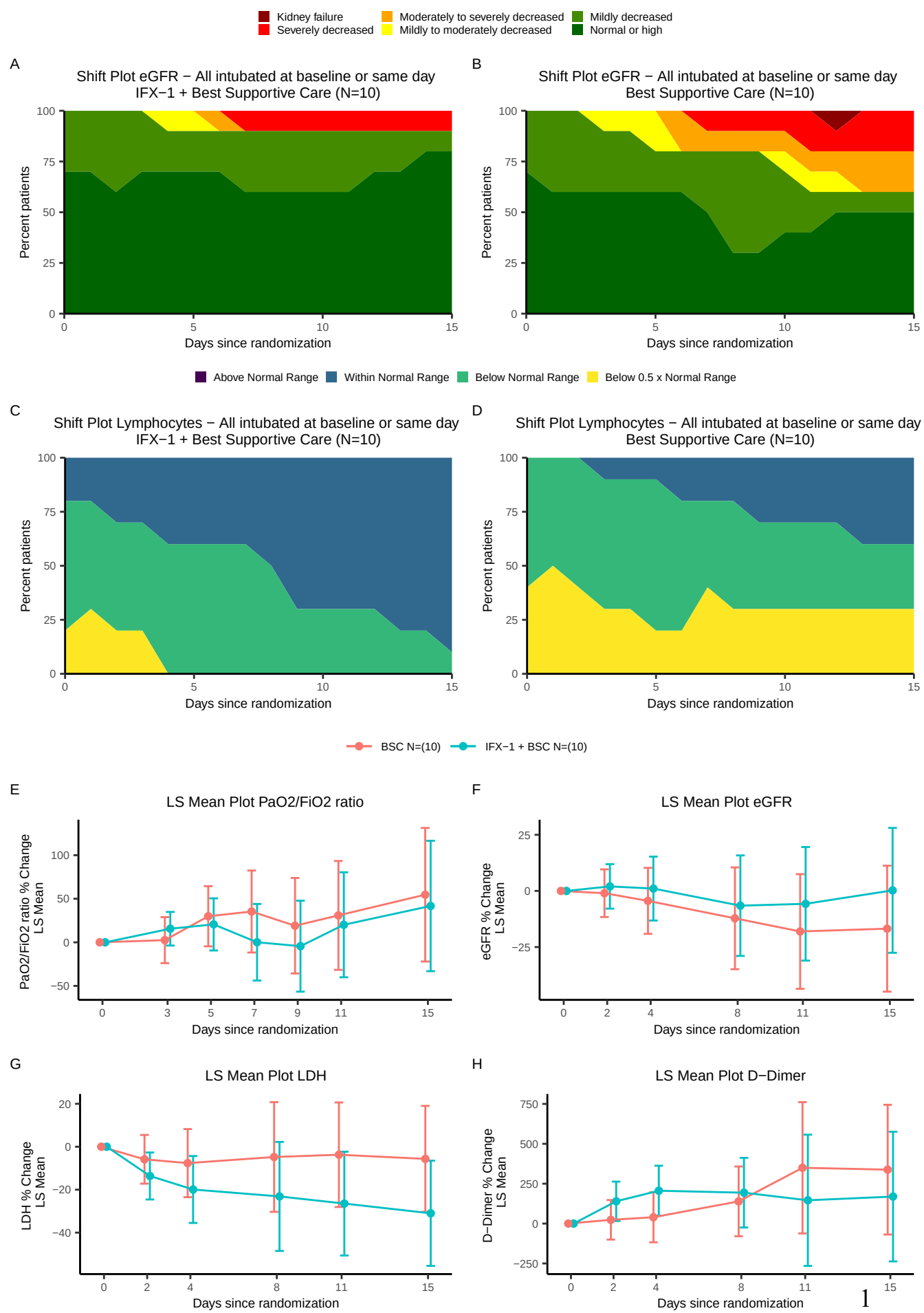
THE LANCET
Rheumatology

