Antivirals for adult patients hospitalized with infection by SARS-CoV-2, randomized, Phase II/III, multicenter, placebo-controlled, adaptive study, with multiple arms and stages. COALITION COVID-19 BRAZIL IX – REVOLUTIOn: statistical analysis plan

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SECTION 1 - ADMINISTRATIVE INFORMATION

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Protocol version 4.0

SAP revisions

Roles and responsibilities

SAP version	Date	Protocol version
V1	01/09/2020	V1
V2	30/10/2020	V2
V3	26/02/2021	V4

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SECTION 2 - INTRODUCTION

2.1 Background

Coronavirus disease 2019 (COVID-19) has had a huge health impact in the world since 2020. March 11, 2020 the World Health Organization (WHO) declared a pandemic,[1] despite the efforts of the scientific community there is still no solid evidence that any therapy can potentially improve health outcomes in suspected or with COVID-19 confirmed.

The COALITION COVID-19 BRASIL IX – REVOLUTIOn study aims to verify whether treatment with isolated or combined antivirals reduces the viral load of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and increases the chance that the patient will not need increased ventilatory support. This is a randomized, Phase II/III, placebo-controlled, adaptive multi-arm clinical study with stages, to be conducted in at least 60 Brazilian hospitals. This document describes the study's statistical analysis plan.

2.2 Objectives

The general objectives of the REVOLUTIOn Coalition IX project are to answer to the following questions:

1. Are isolated antiviral candidates (atazanavir - ATV, daclatasvir - DCV -, sofosbuvir - SOF/DCV) capable of reducing the viral load of SARS-CoV-2 compared to placebo in patients hospitalized with COVID-19 ≤ 7 days of symptoms?
2. Which isolated antiviral has the best effect in reducing the viral load of SARS-CoV-2 in patients hospitalized with COVID-19 with ≤ 7 days of symptoms? And what is the second-best effect?
3. Are combined antiviral candidates able to reduce SARS-CoV-2 viral load compared to isolated antiviral in patients hospitalized with COVID-19 ≤ 7 days of symptoms?
4. Are isolated or combined antiviral candidates safe compared to placebo?
5. Does the isolated antiviral candidate or in combination improve clinical outcomes (days free of respiratory support in 15 days) compared to placebo in patients hospitalized with COVID-19 ≤ 7 days of symptoms?

2.2.1 Primary objectives

1. Evaluate the effect of treatment with isolated antivirals or combined with each other compared to placebo in reducing the viral load of SARS-CoV-2 in nasopharyngeal swab samples obtained at baseline (Day -D - 0) and D3, D6 and D10.
2. Evaluate the efficacy of antivirals isolated or combined compared to placebo in increasing days free of respiratory support defined as the number of days without oxygen, non-invasive ventilation/high flow nasal cannula or mechanical ventilation in 15 days.

2.2.2 Secondary objectives

To evaluate the effect of treatment with antivirals isolated or combined with each other compared to placebo, in adult patients with confirmed COVID-19 on the following secondary/exploratory outcomes:

1. Ordinal 7-stage scale for clinical outcomes on day 15 ((1) not hospitalized with resumption of normal activities; (2) not hospitalized, but unable to resume normal activities; (3) hospitalized, without the need for supplemental oxygen; (4) hospitalized, requiring supplemental oxygen; (5) hospitalized, requiring high-flow nasal oxygen therapy, non-invasive mechanical ventilation or both; (6) hospitalized, requiring blood oxygenation through a membrane system, invasive mechanical ventilation, or both; (7) Death).
2. Ordinal 6-stage scale for clinical outcomes on day 7 ((1) not hospitalized; (2) hospitalized, without the need for supplemental oxygen; (3) hospitalized, requiring supplemental oxygen; (4) hospitalized, requiring high-flow nasal oxygen therapy, non-invasive mechanical ventilation, or both; (5) hospitalized, requiring blood oxygenation through a membrane system, invasive mechanical ventilation or both; (6) Death).
3. Mortality within 28 days.
4. Days free from mechanical ventilation within 28 days.
5. Days out of hospital within 28 days.
6. Time to discharge, defined as the number of days from randomization to discharge, within 28 days.
7. Days free from respiratory support, defined as the number of days without oxygen, non-invasive ventilation/high-flow nasal cannula or the need for mechanical ventilation in 15 days for participants in Phase II, stages 1 and 2.

Secondary objectives are also to assess the effect of treatment with antivirals isolated or combined with each other compared to placebo, in adult patients with confirmed COVID-19 on the following safety outcomes:

1. Grade 2, 3 or 4 adverse events, which were not present at the patient's entrance, defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected version 2.1, July 2017).[2]
2. Serious adverse events (SAE).*
3. Discontinuation of study drug-related treatment.

SECTION 3 - STUDY METHODS

3.1 Trial design

Randomized, multicenter clinical trial, placebo controlled, blinded, multi-arm and stages to study the effects of repurposing drugs ATV, SOF/DCV and DCV alone against their placebo. Trial stages are described in figure 1S.

3.2 Eligibility criteria

Elegibility criteria are described in table 1S.

3.3 Randomization

The randomization list will be generated electronically using appropriate software. Randomization will be performed in blocks and stratified by center. In Phase 2 stage 1, the blocks will have 12 codes (positions), with each treatment group being represented by 3 different codes and each placebo by a single code. In Phase II, stage 2, the blocks will have 6 codes, the treatment groups will be represented by 2 different codes and each placebo by a single code. Block sizes will be adapted if any arm is discontinued. In the third stage of the study, the blocks will have 6 codes, 4 codes representing the treatment group and 2 codes the placebo group

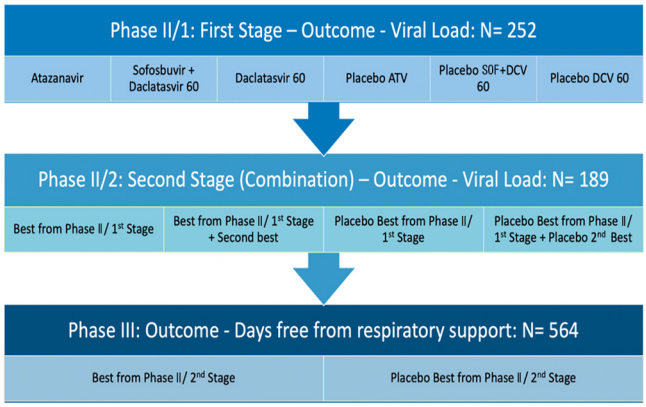

Figure 1S - Study flowchart.
ATV - atazanavir; SOF - sofosbuvir; DCV - daclatasvir.

3.4 Sample size

Based on data from the Wölfel et al. study,[4] the average linear decay rate for patients with SARS-CoV-2 in nasopharyngeal swab samples assessed from the fourth to the fourteenth day of symptoms is about 1.0 $\log_{10}$ (viral load) every 3 days. Assuming this decay rate for the placebo group, under the scenario that all treatments selected in Phase II/1 have a decay rate of 1.20 $\log_{10}$ (viral load), the study will have about 90% power to indicate that at least one of the treatments will be superior to placebo, with a global significance level of 20% for this stage, considering a significance level of 6.7% (Bonferroni correction) for each of the five treatment comparisons in relation to the placebo group.

For Phase II/2, under the scenario that the average decay rate of the group with drug combinations will be 1.30 log (viral load), the experiment will have 90% power to indicate the combined group chosen for the Phase II/2 in relation to the treatment selected in Phase II/1, at a significance level of 10%.

Finally, the 314 patients who used placebo compared to at least 429 patients of the chosen treatment (bringing together patients from all stages) will have 80% power to detect a difference between the groups of 1.5 days without respiratory support, considering that the standard deviation for days without respiratory support should be around 4.2 days[5] and a significance level of 5%, assuming that these times will assume beta-binomial distribution with inflated zeros.

The aforementioned power calculations were performed considering a 20% loss of patients from the intention-to-treat (ITT) population to modified intention-to-treat (ITTm) population, due to the non-confirmation of the real time polymerase chain reaction (RT-PCR) test for SARS-CoV-2. Simulations considering peculiarities of the design with details on the distributions considered for the outcomes and consequent determination of the study's power are found in the Operational Characteristics section of the Statistical Analysis Plan.

3.5 Framework

The Revolution trial is intended do test superiority of antivirals ATV, SOF/DCV or DCV over placebo for decreasing viral load as the primary outcome of Phase II/1 and Phase II/2, as well as days free of respiratory support as primary outcome for Phase III.

3.6 Outcomes

Primary, secondary and safety outcomes are described and defined in table 2S.

