcommittees: the internal safety sub-committee (interacting with the DSMB to review safety summaries provided by the Contract Research Organization [CRO] in charge of the global database), the operations sub-committee (overseeing all direct operational, project-related questions, such as staff training, data entry supervision, or monitoring), and a communication sub-committee (safeguarding common messages, should a decision of stopping a treatment arm be taken, and managing the overall communication on study progress and results).

9.1.4.2 Data and Safety Monitoring Board

The DSMB members were selected by the ANTICOV Consortium JSC based on a set of criteria as defined in the protocol. The DSMB was composed of 5 members independent of the investigators and sponsors, and included a member from the World Health Organization (WHO) as observer. The members had expertise in COVID-19 or respiratory viruses in Africa, antiviral therapies and viral shedding, emerging epidemics, adaptive platform trial design, bayesian statistical methods and analysis, and ethics. The DSMB reviewed the study data at pre-determined intervals and issued recommendations concerning study conduct in order to ensure that risks were minimised and benefits were maximised for participants.

The DSMB charter is provided in Appendix 16.1.9. Please refer to Section 9.8.2.2 for the timing of the DMSB reviews.

9.1.4.3 Ethical Considerations

ANTICOV was conducted in accordance with the protocol and all applicable laws and regulations, including, but not limited to, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP), the ethical principles that have their origins in the Declaration of Helsinki and applicable privacy laws.

Study approval by Regulatory Authorities and Independent Ethics Committees

The ethical approval of the ANTICOV protocol involved two successive steps.

The ANTICOV protocol was submitted to the WHO / Regional Office for Africa (WHO / AFRO) for a joint review using the African Vaccine Regulatory Forum (AVAREF) emergency process for COVID-19, with the participation of national Ethics Committees and Regulatory Authorities of the countries involved in this project. This process took place from 12 June to 08 July 2020. All sponsors submitted the ANTICOV 01-COV Master Protocol in their respective countries (including Appendix 5, outlining the treatment arms available to the clinical sites within each country). Then the Ethics Committees and Regulatory Authorities approved the clinical trial application in their respective country.

The ANTICOV protocol was also submitted to the World Health Organization-Ethics Review Committee (WHO-ERC) due to the Unitaid grant. This process took place from 13 July to 24 November 2020. No substantial changes were made; the Master Protocol and informed consent documents for each country were clarified.

Three countries (DRC, Kenya, and Ghana) initiated the study based on the locally approved version of the protocol, which corresponded to version 5.0 of the Master Protocol (in Kenya and Ghana, recruitment actually started under version 7.0). The other countries initiated the study using version 7.0 of the Master Protocol, which was the first version approved by WHO-ERC (see Section 9.8.1.1).

Following version 7.0 of the Master Protocol, 3 amendments were implemented during the study. All amendments were reviewed via the AVAREF emergency process, and approved by the WHO-ERC as well as the relevant national Ethics Committees and Regulatory Authorities. The protocol amendments are described in Section 9.8.1.1.

Copies of the approved clinical study protocol versions and summaries of protocol amendments are included in Appendix 16.1.1.

Participant information and consent

All participants were included in the study after written informed consent was obtained.

If an arm was to be dropped for futility, participants already randomised to this arm were to be informed of the decision made during their next visit or at the time the Ethics Committees and Regulatory Authorities were informed. Participants were informed that they had the choice to stop their current treatment and to be treated under the current standard of care in their country. In case the arm was stopped for safety reasons, efforts were made to inform participants within 24 to 48 hours after the investigators had been informed.

Any new treatment arm was reviewed through the same two-step procedure describe above (AVAREF emergency process and WHO-ERC review, local approval in each country). Following the addition of a new treatment arm, the participants received an informed consent form (ICF) addendum informing them about the change. For the new treatment arm, the ICF was updated accordingly and approved by Ethics Committees before participants could be randomised to this arm.

Separate ICFs were used for the Immunology and Epidemiology ancillary studies. An adapted ICF was submitted for the Coverage Africa ancillary study.

9.1.5 Study Population

ANTICOV included adult patients with confirmed COVID-19 diagnosis and presenting with viral syndrome (with or without uncomplicated pneumonia).

The 3 key inclusion criteria were the following:

- COVID-19 confirmed by molecular biology [or validated antigenic test available in the country]* for SARS-Cov-2 according to national guidelines, based on result obtained within 24 hours prior to screening [and 2 days maximum after sampling]**

** Added to facilitate recruitment as some countries used the antigen Rapid Diagnostic Test as an alternative to the Polymerase Chain Reaction testing (Protocol Amendment 1, Protocol version 7.1, see Table 5).*

*** It was first specified that the result had to be obtained maximum 48 hours after sampling (Protocol Amendment 2, Protocol version 8.0); this was later changed to 2 days after sampling to avoid unnecessary screen failures (Protocol Amendment 3, Protocol version 13.0).*

- Viral syndrome with or without uncomplicated pneumonia, defined as blood oxygen saturation level (SpO2) ≥94%
- Being at risk*, defined as any of the following at screening:
  - Adults aged ≥18 years and having a history of one or more of the following risk factors: diabetes, heart diseases, chronic renal disease, chronic obstructive pulmonary disease (COPD), cerebrovascular diseases, judged to be overweight or underweight with a body mass index (BMI) >25 or ≤16 kg/m^2
  - Adults aged ≥60 years without any co-morbidity
  - Pregnant women**.

** Initially, adults aged ≥18 years regardless of their medical history were eligible, with the option to include children aged ≥12 years if recommended by the DSMB (inclusion criterion 2). After reviewing the first interim analysis results, the DMSB recommended modifying inclusion criterion 2 (as presented above) to include a higher proportion of participants at risk for adverse evolution (Protocol Amendment 3, Protocol version 12.0, see Table 5).*

*** Pregnancy was initially an exclusion criterion (see Protocol version 5.0). Inclusion of pregnant women was possible following the removal of the hydroxychloroquine (HCQ) treatment arm (Protocol Amendment 1, Protocol version 8.0, see Table 5). Pregnant or breastfeeding women were randomised only to treatment arms without contraindication for pregnancy and breastfeeding.*

Importantly, participants who had declared feeling unwell for more than 7 days prior to screening were not eligible (exclusion criterion 3), in order to limit enrolment to recently affected participants.

Please refer to Section 4.1 and 4.2 of the Master Protocol for the full list of inclusion and exclusion criteria. These criteria evolved during the study, mainly

following the removal or addition of new study treatment arms (see Table 5).

9.1.6 Study Treatments

The selection of treatment arms was expected to evolve with the emergence of new scientific data from other preclinical or clinical studies. The study design allowed the principal investigators and sponsors in each country to select, among the agreed treatment arms, those that could be tested in their country, provided that there would always be a minimum of 2 treatment options for randomisation.

All the investigational products (IPs) selected for the study were affordable, marketed formulations of medicinal products that were registered for use in indications other than COVID-19. The IPs were selected based on their known safety and efficacy profiles in their approved indications. The doses used were within those for the registered indications of the IPs. All IPs were administrated by oral/inhaled route, with a treatment duration for up to 14 days depending on the treatment arm. For study treatments including a combination of two IPs, the drugs were co-administered but not co-packaged.

9.1.6.1 Investigational Products Included in Master Protocol Version 5.0

Hydroxychloroquine (HCQ) sulphate and lopinavir/ritonavir (discontinued as per Amendment 1)

The first two treatment arms to be tested in this study were HCQ sulphate and lopinavir/ritonavir, which were selected based on (i) the *in vitro* evidence of their potential activity against SARS-CoV-2, (ii) their well-known safety in another indication, and (iii) their ability to be manufactured at scale and at an affordable cost. The objective was to provide scientific evidence on their activity in mild patients.

No previous study had been conducted in Africa to inform on the efficacy and safety of the antivirals HCQ sulphate and lopinavir/ritonavir in mild or moderate non-hospitalised COVID-19 patients.

Based on WHO guidelines released on 18 December 2020 and on DSMB recommendations, the HCQ sulphate and lopinavir/ritonavir arms were dropped from the protocol in January 2021 before reaching full sample size (see Protocol Amendment 1 in Table 5).

Paracetamol (control)

The study included a single control arm, paracetamol alone, which was used as the initial reference standard of care. It was investigated when used alone (as the reference arm) and when added to all patients requiring symptomatic treatment for fever and pain in all treatment arms (in which case paracetamol was considered a concomitant medication, see Section 9.1.8.4). During the conduct of the study, if an active arm was found to be superior to paracetamol, paracetamol was to be dropped and the superior active arm was to become the new control arm.

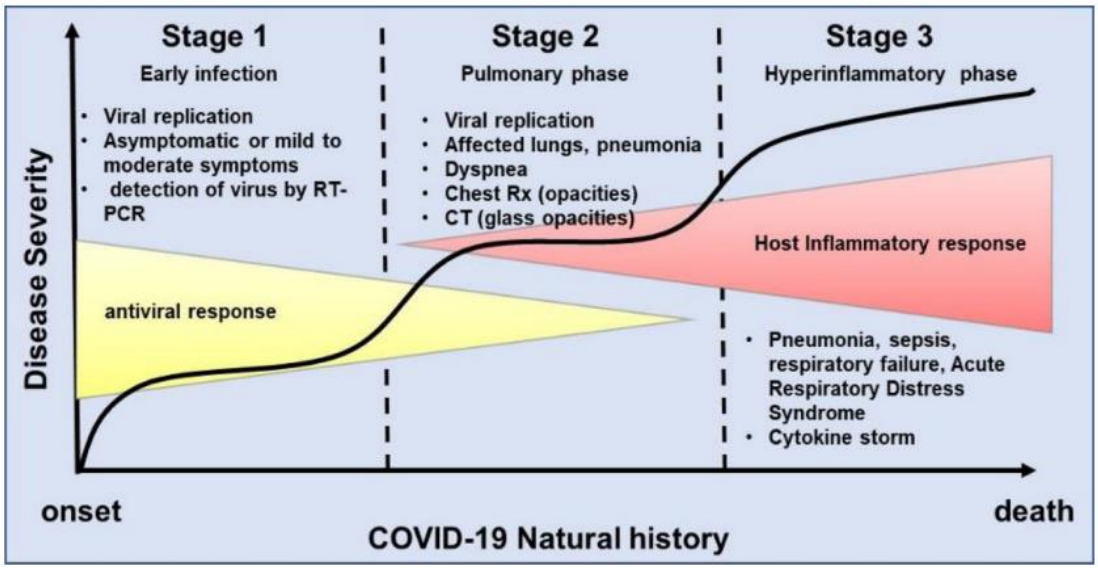
In some countries, the control arm was considered unacceptable and no participants were randomised to this arm (see Section 9.1.6.3 for more details on the adaptation of randomisation in this case).

General information on the IPs included in Master Protocol version 5.0 is provided in Table 2. For more information on these IPs (rationale for choice, safety profile, justification of the dose, precautions of use, prohibited concomitant therapies), please refer to Appendix 1 of the Master Protocol version 5.0 (see Appendix 16.1.1).

9.1.6.2 Investigational Products Implemented in Protocol Amendments 1, 2, and 3

As the study was progressing, SARS-CoV-2 infection got better described and understood. It can typically be divided in two sequential phases. The first phase is characterised by virus replication, followed by the development of clinical symptoms that slowly decrease within 10 to 12 days. The developing inflammatory response starts being uncontrolled after approximately 8 to 10 days, leading to severe pulmonary and systemic complications (Figure 2).

Figure 2: Schematic representation of the natural history of COVID-19



Source: dos Santos W.G., Biomedicine and Pharmacotherapy, Vol 129, 2020 [1].

In real-life setting, patients may be diagnosed at different stages of infection and it is therefore important to combine treatments with complementary mechanisms of action to cover for both stages: a drug with a primary antiviral activity but some level of immune host effect, and a treatment administered locally to primarily control the local inflammation whilst also potentially having an inhibitory effect on SARS-CoV-2 replication.

The IPs implemented in protocol amendments 1, 2, and 3 (see Table 5 for an overview) were therefore combined treatments, which were expected to impact both stages of the disease and decrease any potential risk of viral replication.

Nitazoxanide/ciclesonide (introduced by Amendment 1 and later discontinued due to early futility)

Nitazoxanide is a broad-spectrum antiparasitic drug that is used in medicine for the treatment of primarily helminthic, protozoal infections. Nitazoxanide has also

been identified as a potential pan antiviral agent investigated in clinical trial where it was shown to reduce duration of symptoms and virus burden of uncomplicated influenza [2]. The selection of nitazoxanide was also based on the results of a randomised placebo-controlled clinical study conducted in mild COVID-19 patients in Brazil using a 500 mg three times per day (TID; 1500 mg/day) dosing for 5 days [3]. This study demonstrated, a significant decrease in viral load as well as a significant difference in viral clearance at the 1-week follow-up. Nitazoxanide failed to meet the primary outcome on symptom improvement when evaluated after 5 days of therapy, but when evaluated at the 1-week follow-up, 78% in the nitazoxanide arm and 57% in the placebo arm reported complete resolution of symptoms (p=0.048) [3].

The recommended nitazoxanide dosing in the treatment of diarrhoea caused by *Giardia lamblia* or *Cryptosporidium parvum* is 500 mg twice a day (BID). However, nitazoxanide given at higher doses was being explored in other studies, up to single doses of 4000 mg in dose escalation studies [4]. After examination of the available safety data, a daily dose of 2000 mg nitazoxanide per day was selected for the ANTICOV study. A 1000 mg BID dose was being used in a Nigerian Phase II COVID-19 trial at the time, so there was an opportunity to monitor ongoing safety information and lower the dose if needed.

Ciclesonide is an inhaled corticosteroid (ICS) mainly used to help prevent asthma symptoms. Since the start of the COVID-19 pandemic, the risk of clinical deterioration and hospitalization appeared to be lower among asthma and COPD patients infected with SARS-CoV-2, as compared to the general population [5]. This suggested a possible early protective effect of ICS against SARS-CoV-2 infection. Furthermore, some studies were in favour of an *in vitro* antiviral effect of some ICSs, in addition to their anti-inflammatory effect [6]. Among other ICSs, ciclesonide was selected based on its favourable safety profile.

The selected daily dose of 640 µg ciclesonide per day aimed at optimising the anti-inflammatory and potential antiviral effects. In patients with asthma, this daily dosage allowed a better control of severe asthma from the first day of treatment onwards, compared to the 160 µg dose.

Ivermectin/artesunate-amodiaquine (ASAQ) (introduced by Amendment 2)

Ivermectin is an antiparasitic agent, which is approved for several indications including onchocerciasis due to the nematode parasite *Onchocerca volvulus* and strongyloidiasis of the intestinal tract. Several clinical studies were conducted to test the efficacy of ivermectin in people with COVID-19 [7]. Due to heterogeneous clinical findings, the European Medicines Agency (EMA) concluded in March 2021 that use of ivermectin for prevention or treatment of COVID-19 could not be currently recommended outside controlled clinical trials, and that further well-designed, randomised studies were needed [8].

Amodiaquine (AQ, as hydrochloride)/artesunate (AS) is an artemisinin-based combination therapy, which consists of two blood schizonticides, with independent modes of action and different intraparasitic biochemical targets. This combined therapy is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* strains which are susceptible to AQ as

well as to AS.

In vitro evidence suggested that AQ and its primary active metabolite were active against SARS-CoV-2 [9]. The available data on the activity of AS against SARS-CoV-2 were limited at the time. The inclusion of AS was therefore largely driven by the availability of AQ as existing fixed-dose combinations with AS with established safety, tolerability and efficacy in malaria, as well as a potential antiviral activity.

Fluoxetine/budesonide (introduced by Amendment 3)

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) used in the treatment of major depressive disorder, obsessive-compulsive disorder (OCD), bulimia nervosa, panic disorder, and premenstrual dysphoric disorder. It is considered to hold both antiviral and anti-inflammatory properties, making for an attractive option for mild to moderate COVID-19 patients.

Budesonide is an ICS developed for treatment of asthma by local treatment in the lung. Two clinical studies had shown positive outcome in reducing the risk for disease progression in outpatients with COVID-19 [10,11].

General information on these IPs is provided in Table 3. For more information on these combined treatments (rationale for choice, safety profile, justification of the dose, precautions of use, prohibited concomitant therapies), please refer to Appendix 1 of the Master Protocol version 13.0 (see Appendix 16.1.1).

Table 2: General information on investigational products included in Master Protocol version 5.0

Study treatment label	HCQ sulphate	Lopinavir/Ritonavir	Paracetamol *(control)*
INN of IPs	HCQ sulphate	Lopinavir/Ritonavir	Paracetamol
Dosage form	Film-coated tablet, 200 mg of HCQ sulphate per tablet	Film-coated tablet containing a fixed dose combination of lopinavir 200 mg and ritonavir 50 mg	Tablets, 500 mg of paracetamol per tablet
Route of administration	Oral route	Oral route	Oral route
Dosing instructions	Day 1: loading dose of 800 mg QD (2 daily intakes of 400 mg taken 12 h apart) Day 2-7: maintenance dose of 400 mg QD (2 daily intakes of 200 mg taken 12 h apart)	Day 1: loading dose of lopinavir 1600 mg / ritonavir 400 mg QD (2 daily intakes of lopinavir 800 mg / ritonavir 200 mg taken 12 h apart) Day 2-14: maintenance dose of lopinavir 800 mg / ritonavir 200 mg QD (2 daily intakes of lopinavir 400 mg / ritonavir 100 mg taken 12 h apart)	1 to 2 tablets every 4-6 h as required, to a maximum of 6 tablets (3 g) QD in divided doses
Duration	7 days	14 days	Up to 14 days
Composition	Round, white, film-coated tablets marked ‘HCQ’ on one side and ‘200’on the other side. Active substance: HCQ sulphate 200 mg Excipients: lactose monohydrate, maize starch, magnesium stearate, polyvidone Film-coating: Opadry OY-L-28900 (containing hypromellose, macrogol 4000, titanium dioxide (E171), lactose)	Oval, yellow, biconvex film-coated tablets, measuring approx. 19.0 mm in length and 10.2 mm in width, debossed with “H” on one side and “L3” on other side. Active substance: lopinavir 200 mg, ritonavir 50 mg Excipients: copovidone, sorbitan laurate, colloidal anhydrous silica, sodium stearyl fumarate Film-coating: hypromellose, titanium dioxide, hydroxypropyl cellulose, talc, colloidal anhydrous silica, macrogol, yellow ferric oxide, polysorbate 80	Capsules or white, uncoated tablets. Active substance: 500 mg paracetamol PhEur Excipients: maize starch, pregelatinized; maize starch, stearic acid

HCQ = hydroxychloroquine; INN = International Non-proprietary Name; IP = investigational product; QD = once a day.

Table 3: General information on investigational products implemented in Protocol Amendments 1, 2, and 3

Study treatment label	Nitazoxanide/Ciclesonide (Amendment 1)		Ivermectin/ASAQ (Amendment 2)		Fluoxetine/Budesonide (Amendment 3)	
INN of IPs	Nitazoxanide	Ciclesonide	Ivermectin	AS/AQ (as hydrochloride)	Fluoxetine	Budesonide
Dosage form	Film-coated tablets, 500 mg of nitazoxanide per tablet	Inhalation aerosol, 160 µg per actuation	Tablets, 9 mg of ivermectin per tablet	Tablets containing a fixed dose combination of AS 100 mg and AQ 270 mg	Capsules, 20 mg of fluoxetine per capsule	Inhalation rotacaps, 400 µg per capsule (or 200 µg in Tanzania)
Route of administration	Oral route	Oral inhalation with inhalation chamber	Oral route	Oral route	Oral route	Oral inhalation
Dosing instructions	2000 mg nitazoxanide QD (2 daily intakes of 2 tablets of 500 mg taken 12 h apart with a meal)	640 µg QD (2 daily inhalations of 320 µg)	Single dose QD, 0.4 mg/kg in fasted condition[1]	200 mg AS and 540 mg AQ QD (2 tablets of 100 mg of AS and 270 mg of AQ)	40 mg QD (1 daily intake with 2 capsules of fluoxetine 20 mg)	800 µg QD (2 inhalations of 400 µg or 4 inhalations of 200 µg, daily)
Duration	14 days	14 days	5 days	3 days	7 days	7 days
Composition	Active substance: 500 mg of nitazoxanide Other components: Core: microcrystallone cellulose, lactose, croscarmellose sodium, hydrogenated castor oil, purified talc Coating: Opredy II yellow, purified water	Active ingredient: ciclesonide Inactive ingredients: propellant HFA-134a and ethanol	Ivermectin 9mg Excipients: lactose monohydrate; cellactose 80; sodium starch glycolate; magnesium stearate; talcum powder	Active substances: AS 100 mg and AQ 270 mg Round bilayered tablets (white AS layer engraved with “100”; yellow AQ layer) Excipients: Calcium carbonate, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone and pregelatinised starch	Active ingredient: fluoxetine hydrochloride Excipients: lactose monohydrate, microcrystallinecellulose, anhydrous colloidal silica, magnesium stearate. Shell of the capsule: titanium dioxide (E171), yellow iron oxide (E172), quinoline yellow (E104), indogo carimine (E132), gelatin.	Active ingredient: budesonide Excipients: q.s

AQ = amodiaquine (as hydrochloride); AS = artesunate; ASAQ = artesunate-amodiaquine; BID = twice a day; INN = International Non-proprietary Name; IP = investigational product; QD = once a day; q.s. = quantum satis (as much as needed).
[1] Number of tablets based on body weight: 2 tablets for 45-60 kg; 3 tablets for 61-80 kg; 4 tablets for 81-101 kg; 5 tablets for 102-122 kg; 6 tablets for 123-130 kg.

9.1.6.3 Method of Assigning Participants to Treatment Groups and Data Blinding

Randomisation

At each clinical site, the participants who were eligible to enter the open-label treatment period were randomised to one of the treatment arms available at that country's clinical site. An adaptive randomisation method was used allowing the probability of assignment to each treatment arm to be modified throughout the study based on the results of interim analyses (see Section 9.1.8.1).

Initially (according to version 5.0 of the Master Protocol), the participants were randomised in a 1:1:1 ratio to a control (paracetamol) and to two treatment arms. This ratio was a global ratio across all countries. In Sudan, paracetamol was considered unacceptable and was not a treatment option. As per protocol, participants were initially randomised with equal probability to one of the available active treatment arms in this country (there always had to be a minimum of 2 treatment options for randomisation in each country).

Randomisation could be adapted after the first interim analysis (300 participants randomised in each study arm) or after the subsequent interim analyses (see Section 9.1.8.1). Randomisation was conducted using a centralised online system, the FlexAdvantage Interactive Response Technology (IRT) system, with the country-specific treatment arm availability being updated by DNDi, and the randomisation vector values being updated by the statistical consulting company specialised in adaptive designs (see Section 9.1.8).

Handling of IPs

All IPs were prepared and labelled in accordance with local regulations and laws within each participating country. The IPs were stored at the investigational sites in accordance with GCP and Good Manufacturing Practice (GMP) requirements, in a locked cabinet inaccessible to unauthorised personnel. The investigator or designee maintained appropriate documentation on IP accountability and distribution to study participants.

Data blinding

Since this was an open-label study, participants and investigators were aware of the individual treatment assignments. Investigators were only aware of the treatment assignments and had access to data at their site. This could have introduced an operational bias at the site level because success of a treatment arm was directly related to the probability of allocation to that treatment arm. To minimise this bias, any update of the probability of treatment assignment was kept confidential, being known only to the IRT CRO and statistical consulting company conducting the statistical analysis (see Section 9.1.8).

Access to allocated treatments and to any efficacy and safety data by allocated treatment were not available to the sponsor and clinical study teams until after the database lock, in order to ensure unbiased analysis of interim and final results.

9.1.6.4 Treatment Compliance

For patients quarantined in hospitals or governmental facilities, treatment compliance was recorded directly by study personnel who administered treatment. For outpatients, treatment compliance was assessed by questioning the patients at the time points indicated in Table 4.