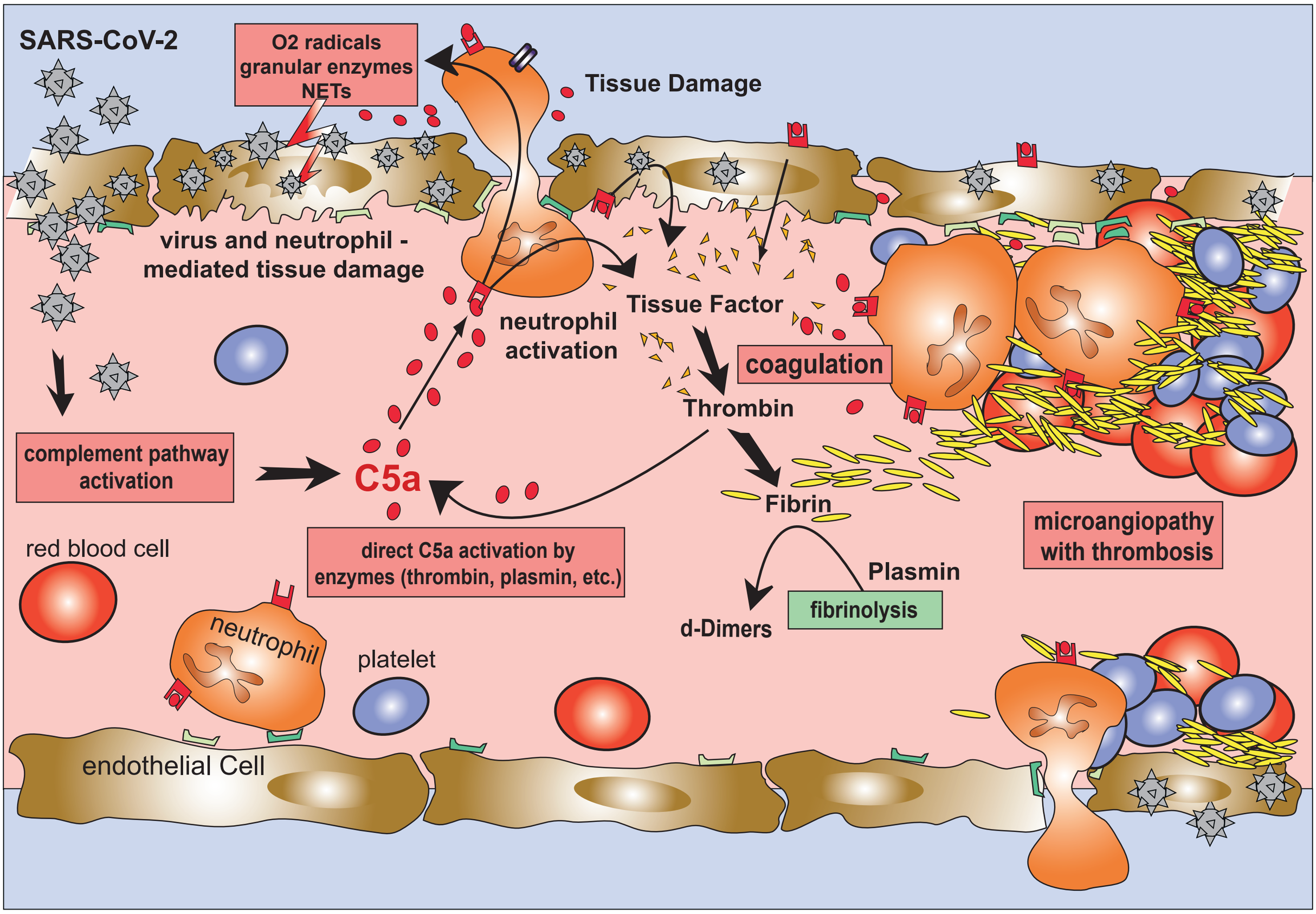
Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

