Tenofovir Disoproxil Fumarate/Emtricitabine and Baricitinib for Patients at High Risk of Severe COVID-19: The PANCOVID Randomized Clinical Trial

Rocío Montejano[1*], Fernando de la Calle-Prieto[1*], María Velasco MD[2], Carlos Guijarro[3], Javier Queiruga-Parada[4], María Jiménez-González[5], Patricia González-Ruano[6], Patricia Martínez[6], Ane Josune Goikoetxea[7], Marta Ibarrola[7], Marianela Ciudad[8], Ángela Gutiérrez[8], Miguel Torralba[9], Ana Díaz-Brasero[9], Pablo Ryan[10], Cristina Marcelo[11], Cristina Díez[12], Sofía Ibarra[13], Esperanza Merino[14], Vicente Estrada[15], Javier Marcos[16], María Novella[17], María A. Rivera[18], Manuel Ruiz-Muñoz[16], Marta de Miguel[19], Llanos Soler[6], Mikel del Álamo[7], Santiago Moreno[20], Antonio J. Carcas[21**], Alberto M. Borobia[21**], José R. Arribas[22**], on behalf of the PANCOVID study Group[‡]

1. Infectious Diseases Unit. Internal Medicine Department. La Paz University Hospital. IdiPAZ. Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC). Madrid, Spain
2. Infectious Diseases. Research Unit. University Hospital Fundación Alcorcón. Madrid. Spain
3. Internal Medicine Unit. University Hospital Fundación Alcorcón. Rey Juan Carlos University. Madrid. Spain
4. Clinical Pharmacology Department, La Paz University Hospital, IdiPAZ. Infectious Diseases Unit. La Paz University Hospital. IdiPAZ. Madrid. Spain
5. Clinical Pharmacology Department, La Paz University Hospital, IdiPAZ. La Paz University Hospital. IdiPAZ. Spanish Clinical Research Network – SCReN. Madrid. Spain
6. Internal Medicine Department. University Hospital Infanta Sofía. Madrid. Spain
7. Infectious Diseases Unit. Cruces University Hospital. Barakaldo. Spain.
8. Infectious Diseases Unit. Internal Medicine Department. La Princesa University Hospital, Madrid, Spain

9. Internal Medicine Department. Guadalajara University Hospital. University of Alcalá. Spain
10. Infanta Leonor University Hospital. Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC). School of Medicine, Complutense University. Madrid, Spain
11. Hospital de Emergencias Enfermera Isabel Zendal. Madrid, Spain
12. Clinical Microbiology and Infectious Diseases Department. Gregorio Marañon University Hospital. Instituto de Investigación Sanitaria Gregorio Marañón. Madrid, Spain
13. Infectious Diseases Department. Basurto University Hospital. Basurto. Spain
14. Infectious Diseases Unit. Alicante General University Hospital. Alicante Institute of Health and Biomedical Research (ISABIAL). Alicante, Spain
15. Infectious Diseases Unit. Internal Medicine Department. Clínico San Carlos University Hospital. IdiSSC. Madrid, Spain
16. Internal Medicine Department. University Hospital Fundación Alcorcón. Madrid, Spain
17. Internal Medicine Department. Príncipe de Asturias University Hospital. Alcalá de Henares, Spain
18. Emergency Department. La Paz University Hospital. Madrid, Spain
19. Fundación SEIMC Gesida. Madrid, Spain
20. Infectious Diseases Department. Ramón y Cajal University Hospital. IRYCIS. University of Alcalá School of Medicine. Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC). Madrid, Spain
21. Clinical Pharmacology Department. La Paz University Hospital. IdiPAZ. School of Medicine, Autonomous University of Madrid. Spanish Clinical Research Network - SCReN. Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC). Madrid, Spain
22. Infectious Diseases Unit. Internal Medicine Department. La Paz University Hospital. IdiPAZ. School of Medicine, Autonomous University of Madrid. Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC). Madrid, Spain

Corresponding author: José R. Arribas, MD Unidad de Enfermedades Infecciosas. Hospital Universitario La Paz. IdiPAZ. Paseo de la Castellana 261, Madrid 28046, Spain. e-mail: joser.arribas@salud.madrid.org

* Both authors contributed equally to this manuscript and should be considered as co-first authors

*** These three authors contributed equally to this manuscript and should be considered as senior authors

‡ Study group members are listed in acknowledgement section

Running title: TDF/FTC and baricitinib for COVID-19

ABSTRACT

Background

This study was designed to evaluate if patients with high risk for severe COVID-19 would benefit from treatment with TDF/FTC followed by baricitinib in case of hypoxemia and systemic inflammation.

Methods

PANCOVID is an open-label, double-randomized, phase 3 pragmatic clinical trial including adults with symptomatic COVID-19 with ≥ 2 comorbidities or older than 60 years conducted between 10 October 2020 and 23 September 2021. In the first randomization patients received TDF/FTC or not TDF/FTC. In the second randomization patients with room-air O_2 saturation <95% and at least one increased inflammatory biomarker received baricitinib plus dexamethasone or dexamethasone alone. The primary endpoint was 28-day mortality. Main secondary endpoint was 28-day disease progression or critical care unit admission or mortality. The trial was stopped before reaching planned sample size due to the decrease in the number of cases and a mortality rate substantially lower than expected EudraCT registration number: 2020-001156-18.

Results

Of the 355 included participants 97% were hospitalized at baseline. Overall, 28-day mortality was 3.1%. The 28-day mortality relative risk (RR) for participants treated with TDF/FTC was 1.76 (95% CI 0.52-5.91; p= 0.379); it was 0.42 (95% CI 0.11-1.59; p= 0.201) for those treated with baricitinib. The 28-day RR for the main secondary combined endpoint for participants treated with TDF/FTC was 0.95 (95% CI 0.66-1.40; p = 0.774); it was 0.90 (95%CI 0.61-1.33; p = 0.687) for those treated with baricitinib.

Conclusions

Our results do not suggest a beneficial effect of TDF/FTC; nevertheless, they are compatible with the beneficial effect of baricitinib already established by other clinical trials.

Key words: COVID-19, tenofovir disoproxil fumarate, emtricitabine, baricitinib

BACKGROUND

There is controversy about the possible efficacy of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) for the prevention and treatment of COVID-19. Several studies reported potential in silico [1] and *in vitro* [2] activity of TDF against SARS-CoV-2, while other in vitro studies found no antiviral activity [3,4]. One animal model reported that ferrets treated with TDF/FTC had lower virus titers in nasal washes at day 8 post infection than the control group [5]. Epidemiological studies have reported that people living with HIV receiving treatment with TDF/FTC compared to those receiving other antiretrovirals have a lower risk of SARS-CoV-2 seropositivity [6] and a lower risk of COVID-19 related hospitalizations [7]. In one cohort of people treated for chronic hepatitis B, better COVID-19 outcomes were reported among TDF/FTC users than for entecavir users [8]. One pilot randomized clinical trial of patients with non-severe COVID-19 found that TDF/FTC appeared to accelerate clearance of nasopharyngeal SARS-CoV-2 virus [9]. One pragmatic trial in hospitalized patients found no effect on mortality or other clinical outcomes in the participants who received treatment with TDF/FTC [10]. However, in this pragmatic trial participants treated with a combination of rosuvastatin plus colchicine plus TDF/FTC had a decrease in 28-day mortality risk and the need for invasive mechanical ventilation Apart from a possible antiviral effect, several studies have reported that TDF/FTC decreases inflammatory cytokine production (interleukin-8, interleukin-10 y MCP-1) in peripheral blood mononuclear cells and might shift cytokine balance towards interleukin-12 [11,12]. This shift would promote a Th1 response leading to production of interferon-γ (IFN-γ) by T and NK cells. This effect may attenuate severe COVID-19 disease characterized by increases of interleukin-8, interleukin-10 and MCP-1 [13].