9.1.6.5 Prior and Concomitant Therapy

Participants were allowed to continue their concomitant treatment or therapy during the study, provided that it was compliant with the study inclusion/exclusion criteria and compatible with the participant's treatment arm. Prohibited treatments, i.e. products contraindicated with the IPs, are listed in Appendix 1 of the Master Protocol (version 5.0 for paracetamol, HCQ sulphate and lopinavir/ritonavir, and version 13.0 for the other IPs). Participants who were receiving prohibited treatments at screening were not included in the study. Participants were instructed to report any new concomitant treatment to the investigator during the study.

9.1.7 Study Assessments

The schedule of events in the Master Study and list of assessments are provided in Table 4.

Study endpoints are listed in Table 1 in Section 9.1.2.

Please refer to the Master Protocol in Appendix 16.1.1 for a full description of the study assessments. Unless otherwise specified, the procedures and assessments were performed by or under the supervision of the investigator.

Efficacy assessments

For the assessment of the primary efficacy endpoint (SpO2 ≤93% on repeated measurement within 21 days), resting SpO2 was collected using a finger pulse oximeter. It was measured twice at 5 minutes intervals. If one value was above or equal to the threshold of 94%, and the other was below that threshold, a third measurement was performed to categorise the participant at inclusion and for failure. A study-specific work instruction was developed, based on WHO's guidance, and was provided to all sites to explain how oximeter had to be used to avoid accuracy issues.

The assessment of 'disease-free' status (secondary endpoint, see Table 1) was based on the normalisation of pre-existing symptoms, according to the WHO clinical progression scale (also see Section 9.8.2.1). The presence of clinical symptoms of COVID-19 was assessed with a set of structured questions. Other efficacy assessments included the modified Medical Research Council (mMRC) dyspnoea scale, the recording of all hospitalisations (along with the reasons for hospitalisation), and the self-assessed questionnaire of warning signs for disease progression.

Safety assessments

Safety was assessed through routine monitoring of adverse events (AEs, also collected via the questionnaire on warning signs for disease progression), physical examination, and vital signs. Pregnancies (present at screening or

occurring during the study) had to be reported by the investigator. Overdoses were also to be reported (regardless of association with an AE).

There were also a number of optional* safety assessments: laboratory safety tests, electrocardiograms (ECGs), chest X-ray, and CT-scan. Optional assessments were only to be performed at investigational centres which were equipped to do those tests and performing them as routine measures for outpatients with COVID-19.

*At screening, human immunodeficiency virus (HIV), tuberculosis and malaria testing were mandatory in Mozambique (HIV testing at screening was also mandatory in Burkina Faso and Guinea).

Table 4: Schedule of events in the Master Study

	Screening		Monitoring				
Time (and window, if allowed)	**Day 0**	**Day 1[1]**	**Days 2-6, 8-13 and 15-20[2]**	**Days 7 and 14**	**Day 21[3]**	**Day 35**	**Unscheduled**
Participant information and informed consent	X						
Demographic data	X						
Medical history	X						
Urine Pregnancy test[4]	X						
Review inclusion and non-inclusion criteria[5]	X	X					
Collection of COVID-19 symptoms	X			X	X		X
Physical examination[6]		X		X	X		X
Height, weight and body-mass index	X						
Vital signs[7]	X	X		X	X		X
SpO2	X	X		X	X		X
mMRC dyspnoea scale		X		X	X		X
WHO clinical progression scale		X		X	X		X
Hospitalisation for aggravation COVID-19				X	X		
Hospitalisation not due to aggravation of COVID-19				X	X		
ECG[8]	X			X	X		X
Blood sampling for laboratory tests[8]	X			X	X		X
Chest X-ray[8]	X			X	X		X
CT-scan[8]	X			X	X		X
Questionnaire on warning signs			X[9]				
Randomisation		X					

	Screening		Monitoring				
Time (and window, if allowed)	**Day 0**	**Day 1[1]**	**Days 2-6, 8-13 and 15-20[2]**	**Days 7 and 14**	**Day 21[3]**	**Day 35**	**Unscheduled**
Start of IP administration		X					
Check treatment compliance				X	X		X
Adverse event monitoring	X	X		X	X		X
Review concomitant treatments	X	X		X	X		X
Participant's status[10]					X		
SAE and/or pregnancy monitoring						X[11]	

ASAQ = artesunate-amodiaquine; COVID-19 = coronavirus disease 2019; CT = computed tomography; ECG = electrocardiogram; IP = investigational product; mMRC = modified Medical Research Council; SAE = serious adverse event; SpO2 = blood oxygen saturation level; WHO = World Health Organization.

1. Day 1 assessments and treatment could be performed at Day 0.
2. Visits via telephone interview and/or telephone application.
3. Day 21 was the end-of-study visit or in the event of early withdrawal from the study (had to be conducted as soon as possible after withdrawal).
4. Only for non-pregnant woman with childbearing potential.
5. Including result for COVID-19 screening test, which had to be performed within 24 hours prior to screening.
6. Physical examination had to include chest examination (auscultation).
7. Vital signs had to include respiratory rate, blood pressure, heart rate and temperature.
8. Optional; only performed at investigational centres which were equipped to do these tests and performing them as routine measures for patients with COVID-19.
9. The questionnaire (completed via telephone interview and/or telephone application) was also used to collect AEs from the participant.
10. Only in participants withdrawn before Day 21. It could be done on site or by telephone, and it was the only assessment performed on Day 21 in these participants.
11. Via telephone

9.1.8 Statistical Methods

Detailed statistical methods and data derivations were described and approved in the SAP. The present section is based on the final version of the SAP (version 3.0, dated 30 November 2023; Appendix 16.1.9), corresponding to Master Protocol version 13.0.

All statistical analyses except the primary analysis were conducted by a CRO, using SAS® version 9.4 or higher.

Unless otherwise stated, all statistical tests were two-sided and performed using a significance level of 0.05. The 95% confidence intervals (CI) were provided when relevant.

The primary analysis of the primary endpoint was conducted by a statistical consulting company specialised in adaptive designs, using the software R. The primary analysis and the adaptive design of the ANTICOV trial are described in a separate SAP, entitled 'Adaptive Design Report' and included in Appendix A of the SAP version 3.0 (Appendix 16.1.9).

9.1.8.1 General Considerations regarding Adaptive Study Design

Each active arm was compared to the control arm (paracetamol). As a platform study, the total number of IPs that were to be compared to control was unknown, so the study was designed to control for type I error/false positive rate on a "per active arm" basis, yielding the same strength of evidence as if a series of separate studies were conducted in which each active arm was compared to the control arm.

Statistical inference for the interim analyses of the primary endpoint was based on an integrated Bayesian model with non-informative prior information, to support comparisons between each active arm and the control arm.

The adaptive platform design of the trial included response-adaptive randomisation (RAR), giving the opportunity to increase the fraction of participants randomised to the better performing IP(s), both to increase the precision of the treatment estimates for those arms and to increase the likely benefit to the individual participants participating in the study.

An overview of RAR is provided in Section 7.1 of Master Protocol version 13.0 (Appendix 16.1.1), and details of calculations and thresholds for dropping arms are contained in the Adaptive Design Report (Appendix 16.1.9).

9.1.8.2 Sample Size

The maximum sample size of 700 per arm was determined by clinical trial simulation. The simulation was carried out for a study evaluating 4 arms, namely one control arm and three active treatment arms (to anticipate the addition of a treatment arm to the 3 starting arms, see Figure 1) with a sample size of 625 participants per arm for a total of 2500 participants. The rate of progression in the control arm (10%) was assumed to be lower than the one observed in other regions of the world (reported to be around 20%), mainly due to the younger population. Assuming a 10% rate of progression (instead of 20%) led to a larger sample size but was expected to better reflect the expected proportion of

participants that would worsen.

9.1.8.3 Types of Planned Analyses

The following statistical analyses were performed:

- ***DSMB interim analyses***

The objective of the interim analyses was to determine the effectiveness of each treatment group in order to decide to continue or discontinue the treatment, and to adjust, if necessary, the randomisation probabilities to each treatment arm (see Section 9.1.8.1). The DSMB was also involved in reviewing the safety data to determine the future use of each study treatment depending on its safety.

The master platform-based approach allowed the integration of data from all sites in the interim analyses, irrespective of their ability to have randomised participants in all treatment arms (see Section 9.1.6.3). All participants' data available at the cut-off date for the interim analysis were considered. This could include data from ongoing participants who had not reached Day 21, and therefore had not been fully monitored.

Reports were generated for DSMB review as described in the DSMB charter (dated 02 September 2020). The DSMB charter, relevant statistical reports for DSMB review, and corresponding DSMB recommendations are presented in Appendix 16.1.9.

The timing of the interim analyses, which changed after the interim analysis on the first 1200 randomised participants, is described in Section 9.8.2.2.

- ***Final analysis***

If an arm reached its maximum sample size, the final analysis for that arm was to occur at the first interim analysis, after the full follow-up on that arm was complete. Efficacy was to be declared if the posterior probability of superiority exceeded 98.5% (this value accounted for the multiple interim analyses in order to obtain overall 2.5% type I error).

The final analysis on all study data was performed using the SAP version 3.0. Guidance on data displays for the final analysis was provided in a separate document on mock tables, figures and listings (Appendix 16.1.9).

9.1.8.4 Study Analysis Sets

The following populations were used in the statistical analyses:

- Full analysis set (FAS) Population: all participants who were randomised (including those not dosed with an IP).
- Intent-to-treat (ITT) Population: all participants who were randomised according to randomised treatment assignment and who received at least one dose of IP.
- Modified ITT Population (used for the interim analyses of the primary endpoint): all ITT participants who completed the study with a known Day 21 outcome (progressed or not progressed), AND all ITT participants who terminated the study early but were known to have progressed prior to termination (also see Section 9.8.2.2).
- Safety Population (Safety): all participants who received at least one dose

of IP.

- Per protocol (PP) Population: all participants in the ITT Population who were free from major protocol violations that could lead to bias.

For the ITT, modified ITT, PP and FAS Populations, the participants were analysed according to the treatment to which they were randomised.

For the Safety Population, the participants were analysed according to the treatment actually received. If a participant was administered both an IP and control, the actual treatment was assigned as the IP treatment and the control treatment was recorded as concomitant medication regardless of randomisation assignment. If a participant was administered 2 IPs, this participant was analysed for both treatments.

9.1.8.5 Analysis of the Primary Endpoint

The primary endpoint was the occurrence of respiratory deterioration defined as SpO2 ≤93% within 21 days after randomisation, including death for any reason (Table 1).

Interim analyses of the primary endpoint

The interim analyses of the primary endpoint were conducted in the modified ITT Population (see Section 9.1.8.4).

The primary analysis was a test of superiority of an intervention vs the control arm (paracetamol). It was tested using a Bayesian logistic regression model that related the rate of respiratory deterioration to intervention arm effects.

The adaptive design pre-specified two statistical triggers within the trial which, if met, would result in public disclosure and declaration of a platform conclusion. The triggers were defined based on the posterior probability that an active arm was super-superior to paracetamol. The posterior probability of super-superiority was determined using a margin of logit(0.10) − logit(0.075) = 0.3151, which was the log-odds difference required for a decrease in respiratory deterioration rate from 10% to 7.5%.

The two statistical triggers were the following:

- Early Futility - posterior probability <0.10: the active failed to demonstrate evidence of clinically meaningful benefit.
- Early Success - posterior probability >0.98: the active arm demonstrated clinically meaningful benefit.

If an active arm met one of the two statistical triggers, enrolment in this active arm stopped at the interim analysis.

The model adjusted for the time period during which a participant was randomised and the baseline risk for progression (defined as high if any of the following risk criteria were met: age >60 years, BMI >30 kg/m^2, ongoing comorbidity of hypertension, coronary artery disease * type 1 diabetes mellitus, or type 2 diabetes mellitus).

Further details on the analysis of the primary endpoint (including power) are provided in the Adaptive Design Report in Appendix A of the SAP version 3.0 (Appendix 16.1.9).

Final (supporting) analysis of the primary endpoint

The primary endpoint was analysed using logistic regression modelling based on a binomial distribution and using the SAS procedure PROC GENMOD. The model included the dichotomous outcome variable (Failure Yes or No) as a function of the fixed categorical effect of treatment group.

The model provided odds ratios of each active treatment group compared with paracetamol (control) and the odds ratios' two-sided 95% CI. Separate models were used for events experienced up to Day 7, Day 14, and Day 21 and for each treatment group comparison.

Subgroup analyses of failure rate with 21 days were performed to investigate the influence of potential confounders. The subgroups are defined below:

- Age: 18-39 years, 40-59 years, and ≥ 60 years
- Sex: male subjects or female subjects
- BMI: ≤16 kg/m^2, 16< to ≤25 kg/m^2, 25< to <30 kg/m^2, ≥30.0 kg/m^2
- Timeframe between onset of symptoms and randomisation: ≤5 days or >5 days
- Use of concomitant medications, considering each of the following categories: fully-vaccinated participants (yes/no), participants who used (or did not used) antiviral medications, antimalarial medications, anti-inflammatory medications, or antidepressive medications
- Country
- Pre-existing, high-risk comorbidities: see the SAP for a full list (Appendix 16.1.9).

9.1.8.6 Analyses of the Secondary Efficacy Endpoints and Safety Data

All secondary efficacy analyses were performed on the ITT Population.

Safety data were descriptively summarised in the Safety Population.

Please refer to the SAP for further details (Appendix 16.1.9).

9.1.8.7 Handling of Missing Data

The efficacy analyses were based on observed cases. There were no imputations of missing data and no outliers excluded from analysis.

A "tipping point" analysis to determine the sensitivity of the primary result, if positive, was to be performed to various patterns of outcomes in participants who were lost to follow-up or with undetermined status at Day 21.

Imputation rules for missing or partial information on AEs are presented in the SAP. If the relationship information was missing, the AE was considered related. If the severity information was missing, the AE was considered as severe.

9.8 CHANGES IN THE STUDY CONDUCT OR PLANNED ANALYSES

9.8.1 Changes in the Conduct of the Study

9.8.1.1 Protocol Amendments

The following approved version of the Master Protocol were used for study initiation:

- Version 5.0 of the Master Protocol in 3 countries (DRC, Kenya*, and Ghana*)
- Version 7.0 of the Master Protocol in the other countries.

*In Kenya and Ghana, recruitment actually started under version 7.0.

After approval of version 7.0, a total of 3 amendments to the Master Protocol were implemented. All amendments were reviewed via the AVAREF emergency process, and approved by WHO-ERC as well as the relevant national Ethics Committees and Regulatory Authorities (see Section 9.1.4.3).

Note: Amendment 1 (in which the nitazoxanide/ciclesonide treatment arm was added) and Amendment 2 (in which the ivermectin/ASAQ treatment arm was added) were not implemented in Tanzania and Brazil; and Amendment 2 was not implemented in Burkina Faso and Guinea.

Also see Section 9.8.1.2 about the enrolment of Brazilian participants.

All amendments were substantial and their content is summarised in Table 5.

Table 5: Summary of amendments to the Master Protocol

Amdt number	Protocol version	Date	Purpose of the amendment
	5.0	09 Jul 2020	First version of the Master Protocol reviewed by all participating countries via AVAREF emergency process. Version used to initiate the study in 3 countries (DRC, Kenya, and Ghana)[1]
	6.0	29 Oct 2020	*The following changes were not formally documented in a Protocol Amendment:* • *Primary endpoint: addition of rationale and mention of study-specific work-instructions* • *Endpoints about hospitalisations: addition of rationale, clarification of hospitalisation due to aggravation of COVID-19, addition of secondary objective no 4 and corresponding endpoint (number of hospitalisations due to other reason than progression of COVID-19)* • *Addition of a rationale for the future selection of new IPs* • *DSMB: clarification of the selection of members, clarification of the conduct of interim analyses* • *Informed consent: clarification of procedures* • *Statistics: clarification of sample size calculation using Bayesian statistics, description of how type I error was addressed* • *Addition of a section on data blinding* • *Addition of a section on ANTICOV governance*
	7.0	16 Nov 2020	First version of the Master Protocol submitted and approved by WHO-ERC. Version used to initiate the study in the countries other than DRC, Kenya, and Ghana • *Clarification of the assessment of benefit-risk ratio to decide on the potential inclusion of pregnant women and children aged ≥12 years*
1	7.1	22 Dec 2020	Version of the protocol including Amendment 1 that was submitted and approved by WHO-ERC.[2] • Addition of nitazoxanide/ciclesonide as new treatment arm: description, rationale for selection, adaptation of inclusion/exclusion criteria, follow-up documents, and informed consent documents • Removal of HCQ sulphate and lopinavir-ritonavir treatment arms • COVID-19 positive patients confirmed by validated antigenic test as an alternative to the molecular biology test • Revision of the SAE definition • Adjustments to the statistical section
	8.0	09 Feb 2021	• Adaptation of inclusion/exclusion criteria following removal of HCQ sulphate and lopinavir-ritonavir treatment arms • Inclusion of pregnant women allowed following the removal of HCQ sulphate: procedures to follow pregnancies up confirmed, removal of pregnant women from the assessment of benefit-risk ratio to decide on potential inclusion

Amdt number	Protocol version	Date	Purpose of the amendment
			• Clarification that ECG was optional
	9.0	18 Feb 2021	Version of the protocol including Amendment 1 reviewed by all participating countries via AVAREF emergency process. • Addition of timing of definitive removal of HCQ sulphate and lopinavir-ritonavir treatment arms • Harmonisation of last protocol changes throughout the document
2	10.0	26 Mar 2021	Version of the protocol including Amendment 2 that was submitted and approved by WHO-ERC.[2] • Addition of ivermectin/ASAQ as new treatment arm: description, rationale for selection, adaptation of inclusion/exclusion criteria, follow-up documents, and informed consent documents • Exclusion criteria added for vaccinated patients against SARS CoV-2. • Clarification of procedures in case of early study withdrawal vs early discontinuation of IPs
	11.0	31 May 2021	Version of the protocol including Amendment 2 reviewed by all participating countries via AVAREF emergency process. • Exclusion criteria 30 (known renal impairment) clarified • Risk evaluation for pregnant women and/or breastfeeding women clarified • Nitazoxanide intake with food clarified
3	12.0	21 Sep 2021	• Addition of fluoxetine and inhaled budesonide as new treatment arm, including rationale for selection • Change to inclusion criterion 2 to include a higher proportion of participants at risk for progression of COVID-19, based on DSMB recommendations following the first interim analysis, which showed a rate of events (=failures) that was lower than anticipated in the protocol) • Adaptation of exclusion criteria following addition of fluoxetine-budesonide treatment arm • Addition of a section on scaling-up diagnostic testing to facilitate early identification of cases • Active screening put in place in some countries to facilitate recruitment • Addition of a phone call at Day 35 for SAE and/or pregnancy monitoring
	13.0	21 Oct 2021	Version of the protocol including Amendment 3 reviewed by all participating countries via AVAREF emergency process and approved by WHO-ERC. • Addition of the possibility to add new countries

Amdt = Amendment; ASAQ = artesunate-amodiaquine; AVAREF = African Vaccine Regulatory Forum; COVID-19 = coronavirus disease 2019; DRC = Democratic Republic of the Congo; DSMB = Data Safety Monitoring Board; ECG = electrocardiogram; HCQ = Hydroxychloroquine; IP = investigational product; SAE = serious adverse event; vs = versus; WHO-ERC = World Health Organization-Ethics Review Committee.

[1] In Kenya and Ghana, recruitment actually started under version 7.0.

[2] The version reviewed and approved included the key changes of the amendment. Further changes were implemented in subsequent protocol versions; however, these were minor points.

The versions of the Master Protocol under which study was initiated (5.0 and 7.0), the versions of the Master Protocol including the 3 amendments (9.0, 11.0, and 13.0), and the summaries of amendments are included in Appendix 16.1.1.

9.8.1.2 Other Changes to the Conduct of the Study

Apart from the changes formally documented in protocol amendments and other changes to the protocol which were implemented in-between amendments (see Table 5), here is a list of other changes that affected the conduct of the study:

- Participating countries where ANTICOV was initiated

It was initially planned to conduct the study in 13 African countries. It was jointly decided not to start any sites in Cameroon and Uganda because obtaining approvals was taking too long. The study was therefore conducted in a total of 11 African countries.

- Inclusion of patients from Brazil (Together trial)

The ANTICOV study was initiated in 11 African countries. As the wave of COVID-19 was slowing down in Africa, ANTICOV JSC was looking for opportunities to expand recruitment for the study. The Together Trial was an international trial that was similar to ANTICOV, aiming at identifying effective repurposed therapies to prevent the disease progression of COVID-19. To increase the ANTICOV study population (and considering the two trials had similar populations), it was agreed to add to the Together trial the last arm implemented in the ANTICOV study (fluoxetine/budesonide) and the control arm (paracetamol). Data from the paracetamol and any tested arm were to be exclusively part of the ANTICOV primary and secondary analyses. The first Brazilian participant was enrolled on 21 June 2022. The data collected included all data requested by the ANTICOV protocol, using the ANTICOV electronic case report form (CRF). The data from participants enrolled in the Together Trial in Brazil under these two arms were added to the database (see Section 11.2 for further information).

- Discontinuation of the ivermectin/ASAQ treatment arm

Based on the recent data on the absence of convincing evidence for an antiviral effect of the ASAQ combination, shared with the JSC by the sponsors of an exploratory trial [12], the JSC decided to stop this arm on 15 September 2022 (see minutes of the JSC meeting in Appendix 16.1.9).

9.8.2 Changes in the Planned Analyses

9.8.2.1 From the Protocol to the Statistical Analysis Plan

The following changes were implemented from the Master Protocol to the SAP version 1.0:

- Analysis sets

The FAS was added as a new set. The type of analysis in each set (according to treatment randomised or actually received) was clarified. The analysis of safety data in case of double administration (i.e. IP and control, or 2 IPs) was clarified (see Section 9.1.8.4).

- SpO2 worsening

Throughout the protocol, there were some inconsistencies in the wording of SpO2 worsening ("SpO2 <93%" in Section 1.2.1, "below the threshold of 94%" in Section 6.4.1.1, where it should have been SpO2 ≤93% throughout). The inconsistencies were fixed in the SAP, where worsening SpO2 was defined as SpO2 ≤93% throughout.

- Disease-free status

Disease-free status was defined as the normalisation of pre-existing symptoms by Day 21, SpO2 maintenance by Day 21 (≥94%), and no hospitalisation for COVID-19 at Day 21. The normalisation of pre-existing symptoms was defined as a score of 0 on the WHO clinical progression scale by Day 21. The mMRC dyspnoea scale and the normalisation of baseline clinical COVID-19 symptoms were not considered for defining disease-free status.

9.8.2.2 Between Versions of the Statistical Analysis Plan

The interim analyses were conducted using two different versions of the SAP (see below). The key changes between SAP versions are summarised in Table 6. The full list of changes in each SAP version is available in the revision history table at the beginning of the document (Appendix 16.1.9).

Clarification on the timing of DSMB interim analyses

DSMB interim analyses were conducted after the first 300 participants had been randomised and every 450 participants thereafter, until 1200 participants had been randomised. The interim analysis on the first 1200 randomised participants was the third interim analysis, which was performed in February 2022 using the SAP version 1.0, corresponding to Master Protocol version 11.0 (see Table 5). Full results of the third interim analysis are presented in the extract of the statistical report (dated 10 February 2022, see Appendix 16.1.9) and summarised in Section 11.4.1.1.1.

After the third interim analysis, the interim analysis plan changed. Interim analyses were to be conducted every 45 total events on the primary endpoint (event = failure, see Table 1), to address the low rate of events seen in the blinded review (see SAP version 2.0, in Appendix 16.1.9). It turned out that no more interim analyses were performed due to the lack of events.

The statistical analyses conducted after February 2022 (i.e. after the first 1200 randomised participants) were performed using SAP version 3.0 (final version), corresponding to Master Protocol version 13.0 (see Table 5). These analyses included an update of the third interim analysis (see results in Section 11.4.1.1.1) and the final analysis of the data (see results in Section 11.4.1.1.2).

