Supplementary Appendix to Manuscript Entitled:

Baricitinib plus Remdesivir for the Treatment of Hospitalized Adults with COVID-19. A Randomized Double-blind Placebo-controlled Trial

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Supplemental Methods:

Additional Study Design Details

The trial was designed, overseen and sponsored by the NIAID's Division of Microbiology and Infectious Diseases (DMID) with input from selected site investigators. Sites entered the data into Advantage eClinical ^{SM}, designed by The Emmes Company LLC. The sponsor and staff from Emmes, which is funded by the sponsor, analyzed the data. The manuscript was revised and approved by all the authors, who agreed to submit the manuscript for publication.

Additional Study population Details

After informed consent was obtained, participants 18 years of age or older who were hospitalized with symptoms suggestive of COVID-19 were assessed for eligibility. Participants had to meet one of the following criteria suggestive of lower respiratory tract infection at the time of enrollment: radiographic infiltrates by imaging study, peripheral oxygen saturation (SpO2) ≤94% on room air, or requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). There was no limit to the duration of symptoms prior to enrollment. Participants had to have a laboratory-confirmed SARS-CoV-2 infection as determined by a positive reverse transcription, polymerase-chain-reaction (RT-PCR) assay result from any respiratory specimen collected <72 hours prior to randomization. During the study, this criterion was modified due to limitations in testing capacity to also allow a RT-PCR positive specimen that was collected ≥72 hours prior to randomization if the site was unable to obtain a repeat sample and if the participant had progressive disease consistent with ongoing SARS-CoV-2 infection. Other inclusion criteria included agreeing not to participate in another COVID-19 treatment clinical trial through Day 29 and practicing heterosexual abstinence or using study-specified contraception through Day 29 for women of childbearing potential. Exclusion criteria included having either an alanine aminotransferase (ALT) or an aspartate aminotransferase (AST) > 5 times the upper limit of the normal range; impaired renal function as determined by calculating an estimated glomerular filtration rate (eGFR), or need for hemodialysis or hemofiltration; allergy to study product; pregnancy or breast-feeding; and anticipated discharge from the hospital or transfer to another hospital within 72 hours of enrollment.

Randomization was stratified by study site and disease severity at enrollment and was performed using a web-based Internet Data Entry System, Advantage eClinical [SM]. Severe disease was defined as participants in ordinal category 7 and 6, and included those on ECMO, invasive or non-invasive mechanical ventilation, or high flow oxygen devices. Mild / moderate disease was defined as ordinal category 5 and 4, and included those on low flow oxygen devices (defined as 15L/min or less) and those not on supplemental oxygen.

Additional Study Procedures Details

Participants were assessed daily from Day 1 through Day 29 while hospitalized. Participants discharged from the hospital had study visits at Days 15 and 29. In-person visits were preferred, although restrictions due to local infection control measures often limited participants from leaving their home and returning to the study sites. Follow-up by phone was acceptable in these circumstances. An additional study visit on Day 22 was conducted by phone. The participant's clinical status was captured daily while hospitalized using an 8-category ordinal scale (defined in the main manuscript) and the National Early Warning Score (NEWS) (1, 2). Participants discharged prior to Day 15 had the ordinal scale assessed at all follow-up visits while the NEWS required in-person visits. Blood samples for safety laboratory tests (white blood cell count with differential, hemoglobin, platelet count, creatinine, glucose, total bilirubin, ALT, AST, and prothrombin time), and oropharyngeal (OP) swab samples (nasopharyngeal [(NP]) could be substituted) were collected on Days 1 (before initial infusion), 3, 5, 8, and 11 while hospitalized, and Days 15 and 29 for participants able to attend an in-person visit or who were still hospitalized.

All serious adverse events (SAE), and grade 3-4 adverse events (AE) that represented an increase in severity from Day 1, and any grade 2 or higher suspected drug-related hypersensitivity reactions associated with study product administration were captured in this trial. AEs were assessed by review of the electronic medical record, physical examinations, vital signs, and laboratory studies from the time the informed consent form was signed through Day 29. AEs were classified in accordance with the Medical Dictionary for Regulatory Activities® (MedDRA version 23.0), and their relationship to study product, severity, and outcome were documented.

Additional Statistical Analysis Details

The primary analysis was a log-rank test of time-to-recovery between remdesivir plus baricitinib and remdesivir plus placebo stratified by disease severity as defined above. The relevant treatment efficacy parameter is the "recovery rate ratio" (for the combination arm relative to control), which is akin to the hazard ratio in survival analysis but for the beneficial outcome of recovery. Two practical considerations result from considering time to a beneficial outcome. First, a recovery rate ratio greater than one indicates an improvement for the combination arm. Second, failure to recover and death are both censored at Day 29. Consequently, participants censored on the last observation day reflect two different states: death and failure to recover by Day 29. Hence, a breakdown of deaths by treatment arm is also important to understanding treatment efficacy. The key secondary analysis tested a difference in the ordinal score distribution between remdesivir plus baricitinib and remdesivir plus placebo at Day 15 using the "common odds ratio" from a proportional odds model, stratifying by baseline disease severity stratum.

The study was designed to achieve 85% power for detecting a recovery rate ratio of 1.35 with a two-sided type-I error rate of 5%. Enrollment continued through April 19, 2020 to ensure at least 400 recoveries and to address subgroup analysis. Because the SAP did not include a provision for correcting for multiplicity when conducting tests for secondary outcomes, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes. More details can be found in the statistical analysis plan. Analyses were conducted using SAS version 9.4 and R version 3.5.1.

Additional Sensitivity Analysis Related to Baseline Ordinal Score Category 6

Due to the potential variation in the definition of high-flow oxygen, a sensitivity analysis was performed combining ordinal score categories 5 and 6. The recovery rate ratio using this stratification (4, 5+6, 7) was 1.18 (95% CI: 1.03-1.35; p=0.018).

Interim Analysis Details

At the first interim analysis, there were 286 recoveries, and the total number of recoveries anticipated by trial's end was 723. Therefore, the information fraction was 286/723=0.3956.

The free WinLD program from the University of Wisconsin shows that the boundary at the first look is 3.378.

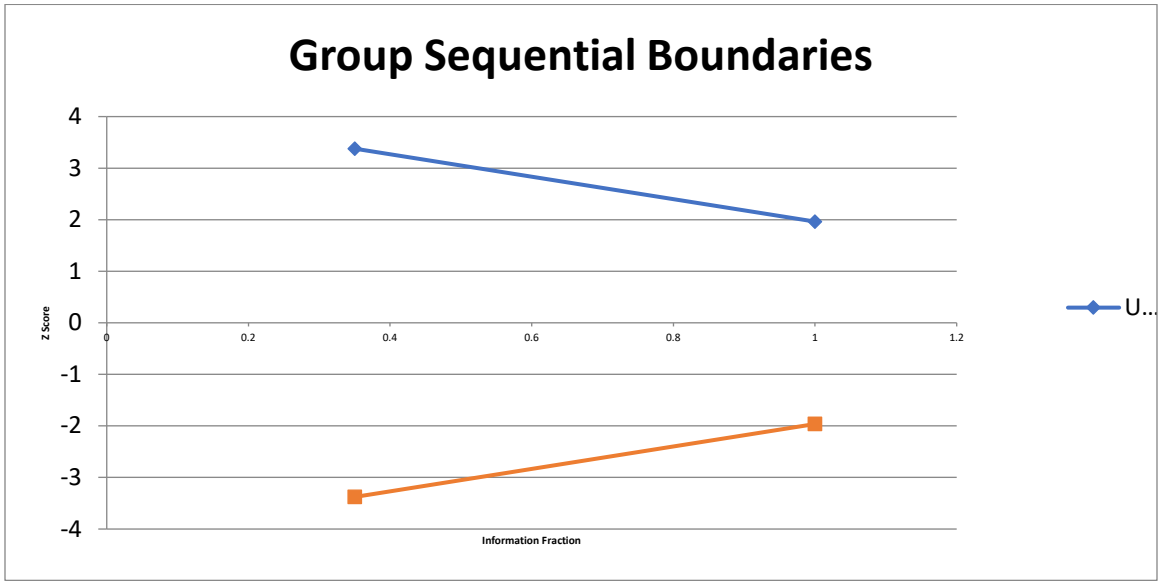
At the second and final interim analysis, the number of recoveries was 817. That is, we over-ran the targeted number of recoveries. That means that the real information fraction at the first interim analysis was not 286/723=0.3956, but 286/817=0.350. Nonetheless, the boundary that was used was 3.378. Therefore, we must find the boundary c such that $P|\{Z(t_1)| > 3.378\ or\ |Z(t_2)| > c\} = 0.05$. It is clear that we should use $t_2 = 1$, but what do we use for t_1, the information fraction we thought at the first analysis, or the actual information fraction at the first analysis? Note that the null joint distribution of the z-scores at the first and second looks is bivariate normal with means (0,0), variances (1,1), and correlation $\sqrt{\left\{\frac{t_1}{t_2}\right\}}$. The joint distribution depends only on the **ratio** of information fractions, so only the actual numbers of recoveries matters. In other words, $t_1\ and\ t_2$ should be the true information fractions at the two looks, (0.350,1). This causes a problem if we use the Compute Bounds option of the WinLD program because if we give it the true information fractions 0.350 and 1, it will give us a different boundary at t_1 than what we actually used. Therefore, use the Compute Probability option instead of Compute Bounds. We give it the true information fractions, 0.350 and 1, and we input the boundary we actually used, 3.378, at the first look. Through trial and error, we try different values for the boundary c at the second look until we find one such that the cumulative exit probability (the last column in the table WinLD provides) by the second look is 0.05. After a few tries, I found that a boundary of 1.963 at the second look gives a cumulative exit probability just slightly under 0.05 (actual cumulative type 1 error rate is 0.04994). See below for the WinLD output.