Baricitinib is an oral selective inhibitor of Janus kinase (JAK) 1 and 2 that has already shown to improve clinical outcomes in randomized clinical trials of hospitalized patients with severe COVID-19 [14–16]. It might potentially exert combined antiviral and anti-inflammatory effects [17]. The antiviral effect is thought to be mediated by interfering with AP2-associated protein kinase 1 which would prevent SARS-CoV-2 cellular entry. Its anti-inflammatory effect is due to the inhibition of intracellular signaling pathways of cytokines such as interleukin-2, interleukin-6, interleukin-10, interferon-γ, and granulocyte–macrophage colony-stimulating factor [18].

Because TDF/FTC might have an antiviral and an immunomodulatory effect that could be synergistic with baricitinib we have conducted a pragmatic randomized clinical trial to evaluate whether patients with high risk for severe COVID-19 would benefit from the possible antiviral/immunomodulatory activity of TDF/FTC followed by baricitinib in case of respiratory insufficiency accompanied by increased biomarkers of systemic inflammation.

METHODS

Study design and participants

The PANCOVID study is an open-label, stratified, double-randomized, phase 3 pragmatic clinical trial conducted in 25 sites in Spain lead by La Paz University Hospital. The scheme of the study design is provided in Supplemental Figure 1. We recruited patients with symptomatic SARS-CoV-2 detected by PCR or antigenic test in nasopharyngeal swabs, aged 60 years or older, or younger if they had at least 2 comorbidities (hypertension, obesity, diabetes, cirrhosis, chronic neurologic disease, active cancer, heart failure, coronary heart disease or COPD). Main exclusion criteria were creatinine clearance <60 mL/min, receiving steroids at immunosuppressive doses (≥ 15 mg/day in the 7 days prior to the onset of symptoms), HIV infection, and severe respiratory failure (requiring a reservoir bag, mechanical ventilation, or acute respiratory distress) at the time of inclusion. The inclusion for the second randomization were to have a room air O_2 blood saturation <95% and at least one increased inflammatory biomarker (Interleukin 6, C-reactive protein, D-dimer and/or ferritin). Full inclusion and exclusion criteria for both randomizations are detailed in the study protocol provided as supplementary material. All participants provided written informed consent before inclusion.

The trial was undertaken in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. The trial protocol was approved by the Spanish Agency of Medicines and Health Products (AEMPS) and by La Paz University Hospital Research Ethics Board. This clinical trial was registered with EudraCT (#2020-001156-18).

Randomization and masking

In the first randomization, eligible participants were randomly assigned in a 1:1 ratio to receive

or not TDF/FTC. At any moment during the trial participants could undergo a second randomization (1:1 ratio) to receive baricitinib plus dexamethasone or dexamethasone alone. The randomization list was centrally generated using SAS, version 9.4; randomization was stratified by age group, symptoms duration (< or ≥ 5 days) and health care setting (hospitalized, long-term care facility, ambulatory) to achieve balanced groups. The randomization list was imported into the secure Research Electronic Data Capture platform (REDCap, version 8.7.4) used for the study electronic case report form.

Procedures

The trial and evaluations followed a pragmatic approach as close as possible to clinical practice in an emergency such as the present pandemic. The dosing for TDF/FTC (200/245 mg) after first randomization were 2 oral tablets on the first day and 1 tablet daily for a total of 14 days. The dosing for baricitinib was based on a prior clinical trial [15] after second randomization was 4-mg once a day for 10-14 days, at the discretion of the investigator. To patients older than 75 years, the dose of baricitinib was reduced to 2-mg once a day. The dosing for dexamethasone was 6-mg daily (oral or intravenously) for 7-10 days, at the discretion of the investigator based on WHO guidelines [19]. At the discretion of the investigator patients could also receive remdesivir. Patients were followed-up on days 7, 14 and 28 after randomization, recording at least vital signs, blood test and documentation of respiratory status. Patients entering the second randomization had an additional visit on day 7 after this randomization. If patients remained hospitalized on day 28, they were followed until discharge or death. Full procedures details are provided in the study protocol (supplementary material).

Outcomes

The primary outcome was 28-day mortality. Main secondary outcome was the combined variable disease progression (defined by increased O_2 requirements or intensified medical therapy including increased steroid dose and/or need for tocilizumab) or critical care unit admission or mortality. Other secondary outcomes were time in days to: death, hospital admission (in ambulatory patients), critical care unit admission, need for second randomization, first negative PCR result for SARS-CoV-2, hospital discharge, disease progression. Primary safety outcomes were percentage of

patients with adverse events leading to discontinuation of treatment and percentage of patients with adverse events.

Statistical Analysis

Based on mortality data during the first COVID-19 wave in Spain, sample size calculations assumed a 20% mortality in this mixed population [20]. We also assumed an alfa error of 0.025, beta error of 0.2 and a 0.7 risk reduction in mortality. resulting in a predefined sample of 1,482 patients for each group (TDF/FTC vs no TDF/FTC). The trial was stopped before reaching the planned sample size due to the decrease in the number of COVID-19 cases during the recruitment period and the much lower global mortality observed

The main results were summarized as absolute and relative frequencies in the case of qualitative variables, and median and interquartile ranges (IQR) in the case of quantitative variables. The main outcome (28-day mortality), main combined secondary endpoint (disease progression/critical care unit admission/28-day mortality) and other secondary outcomes were compared between treatment groups (TDF/FTC vs. not TDF/FTC, baricitinib plus dexamethasone vs. dexamethasone alone) using Fisher's exact test. In addition, their respective relative risks and 95% confidence intervals (95%CI) were calculated.

The comparison of continuous variables between the treatment groups (age, days since first randomization until death, laboratory parameters, etc.) was performed using the Mann-Whitney U test, due to the non-normality of most of the continuous variables. For multiple comparisons of treatment groups, the p-value was adjusted by the Bonferroni method. Subsequently, Tukey and Bonferroni post hoc tests were performed. We performed a logistic regression analysis to evaluate a interaction between TDF/FTC and baricitinib including age, sex, number of comorbidities, simultaneous or deferred randomization and randomization group. Statistical analysis was performed with R software (version 4.1.1., R Core Team (2020), Vienna, Austria). For the primary outcome of 28-day mortality, the results from the PANCOVID trial were subsequently included in a meta-analysis of results from all previous randomized controlled trials of baricitinib for patients hospitalized with COVID-19. Details of the systematic search and meta-analysis methods are provided in supplementary material.