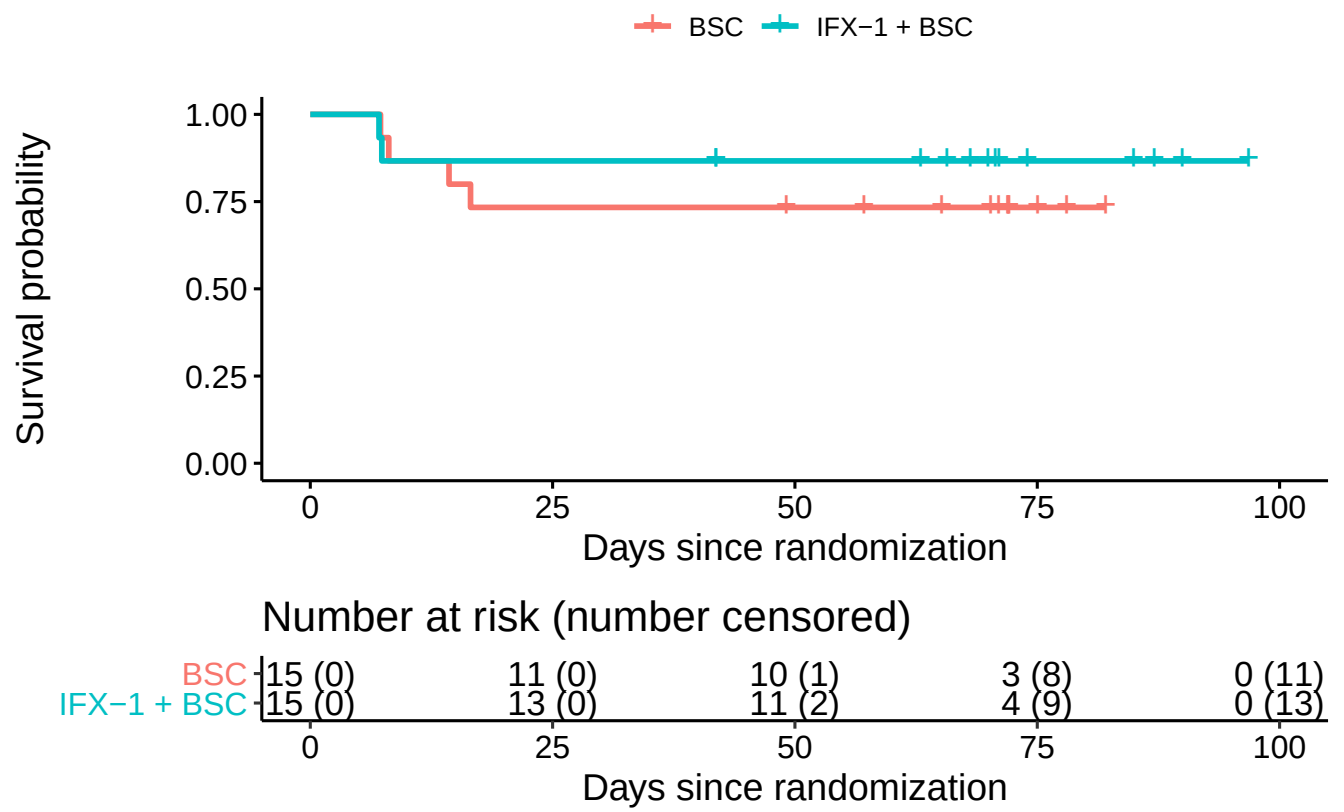
Supplement to: Vlaar APJ, de Bruin S, Busch M, et al. Anti-C5a antibody IFX-1 (vilobelimab) treatment versus best supportive care for patients with severe COVID-19 (PANAMO): an exploratory, open-label, phase 2 randomised controlled trial. *Lancet Rheumatol* 2020; published online Sept 28. https://doi.org/10.1016/S2665-9913(20)30341-6.