Lan-DeMets Group Sequential Boundaries Calculations

Compute Probability
Analysis Parameters
Interim Analyses (k): 2
Information times(t): User Input
Test Boundaries: Two-Sided Symmetric
Probability Parameters
Determine Bounds: User Input
Drift: 0.0

Time	Lower	Upper	Nominal Upr Alpha	Cum exit pr

0.35	-3.3780	3.3780	0.00037	0.00073
1.00	-1.9630	1.9630	0.02482	0.04994



The first stopping boundary was not crossed during the first interim, so the study continued until a final look at 817 recoveries. The analysis gave a recovery-rate ratio of 1.17 (95% CI: 1.02, 1.34; p=0.02) [Table S13], which crossed the stopping boundary. Upon final database lock, with full follow-up of all individuals there were an additional 22 recoveries, for a total of 839 recoveries (RRR: 1.16, 95% CI 1.01, 1.32; p=0.04). The main manuscript reports on the latter results that correspond to the full cohort.

Registration at ClinicalTrials.gov

Enrollment began on May 8, 2020, and the study record was submitted on May 22, 2020. 179 subjects were enrolled prior to submission of the trial information to clinicaltrials.gov. The sponsor uses automated systems for protocol registration and the systems are linked to the protocol number. As ACTT-2 is a platform trial with the same protocol number as ACTT-1, ACTT-2 would have overwritten ACTT-1 registration. The sponsor had to reconfigure the systems to be able to generate a different registration number for ACTT-2 than ACTT-1. This is within the US regulations for clinicaltrial.gov registration (https://clinicaltrials.gov/ct2/manage-recs/faq#fr_5) but does not conform to the recommendations by ICMJE for trial registration. (http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html).

Supplemental Tables and Figures:

Table S1. Ordinal Scale

Recovered	**1**	**Not hospitalized, no limitations on activities**
	2	**Not hospitalized, limitation on activities and/or requiring home oxygen**
	3	**Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care**
Population Enrolled	**4**	**Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care**
	5	**Hospitalized, requiring supplemental oxygen**
	6	**Hospitalized, on non-invasive ventilation or high flow oxygen devices**
	7	**Hospitalized, on mechanical ventilation or ECMO**
	8	**Death**

Table S2. Categorical Demographic and Baseline Characteristics by Treatment Group

		Baricitinib + RDV Subjects (N=515)		Placebo + RDV Subjects s (N=518)		All Subjects (N=1033)	
Demographic Category	**Characteristic**	**n**	**%**	**n**	**%**	**n**	**%**
Sex	Male	319	62	333	64	652	63
	Female	196	38	185	36	381	37
Ethnicity	Not Hispanic or Latino	246	48	240	46	486	47
	Hispanic or Latino	263	51	268	52	531	51
	Not Reported	2	<1	2	<1	4	<1
	Unknown	4	1	8	2	12	1
Race	American Indian or Alaska Native	2	<1	8	2	10	1
	Asian	49	10	52	10	101	10
	Native Hawaiian or Other Pacific Islander	4	1	7	1	11	1
	Black or African American	77	15	79	15	156	15
	White	251	49	245	47	496	48
	Unknown	132	26	127	25	259	25
Geographic Region 1	US Site	441	86	444	86	885	86
	Non-US Site	74	14	74	14	148	14
Geographic Region 2	North America	476	92	477	92	953	92
	Europe	6	1	7	1	13	1
	Asia	33	6	34	7	67	6
Age (years)	<40	87	17	86	17	173	17
	40-64	281	55	274	53	555	54
	>=65	147	29	158	31	305	30

		Baricitinib + RDV Subjects (N=515)		Placebo + RDV Subjects s (N=518)		All Subjects (N=1033)	
Demographic Category	**Characteristic**	**n**	**%**	**n**	**%**	**n**	**%**
Baseline Clinical Status	Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care	70	14	72	14	142	14
	Hospitalized, requiring supplemental oxygen	288	56	276	53	564	55
	Hospitalized, on non-invasive ventilation or high flow oxygen devices	103	20	113	22	216	21
	Hospitalized, on invasive mechanical ventilation or ECMO	54	10	57	11	111	11
Duration of Symptoms prior to enrollment[a]	First Quartile (<= 5 Days)	134	26	130	25	264	26
	Second Quartile (6 to <= 8 Days)	159	31	161	31	320	31
	Third Quartile (9 to <= 10 Days)	96	19	84	16	180	17
	Fourth Quartile (11+ Days)	120	23	133	26	253	24
Duration of Symptoms prior to enrollment[a]	<= 10 Days	389	76	375	72	764	74
	> 10 Days	120	23	133	26	253	24
Duration of Symptoms prior to enrollment[a]	<= Median (8 Days)	293	57	291	56	584	57
	> Median (8 Days)	216	42	217	42	433	42
Comorbidities at baseline[b]	Asthma	53	10	44	9	97	10
	Cancer	20	4	17	3	37	4

		Baricitinib + RDV Subjects (N=515)		Placebo + RDV Subjects s (N=518)		All Subjects (N=1033)	
Demographic Category	**Characteristic**	**n**	**%**	**n**	**%**	**n**	**%**
	Cardiac Valvular Disease	10	2	12	2	22	2
	Chronic Kidney Disease	31	6	33	7	64	6
	Chronic Liver Disease	13	3	15	3	28	3
	Chronic Oxygen Requirement	8	2	9	2	17	2
	Chronic Respiratory Disease	39	8	30	6	69	7
	Coagulopathy	3	1	4	1	7	1
	Congestive Heart Failure	31	6	31	6	62	6
	Coronary Artery Disease	50	10	51	10	101	10
	Diabetes I	5	1	5	1	10	1
	Diabetes II	195	39	175	35	370	37
	Hypertension	258	51	264	52	522	52
	Immune Deficiency	17	3	13	3	30	3
	Obesity	295	58	272	53	567	56
	Any History of DVT or PE	11	2	11	2	22	2
Risk Factors for DVT or PE[b]	Current nicotine consumption	18	4	29	6	47	5
	Major Surgery, Significant Trauma, or Long Hospitalization in one month prior to screening	14	3	2	<1	16	2
	Prolonged Immobility in one month prior to screening	11	2	13	3	24	2

		Baricitinib + RDV Subjects (N=515)		Placebo + RDV Subjects s (N=518)		All Subjects (N=1033)	
Demographic Category	**Characteristic**	**n**	**%**	**n**	**%**	**n**	**%**
	Any risk factor for DVT or PE (excluding COVID-19) not listed above	11	2	18	4	29	3
Comorbidities Group 1[c]	Any Comorbidities	443	86	417	81	860	83
	No Comorbidities	64	12	91	18	155	15
	Unknown	8	2	10	2	18	2
Comorbidities Group 2[c]	No Comorbidities	64	12	91	18	155	15
	1 Comorbidity	148	29	122	24	270	26
	2 or more Comorbidities	284	55	285	55	569	55
	Unknown	19	4	20	4	39	4
Comorbidities Group 3	Obese	295	57	272	53	567	55
	Non-Obese	211	41	238	46	449	43
	Unknown	9	2	8	2	17	2

N = Number of subjects enrolled.
[a]Duration of Symptoms prior to enrollment data was missing for 16 subjects.
[b]Percentages are based on the number of subjects with data available for the individual comorbi dity and risk factors for DVT or PE.
[c]Current nicotine consumption, Major Surgery, Prolonged Immobility and Any risk factor for D VT or PE are excluded from Comorbidities Group 1 and 2