Table 6: Summary of the key changes between versions of the statistical analysis plan

SAP version	Date	Key changes
1.0	01 Sep 2021	Initial version of the SAP used for the interim analyses of the first 1200 participants
2.0	08 Jun	• SAP updated per protocol version 13.0; Adaptive Design Report added

SAP version	Date	Key changes
	2023	to Appendix A of the SAP • SAP updated to match the Publication Analysis delivery (set of analyses performed to prepare publications on ANTICOV data) • SAP updated per comments from the coordinating sponsor and statistical consulting company: analysis of secondary efficacy endpoints updated to match the table shells (see document entitled 'Mock tables, figures, and listings', version 1.0, dated 08 June 2023) and the analyses performed in Publication delivery; language for the AE incidence rate as a secondary endpoint added; language pertaining to site effects in statistical modelling removed; age groups and BMI categories updated to match the risk factor categorisation; derived variables updated to include treatment compliance table for each treatment group
3.0	29 Nov 2023	Version of the SAP used for the update of the third interim analysis and for the final analysis • Secondary efficacy endpoints: time-to-event analysis, additional details specified • Derived variables (Table 2) modified • Treatment compliance (Table 3) modified • Language on DSMB analyses updated per protocol version 13.0 • Language modified from Screen Failure to Eligibility Failure • AE date imputation logic modified/added • Laboratory Evaluations: addition of shift tables according to normal and abnormal • Protocol deviation: addition of the fact that any other protocol deviations could be classified as major per the discretion of the coordinating sponsor and the CRO in charge of the statistical analyses • For all efficacy analyses which took into account the number of days from randomisation, it was added that Coverage Africa participants (i.e. participants enrolled in Burkina Faso and Guinea) were considered through 22 days after randomisation.

AE = adverse event; BMI = body mass index; CRO = Contract Research Organisation; DSMB = Data Safety Monitoring Board; SAP = statistical analysis plan.

The two versions of the SAP that were used to conduct interim analyses (versions 1.0 and 3.0) are included in Appendix 16.1.9.

Please note that the analysis set used for interim analyses (modified ITT, see Section 9.1.8.4) was defined in the Adaptive Design Report appended to the SAP. But the actual term "modified intent-to-treat population" is only used in the statistical reports provided for DSMB review (see in Appendix 16.1.9).

9.8.3 Changes Following Database Lock and Post-hoc Analyses

Database lock was performed on 30 November 2023. There were no changes to the statistical analyses following database lock.

10. STUDY PARTICIPANTS

The study was conducted by different sponsors at 26 sites (with screened participants) in 12 countries: 15 sites in 11 African countries (Burkina Faso, Democratic Republic of the Congo (DRC), Ethiopia, Ghana, Guinea, Ivory Coast, Kenya, Mali, Mozambique, Sudan, and Tanzania), and 11 sites in Brazil (see Section 9.8.1.2). All 15 African sites and 10 of the 11 Brazilian sites randomised participants.

10.1 DISPOSITION OF PARTICIPANTS

The first patient first visit was held on 21 September 2020 and the last patient last visit was held on 21 December 2022 (Table 7).

Table 7: Dates of enrollment by treatment arm

Treatment Arm	First Patient In (Consent)	First Patient In (Randomised)	Last Patient In (Consent)	Last Patient In (Randomised)	Last Patient Out
HCQ sulphate	23 Sep 2020	23 Sep 2020	02 Dec 2020	02 Dec 2020	24 Dec 2020
Lopinavir/ ritonavir	21 Sep 2020	21 Sep 2020	02 Dec 2020	02 Dec 2020	22 Dec 2020
Nitazoxanide/ ciclesonide	14 Apr 2021	14 Apr 2021	21 Feb 2022	21 Feb 2022	27 Mar 2022
Ivermectin/ ASAQ	28 Jul 2021	28 Jul 2021	07 Sep 2022	07 Sep 2022	11 Oct 2022
Fluoxetine/ budesonide	02 May 2022	02 May 2022	16 Nov 2022	16 Nov 2022	20 Dec 2022
Paracetamol	11 Nov 2020	11 Nov 2020	17 Nov 2022	17 Nov 2022	21 Dec 2022

ASAQ = artesunate-amodiaquine ; HCQ = hydroxychloroquine.

Participant disposition is presented in Figure 3. A total of 2328 participants were screened, of whom 1942 participants (83.4%) were randomised to one of the following treatment arms (Table 14.1.1.2):

- HCQ sulphate: n=83 (4.3%)
- Lopinavir/ritonavir: n=83 (4.3%)
- Nitazoxanide/ciclesonide: n=603 (31.1%)
- Ivermectin/ASAQ: n=190 (9.8%)
- Fluoxetine/budesonide: n=149 (7.7%)
- Paracetamol (reference treatment): n=834 (42.9%).

The first two active arms (HCQ sulphate and lopinavir/ritonavir) were discontinued as per Amendment 1, while the last three active arms (nitazoxanide/ciclesonide, ivermectin/ASAQ, fluoxetine/budesonide) were introduced as per Amendments 1, 2, and 3, respectively (see Section 9.1.6).

Of the 2328 screened participants, 402 (17.3%) were screen failures (Table 14.1.1.2). The main reason for screening failure was participant not

meeting the inclusion criteria/exclusion criteria (395 participants, 98.0% of all screen failures). Other screen failures were due to participant who withdrew consent (5 participants) and other reasons (2 participants with behavioural disorder with temporal and spacial disorientation leading to difficulty in complying with study schedule) (Listing 16.2.1.2).

The reasons for not meeting the inclusion/exclusion criteria are detailed in Listing 16.2.1.3.

A total of 386 participants were not randomised (Figure 3). Sixteen participants were randomised despite being non-eligible because their non-eligibility was confirmed after randomisation. These participants were enrolled in different countries, confirming the absence of site effect in the randomisation of non-eligible participants (Listing 16.2.1.4).

Of the 1942 randomised participants, 1893 (97.5%) received at least one dose of IP (Table 14.1.1.3.1; also see Section 11.1).

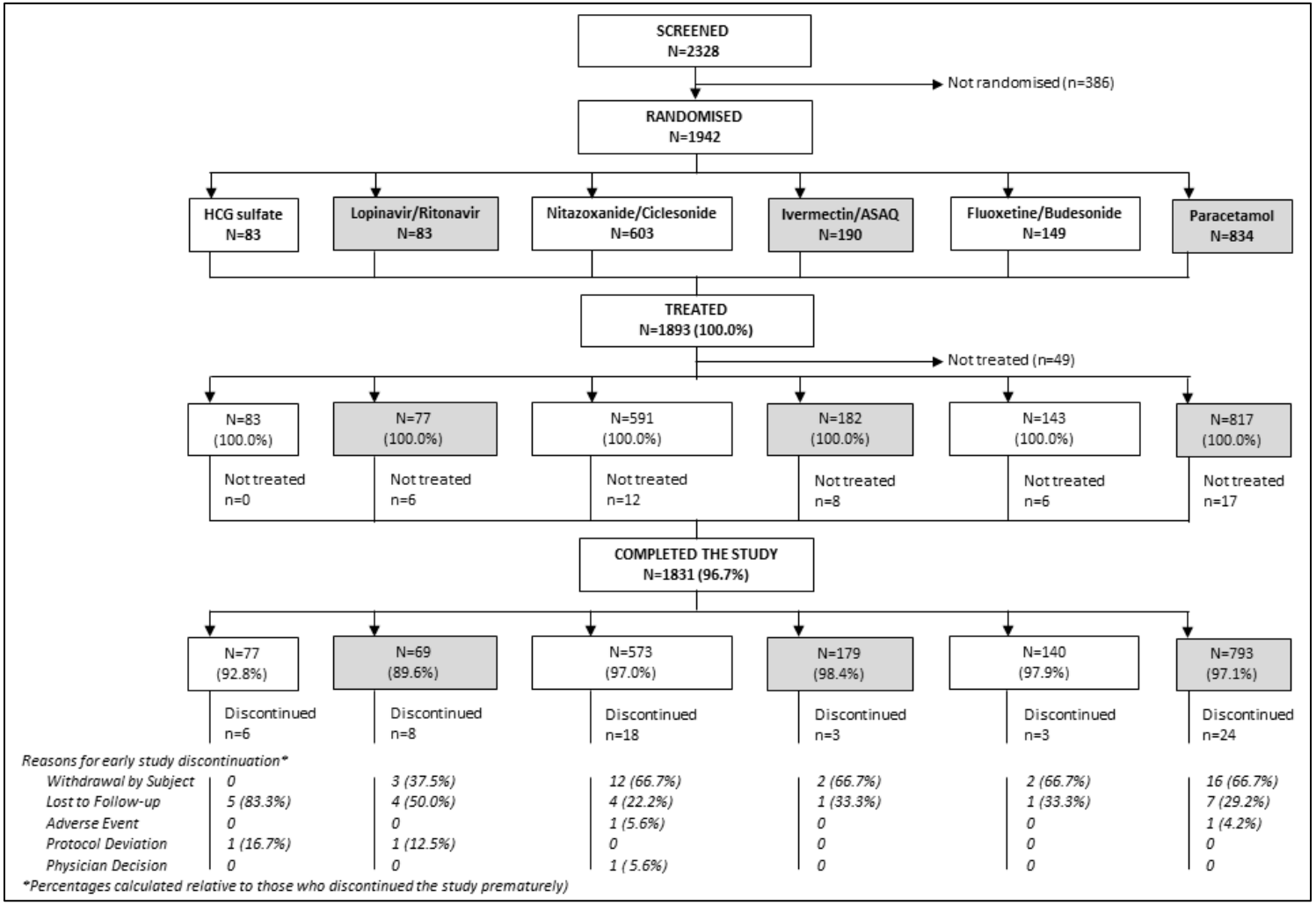
Of the 1893 exposed participants, 1831 (96.7%) completed the study (Figure 3). Study completers were either participants who reached the end of study (defined as reaching Day 21 for participants enrolled under protocol versions 5.0 to 12.0, or reaching Day 35 for participants enrolled under version 13.0, regardless of treatment administration and missed visits before end of study), or participants who died during the study (Table 14.1.1.3.2). The main reasons for not completing the study were consent withdrawal (n=35, 56.5% of all discontinuations) or being lost to follow-up (n=22, 35.5%) (Table 14.1.1.3.2). Study completion rate was lower in the lopinavir/ritonavir (89.6%) and the HCG sulphate (92.8%) treatment arms than in the other arms (≥97.0%, Figure 3).

Of the 1893 exposed participants, 1749 (92.4%) completed study treatment (Figure 4). The main reasons for not completing study treatment were consent withdrawal (n=79, 54.9% of all discontinuations) and occurrence of an AE (n=43, 29.9%) (Table 14.1.1.3.2). Treatment completion rate was lower in the lopinavir/ritonavir (77.9%) and the nitazoxanide/ciclesonide (85.3%) treatment arms than in the other arms (≥94.0%; Figure 4). AE as a cause of early discontinuation of treatment was more frequent in the nitazoxanide/ciclesonide (32 of 87 discontinuations in this arm, 36.8%) and the ivermectin/ASAQ (4 of 11 discontinuations, 36.4%) treatment arms than in the other arms (from 0 to 21.1%).

A total of 7 participants (0.4%) died (3 randomised to paracetamol, 2 randomised to nitazoxanide/ciclesonide, 1 randomised to lopinavir/ritonavir, and 1 randomised to ivermectin/ASAQ). Five of the 7 fatal serious AEs (SAEs) started during study treatment and led to treatment discontinuation. For more information on deaths, see Section 12.3.1.1.

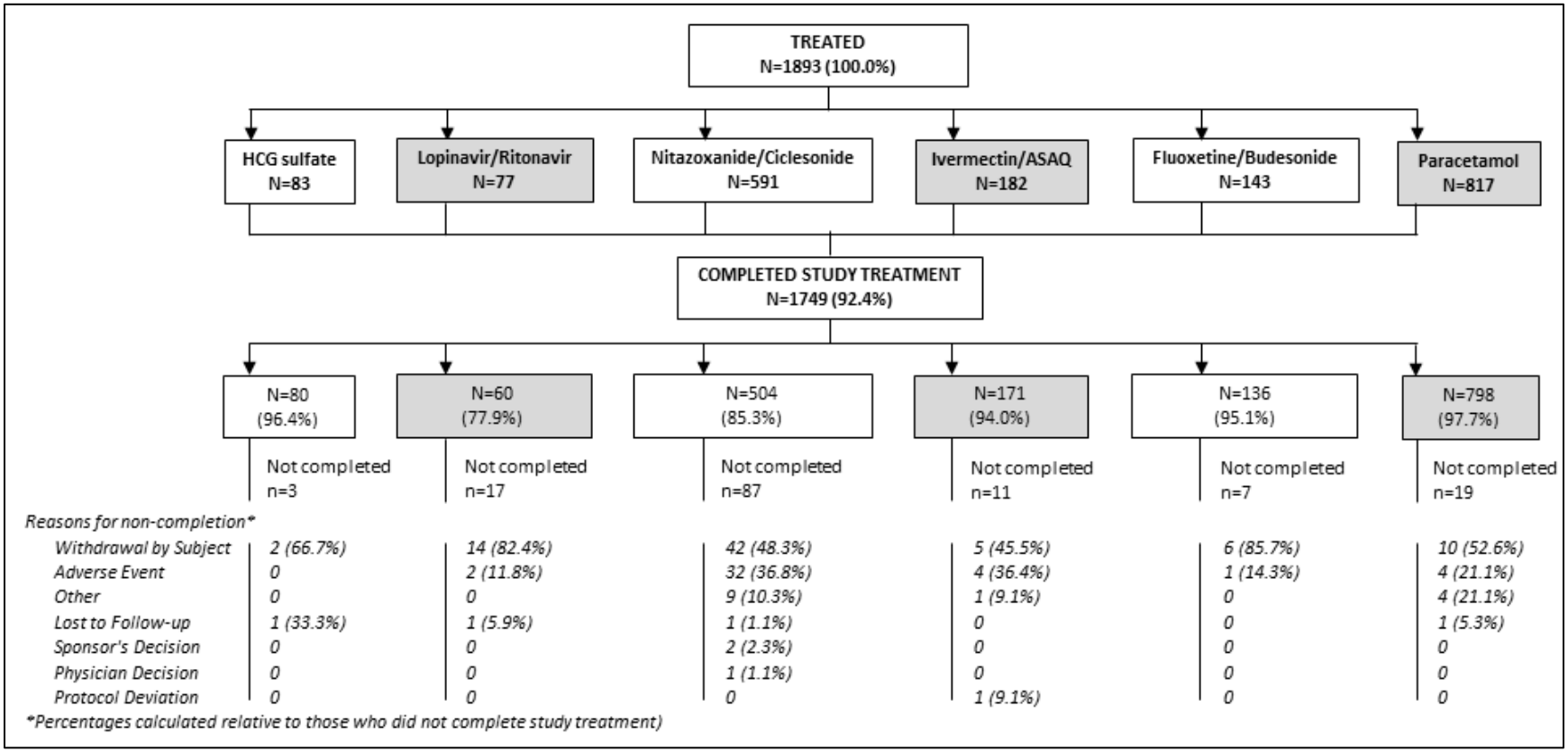
A by-participant listing of participant disposition, including completion of study, completion of study treatment and reasons for non-completion is provided in Listing 16.2.1.1.

Figure 3: Participant disposition and reasons for early study discontinuation (all screened participants)



ASAQ = artesunate-amodiaquine ; HCQ = hydroxychloroquine.
Sources: Tables 14.1.1.2, 14.1.1.3.1, and 14.1.1.3.2.

Figure 4: Treatment completion rate and reasons for not completing treatment (ITT Population)



ASAQ = artesunate-amodiaquine; HCQ = hydroxychloroquine; ITT = intent-to-treat.
Source: Table 14.1.1.3.2.

11. EFFICACY EVALUATION

11.1 DATA SETS ANALYSED

The data sets analysed are defined in Section 9.1.8.4. The number of participants in each analysis set is summarized, by treatment arm and overall, in Table 8. For details on the participants included in the modified ITT (interim analyses), please see Section 11.4.1.1.

Of the 1942 randomised participants, 1893 (97.5%) received at least one dose of IP and were included in the ITT. The main reason for not being dosed was participant's withdrawal (36 of 49 patients not dosed, Listing 16.2.1.5).

ITT and Safety Populations were identical because all participants received treatment as randomised (i.e. no misallocation).

Of the 1893 participants included in the ITT, 141 (7.4%) had at least one major protocol deviation and were therefore excluded from the PP Population (Table 14.1.1.4). The most frequent major protocol deviations were deviations regarding the use of IPs (3.5% of all participants included in the ITT; mainly due to non-compliance, i.e. <80% or >120%), deviations regarding the collection of informed consent (2.1%), and deviations regarding the participant's eligibility (1.9%). Among the deviations regarding the participant's eligibility, a total of 12 participants (0.6%) started to have the first COVID-19 symptoms more than 7 days prior to the date of informed consent (4 randomised to nitazoxanide/ciclesonide and 8 randomised to paracetamol, also see Section 11.2). There was one major GCP deviation in the study: Participant ET100093, who was randomised to paracetamol, was enrolled despite being a study staff.

The percentage of participants with a major deviation was higher in the HCQ sulphate (25.3%), lopinavir/ritonavir (22.1%), and ivermectin/ASAQ (19.2%) treatment arms than the other arms (from 0.7% to 5.6%), mainly due to deviations regarding the use/compliance of IPs.

A by-participant listing of all protocol deviations (major and minor) is provided in Listing 16.2.2.

Table 8: Data sets analysed by treatment arm and overall (FAS Population)

	HCQ sulphate (n=83)	Lopinavir/ Ritonavir (n=83)	Nitazoxanide/ Ciclesonide (n=603)	Ivermectin/ ASAQ (n=190)	Fluoxetine/ Budesonide (n=149)	Paracetamol *(control)* (n=834)	Total (n=1942)
FAS Population, n (%)	83 (100.0)	83 (100.0)	603 (100.0)	190 (100.0)	149 (100.0)	834 (100.0)	1942 (100.0)
ITT Population, n (%)	83 (100.0)	77 (92.8)	591 (98.0)	182 (95.8)	143 (96.0)	817 (98.0)	1893 (97.5)
Safety Population, n (%)	83 (100.0)	77 (92.8)	591 (98.0)	182 (95.8)	143 (96.0)	817 (98.0)	1893 (97.5)
PP Population, n (%)	62 (74.7)	60 (72.3)	558 (92.5)	147 (77.4)	142 (95.3)	783 (93.9)	1752 (90.2)

ASAQ = artesunate-amodiaquine; FAS = full analysis set; HCQ = hydroxychloroquine; ITT = intent-to-treat; PP = per protocol.
Source: Table 14.1.1.1.

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics

The study was conducted in 11 African countries and in Brazil.

Mean age of the population was 42.1 years (standard deviation [SD] 14.39), with the oldest participant being 89 years old (Table 9). No children were enrolled. Overall, there was a similar percentage of male (50.8%) and female (49.2%) participants, and almost all participants were black (94.0%), with a lower percentage in the fluoxetine/budesonide treatment arm due to the inclusion of participants from Brazil (see Section 9.8.1.2). Mean BMI was 26.3 kg/m^2 (SD 5.79). The countries that contributed the most to study population were DRC (22.7%), Burkina Faso (21.1%), Ethiopia (16.2%), Mali (11.1%) and Ghana (10.2%). Other countries enrolled fewer than 10% of the population.

There were no major differences in demographics between treatment arms. The percentage of male participants was higher in the HCQ sulphate (73.5%) and lopinavir/ritonavir (66.2%) treatment arms, and lower in the fluoxetine/budesonide treatment arm (39.9%), compared to the paracetamol treatment arm (48.8%).

When considering the risk factors for COVID-19 progression to severe disease (age >60 years, BMI >30 kg/m^2; see Section 9.1.8.5) and the potential differences between active treatment arms and control arm (paracetamol), the following features were observed:

- The percentage of participants over the age of 60 years (13.8% overall) was similar among all treatment arms
- Mean BMI was higher in the fluoxetine/budesonide treatment arm (28.7 kg/m^2) and lower in the ivermectin/ASAQ treatment arm (24.1 kg/m^2), compared to the paracetamol treatment arm (26.5 kg/m^2).

A by-participant listing of demographics and baseline characteristics is provided in Listing 16.2.4.1.

COVID-19 Disease Characteristics and Vital Signs

Vital signs at baseline were similar between treatment arms (Table 10). SpO2 ranged from 94% to 100% (except for 1 patient, see Table 10), with a mean value ≥97% in all treatment arms except the HCQ sulphate (96.8%) and ivermectin/ASAQ (96.6%) treatment arms.

Overall, randomisation occurred 3.9 days (SD 2.79), on average, after the onset of COVID-19 symptoms, with no major differences between treatment arms (Table 9). A total of 12 participants (0.6%) started to have the first COVID-19 symptoms more than 7 days prior to the date of informed consent, which was considered a major protocol deviation (see Section 11.1). The following COVID-19 symptoms were most commonly reported at baseline (Table 10):

- >50% of participants: cough (69.8%), headache (59.9%), fatigue/malaise (55.7%), runny nose (51.0%)
- >20%-50% of participants: muscle aches (46.3%), fever (42.3%), sore throat (35.1%), loss of taste (29.8%), loss of smell (28.6%)

- ~10% of participants: shortness of breath (11.8%) and vomiting/nausea (9.8%).

The other symptoms were reported in <6% of participants overall.

The participant's clinical status was assessed using the WHO clinical progression scale. At baseline, most participants (93.9%) had a score of 2, i.e. they were ambulatory, symptomatic but independent (disease was mild). A few participants had a worse clinical status, with 2.9% having a score of 3 (assistance needed, but disease still mild), and 2.1% having a score of 4 (hospitalisation without oxygen therapy; disease considered moderate). There were no major differences between the active treatment arms and the control arm regarding the distribution of participants across the WHO clinical progression scores (Table 10).

Regarding the participants' respiratory status (assessed using the mMRC dyspnoea scale), more than 95% of participants only got breathless during strenuous exercise (Grade 0; 72.5%) or moderate exercise (Grade 1; 23.0%). But the distribution of participants within these 2 categories varied between treatment arms. For example, the percentage of participants who only got breathless during strenuous exercise (Grade 0) ranged from 57.3% in the fluoxetine/budesonide treatment arm to 96.1% in the lopinavir/ritonavir treatment arm (vs 69.3% in the paracetamol control arm). Few participants (<5% overall) had worse dyspnoea symptoms at baseline (Grade 2 to 4); this percentage was also lower than 5% in each treatment arm except fluoxetine/budesonide (8.4%).

Optional safety assessments were performed in a small subset of participants at baseline (Table 14.1.2.2): 293 participants had an ECG, 37 participants had a chest X-ray, and 2 participants had a CT scan. All results were normal or abnormal but clinically unsignificant, except for 2 participants who had abnormal chest X-ray findings showing the presence of infiltrates (Listing 16.2.10.3): Participant ET110115, randomised to ivermectin/ASAQ, who had atypical pneumonia, pulmonary tuberculosis, visceral leishmaniasis, and HIV at baseline (Listing 16.2.4.2 and Listing 16.2.4.3) and Participant ET100073, randomised to paracetamol, who had pneumonia at baseline (Listing 16.2.4.2).

By-participant listings of COVID-19 symptoms, mMRC dyspnoea scale, and vital signs are provided in Listing 16.2.6.1, Listing 16.2.6.2, and Listing 16.2.9, respectively. By-participant listings of the optional safety assessments are provided in Listing 16.2.10.1 (ECG), Listing 16.2.10.2 (CT scan), and Listing 16.2.10.3 (chest X-ray).

Medical History and Concomitant Illness

There were no major differences between treatment arms regarding the medical history (Table 11), apart from a higher percentage of obese participants in the fluoxetine/budesonide treatment arm (15.4%) compared to the other arms (0 to 4.4%).

Ongoing comorbidities at baseline were reported in 26.3% of participants overall (Table 14.1.3.2). Hypertension, coronary artery disease, type 1 and type 2 diabetes mellitus were identified risk factors of COVID-19 progression to severe disease (see Section 9.1.8.5). Hypertension was the most common ongoing comorbidity, being reported in 17.6% of participants overall. Type 1 and type 2

diabetes mellitus were reported in 1.7% and 3.9% of participants, respectively, while coronary artery disease was very rare (0.1%).

Asthma was the most frequently reported respiratory disorder at baseline (5.0% of participants overall), while other respiratory disorders were very rare (≤0.2%).