RESULTS

From October 10th, 2020 to September 23rd, 2021, a total of 355 patients from 25 hospitals in Spain were enrolled in the trial and underwent the first randomization. Of these 355 patients 344 were hospitalized, 4 were residents of long-term care facilities and 7 were ambulatory. In this first randomization 177 and 178 patients were respectively assigned to receive or not TDF/FTC. Out of these 355 patients, 287 underwent the second randomization to receive baricitinib plus dexamethasone or dexamethasone alone, 264 immediately after the first randomization and 23 subsequently. A total of 45 patients also received remdesivir. A total of 338 patients (TDF/FTC, n= 167; no TDF/FTC, n= 171), completed the 28-day follow-up, whereas 11 died and 6 patients discontinued the study (Figure 1).

Baseline demographic and disease characteristics were generally balanced between the first randomization treatment groups (Table 1). Most patients were men (64%), and the median age was 67 years (IQR 62-73). On average, patients were randomized 7 days after symptom onset. Twenty-three percent patients did not have any comorbidities, 30% had one and 47% had at least two comorbidities. The most frequent comorbidity was hypertension (61% patients) followed by diabetes (27%) and obesity (16%). Thirty-seven percent patients did not need ventilation support, while 60% needed nasal prongs, 1% conventional mask, 1% high-flow device and only one patient needed rebreathing mask. Inflammatory biomarkers were also similar between groups. Out of the 291 participants for whom vaccination status was known, 267 (91%) had received at least one dose of a SARS-CoV-2 vaccine. Baseline demographic and disease characteristics were in general also well balanced between the second randomization treatment groups except for the number of comorbidities that were numerically higher in the dexamethasone group without reaching statistical significance (Table 2). Patients undergoing the second randomization had similar characteristics to the whole group, apart from oxygen support (any kind) and inflammatory biomarkers levels. Oxygen support was needed by 62% of patients included in the first randomization and by 74% of those patients included in the second one. Also, median levels of inflammatory biomarkers were slightly higher in patients who underwent the second randomization.

Regarding primary and secondary efficacy outcomes of the first randomization, i.e. TDF/FTC compared to no TDF/FTC, overall 28-day mortality was 3.1%, with no statistical difference between groups (Table 3). The primary outcome occurred in 7 patients in the TDF/FTC group (4.0%) and 4 in the no TDF/FTC group (2.2%). The relative risk (RR) for 28-day mortality was 1.76 (95% CI 0.52-5.91; p= 0.379) (Table 3). The main combined secondary outcome, including disease progression or critical care unit admission or 28-day mortality, was similar between groups (TDF/FTC, 22.0%; no TDF/FTC, 23.6%). The RR for the composite outcome was 0.95 (95% CI 0.66-1.40; p= 0.774) (Table 3). The other secondary efficacy outcomes did not reach statistical difference between groups (Table 3).

Regarding primary and secondary efficacy outcomes of the second randomization, i.e. baricitinib plus dexamethasone compared to dexamethasone alone, overall 28-day mortality in 287 patients entering in the second randomization was 3.5% (Table 4). The primary outcome occurred in 3 patients in the baricitinib plus dexamethasone group (2.1%) and 7 in the dexamethasone alone group (4.9%). Despite a RR of 0.42 for mortality in the baricitinib plus dexamethasone group, statistical significance was not achieved (95% CI 0.11-1.59; p= 0.201 (Table 4). The occurrence of the main combined secondary outcome in the baricitinib plus dexamethasone and the dexamethasone alone groups were 24.8% and 27.5% respectively. The RR for the composite outcome was 0.90 (95% CI 0.61-1.33; p=0.687) (Table 4). Results of the rest of secondary efficacy outcomes did not achieve statistically significant difference between groups. (Table 4). Comparison of main outcomes of this randomization stratified by the group of the first randomization are presented in Supplemental Table 1. No statistically significant differences were found among the four groups. No interaction between TDF/FTC and baricitinib were identified according to results from the logistic regression model.

Regarding safety, 208 patients presented a total of 233 adverse events (Supplemental Tables 2 and 3). Adverse events were more frequent in patients who underwent the second randomization. Serious adverse events were reported in 13 (Supplemental Table 2). The most common adverse event was hyperglycemia, followed by increased ALT/AST, diarrhea and constipation (Supplemental

Table 3). Eight patients developed an adverse event leading to discontinuation of treatment (Supplemental Table 2).

Our systematic search identified 4 previous trials and one meta-analysis [21] of baricitinib, involving a total of 10,815 randomized patients and 1,331 deaths[14–16,22] (Figure 2). After inclusion of the results from PANCOVID trial into this meta-analysis, the overall mortality risk ratio from all 5 trials – now involving 11,102 randomized patients and 1,341 deaths – was 0.73 (0.57-0.92; p=0.008. Fig.2).

DISCUSSION

In this pragmatic randomized clinical trial, we have not found evidence that treatment with TDF/FTC improves clinical outcomes in hospitalized patients with COVID-19 at high risk of disease progression. There were no statistical significant differences between participants treated and not treated with TDF/FTC for the primary endpoint of reduction of mortality at day 28, neither for the combined secondary endpoint of disease progression or ICU admission or 28th day mortality. For both outcomes, the lower limit of the 95% confidence interval was above the 0.7 risk reduction established as the difference to detect in our sample size calculations.

In our trial, patients who needed oxygen therapy and had at least one increased inflammatory biomarker were additionally randomized to dexamethasone with or without baricitinib. For this second randomization, there were no statistically significant differences between the groups for the primary endpoint of reduction of mortality at day 28 or for the main combined secondary endpoint of disease progression or critical care unit admission or 28-day mortality.

Our study is limited mainly because our estimates of the efficacy of treatment with TDF/FTC and bariticinib are imprecise with wide confidence intervals. This limitation derives from our limited sample size and the unexpected low mortality observed in our trial. The overall mortality in our trial was 3.1% even though our participants had a median age of 67 years, 76.9% had at least one comorbidity predisposing to severe COVID-19 and almost all of them were hospitalized when randomized. Taking this low mortality into account, we would have needed more than 5,000 patients per group to detect a 30% reduction in mortality between groups (3.1 vs 2.17). Our results are also limited by the lack of virological data. Although the protocol planned to study virological endpoints, due to the situation in most hospitals required samples were not collected. Another limitation is our

open label design which is common in pragmatic clinical trials [23] with hard endpoints such as mortality.

In three other trials of baricitinib for hospitalized patients with COVID-19 not requiring mechanical ventilation, overall reported mortality at day 28 was higher than in PANCOVID. In the ACTT-2 trial[15] mean patient age was 55.4 years and mortality was 5.9%. In the COV-BARRIER trial [14] patients´ mean age was 57.6 years and mortality was 10.6%. In the RECOVERY trial [16], mean age was 58.1 years and mortality at day 28 was 13%. One possible explanation for the lower mortality (3.1%) in PANCOVID is that 25.8% of our participants did not need oxygen therapy at baseline while this proportion was 13.7% in ACTT-2, 12.2% in COV-BARRIER and very small (exact data not provided) in the RECOVERY trial. Although patients in PANCOVID were almost one decade older than those enrolled in ACTT-2, COV-BARRIER and RECOVERY, it is possible that they could have had less severe disease at baseline. It is also possible that, being a more recent trial, the higher proportion of patients in PANCOVID who had received at least on dose of a SARS-CoV-2 vaccine might have contributed to a decreased mortality. Vaccination status was only reported in the RECOVERY trial where 42% patients had received at least one dose of a SARS-CoV-2 vaccine compared to 91.2% in PANCOVID.