Table S3. Continuous Demographic and Baseline Characteristics by Treatment Group

Variable	Statistic	Baricitinib + RDV (N=515)	Placebo + RDV (N=518)	All Subjects (N=1033)
Age (years)	n	515	518	1033
	Mean	55.0	55.8	55.4
	Standard Deviation	15.4	16.0	15.7
	Median	55.0	56.0	56.0
	IQR	23	24	24
	Minimum	18	18	18
	Maximum	101	96	101
Height (cm)	n	497	494	991
	Mean	167.81	168.18	167.99
	Standard Deviation	10.75	10.97	10.86
	Median	167.60	167.60	167.60
	IQR	15	15	15
	Minimum	134.6	119.4	119.4
	Maximum	200.7	198.1	200.7
Weight (kg)	n	503	506	1009
	Mean	90.78	91.00	90.89
	Standard Deviation	24.77	25.07	24.91
	Median	87.00	86.20	87.00
	IQR	31	28	30
	Minimum	38.6	33.0	33.0
	Maximum	213.6	219.8	219.8
BMI (kg/m^2)	n	496	494	990
	Mean	32.16	32.25	32.21

Variable	Statistic	Baricitinib + RDV (N=515)	Placebo + RDV (N=518)	All Subjects (N=1033)
	Standard Deviation	8.17	8.41	8.29
	Median	30.80	30.55	30.70
	IQR	9	10	10
	Minimum	16.9	16.1	16.1
	Maximum	91.9	66.8	91.9
Duration of Symptoms prior to Enrollment (days)	n	509	508	1017
	Mean	8.3	8.6	8.5
	Standard Deviation	4.4	4.6	4.5
	Median	8.0	8.0	8.0
	IQR	5	6	5
	Minimum	0	1	0
	Maximum	35	32	35

IQR is the inter-quartile range.

Table S4. Summary of Demographic and Clinical Characteristics at Baseline - US Sites

Characteristic	All Subjects (N=885)	Baricitinib + RDV Subjects (N=441)	Placebo + RDV Subjects (N=444)
Age - mean +/- standard deviation, yr	55.9 +/- 15.7	55.7 +/- 15.5	56.1 +/- 15.8
Age Category - no.(%)			
40-64	481 (54.4)	239 (54.2)	242 (54.5)
<40	137 (15.5)	68 (15.4)	69 (15.5)
>=65	267 (30.2)	134 (30.4)	133 (30.0)
Sex - no.(%)			
Female	342 (38.6)	177 (40.1)	165 (37.2)
Male	543 (61.4)	264 (59.9)	279 (62.8)
Race or ethnic group - no.(%)			
American Indian or Alaskan Native	8 (0.9)	1 (0.2)	7 (1.6)
Asian	32 (3.6)	15 (3.4)	17 (3.8)
Black or African American	156 (17.6)	77 (17.5)	79 (17.8)
Native Hawaiian or Other Pacific Islander	11 (1.2)	4 (0.9)	7 (1.6)
White	487 (55.0)	247 (56.0)	240 (54.1)
Unknown	191 (21.6)	97 (22.0)	94 (21.2)
Ethnicity - no.(%)			
Hispanic or Latino	461 (52.1)	227 (51.5)	234 (52.7)
Not Hispanic or Latino	408 (46.1)	208 (47.2)	200 (45.0)
Not Reported	4 (0.5)	2 (0.5)	2 (0.5)
Unknown	12 (1.4)	4 (0.9)	8 (1.8)
BMI - mean +/- standard deviation	32.9 +/- 8.5	32.9 +/- 8.4	32.9 +/- 8.6
Median time (Q1, Q3) from symptom onset to randomization – days	8 (5,10)	8 (5,10)	8 (5,11)
Disease severity - no.(%)			
Moderate Disease	601 (67.9)	306 (69.4)	295 (66.4)
Severe Disease	284 (32.1)	135 (30.6)	149 (33.6)
Summary of coexisting conditions - no./total no.(%)			

Characteristic	All Subjects (N=885)	Baricitinib + RDV Subjects (N=441)	Placebo + RDV Subjects (N=444)
None	103/848 (11.6)	39/423 (8.8)	64/425 (14.4)
One	218/848 (24.6)	121/423 (27.4)	97/425 (21.8)
Two or More	527/848 (59.5)	263/423 (59.6)	264/425 (59.5)
Coexisting conditions - no./total no.(%)			
Asthma	92/859 (10.7)	50/433 (11.5)	42/426 (9.9)
Cancer	34/862 (3.9)	20/434 (4.6)	14/428 (3.3)
Cardiac Valvular Disease	20/852 (2.3)	9/427 (2.1)	11/425 (2.6)
Chronic Kidney Disease	62/860 (7.2)	30/432 (6.9)	32/428 (7.5)
Chronic Liver Disease	25/859 (2.9)	10/432 (2.3)	15/427 (3.5)
Chronic Oxygen Use	17/871 (2.0)	8/436 (1.8)	9/435 (2.1)
Chronic Respiratory Disease	65/863 (7.5)	37/434 (8.5)	28/429 (6.5)
Coagulopathy	6/860 (0.7)	2/433 (0.5)	4/427 (0.9)
Congestive Heart Failure	61/860 (7.1)	31/432 (7.2)	30/428 (7.0)
Coronary Artery Disease	97/839 (11.6)	48/420 (11.4)	49/419 (11.7)
Current Nicotine Use	40/863 (4.6)	17/434 (3.9)	23/429 (5.4)
Diabetes I	10/869 (1.2)	5/435 (1.1)	5/434 (1.2)
Diabetes II	333/863 (38.6)	174/433 (40.2)	159/430 (37.0)
Hypertension	481/859 (56.0)	240/427 (56.2)	241/432 (55.8)
Immune Deficiency (acquired or innate)	30/861 (3.5)	17/434 (3.9)	13/427 (3.0)
Obesity	518/869 (59.6)	269/432 (62.3)	249/437 (57.0)
Score on ordinal scale - no.(%)			
4.Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (COVID-19 related or otherwise)	107 (12.1)	51 (11.6)	56 (12.6)

Characteristic	All Subjects (N=885)	Baricitinib + RDV Subjects (N=441)	Placebo + RDV Subjects (N=444)
5. Hospitalized, requiring supplemental oxygen	494 (55.8)	255 (57.8)	239 (53.8)
6.Hospitalized, on non-invasive ventilation or high flow oxygen devices	185 (20.9)	89 (20.2)	96 (21.6)
7.Hospitalized, on invasive mechanical ventilation or ECMO	99 (11.2)	46 (10.4)	53 (11.9)

Table S5. Table of missing values for recovery, mortality and ordinal scale at Day 15

Recovery status unknown—n (%)		
Visit Day	Baricitinib N=515	Placebo N=518
Day 15	17 (3.3%)	21 (4.1%)
Day 22	17 (3.3%)	22 (4.2%)
Day 29 (+/-3 days)	20 (3.9%)	26 (5.0%)
Mortality status unknown—n (%)		
Day 15	37 (7.2%)	36 (6.9%)
Day 22	46 (8.9%)	52 (10.0%)
Day 29 (+/-3 days)	67 (13.0%)*	75 (14.5%)*
Day 15 Ordinal score imputations		
Type 1. In hospital for initial hospitalization and no clinical status score was reported (last observation carried forward to impute ordinal score)	0	0
Type 2. Discharged from the hospital and still in study and no clinical status score was reported – values imputed as the worst possible discharge score of "2."	20 (3.9%)	26 (5.0%)
Type 3. Discontinued from the study (last observation carried forward to impute ordinal score)	35 (6.8%)	35 (6.8%)

* Of the subjects that had missing death status, 49 and 52 randomized to Baricitinib and Placebo, respectively, met recovery criteria and therefore had data for the primary analysis. Death after discharge is very uncommon in ACTT-2. Indeed, only one subject in each study arm met the recovery criteria and later died.

Table S6. Primary analysis using "as randomized" disease severity.