Table 1S - Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Adults (≥ 18 years) hospitalized with COVID-19 with one of the following conditions: - Positive RT-PCR test for SARS-CoV-2 OR - Typical clinical history AND chest CT with typical findings, pending the results of the RT-PCR test for SARS-CoV-2 2. Time between symptom onset and inclusion ≤ 9 days 3. SpO_2 ≤ 94% in room air or need for supplemental oxygen to maintain an SpO_2 > 94% 4. The patient consents to participate in the study and is willing to comply with all study procedures, including the collection of virology samples	Presence of any of the following conditions: - Patients requiring invasive mechanical ventilation - ALT or AST level > 5 times the upper limit of normal - Total bilirubin level > 2mg/dL - Platelet count < 50,000 cells/L - Total neutrophil count < 750 cells/L - Renal failure (eGFR < 30mL/min/1.73m², using the MDRD or CKD-EPI method); and predefined renal failure Stage 3 according to the AKIN[9] classification with a serum creatinine level > 4mg/dL or patient already on renal replacement therapy - History of liver disease with moderate to severe impairment (liver cirrhosis with Child Pugh B and C classification) previously known* - Decompensated congestive heart failure* - Pregnant or breastfeeding patients - Known allergy or hypersensitivity to any study drug - Carrier of hepatitis C (positive HCV RNA), active hepatitis B (positive surface antigen in the past), or HIV (ELISA and confirmatory Western blot in the past) - Patients currently using nucleoside or nucleotide analog drugs for any indication - Corrected QT interval > 480 on the electrocardiogram - Heart rate < 55 bpm - Patients using or who recently used (< 90 days) amiodarone - Women of childbearing potential* or men with a partner of childbearing potential who do **NOT** agree to use two contraceptive methods (including barrier method) for 100 days

RT-PCR - real time polymerase chain reaction; CT - computed tomography; SpO2 - oxygen saturation; ALT - alanine aminotransferase; AST - aspartate aminotransferase; eGFR - estimated glomerular filtration rate; MDRD - Modification of Diet in Renal Disease; CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration; AKIN - Acute Kidney Injury Network; HCV - hepatitis C virus; ELISA - enzyme-linked immunosorbent assay. * Defined in Supplementary material 1.

Table 2S - Objectives and outcomes

Primary objective	**Outcome/primary variables**
Phase II first stage (II/1): compare the effect of treatment with single antivirals to the placebo in reducing the load of SARS-CoV-2 in nasopharyngeal swab samples	Decay rate (slope) of the SARS-CoV-2 load logarithm in nasopharyngeal and swab samples evaluated at D0, D3, D6 and D10 after randomization
Phase II second stage (II/2): compare the effect of treatment with combinations of antivirals compared to isolated antivirals in reducing the SARS-CoV-2 load in nasopharyngeal swab samples	Decay rate (slope) of the SARS-CoV-2 load logarithm in nasopharyngeal and swab samples evaluated at D0, D3, D6 and D10 after randomization
Phase III: compare the efficacy of antivirals alone or in combination to the placebo in increasing the number of days free of respiratory support	Days free of respiratory support, defined as the number of days without oxygen, noninvasive ventilation/high-flow nasal cannula or the need for mechanical ventilation within 15 days from randomization 1. This parameter is counted as follows: - D = zero (if the patient dies within 15 days (either in the hospital or at home or remains on respiratory support with oxygen through a nasal catheter, noninvasive ventilation, high-flow nasal catheter, or mechanical ventilation ≥ 15 days) - D = 15 - x (if the patient is released from the hospital in < 15 days, where x represents the number of days with respiratory support during hospitalization)
Secondary objectives	**Outcomes/secondary variables**
Evaluate the status using the 7-stage ordinal scale for clinical outcomes on D15	Percentage of patients in various stages: 1. Not hospitalized with resumption of normal activities 2. Not hospitalized, but unable to resume normal activities 3. Hospitalized, with no need for supplemental oxygen 4. Hospitalized, requiring supplemental oxygen 5. Hospitalized, requiring high-flow nasal oxygen therapy, noninvasive mechanical ventilation, or both 6. Hospitalized, requiring blood oxygenation through a membrane system, invasive mechanical ventilation or both 7. Death
Evaluate the status using the 6-stage ordinal scale for clinical outcomes on D7	Percentage of patients in various stages: 1. Nonhospitalized 2. Hospitalized, with no need for supplemental oxygen 3. Hospitalized, requiring supplemental oxygen 4. Hospitalized, requiring high-flow nasal oxygen therapy, noninvasive mechanical ventilation, or both 5. Hospitalized, requiring blood oxygenation through a membrane system, invasive mechanical ventilation or both 6. Death
Evaluate 28-day mortality	Percentage of deaths in 28 days
Evaluate the number of days free from mechanical ventilation within 28 days	D = 28 - number of days requiring mechanical ventilation D = zero if death occurs or the patient continues to require mechanical ventilation after 28 days
Evaluate the number of days out of the hospital within 28 days	D = 28 - number of days after admission to the hospital D = zero if death occurs or the patient remains hospitalized after 28 days
Evaluate the time to discharge	Number of days from randomization to discharge, within 28 days D = 28 - number of days from randomization to hospital discharge D = zero if death occurs or the patient remains hospitalized after 28 days
Evaluate the number of days free of respiratory support within 15 days for Phases II/1 and II/2	D = 15 - number of days with respiratory support on hospitalization D = zero if death occurs or the patient remains hospitalized with a need for respiratory support defined as the use of low-flow, high-flow oxygen, IMV, or MV in 15 days
Safety objective	**Outcomes/safety variables**
Evaluate Grade 2, 3 or 4 adverse events, which were not present at the patient's entrance, defined by the Division of AIDS table for Grading the Severity of Adult and Pediatric Adverse Events[8]	Percentage of Grade 2, 3, or 4 adverse events in the Division of AIDS table
Evaluate serious adverse events	Percentage of serious adverse events
Evaluate discontinuation of study drug-related treatment	Percentage of patients who needed to discontinue the intervention (study drug)

D - day; IMV - invasive mechanical ventilation; MV - mechanical ventilation.

3.7 Study hypothesis

Does treatment with antivirals (ATV, DCV, SOF/DCV) alone or in combination in adult patients with confirmed COVID-19 reduces the viral load of SARS-CoV-2 and increases days free of respiratory support?

3.8 Recruitment and patient retention

Recruitment will be granted for every COVID-19 patient hospitalized which will be screened for eligibility criteria, sign the informed consent form and followed up by a local study team properly trained until discharge. Loss to follow up is not expected in this period. If hospital discharge occurs before 15 days after the randomization date, these patients will be evaluated by telephone call, performed by the center in 15 days after randomization and in 28 days. Those delivered home before day 10 will be assessed daily until completion of the study drug treatment time (10 days) by telephone call or in person on D3, D6 or D10 to collect swab nasal and to check treatment compliance.

3.9 Allocation concealment

The concealment of the randomization list will be maintained through a centralized, automated, Internet-based randomization system, available 24 hours a day, developed by a team of programmers and researchers from the Research Institute of *HCor-Hospital do Coração* (HCor).

3.10 Blinding

This study is not a global double-blind in stage 1 and 2, as we have 3 drugs with different physical characteristics, which makes global blindness impossible. Both participant and investigator can know, after randomization, which drug group was allocated. However, none will know whether the capsule or coated tablet to be administered is the active drug or placebo, ensuring blinding within that specific group, as well as the outcome assessors.

In Phase III, the global blinding of the stage is possible, since we will have only one active group and a placebo.

A partnership will be carried out with a handling pharmacy duly licensed to carry out the fractioning, repacking, labeling and blinding process of the drugs. The pharmacy will deliver all the drugs to a logistic contractor which will deliver it to the centers.

3.11 Statistical interim analyses and stopping guidance. Statistical methods

The main analysis of the study will be performed on patients of the ITTm population (intention to treat modified), the definition of the analysis populations and more details on statistical methods can be found in the Statistical Analysis Plan. The analyses will be performed with the aid of the R software (R Core Team, 2020).[6]

All the different placebos for ATV, DCV and SOF will always be analyzed together as a single placebo group.

3.11.1 Analysis of primary outcomes

3.11.1.1 Phase II/1

In Phase II/1 patients will be allocated in an allocation ratio 3:3:3:1:1:1 (3 for each treatment group and 1 for placebo). For Phase II/1, and the parameter of interest for the decision will be the comparison of the decay rates of the viral load logarithm from RT-PCR to COVID-19 in 9 days between the treatment groups in comparison with the control using a mixed linear model, defined as:

$$Y_{kl} = \beta_0 + \beta_1 x_{1k} + \beta_2 x_{2k} + \beta_3 x_{3k} + \alpha x_{6kl} + \pi_1 x_{1k} x_{4kl} + \pi_2 x_{2k} x_{4kl} + \pi_3 x_{3k} x_{4kl} + \delta_k + \gamma_k x_{4kl} + \epsilon_{kl}$$

Where k is the index for the k-th individual and l is the index for the repetition of the RT-PCR exam for each individual. x_{1k},x_{2k} and x_{3k} are indicator variables assuming 1 if patient k has been allocated to group 1, 2 or 3, respectively and 0, otherwise. $_4$ is the day of the examination l ($l \in [1,4]$) of patient k. δ_k and γ_k are respectively the random effects for the intercept and for the linear decay rate associated with patient k, assuming normal distributions:

$$\delta_k \sim N(0, \sigma_0^2) \; e \; \gamma_k \sim N(0, \sigma_s^2)$$

And, finally,

$$\epsilon_{kl} \sim N(0, \sigma^2)$$

Thus, coefficients β_1, β_2 and β_3 are the fixed effects of treatments 1, 2 and 3; α the average linear decay rate of viral load for the control group; and the parameters π_1, π_2 and π_3, are the coefficients of interest, the increments of the linear decay rate for each possible treatment of the Phase II/1.

Thus, the hypotheses to be tested in the interim analysis and at the end of Phase II/1 will be:

H_0: $\pi_i \geq 0$,

H_1: $\pi_i < 0$

Where $i = \{1, 2, 3\}$.