Despite the imprecision of our estimate for the efficacy of TDF/FTC our interpretation of the results is that it is unlikely that TDF/FTC can have a relevant beneficial effect when used in hospitalized patients with COVID-19. This interpretation agrees with another recent pragmatic trial that did not find a positive effect of TDF/FTC in hospitalized patients with COVID-19 [10]. Our study does not rule out a possible beneficial effect of TDF/FTC when used earlier during infection. Of note, participants in our trial started treatment with TDF/FTC a median time of 7 days after symptom onset. Other antivirals such as molnupiravir have demonstrated to improve outcomes only in ambulatory patients when started within 5 days after the onset of signs or symptoms of COVID-19 [24] but not in hospitalized patients with a longer duration of symptoms [25]. Our initial goal when we designed the trial was to include a substantial number of ambulatory participants. Unfortunately, the situation in primary care settings during the beginning of the trial did not permit to include a significant number of them.

Our estimates about the efficacy of bariticinib are also imprecise. For this reason we included our results in a meta-analysis of all published trials of baricitinib for treatment of COVID-19 [14–16,22]. The results of this updated meta-analysis confirm the positive effect of baricitinib on mortality as shown by a 27% decrease in mortality. Currently the WHO guidelines [19] provide a strong recommendation for the use of baricitinib as an alternative to interleukin-6 receptor blockers, in combination with corticosteroids, in patients with severe or critical COVID-19.

In summary, results of this randomized clinical trial exploring the efficacy of TDF/FTC for the treatment of hospitalized patients with COVID-19 at high risk of disease progression do not suggest a beneficial effect of TDF/FTC although our estimate of its effect is imprecise. The results of our updated meta-analysis of 5 clinical trials including PANCOVID support a substantial beneficial effect of baricitinib for the treatment of severe COVD-19.

NOTES

Author contributions

Trial conceptualization and design was done by AJC, AMB, and JRA.

Analysis and interpretation of the data was done by RM, FC-P, MV, CG, MJ-G, AJC, AMB and JRA.

Critical revision of the article for important intellectual content was provided by RM, FC-P, MV, CG, JQ-P, MJ-G, PG-R, PM, MI, AJG, MC, AG, AD-B, MT, PR, CM, CD, SI, EM, VE, JM, MN, MAR, MR-M, MdM, SC, LS, MdA, SM, MS, AJC, AMB, and JRA.

Provision of study materials for patients was done by RM, FC-P, MV, CG, PG-R, PM, MI, AJG, MC, AG, AD-B, PR, CM, CD, SI, EM, VE, JM, MN, MAR, MR-M, SC, LS, SM, MS and JRA.

Statistical expertise was provided by MJ-G, AJC, AMB, and JRA.

Obtaining of funding was managed by AJC, AMB, and JRA.

Administrative, technical, or logistical support was provided by JQ-P and MdM.

Collection and assembling of data was carried out by JQ-P, MJ-G, MdM, AJC, AMB, and JRA.

All authors reviewed and edited the manuscript, and approved the manuscript for submission. All authors reviewed and approved the original draft. All authors had full access to the full data in the study and accept responsibility to submit for publication.

Acknowledgements

The authors thank the members of PanCOVID team for their many contributions in conducting the trial, the members of scientific committee (Infectious Diseases Unit, Clinical Pharmacology Department, Emergency Department and Geriatric Department of La Paz University Hospital, Primary Care Direction of Comunidad de Madrid, and Fundación SEIMC-GESIDA), the members of the monitoring team (Fundación SEIMC-GESIDA), members of management and coordination center (Clinical Trial Unit of La Paz University Hospital), members of data management center (Instituto de Investigación Biosanitaria del Hospital 12 de Octubre), physicians and health care workers of participating institutions, as well as the and the patients for their altruism in participating in this trial. The authors thank Esther Prieto for editorial assistance (employed by Hospital Universitario La Paz; funded by the Instituto de Salud Carlos III [grant number COV20/00023]).

PANCOVID Trial Group

1. Gonzalo Sierra-Torres, MD. Internal Medicine Department. University Hospital Fundación Alcorcón. Madrid, Spain
2. Antonio Pablo-Esteban, MD. Internal Medicine Department. University Hospital Fundación Alcorcón. Madrid, Spain
3. Javier Villanueva, MD. Internal Medicine Department. University Hospital Fundación Alcorcón. Madrid, Spain
4. Marta Mora-Rillo, MD. Infectious Diseases Unit. Internal Medicine Department. La Paz University Hospital. IdiPAZ. Madrid, Spain
5. Enrique Seco-Messeguer, MD. Clinical Pharmacology Department, La Paz University Hospital, IdiPAZ, Madrid, Spain
6. Sara Castro, MD. Hospital de Emergencias Enfermera Isabel Zendal. Madrid, Spain
7. Jose Luis Valle-López, MD. Infanta Sofia University Hospital. FIIB HUIS HHEN. San Sebastián de los Reyes, Madrid, Spain
8. Pepa Muñoz, MD, PhD. Infectious Diseases Department. Basurto University Hospital. Basurto, Spain

9. Gorane Euba, MD, PhD. Infectious Diseases Department, Gurutzeta/Cruces University Hospital. Barakaldo, Bizkaia, Spain

10. Asunción Costa, MD. Internal Medicine Department. Guadalajara University Hospital. Guadalajara, Spain

11. Filomena Ceres, MD. Guadalajara University Hospital. Guadalajara, Spain

12. Azucena Bautista, MD. Internal Medicine and Infectious Diseases Department. Hospital de la Princesa, IIS-IP. Madrid, Spain

13. Jesús Sanz, MD. Internal Medicine/Infectious Diseases Department, La Princesa University Hospital, Madrid, Spain. Instituto de Investigación La Princesa. Madrid, Spain

14. Jorge Valencia, MD, PhD. Infanta Leonor University Hospital. Madrid, Spain

15. Gerardo Redondo. Infanta Leonor University Hospital. Madrid, Spain

16. Matilde Sánchez, MD, PhD. Infectious Diseases Department. Ramón y Cajal University Hospital. IRYCIS. Madrid, Spain

17. Pedro Gil. Fundación SEIMC Gesida. Madrid, Spain

18. Samantha García Díaz. Fundación SEIMC Gesida. Madrid, Spain

19. Noemí Cabello-Clotet, MD. Medicina Interna-Enfermedades Infecciosas.Hospital Universitario Clínico San Carlos. Universidad Complutense de Madrid. Madrid, Spain