				First Quartile Time to Recovery (Days)		Median Time to Recovery (Days)		Third Quartile Time to Recovery (Days)		HR		
Analysis Population	**Treatment Group**	**Disease Severity**	**n**	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**P-value**
As randomized and ITT*	Baricitinib + RDV (N=339)	Moderate	311	4.0	3.0, 4.0	5.0	5.0, 6.0	9.0	8.0, 10.0	1.10	0.93, 1.29	-
	Placebo + RDV (N=327)		292	3.0	3.0, 4.0	6.0	5.0, 6.0	10.0	9.0, 11.0			
	Baricitinib + RDV (N=176)	Severe	122	7.0	6.0, 9.0	13.0	10.0, 16.0	NE	25.0, NE	1.29	1.00, 1.66	-
	Placebo + RDV (N=191)		114	9.0	6.0, 11.0	20.0	15.0, 23.0	NE	NE			
	Baricitinib + RDV (N=515)	Any Severity	433	4.0	NE	7.0	6.0, 8.0	13.0	12.0, 16.0	1.15	1.00, 1.31	0.047
	Placebo + RDV (N=518)		406	4.0	4.0, 5.0	8.0	7.0, 9.0	20.0	16.0, 23.0			
	Placebo + RDV (N=509)		406	4.0	4.0, 5.0	8.0	7.0, 9.0	20.0	16.0, 23.0			

N = Number of subjects in specified treatment group, disease severity, and analysis population.
n = Number of recovered subjects.
HR is the ratio of the hazard of recovery in each treatment group estimated from the Cox Model. The ratio is Baricitinib + RDV to Placebo + RDV.
HR for the 'Any Severity' group is the hazard ratio from the stratified Cox Model.
P-value calculated using the stratified log-rank test.

*This analysis treats 40 baseline ordinal scale values that were truly "moderate" at baseline as their incorrectly initial entry of "severe" for summary statistics and stratified testing.

Table S7. Serious Adverse Events Occurring in 5 or More Participants in Any Preferred Term by Treatment Group

MedDRA System Organ Class	Preferred Term	Baricitinib + RDV (N = 507) No.(%)	Placebo + RDV (N = 509) No.(%)
Any System Organ Class	Any Preferred Term	81 (16.0)	107 (21.0)
Cardiac disorders	Cardiac arrest	2 (0.4)	3 (0.6)
General disorders and administration site conditions	Multiple organ dysfunction syndrome	1 (0.2)	6 (1.2)
Infections and infestations	Septic shock	4 (0.8)	8 (1.6)
	Pneumonia	2 (0.4)	8 (1.6)
	Sepsis	1 (0.2)	5 (1.0)
Renal and urinary disorders	Acute kidney injury[a]	5 (1.0)	11 (2.2)
	Renal failure[a]	0 (-)	5 (1.0)
Respiratory, thoracic and mediastinal disorders	Respiratory failure[b]	26 (5.1)	37 (7.3)
	Acute respiratory failure[b]	18 (3.6)	13 (2.6)
	Acute respiratory distress syndrome	4 (0.8)	10 (2.0)
	Respiratory distress[c]	4 (0.8)	6 (1.2)
	Pulmonary embolism	5 (1.0)	2 (0.4)
	Hypoxia[c]	3 (0.6)	3 (0.6)
	Dyspnoea[c]	1 (0.2)	4 (0.8)
	Pneumothorax	1 (0.2)	4 (0.8)
Vascular disorders	Hypotension	5 (1.0)	5 (1.0)
	Shock	2 (0.4)	4 (0.8)

No. = number of subjects reporting at least one event.
[a] The combined number of subjects with acute kidney injury or renal failure are 5 for Baricitinib + RDV and 16 for Placebo + RDV.
[b] The combined number of subjects with respiratory failure or acute respiratory failure is 44 for Baricitinib + RDV and 50 for Placebo + RDV.
[c] The combined number of subjects with dyspnoea, hypoxia or respiratory distress are 8 for Baricitinib + RDV and 13 for Placebo + RDV.

Table S8. Non-Serious Adverse Events Occurring in 5 or More Participants in Any Preferred Term by Treatment Group

MedDRA System Organ Class	Preferred Term	Baricitinib + RDV (N = 507) No.(%)	Placebo + RDV (N = 509) No.(%)
Any System Organ Class	Any Preferred Term	187 (36.9)	220 (43.2)
Blood and lymphatic system disorders	Anaemia[a]	24 (4.7)	31 (6.1)
	Lymphopenia[b]	11 (2.2)	23 (4.5)
Cardiac disorders	Atrial fibrillation	1 (0.2)	7 (1.4)
General disorders and administration site conditions	Pyrexia	10 (2.0)	9 (1.8)
Infections and infestations	Pneumonia	10 (2.0)	14 (2.8)
	Pneumonia bacterial	3 (0.6)	9 (1.8)
	Sepsis	3 (0.6)	7 (1.4)
	Urinary tract infection	5 (1.0)	2 (0.4)
	Bacteraemia	2 (0.4)	5 (1.0)
	Septic shock	3 (0.6)	2 (0.4)
Investigations	Glomerular filtration rate decreased[c]	49 (9.7)	42 (8.3)
	Haemoglobin decreased[a]	30 (5.9)	30 (5.9)
	Lymphocyte count decreased[b]	23 (4.5)	35 (6.9)
	Blood glucose increased[e]	22 (4.3)	27 (5.3)
	Aspartate aminotransferase increased[d]	9 (1.8)	16 (3.1)
	Blood creatinine increased[c]	10 (2.0)	8 (1.6)
	Transaminases increased[d]	6 (1.2)	10 (2.0)
	Alanine aminotransferase increased[d]	6 (1.2)	9 (1.8)
	International normalised ratio increased	3 (0.6)	8 (1.6)
	Blood bilirubin increased	2 (0.4)	8 (1.6)
	Blood albumin decreased	5 (1.0)	3 (0.6)
	Creatinine renal clearance decreased[c]	3 (0.6)	3 (0.6)
	Prothrombin time prolonged	4 (0.8)	1 (0.2)
Metabolism and nutrition disorders	Hyperglycaemia[e]	25 (4.9)	40 (7.9)
Renal and urinary disorders	Acute kidney injury[c]	15 (3.0)	27 (5.3)
Respiratory, thoracic and mediastinal disorders	Respiratory distress[f]	9 (1.8)	9 (1.8)
	Hypoxia[f]	6 (1.2)	4 (0.8)
	Pneumonia aspiration	4 (0.8)	2 (0.4)
	Dyspnoea[f]	3 (0.6)	3 (0.6)
	Acute respiratory failure	0 (-)	6 (1.2)
	Pneumothorax	3 (0.6)	2 (0.4)
Vascular disorders	Deep vein thrombosis	11 (2.2)	9 (1.8)
	Hypertension	11 (2.2)	6 (1.2)

MedDRA System Organ Class	Preferred Term	Baricitinib + RDV (N = 507) No.(%)	Placebo + RDV (N = 509) No.(%)
	Hypotension	4 (0.8)	13 (2.6)

No. = number of subjects reporting at least one event.
[a] The combined number of subjects with anaemia or haemoglobin decreased are 54 for Baricitinib + RDV and 59 for Placebo + RDV.
[b] The combined number of subjects with lymphopenia or lymphocyte count decreased are 34 for Baricitinib + RDV and 58 for Placebo + RDV.
[c] The combined number of subjects with glomerular filtration rate decreased, acute kidney injury, blood creatinine increased or creatinine renal clearance decreased are 71 for Baricitinib + RDV and 75 for Placebo + RDV.
[d] The combined number of subjects with transaminases increased, aspartate aminotransferase increased or alanine aminotransferase increased are 15 for Baricitinib + RDV and 30 for Placebo + RDV.
[e] The combined number of subjects with hyperglycaemia or blood glucose increased are 47 for Baricitinib + RDV and 66 for Placebo + RDV.
[f] The combined number of subjects with hypoxia, dyspnea or respiratory distress are 18 for Baricitinib + RDV and 16 for Placebo + RDV.

Table S9. ACTT-2 results of Cox proportional hazards models testing for interactions between treatment effect and baseline ordinal score with respect to recovery and mortality.

Cox Proportional Hazards Model	Group	HR (95% CI)*
Recovery		
Model 1 – Time to recovery with interaction term for treatment effect by baseline ordinal score; • Baseline ordinal score treated as continuous • Model terms: treatment, continuous baseline ordinal score, interaction between treatment and ordinal score	Baseline Score 4	0.99 (0.79,1.25)
	Baseline Score 5	1.14 (0.99,1.30)
	Baseline Score 6	1.30 (1.07,1.59)
	Baseline Score 7	1.49 (1.06,2.10)
Model 2 – Time to recovery with interaction term for treatment effect by baseline ordinal score; • Baseline ordinal scores grouped as 4/5 versus 6/7 • Model terms: treatment, grouped baseline ordinal score, interaction between treatment and grouped ordinal score	Baseline Score 4/5	1.13 (0.97,1.32)
	Baseline Score 6/7	1.28 (0.97,1.70)
Model 3 – Time to recovery with interaction term for treatment effect by baseline ordinal score; • Baseline ordinal score treated as categorical • Model terms: treatment, categorical baseline ordinal score, interaction between treatment and categorical ordinal score	Baseline Score 4	0.85 (0.61,1.19)
	Baseline Score 5	1.21 (1.01,1.44)
	Baseline Score 6	1.43 (1.04,1.96)
	Baseline Score 7	1.07 (0.59,1.95)
Mortality		
Model 4 – Mortality with interaction term for treatment effect by baseline ordinal score; • Baseline ordinal score treated as continuous • Model terms: treatment, continuous baseline ordinal score, interaction between treatment and ordinal score	Baseline Score 4	0.27 (0.07,1.12)
	Baseline Score 5	0.41 (0.17,0.98)
	Baseline Score 6	0.61 (0.36,1.03)
	Baseline Score 7	0.91 (0.44,1.86)
Model 5 – Mortality with interaction term for treatment effect by baseline ordinal score; • Baseline ordinal scores grouped as 4/5 versus 6/7 • Model terms: treatment, grouped baseline ordinal score, interaction between treatment and grouped ordinal score	Baseline Score 4/5	0.40 (0.14,1.14)
	Baseline Score 6/7	0.77 (0.42,1.40)
Model 6 – Mortality with interaction term for treatment effect by baseline ordinal score; • Baseline ordinal score treated as categorical • Model terms: treatment, categorical baseline ordinal score, interaction between treatment and categorical ordinal score	Baseline Score 4	1 (0,Inf)
	Baseline Score 5	0.40 (0.14,1.13)
	Baseline Score 6	0.55 (0.22,1.38)
	Baseline Score 7	0.99 (0.45,2.21)