Within those 0 days, it was established that the individual will be evaluated at the time of randomization, after 3, 6 and 10 days, totaling 4 measures of viral load based on viral load information over time in patients with self-limited and severe disease as shown in the figure 2S.

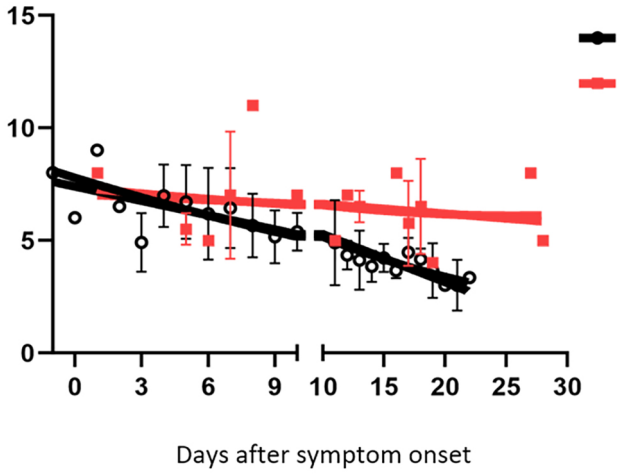

Figure 2S - Comparison of the viral load of patients with COVID-19 according to the date of onset of symptoms until collection.

If patients collect the exam outside the specified day (for example, assume that the patient collected four measurements on D0, D2, D5 and D10; as the assessments on D3 and D6 were anticipated, the model will consider the covariate as continuous variable and will use the values of days, actually observed, for the calculations, x_{6k}= (0,2,5,10).

The imputation will be carried out using only one estimate by the method of multiple imputation by chained equations (package MICE, van Buuren).[7] We opted to perform the primary outcome assessment based on multiple imputations to eventually correct the values of viral loads due to loss of information due to mortality, although based on data by Cavalcanti et al.,[5] the expected mortality during the exam collection period is minimal (< 3%).

The interim analysis, planned to happen when 126 patients are randomized and followed for at least 10 days, will be exclusively for patient safety assessment (based on safety outcomes and adverse events). There is no intention to interrupt the study due to its efficacy or futility in the interim analyses based on the viral load decay outcome within 10 days of randomization.

At the end of Phase II/1, each group will be compared with the placebo considering a significance level for each comparison of 0.067 (Bonferroni correction for multiple comparisons), such that the global type I error of Phase II/1 will be 0.20. If no treatment is significantly different from the placebo group at the stipulated level of significance, the study will be terminated at this stage.

Among the treatments significantly different from the placebo group in relation to the linear rate of viral load decay, the one with the highest rate of decay and considered safe by the independent study safety committee, will be a candidate treatment for Phase II/2 of the study. It will be combined with the drug responsible for the second highest linear decay rate to make up the second Phase II/2 treatment group according to the rules in section 4.1.

If placebo is the group with the second highest rate of decay, the study will move from Phase II/1 directly to Phase III, without combining any drug.

3.11.1.2 Phase II/2

In the 2nd stage, the patients in the ratio 2:2:1:1, 2 for each active arm and 1 for each placebo and the same statistic used in Phase II/1, π_{F2}, now comparing combined treatment against the treatment selected in Phase II/1, since Phase II/1 treatment is necessarily effective in reducing viral load against placebo by the stipulated criteria. In this phase, the tested hypothesis for efficacy will be:

$$H_0: \pi_{F2} - \pi_{F1} \geq 0,$$
$$H_1: \pi_{F2} - \pi_{F1} < 0$$

Where π_{F2} is the linear decay rate of the mixed model of the new suggested treatment, assuming one of the possible combinations of Phase II/2 (ATV/DCV 60mg, ATV/SOF/DCV 60mg, SOF/DCV 60mg), and π_{F1} if refers to the treatment chosen in Phase II/1 (ATV or DCV or SOF/DCV).

Note that the Phase II/2 efficacy hypothesis does not consider patients in the placebo group. These are important to maintain the blindness of the study and its data will be used for safety comparison only. Additionally, it is noteworthy that the patients already collected for the placebo and F1 group will be loaded into Phase II/2. Therefore, necessarily, the F1 and placebo groups will have a larger sample size than the F2 group.

As in Phase II/1, the interim analysis planned after inclusion and data collected from half of the planned patients will only assess safety data. And the study will not be discontinued by futility or efficacy. At the end of Phase II/2 the choice of treatment that will proceed to Phase III will consider a significance level of 10% following the same rules of phase change and choice of drugs in section 4.5.2 and 4.5.3.

3.11.1.3 Phase III

The third stage of the study will proceed in a 2:1 allocation (2 active treatments for each placebo), with a minimum inclusion of 189 patients and a maximum of 564. And the study will perform interim analyses as described in the table below, which can be interrupted by safety, futility or efficacy, using all participants already randomized in Phases II/1 and II/2, since the primary efficacy outcome of Phase III (time of use of ventilatory support within 15 days) will be collected in all patients from these earlier phases as well. This outcome is still called in φ_j , where j = {T-treatment, P-placebo}. The hypothesis tested in each predefined analysis will be:

$$H_0: \varphi_T - \varphi_P = 0,$$
$$H_1: \varphi_T - \varphi_P \neq 0$$

Based on data from previous studies by Coalition Covid Brazil,[5] the distribution of days without ventilatory support up to 15 days, behaves like a beta-binomial with inflated zeros. Thus, the hypothesis test for the treatment effect will be performed using a generalized additive model of location and scale considering the distribution of a beta-binomial mixture with inflated zeros for the data adjusted by age and considering the random effect of the center for each intercept (model for the beta-binomial part and for the probability of zeros).

Phase III has three interim analyses planned, m = {1,2,3}, for each third of the collected sample. In order to maintain the level of global significance at 5%, the interim analyses will consider stop limits according to O'Brien Fleeming criterion, with significance levels of 0.06%, 1.51% and 4.71%, respectively. In Phase III, discontinuations by futility will be allowed and consider the same stopping criteria defined for efficacy.

The placebo group, although made up of placebos of three separate drugs (sometimes in combination) will always be evaluated as a single group, gathering information from all "placebo arms".

3.11.2 Secondary/exploratory outcomes

The models for the clinical outcome ordinal schools on day 15 and 28 of follow-up after randomization will be logistic regression models for ordinal models assuming proportional odds ratios.

The 28-day mortality will also be assessed by logistic regression model. It is expected that there will be no loss of follow-up to mortality in 28 days, however, if any subject is discharged and their follow-up in 28 days is not performed, we will evaluate mortality up to 28 days by proportional risk survival model, considering the censored data at the date of hospital discharge.

All models will be adjusted by the patient's age.

The models for days without mechanical ventilation on 28 days and days outside the hospital will also be Beta-Binomial regressions with inflated zeros (with parameter n = 28) with a structure similar to the model for the primary outcome for Phase III efficacy.

Time to discharge, defined as the number of days from randomization to discharge will be adjusted by generalized linear regression models assuming Gamma distribution with logarithmic link for the response variable. And the effect will be presented as a ratio of averages.

SECTION 4 - STATISTICAL PRINCIPALS

4.1 Operational characteristics

To assess the power of decisions taken at each stage given the proposed design, simulations were carried out in different scenarios. Each scenario was simulated 2000 times and the results of the decisions described below.

All simulations consider a loss of 20% of cases (due to non-confirmation of the post-randomization polymerase chain reaction - PCR - test). This means that for the Phase II/1 simulation, although the sample size is 63 patients randomized per active arm, only 50 cases per active arm were simulated. For Phase II/2 also. And for Phase III, valid inclusions of 150 patients for the control group and 300 patients for the selected treatment group were considered in the simulations.

For Phases II/1 and II/2, simulations of log10 measurements (viral load) were performed for days 0, 3, 6 and 9 from a multivariate normal distribution with different means and covariance matrix Σ, such what:

$$\Sigma = \begin{bmatrix} 3,1 & 1,7 & 1,4 & 0,4 \\ 1,7 & 1,3 & 1,1 & 0,3 \\ 1,4 & 1,1 & 1,2 & 0,3 \\ 0,4 & 0,3 & 0,3 & 0,1 \end{bmatrix}$$

The choice of the covariance matrix was derived from data published in Wölfel et al.[4] The cohort of patients with moderate severity from the seventh day of symptom on (considered as day 0) was used, and then the matrix was derived considering the standard deviations of D0, D3, D6 and D9 and assuming an autoregressive correlation of parameter 0.85. The evaluated scenarios varied the mean viral load at distinct linear decay rates between the treatment and control groups as described in table 3S.

The variable for days free from oxygen support up to 15 days, called Y, was assumed to follow a Beta-Binomial distribution with inflated zeros, theoretically distributed as shown in figure 3S, based on the assessment of patients in the Coalition I study (Cavalcanti et al.).[5]

The distribution has the following probability density function:

$$f(y|n,\pi,\alpha_1,\alpha_2) = I_{X=0} + I_{X=1} * \binom{n}{y} \frac{B(y+\alpha_1, n-y+\alpha_2)}{B(\alpha_1,\alpha_2)}$$

Where IX is an indicator function that assumes 0 with probability π and 1 with probability 1 – π, n is the number of days evaluated (n = 15 fixed, in this case), B() is the Beta function, and the parameters $\alpha 1$ e $\alpha 2$ are called scale parameters, such that the mean of the distribution, the statistic used for the tested hypothesis, the mean of the number of days free of oxygen support up to 15 days, is given by:

$$\varphi = (1-\pi)\frac{n\alpha_1}{\alpha_1+\alpha_2}$$

Thus, from generalized additive model adjustments with Beta-Binomial distribution with inflated zeros in the population of the Coalition I study, estimates of $\alpha 1$, $\alpha 2 e$ π were arrived at, which were considered as expected values for the Control group in scenario 1 (Null) and that suffered small variations for scenarios 2 to 7 to assess the operational characteristics of the study design.