20. María José Núñez Orantos., MD. Unidad de Infecciosas (Medicina Interna) Hospital Clínico San Carlos. Madrid, Spain

21. Pilar González-de-la-Aleja García-Luengo. Hospital General de Alicante. Alicante, Spain

22. Antonio Amo-Lozano, MD. Servicio de Medicina Interna. Hospital General Universitario de Alicante. Alicante, Spain

23. Rebeca Fuerte Martínez, MD. Hospital Universitario Infanta Sofia. Madrid, Spain

24. Beatriz Pérez-Monte Minguez, MD. Hospital Universitario Infanta Sofia. Madrid, Spain

25. Victor Polo San Ricardo. Hospital Universitario de Basurto. Basurto, Spain

26. Zuriñe Zubero, MD. Hospital Universitario de Basurto. Basurto, Spain

27. Regino Rodriguez-Alvarez, MD. Unidad de enfermedades Infecciosas, Hospital Universitario Cruces. Barakaldo, Spain

28. Javier Nieto Arana, MD. Servicio de Enfermedades Infecciosas, Hospital Universitario Cruces. Barakaldo, Spain

29. Rodríguez-Miñón, Isabel, MD. Adjunto del Servicio de Geriatría del Hospital Universitario de Guadalajara. Guadalajara, Spain

30. Saray Gil, MD. Servicio de Urgencias Hospital Universitario de Guadalajara. Guadalajara, Spain

31. JJ Martínez-Simón, PharmD. Servicio de Farmacia, Hospital Universitario Fundación Alcorcón. Madrid, Spain

32. Rosario Torres Santos Olmo, MD, PhD. Servicio de Urgencias de adultos, Hospital Universitario La Paz. Madrid, Spain

33. Carrme Busca, MD. HIV Unit. Internal Medicine Department. Idipaz. Hospital La Paz. Madrid, Spain

34. Ana Barrios Blandino, MD. Sección de Infecciosas. Servicio de Medicina Interna. Hospital Universitario de La Princesa. Madrid, Spain

35. Lucio J García Fraile Fraile, MD. Unidad de E. Infecciosas / Medicina Interna. Hospital Universitario de La Princesa. Madrid, Spain

36. Chiara Fanciulli, MD. Servicio de Microbiología Clínica y Enfermedades Infecciosas, Hospital General Universitario Gregorio Marañon. Instituto de investigación sanitaria Gregorio Marañón. CIBERINFEC. Madrid, Spain

37. Leire Pérez-Latorre, MD, PhD. Servicio de Microbiología Clínica y Enfermedades Infecciosas, Hospital General Universitario Gregorio Marañón. Madrid, Spain

38. Irene Cañamares. Hospital Universitario Infanta Leonor. Madrid, Spain

39. Juan Torres-Macho, MD, PhD. Internal medicine Deparment. Infanta Leonor-Virgen de la Torre University Hospital. Madrid, Spain

40. José Sanz Moreno, MD, PhD. Servicio Medicina Interna/Unidad de Enfermedades Infecciosas, Hospital Universitario Príncipe de Asturias. Alcalá de Henares, Madrid, Spain

41. Cristina Hernández Gutiérrez, MD. Hospital Universitario Príncipe de Asturias Servicio Medicina Interna, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid, Spain

42. Pilar Vizcarra, MD. Department of Infectious Diseases, IRyCIS, Ramon y Cajal University Hospital. Madrid, Spain

43. Clara Crespillo-Andújar, PhD. National Referral Centre for Tropical Diseases, Infectious Diseases Department, Hospital Universitario Ramón y Cajal. Madrid Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), CIBER de Enfermedades infecciosas. Madrid, Spain

44. Carlos Bea, MD. Hospital Clínico Universitario de Valencia. Valencia, Spain

45. Carolina Pinto Plá. Hospital Clínico de Valencia. Valencia, Spain

46. María Rosa Oltra Sempere, MD, PhD. Unidad Enfermedades Infecciosas. Servicio Medicina Interna. Hospital Clínic Universitari Valencia. Valencia, Spain

47. José Luis Mostaza-Fernández, MD. Complejo Asistencial Universitario de León. León, Spain

48. Alberto Muela Molinero, MD, PhD. Complejo Asistencial Universitario de León. León, Spain

49. Manuel Martín Regidor, MD. Complejo Asistencial Universitario de León. León, Spain

50. Pelazas González, R. MD, PhD. Servicio de Infecciones, Complejo Hospitalario Universitario de Canarias. Santa Cruz de Tenerife, Spain

51. Jose Luis Gómez Sirvent MD, PhD. Servicio de Infecciones, Complejo Hospitalario Universitario de Canarias. Santa Cruz de Tenerife, Spain

52. María Remedios Alemán Valls, MR. MD, PhD. Servicio de Infecciones, Complejo Hospitalario Universitario de Canarias. Santa Cruz de Tenerife, Spain

53. Mónica Martínez Martínez. Hospital Reina Sofía de Murcia. Murcia, Spain

54. Antonia Alcaraz PhD. Hospital General Universitario Reina Sofía de Murcia. Murcia, Spain

55. Enrique Bernal Morell. Hospital Reina Sofía de Murcia. Murcia, Spain

56. Marta Montero-Alonso, MD. Unidad de Enfermedades Infecciosas, Hospital Universitario y Politécnico La Fe. Valencia, Spain

57. Jon Ortiz Carrera, MD. Medicina Interna. Hospital Universitari i Politecnic La Fe. Valencia, Spain

58. Maria Tasias Pitarch, MD. Unidad de Enfermedades Infecciosas, Hospital Universitario La Fe. Valencia, Spain

59. E. Nuño-Álvarez, MD. UGC Enfermedades Infecciosas, Hospital Universitario Virgen de la Victoria. Málaga, Spain

60. Cristobal Rodriguez-Leal, MD. Servicio de Urgencias, Hospital Universitario del Henares. Madrid, Spain

61. Lourdes Iglesias Vázquez, MD. Centro Asistencial San Camilo. Madrid, Spain

62. María Franco Huerta, PhD. Servicio de Enfermedades Infecciosas Hospital Juan Ramón Jimenez. Huelva, Spain

63. Juan Flores Cid. Hospital Arnau de Vilanova. Valencia, Spain

64. Lourdes Muñoz Abril. Hospital de Fuenlabrada. Madrid, Spain

65. María Teresa García Morales, MSc. Instituto de Investigación Hospital 12 de Octubre (imas12). Plataforma Española de Unidades de Investigación Clínica y Ensayos Clínicos (SCReN). Madrid, Spain

66. Rocío Prieto. Gestión SCReN. Madrid, Spain

67. Miguel Galán de Juana, M.D. Internal Medicine Unit. Hospital Universitario Fundación Alcorcón. Madrid, Spain

68. Carmen Jimeno Griñó, MD. Internal Medicine Unit. Hospital Universitario Fundación Alcorcón. Madrid, Spain

69. José Luis Narro. Hospital Universitario La Paz. IdiPAZ. Madrid. Spain

Data sharing

The following supporting documents will be made available with publication: informed consent form, statistical analysis plan and statistical analysis report. The following data will be made available with publication: complete anonymized patient data set (available from María Jiménez-González; e-mail: maria.jimenez.gonzalez@salud.madrid.org). Individual participant data will be made available when the trial is complete, on request to the corresponding authors. After approval of the proposal, data will be shared through a secure online procedure.

Funding

This clinical trial was funded by the Instituto de Salud Carlos III (ISCIII), Minister of Innovation and Science of Spain in a competitive and public grant (Royal Decree-Law 8/2020, of March 17, on extraordinary urgent measures to face the economic and social impact of COVID-19).
Project code: COV20/00023. (Co-funded by European Regional Development Fund/European Social Fund "A way to make Europe"/"Investing in your future"). Baricitinib was provided by Eli Lilly and TDF/FTC was partially provided by Teva. The clinical trial was designed, and the data analyzed by the senior authors and the biostatistician. The funder had no influence on the design or conduct of the trial and were not involved in data collection or analysis, manuscript writing, or the decision to submit it for publication.