***Estimates represent model-based recovery-/hazard-rate ratios. For completeness, three approaches to modelling ordinal score were included: categorical, binary (baseline 4/5 vs baseline 6/7), or continuous.**

Table S10. Treatment Emergent Related Grade 3-4 AEs (Serious and Non-Serious) by MedDRA System Organ Class, Preferred Term and Treatment Group

MedDRA System Organ Class	Preferred Term	Baricitinib + RDV (N = 508) No.(%)	Placebo + RDV (N = 509) No.(%)
Any System Organ Class	Any Preferred Term	25 (4.9)	28 (5.5)
Blood and lymphatic system disorders	Lymphopenia	0 (-)	1 (0.2)
	Neutropenia	0 (-)	1 (0.2)
Gastrointestinal disorders	Nausea	2 (0.4)	1 (0.2)
	Vomiting	0 (-)	2 (0.4)
General disorders and administration site conditions	Oedema peripheral	0 (-)	1 (0.2)
Hepatobiliary disorders	Hepatitis	0 (-)	1 (0.2)
Immune system disorders	Hypersensitivity	0 (-)	1 (0.2)
Infections and infestations	Intervertebral discitis	1 (0.2)	0 (-)
	Lung abscess	0 (-)	1 (0.2)
	Pneumonia	0 (-)	1 (0.2)
Investigations	Alanine aminotransferase increased	4 (0.8)	3 (0.6)
	Aspartate aminotransferase increased	7 (1.4)	3 (0.6)
	Bilirubin conjugated increased	1 (0.2)	0 (-)
	Glomerular filtration rate decreased	0 (-)	2 (0.4)
	Liver function test increased	1 (0.2)	0 (-)
	Lymphocyte count decreased	6 (1.2)	5 (1.0)
	Platelet count decreased	1 (0.2)	0 (-)
	Prothrombin time prolonged	1 (0.2)	1 (0.2)
	Transaminases increased	2 (0.4)	4 (0.8)
Renal and urinary disorders	Acute kidney injury	1 (0.2)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	4 (0.8)	0 (-)
Skin and subcutaneous tissue disorders	Rash	0 (-)	1 (0.2)
Vascular disorders	Brachiocephalic vein thrombosis	0 (-)	1 (0.2)
	Deep vein thrombosis	1 (0.2)	3 (0.6)
	Peripheral ischaemia	0 (-)	1 (0.2)
	Thrombosis	0 (-)	1 (0.2)

No. = number of subjects reporting at least one event.

Table S11. Treatment Emergent Grade 3-4 AEs (Serious and Non-Serious) by MedDRA System Organ Class, Preferred Term and Treatment Group

MedDRA System Organ Class	Preferred Term	Baricitinib + RDV (N = 508) No.(%)	Placebo + RDV (N = 509) No.(%)
Any System Organ Class	Any Preferred Term	207 (40.7)	238 (46.8)
Blood and lymphatic system disorders	Anaemia	25 (4.9)	33 (6.5)
	Anaemia macrocytic	0 (-)	1 (0.2)
	Heparin-induced thrombocytopenia	1 (0.2)	1 (0.2)
	Hypercoagulation	0 (-)	1 (0.2)
	Leukocytosis	2 (0.4)	0 (-)
	Leukopenia	1 (0.2)	1 (0.2)
	Lymphocytosis	0 (-)	1 (0.2)
	Lymphopenia	11 (2.2)	24 (4.7)
	Neutropenia	1 (0.2)	2 (0.4)
	Sickle cell anaemia with crisis	1 (0.2)	0 (-)
	Thrombocytopenia	0 (-)	2 (0.4)
Cardiac disorders	Aortic valve stenosis	0 (-)	1 (0.2)
	Arrhythmia	1 (0.2)	1 (0.2)
	Atrial fibrillation	1 (0.2)	8 (1.6)
	Atrioventricular block	0 (-)	1 (0.2)
	Bradycardia	1 (0.2)	1 (0.2)
	Cardiac arrest	1 (0.2)	1 (0.2)
	Cardiac failure	2 (0.4)	0 (-)
	Myocardial ischaemia	0 (-)	1 (0.2)
	Pulseless electrical activity	1 (0.2)	1 (0.2)
	Right ventricular dysfunction	0 (-)	1 (0.2)
	Sinus bradycardia	1 (0.2)	0 (-)
	Tachycardia	0 (-)	1 (0.2)
Eye disorders	Visual impairment	1 (0.2)	0 (-)
Gastrointestinal disorders	Abdominal distension	0 (-)	1 (0.2)
	Abdominal pain	0 (-)	1 (0.2)
	Dysphagia	3 (0.6)	0 (-)
	Gastrointestinal haemorrhage	0 (-)	2 (0.4)
	Ileus	0 (-)	3 (0.6)
	Lower gastrointestinal haemorrhage	0 (-)	1 (0.2)
	Nausea	2 (0.4)	1 (0.2)
	Pancreatitis acute	1 (0.2)	0 (-)
	Toothache	1 (0.2)	0 (-)
	Vomiting	0 (-)	2 (0.4)
General disorders and administration site conditions	Asthenia	1 (0.2)	0 (-)

MedDRA System Organ Class	Preferred Term	Baricitinib + RDV (N = 508) No.(%)	Placebo + RDV (N = 509) No.(%)
	Chest pain	3 (0.6)	0 (-)
	Complication associated with device	0 (-)	1 (0.2)
	Injection site induration	0 (-)	1 (0.2)
	Multiple organ dysfunction syndrome	2 (0.4)	4 (0.8)
	Non-cardiac chest pain	1 (0.2)	0 (-)
	Oedema peripheral	0 (-)	1 (0.2)
	Pain	1 (0.2)	1 (0.2)
	Pyrexia	9 (1.8)	9 (1.8)
Hepatobiliary disorders	Hepatic haemorrhage	0 (-)	1 (0.2)
	Hepatitis	0 (-)	1 (0.2)
	Hyperbilirubinaemia	2 (0.4)	1 (0.2)
	Hypertransaminasaemia	1 (0.2)	0 (-)
	Liver injury	0 (-)	1 (0.2)
Immune system disorders	Cytokine storm	1 (0.2)	1 (0.2)
	Hypersensitivity	1 (0.2)	1 (0.2)
Infections and infestations	Abscess	0 (-)	1 (0.2)
	Aspergillus infection	1 (0.2)	1 (0.2)
	Bacteraemia	2 (0.4)	5 (1.0)
	Bronchopulmonary aspergillosis	1 (0.2)	1 (0.2)
	Candida infection	1 (0.2)	0 (-)
	Candida sepsis	0 (-)	1 (0.2)
	Clostridium difficile infection	2 (0.4)	0 (-)
	Enterococcal infection	0 (-)	1 (0.2)
	Fungaemia	1 (0.2)	0 (-)
	Fungal infection	1 (0.2)	0 (-)
	Intervertebral discitis	1 (0.2)	0 (-)
	Klebsiella infection	0 (-)	1 (0.2)
	Lower respiratory tract infection	1 (0.2)	0 (-)
	Lung abscess	0 (-)	1 (0.2)
	Mastoiditis	0 (-)	1 (0.2)
	Oesophageal candidiasis	1 (0.2)	0 (-)
	Pneumonia	12 (2.4)	21 (4.1)
	Pneumonia bacterial	3 (0.6)	9 (1.8)
	Pneumonia Escherichia	0 (-)	1 (0.2)
	Pneumonia klebsiella	0 (-)	1 (0.2)
	Pneumonia staphylococcal	0 (-)	3 (0.6)
	Pneumonia streptococcal	0 (-)	1 (0.2)
	Prostatic abscess	1 (0.2)	0 (-)
	Respiratory tract infection bacterial	0 (-)	1 (0.2)