CONTENT APPENDIX


Kidney failure
Severely decreased
Moderately to severely decreased
Mildly to moderately decreased
Mildly decreased
Normal or high
A
Shift Plot eGFR − All intubated at baseline or same day
IFX−1 + Best Supportive Care (N=10)
B
Shift Plot eGFR − All intubated at baseline or same day
Best Supportive Care (N=10)
Percent patients
Days since randomization
Above Normal Range
Within Normal Range
Below Normal Range
Below 0.5 x Normal Range
C
Shift Plot Lymphocytes − All intubated at baseline or same day
IFX−1 + Best Supportive Care (N=10)
D
Shift Plot Lymphocytes − All intubated at baseline or same day
Best Supportive Care (N=10)
BSC N=(10)
IFX−1 + BSC N=(10)
E
LS Mean Plot PaO2/FiO2 ratio
PaO2/FiO2 ratio % Change
LS Mean
F
LS Mean Plot eGFR
eGFR % Change
LS Mean
G
LS Mean Plot LDH
LDH % Change
LS Mean
H
LS Mean Plot D−Dimer
D−Dimer % Change
LS Mean

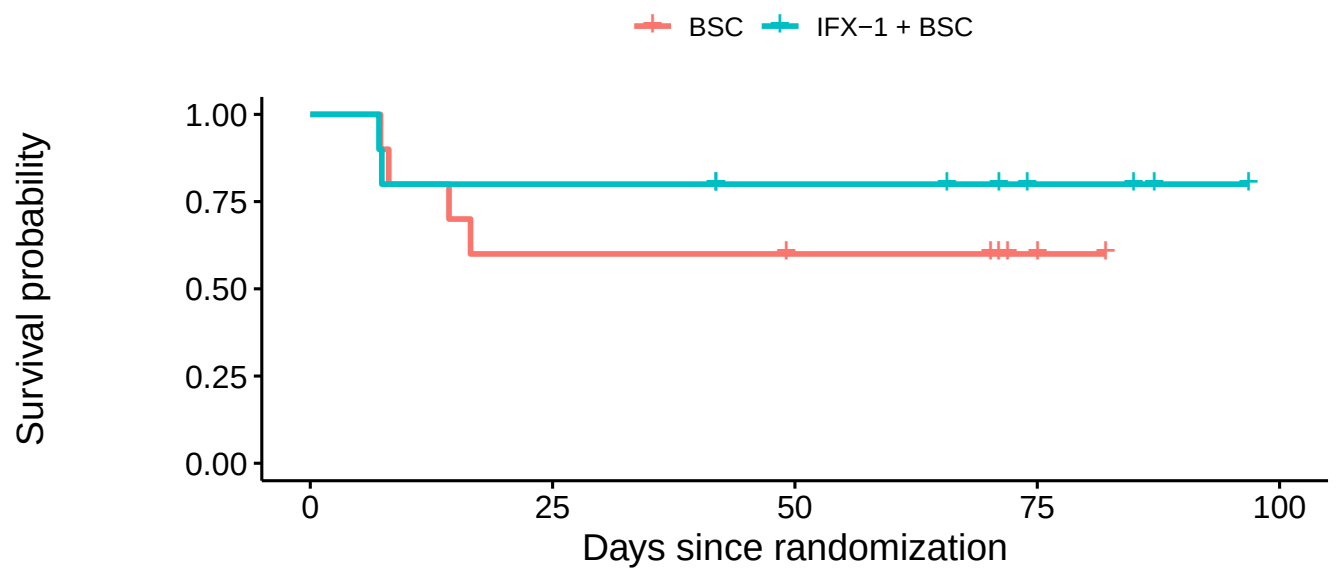

SARS-CoV-2
O2 radicals
granular enzymes
NETs
Tissue Damage
virus and neutrophil -
mediated tissue damage
neutrophil
activation
Tissue Factor
coagulation
Thrombin
complement pathway
activation
C5a
Fibrin
microangiopathy
with thrombosis
direct C5a activation by
enzymes (thrombin, plasmin, etc.)
Plasmin
fibrinolysis
d-Dimers
red blood cell
neutrophil
platelet
endothelial Cell