There were no major differences between treatment arms regarding the prevalence of ongoing comorbidities.

By-participant listings of medical history and ongoing comorbidities are provided in Listing 16.2.4.2 and Listing 16.2.4.3, respectively.

Prior and Concomitant Therapies

At baseline, 18.1% of participants overall reported using prior medications, most frequently systemic anti-infectives (6.0%), agents acting on the cardiovascular system (5.8%), and agents acting on the alimentary tract and metabolism (5.5%) (Table 14.1.4).

Overall, 34.9% of participants used concomitant medications (Table 14.1.4). Concomitant medications for the respiratory system were used by 13.5% of participants, and included cough and cold preparations (8.2%), systemic antihistamines (4.6%), nasal preparations (2.7%), drugs for obstructive airway diseases (0.7%), and caffeine (0.1%).

Regarding the use of concomitant medications that were considered in the subgroup analysis of failures (see Section 9.1.8.5), none of the participants were fully vaccinated against COVID-19. Antimalarial medications were used by 14 participants (0.7%): 10 used artemether-lumefantrine and 4 used artesunate. Anti-inflammatory medications were used by 37 participants (2.0%), mainly for the management of COVID-19 symptoms. Antidepressive medications were used by 17 participants (0.9%) to treat depression, major depressive disorder, anxiety, or insomnia. Antiviral medications were used by 31 participants (1.6%). No difference in the frequency of use of these concomitant medications were seen between groups.

Concomitant procedures or surgeries are summarised in Table 14.1.5, with no relevant data to report, apart from a positive pregnancy test (see Section 12.5.3)

By-participant listings of prior and concomitant medications, as well as concomitant procedures or surgeries are provided in Listing 16.2.4.4 and Listing 16.2.4.5, respectively.

Table 9: Demographic characteristics at baseline by treatment arm and overall (ITT Population)

	HCQ sulphate (n=83)	Lopinavir/ Ritonavir (n=77)	Nitazoxanide/ Ciclesonide (n=591)	Ivermectin/ ASAQ (n=182)	Fluoxetine/ Budesonide (n=143)	Paracetamol *(control)* (n=817)	Total (n=1893)
Age (years)							
Mean (SD)	45.5 (12.67)	42.6 (10.94)	42.7 (14.77)	38.4 (15.66)	43.3 (13.32)	41.9 (14.31)	42.1 (14.39)
Median	46.0	41.0	42.0	36.0	43.0	40.0	41.0
Min, Max	20, 77	21, 65	18, 89	18, 84	18, 80	18, 83	18, 89
Age group, n (%)							
18-39 years	31 (37.3)	32 (41.6)	267 (45.2)	110 (60.4)	59 (41.3)	394 (48.2)	893 (47.2)
40-59 years	39 (47.0)	37 (48.1)	239 (40.4)	50 (27.5)	66 (46.2)	308 (37.7)	739 (39.0)
≥60 years	13 (15.7)	8 (10.4)	85 (14.4)	22 (12.1)	18 (12.6)	115 (14.1)	261 (13.8)
Sex, n (%)							
Male	61 (73.5)	51 (66.2)	296 (50.1)	98 (53.8)	57 (39.9)	399 (48.8)	962 (50.8)
Female	22 (26.5)	26 (33.8)	295 (49.9)	84 (46.2)	86 (60.1)	418 (51.2)	931 (49.2)
Race, n (%)							
White	0	0	9 (1.5)	0	2 (1.4)	8 (1.0)	19 (1.0)
Black	82 (98.8)	77 (100)	581 (98.3)	182 (100)	108 (75.5)	750 (91.8)	1780 (94.0)
Asian	0	0	1 (0.2)	0	0	0	1 (0.1)
Other	1 (1.2)	0	0	0	33 (23.1)	59 (7.2)	93 (4.9)
Country, n (%)[1]							
Brazil	0	0	0	0	35 (24.5)	64 (7.8)	99 (5.2)
Burkina Faso	0	0	160 (27.1)	0	40 (28.0)	199 (24.4)	399 (21.1)
Ivory Coast	0	0	13 (2.2)	10 (5.5)	0	18 (2.2)	41 (2.2)
DRC	83 (100)	77 (100)	87 (14.7)	41 (22.5)	18 (12.6)	123 (15.1)	429 (22.7)
Ethiopia	0	0	111 (18.8)	59 (32.4)	0	136 (16.6)	306 (16.2)
Ghana	0	0	55 (9.3)	26 (14.3)	23 (16.1)	89 (10.9)	193 (10.2)
Guinea	0	0	20 (3.4)	0	0	19 (2.3)	39 (2.1)
Kenya	0	0	6 (1.0)	0	0	11 (1.3)	17 (0.9)

	HCQ sulphate (n=83)	Lopinavir/ Ritonavir (n=77)	Nitazoxanide/ Ciclesonide (n=591)	Ivermectin/ ASAQ (n=182)	Fluoxetine/ Budesonide (n=143)	Paracetamol *(control)* (n=817)	Total (n=1893)
Country, n (%) cont'd							
Mali	0	0	81 (13.7)	31 (17.0)	16 (11.2)	82 (10.0)	210 (11.1)
Mozambique	0	0	55 (9.3)	10 (5.5)	0	62 (7.6)	127 (6.7)
Sudan	0	0	3 (0.5)	5 (2.7)	1 (0.7)	0	9 (0.5)
Tanzania	0	0	0	0	10 (7.0)	14 (1.7)	24 (1.3)
BMI (kg/m^2)							
n	78	72	575	182	142	801	1850
Mean (SD)	27.4 (5.31)	27.0 (4.96)	25.9 (5.65)	24.1 (5.27)	28.7 (5.68)	26.5 (5.94)	26.3 (5.79)
Median	26.85	26.30	25.10	22.85	28.70	25.80	25.60
Min, Max	17.8, 42.8	17.0, 44.1	16.2, 51.9	16.1, 47.3	15.3, 51.9	15.4, 50.0	15.3, 51.9
Time from onset of symptoms to randomisation (days)[2]							
n	83	77	589	182	143	814	1888
Mean (SD)	3.2 (1.81)	3.4 (1.61)	4.2 (2.09)	3.4 (1.60)	3.2 (1.30)	4.1 (3.62)	3.9 (2.79)
Median	3.0	3.0	4.0	3.0	3.0	4.0	4.0
Min, Max	0, 7	0, 7	0, 23	0, 7	0, 6	0, 82	0, 82

ASAQ = artesunate-amodiaquine; BMI = body mass index; COVID-19 = Coronavirus disease 2019; DRC = Democratic Republic of the Congo; HCQ = hydroxychloroquine; ITT = intent-to-treat; Max = maximum; Min = minimum; SD = standard deviation.
[1] DRC is the only country that started recruitment under Master Protocol version 5.0, which included the two initial treatment arms (HCQ sulphate and lopinavir/ritonavir); these two arms were dropped in Amendment 1. Amendment 1 (in which the nitazoxanide/ciclesonide treatment arm was added) and Amendment 2 (in which the ivermectin/ASAQ treatment arm was added) were not implemented in Tanzania and Brazil; and Amendment 2 was not implemented in Burkina Faso and Guinea. The paracetamol arm was not implemented in Sudan.
[2] The onset of symptoms is the earliest COVID-19 symptom's start date, relative to the date of randomisation. Please note that negative values are possible if the earliest reported symptom happened after the randomisation.
Source: Table 14.1.2.1.1.

Table 10: Vital signs and disease characteristics at baseline by treatment arm and overall (ITT Population)

	HCQ sulphate (n=83)	Lopinavir/ Ritonavir (n=77)	Nitazoxanide/ Ciclesonide (n=591)	Ivermectin/ ASAQ (n=182)	Fluoxetine/ Budesonide (n=143)	Paracetamol *(control)* (n=817)	Total (n=1893)
Heart rate (bpm)							
n	83	77	591	182	143	815	1891
Mean (SD)	82.6 (12.34)	82.7 (12.17)	82.5 (11.32)	86.2 (11.75)	84.7 (12.44)	84.1 (12.40)	83.7 (12.04)
Median	80.0	80.0	81.0	87.0	85.0	84.0	83.0
Min, Max	56, 112	57, 105	55, 114	60, 120	57, 117	53, 127	53, 127
DBP (mmHg)							
n	83	77	585	182	143	812	1882
Mean (SD)	83.0 (11.18)	80.2 (9.95)	79.4 (10.26)	76.7 (10.26)	81.5 (9.99)	80.2 (10.37)	79.9 (10.39)
Median	83.0	80.0	80.0	74.0	81.0	80.0	80.0
Min, Max	50, 100	60, 100	56, 119	60, 100	58, 107	50, 117	50, 119
SBP (mmHg)							
n	83	77	585	182	143	812	1882
Mean (SD)	136.6 (17.17)	126.4 (14.59)	122.8 (14.77)	120.4 (14.84)	124.2 (15.27)	123.5 (15.48)	123.7 (15.50)
Median	140.0	126.0	121.0	120.0	122.0	122.0	121.5
Min, Max	100, 160	93, 160	90, 176	96, 160	93, 159	90, 195	90, 195
SpO2 (%)[1]							
n	83	76	578	182	140	799	1858
Mean (SD)	96.8 (1.71)	97.0 (1.56)	97.3 (1.66)	96.6 (1.64)	97.9 (1.22)	97.3 (1.65)	97.2 (1.65)
Median	97.0	97.0	98.0	97.0	98.0	98.0	97.0
Min, Max[1]	94, 100	93, 100	94, 100	94, 100	94, 100	94, 100	93, 100
Temperature (°C)							
n	81	75	591	182	143	810	1882
Mean (SD)	36.75 (0.360)	36.77 (0.305)	36.89 (0.493)	36.89 (0.459)	36.92 (0.524)	36.93 (0.540)	36.90 (0.504)
Median	36.70	36.70	36.80	36.80	36.80	36.80	36.80
Min, Max	36.0, 38.3	36.2, 37.5	35.1, 39.3	36.0, 38.4	35.5, 38.8	34.6, 40.1	34.6, 40.1

	HCQ sulphate (n=83)	Lopinavir/ Ritonavir (n=77)	Nitazoxanide/ Ciclesonide (n=591)	Ivermectin/ ASAQ (n=182)	Fluoxetine/ Budesonide (n=143)	Paracetamol *(control)* (n=817)	Total (n=1893)
Respiratory rate (breaths/min)							
n	83	77	591	182	143	813	1889
Mean (SD)	19.2 (1.69)	19.2 (2.50)	18.7 (1.94)	18.9 (1.85)	18.4 (1.95)	18.7 (2.04)	18.8 (2.00)
Median	20.0	19.0	18.0	18.0	18.0	18.0	18.0
Min, Max	16, 28	16, 36	13, 26	15, 24	13, 25	12, 24	12, 36
COVID-19 symptoms, n (%)							
Cough[2]	45 (54.2)	40 (51.9)	406 (68.7)	137 (75.3)	109 (76.2)	585 (71.6)	1322 (69.8)
Headache	27 (32.5)	33 (42.9)	341 (57.7)	107 (58.8)	106 (74.1)	520 (63.6)	1134 (59.9)
Fatigue / Malaise[2]	30 (36.1)	31 (40.3)	337 (57.0)	86 (47.3)	92 (64.3)	478 (58.5)	1054 (55.7)
Runny Nose (Rhinorrhoea)	25 (30.1)	18 (23.4)	281 (47.5)	112 (61.5)	104 (72.7)	425 (52.0)	965 (51.0)
Muscle Aches (Myalgia)	21 (25.3)	18 (23.4)	263 (44.5)	102 (56.0)	78 (54.5)	394 (48.2)	876 (46.3)
Fever	20 (24.1)	27 (35.1)	235 (39.8)	90 (49.5)	72 (50.3)	356 (43.6)	800 (42.3)
Sore Throat	13 (15.7)	10 (13.0)	193 (32.7)	77 (42.3)	78 (54.5)	293 (35.9)	664 (35.1)
Loss of Taste (Ageusia)	15 (18.1)	17 (22.1)	188 (31.8)	58 (31.9)	33 (23.1)	254 (31.1)	565 (29.8)
Loss of Smell (Anosmia)	11 (13.3)	13 (16.9)	185 (31.3)	60 (33.0)	28 (19.6)	244 (29.9)	541 (28.6)
Shortness of Breath	4 (4.8)	4 (5.2)	68 (11.5)	24 (13.2)	23 (16.1)	101 (12.4)	224 (11.8)
Vomiting / Nausea[2]	3 (3.6)	3 (3.9)	67 (11.3)	7 (3.8)	23 (16.1)	82 (10.0)	185 (9.8)
Diarrhoea	4 (4.8)	6 (7.8)	21 (3.6)	4 (2.2)	17 (11.9)	60 (7.3)	112 (5.9)
Conjunctivitis	0	0	15 (2.5)	3 (1.6)	2 (1.4)	20 (2.4)	40 (2.1)
Skin Rash	0	1 (1.3)	2 (0.3)	1 (0.5)	1 (0.7)	6 (0.7)	11 (0.6)
WHO clinical progression scale, n (%)[3]							
Score 0	0	0	1 (0.2)	0	1 (0.7)	4 (0.5)	6 (0.3)
Score 1	0	0	2 (0.3)	2 (1.1)	0	3 (0.4)	7 (0.4)
Score 2	79 (95.2)	77 (100)	544 (92.0)	171 (94.0)	139 (97.2)	768 (94.0)	1778 (93.9)
Score 3	1 (1.2)	0	22 (3.7)	9 (4.9)	2 (1.4)	21 (2.6)	55 (2.9)
Score 4	0	0	20 (3.4)	0	0	19 (2.3)	39 (2.1)
Score ≥5	0	0	0	0	0	0	0

	HCQ sulphate (n=83)	Lopinavir/ Ritonavir (n=77)	Nitazoxanide/ Ciclesonide (n=591)	Ivermectin/ ASAQ (n=182)	Fluoxetine/ Budesonide (n=143)	Paracetamol *(control)* (n=817)	Total (n=1893)
mMRC dyspnoea scale, n (%)[4]							
Grade 0	79 (95.2)	74 (96.1)	451 (76.3)	120 (65.9)	82 (57.3)	566 (69.3)	1372 (72.5)
Grade 1	1 (1.2)	0	111 (18.8)	56 (30.8)	49 (34.3)	219 (26.8)	436 (23.0)
Grade 2	0	0	26 (4.4)	6 (3.3)	8 (5.6)	22 (2.7)	62 (3.3)
Grade 3	0	0	0	0	4 (2.8)	7 (0.9)	11 (0.6)
Grade 4[5]	0	0	0	0	0	1 (0.1)[5]	1 (0.1)

ASAQ = artesunate-amodiaquine; BMI = body mass index; bpm = beats per minute; COVID-19 = coronavirus disease 2019; CRF = case report form; DBP = diastolic blood pressure; HCQ = hydroxychloroquine; ITT = intent-to-treat; Max = maximum; Min = minimum; mMRC = modified Medical Research Council; SBP = systolic blood pressure; SD = standard deviation; SpO2 = blood oxygen saturation level; WHO = World Health Organization.

[1] At screening, Participant CD110007 had two successive measurements of SpO2: the first value was 97% and the second value was 93%. The third measurement was not performed.

[2] These symptoms were collected slightly differently in the Coverage Africa CRF (the CRF used in Burkina Faso and Guinea). Data of all redundant symptoms were merged into one single category to provide the incidence of the symptom in the overall population (e.g. the Coverage Africa CRF collected “fatty cough” and “dry cough” whereas the ANTICOV CRF collected “cough; all 3 categories were merged under the label “cough” and the incidence of cough was calculated for the overall population.

[3] The scale from 0 to 10 defines 5 states: Uninfected (Score 0), Ambulatory -mild disease (Scores 1-3), Hospitalised – moderate disease (Scores 4-5), Hospitalised – severe disease (Scores 6-9), and Dead (Score 10), with various grades within each participant’s state.

[4] The scale from 0 to 4 defines the following dyspnoea symptoms: “I only get breathless on strenuous exercise” (Grade 0); “I get short of breath when hurrying on level ground or walking up a slight hill” (Grade 1); “On level ground, I walk slower than other people the same age because of breathlessness or I have to stop for breath when walking at my own pace” (Grade 2); “I stop for breath after walking 100 m or after a few minutes on level ground” (Grade 3); “I am too breathless to leave the house or I am breathless when dressing” (Grade 4).

[5] Participant BR170041’s dyspnoea score went from 4 at baseline to zero at Day 7, 14, and 21. The female participant, who was 20 years old, had a history of severe obesity (her BMI was 39.9 kg/m^2 at baseline).

Source: Table 14.1.2.2, Listing 16.2.4.1, Listing 16.2.6.2, Listing 16.2.9.

Table 11: Medical history reported in ≥0.5% of participants by SOCs and PTs (Safety Population)

SOC PT	HCQ sulphate (n=83)	Lopinavir/ Ritonavir (n=77)	Nitazoxanide/ Ciclesonide (n=591)	Ivermectin/ ASAQ (n=182)	Fluoxetine/ Budesonide (n=143)	Paracetamol *(control)* (n=817)	Total (n=1893)
Any medical history	**5 (6.0)**	**8 (10.4)**	**111 (18.8)**	**36 (19.8)**	**55 (38.5)**	**192 (23.5)**	**407 (21.5)**
Social circumstances	**5 (6.0)**	**6 (7.8)**	**41 (6.9)**	**13 (7.1)**	**16 (11.2)**	**47 (5.8)**	**128 (6.8)**
Menopause	5 (6.0)	6 (7.8)	38 (6.4)	12 (6.6)	15 (10.5)	46 (5.6)	122 (6.4)
Infections and infestations	**0**	**0**	**28 (4.7)**	**16 (8.8)**	**3 (2.1)**	**45 (5.5)**	**92 (4.9)**
HIV infection	0	0	11 (1.9)	4 (2.2)	0	11 (1.3)	26 (1.4)
Pneumonia	0	0	2 (0.3)	5 (2.7)	0	9 (1.1)	16 (0.8)
Malaria	0	0	4 (0.7)	0	0	6 (0.7)	10 (0.5)
Metabolism and nutrition disorders	**0**	**0**	**3 (0.5)**	**1 (0.5)**	**26 (18.2)**	**62 (7.6)**	**92 (4.9)**
Obesity	0	0	1 (0.2)	0	22 (15.4)	36 (4.4)	59 (3.1)
Overweight	0	0	0	0	3 (2.1)	21 (2.6)	24 (1.3)
Gastrointestinal disorders	**0**	**1 (1.3)**	**11 (1.9)**	**2 (1.1)**	**1 (0.7)**	**18 (2.2)**	**33 (1.7)**
Gastritis	0	0	3 (0.5)	1 (0.5)	0	8 (1.0)	12 (0.6)
Peptic ulcer	0	0	3 (0.5)	0	1 (0.7)	8 (1.0)	12 (0.6)
Surgical and medical procedures	**0**	**1 (1.3)**	**7 (1.2)**	**0**	**6 (4.2)**	**18 (2.2)**	**32 (1.7)**
Caesarean section	0	0	5 (0.8)	0	1 (0.7)	6 (0.7)	12 (0.6)
Pregnancy, puerperium and perinatal conditions	**0**	**0**	**4 (0.7)**	**0**	**3 (2.1)**	**6 (0.7)**	**13 (0.7)**
Pregnancy	0	0	4 (0.7)	0	2 (1.4)	3 (0.4)	9 (0.5)

ASAQ = artesunate-amodiaquine; HCQ = hydroxychloroquine; HIV = human immunodeficiency virus; PT = preferred term; SOC = system organ class.
Source: Table 14.1.3.1.

11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

Treatment compliance is summarised by treatment arm in Table 14.1.6. The calculation of compliance, which was specific to each treatment arm, is provided in the SAP (Appendix 16.1.9).

The percentage of participants with satisfactory compliance (i.e. 80-120%) was heterogeneous between treatment arms, as described below:

- Paracetamol: 90.0%
- Fluoxetine/budesonide: 87.4%
- Ivermectin/ASAQ: 76.9%
- Nitazoxanide/ciclesonide: 73.6%
- HCQ sulphate: 61.4%
- Lopinavir/ritonavir: 53.2%.

Low compliance (<80%) was observed in almost half the participants in the lopinavir/ritonavir treatment arm (46.8%), whereas this percentage was lower than 30% in the other active treatment arms: nitazoxanide/ciclesonide (26.2%), HCQ sulphate (22.9%), ivermectin/ASAQ (22.5%), and fluoxetine/budesonide (11.9%). In the control group (paracetamol), low compliance was observed in 10.0% of the participants.

A total of 43 protocol deviations of overdosing were observed during the study: 28 in the HCQ sulphate treatment arm (including 17 considered major), 8 in the ivermectin/ASAQ treatment arm (7 major), 5 in the nitazoxanide/ciclesonide treatment arm (all minor), and 2 in the lopinavir/ritonavir treatment arm (all minor, see Listing 16.2.2).

Treatment duration and exposure are presented in Section 12.1. A by-participant listing of treatment duration, exposure, and compliance is provided in Listing 16.2.5.

11.4 EFFICACY RESULTS AND TABULATIONS OF PARTICIPANT DATA

11.4.1 Analysis of Efficacy

11.4.1.1 Primary Endpoint – Failure Rate within 21 days

The primary endpoint was the occurrence of respiratory deterioration, defined as SpO2 ≤93% within 21 days after randomisation, including death for any reason.

Respiratory deterioration and death within 21 days were considered as failures.

11.4.1.1.1 Interim Analyses of the Primary Endpoint

The primary analysis model was a Bayesian logistic regression model for the binary primary endpoint. The model adjusted for time period during which a participant had been randomised and the baseline risk (see Section 9.1.8.5).

The primary analysis was conducted in the modified ITT Population (see Section 9.1.8.4) during the third interim analysis scheduled after 1200 participants had been randomised (see Section 9.8.2.2).

This third interim analysis demonstrated early futility of the nitazoxanide/ciclesonide treatment arm, which was immediately discontinued,

in accordance with the pre-specified statistical design (see recommendations from the DSMB, dated 18 February 2022, in Appendix 16.1.9). The statistical comparison of failure rate within 21 days vs the control arm (paracetamol) could not be performed for the other treatment active arms as the required sample size was not reached and the number of events (i.e. failures) was insufficient.

The analysis conducted at the third interim analysis was the primary analysis for the nitazoxanide/ciclesonide treatment arm. Full results are presented in the extract of the statistical report of the third interim analysis (dated 10 February 2022, see Appendix 16.1.9).

Data availability and model-estimated odds ratio of the primary analysis are presented in Table 12. Deterioration rate was 3.25% in the nitazoxanide/ciclesonide active treatment arm (15 of 462 participants analysed) vs 1.13% in the paracetamol control arm (5 of 443 participants analysed). The median of the model-estimated odds ratio was 2.58 (95% credible interval 1.05 – 7.05). The model was structured such that an odds ratio less than one implied benefit.

In the primary analysis, the posterior probability of super-superiority for nitazoxanide/ciclesonide was 0.0026 (which was <0.10, therefore triggering early futility see Section 9.1.8.5).

Table 12: Primary analysis (third interim analysis) - Summary of respiratory deterioration and treatment effect of nitazoxanide/ciclesonide compared to paracetamol (Modified ITT Population)

	Descriptive summary of respiratory deterioration		Treatment effect of nitazoxanide/ciclesonide compared to paracetamol
	Paracetamol	Nitazoxanide/ Ciclesonide	Model-estimated Odds ratio[1]
N assigned	545	579	Median = 2.58
N ongoing[2]	65	83	
N terminated[3] **and excluded**	36	33	95% credible interval 1.05 – 7.05
N in the analysis set (n)	443	462	
N of deteriorations (y)	5	15	Mean = 2.95
Deterioration rate (y/n)	0.0113	0.0325	SD = 1.60

DSMB = Data Safety Monitoring Committee; ITT = intent-to-treat; N = number; SD = standard deviation.

[1] The table presents posterior means, SDs, medians, and 95% Bayesian credible intervals for the odds ratios of the third interim analysis.

[2] At the time of the primary analysis (interim analysis), a number of participants were still in their follow-up period.

[3] The status “terminated” refers to participants who were lost to follow-up or who had discontinued before the end of the 21-day follow-up period.