Potential conflicts of interest

None of them related to this work. Pablo Ryan has received grant support and honoraria from Gilead and MSD, consulting fees from Abbvie SL, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from ViiV and Gilead Sciences, and support for attending meetings and/or travel from Abbvie and GSK (ViiV). Jorge Valencia has received scholarships and honorarium as speaker for Gilead sciences. Matilde Sánchez has received honoraria from Gilead, has developed educational material for MSD and ViiV Healthcare and has served on an advisory board for MSD and Gilead. Alberto M. Borobia reports grants or contracts from GSK, Moderna, and Jannssen (paid to institution), has received advisory fees from Janssen and Pfizer (paid to author), including participation on a Data Safety Monitoring Board for Pfizer, Janssen and Medical Developments International (MDI) (paid to author), payment or honoraria for lectures, presentations, manuscript writing or educational events from Gilead and Pfizer (paid to author), and speaker fees from Janssen (paid to author). Jose R. Arribas reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Merck (paid to author), support for attending meetings and/or travel from MSD (paid to author), and has received consulting fees, advisory fees and speaker fees from Gilead, Merck, Pfizer, Sobi, GSK, MSD, Serono, Lilly, and Roche (paid to author); he is member of the Infectious Diseases and Clinical Microbiology Society COVID-19 treatment guidelines. Ángela

Gutierrez Liarte reports payment or honoraria for presentation from Gilead Sciences (Educational event. “Unfollow the virus”. Apoyo positivo), and support for attending meetings and/or travel from ANGELINI PHARMA ESPAÑA (SEICAV CONGRESS 2021). Antonio J. Carcas reports grants or contracts from Instituto de Salud Carlos III (ISCIII), Minister of Innovation and Science of Spain (PI21/01507, PI18/00136, CM19/00243, ICI21/00065) and Vaccelerate (Clinical trial name: EU-Covat-1 Aged), including payment or honoraria for a Course on Clinical Investigation (institution) from Abbvie, and participation on a Data Safety Monitoring Board or Advisory Board for AMR Inshights (Project: Bacterial infections and antimicrobial resistance in the era of the covid-19 pandemic A Multi-Country Retrospective Analysis (HULP:PI-4931 (institution)). Carlos Guijarro reports consulting fees, participation on a Data Safety Monitoring Board or Advisory Board and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AMGEN, DAIICHI SANKYO, FERRER, and SANOFI, and support for attending meetings and/or travel from SANOFI and FERRER. Llanos Soler reports grants or contracts from NOVARTIS and BOEHRINGER, and support for attending meetings and/or travel from NOVARTIS. Manuel Ruiz Muñoz reports support for attending meetings and/or travel from ROCHE Farma SA. María Novella Mena reports support for attending meetings and/or travel and payment or honoraria for presentations, and educational events from Gilead (PRESENTATION OF HIV and SUPPORT FOR ATTENDING TO THE CONGRESS OF INFECTIOUS DISEASE OF SPANISH INFECTIOUS DISEASE SOCIETY, JUNE 2002). Maria Velasco Arribas reports grants or contracts from Gilead and ViiV (paid to institution), payment or honoraria for lectures and educational events for Gilead and Janssen (paid to author and institution) and payment or honoraria for educational events from ViiV and MSD (paid to institution), and support for attending meetings and/or travel from Angelini, Gilead, and Janssen (paid to author). Patricia González-Ruano Perez reports support for attending meetings and/or travel from Gilead and Angelini. Patricia Martínez reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from SANOFI (paid to author). Rocío Montejano reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Gilead, ViiV, Merck Sharp Dome, and Thera Technologies (paid to author), payment for expert testimony

from Gilead and Viiv (paid to author), support for attending meetings and/or travel from Gilead and Jannsen (paid to author), and participation on a Data Safety Monitoring Board or Advisory Board for ViiV (paid to author). Santiago Moreno reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Pfizer, Gilead, Roche, Sobi, and MSD (paid to author), and participation on a Data Safety Monitoring Board or Advisory Board for Pfizer, Gilead, and MSD (paid to author). Vicente Estrada reports consulting fees from Gilead, Janssen, and MSD (paid to author); payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Gilead and Janssen (paid to author), support for attending meetings and/or travel from Gilead (paid to author), and participation on a Data Safety Monitoring Board or Advisory Board for Gilead, Janssen, and Synairgen (paid to author). All other authors declare no competing interests.

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1 **Table 1. Patient Characteristics and Baseline Values. First Randomization: TDF/FTC vs. no TDF/FTC**

Characteristic	All patients N=355	TDF/FTC N=177	No TDF/FTC N=178
Sex, Female, n (%)	126 (35.5)	64 (36.2)	62 (34.8)
Age, median (IQR)	67.0 (62.0, 73.0)	68.0 (62.0, 74.0)	67.0 (62.2, 73.0)
≤60 years, n (%)	61 (17.2)	28 (15.8)	33 (18.5)
>60 years, n (%)	294 (82.8)	149 (84.2)	145 (81.5)
Time from symptom onset to 1st randomization, median (IQR)	7.0 (5.0, 10.0)	8.0 (5.0, 10.0)	7.0 (5.0, 10.0)
≤5 days, n (%)	106 (29.9)	52 (29.4)	54 (30.3)
>5 days, n (%)	249 (70.1)	125 (70.6)	124 (69.7)
Comorbidities, n (%)			
None	82 (23.1)	37 (20.9)	45 (25.3)
One	105 (29.6)	55 (31.1)	50 (28.1)
Two or more	168 (47.3)	85 (48.0)	83 (46.6)
Hypertension	217 (61.1)	112 (63.3)	105 (59.0)
Diabetes	97 (27.3)	52 (29.4)	45 (25.3)
Obesity	57 (16.1)	27 (15.3)	30 (16.9)
O2 Saturation, median (IQR)	95.0 (94.0, 96.0)	95.0 (94.0, 96.5)	95.0 (94.0, 96.0)

O2 support, n (%)			
None	133 (37.5)	65 (36.7)	68 (38.2)
Nasal prongs	214 (60.3)	108 (61.0)	106 (59.6)
Conventional mask	3 (0.8)	2 (1.1)	1 (0.6)
High-flow device	4 (1.1)	1 (0.6)	3 (1.7)
Rebreathing mask	1 (0.3)	1 (0.6)	0 (0.0)
Inflammatory biomarkers, median (IQR)			
C Reactive Protein (mg/L)	61.7 (30.3, 107.5)	63.80 (30.7, 117.0)	58.40 (30.1, 96.9)
Lactate Dehydrogenase (UI/L)	285.0 (232.5, 371.5)	299.0 (235.7, 374.7)	280.00 (232.0, 356.0)
D-Dimer (ng/mL)	406.00 (12.3, 650.0)	417.00 (9.9, 700.0)	380.00 (12.4, 590.7)
Interleukin-6 (pg/mL)	17.40 (6.8, 37.2)	20.00 (7.1, 36.1)	14.00 (6.8, 38.1)
Remdesivir prior/after 1st randomization, n (%)	45 (12.7)	23 (12.9)	22 (12.4)
Anti-inflammatory treatment (2nd randomization), n (%)	287 (80.8)	141 (79.7)	146 (82.0)
Simultaneous with 1st randomization			
Dexamethasone	135 (47.0)	67 (47.5)	68 (46.6)
Dexamethasone + Baricitinb	129 (44.9)	63 (44.7)	66 (45.2)
Deferred after 1st randomization			
Dexamethasone	7 (2.4)	4 (2.8)	3 (2.1)