A All cause mortality
(All randomized)

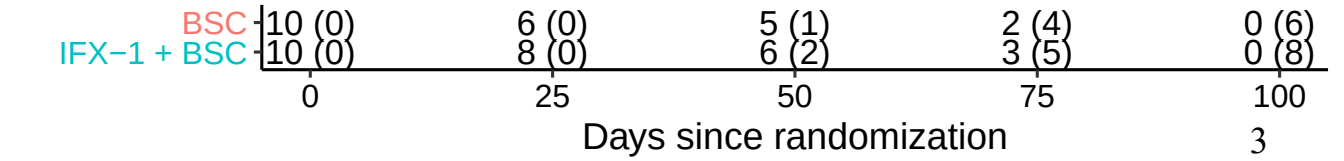


Number at risk (number censored)

B All cause mortality
(All intubated at baseline or same day)



Number at risk (number censored)



Legends supplementary files

Figure 1. Shift Plots for Estimated Glomerular Filtration Rates and Lymphocytes Concentrations and LS Mean Plots for relative changes in selected outcome parameters in intubated patients at baseline or same day.
Legend: Categories of eGFR (%) in the IFX-1 treated group (panel A) and best standard care group (B), and categories of lymphocyte counts in the IFX-1 treated group (panel C) and best standard care group (D).Plotted relative change in mean PaO2/FiO2 ratioand 95% confidence interval for the mean (panel E), eGFR (panel F), LDH (Panel G) and D-Dimers (Panel H). LRMM=Linear repeated measures model

Figure 2. Proposed Role of C5a in COVID-19-induced Vascular Disease

Endothelial damage is induced by SARS-CoV-2 infection which also activates the complement system leading to C5a generation. C5a activates neutrophils via C5aR leading to increased adherence to endothelial cells and damage through generation of oxidative radicals, granular enzyme release and neutrophil extracellular traps (NETs). C5a induces release of tissue factor release from neutrophils as well as endothelial cells, which promotes coagulation leading to Fibrin formation. Thrombin, plasmin and other enzymes can further induce direct C5a activation (through direct cleavage of C5) which may establish a viscious cycle leading to microangiopathy with thrombosis.

Figure 3. Kaplan-Meier Curves for 28-day All-cause Mortality.

Kaplan-Meier estimates of mortality by 28 days were 13% (95% CI, 0% to 31%) for IFX-1 and 27% (95% CI, 4% to 49%) for controls (Figure 3A; adjusted hazard ratio for death, 0.65; 95% CI, 0.10 to 4.14). For those intubated within six hours after randomization, estimates of mortality by 28 days were 20% (95% CI, 0% to 45%) for IFX-1 and 40% (95% CI, 10% to 70%) for the best supportive care group (hazard ratio for death, 0.48; 95% CI, 0.07 to 3.35).