MedDRA System Organ Class	Preferred Term	Baricitinib + RDV (N = 508) No.(%)	Placebo + RDV (N = 509) No.(%)
	Sepsis	4 (0.8)	11 (2.2)
	Septic shock	5 (1.0)	9 (1.8)
	Sinusitis	0 (-)	1 (0.2)
	Staphylococcal bacteraemia	0 (-)	1 (0.2)
	Staphylococcal infection	1 (0.2)	1 (0.2)
	Systemic candida	0 (-)	1 (0.2)
	Upper respiratory tract infection bacterial	0 (-)	2 (0.4)
	Urinary tract infection	6 (1.2)	2 (0.4)
	Urinary tract infection fungal	1 (0.2)	0 (-)
	Urosepsis	0 (-)	1 (0.2)
	Vascular device infection	2 (0.4)	1 (0.2)
	Vulvovaginal mycotic infection	0 (-)	1 (0.2)
Injury, poisoning and procedural complications	Endotracheal intubation complication	1 (0.2)	1 (0.2)
	Fall	0 (-)	1 (0.2)
	Overdose	0 (-)	1 (0.2)
	Procedural hypotension	1 (0.2)	0 (-)
Investigations	Activated partial thromboplastin time prolonged	1 (0.2)	1 (0.2)
	Alanine aminotransferase increased	6 (1.2)	12 (2.4)
	Aspartate aminotransferase increased	9 (1.8)	18 (3.5)
	Bacterial test positive	1 (0.2)	0 (-)
	Bilirubin conjugated increased	1 (0.2)	0 (-)
	Blood albumin decreased	5 (1.0)	3 (0.6)
	Blood alkaline phosphatase increased	0 (-)	2 (0.4)
	Blood bilirubin increased	2 (0.4)	8 (1.6)
	Blood calcium decreased	1 (0.2)	0 (-)
	Blood creatine phosphokinase increased	2 (0.4)	2 (0.4)
	Blood creatinine decreased	2 (0.4)	1 (0.2)
	Blood creatinine increased	10 (2.0)	9 (1.8)
	Blood glucose decreased	0 (-)	1 (0.2)
	Blood glucose increased	22 (4.3)	27 (5.3)
	Blood phosphorus decreased	0 (-)	1 (0.2)
	Blood pressure increased	1 (0.2)	2 (0.4)
	Blood pressure systolic increased	0 (-)	1 (0.2)
	Blood sodium increased	1 (0.2)	0 (-)
	Blood triglycerides increased	1 (0.2)	2 (0.4)
	Candida test positive	1 (0.2)	0 (-)
	Creatinine renal clearance decreased	3 (0.6)	3 (0.6)
	Electrocardiogram QT prolonged	1 (0.2)	1 (0.2)
	Fibrin D dimer increased	0 (-)	1 (0.2)

MedDRA System Organ Class	Preferred Term	Baricitinib + RDV (N = 508) No.(%)	Placebo + RDV (N = 509) No.(%)
	Glomerular filtration rate decreased	49 (9.6)	42 (8.3)
	Glomerular filtration rate increased	0 (-)	1 (0.2)
	Haemoglobin decreased	30 (5.9)	30 (5.9)
	Haemophilus test positive	0 (-)	1 (0.2)
	International normalised ratio increased	3 (0.6)	8 (1.6)
	Liver function test increased	1 (0.2)	0 (-)
	Lymphocyte count decreased	24 (4.7)	35 (6.9)
	Neutrophil count decreased	1 (0.2)	0 (-)
	Platelet count decreased	2 (0.4)	1 (0.2)
	Prothrombin time prolonged	4 (0.8)	1 (0.2)
	Serratia test positive	0 (-)	1 (0.2)
	Sputum culture positive	1 (0.2)	0 (-)
	Transaminases increased	6 (1.2)	10 (2.0)
	Troponin increased	1 (0.2)	1 (0.2)
	White blood cell count decreased	0 (-)	1 (0.2)
Metabolism and nutrition disorders	Acidosis	1 (0.2)	4 (0.8)
	Alkalosis	2 (0.4)	0 (-)
	Decreased appetite	1 (0.2)	0 (-)
	Dehydration	1 (0.2)	0 (-)
	Diabetic ketoacidosis	0 (-)	1 (0.2)
	Fluid overload	0 (-)	2 (0.4)
	Hyperglycaemia	25 (4.9)	40 (7.9)
	Hyperkalaemia	0 (-)	2 (0.4)
	Hypernatraemia	1 (0.2)	1 (0.2)
	Hypertriglyceridaemia	1 (0.2)	0 (-)
	Hypoalbuminaemia	2 (0.4)	1 (0.2)
	Hypocalcaemia	0 (-)	3 (0.6)
	Hypoglycaemia	1 (0.2)	1 (0.2)
	Hypokalaemia	0 (-)	1 (0.2)
	Hypophosphataemia	0 (-)	1 (0.2)
	Metabolic acidosis	0 (-)	2 (0.4)
	Metabolic alkalosis	0 (-)	4 (0.8)
Musculoskeletal and connective tissue disorders	Compartment syndrome	0 (-)	1 (0.2)
	Diabetic amyotrophy	1 (0.2)	0 (-)
	Haematoma muscle	0 (-)	1 (0.2)
Nervous system disorders	Cerebrovascular accident	1 (0.2)	2 (0.4)
	Encephalopathy	3 (0.6)	3 (0.6)
	Guillain-Barre syndrome	1 (0.2)	0 (-)
	Haemorrhage intracranial	0 (-)	1 (0.2)

MedDRA System Organ Class	Preferred Term	Baricitinib + RDV (N = 508) No.(%)	Placebo + RDV (N = 509) No.(%)
	Headache	1 (0.2)	1 (0.2)
	Metabolic encephalopathy	1 (0.2)	0 (-)
	Nervous system disorder	1 (0.2)	0 (-)
	Presyncope	0 (-)	1 (0.2)
	Seizure	1 (0.2)	0 (-)
	Sensory loss	0 (-)	1 (0.2)
	Vocal cord paralysis	0 (-)	1 (0.2)
Psychiatric disorders	Acute psychosis	1 (0.2)	0 (-)
	Agitation	1 (0.2)	0 (-)
	Anxiety	0 (-)	1 (0.2)
	Delirium	0 (-)	3 (0.6)
	Intensive care unit delirium	1 (0.2)	0 (-)
	Mental status changes	1 (0.2)	0 (-)
Renal and urinary disorders	Acute kidney injury	20 (3.9)	36 (7.1)
	Azotaemia	0 (-)	1 (0.2)
	Chronic kidney disease	0 (-)	1 (0.2)
	Haematuria	0 (-)	1 (0.2)
	Pollakiuria	0 (-)	1 (0.2)
	Renal failure	0 (-)	6 (1.2)
	Urinary retention	1 (0.2)	2 (0.4)
	Urinary tract obstruction	1 (0.2)	0 (-)
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	5 (1.0)	6 (1.2)
	Acute respiratory failure	13 (2.6)	10 (2.0)
	Asthma	2 (0.4)	0 (-)
	Bronchospasm	0 (-)	2 (0.4)
	Dyspnoea	4 (0.8)	7 (1.4)
	Epistaxis	0 (-)	2 (0.4)
	Haemoptysis	0 (-)	1 (0.2)
	Haemothorax	0 (-)	1 (0.2)
	Hypoxia	8 (1.6)	7 (1.4)
	Lung infiltration	1 (0.2)	0 (-)
	Oropharyngeal pain	1 (0.2)	0 (-)
	Pneumomediastinum	0 (-)	1 (0.2)
	Pneumonia aspiration	4 (0.8)	2 (0.4)
	Pneumothorax	4 (0.8)	6 (1.2)
	Pulmonary embolism	5 (1.0)	1 (0.2)
	Respiratory acidosis	0 (-)	1 (0.2)
	Respiratory disorder	0 (-)	1 (0.2)
	Respiratory distress	12 (2.4)	14 (2.8)

MedDRA System Organ Class	Preferred Term	Baricitinib + RDV (N = 508) No.(%)	Placebo + RDV (N = 509) No.(%)
	Respiratory failure	19 (3.7)	32 (6.3)
	Respiratory tract oedema	0 (-)	1 (0.2)
	Tachypnoea	0 (-)	1 (0.2)
Skin and subcutaneous tissue disorders	Angioedema	0 (-)	1 (0.2)
	Decubitus ulcer	3 (0.6)	1 (0.2)
	Rash	0 (-)	2 (0.4)
Surgical and medical procedures	Extubation	0 (-)	1 (0.2)
Vascular disorders	Brachiocephalic vein thrombosis	0 (-)	1 (0.2)
	Deep vein thrombosis	11 (2.2)	7 (1.4)
	Distributive shock	1 (0.2)	4 (0.8)
	Dry gangrene	0 (-)	1 (0.2)
	Embolism venous	1 (0.2)	1 (0.2)
	Essential hypertension	0 (-)	1 (0.2)
	Hypertension	11 (2.2)	6 (1.2)
	Hypotension	9 (1.8)	18 (3.5)
	Peripheral artery occlusion	1 (0.2)	0 (-)
	Peripheral ischaemia	1 (0.2)	1 (0.2)
	Phlebitis	0 (-)	1 (0.2)
	Shock	3 (0.6)	4 (0.8)
	Thrombophlebitis	1 (0.2)	0 (-)
	Thrombophlebitis superficial	1 (0.2)	0 (-)
	Thrombosis	2 (0.4)	2 (0.4)

No. = number of subjects reporting at least one event.