Source: Extract of the statistical report on the third interim analysis (delivered to DSMB on 10 February 2022), see Appendix 16.1.9.

At the time of the primary analysis, a number of participants were still in their follow-up period. A supporting analysis was conducted using the full follow-up data of all participants randomised on or before the date of discontinuation of the nitazoxanide/ciclesonide treatment arm (see Table 13) and did not change the observed futility: the posterior probability of super-superiority for

nitazoxanide/ciclesonide was 0.0065 (<0.10).

The effects of covariates (time period during which a participant had been randomised and the baseline risk baseline risk) are presented in the Nitazoxanide/Ciclesonide Publication Report (dated 23 September 2022, see Appendix 16.1.9).

Table 13: Supporting analysis (third interim analysis updated with full follow-up data for all participants) - Summary of respiratory deterioration and treatment effect of nitazoxanide/ciclesonide compared to paracetamol (Modified ITT Population)

	Descriptive summary of respiratory deterioration		Treatment effect of nitazoxanide/ciclesonide compared to paracetamol
	Paracetamol	Nitazoxanide/ Ciclesonide	Model-estimated Odds ratio[1]
N assigned	557	591	Median = 2.07
N ongoing[2]	0	0	
N terminated[3] and excluded	27	24	95% credible interval 0.91 – 5.04
N in the analysis set (n)	529	567	
N of deteriorations (y)	7	16	Mean = 2.30
Deterioration rate (y/n)	0.0132	0.0282	SD = 1.09

ITT = intent-to-treat; N = number; SD = standard deviation.
[1] The table presents posterior means, SDs, medians, and 95% Bayesian credible intervals for the odds ratios of the third interim analysis.
[2] The supporting analysis used the full follow-up data of all participants randomised on or before the date of discontinuation of the nitazoxanide/ciclesonide treatment arm. Therefore, none of the participants were ongoing in their follow-up period.
[3] The status “terminated” refers to participants who were lost to follow-up or who had discontinued before the end of the 21-day follow-up period.
Source: Nitazoxanide/Ciclesonide Publication Report (23 September 2022), see Appendix 16.1.9.

11.4.1.1.2 Final (Supporting) Analysis of the Primary Endpoint

The final analysis of the primary endpoint was conducted in ITT Population (see Section 9.1.8.4). Full results are presented in Section 14.2. The number (%) of failures within 21 days in each treatment arm was the following (Table 14.2.2.1):

- HCQ sulphate: no failure
- Lopinavir/ritonavir: 1 failure (1.3%)
- Nitazoxanide/ciclesonide: 16 failures (2.7%)
- Ivermectin/ASAQ: no failure
- Fluoxetine/budesonide: no failure
- Paracetamol: 9 failures (1.1%).

Results of the final analysis comparing the failure rate between the nitazoxanide/ciclesonide treatment arm and the paracetamol control arm are provided in Table 14.2.2.1 and Figure 14.2.2.

Statistical results regarding the subgroup analyses of failure rate with 21 days are presented in the following outputs: age (Table 14.2.2.2), sex (Table 14.2.2.3), BMI (Table 14.2.2.4), timeframe between onset of symptoms and randomisation

(Table 14.2.2.5), use of concomitant medications (Table 14.2.2.6), country (Table 14.2.2.7), and pre-existing, high-risk comorbidities (Table 14.2.2.8). The results of the subgroup analyses are also presented graphically in the forest plots of the odds ratio for failure rate within 21 days (Figure 14.2.2).

The participants who withdrew before Day 21 were contacted at Day 21 to determine their status, either on site or by phone (Table 4). The participants with known status at Day 21, who were considered as study completers, are listed in Listing 16.2.6.5.

11.4.1.2 Other Efficacy Endpoints

Locations of the statistical results regarding the other efficacy endpoints (listed in Table 1) are provided below.

- Number of hospitalisations

The number of hospitalisations due to severe progression of COVID-19 is summarised in Table 14.2.2.9, while the number of hospitalisations due to other reason than progression of COVID-19 is summarised in Table 14.2.2.10.

Comparisons between each active treatment arm and paracetamol is provided in Table 14.2.2.13 (number of hospitalisations) and Table 14.2.2.11 (time to hospitalisation). A by-participant listing of all hospitalisations is provided in Listing 16.2.6.4.

Hospitalisations due to COVID-19 were defined as hospitalisations due to the worsening of COVID-19 symptoms, which are listed by participant in Listing 16.2.6.1.

- Disease-free status

Disease-free status was defined as the normalisation of pre-existing symptoms by Day 21 (based on a score of 0 on the WHO clinical progression scale), SpO2 maintenance by Day 21 (≥94%), and no hospitalisation for COVID-19 at Day 21 (see Section 9.8.2.1). Comparisons between each active treatment arm and paracetamol regarding disease-free status is provided in Table 14.2.2.13.

WHO clinical progression scales scores are summarised by visit in Table 14.2.2.16 (the normalisation of pre-existing symptoms was defined as a WHO clinical progression scale score of 0 by Day 21), and listed by participant in Listing 16.2.6.6.

- Occurrence of death up to Day 21

Comparisons between each active treatment arm and paracetamol regarding the occurrence of deaths up to Day 21 is provided in Table 14.2.2.13. All deaths (including those occurring after Day 21) are listed in Listing 16.2.7.5.

- Time to worsening of SpO2 ≤93% (or death) within 21 days

Comparisons between each active treatment arm and paracetamol regarding the time to worsening of SpO2 ≤93% (or death) within 21 days is provided in Table 14.2.2.12.

- Occurrence of SpO2 ≤93%, death, or hospitalisation due to COVID-19

Comparisons between each active treatment arm and paracetamol regarding the occurrence of SpO2 ≤93%, death, or hospitalisation due to COVID-19 are

provided in Table 14.2.2.14.

- Mean number of incidence rate of certain AE categories

Comparisons between each active treatment arm and paracetamol regarding the mean number and incidence rate of SAEs, severe AEs, and AEs leading to permanent or temporary discontinuation of study treatment are reported in Table 14.2.2.15. Corresponding by-participant listings are provided in Listings 16.2.7.2 (all SAEs), 16.2.7.1 (all AEs, including severe AEs), and 16.2.7.4 (all AEs leading to treatment discontinuation or temporary suspension).

These categories of AEs are also descriptively summarised in Sections 12.3.1.2 (all SAEs), 12.2.3.2 (severe AEs), and 12.3.1.3 (all AEs leading to treatment discontinuation or temporary suspension).

11.4.2 Statistical/Analytical Issues

11.4.2.1 Adjustments for Covariates

The primary analysis of the primary endpoint adjusted for two baseline covariates: time (depending on when the participant was randomised relative to the data locks of interim analyses) and the risk for progression (defined as high or low depending on risk criteria such as age >60 years or BMI >30 kg/m^2; for the full list of risk criteria, see the SAP in Appendix 16.1.9).

11.4.2.2 Handling of Dropouts or Missing Data

The handling of missing data is summarised in Section 9.1.8.7. A “tipping point” analysis to determine the sensitivity of the primary result, if positive, was planned to be performed to various patterns of outcomes in participants who were lost to follow-up or with undetermined status at Day 21 (see SAP in Appendix 16.1.9). Since the primary result was not positive, the tipping point analysis was not performed. All analyses were based on observed cases.

11.4.2.3 Interim Analyses and Data Monitoring

An independent DSMB reviewed efficacy and safety data (see Section 9.1.4.2) for the interim analyses conducted at prespecified time points (see Section 9.8.2.2). Results of the third interim analysis demonstrating the futility of the nitazoxanide/ciclesonide treatment arm are summarised in Section 11.4.1.1.1.

11.4.2.4 Multicentre Studies

An adjustment for potential site effect on the proportion of participants with progression to severe disease at 21 days was initially planned (see SAP version 1.0 in Appendix 16.1.9), as some sites did not have the capability to randomise across all available treatment arms. This adjustment was removed in the next version of the SAP (version 2.0, see Appendix 16.1.9).

11.4.2.5 Multiple Comparison/Multiplicity

The primary analysis threshold for success of 0.985 accounted for the multiple interim analyses performed on each arm (see Adaptive Design Report appended to the SAP, Appendix 16.1.9). The secondary analyses did not account for any multiplicity adjustments.

11.4.2.6 Use of an "Efficacy Subset" of Participants

The primary analysis of the primary endpoint (interim analyses) was conducted in the modified ITT Population (see Section 9.1.8.4). To be included, participants from the ITT Population had to have a known Day 21 outcome (progressed or not progressed), or -for those who had terminated the study early- had to have progressed prior to termination. The tipping point analysis considering various patterns of outcomes in participants who were lost to follow-up or with undetermined status at Day 21 was not performed (see Section 11.4.2.2).

The final analysis of the primary endpoint and the analyses of the secondary endpoints were conducted in the ITT Population. No other populations were used for efficacy analyses.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

Not applicable. This study was not intended to show equivalence.

11.4.2.8 Examination of Subgroups

The subgroup analyses conducted on failure rate within 21 days to investigate the influence of potential confounders are presented in Section 11.4.1.1.

11.4.3 Tabulation of Individual Response Data

Individual participant data for the efficacy analyses are presented in the following listings: Listing 16.2.6.1 (COVID-19 symptoms), Listing 16.2.6.2 (mMRC dyspnoea scale), Listing 16.2.6.3 (warning signs of COVID-19 progression), Listing 16.2.6.4 (all hospitalisations), Listing 16.2.6.5 (participants who withdrew before the primary time point, i.e. Day 21), and Listing 16.2.6.6 (WHO clinical progression scales scores).

11.4.4 Drug Dose, Drug Concentration, and Relationships to Response

Drug dose, drug concentration, and relationships to response were not assessed in this study.

11.4.5 Drug-Drug and Drug-Disease Interactions

Drug-drug and drug-disease interactions were not assessed in this study.

11.4.6 By-Participant Displays

By-participant displays are not presented for this study. Individual participant data for efficacy endpoints are presented in Appendix 16.2.6.

11.4.7 Efficacy Conclusions

The primary endpoint, e.g. the occurrence of respiratory deterioration (SpO2 ≤93% within 21 days, including death for any reason), was analysed in successive planned interim analyses using Bayesian statistics.

The third interim analysis demonstrated early futility of the nitazoxanide/ciclesonide treatment arm, vs paracetamol. This treatment arm was immediately discontinued, as per protocol.

The statistical comparison of failure rate within 21 days vs the concurrently

randomised control arm (paracetamol) could not be performed for the other active arms as the required sample size was not reached and the number of events (i.e. failures) was insufficient.

In the primary analysis, deterioration rate was 3.25% in the nitazoxanide/ciclesonide arm (15 of 462 participants analysed) vs 1.13% in the paracetamol control arm (5 of 443 participants analysed). The median of the model-estimated odds ratio was 2.58 (95% credible interval 1.05 – 7.05). The model of this primary analysis was structured such that an odds ratio less than one implied benefit.

The posterior probability of super-superiority for nitazoxanide/ciclesonide (vs paracetamol) was 0.0026, which was lower than the statistical trigger for early futility (<0.10).

This result was confirmed by the supporting analysis conducted with all follow-up data for all participants in the paracetamol and nitazoxanide/ciclesonide arms, (posterior probability of super-superiority for nitazoxanide/ciclesonide was 0.0065).

Overall, based on the final analysis of all available data, the deterioration rate within 21 days was 2.7% in the nitazoxanide/ciclesonide arm and 1.1% in the paracetamol arm.

12. SAFETY EVALUATION

All safety analyses were conducted in the Safety Population.

In this section, the timing of AEs (and more generally, the timing of any safety assessment) is given relative to the first dose of study treatment, which is defined as “Day 1” in the text. According to the schedule of assessment (see Table 4), the first dose of study treatment could actually be administered on D0 Visit or D1 Visit. In the statistical outputs (provided in Section 14 for tables and figures, and Section 16.2 for listings), the timing is provided in two forms: [a] relative to the date of randomisation, and [b] relative to treatment start date. For the purpose of safety analyses, the time since the first dose was considered the most relevant.

12.1 EXTENT OF EXPOSURE

Treatment duration and exposure (number of doses received) are presented by treatment arm in Table 14. Overall, the median treatment duration in each arm was consistent with the planned duration as per protocol (see Table 2 and Table 3): 7 days for HCQ sulphate treatment, 14 days for lopinavir/ritonavir treatment, 14 days for nitazoxanide/ciclesonide treatment, 5 days for ivermectin/ ASAQ treatment, 8 days for fluoxetine/budesonide treatment (instead of 7 days as per protocol), and 10 days for paracetamol treatment (up to 14 days as per protocol).

Treatment compliance is presented in Section 11.3.

A by-participant listing of treatment duration, exposure, and compliance is provided in Listing 16.2.5.

Table 14: Treatment duration and exposure, by treatment arm (Safety Population)

	HCQ sulphate (n=83)	Lopinavir/ Ritonavir (n=77)	Nitazoxanide/ Ciclesonide (n=591)	Ivermectin/ ASAQ (n=182)	Fluoxetine/ Budesonide (n=143)	Paracetamol *(control)* (n=817)	Total (n=1893)
Treatment duration (days)[1]							
Mean (SD)	8.4 (2.17)	12.4 (3.91)	13.6 (3.10)	4.9 (0.65)	7.6 (2.90)	9.6 (4.65)	10.3 (4.59)
Median	7.0	14.0	14.0	5.0	8.0	10.0	12.0
Min, Max	6, 15	1, 15	1, 25	1, 7	1, 39	1, 35	1, 39
Total number of days of exposure for all participants	701	958	8035	893	1082	7870	19539
Number of doses received							
Mean (SD)	18.0 (4.23)	52.2 (16.16)	99.2 (27.84)	19.2 (5.25)	28.4 (5.92)	29.7 (18.67)	50.7 (38.92)
Median	16.0	60.0	112.0	16.0	28.0	30.0	40.0
Min, Max	14, 30	4, 62	0, 140	2, 36	3, 42	1, 84	0, 140

ASAQ = artesunate-amodiaquine; HCQ = hydroxychloroquine; Max = maximum; Min = minimum; SD = standard deviation.
[1] Treatment duration was calculated as follows: Date of last randomised study medication intake – Date of first randomised study medication intake +1.
Source: Table 14.1.6.

12.2 ADVERSE EVENTS

The analysis of AEs was performed in the Safety Population, based on treatment-emergent AEs, defined as any event that was not present before exposure to IP, or any event that was already present but worsened in intensity after exposure.

Pre-treatment events, which started before the first dose of IP, are not discussed in this report (see Table 14.3.2.1.1 for a summary of these events).

An AE was considered as serious if it resulted in death, was life-threatening, required hospitalisation or prolongation of hospitalisation, resulted in persistent disability, congenital anomaly, or was medically significant.

12.2.1 Brief Summary of Adverse Events

A total of 560 treatment-emergent AEs were reported in 17.7% of participants overall (Table 15), with heterogeneous incidence between treatment arms (higher in the nitazoxanide/ciclesonide and lopinavir/ritonavir treatment arms), as shown below:

- Nitazoxanide/ciclesonide: 32.8% of participants
- Lopinavir/ritonavir: 27.3%
- Ivermectin/ASAQ: 12.1%
- Paracetamol: 10.4%
- Fluoxetine/budesonide: 6.3%
- HCQ sulphate: 6.0%.

Most AEs were mild or moderate in severity (537 of 560 events, 95.9%). A total of 23 severe AEs were reported in 16 participants (0.8%) overall: 2 participants (2.6%) treated with lopinavir/ritonavir, 8 participants (1.4%) treated with nitazoxanide/ciclesonide, 5 participants (0.6%) treated with paracetamol, and 1 participant (0.5%) treated with ivermectin/ASAQ.

Treatment-related AEs were reported in 9.1% of participants. The incidence in each treatment was heterogeneous, going from 22.8% of participants treated with nitazoxanide/ciclesonide and 16.9% of participants treated with lopinavir/ritonavir, down to 0.7% of participants treated with fluoxetine/budesonide.

Study discontinuation due to an AE was rare, with 3 AEs reported in 3 participants (0.2%) overall (1 treated with nitazoxanide/ciclesonide, 1 treated with ivermectin/ASAQ, and 1 treated with paracetamol). A total of 58 AEs reported in 44 participants (2.3%) led to permanent discontinuation of study treatment, with an incidence of 5.8% in the nitazoxanide/ciclesonide treatment arm and <3% in the other arms.

A total of 34 SAEs were reported in 28 participants (1.5%) overall, with

heterogeneous incidence between treatment arms, as shown below:

- Lopinavir/ritonavir: 2 events in 2 participants (2.6%)
- Nitazoxanide/ciclesonide: 18 events in 14 participants (2.4%)
- Ivermectin/ASAQ: 5 events in 3 participants (1.6%)
- Paracetamol: 8 events in 8 participants (1.0%)
- Fluoxetine/budesonide: 1 event in 1 participant (0.7%)
- HCQ sulphate: no SAEs reported.

Of the 34 SAEs reported during the study, 7 led to the death of 7 participants (0.4%): 3 participants who received paracetamol, 2 who received nitazoxanide/ciclesonide, 1 who received lopinavir/ritonavir, and 1 who received ivermectin/ASAQ. None of the fatal AEs were considered treatment-related by the investigator.

Statistical comparisons between each active treatment arm and paracetamol regarding the mean number and incidence rate of SAEs, severe AEs, and AEs leading to permanent or temporary discontinuation of study treatment are reported in Table 14.2.2.15.

Table 15: Summary of treatment-emergent adverse events (Safety Population)

	HCQ sulphate (n=83)	Lopinavir/ Ritonavir (n=77)	Nitazoxanide/ Ciclesonide (n=591)	Ivermectin/ ASAQ (n=182)	Fluoxetine/ Budesonide (n=143)	Paracetamol *(control)* (n=817)	Total (n=1893)
Any AE	5 (6.0), *7*	21 (27.3), *34*	194 (32.8), *330*	*22* (12.1), *38*	9 (6.3), *12*	85 (10.4), *139*	336 (17.7), *560*
Any AE by maximum severity							
Mild	4 (4.8), *6*	11 (14.3), *19*	110 (18.6), *210*	9 (4.9), *22*	8 (5.6), *11*	51 (6.2), *90*	193 (10.2), *358*
Moderate	1 (1.2), *1*	8 (10.4), *13*	76 (12.9), *106*	12 (6.6), *15*	1 (0.7), *1*	29 (3.5), *43*	127 (6.7), *179*
Severe	0	*2* (2.6), *2*	8 (1.4), *14*	1 (0.5), *1*	0	5 (0.6), *6*	16 (0.8), *23*
Any treatment-related AE[1]	3 (3.6), *3*	13 (16.9), *18*	135 (22.8), *170*	10 (5.5), *17*	1 (0.7), *1*	10 (1.2), *11*	172 (9.1), *220*
Any severe treatment-related AE	0	1 (1.3), *1*	2 (0.3), *2*	0	0	0	3 (0.2), *3*
Any SAE[2]	0	2 (2.6), *2*	14 (2.4), *18*	3 (1.6), *5*	1 (0.7), *1*	8 (1.0), *8*	28 (1.5), *34*
Any AE leading to study discontinuation	0	0	1 (0.2), *1*	1 (0.5), *1*	0	1 (0.1), *1*	3 (0.2), *3*
Any AE leading to treatment discontinuation	0	2 (2.6), *2*	34 (5.8), *45*	4 (2.2), *6*	1 (0.7), *1*	3 (0.4), *4*	44 (2.3), *58*
Any treatment-related AE leading to treatment discontinuation[1]	0	1 (1.3), *1*	29 (4.9), *38*	4 (2.2), *6*	1 (0.7), *1*	2 (0.2), *3*	37 (2.0), *49*
Any AE leading to death	0	1 (1.3), *1*	2 (0.3), *2*	1 (0.5), *1*	0	3 (0.4), *3*	7 (0.4), *7*
Any treatment-related AE leading to death	0	0	0	0	0	0	0

AE = adverse event; ASAQ = artesunate-amodiaquine; HCQ = hydroxychloroquine; SAE = serious adverse event.
Data are presented as: number of participants with any AE (% of participants), *number of events*.
[1] The SAE of hypoxia in Participant GNCO0015 was listed as “probably related” to study treatment by mistake (clinical database incorrect); both the investigator and the sponsor considered the AE as “not related” (as indicated in the safety database). This affects the number of treatment-related AEs in the nitazoxanide/ciclesonide treatment arm (169 instead of 170) and in the overall Safety Population (219 instead of 220), but not the number (%) of participants with any related AE as this participant had multiple related AEs. The event was moderate in intensity and led to study treatment discontinuation.
[2] Including fatal SAEs.
Source: Table 14.3.2.1.1.

12.2.2 Display of Adverse Events

A summary of all treatment-emergent AEs in the Safety Population is presented by system organ class (SOC) and preferred term (PT) in Table 14.3.2.1.2. These data are analysed in Section 12.2.3.1.

Treatment-emergent AEs are presented by severity, by SOC and PT, in Table 14.3.2.1.3. These data are analysed in Section 12.2.3.2.

Treatment-emergent AEs that led to study treatment discontinuation are presented by SOC and PT in Table 14.3.2.1.4. These data are analysed in Section 12.3.1.3.

Treatment-emergent AEs considered by the investigator as related to study treatment are presented by SOC and PT in Table 14.3.2.1.5. These data are analysed in Section 12.2.3.3.

12.2.3 Analysis of Adverse Events

12.2.3.1 Analysis of Adverse Events by System Organ Class and Preferred Term

A total of 560 AEs were reported in 17.7% of participants overall, with a higher incidence in the nitazoxanide/ciclesonide (32.8%) and lopinavir/ritonavir (27.3%) treatment arms, compared to the ivermectin/ASAQ (12.1%), paracetamol (10.4%), fluoxetine/budesonide (6.3%), and HCQ sulphate (6.0%) treatment arms (Table 16).

AEs were most frequently reported in the following SOCs: gastrointestinal disorders (8.8% overall), nervous system disorders (2.7%), general disorders and administration site conditions (2.5%), and respiratory, thoracic, and mediastinal disorders (2.5%).

The most common AEs (reported in ≥1% of participants overall) were:

- Diarrhoea (3.5% overall), with a higher incidence in the lopinavir/ritonavir (11.7%) and nitazoxanide/ciclesonide (8.0%) treatment arms than the other arms (0 to 1.6%)
- Dyspepsia (2.0%), with a higher incidence in the nitazoxanide/ciclesonide (4.7%) and ivermectin/ASAQ (2.7%) treatment arms then the other arms (0 to 0.5%)
- Headache (1.6%), with a higher incidence in the nitazoxanide/ciclesonide (2.9%) treatment arm than the other arms (0 to 1.3%)
- Abdominal pain (1.5%), with a higher incidence in the nitazoxanide/ciclesonide (3.0%) treatment arm than the other arms (0 to 1.6%)
- Abdominal pain upper (1.1%), with a higher incidence in the lopinavir/ritonavir (5.2%) and nitazoxanide/ciclesonide (2.0%) treatment arms than the other arms (0.2 to 1.2%)
- Chromaturia (1.3%), with a higher incidence in the nitazoxanide/ciclesonide (4.1%) treatment arm than the other arms (0 to 0.1%).