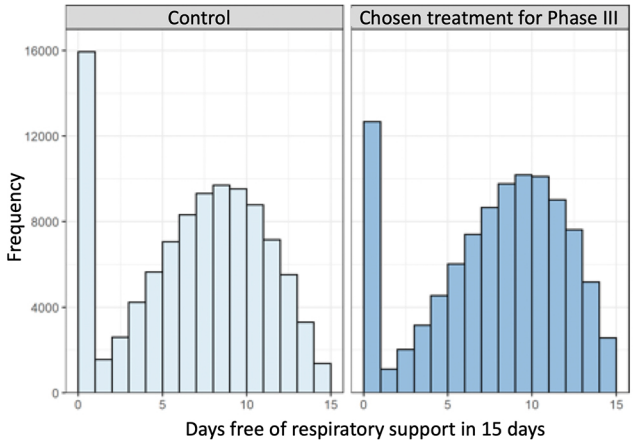

Figure 3S - Theoretical probability density function for days free from ventilatory support up to 15 days.

Table 3S describes the three parameters ($\alpha 1$, $\alpha 2$ e π) considered for each study group and how these parameters reflect the expected mean of the distribution of interest in the last lines that will be used to compare treatments in Phase III of the study, and the respective linear decay rates for the log of the viral load of the comparisons used in Phases II/1 and II/2.

Table 4S describes the proportion of cases significantly higher than placebo at the level of 4% recommended for this phase at the end of each of the scenarios simulated in Phase II/1. Note that in the null scenario the level of global significance simulated was 14.4%, lower than the theoretical 20% defined by the Bonferroni method. This happens because not all the two-by-two combinations between the factor levels are being considered, but the comparisons of each group in relation to placebo, and thus, the specification of the global significance level of 20% for Phase II/ 1 is conservative.

The results presented in scenario 6 indicate that the study will have about 90% power to detect at least one group superior to placebo when the reduction in the viral load log decay rate is expected to be 0.2 units smaller (1.0 to 1.2) in all Phase II/1 treatment groups compared to placebo. Each treatment alone would have about 70% of the power to be considered superior to placebo alone. Simulations with a decay rate of 1.5 for the treatment groups had at least one of the groups chosen for Phase II/2 in all simulated databases (Scenario 2).

Proportions of simulated scenarios where the intervention group was superior to placebo for viral load.

For the second stage (Phase II/2), the comparison of interest is between the two treatment groups (and not against placebo).

Table 3S - Parameters used for simulation scenarios

Parameters	Scenarios						
	1 - Null	2	3	4	5	6	7
Mean decay each 3 days							
Placebo	1,0	1,0	1,0	1,0	1,0	1,0	1,0
Phase II/1 treatment	1,0	1,5	1,25	1,10	1,15	1,20	1,10
Phase II/2 combined treatment	1,0	1,5	1,25	1,10	1,30	1,30	1,20
Parameters for beta-binomial with zeros inflated (distribution of vent support free days)							
φ (proportion of death; Free days equal zero)							
Placebo	0,15	0,15	0,15	0,15	0,15	0,15	0,15
All treatments	0,15	0,15	0,15	0,10	0,10	0,12	0,12
α 1 (1st parameter of scale Beta distribution)							
Placebo	4,1	4,1	4,1	4,1	4,1	4,1	4,1
All treatments	4,1	4,1	4,1	4,1	4,1	4,1	4,1
α 2 (2nd parameter of scale beta distribution)							
Placebo	2,5	2,5	2,5	3,0	3,0	3,0	3,0
Todos os tratamentos	2,5	2,5	2,5	1,5	2,0	2,0	2,5
Mean of free days of support							
Placebo	7,9	7,9	7,9	7,4	7,4	7,4	7,4
All treatments	7,9	7,9	7,9	9,9	9,1	8,9	8,2

Table 4S - Simulations results for Phase II/1

Scenarios	Group 1	Group 2	Group 3	One of the groups at least
1	0,069	0,058	0,067	0,144
2	1,000	0,999	1,000	1,000
3	0,849	0,833	0,828	0,963
4	0,294	0,306	0,307	0,530
5	0,505	0,477	0,510	0,746
6	0,708	0,698	0,706	0,899
7	0,313	0,299	0,297	0,533

Proportions of simulated scenarios where the intervention group was superior to placebo for viral load.

The power of the study in the last three scenarios (5, 6 and 7) where the combined treatment (ATV + some combination of Daclastavir) has a decay rate about 0.1 lower than the treatment selected in Phase II/2 will have more than 90 % of power to proceed to Phase III, at the 10% unilateral significance level.

Finally, the Phase III scenarios, although there are analytical means for comparisons of means and scales to calculate power and sample size considering corrections for skewed distributions, there was a need to consider possible different sample sizes for Phase III comparisons depending on the chosen treatment and whether or not to carry out Phase II/2.

Table 5S presents the results of these comparisons between groups in each interim analysis considering the limits of O'Brian Flemming in each interim analysis. Note that in scenarios (1 to 3), which are null for the efficacy outcome, the global significance level is around 5% analytical.

Scenario 6, which considers a mortality difference of 3% absolute and beta-binomial distribution parameters that imply a mean difference of 1.5 days between the methods, has 95% power to detect differences at the global significance level of 5 %.

4.2 Treatment adherence

Treatment adherence will be reported in daily proportions for each patient and summarized by group by treatment incidence per patient-day.

In addition to the data indicated above, adherence to treatment will be assessed after hospital discharge, if it occurred during the duration of the study intervention. The adherence data will be verified through a participant's diary with information on dosage, storage and time of day that took the drug. This diary will be evaluated during trips to the institution for the expected swab collection.

Table 5S - Simulated power for scenarios 1 to 7

Scenarios	Null hypothesis rejection between treatment and placebo			
	1st interim analysis	2nd interim analysis	3rd interim analysis	One of the groups at least
1	0,005	0,016	0,048	0,051
2	0,005	0,013	0,043	0,048
3	0,009	0,017	0,042	0,051
4	0,992	1	1	1
5	0,771	0,965	1	1
6	0,582	0,857	0,946	0,952
7	0,148	0,347	0,623	0,631

Protocol deviations and violations: We will daily record data on adherence to treatment and eventual crossing of study groups and protocol violations. All deviations and violations will be reported to the Research Ethics Committee of the participating center. Changes in dosage as described in this protocol will not be considered deviations.

4.3 Sensitivity analysis

All analyzes performed will also be performed for the ITT and PP population in all phases of the study.

In addition, it is intended to evaluate as an alternative outcome, the area under the curve of the log of viral load defined by θ

por $\theta_i = \int_0^9 log_{10}(\mu_{T_i})xdx - \int_0^9 log_{10}(\mu_P)xdx$

being μg the viral load for RT-PCR for CODIV-19 after randomization, and g the index for group P (Placebo) and Ti treatment with i = {1, 2, 3}. And the tests for the primary outcome will be performed considering an a priori neutral scenario, $\theta i \sim N(0, 10)$.

Within these 10 days, it was established that the individual will be evaluated at the time of randomization, after 3, 6 and 10 days, totaling 4 measurements of viral load. This area will then be approximated by the Riemman sum of these assessments: $\theta i = \sum log10(\mu Ti)\Delta x - \sum log10(\mu P)\Delta x$. The same comparison considering the two treatments considered in Phase II/2 will also be compared by the same statistic.

If patients collect the swab outside the established day, this area will be calculated considering exactly the measurement day (for example, assume that the patient collected 4 measurements on days 0, 2, 5 and 10; like the assessments on days 3 and 6 were anticipated, the area calculations will consider the real time differences between measurements, Δx = 2, 3 and 5 days, and not the recommended days).

Additionally, as the efficacy outcome for Phase II/1 and II/2 assume imputations for possible missing data from the swabs collections, it is intended to carry out the analyzes for the mITT population considering only the observed data as an outcome.

In addition, all models do not take the study center effect into account, and hierarchical model fits to the center for the intercepts of the primary and secondary outcome models will also be fitted as a sensitivity analysis.

A sensitivity analysis will also be provided for those patients who used cytokine modulators prescribed by the attending physician without belonging, however, to any other clinical study.

4.4 Additional analyses

Subgroup analyses of patients with COVID-19 will be performed by comparing cases only in Phase III of the study:

- Age (above or below 60 years).
- Initial symptoms ≤ 4 and > 4 days.
- Supplemental oxygen need: ≤ 4L/min *versus* > 4L/min.
- Use of full-dose anticoagulation.

Subgroup assessments will be performed with the inclusion of interaction parameters in the models previously defined for the viral load log. A sensitivity analysis in all phases of the study is also foreseen for those patients who made use of cytokine modulators prescribed by the attending physician without, however, belonging to any other clinical study. Other sensitivity analyses are not foreseen.