Table S12. Post-randomization corticosteroid use

	Percent post-randomization corticosteroid use		
Baseline category	Bari + RDV (n/N)	Placebo + RDV (n/N)	Difference (95% CI)
Overall	10.9% (56/515)	12.9% (67/518)	-2.1% (-6.0%, 1.9%)
OS-4	1.4% (1/70)	1.4% (1/72)	0.04% (-3.8%, 3.9%)
OS-5	10.1% (29/288)	9.4% (26/276)	0.6% (-4.2%, 5.5%)
OS-6	11.7% (12/103)	21.2% (24/113)	-9.6% (-19.3%, 0.2%)
OS-7	25.9% (14/54)	28.1% (16/57)	-2.1% (-18.7%, 14.4%)
	Post-randomization dexamethasone use		
Baseline category	Bari + RDV (n/N)	Placebo + RDV (n/N)	Difference (95% CI)
Overall	6.0% (31/515)	7.1% (37/518)	-1.1% (-4.1%, 1.9%)
OS-4	0 (0/70)	0 (0/72)	NA
OS-5	6.9% (20/288)	6.5% (18/276)	0.4% (-3.7%, 4.6%)
OS-6	5.8% (6/103)	11.5% (13/113)	-5.7% (-13.1%, 1.7%)
OS-7	9.3% (5/54)	10.5 (6/56)	-1.3% (-12.4%, 9.8%)

Table S13. Sensitivity analysis of time to recovery with random effects for site

Random effects model estimates	1.1564 (95% CI: 1.009, 1.325)	p=0.0364
Original model estimates	1.1567 (95% CI: 1.010, 1.325)	p=0.0354

Table S14. Primary Analysis of Time to Recovery by Baseline Ordinal Score at Final Alpha Spending Look

Baseline Ordinal Score	Overall		4		5		6		7	
	Placebo (n=518)	Baricitinib (n=516)	Placebo (n=73)	Baricitinib (n=71)	Placebo (n=259)	Baricitinib (n=271)	Placebo (n=130)	Baricitinib (n=120)	Placebo (n=56)	Baricitinib (n=54)
Days to Recovery										
Number of Recoveries	390	427	66	67	222	240	83	98	19	22
Median (95% CI)	8 (7, 9)	7 (6, 8)	4 (4, 6)	5 (4, 6)	6 (5, 7)	5 (5, 6)	15 (11, 19)	10 (8, 11)	NE*	NE*
Recovery Rate Ratio (95% CI); p-value	1.17 (1.02, 1.34); 0.02		0.87 (0.62, 1.22)		1.16 (0.97, 1.40)		1.56 (1.16, 2.09)		1.18 (0.64, 2.18)	

*Indicates that the value was not estimable.

Note that data cleaning was ongoing during the final alpha spending look. One participant included in the baricitinib+RDV arm during the final alpha spending look was subsequently determined to be ineligible and data cleaning related to baseline ordinal scores occurred after the final alpha spending look.

Table S15. Restricted Mean Survival Time Analysis

					Restricted Mean Survival Time (Days)		Difference	
Analysis Population	**Actual Disease Severity**	**Treatment Group**	**n**	**Tau**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Recovery	Ordinal Score 4	Baricitinib + RDV (N=70)	67	22.0	6.44	5.31, 7.57	0.66	-0.81, 2.14
		Placebo + RDV (N=72)	69	22.0	5.77	4.82, 6.72		
	Ordinal Score 5	Baricitinib + RDV (N=288)	262	30.0	7.73	6.94, 8.53	-1.29	-2.55, -0.02
		Placebo + RDV (N=276)	243	30.0	9.02	8.04, 10.01		
	Ordinal Score 6	Baricitinib + RDV (N=103)	82	30.0	14.26	12.50, 16.03	-3.74	-6.29, -1.19
		Placebo + RDV (N=113)	73	30.0	18.00	16.16, 19.84		
	Ordinal Score 7	Baricitinib + RDV (N=54)	22	30.0	24.46	22.41, 26.51	-0.38	-3.30, 2.54
		Placebo + RDV (N=57)	21	30.0	24.84	22.77, 26.91		
	Overall	Baricitinib + RDV (N=515)	433	30.0	10.67	9.87, 11.46	-1.54	-2.73, -0.36
		Placebo + RDV (N=518)	406	30.0	12.21	11.33, 13.09		
Mortality	Ordinal Score 4	Baricitinib + RDV (N=70)	0	-	-	-	-	-
		Placebo + RDV (N=72)	0	-	-	-		

					Restricted Mean Survival Time (Days)		Difference	
Analysis Population	**Actual Disease Severity**	**Treatment Group**	**n**	**Tau**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
	Ordinal Score 5	Baricitinib + RDV (N=288)	5	28.0	27.77	27.57, 27.98	0.32	-0.07, 0.71
		Placebo + RDV (N=276)	12	28.0	27.45	27.12, 27.78		
	Ordinal Score 6	Baricitinib + RDV (N=103)	7	28.0	27.28	26.65, 27.92	0.58	-0.46, 1.62
		Placebo + RDV (N=113)	13	28.0	26.71	25.88, 27.53		
	Ordinal Score 7	Baricitinib + RDV (N=54)	12	28.0	25.30	23.59, 27.02	0.32	-2.07, 2.72
		Placebo + RDV (N=57)	12	28.0	24.98	23.31, 26.65		
	Any Severity	Baricitinib + RDV (N=515)	24	28.0	27.44	27.18, 27.70	0.34	-0.07, 0.75
		Placebo + RDV (N=518)	37	28.0	27.10	26.78, 27.42		

N = Number of subjects in specified treatment group and disease severity.
n = Number of recoveries/deaths.
Difference is the difference in the restricted mean survival time between Baricitinib + RDV and Placebo + RDV.

Table S16. Time to Recovery by Treatment Group and Baseline Ordinal Score: Fine-Gray Modeling

		HR	
Model	**Baseline Clinical Ordinal Score**	**Estimate**	**95% CI**
Fine-Gray	Baseline Clinical Status Score 7	1.08	0.60, 1.94
	Baseline Clinical Status Score 6	1.51	1.11, 2.06
	Baseline Clinical Status Score 5	1.17	1.00, 1.37
	Baseline Clinical Status Score 4	0.88	0.65, 1.18
	Overall	1.16	1.02, 1.31
HR is the ratio of the hazard of recovery in each treatment group estimated from the Cox Model. The ratio is Baricitinib + RDV to Placebo + RDV.			

Figure S1. Day 15 outcomes by baseline ordinal scale in the intent-to-treat population.
Bar plots are shifted to compare improvement versus no improvement / worsening compared to the baseline ordinal score category (i.e., the "Enrollment Score"). Movement to the right of the enrollment score line reflect improvement by Day 15. Movement to the left of the enrollment line reflect no change in ordinal status or worsening by Day 15.