Table 16: Treatment-emergent adverse events reported in at least 0.5% of participants overall, by system organ class and preferred term (Safety Population)

SOC PT	HCQ sulphate (n=83)	Lopinavir/ Ritonavir (n=77)	Nitazoxanide/ Ciclesonide (n=591)	Ivermectin/ ASAQ (n=182)	Fluoxetine/ Budesonide (n=143)	Paracetamol *(control)* (n=817)	Total (n=1893)
Any AE	**5 (6.0), *7***	**21 (27.3), *34***	**194 (32.8), *330***	**22 (12.1), *38***	**9 (6.3), *12***	**85 (10.4), *139***	**336 (17.7), *560***
Gastrointestinal disorders	**2 (2.4), *2***	**13 (16.9), *17***	**115 (19.5), *138***	**11 (6.0), *15***	**3 (2.1), *3***	**23 (2.8), *25***	**167 (8.8), *200***
Diarrhoea	0	9 (11.7), *9*	47 (8.0), *48*	3 (1.6), *3*	1 (0.7), *1*	6 (0.7), *6*	66 (3.5), *67*
Dyspepsia	0	0	28 (4.7), *28*	5 (2.7), *5*	0	4 (0.5), *4*	37 (2.0), *37*
Abdominal pain	0	1 (1.3), *1*	18 (3.0), *18*	3 (1.6), *3*	1 (0.7), *1*	5 (0.6), *5*	28 (1.5), *28*
Abdominal pain upper	1 (1.2), *1*	4 (5.2), *4*	12 (2.0), *12*	1 (0.5), *1*	1 (0.7), *1*	2 (0.2), *2*	21 (1.1), *21*
Vomiting	0	0	8 (1.4), *8*	2 (1.1), *2*	0	2 (0.2), *2*	12 (0.6), *12*
Abdominal discomfort	0	0	7 (1.2), *7*	0	0	2 (0.2), *2*	9 (0.5), *9*
Nervous system disorders	**0**	**1 (1.3), *1***	**28 (4.7), *32***	**2 (1.1), *2***	**1 (0.7), *1***	**19 (2.3), *21***	**51 (2.7), *57***
Headache	0	1 (1.3), *1*	17 (2.9), *17*	1 (0.5), *1*	1 (0.7), *1*	10 (1.2), *12*	30 (1.6), *32*
Dizziness	0	0	6 (1.0), *7*	0	0	5 (0.6), *5*	11 (0.6), *12*
General disorders and administration site conditions	**1 (1.2), *1***	**6 (7.8), *7***	**21 (3.6), *24***	**4 (2.2), *4***	**1 (0.7), *1***	**14 (1.7), *16***	**47 (2.5), *53***
Pyrexia	0	0	6 (1.0), *6*	1 (0.5), *1*	0	6 (0.7), *6*	13 (0.7), *13*
Chest pain	0	1 (1.3), *1*	4 (0.7), *5*	0	0	7 (0.9), *7*	12 (0.6), *13*
Asthenia	1 (1.2), *1*	6 (7.8), *6*	1 (0.2), *1*	0	0	1 (0.1), *1*	9 (0.5), *9*
Respiratory, thoracic, and mediastinal disorders	**1 (1.2), *1***	**2 (2.6), *2***	**24 (4.1), *29***	**3 (1.6), *3***	**0**	**17 (2.1), *21***	**47 (2.5), *56***
Dyspnoea	0	1 (1.3), *1*	6 (1.0), *6*	2 (1.1), *2*	0	7 (0.9), *8*	16 (0.8), *17*
Infections and infestations	**1 (1.2), *1***	**1 (1.3), *1***	**14 (2.4), *14***	**4 (2.2), *5***	**1 (0.7), *1***	**19 (2.3), *20***	**40 (2.1), *42***
COVID-19 pneumonia	0	1 (1.3), *1*	2 (0.3), *2*	0	0	6 (0.7), *6*	9 (0.5), 9
Renal and urinary disorders	**0**	**0**	**26 (4.4), *26***	**1 (0.5), *1***	**1 (0.7), *1***	**1 (0.1), *1***	**29 (1.5), *29***
Chromaturia	0	0	24 (4.1), *24*	0	0	1 (0.1), *1*	25 (1.3), *25*

SOC PT	**HCQ sulphate (n=83)**	**Lopinavir/ Ritonavir (n=77)**	**Nitazoxanide/ Ciclesonide (n=591)**	**Ivermectin/ ASAQ (n=182)**	**Fluoxetine/ Budesonide (n=143)**	**Paracetamol *(control)* (n=817)**	**Total (n=1893)**
Vascular disorders	**0**	**0**	**5 (0.8), *5***	**1 (0.5), *1***	**0**	**8 (1.0), *8***	**14 (0.7), *14***
Hypertension	0	0	4 (0.7), *4*	1 (0.5), *1*	0	7 (0.9), *7*	12 (0.6), *12*

AE = Adverse event; ASAQ = artesunate-amodiaquine; COVID-19 = Coronavirus disease 2019; HCQ = hydroxychloroquine; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class.
Data are presented as: number of participants with any AE (% of participants), *number of events*.
AEs were coded using MedDRA, Version 23.0.
Source: Table 14.3.2.1.2.

12.2.3.2 Analysis of Adverse Events by Severity

A total of 23 severe AEs were reported in 16 participants (0.8%) overall: 2 participants (2.6%) treated with lopinavir/ritonavir, 8 participants (1.4%) treated with nitazoxanide/ciclesonide, 5 participants (0.6%) treated with paracetamol, and 1 participant (0.5%) treated with ivermectin/ASAQ (Table 17).

The most common severe AEs (reported in 2 participants overall, 0.1%) were:

- Dyspnoea (2 participants who received nitazoxanide/ciclesonide)
- COVID-19 pneumonia (1 participant who received lopinavir/ritonavir and 1 who received paracetamol)
- Pyrexia (1 participant who received nitazoxanide/ciclesonide and 1 who received paracetamol)
- Hypertension (2 participants who received paracetamol)
- Headache (1 participant who received nitazoxanide/ciclesonide and 1 who received paracetamol).

All the aforementioned severe AEs were considered as serious (see Section 12.3.1.2), except one AE of hypertension and the 2 AEs of headache.

All other severe AEs (13 in total) were single occurrences, and 7 out of 13 were considered as serious.

Table 17: Summary of severe adverse events, by preferred term (Safety Population)

PT	HCQ sulphate (n=83)	Lopinavir/ Ritonavir (n=77)	Nitazoxanide/ Ciclesonide (n=591)	Ivermectin/ ASAQ (n=182)	Fluoxetine/ Budesonide (n=143)	Paracetamol *(control)* (n=817)	Total (n=1893)
Any severe AE	**0**	**2 (2.6), *2***	**8 (1.4), *14***	**1 (0.5), *1***	**0**	**5 (0.6), *6***	**16 (0.8), *23***
Dyspnoea	0	0	2 (0.3), *2*	0	0	0	2 (0.1), *2*
COVID-19 pneumonia	0	1 (1.3), *1*	0	0	0	1 (0.1), *1*	2 (0.1), *2*
Pyrexia	0	0	1 (0.2), *1*	0	0	1 (0.1), *1*	2 (0.1), *2*
Hypertension	0	0	0	0	0	2 (0.2), *2*	2 (0.1), *2*
Headache	0	0	1 (0.2), *1*	0	0	1 (0.1), *1*	2 (0.1), *2*
Death	0	0	1 (0.2), *1*	0	0	0	1 (0.1), *1*
Sepsis	0	0	0	1 (0.5), *1*	0	0	1 (0.1), *1*
Acute respiratory distress syndrome	0	0	1 (0.2), *1*	0	0	0	1 (0.1), *1*
Shock	0	0	1 (0.2), *1*	0	0	0	1 (0.1), *1*
Abdominal pain	0	0	1 (0.2), *1*	0	0	0	1 (0.1), *1*
Abdominal discomfort	0	0	1 (0.2), *1*	0	0	0	1 (0.1), *1*
Anaemia	0	0	1 (0.2), *1*	0	0	0	1 (0.1), *1*
Transaminases increased	0	1 (1.3), *1*	0	0	0	0	1 (0.1), *1*
Hyperglycaemia	0	0	1 (0.2), *1*	0	0	0	1 (0.1), *1*
Arthralgia	0	0	1 (0.2), *1*	0	0	0	1 (0.1), *1*
Uterine leiomyoma	0	0	1 (0.2), *1*	0	0	0	1 (0.1), *1*
Abortion	0	0	0	0	0	1 (0.1), *1*	1 (0.1), *1*
Haematuria	0	0	1 (0.2), *1*	0	0	0	1 (0.1), *1*

AE = Adverse event; ASAQ = artesunate-amodiaquine; COVID-19 = Coronavirus disease 2019; HCQ = hydroxychloroquine; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term.
Data are presented as: number of participants with any AE (% of participants), *number of events*.
AEs were coded using MedDRA, Version 23.0.
Source: Table 14.3.2.1.3.

12.2.3.3 Analysis of Adverse Events by Relatedness

Treatment-related AEs were reported in 9.1% of participants overall, with a higher incidence in the nitazoxanide/ciclesonide (22.8%) and lopinavir/ritonavir (16.9%) treatment arms, compared to the ivermectin/ASAQ (5.5%), HCQ sulphate (3.6%), paracetamol (1.2%), and fluoxetine/budesonide (0.7%) treatment arms (Table 18).

Treatment-related AEs were most frequently reported in the following SOCs: gastrointestinal disorders (6.1% overall), renal and urinary disorders (1.3%), general disorders and administration site conditions (0.8%), respiratory, thoracic, and mediastinal disorders (0.5%), and nervous system disorders (0.5%).

The most common related AEs (reported in ≥1% of participants overall) were:

- Diarrhoea (2.9% overall), with a higher incidence in the lopinavir/ritonavir (10.4%) and nitazoxanide/ciclesonide (7.4%) treatment arms than the other arms (0 to 1.1%)
- Dyspepsia (1.6%), with a higher incidence in the nitazoxanide/ciclesonide (4.4%) treatment arm than the other arms (0 to 1.1%)
- Chromaturia (1.3%), with a higher incidence in the nitazoxanide/ciclesonide (4.1%) treatment arm than the other arms (0 to 0.1%)
- Abdominal pain (1.0%), only reported in the nitazoxanide/ciclesonide (2.5%) and ivermectin/ASAQ (1.6%) treatment arms.

Table 18: Treatment-related adverse events reported in ≥0.2% of participants overall, by system organ class and preferred term (Safety Population)

SOC PT	HCQ sulphate (n=83)	Lopinavir/ Ritonavir (n=77)	Nitazoxanide/ Ciclesonide (n=591)	Ivermectin/ ASAQ (n=182)	Fluoxetine/ Budesonide (n=143)	Paracetamol *(control)* (n=817)	Total (n=1893)
Any related AE[1]	**3 (3.6), *3***	**13 (16.9), *18***	**135 (22.8), *170***	**10 (5.5), *17***	**1 (0.7), *1***	**10 (1.2), *11***	**172 (9.1), *220***
Gastrointestinal disorders	**1 (1.2), *1***	**10 (13.0), *13***	**96 (16.2), *110***	**6 (3.3), *10***	**0**	**3 (0.4), *3***	**116 (6.1), *137***
Diarrhoea	0	8 (10.4), *8*	44 (7.4), *44*	2 (1.1), *2*	0	0	54 (2.9), *54*
Dyspepsia	0	0	26 (4.4), *26*	2 (1.1), *2*	0	3 (0.4), *3*	31 (1.6), *31*
Abdominal pain	0	0	15 (2.5), *15*	3 (1.6), *3*	0	0	18 (1.0), *18*
Abdominal pain upper	0	4 (5.2), *4*	3 (0.5), *3*	1 (0.5), *1*	0	0	8 (0.4), *8*
Vomiting	0	0	6 (1.0), *6*	2 (1.1), *2*	0	0	8 (0.4), *8*
Gastrointestinal disorder	0	0	7 (1.2), *7*	0	0	0	7 (0.4), *7*
Abdominal discomfort	0	0	6 (1.0), *6*	0	0	0	6 (0.3), *6*
Renal and urinary disorders	**0**	**0**	**24 (4.1), *24***	**0**	**0**	**1 (0.1), *1***	**25 (1.3), *25***
Chromaturia	0	0	24 (4.1), *24*	0	0	1 (0.1), *1*	25 (1.3), *25*
General disorders and administration site conditions	**0**	**3 (3.9), *3***	**7 (1.2), *7***	**2 (1.1), *2***	**0**	**3 (0.4), *3***	**15 (0.8), *15***
Asthenia	0	3 (3.9), *3*	1 (0.2), *1*	0	0	0	4 (0.2), *4*
Chest pain	0	0	1 (0.2), *1*	0	0	3 (0.4), *3*	4 (0.2), *4*
Fatigue	0	0	3 (0.5), *3*	0	0	0	3 (0.2), *3*
Respiratory, thoracic and mediastinal disorders	**1 (1.2), *1***	**0**	**5 (0.8), *5***	**3 (1.6), *3***	**0**	**1 (0.1), *1***	**10 (0.5), *10***
Dyspnoea	0	0	2 (0.3), *2*	2 (1.1), *2*	0	0	4 (0.2), *4*
Nervous system disorders	**0**	**0**	**8 (1.4), 9**	**0**	**0**	**1 (0.1), *1***	**9 (0.5), 10**
Dizziness	0	0	3 (0.5), *3*	0	0	1 (0.1), *1*	4 (0.2), *4*
Headache	0	0	4 (0.7), *4*	0	0	0	4 (0.2), *4*

SOC PT	**HCQ sulphate (n=83)**	**Lopinavir/ Ritonavir (n=77)**	**Nitazoxanide/ Ciclesonide (n=591)**	**Ivermectin/ ASAQ (n=182)**	**Fluoxetine/ Budesonide (n=143)**	**Paracetamol *(control)* (n=817)**	**Total (n=1893)**
Skin and subcutaneous tissue disorders	**1(1.2), *1***	**1 (1.3), *1***	**4 (0.7), *4***	**0**	**0**	**0**	**6 (0.3), *6***
Pruritus	1(1.2), *1*	1 (1.3), *1*	1 (0.2), *1*	0	0	0	3 (0.2), *3*
Eye disorders	**0**	**0**	**1 (0.2), *1***	**2 (1.1), *2***	**0**	**0**	**3 (0.2), *3***
Vision blurred	0	0	1 (0.2), *1*	2 (1.1), *2*	0	0	3 (0.2), *3*

AE = Adverse event; ASAQ = artesunate-amodiaquine; HCQ = hydroxychloroquine; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event; SOC = system organ class.
Data are presented as: number of participants with any AE (% of participants), *number of events*.
AEs were coded using MedDRA, Version 23.0.
[1] The SAE of hypoxia in Participant GNCO0015 was listed as “probably related” to study treatment by mistake (clinical database incorrect); both the investigator and the sponsor considered the AE as “not related” (as indicated in the safety database). This affects the number of treatment-related AEs in the nitazoxanide/ciclesonide treatment arm (169 instead of 170) and in the overall Safety Population (219 instead of 220), but not the number (%) of participants with any related AE as this participant had multiple related AEs. The event was moderate in intensity and led to study treatment discontinuation.

Source: Table 14.3.2.1.5.

12.2.4 Listing of Adverse Events by Participant

By-participant listings of all AEs and treatment-related AEs are presented for the Safety Population in Listing 16.2.7.1 and Listing 16.2.7.3, respectively.

12.3 DEATHS, SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS

12.3.1 Listing of Deaths, Serious Adverse Events and Other Significant Adverse Events

By-participant listings of all SAEs (including deaths) and all AEs that led to treatment discontinuation are presented for the Safety Population in Listing 16.2.7.2 and Listing 16.2.7.4, respectively. A listing of all deaths is presented in Listing 16.2.7.5.

12.3.1.1 Deaths

A total of 7 participants died during the study: 3 who received paracetamol, 2 who received nitazoxanide/ciclesonide, 1 who received lopinavir/ritonavir, and 1 who received ivermectin/ASAQ (Table 19). All deceased participants but one were men, and all were Black. Three participants were older than 70 years with a normal BMI, whereas the remaining participants, who were younger than 70 years, had a high BMI (>30 kg/m^2, Listing 16.2.4.1). Five fatal SAEs started during study treatment and led to treatment discontinuation. None of the fatal AEs were considered treatment-related by the investigator, nor the sponsor. Four deaths were considered as related to disease progression (COVID-19 pneumonia or acute respiratory distress syndrome).

Table 19: Listing of all fatal SAEs, from earliest to latest onset within each arm (Safety Population)

Participant's ID (sex, age)	Treatment arm	Preferred term	Intensity	Start day – End day[1]	Related to treatment?[2]
BFBO0132 (F, 75 years)[3]	Paracetamol (control)	Loss of consciousness (later updated to septicaemia)[4]	Moderate	2-2	No
BFBO0064 (M, 86 years)[3]	Nitazoxanide/ Ciclesonide	Death[5]	Severe	4-4	No
CD110007 (M, 65 years)	Lopinavir/ Ritonavir	COVID-19 pneumonia	Severe	2-8	No
ET110010 (M, 52 years)	Nitazoxanide/ Ciclesonide	Acute respiratory distress syndrome	Severe	7-8	No
CD110085 (M, 61 years)	Paracetamol (control)	COVID-19 pneumonia	Severe	11-11[6]	No
BFOU0037 (M, 51 years)[3]	Paracetamol (control)	Pyrexia (later updated to COVID-19 pneumonia)[4]	Severe	3-18	No
GH100197 (M, 84 years)[7]	Ivermectin/ ASAQ	Sepsis	Severe	20-24[6]	No

ASAQ = artesunate-amodiaquine; CIOMS = Council for International Organizations of Medical Sciences; COVID-19 = coronavirus disease 2019; F = female; ID = identification; M = male; MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event.
Adverse Events were coded using MedDRA, Version 23.0.
[1] Start/End day was calculated relative to the study treatment start date (End date = date of death).
[2] Causal relationship to study treatment was assessed by the investigator.
[3] Age corrected based on the correct date of birth provided in the CIOMS form (see Section 14.3.3).
[4] AE term in the clinical database was later corrected in the safety database.
[5] On Day 4, the participant had an unexplained malaise and cardiac arrest, and died at home.
[6] The fatal SAE did not lead to study discontinuation, as study treatment had already been completed at SAE onset.
[7] Death which was not considered a failure since it occurred after Day 21, i.e. outside the time window of the primary endpoint.
Sources: Listings 16.2.4.1, 16.2.5, and 16.2.7.5.

Short narratives of all deaths are provided below (Listings 16.2.4.1, 16.2.4.2, 16.2.4.3, 16.2.4.4, 16.2.5, 16.2.7.1, 16.2.7.5, and 16.2.9).

Participant BFBO0132 (paracetamol treatment arm)

This 75-year-old woman had an SAE of loss of consciousness, which started on Day 2 of treatment and was moderate in intensity. She died on the same day following septicaemia. The investigator reported that the death was sudden, in a context of an altered general condition with disturbed consciousness and fever. The participant had received paracetamol treatment on Day 1 (1 tablet of 500 mg TID), then treatment was discontinued due to the AE. On Day 2, the participant received intravenous ceftriaxone 2 g once a day (QD) for septicaemia and nasal oxygen 3L/min for hypoxemia.

From Day 1 to Day 2, heart rate rose from 65 to 110 beats per minute (bpm), respiratory rate from 19 to 40 breaths per minute and body temperature from 36.5 to 39.0°C. Blood pressure was 129/62 mmHg on Day 1 and 110/82 mmHg

on Day 2. SpO2 was 95% on Day 1 and 96% on Day 2. The participant had had moderate arterial hypertension for 12 years and had no other medical history. BMI was normal (18.4 kg/m^2). The investigator confirmed that the probable cause of the sepsis was of pulmonary origin because the X-ray showed a pleuropneumopathy. The AE term in the safety database was updated to septicaemia.

Participant BFBO0064 (nitazoxanide/ciclesonide treatment arm)

This 86-year-old man had an AE of death, which started on Day 4 of treatment and was severe in intensity. He had an unexplained malaise and cardiac arrest, and died at home. According to the investigator, the participant had presented anorexia two days before and had received glucose serum 5% for rehydration.

The participant had no other AEs. He had received nitazoxanide/ciclesonide treatment on Day 1 (2 daily intakes of 2 tablets of nitazoxanide 500 mg, and 2 daily inhalations of ciclesonide 320 µg; timing unknown), then treatment was discontinued due to the AE. On Day 1, vital signs were: blood pressure 120/59 mmHg, heart rate 68 bpm, SpO2 98%, respiratory rate 15 breaths per minute, body temperature 37.5°C. The participant had no relevant medical history and his BMI was normal (22.8 kg/m^2). The AE term in the safety database is “unknown cause of death”. Additional test results that could explain the cause of death are pending.

Participant CD110007 (lopinavir/ritonavir treatment arm)

This 65-year-old man had an SAE of COVID-19 pneumonia, which started on Day 2 of treatment and was severe in intensity. He had no other AEs and died on Day 8. The AE term was “aggravation of the clinical picture, marked by respiratory distress in COVID-19 pneumopathy”. He had received lopinavir/ritonavir treatment from the evening of Day 1 to the morning of Day 5 as per protocol (2 daily intakes of 4 tablets of lopinavir 200 mg/ritonavir 50 mg, 12 hof 2 tablets of lopinavir 200 mg/ritonavir 50 mg, 12 h). Study treatment was discontinued in the evening of Day 5 due to the AE. During the duration of the AE, the participant received intravenous ceftriaxone 2 g BID (Day 2-8) and oral azithromycin 500 mg QD (Day 5-7) for pneumopathy, oral paracetamol 1000 mg as needed for fever or headaches (Day 3-7), intravenous dexamethasone for respiratory distress (Day 3-7), and oral terpin-codein 100 mg BID for cough (Day 5-7).

On Day 1, blood pressure was 128/72 mmHg, heart rate 99 bpm, respiratory rate was 36 breaths per minute, and SpO2 was 97% and later 93%. On Day 7, SpO2 had decreased to 88% at 9:00 am, and down to 12% at 10:00 pm; other vital signs remained stable. The participant died the next day following septic shock. The participant had a high BMI (32.3 kg/m^2) and had had moderate arterial hypertension (treated with ramipril and amlodipine) and moderate type 2 diabetes (treated with metformin) for 1 year.

Participant ET110010 (nitazoxanide/ciclesonide treatment arm)

This 52-year-old man had an SAE of acute respiratory distress syndrome, which started on Day 7 of treatment and was severe in intensity. The participant died on Day 8. The AE term was “acute respiratory distress syndrome secondary to

critical COVID". He had received nitazoxanide/ciclesonide treatment from the evening of Day 1 to the morning of Day 7 as per protocol (2 daily intakes of 2 tablets of nitazoxanide 500 mg, 12 h apart, and 2 daily inhalations of ciclesonide 320 µg). Study treatment was discontinued in the evening of Day 7 due to the AE. The following intravenous treatments were given on Day 7 to treat the AE: ceftazidime 2 g TID, vancomycin 1 g BID, and dexamethasone 6 mg QD (+ subcutaneous unfractionated heparin 5000 IU BID to prevent aggravation of COVID-19).

On Day 7, the participant also had AEs of moderate leukocytosis (not treated), severe hyperglycaemia (treated with subcutaneous insulin 10 IU QD), and severe shock (AE term "severe hypotension with shock", treated with 1 L of intravenous fluid), none of which were serious nor related to study treatment.

From Day 1 to Day 7, blood pressure had dropped from 120/70 mmHg to 70/40 mmHg, heart rate from 80 to 59 bpm, SpO2 from 97% to 57%, and body temperature from 36.5 to 35.9°C, while respiratory rate had increased from 16 to 40 breaths per minute. On Day 8, respiratory rate increased up to 52 breaths per minute. The participant had a high BMI (33.3 kg/m^2) and had had moderate hypertension for 2 years.

Participant CD110085 (paracetamol treatment arm)

This 61-year-old man had an SAE of COVID-19 pneumonia, which started on Day 11 and was severe in intensity. He had no other AEs and died on the same day. The AE term was "acute respiratory distress secondary to SARS-CoV-2 viral pneumonia". He had received paracetamol treatment from the evening of Day 1 to the morning of Day 5 as per protocol (2 tablets of 500 mg BID, 4-6 h apart).

Before the fatal AE started, the participant had received oral terpin-codein 100 mg QD for cough (Day 4-8), oral amboxol 10 mL TID for productive cough (Day 8), and oral amoxycillin 1 g TID for the presence of slight crackles in the two pulmonary fields (Day 8-11). On the day the participant died, he received intravenous ceftriaxone 2 g BID for respiratory distress, intravenous dexamethasone 6 mg QD due to the risk of embolism, and subcutaneous fraxiparine 0.8 mL BID for pulmonary embolism (and also subcutaneous insulin 10 IU TID for hyperglycaemia).

On Day 1, vital signs were: blood pressure 133/82 mmHg, heart rate 83 bpm, respiratory rate 20 breaths per minutes, SpO2 95% and later 96%, and body temperature 36.7°C. They remained stable on Day 8. From Day 8 to Day 11, blood pressure remained high, heart rate had increased from 82 to 130 bpm and respiratory rate from 22 to 32 breaths per minute, while SpO2 had decreased from 96% to 82% and body temperature from 36.7 to 36.2°C. The participant had a high BMI (36.8 kg/m^2), but no medical history or ongoing comorbidities.