4.5 Screening data

The number of patients screened, the number of patients recruited and the reason for non-recruitment will be collected. This information will be provided overall and presented in a study flow diagram.

4.6 Study populations

1. Modified intention-to-treat population (ITTm). Defined by all randomized patients with positive RT-PCR for SARS-CoV-2, regardless of whether or not they were treated with the allocated medication.

2. Intention-to-treat (ITT) population. Defined by all randomized patients, regardless of whether or not they were treated with the allocated medication.

3. Population per protocol (PP). Defined by all randomized patients with positive RT-PCR for SARS-CoV-2, with at least 80% drug adherence to the allocated treatment.

4. Security population (SP). Defined by all randomized patients, being compared according to the medications actually administered in at least one dose.

SECTION 5 - TRIAL POPULATION

5.0 Descontinuation of the drug treatment and safety criteria

The set of primary analyses for safety and efficacy will include individuals who received at least one dose of the study drug. Emerging treatment data will be analyzed and defined as data collected from the first study drug dose to the date of the last study drug dose plus 30 days.

At medical discretion, the study drug(s) will be discontinued if a research participant meets one of the following criteria:

1. The researcher considers that the discontinuation of the study drug is in the best interest of the research participant.

2. Elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above ten times the value of upper limit of normality (ULN). Elevations in ALT or AST often follow COVID-19's clinical picture, whether due to shock, sepsis or even direct SARS-CoV-2 infection in liver cells.[8] This can happen in the two study groups: active drug or placebo.

3. Elevation of ALT or AST above three times the ULN **WITHOUT** an increase in Alkaline Phosphatase confirmed in a new test in 48 hours **AND** one of the criteria below:

a. Total bilirubin > 2 times the ULN;

b. International Normalized Ratio (INR) > 2.

4. Elevation of ALT or AST above three times the ULN accompanied by the following two criteria:

a. Onset or worsening of fatigue, nausea, vomiting, discomfort in the upper abdomen, fever;

b. Rash and/or peripheral eosinophilia (>5%).

5. Any rash grade 3 or greater accompanied by symptoms;

6. Any grade 4 AE or laboratory abnormality considered to be related to the study drug.

5.1 Data collection, management and analysis

Collection and management methods

The data collection system to be adopted in the development of this study is widely used in research projects and with easy access via the web with Redcap® sofware. Only users qualified by the system administrator can have access and each registered user can access the system only with their login and password, and the sharing of this information between project collaborators is prohibited.

Statistical Analysis Plan cheklist is described in the appendix 1S. Dummy tables S1 to S9 are described in the appendix 2S.

REFERENCES

1. World Health Organization (WHO). WHO Coronavirus (COVID-19) Dashboard. [cited 2022 Feb 2]. Available from: https://covid19.who.int/
2. National Institute of Allergy and Infectious Diseases (NIH). Division of AIDS (DAIDS). Regulatory Support Center (RSC). DAIDS Adverse Event Grading Tables. DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 - July 2017. Available from: https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables
3. Mehta R, Kellum J, Shah S, Molitoris BA, Ronco C, Warnock DG, Levin A; Acute Kidney Injury Network. Acute Kidney Injury Network: a report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.
4. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020;581(7809):465-9.
5. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LC, Veiga VC, Avezum A, Damiani LP, Marcadenti A, Kawano-Dourado L, Lisboa T, Junqueira DLM, de Barros E Silva PGM, Tramujas L, Abreu-Silva EO, Laranjeira LN, Soares AT, Echenique LS, Pereira AJ, Freitas FGR, Gebara OCE, Dantas VCS, Furtado RHM, Milan EP, Golin NA, Cardoso FF, Maia IS, Hoffmann Filho CR, Kormann APM, Amazonas RB, Bocchi de Oliveira MF, Serpa-Neto A, Falavigna M, Lopes RD, Machado FR, Berwanger O; Coalition Covid-19 Brazil I Investigators. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. N Engl J Med. 2020;383(21):2041-52
6. R Foundation for Statistical Computing. R: A language and environment for statistical computing. Vienna, Austria: R Core Team; 2020. Available from: https://www.r-project.org/.
7. van Buuren S. MICE: multivariate imputation by chained equations in R. J Stat Softw. 2011;45(3):1-67.
8. Wang Y, Liu S, Liu H, Li W, Lin F, Jiang L, et al. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. J Hepatol. 2020;73(4):807-16.

Appendix 1S - Statistical Analysis Plan (SAP) Checklist v 1.0 2019

Section/item	Index	Description	Reported on page #
Section 1: Administrative information			
Trial and trial registration	1a	Descriptive title that matches the protocol, with SAP either as a forerunner or subtitle, and trial acronym (if applicable)	2
	1b	Trial registration number	2
SAP version	2	SAP version number with dates	2
Protocol version	3	Reference to version of protocol being used	2
SAP revisions	4a	SAP revision history	2
	4b	Justification for each SAP revision	2
	4c	Timing of SAP revisions in relation to interim analyses, etc.	2
Roles and responsibility	5	Names, affiliations, and roles of SAP contributors	3
Signatures of	6a	Person writing the SAP	3
	6b	Senior statistician responsible	3
	6c	Chief investigator/clinical lead	3
Section 2: Introduction			
Background and rationale	7	Synopsis of trial background and rationale including a brief description of research question and brief justification for undertaking the trial	4
Objectives	8	Description of specific objectives or hypotheses	4

Continue...

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Section/item	Index	Description	Reported on page #
Section 3: Study methods			
Trial design	9	Brief description of trial design including type of trial (e.g., parallel group, multi-arm, crossover, factorial) and allocation ratio and may include brief description of interventions	6
Randomization	10	Randomization details, e.g., whether any minimization or stratification occurred (including stratifying factors used or the location of that information if it is not held within the SAP)	6
Sample size	11	Full sample size calculation or reference to sample size calculation in protocol (instead of replication in SAP)	6
Framework	12	Superiority, equivalence, or noninferiority hypothesis testing framework, including which comparisons will be presented on this basis	7
Statistical interim analysis and stopping guidance	13a	Information on interim analyses specifying what interim analyses will be carried out and listing of time points	8-11,15
	13b	Any planned adjustment of the significance level due to interim analysis	8-11,15
	13c	Details of guidelines for stopping the trial early	8-11,15
Timing of final analysis	14	Timing of final analysis, e.g., all outcomes analysed collectively or timing stratified by planned length of follow-up	8,9,11
Timing of outcome assessments	15	Time points at which the outcomes are measured including visit "windows"	7,12
Section 4: Statistical principals			
Confidence intervals and p values	16	Level of statistical significance	6,15
	17	Description and rationale for any adjustment for multiplicity and, if so, detailing how the type 1 error is to be controlled	10
	18	Confidence intervals to be reported	10
Adherence and protocol deviations	19a	Definition of adherence to the intervention and how this is assessed including extent of exposure	16
	19b	Description of how adherence to the intervention will be presented	16
	19c	Definition of protocol deviations for the trial	16
	19d	Description of which protocol deviations will be summarized	16
Analysis populations	20	Definition of analysis populations, e.g., intention to treat, per protocol, complete case, safety	17
Section 5: Trial population			
Screening data	21	Reporting of screening data (if collected) to describe representativeness of trial sample	7
Eligibility	22	Summary of eligibility criteria	6
Recruitment	23	Information to be included in the CONSORT flow diagram	17
Withdrawal/follow-up	24a	Level of withdrawal, e.g., from intervention and/or from follow-up	18
	24b	Timing of withdrawal/lost to follow-up data	18
	24c	Reasons and details of how withdrawal/lost to follow-up data will be presented	18
Baseline patient characteristics	25a	List of baseline characteristics to be summarized	27
	25b	Details of how baseline characteristics will be descriptively summarized	27
Section 6: Analysis			
Outcome definitions		List and describe each primary and secondary outcome including details of:	Table 2S
	26a	Specification of outcomes and timings. If applicable include the order of importance of primary or key secondary end points (e.g., order in which they will be tested)	Table 2S
	26b	Specific measurement and units (e.g., glucose control, hbA1c [mmol/mol or %])	Table 2S
	26c	Any calculation or transformation used to derive the outcome (e.g., change from baseline, QoL score, Time to event, logarithm, etc.)	Table 2S
Analysis methods	27a	What analysis method will be used and how the treatment effects will be presented	8,9
	27b	Any adjustment for covariates	8,9
	27c	Methods used for assumptions to be checked for statistical methods	8,9
	27d	Details of alternative methods to be used if distributional assumptions do not hold, e.g., normality, proportional hazards, etc.	9,11-15
	27e	Any planned sensitivity analyses for each outcome where applicable	16
	27f	Any planned subgroup analyses for each outcome including how subgroups are defined	17
Missing data	28	Reporting and assumptions/statistical methods to handle missing data (e.g., multiple imputation)	16
Additional analyses	29	Details of any additional statistical analyses required, e.g., complier-average causal effect10 analysis	16
Harms	30	Sufficient detail on summarizing safety data, e.g., information on severity, expectedness, and causality; details of how adverse events are coded or categorized; how adverse event data will be analysed, i.e., grade 3/4 only, incidence case analysis, intervention emergent analysis	18
Statistical software	31	Details of statistical packages to be used to carry out analyses	8,10
References	32a	References to be provided for nonstandard statistical methods	21
	32b	Reference to Data Management Plan	21
	32c	Reference to the Trial Master File and Statistical Master File	21
	32d	Reference to other standard operating procedures or documents to be adhered to	21

SAP - statistical analysis plan; CONSORT - Consolidated Standards of Reporting Trials; hbA1c - haemoglobin A1c; QoL - quality of life. Taken from the paper: Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017;318(23):2337-43. For more information visit: *Vj g"f gxgmpr o gpv"qh"vj ku"ej gemkuv/y cu"hvpf gf "d{"\j g O TE"Jvdu"hqt"Vkcnu"O gy qf qmpi {"Tgugctej 0*

Appendix 2S - Dummy tables.