Dexamethasone + Baricitinb	16 (5.6)	7 (5.0)	9 (6.2)

1

Table 2. Patient Characteristics and Baseline Values. Second Randomization: Baricitinib plus Dexamethasone vs. Dexamethasone

Characteristic	All patients N=287	Baricitinib plus Dexamethasone N=145	Dexamethasone N=142
Sex, Female, n (%)	99 (34.5)	51 (35.2)	48 (33.8)
Age, median (IQR)	67.0 (62.0, 74.0)	68.0 (63.0, 75.0)	67.0 (61.0, 72.7)
≤60 years, n (%)	61 (17.2)	23 (15.9)	30 (21.1)
>60 years, n (%)	294 (82.8)	122 (84.1)	112 (78.9)
Time from symptom onset to 2nd randomization, median (IQR)	7.0 (5.0, 10.0)	8.0 (5.0, 11.0)	7.0 (5.0, 9.7)
≤5 days, n (%)	83 (28.9)	37 (25.5)	46 (32.4)
>5 days, n (%)	204 (71.1)	108 (74.5)	96 (67.6)
Time from 1st to 2nd randomization (excluding simultaneous randomization), median (IQR)	1.0 (1.0, 2.0)	1.00 (1.0, 2.0)	2.0 (1.0, 2.5)
Comorbidities, n (%)			
None	76 (26.5)	43 (29.7)	33 (23.2)
One	83 (28.9)	44 (30.3)	39 (27.5)
Two or more	128 (44.6)	58 (40.0)	70 (49.3)
Diabetes	85 (29.6)	37 (25.5)	48 (33.8)

Hypertension	165 (57.5)	78 (53.8)	87 (61.3)
Obesity	54 (18.8)	27 (18.6)	27 (19.0)
O2 Saturation, median (IQR)	95.0 (94.0, 96.0)	95.00 (94.0, 96.0)	95.00 (93.0, 96.0)
O2 support, n (%)			
None	74 (25.8)	42 (29.0)	32 (22.5)
Nasal prongs	205 (71.4)	99 (68.3)	106 (74.6)
Conventional Mask	3 (1.0)	3 (2.1)	0 (0.0)
High-flow device	4 (1.4)	1 (0.7)	3 (2.1)
Rebreathing mask	1 (0.3)	0 (0.0)	1 (0.7)
Inflammatory biomarkers, median (IQR)			
C Reactive Protein (mg/L)	66.7 (33.6, 113.7)	68.1 (33.8, 113.6)	65.4 (33.6, 113.6)
Lactate Dehydrogenase (Ul/L)	304.0 (242.0, 378.0)	303.5 (238.5, 371.7)	305.0 (247.0, 379.0)
D-Dimer (ng/mL)	417.5 (15.4, 655.5)	430.0 (35.0, 665.0)	410.0 (9.4, 640.0)
Interleukin-6 (pg/mL)	17.7 (6.5, 37.3)	19.2 (7.8, 43.4)	12.0 (6.0, 29.9)
Remdesivir prior to/at 1st randomization, n (%)	44 (15.3)	22 (15.2)	22 (15.5)
TDF/FTC prior to/at 2nd randomization, n (%)	141 (49.1)	71 (48.9)	70 (49.3)

1

Table 3. Disease Outcomes. First Randomization: TDF/FTC vs. No TDF/FTC

Variable	TDF/FTC N=177	No TDF/FTC N=178	RR (95%CI)	p-value
Primary outcome				
28-day mortality, n (%)	7 (4.0)	4 (2.2)	1.76 (0.52,5.91)	0.379
Secondary outcomes				
Disease progression/critical care unit admission/28-day mortality (combined), n (%)	39 (22.0)	42 (23.6)	0.95 (0.66,1.40)	0.774
Disease Progression, n (%)	39 (22.0)	42 (23.6)	0.94 (0.66,1.35)	0.774
Increase of O2 support	36 (35.6)	40 (37.7)	0.95 (0.71, 1.28)	0.867
Increase of steroid dose	19 (19.0)	19 (17.9)	0.94 (0.53,1.68)	0.859
Need for new medication	21 (21.0)	27 (25.5)	0.82 (0.50,1.36)	0.511
Tocilizumab	7 (4.0)	12 (6.7)		
Other medication	14 (7.9)	15 (8.4)		
Mechanical Ventilation, n (%)				
Non-invasive (BIPAP, CPAP, high flow nasal prongs)	8 (4.5)	5 (2.8)	0.90 (0.51,1.59)	0.589
Invasive	8 (4.5)	13 (7.3)		
Days since 1st randomization until death, median (IQR)	17.0 (10.5, 26.5)	25.5 (24.7, 34.7)	8.5 (-10.0,31.5)	0.218

Days since 1st randomization until discharge, median (IQR)	6.0 (4.0, 12.0)	7.0 (5.0, 14.0)	1.0 (-2.0,1.0)	0.369
Discharge ≤ 28 days, n (%)	148 (89.7)	159 (91.9)	1.27 (0.65,2.50)	0.573
Discharge > 28 days, n (%)	17 (10.3)	14 (8.1)		

1 Mann Whitney U test for continuous variables and Chi-square test for qualitative variables. RR: Relative Risk

2

Table 4. Disease Outcomes. Second Randomization: Baricitinib plus Dexamethasone vs. Dexamethasone

Variable	Baricitinib plus Dexamethasone N=145	Dexamethasone N=142	RR (95%CI)	p-value
Primary outcome.				
28-day mortality, n (%)	3 (2.1)	7 (4.9)	0.42 (0.11,1.59)	0.201
Secondary Outcomes				
Disease progression/critical care unit admission/28-day mortality (combined), n (%)	36 (24.8)	39 (27.5)	0.90 (0.61,1.33)	0.687
Disease Progression, n (%)	36 (24.8)	39 (27.5)	0.90 (0.61,1.33)	0.687
Increase of O2 support	34 (37.0)	36 (39.6)	0.93 (0.65,1.35)	0.762
Increase of steroid dose	20 (21.7)	15 (16.7)	1.30 (0.71,2.38)	0.453
Need for new medication	22 (23.9)	21 (23.3)	1.02 (0.61,1.73)	1.000
Tocilizumab	5 (3.4)	13 (9.2)		
Other medication	17 (11.7)	8 (5.6)		
Mechanical Ventilation, n (%)				
Non-invasive (BIPAP, CPAP, high flow nasal prongs)	3 (2.1)	8 (5.6)	0.64 (0.33,1.27)	0.378
Invasive	9 (6.2)	11 (7.7)		

Days since 1st randomization until death, median (IQR)	28.0 (26.5, 44.5)	24.0 (14.5, 25.5)	-4.0 (-49.0,1) *	0.110
Time since 1st randomization until discharge, median (IQR)	7.0 (5.0, 13.5)	7.00 (5.0, 12.0)	0.0 (-3.0,0.0) *	0.596
Discharge ≤ 28 days, n (%)	131 (94.2)	121 (89.0)	0.52 (0.22,1.19)	0.131
Discharge > 28 days, n (%)	8 (5.8)	15 (11.0)		

1 Mann Whitney U test for continuous variables and Chi-square test for qualitative variables. RR: Relative Risk *Median difference

2

Figure legends

Figure 1. Trial profile.