Participant BFOU0037 (paracetamol treatment arm)

This 51-year-old man had an SAE of pyrexia, which started on Day 3 of treatment and was severe in intensity. He had no other AEs and died on Day 18. The AE term in the clinical database was "persistent fever" and the AE was intermittent. He had received paracetamol treatment on Day 1 (1 tablet of 500 mg TID), then treatment was discontinued due to the AE.

Before the fatal AE started, the participant had received oral vitamin C 500 mg QD for asthenia (Day 1-unknown), oral fluoxetine 200 mg QD for anxiety (Day 1-2), and oral carbocysteine 750 mg every 3 days for cough (Day 1-3).

On Day 1, vital signs were: blood pressure 143/87 mmHg, heart rate 114 bpm, respiratory rate 24 breaths per minutes, SpO2 95%, and body temperature 37.5°C. On Day 3, the participant was hospitalised for fever. On Day 4, he had difficulty breathing, with SpO2 at 89%. On Day 5, he was referred to the Intensive Care Unit and was intubated (SpO2 95%). On Day 8, blood pressure had decreased to 107/87 mmHg and heart rate to 98 bpm, while other vital signs remained stable (including body temperature at 37.7°C). On Day 11, he was evacuated to his home country. On Day 13, he developed a fever which was treated as acquired pneumonia under mechanical ventilation, which was treated with levofloxacin and amykacin. On Day 18, the participant died following COVID-19 complications. The AE term in the safety database was later updated to COVID-19 pneumonia. The participant had a high BMI (31.6 kg/m^2), but no medical history or ongoing comorbidities.

Participant GH100197 (ivermectin/ASAQ treatment arm)

This 84-year-old man had an SAE of sepsis, which started on Day 20 and was severe in intensity. He had no other AE and died on Day 24. The AE term was “sepsis from chronic leg ulcer”. He had received ivermectin/ASAQ treatment from the morning of Day 1 to the morning of Day 5 as per protocol (2 tablets of ivermectin 9 mg for 5 days, and 2 tablets of ASAQ 100 mg/270 mg for 3 days).

At screening (one day before the first dose), the participant had had a mild ulcer in the right leg for 12 days. The ulcer had been treated with oral clindamycin 300 mg four times a day (from Day -5 to Day -6). The participant however remained in good health and had a daily dressing of the ulcer. He also had a history of hypertension. On Day -1, vital signs were: blood pressure 111/78 mmHg, heart rate 91 bpm, respiratory rate 23 breaths per minute, SpO2 95% and later 98%, and body temperature 36.7°C. On Day 20, after a week of not eating well, the participant was found very weak at home in the evening and rushed to the hospital. Blood pressure had decreased to 104/47 mmHg, heart rate to 57 bpm, and SpO2 to 94%. The participant was managed for severe sepsis with hypotension secondary to chronic leg ulcer and despite intensive treatment, he developed very low SpO2 (68% on Day 24), hypokalaemia, hyponatremia, and possible lobar pneumonia. On Day 24, oxygen therapy was initiated but SpO2 kept fluctuating and the participant died on the same day. He had a normal BMI (20.3 kg/m^2) and no other ongoing comorbidities.

12.3.1.2 All Serious Adverse Events

A total of 34 SAEs were reported in 28 participants (1.5%) overall, with the following incidence in each treatment arm (Table 15):

- Lopinavir/ritonavir: 2 events in 2 participants (2.6%)
- Nitazoxanide/ciclesonide: 18 events in 14 participants (2.4%)
- Ivermectin/ASAQ: 5 events in 3 participants (1.6%)
- Paracetamol: 8 events in 8 participants (1.0%)

- Fluoxetine/budesonide: 1 event in 1 participant (0.7%)
- HCQ sulphate: no SAEs reported.

SAEs were most frequently reported in the following SOCs (Table 14.3.2.2.1):

- Respiratory, thoracic and mediastinal disorders: 11 events in 11 participants (0.6%)
- Infections and infestations: 7 events in 7 participants (0.4%)
- General disorders and administration site conditions: 5 events in 4 participants (0.2%)
- Gastrointestinal disorders: 3 events in 3 participants (0.2%)
- Nervous system disorders: 2 events in 2 participants (0.1%).

Other SOCs did not include more than 1 SAE.

At the PT level, the most frequently reported SAEs were: dyspnoea (6 events in 6 participants, 0.3%), hypoxia, COVID-19, and COVID-19 pneumonia (2 events for each PT, in 2 participants, 0.1%). There were also 2 SAEs with similar definition: 1 SAE of loss of consciousness and 1 SAE of syncope. Other PTs were reported in no more than 1 participant (0.1%) overall. The description of the SAEs of COVID-19 and COVID-19 pneumonia (AE terms) indicate that the participants had acute respiratory distress.

A total of 7 SAEs led to the death of 7 participants (see Section 12.3.1.1).

Most non-fatal SAEs started during the treatment period, and only 4 events were considered by the investigator as possibly related to study treatment:

- Lopinavir/ritonavir treatment arm: transaminases increased
- Nitazoxanide/ciclesonide treatment arm: syncope and dehydration (in the same participant); vomiting.

All non-fatal SAEs resolved by the end of the study, except the SAE of transaminases increased in Participant CD110008 (outcome unknown, but the participant indicated he was doing well when contacted more than 1 year after the first dose).

No clear patterns were observed between treatment arms regarding SAE PTs, timing, intensity, relationship to treatment, and outcome.

Please refer to Section 12.5.3 for more details on the SAE of abortion (Participant CD100175).

An additional SAE of hypospadias was reported in the child of Participant CD110142, who was exposed to nitazoxanide/ciclesonide during pregnancy. This event is not included in the statistical outputs and in Table 20; please refer to Section 12.5.3 for a short narrative.

Table 20: Listing of all SAEs, from earliest to latest onset within each arm (Safety Population)

Participant's ID	Sex, age (years)	Preferred term	Intensity	Start–End day[1]	Related to tx?[2]	Action on treatment	Outcome
Lopinavir/ritonavir							
CD110007	M, 65	COVID-19 pneumonia *(AE term: "aggravation of the clinical picture, marked by respiratory distress in COVID-19 pneumopathy")*	Severe	2-8	No	Discontinued	Death
CD110008	M, 29[5]	Transaminases increased[3]	Severe	14-34	Yes	Discontinued	Unknown[3]
Nitazoxanide/ciclesonide							
CD110159	M, 55	Syncope *(AE term: "syncope due to dehydration")*[4]	Moderate	4-8[4]	Yes	None	Recovered
		Dehydration	Moderate	4-4	Yes	None	Recovered
BFBO0055	M, 61	Dyspnoea	Severe	3-10	No	None	Recovered
BFBO0086	M, 44	Respiratory distress	Moderate	3-17	No	Discontinued	Recovered
BFBO0064	M, 86[5]	Death	Severe	4-4	No	Discontinued	Death
GNCO0015	F, 81[5]	Hypoxia	Moderate	4-16	No[6]	Discontinued	Recovered
GNCO0055	M, 75	Hypoxia	Mild	6-6	No	Interrupted	Recovered
BFBO0011	F, 45[5]	Vomiting	Moderate	6-8	Yes	Interrupted	Recovered
ET110010	M, 52	Acute respiratory distress syndrome	Severe	7-8	No	Discontinued	Death
CD110125	M, 77	COVID-19 *(AE term: "moderate acute respiratory distress syndrome secondary to SARS-CoV-2 infection")*	Moderate	7-18	No	None	Recovered
BFBO0025	F, 68	Dyspnoea	Mild	8-12	No	None	Recovered
BFBO0023	F, 59	Dyspnoea	Moderate	9-10	No	None	Recovered
BFOU0004	M, 32	Chest pain	Mild	9-10	No	None	Recovered
		Chest pain	Moderate	10-27	No	None	Recovered
BFOU0053	F, 75	Pyrexia	Severe	10-12	No	None	Recovered
		Haematuria	Severe	10-17	No	None	Recovered
		Dyspnoea	Severe	10-11	No	None	Recovered
MZ100043	F, 47	Anaemia	Severe	12-16	No	Discontinued	Recovered

Participant's ID	Sex, age (years)	Preferred term	Intensity	Start–End day[1]	Related to tx?[2]	Action on treatment	Outcome
Ivermectin/ASAQ							
CD110198	F, 29	Dyspepsia	Moderate	4-5	No	None	Recovered
		Gastroenteritis viral	Moderate	4-5	No	None	Recovered
GH100204	F, 43	Gastritis	Mild	13-18	No	NA	Recovered
		Urinary tract infection	Mild	13-18	No	NA	Recovered
GH100197	M, 84	Sepsis[7]	Severe	20-24	No	NA	Death
Fluoxetine/budesonide							
CD110213	F, 55	COVID-19 *(AE term: "acute respiratory distress syndrome secondary to moderate SARS-CoV-2 infection")*	Moderate	3-4	No	None	Recovered
Paracetamol (control)							
BFBO0132	F, 75[5]	Loss of consciousness[8]	Moderate	2-2	No	Discontinued	Death
BFOU0008	M, 61	Dyspnoea	Mild	2-9	No	None	Recovered
BFOU0037	M, 51[5]	Pyrexia[8]	Severe	3-18	No	Discontinued	Death
CD110071	F, 27	Haemoptysis	Mild	4-5	No	None	Recovered
BFBO0049	F, 67	Dyspnoea	Moderate	7-19	No	None	Recovered
BFOU0061	F, 51	Hypertension	Severe	9-17	No	None	Recovered
CD110085	M, 61	COVID-19 pneumonia *(AE term: "acute respiratory distress secondary to SARS-CoV-2 viral pneumonia")*	Severe	11-11	No	NA	Death
CD100175	F, 37	Abortion	Severe	11-15	No	NA	Recovered

AE = adverse event; ASAQ = artesunate-amodiaquine; COVID-19 = coronavirus disease 2019; F = female; ID = identification; M = male; NA = not applicable (treatment had been stopped before SAE onset); SAE = serious adverse event; tx = study treatment. Adverse Events were coded using MedDRA, Version 23.0.
[1] Start/End day was calculated relative to the study treatment start date. End date corresponded to the date of death.
[2] Causal relationship to study treatment was assessed by the investigator.
[3] The participant indicated he was doing well when contacted more than 1 year after the first dose.
[4] The participant had the first symptoms of syncope on Day 2, and the event was considered as serious on Day 4 when it led to the participant's hospitalisation.
[5] Age corrected based on the correct date of birth provided in the CIOMS form (see Section 14.3.3)
[6] This AE was listed as "probably related" to study treatment by mistake. Both the investigator and the sponsor considered the AE as "not related" (see CIOMS).
[7] Death which was not considered a failure since it occurred after Day 21, i.e. outside the time window of the primary endpoint.
[8] AE term was later corrected in the safety database (see the in-text short narratives of deaths in Section 12.3.1.1).
Sources: Table 14.3.2.2.1, Listings 16.2.4.1, 16.2.7.1, and 16.2.7.2.

Short narratives of the 4 related SAEs reported in 3 participants are provided below (Listings 16.2.4.1, 16.2.4.2, 16.2.4.3, 16.2.4.4, 16.2.5, 16.2.7.1, 16.2.7.5, and 16.2.9).

Participant CD110008 (lopinavir/ritonavir treatment arm)

This 29-year-old man had an SAE of transaminases increased, which started on Day 14 of treatment and was severe in intensity. At baseline, aspartate aminotransferase (AST) was 41.7 UI/L and alanine aminotransferase (ALT) was 59.8 IU/L, which was high but not clinically significant (Listing 16.2.8.1). On Day 14, both enzymes increased to a clinically significantly high level, with AST at 130.8 IU/L and ALT at 652.5 IU/L. The participant was tested for viral hepatitis and the results showed the presence of hepatitis B surface antigen, suggestive of hepatitis B infection. He had no other AEs and no ongoing comorbidities. He had received lopinavir/ritonavir treatment from the evening of Day 1 to the evening of Day 13 as per protocol (2 daily intakes of 4 tablets of lopinavir 200 mg/ritonavir 50 mg, 12 hof 2 tablets of lopinavir 200 mg/ritonavir 50 mg, 12 h). Study treatment was discontinued in the morning of Day 14 (before the last scheduled dose) due to the AE. The event was not treated and further hepatic check-up at the hospital could not be performed due to the lockdown situation at the time. At the follow-up performed approximately 1 year and 3 months after the first dose, the participant asked not to be contacted again by the site and confirmed that he was doing well. The investigator decided to close the follow-up of this SAE.

End date for the SAE of transaminases increased was Day 34, with an unknown outcome. The event was considered by the investigator (and the sponsor) as probably related to study treatment due to the temporal relationship between the study treatment and the event (increase in transaminases is usually seen after 15 to 30 days of treatment).

Participant CD110159 (nitazoxanide/ciclesonide treatment arm)

This 55-year-old man had an SAE of syncope and an SAE of dehydration, which both started on Day 4 and were of moderate intensity (AE term: “syncope due to dehydration”). He had no other AEs and no ongoing comorbidities. He received the full course of nitazoxanide/ciclesonide treatment, from the evening of Day 1 to the morning of Day 15, as per protocol (2 daily intakes of 2 tablets of nitazoxanide 500 mg, 12 h apart, and 2 daily inhalations of ciclesonide 320 µg).

The participant had the first symptoms of syncope due to dehydration on Day 2 (including dizziness, diarrhoea, malaise, vomiting twice, and anorexia), and the AE of syncope was considered as serious on Day 4 when the participant lost consciousness and had to be hospitalised. The SAE of dehydration, which started on Day 4, was treated with 1 L of intravenous lactated ringer solution and resolved on the same day. On Day 4, the participant also received 1L of intravenous physiological serum for low blood pressure and 1 g of intravenous paracetamol for pyrexia, and subcutaneous enoxaparin sodium treatment was initiated to prevent embolism (given until Day 7).

After Day 4, the participant received the following treatments: intravenous omeprazole for dyspepsia (Day 5-7), intravenous ceftriaxone for infectious syndrome (Day 4-8), as well as intravenous artesunate (Day 5-6) and oral

artemether-lumefantrine (Day 7-9) for malaria.

On Day 8, the participant had recovered and was discharged from the hospital for continued treatment at home. The SAE of syncope was considered as resolved. Both SAEs (syncope and dehydration) were considered by the investigator as possibly related to study treatment. The sponsor disagreed with the investigator and assessed the event as unrelated. According to the sponsor, dehydration occurred due to insufficient fluid intake, vomiting and diarrhoea in the context of COVID-19 and malaria. This resulted in hypotension, which led to the SAE.

Participant BFBO0011 (nitazoxanide/ciclesonide treatment arm)

This 45-year-old woman had an SAE of vomiting, which started on Day 6 of treatment and was moderate in intensity. She had received nitazoxanide/ciclesonide treatment intermittently. She received the per-protocol dose on Day 1 (2 daily intakes of 2 tablets of nitazoxanide 500 mg, no indication of timing, and 2 daily inhalations of ciclesonide 320 µg), then treatment was interrupted on Day 6 due to the AE. On Day 6, the participant was hospitalised for uncontrollable vomiting, associated with a fever and a deterioration of general state. The event was treated with intravenous lederfoline and metamizole (with isotonic saline solution). Lovenox and antibiotics were given as concomitant treatments. On Day 8, the event had resolved. Treatment resumed with the per-protocol dose and ended on Day 15, as scheduled, without vomiting.

The participant also had non-serious AEs of bilateral crepitus rales (Day 1-15), pyrexia (Day 6-7), abdominal pain (Day 6-9), and productive cough (Day 6-22). During the treatment of the SAE (Day 6-Day 8), she also received antibacterials for systemic use to treat superinfection and antithrombotic agent to treat pulmonary embolism. Pyrexia was treated with analgesics from Day 8 to Day 11. She had had hepatitis B for 3 years and 8 months, and no other ongoing comorbidities. The SAE of vomiting and was considered by the investigator (and the sponsor) as possibly related to study treatment.

12.3.1.3 Other Significant Adverse Events

A total of 58 AEs reported in 44 participants (2.3%) led to permanent discontinuation of study treatment, with a higher incidence in the nitazoxanide/ciclesonide arm (Table 15):

- Nitazoxanide/ciclesonide: 45 events in 34 participants (5.8%)
- Lopinavir/ritonavir: 2 events in 2 participants (2.6%)
- Ivermectin/ASAQ: 6 events in 4 participants (2.2%)
- Fluoxetine/budesonide: 1 event in 1 participant (0.7%)
- Paracetamol: 4 events in 3 participants (0.4%)
- HCQ sulphate: no AEs reported.

AEs that led to permanent treatment discontinuation were most frequently reported in the following SOCs (Table 14.3.2.1.4):

- Gastrointestinal disorders: 28 events in 25 participants (1.3%)
- Respiratory, thoracic and mediastinal disorders: 7 events in 7 participants (0.4%)

- General disorders and administration site conditions: 6 events in 6 participants (0.3%)
- Cardiac disorders: 3 events in 3 participants (0.2%)
- Nervous system disorders: 3 events in 3 participants (0.2%).

Other SOCs did not include more than 2 AEs that led to discontinuation.

At the PT level, the most frequently reported AEs that led to permanent treatment discontinuation were: dyspepsia (16 participants, 0.8%), diarrhoea (6 participants, 0.3%), abdominal pain (4 participants, 0.2%), dyspnoea (3 participants, 0.2%), palpitations (2 participants, 0.1%), and chromaturia (2 participants, 0.1%). Other PTs were reported in no more than 1 participant (0.1%) overall.

Regarding the 3 AEs reported in the cardiac disorders SOC (all non-serious), 2 AEs of palpitations led to the discontinuation of nitazoxanide/ciclesonide treatment in 2 participants, and 1 AE of tachycardia led to the discontinuation of fluoxetine/budesonide treatment in 1 participant.

Regarding hepatic toxicity, 1 AE of transaminases increased (considered serious) led to the discontinuation of lopinavir/ritonavir treatment in 1 participant, and 1 AE of hepatitis (considered non-serious) led to the discontinuation of nitazoxanide/ciclesonide treatment in 1 participant.

Regarding renal function, 2 AEs of chromaturia (both non-serious) led to the discontinuation of nitazoxanide/ciclesonide treatment in 2 participants.

AE as a cause of early discontinuation of treatment was more frequent in the nitazoxanide/ciclesonide treatment arm (32 of 87 discontinuations, 36.8%), as opposed to other causes of discontinuation (see Section 10.1). AEs causing early discontinuation of nitazoxanide/ciclesonide were mainly dyspepsia and diarrhoea (19 out of 45 events, Table 14.3.2.1.4).

No other clear patterns were observed between treatment arms regarding the PTs of AEs that led to permanent treatment discontinuation, as well as their timing, intensity, relationship to treatment, and outcome.

There were no other significant AEs.

12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

The Council for International Organizations of Medical Sciences (CIOMS) forms of all deaths and other non-fatal SAEs are included in Section 14.3.3. Short narratives of deaths and related SAEs are provided in Section 12.3.1.1 and Section 12.3.1.2, respectively.

The CIOMS forms of cases of exposure during pregnancy are also included in Section 14.3.3. Corresponding short narratives are presented in Section 12.5.3.

12.3.3 Analysis and Discussion of Deaths, Serious Adverse Events and Other Significant Adverse Events

There were 7 deaths during the study: 3 participants who received paracetamol, 2 who received nitazoxanide/ciclesonide, 1 who received lopinavir/ritonavir, and

1 who received ivermectin/ASAQ. Death was due to COVID 19 pneumonia (n=3), acute respiratory distress syndrome (n=1), sepsis (n=1), septicaemia (n=1), and unexplained malaise and cardiac arrest (n=1). Deaths occurred 2 to 24 days after the first dose of treatment, and none of the fatal AEs were considered treatment-related by the investigator, nor the sponsor.

Three participants who died were older than 70 years (75 to 89 years), with a normal BMI. The 4 remaining participants were all younger than 70 years (51 to 65 years) and presented a high BMI (>30 kg/m^2). Three of these 4 participants also had other comorbidities such as arterial hypertension and/or diabetes.

A total of 34 SAEs (fatal or not) were reported in 28 participants (1.5%) overall, with no marked differences in incidence between treatment arms. The most common SAEs were dyspnoea, hypoxia, COVID-19, COVID-19 pneumonia, and loss of consciousness/syncope.

Most non-fatal SAEs started during the treatment period, and only 4 events were considered by the investigator as possibly related to study treatment: transaminases increased which started before the last scheduled dose of lopinavir/ritonavir treatment (Day 14), leading to treatment discontinuation; syncope and dehydration in a participant who could complete the full course of nitazoxanide/ciclesonide treatment despite the SAEs, and vomiting which caused treatment interruption/discontinuation in 1 participant who received nitazoxanide/ciclesonide.

All non-fatal SAEs resolved by the end of the study, except the SAE of transaminases increased (outcome unknown, but the participant indicated he was doing well when contacted more than 1 year after the first dose).

An additional SAE of hypospadias was reported in the child of a participant exposed to nitazoxanide/ciclesonide during pregnancy. The event was considered by the investigator (and the Sponsor) as unrelated to study treatment (see Section 12.5.3).

None of the SAEs raised any new safety signals concerning the IPs which were investigated in this study.

12.4 CLINICAL LABORATORY EVALUATION

Clinical laboratory evaluation was an optional safety assessment.

Available laboratory data at each visit and changes over time are presented by treatment arm in Table 14.3.4.1.1 (blood chemistry), Table 14.3.4.1.2 (blood haematology), Table 14.3.4.1.3 (coagulation), and Table 14.3.4.1.4 (lipids).

At baseline, laboratory data were obtained for up to 967 participants (blood chemistry), 991 participants (blood haematology), 492 participants (coagulation), and 431 participants (lipids).

Shift tables were prepared for each category of clinical laboratory data using two types of interpretation: the collected interpretation when no local laboratory normal ranges were provided, and the derived interpretation when local laboratory normal ranges were provided. Shift tables based on derived and collected interpretation are provided in Table 14.3.4.2.1.1 and Table 14.3.4.2.1.2

(blood chemistry), Table 14.3.4.2.2.1 and Table 14.3.4.2.2.2 (blood haematology), Table 14.3.4.2.3.1 and Table 14.3.4.2.3.2 (coagulation), Table 14.3.4.2.4.1 and Table 14.3.4.2.4.2 (lipids).

Individual clinically significant abnormalities were reported as AEs (see Section 12.2).

Two non-fatal SAEs related to laboratory abnormalities were observed:

- Transaminases increased in Participant CD110008, which was considered related to study treatment lopinavir/ritonavir (see Section 12.3.1.2 for further information).
- Anaemia in Participant MZ100043 (47-year-old female, nitazoxanide/ciclesonide treatment arm): the event started on Day 12, was of severe intensity, and led to discontinuation of treatment. On that day, the participant was hospitalised, with haemoglobin at 2.6 g/dL, leukocytes at $5.4x10^3$ /µL, and platelets at $195x10^3$ /µL. From Day 12 to Day 16, the participant received a transfusion of 5 units of 500 mL of packed red blood cells. From Day 12, anaemia was also treated with ferrous sulphate, folic acid, and multivitamins for 30 days. On Day 16, the participant was discharged from hospital and the event was considered as resolved. On the same day, the participant was diagnosed with uterine myoma, which probably caused anaemia (due to vaginal bleeding).

By-participants listings of clinical laboratory results are provided in Listing 16.2.8.1 (blood chemistry), Listing 16.2.8.2 (blood haematology), Listing 16.2.8.3 (coagulation), and Listing 16.2.8.4 (lipids).

12.5 VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

12.5.1 Vital Signs

Vital signs at each visit and changes over time are presented by treatment arm in Table 14.3.4.4. Baseline values are summarised in Table 10 in Section 11.2.

There were no major changes in the mean values of vital signs over the 21 days of follow-up.

The following abnormalities regarding vital signs were reported as AEs (Table 14.3.2.1.2):

- Elevated body temperature

A total of 13 AEs of pyrexia were reported in 13 participants (0.7%), one of which led to death in a participant treated with paracetamol (the AE term was later updated to COVID-19 pneumonia, see Section 12.3.1.1).