Table 1S - Baseline clinical characteristics per group Phase II/1

	Atazanavir	**Daclatasvir 60mg**	**Sofusbuvir + Daclatasvir 60mg**	**Placebo**
	n = xxx	**n = xxx**	**n = xxx**	**n = xxx**
Age	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Sex female	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
COVID-19				
Positive	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Negative	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Comorbidities				
Hipertension	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Diabetes	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Ex smoker	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Smoker	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Obesity	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Solid tumor	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Hematological malignancies	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Heart failure	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
COPD	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
AIDS	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Chronic renal failure	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
RRT	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Cyrrosis	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Asthma	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Neuromuscular disease	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Previous MI	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Previous medication				
Corticosteroids	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Angiotensin conversion enzyme inhibitors	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Angiotensin receptor antagonist II	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Acetylsalicylic acid	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Hydroxicloroquine	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Azytromicin	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Clinical data				
Systolic blood pressure, mmHg	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Diastolic blood pressure, mmHg	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Heart rate, bpm	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Respiratory rate, rpm	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
SpO_2, %,	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Oxygen support				
None	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Low flow oxygen catheter	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Venturi mask	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Blood samples				
Creatinine, mg/dL	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
D-dimer, ng/dL	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Hemoglobin, g/dL	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Total leucocytes, 1/mL,	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]
Platelets, 1/mm^3,	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Linphocytes, 1/mL	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]
Lactate (mg/dL)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x

Continue...

...continuation

	Atazanavir n = xxx	Daclatasvir 60mg n = xxx	Sofusbuvir+Daclatasvir 60mg n = xxx	Placebo n = xxx
Additional medication				
Ceftriaxone	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Ceftaroline	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
PiperacilinaTazobactan	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Oxacylin	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Vancomycin	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Carbapenemic	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Quinolone	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Corticosteroids				
Hydrocortisone	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Dexametasone	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Collected swabs				
D0	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
D3	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
D6	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
D9	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Time between symptoms and randomization	xx.x [xx.x - xx.x]	xx.x [xx.x - xx.x]	xx.x [xx.x - xx.x]	xx.x [xx.x - xx.x]
Time between admission and randomization	xx.x [xx.x - xx.x]	xx.x [xx.x - xx.x]	xx.x [xx.x - xx.x]	xx.x [xx.x - xx.x]

COPD - chronic obstructive pulmonary disease; RRT - renal replacement therapy; MI - myocardial infarction; SpO_2 – oxygen saturation; D - day. Results expressed as mean ± standard deviation, n (%) or median [interquartile range].

Table 2S - Baseline clinical characteristics per group Phase II/2

	Best Phase II/1 n = xxx	Best + Second best Phase II/1 n = xxx	Placebo n = xxx
Age	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Sex female	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
COVID-19			
Positive	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Negative	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Comorbidities			
Hipertension	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Diabetes	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Ex smoker	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Smoker	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Obesity	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Solid tumor	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Hematological malignancies	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Heart failure	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
COPD	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
AIDS	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Chronic renal failure	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
RRT	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Cyrrosis	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Asthma	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Neuromuscular disease	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Previous MI	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Previous medication			
Corticosteroids	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Angiotensin conversion enzyme inhibitors	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Angiotensin receptor antagonist II	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Acetylsalicylic acid	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Hydroxicloroquine	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Azytromicin	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

Continue...

...continuation

	Best Phase II/1 n = xxx	Best + Second best Phase II/1 n = xxx	Placebo n = xxx
Clinical data			
Systolic blood pressure, mmHg	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Diastolic blood pressure, mmHg	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Heart rate, bpm	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Respiratory rate, rpm	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
SpO_2, %	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Oxygen support			
None	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Low flow oxygen catheter	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Venturi mask	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Blood samples			
Creatinine, mg/dL	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
D-dimer, ng/dL	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Hemoglobin, g/dL	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Total leucocytes, 1/mL	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]
Platelets, $1/mm^3$	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Linphocytes, 1/mL	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]
Lactate (mg/dL)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Additional medication			
Ceftriaxone	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Ceftaroline	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Piperacilina tazobactan	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Oxacylin	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Vancomycin	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Carbapenemic	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Quinolone	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Corticosteroids			
Hydrocortisone	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Dexametasone	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Collected swabs			
D0	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
D3	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
D6	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
D9	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Time between symptoms and randomization	xx.x [xx.x - xx.x]	xx.x [xx.x - xx.x]	xx.x [xx.x - xx.x]
Time between admission and randomization	xx.x [xx.x - xx.x]	xx.x [xx.x - xx.x]	xx.x [xx.x - xx.x]

COPD - chronic obstructive pulmonary disease; RRT - renal replacement therapy; MI - myocardial infarction; SpO_2 – oxygen saturation; D - day. Results expressed as mean ± standard deviation, n (%) or median [interquartile range]..

Table 3S - Baseline clinical characteristics per group Phase III

	Best Phase II/1/2 n = xxx	Placebo n = xxx
Age	xx.x ± xx.x	xx.x ± xx.x
Sex female	xx.x (xx.x)	xx.x (xx.x)
COVID-19		
Positive	xx.x (xx.x)	xx.x (xx.x)
Negative	xx.x (xx.x)	xx.x (xx.x)
Comorbidities		
Hipertension	xx.x (xx.x)	xx.x (xx.x)
Diabetes	xx.x (xx.x)	xx.x (xx.x)
Ex smoker	xx.x (xx.x)	xx.x (xx.x)

Continue...

...continuation

	Best Phase II/1/2 **n = xxx**	**Placebo** **n = xxx**
Smoker	xx.x (xx.x)	xx.x (xx.x)
Obesity	xx.x (xx.x)	xx.x (xx.x)
Solid tumor	xx.x (xx.x)	xx.x (xx.x)
Hematological malignancies	xx.x (xx.x)	xx.x (xx.x)
Heart failure	xx.x (xx.x)	xx.x (xx.x)
COPD	xx.x (xx.x)	xx.x (xx.x)
AIDS	xx.x (xx.x)	xx.x (xx.x)
Chronic renal failure	xx.x (xx.x)	xx.x (xx.x)
RRT	xx.x (xx.x)	xx.x (xx.x)
Cyrrosis	xx.x (xx.x)	xx.x (xx.x)
Asthma	xx.x (xx.x)	xx.x (xx.x)
Neuromuscular disease	xx.x (xx.x)	xx.x (xx.x)
Previous MI	xx.x (xx.x)	xx.x (xx.x)
Previous medication		
Corticosteroids	xx.x (xx.x)	xx.x (xx.x)
Angiotensin conversion enzyme inhibitors	xx.x (xx.x)	xx.x (xx.x)
Angiotensin receptor antagonist II	xx.x (xx.x)	xx.x (xx.x)
Acetylsalicylic acid	xx.x (xx.x)	xx.x (xx.x)
Hydroxicloroquine	xx.x (xx.x)	xx.x (xx.x)
Azytromicin	xx.x (xx.x)	xx.x (xx.x)
Clinical data		
Systolic blood pressure, mmhg	xx.x ± xx.x	xx.x ± xx.x
Diastolic blood pressure, mmhg	xx.x ± xx.x	xx.x ± xx.x
Heart Rate, bpm	xx.x ± xx.x	xx.x ± xx.x
Respiratory rate, rpm	xx.x ± xx.x	xx.x ± xx.x
SpO_2, %	xx.x ± xx.x	xx.x ± xx.x
Oxygen support		
None	xx.x (xx.x)	xx.x (xx.x)
Low flow oxygen catheter	xx.x (xx.x)	xx.x (xx.x)
Venturi mask	xx.x (xx.x)	xx.x (xx.x)
Blood samples		
Creatinine, mg/dL	xx.x ± xx.x	xx.x ± xx.x
D-dímer, ng/dL	xx.x ± xx.x	xx.x ± xx.x
Hemoglobin, g/dL	xx.x ± xx.x	xx.x ± xx.x
Total leucocytes, 1/mL	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]
Platelets, $1/mm^3$	xx.x ± xx.x	xx.x ± xx.x
Linphocytes, 1/mL	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]
Lactate (mg/dL)	xx.x ± xx.x	xx.x ± xx.x
Additional medication		
Ceftriaxone	xx.x (xx.x)	xx.x (xx.x)
Ceftaroline	xx.x (xx.x)	xx.x (xx.x)
Piperacilina tazobactan	xx.x (xx.x)	xx.x (xx.x)
Oxacylin	xx.x (xx.x)	xx.x (xx.x)
Vancomycin	xx.x (xx.x)	xx.x (xx.x)
Carbapenemic	xx.x (xx.x)	xx.x (xx.x)
Quinolone	xx.x (xx.x)	xx.x (xx.x)
Corticosteroids		
Hydrocortisone	xx.x (xx.x)	xx.x (xx.x)
Dexametasone	xx.x (xx.x)	xx.x (xx.x)
Collected swabs		
D0	xx.x (xx.x)	xx.x (xx.x)
D3	xx.x (xx.x)	xx.x (xx.x)
D6	xx.x (xx.x)	xx.x (xx.x)
D9	xx.x (xx.x)	xx.x (xx.x)
Time between symptoms and randomization	xx.x [xx.x - xx.x]	xx.x [xx.x - xx.x]
Time between admission and randomization	xx.x [xx.x - xx.x]	xx.x [xx.x - xx.x]

COPD - chronic obstructive pulmonary disease; RRT - renal replacement therapy; MI - myocardial infarction; SpO_2 – oxygen saturation; D - day. Results expressed as mean ± standard deviation, n (%) or median [interquartile range]..