Figure 2. Baricitinib vs usual care in patients hospitalized with COVID-19 - Meta−analysis of mortality in PANCOVID and other trials, including weight and risk ratio (95% CI) of each trial, heterogeneity analysis and pooled risk ratio with a 95% confidence interval using the Mantel-Haenszel method under a random-effects model.

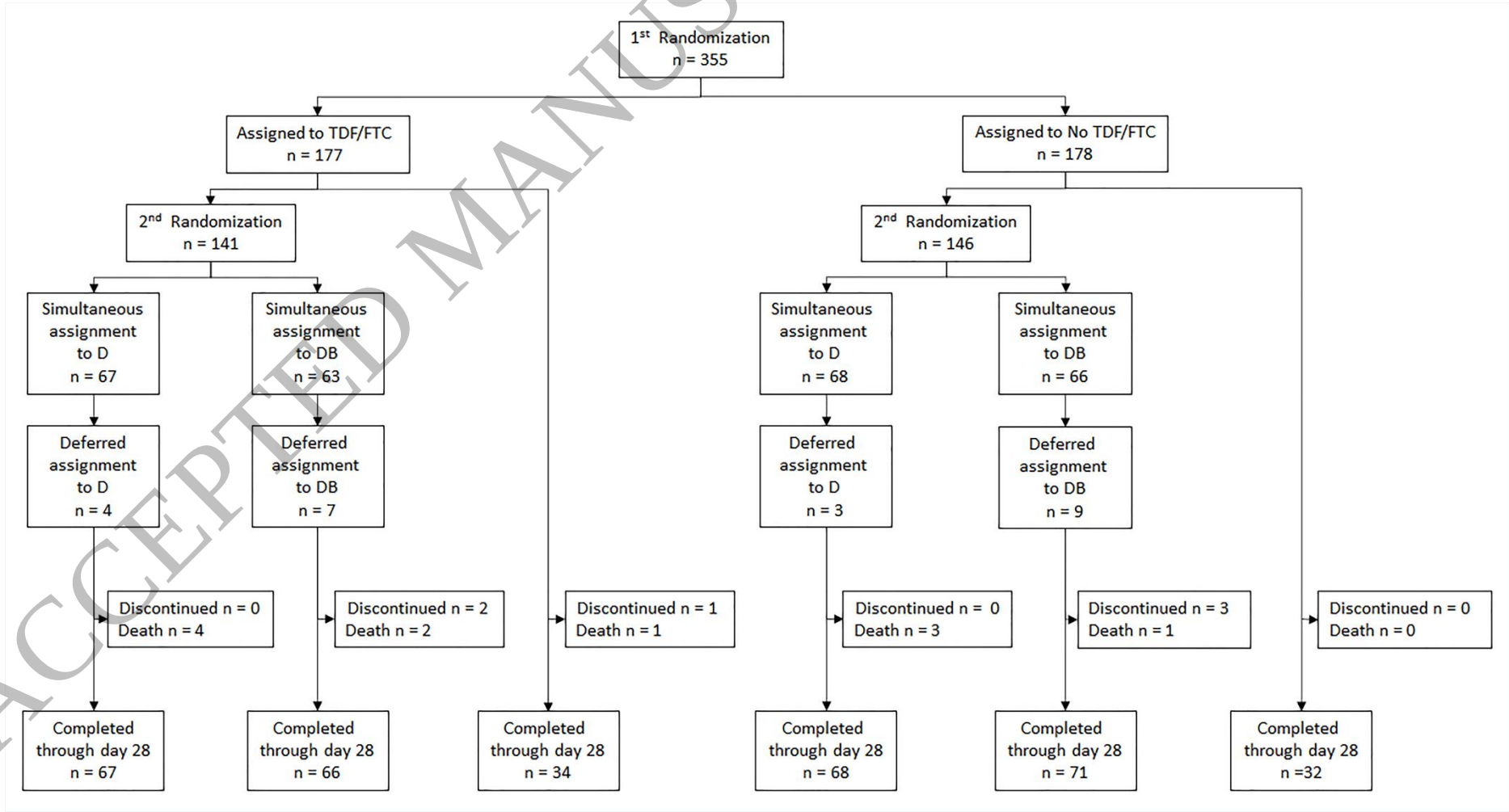

Figure 1
456x245 mm (x DPI)

Study or Subgroup	Baricitinib Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ACTT2	24	515	37	518	14.8%	0.65 [0.40, 1.07]
Cao et al.	0	20	3	21		Not estimable
COV-BARRIER	62	764	100	761	25.2%	0.62 [0.46, 0.83]
COV-BARRIER (critically ill)	20	51	29	50	18.5%	0.68 [0.45, 1.02]
Guimaraes et al.	4	144	8	145		Not estimable
Murugesan	0	50	0	50		Not estimable
PANCOVID	3	145	7	142	3.0%	0.42 [0.11, 1.59]
RECOVERY	513	4148	546	4008	38.5%	0.91 [0.81, 1.02]
RUXCOVID	9	287	3	145		Not estimable
RUXCOVID-DEVENT	0	0	0	0		Not estimable
Total (95% CI)		**5623**		**5479**	**100.0%**	**0.73 [0.57, 0.92]**
Total events	622		719			

Heterogeneity: Tau² = 0.04; Chi² = 8.94, df = 4 (P = 0.06); I² = 55%

Test for overall effect: Z = 2.63 (P = 0.008)

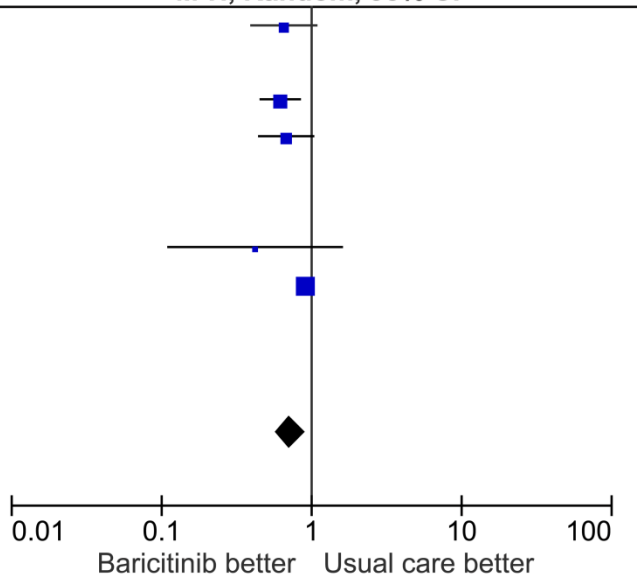

Figure 2
285x102 mm (x DPI)