- High blood pressure

A total of 12 AEs of hypertension were reported in 12 participants (0.6%), one of which was considered as serious in a participant treated with paracetamol (see Section 12.3.1.2).

- Low SpO2

A total of 2 AEs of hypoxia were reported in 2 participants (0.1%). Both were

reported in participants treated with nitazoxanide/ciclesonide and were serious (see Section 12.3.1.2).

- Elevated heart rate

A total of 2 AEs of tachycardia were reported in 2 participants (0.1%), one of which led to the discontinuation of fluoxetine/budesonide treatment in 1 participant (see Section 12.3.1.3).

- Slow heart rate

One AE of bradycardia was reported in 1 participant (0.1%). The event was mild in intensity, not considered related to nitazoxanide/ciclesonide treatment, and the participant was recovering at the last follow-up visit (Listing 16.2.7.1).

There were no clear differences between treatment arms regarding the incidence of these AEs.

A by-participant listing of vital signs is provided in Listing 16.2.9.

12.5.2 Physical Examination

Physical examination findings are listed in Listing 16.2.11. Individual clinically significant abnormalities were reported as AEs (see Section 12.2).

12.5.3 Exposure to Study Treatment During Pregnancy

The results of urine pregnancy tests are summarised in Table 14.3.4.3 and listed in Listing 16.2.8.5. Of note, the urine sample could not be collected in 31 women of childbearing potential (1.6%).

There were 5 cases of exposure to study treatment during pregnancy (from first to third trimester). Exposure started 8 to 213 days after pregnancy start, defined as the date of last menstruation period (LMP), and lasted for 1 to 8 days.

- 1 participant (CD100175) was randomised to paracetamol before obtaining the result of the pregnancy test and consequently the pregnancy was not declared in the randomisation system (Listing 16.2.2). The participant had an SAE of abortion on Day 11 (see below).
- 1 participant (CD110142), who was randomised to nitazoxanide/ciclesonide, was 7-month pregnant at baseline.
- 3 other participants had a positive pregnancy test at baseline (Table 14.3.4.3 and Listing 16.2.8.5) or during the study (Listing 16.2.4.5): 1 randomised to paracetamol, 1 randomised to fluoxetine/budesonide, and 1 randomised to ivermectin/ASAQ.

Short narratives of these 5 cases of pregnancy are provided below (Listings 16.2.4.1, 16.2.4.2, 16.2.4.3, 16.2.5, and 16.2.7.1).

Participant CD100175 (paracetamol treatment arm)

This 37-year-old woman was randomised before obtaining the result of the pregnancy test and consequently the pregnancy was not declared in the randomisation system. She received paracetamol treatment on Day 1 and Day 3 (2 tablets of 500 mg QD). Exposure to paracetamol started 8 days after

pregnancy start (first trimester). She had an SAE of abortion (AE term "involuntary termination of pregnancy"), that started on Day 11 and was severe in intensity. It was reported that "she had slipped on the steps of the stairs and had genital haemorrhage with clots" 2 days before. The participant recovered on Day 15.

The participant's obstetric history included 6 previous pregnancies with 4 deliveries and 2 therapeutic abortions. She had had severe eclampsia during a previous pregnancy, approximately 9 months before receiving the first dose of study treatment. She had no ongoing comorbidities and no other AEs. Family medical history included arterial hypertension.

Follow-up echography done approximately 2 months after the SAE showed normal gynaecologic status with empty uterus. The SAE was considered unrelated to study treatment by the investigator and the sponsor.

Participant CD110142 (nitazoxanide/ciclesonide treatment arm) **and child**

This 29-year-old woman received nitazoxanide/ciclesonide treatment on Day 1, (2 tablets of nitazoxanide 500 mg and 2 inhalations of ciclesonide 160 µg), then decided to stop treatment. Exposure to nitazoxanide/ciclesonide started 213 days after pregnancy start (third trimester).

No relevant medical history was reported in the study participant. She had no prior pregnancies. Previous medications and concomitant medications administered during the pregnancy included intravenous artesunate (for malaria), as well as oral azithromycin, oral vitamin C and oral zinc (for COVID-19). Start dates, end dates, and dosage regimens of these medications were not reported.

The participant discontinued the study treatment on Day 2 (214 days after LMP) as per her father's request, who was also a physician, after experiencing diarrhoea and physical asthenia. The echography at 8 months of pregnancy (246 days after LMP) was normal.

A total of 56 days after the last dose of study treatment (approximately 2 months), the participant gave birth to a male, 3.1 kg, by caesarean section. His height was 50 cm and head circumference 35 cm. The child's general condition was normal and the Apgar score after 1, 5 and 10 minutes was 10. A blood transfusion was administered to the participant after the delivery.

The newborn's neurologic exam at birth was good. Somatic exam at birth was primarily marked by the finding of a connection of the penile urethra to the underside of the penis. The newborn was diagnosed with an SAE of hypospadias, which was moderate in intensity and considered as a congenital anomaly. There were no congenital anomalies or reproductive disorders in the participant's family medical history.

At the 6-month follow-up visit of the child, his general condition was good, physical and motor development was normal, as well as his language development. Child's weight was 8.2 kg, length was 71 cm, and head circumference was 46 cm.

Approximately 1 year later, the child's father was contacted by phone. He reported that the child, aged 19 months, had a good general evaluation with

normal language development. Weight, height and head circumference were not reported. No diagnostic tests had been performed and the child had had no medical events or medical/surgical treatment administered since birth. He was not administered any medication since the last visit.

The SAE of hypospadias had not resolved. The repair surgery was planned for when the child is 2 years old. The SAE of hypospadias was considered by the investigator (and the Sponsor) as unrelated to study treatment.

Participant TZ100009 (paracetamol treatment arm)

This 23-year-old woman received paracetamol treatment from Day 1 to Day 8 (2 tablets of 500 mg BID on Day 1, then 2 tablets TID from Day 2 to Day 7, and 2 tablets QD on Day 8). Exposure to paracetamol started 55 days after pregnancy start (first trimester).

A total of 212 days after the last dose of study treatment (approximately 7 months), the participant gave birth to a female, 2.8 kg, via normal delivery. The child's general condition was normal and the Apgar score was 9 and 10 after 1 and 5 minutes, respectively. Height and head circumference were not reported. No deformity or illness were detected at birth and the child was healthy and developing normally at one month of age.

Participant TZ100028 (fluoxetine/budesonide treatment arm)

This 39-year-old woman received fluoxetine/budesonide treatment from Day 1 to Day 7, as per protocol (1 daily intake with 2 capsules of fluoxetine 20 mg, and 2 inhalations of budesonide 200 µg, BID – participant only took budesonide on Day 1 and only took fluoxetine on Day 7). Exposure to fluoxetine/budesonide started 94 days after pregnancy start (second trimester).

A total of 114 days after the last dose of study treatment (approximately 4 months), the participant gave birth to a male, 1.0 kg, by caesarean section. The child had a low birth weight and gestational age was 28 weeks. Apgar score was 7 and 8 after 1 and 5 minutes, respectively. Height and head circumference were not reported. No relevant medical history was reported for the mother. The newborn was kept under Kangaroo mother care for 2 months. At 2 months of age, the child was healthy, his weight was 1.5 kg, and the mother was discharged home. At 6 months of age, the child's weight was 3.5 kg. No other complications were reported concerning the child's developmental milestones.

Participant CD110211 (ivermectin/ASAQ treatment arm)

This 37-year-old woman received ivermectin/ASAQ treatment from the evening of Day 1 to the morning of Day 5 as per protocol (4 tablets of ivermectin 9 mg for 5 days, and 2 tablets of ASAQ 100 mg/270 mg for 3 days). She had a positive pregnancy test during the study, at Day 17 (Listing 16.2.4.5). Exposure to ivermectin/ASAQ started 29 days after pregnancy start (first trimester). A total of 150 days after the last dose of study treatment (approximately 5 months), the participant gave birth to a male, 3.8 kg, via normal delivery. At the 12-month follow-up (child aged 4.5 months), the participant was contacted by phone as she failed to bring her child to the site. According to her, the child was doing well and had normal physical and motor development. Weight, height and head circumference were not reported. No diagnostic tests had been performed and

the child had had no medical events or medical/surgical treatment administered since birth.

12.5.4 Exposure to Study Treatment During Breastfeeding

A total of 17 participants were exposed to study treatment while breastfeeding: 5 who received nitazoxanide/ciclesonide and 12 who received paracetamol (Table 14.3.4.3).

All 17 participants completed study treatment, with exposure to nitazoxanide/ciclesonide of 14 days as per protocol (15 days if treatment was initiated in the evening) and exposure to paracetamol from 2 to 14 days.

It was not planned to collect follow-up information on exposure during breastfeeding. As a result, the safety database does not include any further information on the infants of these 17 participants.

One case was also exposed during pregnancy (CD100175, see Section 12.5.3 for a narrative).

A by-patient listing of all cases of exposure during breastfeeding is provided in Listing 16.2.8.7.

12.5.5 Optional Safety Assessments

ECGs, chest X-ray, and CT-scan were optional assessments. Results are presented in Listing 16.2.10.1 (ECG), Listing 16.2.10.2 (CT scan), and Listing 16.2.10.3 (chest X-ray).

At baseline, 293 participants had an ECG, 37 participants had a chest X-ray, and 2 participants had a CT scan. The 2 participants who had clinically significant abnormal findings (presence of infiltrates on chest X-ray) at baseline (see Section 11.2) did not have any further chest X-ray.

New clinically significant abnormalities (presence of infiltrates on X-ray) were reported in 2 participants during the study, all on chest X-ray:

- ET110010: abnormality was reported on Day 7, the day the participant had an SAE of acute respiratory distress syndrome that was fatal (see Section 12.3.1.1)
- ET100041: abnormality was reported on Day 7; the participant had had an AE of non-serious COVID-19 pneumonia from day 2 to Day 7 (Listing 16.2.7.1).

12.6 SAFETY CONCLUSIONS

A total of 1893 participants were exposed to study treatments during this study (Table 8):

- HCQ sulphate: n=83 (4.4%)
- Lopinavir/ritonavir: n=77 (4.1%)
- Nitazoxanide/ciclesonide: n=591 (31.2%)
- Ivermectin/ASAQ: n=182 (9.6%)
- Fluoxetine/budesonide: n=143 (7.6%)
- Paracetamol (reference treatment): n=817 (43.2%).

The incidence of treatment-emergent AEs was heterogenous between treatment arms, going from 32.8% in the nitazoxanide/ciclesonide treatment arm down to 6.0% in the HCQ sulphate treatment arm.

Most AEs (95.9% of events) were mild or moderate in severity.

The most common AEs (reported in ≥1% of participants overall) were:

- Diarrhoea (3.5% overall), with a higher incidence in the lopinavir/ritonavir (11.7%) and nitazoxanide/ciclesonide (8.0%) treatment arms (compared to other arms)
- Dyspepsia (2.0%), with a higher incidence in the nitazoxanide/ciclesonide (4.7%) and ivermectin/ASAQ (2.7%) treatment arms
- Headache (1.6%), with a higher incidence in the nitazoxanide/ciclesonide (2.9%) treatment arm
- Abdominal pain (1.5%), with a higher incidence in the nitazoxanide/ciclesonide (3.0%) treatment arm
- Abdominal pain upper (1.1%), with a higher incidence in the lopinavir/ritonavir (5.2%) and nitazoxanide/ciclesonide (2.0%) treatment arms
- Chromaturia (1.3%), with a higher incidence in the nitazoxanide/ciclesonide (4.1%) treatment arm.

The incidence of treatment-related AEs was heterogeneous between treatment arms, going from 22.8% in the nitazoxanide/ciclesonide treatment arm, 16.9% in the lopinavir/ritonavir treatment arm, down to 0.7% in the fluoxetine/budesonide treatment arm.

The most common related AEs (reported in ≥1% of participants overall) were:

- Diarrhoea (2.9% overall), with a higher incidence in the lopinavir/ritonavir (10.4%) and nitazoxanide/ciclesonide (7.4%) treatment arms than the other arms (0 to 1.1%)
- Dyspepsia (1.6%), with a higher incidence in the nitazoxanide/ciclesonide (4.4%) treatment arm than the other arms (0 to 1.1%)
- Chromaturia (1.3%), with a higher incidence in the nitazoxanide/ciclesonide (4.1%) treatment arm than the other arms (0 to 0.1%)
- Abdominal pain (1.0%), only reported in the nitazoxanide/ciclesonide (2.5%) and ivermectin/ASAQ (1.6%) treatment arms.

Permanent discontinuation of study treatment due to an AE was reported in 2.3% of participants overall, with an incidence of 5.8% in the nitazoxanide/ciclesonide treatment arm and <3% in the other arms.

A total of 34 SAEs were reported in 28 participants (1.5%) overall, with heterogeneous incidence between treatment arms (from 2.6% in the lopinavir/ritonavir treatment arm, 2.4% in the nitazoxanide/ciclesonide treatment arm, down to 0% in the HCQ sulphate treatment arm).

Of the 34 SAEs reported during the study, 7 were fatal. Five fatal SAEs started during study treatment and led to treatment discontinuation. Death was due to COVID-19 pneumonia (2 participants who received paracetamol and 1 who

received lopinavir/ritonavir), acute respiratory distress syndrome (1 participant who received nitazoxanide/ciclesonide), sepsis (1 participant who received ivermectin/ASAQ), septicaemia (1 participant who received paracetamol), and unexplained malaise and cardiac arrest (1 participant who received nitazoxanide/ciclesonide). Of the 7 participants (0.4%) who died, 3 were older than 70 years with a normal BMI, and 4 were younger than 70 years but with a high BMI (3 of whom had other comorbidities such as arterial hypertension and/or diabetes). None of the fatal AEs were considered related to treatment.

Most non-fatal SAEs started during the treatment period, and only 4 events in 3 participants were considered by the investigator as possibly related to study treatment: transaminases increased in a participant treated with lopinavir/ritonavir, as well as syncope and dehydration (same participant) and vomiting in 2 participants treated with nitazoxanide/ciclesonide.

All non-fatal SAEs resolved by the end of the study, except the SAE of transaminases increased (outcome unknown, but the participant indicated he was doing well when contacted more than 1 year after the first dose).

An additional SAE of hypospadias was reported in the child of a participant exposed to nitazoxanide/ciclesonide during pregnancy. The child was otherwise healthy and the repair surgery was planned for when the child is 2 years old. The event was considered by the investigator (and the Sponsor) as unrelated to study treatment.

Of the 5 participants who were exposed to study treatment during pregnancy (2 randomised to paracetamol, 1 to nitazoxanide/ciclesonide, 1 to fluoxetine/budesonide, and 1 to ivermectin/ASAQ), 3 had newborns who were healthy and developing normally (including 1 who had a low birthweight) and 1 had a newborn diagnosed with hypospadias at birth (see above). The remaining participant had to have an abortion, which was considered an SAE. The SAE was considered unrelated to study treatment by the investigator and the sponsor (the participant had fell 2 days before the event, and she had had 2 therapeutic abortions in the past).

A total of 17 participants were exposed to study treatment while breastfeeding.

There were no major changes in vital signs over the 21 days of follow-up. Physical examinations and ECGs did not raise any specific safety concerns.

13. DISCUSSION AND OVERALL CONCLUSIONS

ANTICOV was designed as a large, multicentre, multiple-country, randomised, open-label, adaptive, platform clinical study, aiming to determine the efficacy and safety of various treatment regimens in outpatients with mild/moderate COVID-19 to prevent the need for hospitalisation for specialised care due to severe progression of the disease.

ANTICOV included adult patients (≥18 years) with confirmed COVID-19 diagnosis and presenting with viral syndrome (with or without uncomplicated pneumonia) with symptom onset up to 7 days before randomisation and an SpO2 of 94% or more at baseline. Despite the possibility to include children aged ≥12 years, none were enrolled in the study.

The study was initiated with 2 active treatments arms (HCQ sulphate and lopinavir/ritonavir) and one control arm (paracetamol). The first two active arms were discontinued due to external reasons as per Amendment 1 and new active arms were implemented over time (nitazoxanide/ciclesonide as per Amendment 1, ivermectin/ASAQ as per Amendment 2, and fluoxetine/budesonide as per Amendment 3).

The open-label treatment period lasted up to 14 days, depending on treatment arm, and the follow-up period ended 21 or 35 days after treatment start, depending on the protocol version.

A total of 2328 participants were screened, of whom 1942 participants (83.4%) were randomised to one of the following treatment arms HCQ sulphate (4.3%), lopinavir/ritonavir (4.3%), nitazoxanide/ciclesonide (31.1%), ivermectin/ASAQ (9.8%), fluoxetine/budesonide (7.7%), and paracetamol (42.9%).

Of the 1942 randomised participants, 1893 (97.5%) received at least one dose of IP and 1749 (90.1%) completed study treatment. Early discontinuation of treatment due to an AE was more frequent in the nitazoxanide/ciclesonide (36.8% of all discontinuations in this arm) and the ivermectin/ASAQ (36.4%) treatment arms than in the other arms (from 0 to 21.1%). The tablets of nitazoxanide/ciclesonide were difficult to swallow, which may explain that some participants did not complete the treatment. Based on pharmacokinetic/pharmacodynamic modelling, the dose of nitazoxanide/ciclesonide was selected as slightly higher than the recommended dose, which could explain the relatively higher incidence of early discontinuation of treatment due to dyspepsia and diarrhoea in this arm. Similarly, the first dose of lopinavir was super-boosted with ritonavir (to increase the early effective pharmacokinetics).

Study population

The study was conducted in 11 African countries and Brazil. Two additional African countries participated to the preparation but could not enroll patients. Almost all participants were black (94.0%), with a balanced ratio of male (50.8%) and female (49.2%) participants. Mean age was 42.1 years, with the oldest participant being 89 years old and no children. Mean BMI was 26.3 kg/m^2. The countries that contributed the most to study population (>10% each) were DRC, Burkina Faso, Ethiopia, Mali, and Ghana.

Brazil started enrolling later and only in the fluoxetine/budesonide arm, which impacted the baseline demographic findings in that arm.

No major differences in demographics were noted between treatment arms. The percentage of participants over the age of 60 years (which is a risk factor for COVID-19 progression to severe disease) was similar among all treatment arms (13.8% overall). Mean BMI was higher in the fluoxetine/budesonide treatment arm (28.7 kg/m^2) and lower in the ivermectin/ASAQ treatment arm (24.1 kg/m^2), compared to the paracetamol treatment arm (26.5 kg/m^2). This was confirmed by the higher percentage of obese participants in the fluoxetine/budesonide treatment arm (15.4%) compared to the other arms (0 to 4.4%).

The objective to recruit recently affected participants with mild/moderate COVID-19 disease was fulfilled. All participants started to have COVID-19 symptoms no more than 7 days prior to the date of informed consent, as per protocol, except 12 participants (4 randomised to nitazoxanide/ciclesonide and 8 randomised to paracetamol). Randomisation occurred, on average, 3.9 days after the onset of COVID-19 symptoms, which is longer than in other outpatient trials restricting entry to 3 days after symptom onset.

SpO2 ranged from 94% to 100% at baseline, as per protocol (except for 1 patient), with a mean value ≥97% in all treatment arms except the HCQ sulphate (96.8%) and ivermectin/ASAQ (96.6%) treatment arms. Most participants (93.9%) were ambulatory, symptomatic but independent (WHO clinical progression scale score of 2), indicating that the disease was mild. More than 95% of participants only got breathless during strenuous exercise (Grade 0; 72.5%) or moderate exercise (Grade 1; 23.0%).

Considering the comorbidities identified as risk factors of COVID-19 progression to severe disease, hypertension was the most common one (17.6% of participants overall), with no major differences between treatment arms. Type 1 and type 2 diabetes mellitus were rare (1.7% and 3.9% of participants, respectively) and coronary artery disease was very rare (0.1%).

Discussion on efficacy

At the time of designing the study, the management of COVID-19 was essentially symptomatic, as no antiviral treatment had demonstrated a clinical benefit in the outpatient setting. The aim of ANTICOV was to determine the efficacy and safety of various treatment regimens to prevent the need for hospitalisation for specialised care due to severe progression of COVID-19.

The selection of the primary efficacy endpoint (SpO2 ≤93% on repeated measurement within 21 days considered as a failure) was based on the experience of the African investigators actively involved in the COVID-19 response and recommendation from the US Food and Drug Administration (FDA). Respiratory complication was the most commonly critical observed complication responsible for the majority of COVID-19-related hospitalisations with oxygen saturation chosen as the most measurable and objective primary endpoint. Death for any reasons occurring within 21 days was added as a co-primary endpoint of failure.

The trial did not allow to identify an alternative treatment to paracetamol to better

prevent the progression of COVID-19 to severe respiratory disease. A total of 5 treatments were tested in the ANTICOV study. The predefined conditions to demonstrate either early futility or early success of a tested arm (vs control) were only met for one treatment: nitazoxanide/ciclesonide, which showed early futility in the third interim analysis.

The statistical comparison of the failure rate vs paracetamol could not be performed for the other treatment active arms as the required sample size was not reached and the number of failures was insufficient. This is due to the lower-than-expected rate of failures, and to the early discontinuation of the treatment arms based on the accumulated scientific data (as allowed by the adaptive platform design). HCQ sulphate and lopinavir/ritonavir were dropped early based on WHO recommendations, and ivermectin/ASAQ was discontinued early by the ANTICOV Consortium JSC. As for the last arm (fluoxetine/budesonide), the study was terminated before it reached the required sample size and number of failures.

Patients were enrolled from 21 September 2020 to 17 November 2022 and were exposed to Delta, Alpha and Omicron SARS-CoV-2 variants successively. Patients in the HCQ sulphate and lopinavir/ritonavir arms were enrolled from September to December 2020, at the time of the Delta variant pandemic. However, the majority of patients in this trial (55%) were enrolled during the Omicron wave of COVID-19. The Omicron variant was first reported to the WHO towards the end of November 2021. This may partly explain the lower-than-expected rate of failures during this trial.

Discussion on safety

There were no new safety signals identified in this trial and safety results were consistent with the known safety profile of the included IPs.

Of the most common AEs (reported in ≥1% of participants overall), the higher incidence of diarrhoea in the lopinavir/ritonavir treatment arm (11.7%, versus 3.5% overall) was expected as it is an expected side effect of this treatment. Likewise, the higher incidence observed in the nitazoxanide/ciclesonide treatment arm regarding chromaturia (4.1%, versus 1.3% overall) and abdominal pain (3.0%, versus 1.5% overall) was expected due to the safety profile of the drugs.

A total of 7 participants (0.4%) died during the study, 3 of whom were older than 70 years with a normal BMI, and 4 of whom were younger than 70 years but with a high BMI (and other comorbidities such as arterial hypertension and/or diabetes in 3 cases). None of the fatal AEs were considered related to treatment.

A total of 34 SAEs were reported in 28 participants (1.5%) overall. The analysis of these events did not raise any safety concerns. Regarding liver toxicity, one SAE of increased transaminases was reported in 1 participant treated with lopinavir/ritonavir. The event was considered as probably related to study treatment. Liver disorders are known possible side effects of lopinavir/ritonavir treatment. No SAEs indicating potential cardiac toxicity were reported.

There were no safety findings from the cases of exposure to study treatment during pregnancy.

Assessments of vital signs, physical examinations, and ECGs did not raise any specific safety concerns.

Overall conclusion

In a large population of recently affected outpatients with mild/moderate COVID-19 disease across Africa and Brazil, the trial did not allow to identify an alternative treatment to paracetamol to better prevent the progression of COVID-19 to severe respiratory disease. The large majority of patients were enrolled during the Omicron wave of COVID-19, which may partly explain that fewer severe progressions than expected were identified.

Early futility (vs paracetamol) could however be demonstrated for one treatment arm (nitazoxanide/ciclesonide), and the number of failures in the other arms (HCQ sulphate, lopinavir/ritonavir, ivermectin/ASAQ, and fluoxetine/budesonide) was insufficient to allow a statistical comparison.

No new safety signals were identified in this trial on repurposed medications and safety results were consistent with the known safety profiles of the tested drugs.