Table 4S - Outcomes Phase II/1

Outcomes	Atazanavir	Daclatasvir 60mg	Sofusbuvir + daclatasvir 60mg	Placebo	Effect size		
					Atazanavir *versus* placebo	Davlatasvir *versus* placebo	Sofusbuvir + daclatasvir 60mg *versus* placebo
	n = xxx	n = xxx	n = xxx	n = xxx	[IC95%]	[IC95%]	[IC95%]
Viral load linear log decay rate in 9 days	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	x.xx [x.xx; x.xx]	x.xx [x.xx; x.xx]	x.xx [x.xx; x.xx]
Respiratory support free days in 15 days	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	x.xx [x.xx; x.xx]	x.xx [x.xx; x.xx]	x.xx [x.xx; x.xx]
7 stages ordinal scale in 15 days	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]	x.xx [x.xx; x.xx]	x.xx [x.xx; x.xx]	x.xx [x.xx; x.xx]
Category 1 - Not hospitalized with return to normal activities	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)			
Category 2 - Not hospitalized unable to return to normal activities)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)			
Category 3 - Hospitalized without supplemental oxigen support	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)			
Category 4 - Hospitalized with suplemental oxygen support)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)			
Category 5 - Hospitalized with HFOT or NIV support or both	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)			
Category 6 - Hospitalized, with MV or ECMO or both	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)			
Category 7 - Death, n (%)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)			
6 Stages ordinal scale in 7 days	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]	x.xx [x.xx; x.xx]	x.xx [x.xx; x.xx]	x.xx [x.xx; x.xx]
Category 1 - Not hospitalized	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)			
Category 2 - Hospitalized, without supplemental oxygen	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)			
Category 3 - Hospitalized, with supplemental oxygen	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)			
Category 4 - Hospitalized with HFOT or NIV support or both	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)			
Category 5 - Hospitalized, with MV or ECMO or both	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)			
Category 6 - Death	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)			
28 day Mortality	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx [x.xx; x.xx]	x.xx [x.xx; x.xx]
MV free days within 28 days	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	x.xx [x.xx; x.xx]	x.xx [x.xx; x.xx]	x.xx [x.xx; x.xx]
Days out of hospital within 28 days	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx [x.xx; x.xx]	x.xx [x.xx; x.xx]
Time to discharge, days	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx [x.xx; x.xx]	x.xx [x.xx; x.xx]

IC95% - 95% confidence interval; HFOT - high flow oxygen therapy; NIV - noninvasive ventilation; MV - mechanical ventilation; ECMO - extracorporeal membrane oxygenation. Results expressed as mean ± standard deviation, n (%) or median [interquartile range].

Table 5S - Outcomes Phase II/2

Outcomes	Best Phase II/1	Best + Second best Phase II/1	Placebo	Effect size
				Best Phase II/1 *versus* Best + Second Best Phase II/1
	n=xxx	n=xxx	n=xxx	[IC 95%]
Viral Load Linear Log Decay Rate in 9 days	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	x.xx [x.xx; x.xx]
Respiratory Support free days in 15 days	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	x.xx [x.xx; x.xx]
7 Stages Ordinal Scale in 15 days	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]	x.xx [x.xx; x.xx]
Category 1 - Not hospitalized with return to normal activities	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	
Category 2 - Not hospitalized unable to return to normal activities	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	
Category 3 - Hospitalized without supplemental oxigen support	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	
Category 4 - Hospitalized with suplemental oxygen support	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	
Category 5 - Hospitalized with HFOT or NIV support or both	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	
Category 6 - Hospitalized, with MV or ECMO or both	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	
Category 7 - Death	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	
6 Stages Ordinal Scale in 7 days	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]	x.xx [x.xx; x.xx]
Category 1 - Not hospitalized	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	
Category 2 - Hospitalized, without supplemental oxygen	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	
Category 3 - Hospitalized, with supplemental oxygen	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	
Category 4 - Hospitalized with HFOT or NIV support or both	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	
Category 5 - Hospitalized, with MV or ECMO or both	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	
Category 6 - Death	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	
28 day Mortality	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]
MV free days within 28 days	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	x.xx [x.xx; x.xx]
Days out of hospital within 28 days	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]
Time to discharge, days	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]

IC95% - 95% confidence interval; HFOT - high flow oxygen therapy; NIV - noninvasive ventilation; MV - mechanical ventilation; ECMO - extracorporeal membrane oxygenation. Results expressed as mean ± standard deviation, n (%) or median [interquartile range].

Table 6S - Outcomes Phase III

Outcomes	Best Phase II/1 or 2	Placebo	Effect Size Best Phase II/1 *versus* Best + Second Best Phase II/1
	n = xxx	n = xxx	[IC 95%]
Respiratory support free days in 15 days	xx.x ± xx.x	xx.x ± xx.x	x.xx [x.xx - x.xx]
7 Stages ordinal scale in 15 days	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]
Category 1 - Not hospitalized with return to normal activities	x.xx (x.xx)	x.xx (x.xx)	
Category 2 - Not hospitalized unable to return to normal activities	x.xx (x.xx)	x.xx (x.xx)	
Category 3 - Hospitalized without supplemental oxigen support	x.xx (x.xx)	x.xx (x.xx)	
Category 4 - Hospitalized with suplemental oxygen support	x.xx (x.xx)	x.xx (x.xx)	
Category 5 - Hospitalized with HFOT or NIV support or both	x.xx (x.xx)	x.xx (x.xx)	
Category 6 - Hospitalized, with MV or ECMO or both	x.xx (x.xx)	x.xx (x.xx)	
Category 7 - Death	x.xx (x.xx)	x.xx (x.xx)	
6 Stages ordinal scale in 7 days	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]
Category 1 - Not hospitalized	x.xx (x.xx)	x.xx (x.xx)	
Category 2 - Hospitalized, without supplemental oxygen	x.xx (x.xx)	x.xx (x.xx)	
Category 3 - Hospitalized, with supplemental oxygen	x.xx (x.xx)	x.xx (x.xx)	
Category 4 - Hospitalized with HFOT or NIV support or both	x.xx (x.xx)	x.xx (x.xx)	
Category 5 - Hospitalized, with MV or ECMO or both	x.xx (x.xx)	x.xx (x.xx)	
Category 6 - Death	x.xx (x.xx)	x.xx (x.xx)	
28 day Mortality	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx - x.xx]
MV free days within 28 days	xx.x ± xx.x	xx.x ± xx.x	x.xx [x.xx - x.xx]
Days out of hospital within 28 days	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx - x.xx]
Time to discharge, days	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx - x.xx]

IC95% - 95% confidence interval; HFOT - high flow oxygen therapy; NIV - noninvasive ventilation; MV - mechanical ventilation; ECMO - extracorporeal membrane oxygenation. Results expressed as mean ± standard deviation, n (%) or median [interquartile range].

Table 7S - Adverse events per treatment group

Serious adverse event	Atazanavir	Daclatasvir, 60mg	Sofusbuvir + Daclatasvir, 60mg	Placebo
Serious adverse event	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Any adverse event	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Cardiovascular	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Arrhythmia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Hypertension	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Hypotension	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Miocardial infartion	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Heart failure	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Major bleeding in any site	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Prolonged PR interval or AV block	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Prolonged QTc interval 2	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Thrombosis or embolism	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Dermatologic	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Alopecia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Bruising	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Cellulitis	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Hyperpigmentation	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Petechiae	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Pruritus	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Rash	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Endocrine and metabolic	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Diabetes Mellitus	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Gynecomastia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Hyperthyroidism	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Hypothyroidism	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Lipoatrophy	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Lipohypertrophy	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)

Continue...

...continuation

Serious adverse event	Atazanavir	Daclatasvir, 60mg	Sofusbuvir + Daclatasvir, 60mg	Placebo
Gastrointestinal	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Anorexia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Ascites	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Bloating or distension	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Cholecystitis	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Constipation	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Diarrhea	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Dysphagia or odynophagia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Gastrointestinal bleeding	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Mucositis or stomatitis	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Nausea	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Pancreatitis	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Perforation (colon or rectum)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Proctitis	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Rectal discharge	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Vomiting	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Musculoskeletal	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Arthralgia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Arthritis	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Myalgia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Osteonecrosis	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Osteopenia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Osteoporosis	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Neurologic	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Acute CNS ischemia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Altered mental status	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Ataxia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Cognitive, behavioral, or attentional disturbance	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Headache	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Neuromuscular weakness	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Neurosensory alteration	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Seizures	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Syncope	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Psychiatric	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Insomnia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Psychiatric disorders	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Suicidal ideation or attempt	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Respiratory	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Bronchospasm	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Dispnea or respiratory distress	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Sensorial	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Hearing loss	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Tinnitus	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Uveitis	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Vertigo	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Visual changes	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Systemic	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Acute allergic reaction	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Chills	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Cytokine release syndrome	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Fatigue or malaise	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Fever	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Pain	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Serum sickness	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Underweight	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Unintentional weight loss	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)

PR - PR interval; AV - atrioventricular; CNS - central nervous system. Results expressed as n (%).