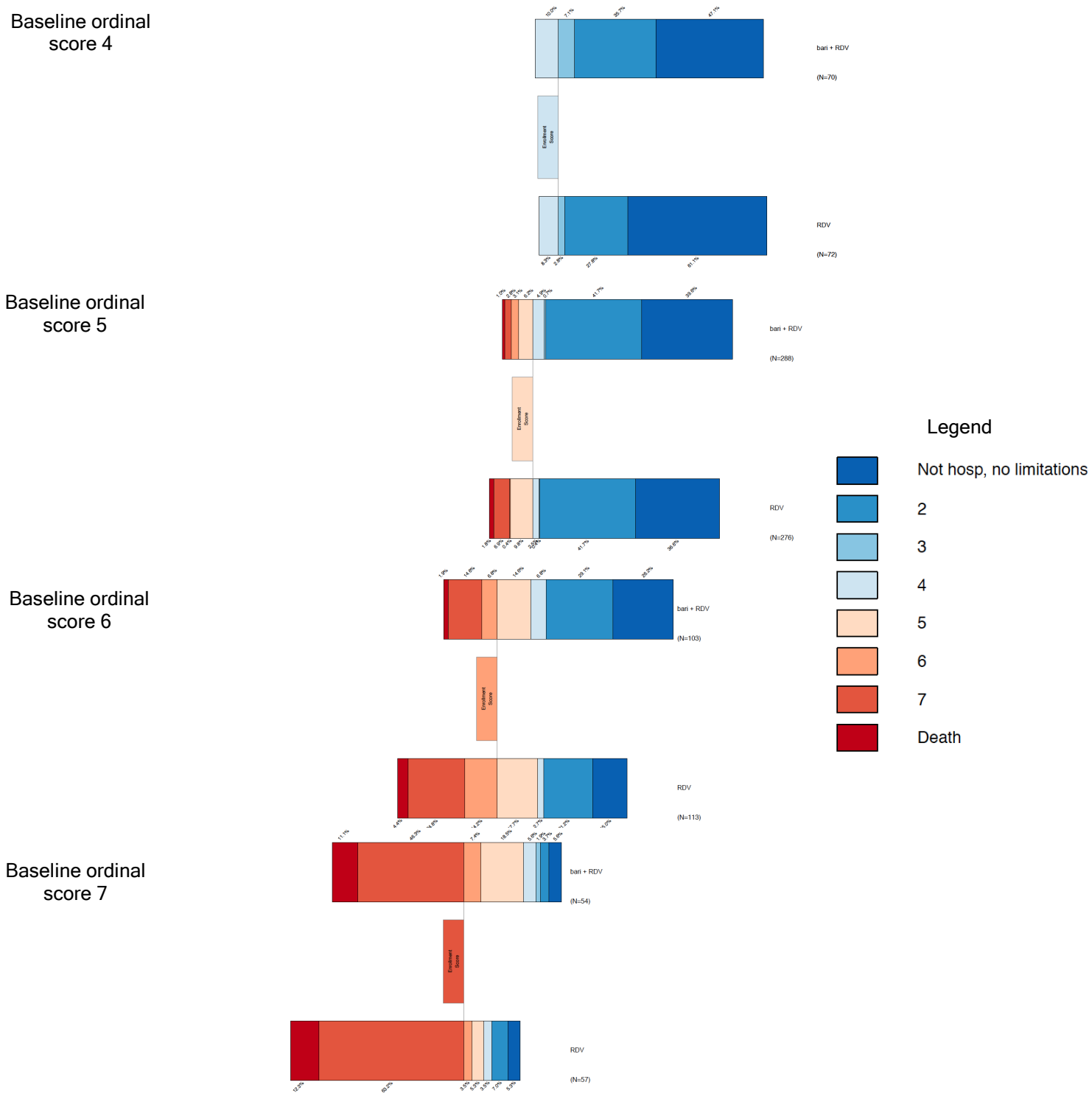
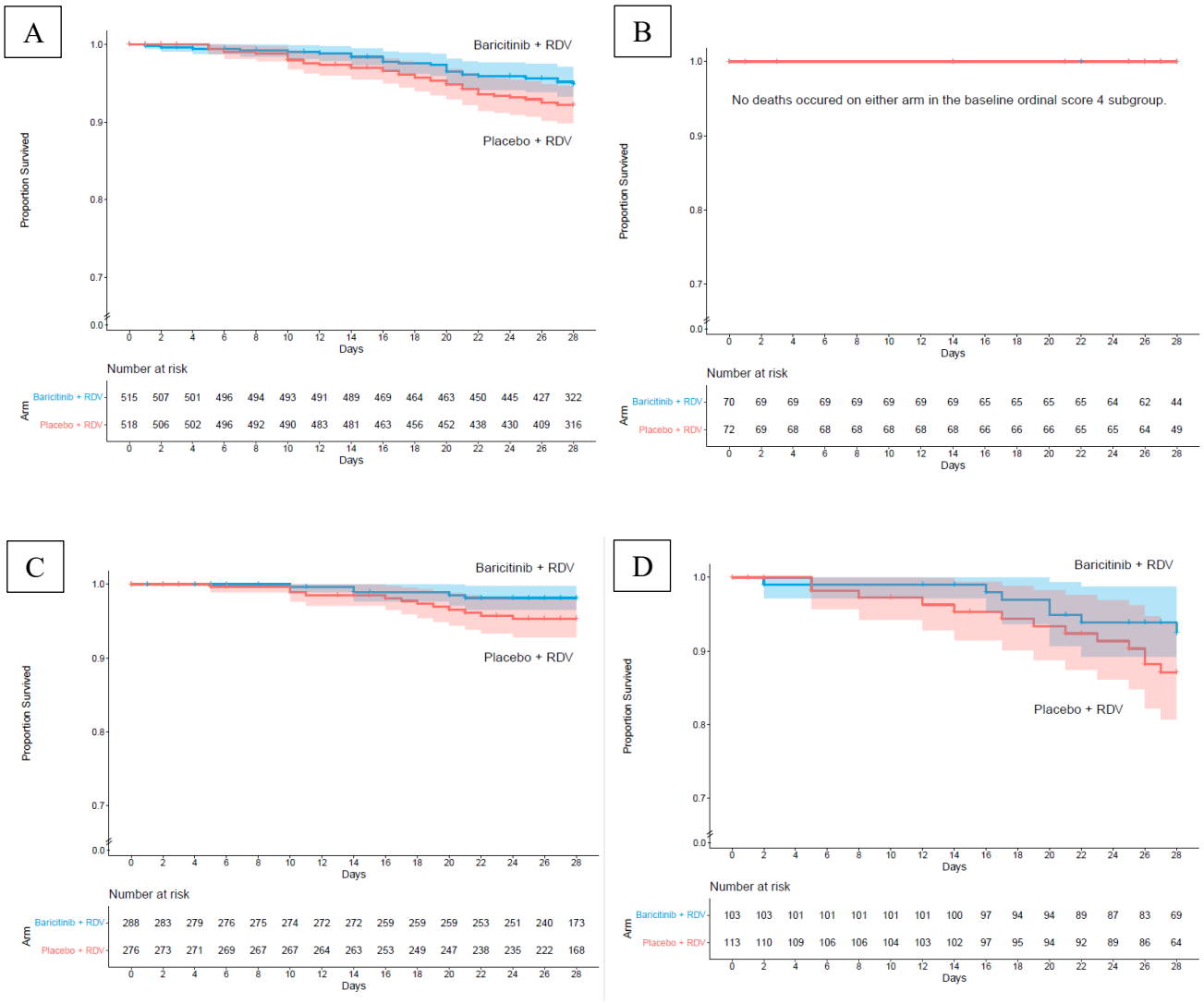
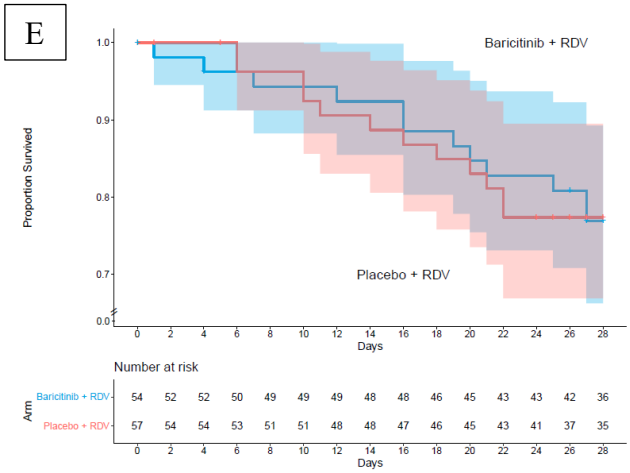


Figure S2. Kaplan–Meier Estimates of Survival by Baseline Ordinal Scale.
Panel A shows the estimates (and 95% confidence bands) in the overall population, Panel B in those with baseline ordinal scale = 4, Panel C in those with baseline ordinal scale = 5, Panel D in those with baseline ordinal scale = 6, and Panel E in those with baseline ordinal scale = 7.





Note: the widths of confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.

References:

1. Royal College of Physicians. National Early Warning Score (NEWS) 2 2017 [Available from: https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2.
2. King JC, Beigel JH, Ison MG, Rothman RE, Uyeki TM, Walker RE, et al. Clinical Development of Therapeutic Agents for Hospitalized Patients With Influenza: Challenges and Innovations. Open Forum Infect Dis. 2019;6(4):ofz137.