Table 8S - Adverse events per treatment group Phase II/2

Serious adverse event	Best Phase II/1	Best + Second Best Phase II/1	Placebo
Serious adverse event	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Any adverse event	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Cardiovascular	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Arrhythmia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Hypertension	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Hypotension	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Miocardial infartion	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Heart failure	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Major bleeding in any site	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Prolonged PR interval or AV block	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Prolonged QTc interval 2	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Thrombosis or embolism	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Dermatologic	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Alopecia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Bruising	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Cellulitis	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Hyperpigmentation	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Petechiae	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Pruritus	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Rash	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Endocrine and metabolic	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Diabetes Mellitus	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Gynecomastia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Hyperthyroidism	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Hypothyroidism	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Lipoatrophy	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Lipohypertrophy	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Gastrointestinal	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Anorexia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Ascites	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Bloating or distension	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Cholecystitis	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Constipation	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Diarrhea	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Dysphagia or odynophagia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Gastrointestinal bleeding	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Mucositis or stomatitis	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Nausea	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Pancreatitis	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Perforation (colon or rectum)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Proctitis	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Rectal discharge	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Vomiting	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Musculoskeletal	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Arthralgia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Arthritis	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Myalgia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Osteonecrosis	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Osteopenia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Osteoporosis	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)

Continue...

...continuation

Serious adverse event	Best Phase II/1	Best + Second Best Phase II/1	Placebo
Neurologic	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Acute CNS ischemia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Altered mental status	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Ataxia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Cognitive, behavioral, or attentional disturbance	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Headache	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Neuromuscular weakness	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Neurosensory alteration	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Seizures	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Syncope	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Psychiatric	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Insomnia	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Psychiatric disorders	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Suicidal ideation or attempt	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Respiratory	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Bronchospasm	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Dispnea or respiratory distress	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Sensorial	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Hearing loss	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Tinnitus	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Uveitis	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Vertigo	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Visual changes	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Systemic	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Acute allergic reaction	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Chills	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Cytokine release syndrome	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Fatigue or malaise	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Fever	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Pain	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Serum sickness	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Underweight	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Unintentional weight loss	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)

PR - PR interval; AV - atrioventricular; CNS - central nervous system. Results expressed as n (%).

Table 9S - Adverse events per treatment group Phase III

Serious adverse event	Best Phase II/1 or 2	Placebo
Serious adverse event	x.xx (x.xx)	x.xx (x.xx)
Any adverse event	x.xx (x.xx)	x.xx (x.xx)
Cardiovascular	x.xx (x.xx)	x.xx (x.xx)
Arrhythmia	x.xx (x.xx)	x.xx (x.xx)
Hypertension	x.xx (x.xx)	x.xx (x.xx)
Hypotension	x.xx (x.xx)	x.xx (x.xx)
Miocardial infartion	x.xx (x.xx)	x.xx (x.xx)
Heart failure	x.xx (x.xx)	x.xx (x.xx)
Major bleeding in any site	x.xx (x.xx)	x.xx (x.xx)
Prolonged PR interval or AV block	x.xx (x.xx)	x.xx (x.xx)
Prolonged QTc interval 2	x.xx (x.xx)	x.xx (x.xx)
Thrombosis or embolism	x.xx (x.xx)	x.xx (x.xx)

Continue...

...continuation

Serious adverse event	Best Phase II/1 or 2	Placebo
Dermatologic	x.xx (x.xx)	x.xx (x.xx)
Alopecia	x.xx (x.xx)	x.xx (x.xx)
Bruising	x.xx (x.xx)	x.xx (x.xx)
Cellulitis	x.xx (x.xx)	x.xx (x.xx)
Hyperpigmentation	x.xx (x.xx)	x.xx (x.xx)
Petechiae	x.xx (x.xx)	x.xx (x.xx)
Pruritus	x.xx (x.xx)	x.xx (x.xx)
Rash	x.xx (x.xx)	x.xx (x.xx)
Endocrine and metabolic	x.xx (x.xx)	x.xx (x.xx)
Diabetes mellitus	x.xx (x.xx)	x.xx (x.xx)
Gynecomastia	x.xx (x.xx)	x.xx (x.xx)
Hyperthyroidism	x.xx (x.xx)	x.xx (x.xx)
Hypothyroidism	x.xx (x.xx)	x.xx (x.xx)
Lipoatrophy	x.xx (x.xx)	x.xx (x.xx)
Lipohypertrophy	x.xx (x.xx)	x.xx (x.xx)
Gastrointestinal	x.xx (x.xx)	x.xx (x.xx)
Anorexia	x.xx (x.xx)	x.xx (x.xx)
Ascites	x.xx (x.xx)	x.xx (x.xx)
Bloating or distension	x.xx (x.xx)	x.xx (x.xx)
Cholecystitis	x.xx (x.xx)	x.xx (x.xx)
Constipation	x.xx (x.xx)	x.xx (x.xx)
Diarrhea	x.xx (x.xx)	x.xx (x.xx)
Dysphagia or odynophagia	x.xx (x.xx)	x.xx (x.xx)
Gastrointestinal bleeding	x.xx (x.xx)	x.xx (x.xx)
Mucositis or stomatitis	x.xx (x.xx)	x.xx (x.xx)
Nausea	x.xx (x.xx)	x.xx (x.xx)
Pancreatitis	x.xx (x.xx)	x.xx (x.xx)
Perforation (colon or rectum)	x.xx (x.xx)	x.xx (x.xx)
Proctitis	x.xx (x.xx)	x.xx (x.xx)
Rectal discharge	x.xx (x.xx)	x.xx (x.xx)
Vomiting	x.xx (x.xx)	x.xx (x.xx)
Musculoskeletal	x.xx (x.xx)	x.xx (x.xx)
Arthralgia	x.xx (x.xx)	x.xx (x.xx)
Arthritis	x.xx (x.xx)	x.xx (x.xx)
Myalgia	x.xx (x.xx)	x.xx (x.xx)
Osteonecrosis	x.xx (x.xx)	x.xx (x.xx)
Osteopenia	x.xx (x.xx)	x.xx (x.xx)
Osteoporosis	x.xx (x.xx)	x.xx (x.xx)
Neurologic	x.xx (x.xx)	x.xx (x.xx)
Acute CNS ischemia	x.xx (x.xx)	x.xx (x.xx)
Altered mental status	x.xx (x.xx)	x.xx (x.xx)
Ataxia	x.xx (x.xx)	x.xx (x.xx)
Cognitive, behavioral, or attentional disturbance	x.xx (x.xx)	x.xx (x.xx)
Headache	x.xx (x.xx)	x.xx (x.xx)
Neuromuscular weakness	x.xx (x.xx)	x.xx (x.xx)
Neurosensory alteration	x.xx (x.xx)	x.xx (x.xx)
Seizures	x.xx (x.xx)	x.xx (x.xx)
Syncope	x.xx (x.xx)	x.xx (x.xx)
Psychiatric	x.xx (x.xx)	x.xx (x.xx)
Insomnia	x.xx (x.xx)	x.xx (x.xx)
Psychiatric disorders	x.xx (x.xx)	x.xx (x.xx)
Suicidal ideation or attempt	x.xx (x.xx)	x.xx (x.xx)

Continue...

...continuation

Serious adverse event	Best Phase II/1 or 2	Placebo
Respiratory	x.xx (x.xx)	x.xx (x.xx)
Bronchospasm	x.xx (x.xx)	x.xx (x.xx)
Dispnea or respiratory distress	x.xx (x.xx)	x.xx (x.xx)
Sensorial	x.xx (x.xx)	x.xx (x.xx)
Hearing loss	x.xx (x.xx)	x.xx (x.xx)
Tinnitus	x.xx (x.xx)	x.xx (x.xx)
Uveitis	x.xx (x.xx)	x.xx (x.xx)
Vertigo	x.xx (x.xx)	x.xx (x.xx)
Visual changes	x.xx (x.xx)	x.xx (x.xx)
Systemic	x.xx (x.xx)	x.xx (x.xx)
Acute allergic reaction	x.xx (x.xx)	x.xx (x.xx)
Chills	x.xx (x.xx)	x.xx (x.xx)
Cytokine release syndrome	x.xx (x.xx)	x.xx (x.xx)
Fatigue or malaise	x.xx (x.xx)	x.xx (x.xx)
Fever	x.xx (x.xx)	x.xx (x.xx)
Pain	x.xx (x.xx)	x.xx (x.xx)
Serum sickness	x.xx (x.xx)	x.xx (x.xx)
Underweight	x.xx (x.xx)	x.xx (x.xx)
Unintentional weight loss	x.xx (x.xx)	x.xx (x.xx)

PR - PR interval; AV - atrioventricular; CNS - central nervous system. Results expressed as n (%).