Supplemental table 1: Symptoms

Symptom	Total (N=30)		IFX-1 + BSC (N=15)		BSC (N=15)	
Dyspnoea	28	(93.3%)	14	(93.3%)	14	(93.3%)
Cough	21	(70.0%)	10	(66.7%)	11	(73.3%)
Pyrexia	11	(36.7%)	5	(33.3%)	6	(40.0%)
Fatigue	4	(13.3%)	1	(6.7%)	3	(20.0%)
Malaise	4	(13.3%)	3	(20.0%)	1	(6.7%)
Decreased appetite	3	(10.0%)	1	(6.7%)	2	(13.3%)
Headache	3	(10.0%)	1	(6.7%)	2	(13.3%)
Nausea	3	(10.0%)	1	(6.7%)	2	(13.3%)
Ageusia	2	(6.7%)	1	(6.7%)	1	(6.7%)
Chest pain	2	(6.7%)	1	(6.7%)	1	(6.7%)
Diarrhoea	2	(6.7%)	1	(6.7%)	1	(6.7%)
Hypoxia	2	(6.7%)	2	(13.3%)	0	(0.0%)
Anosmia	1	(3.3%)	0	(0.0%)	1	(6.7%)
Back pain	1	(3.3%)	1	(6.7%)	0	(0.0%)
Constipation	1	(3.3%)	0	(0.0%)	1	(6.7%)
Delirium	1	(3.3%)	0	(0.0%)	1	(6.7%)
Dysgeusia	1	(3.3%)	0	(0.0%)	1	(6.7%)
Dyspnoea at rest	1	(3.3%)	0	(0.0%)	1	(6.7%)
Dyspnoea exertional	1	(3.3%)	0	(0.0%)	1	(6.7%)
Fall	1	(3.3%)	0	(0.0%)	1	(6.7%)
Hypertension	1	(3.3%)	0	(0.0%)	1	(6.7%)
Hyponatraemia	1	(3.3%)	0	(0.0%)	1	(6.7%)
Myalgia	1	(3.3%)	1	(6.7%)	0	(0.0%)
Neck pain	1	(3.3%)	1	(6.7%)	0	(0.0%)
Oropharyngeal pain	1	(3.3%)	1	(6.7%)	0	(0.0%)
Painful respiration	1	(3.3%)	0	(0.0%)	1	(6.7%)
Pulmonary haemorrhage	1	(3.3%)	0	(0.0%)	1	(6.7%)
Taste disorder	1	(3.3%)	1	(6.7%)	0	(0.0%)
Vomiting	1	(3.3%)	0	(0.0%)	1	(6.7%)

Supplemental table 2: Demographic and Clinical Characteristics at Baseline stratified by site.

Characteristic	Site 1 (N=17)	Site 2 (N=12)	Site 3 (N=1)
Randomized to IFX-1	8 (47)	7 (58)	0 (0)
Age - yr – mean+-SD	60±9	60±8	70
Male sex – no. (%)	11 (65)	10 (83)	1 (100)
Race – no. (%)			
White	7 (41)	11 (92)	1 (100)
Asian	5 (29)	1 (8)	0 (0)
Black	4 (24)	0 (0)	0 (0)
Median time (IQR) from symptom onset to randomization – days	12 (8-13)	10 (9-14)	8
Median time (IQR) from COVID-19 diagnosis to randomization (days)	4 (1-4)	2 (0-3)	1
No. of risk-relevant coexisting conditions* – no. total no. (%)			
None	5 (29)	5 (42)	0 (0)
One	9 (53)	5 (42)	1 (100)
Two or more	3 (18)	2 (17)	0 (0)
Selected coexisting conditions – no./total no. (%)			
Hypertension	6 (35)	3 (25)	0 (0)
Diabetes	6 (35)	1 (8)	1 (100)
Obesity	6 (35)	0 (0)	0 (0)
Intubated at randomization – no. (%)	14 (82)	3 (25)	1 (100)
Oxygen mask – no. (%)	2 (12)	6 (50)	0 (0)
Nasal cannula – no. (%)	1 (6)	3 (25)	0 (0)
Admission department at randomization – no. (%)			
Intensive care unit	14 (82)	3 (25)	1 (100)
Intermediate care unit	2 (12)	5 (42)	0 (0)
COVID ward	1 (6)	4 (33)	0 (0)

Supplemental table 3: Comparison of model based analysis results without and with adjusting for relevant comorbidities (relative and absolute change from baseline).

Result	Adjustment according to protocol	Adjustment according to protocol + relevant comorbidities
Hazard ratio for all cause mortality	0.651 (0.103; 4.135)	0.584 (0.071; 4.789)
LS Means Difference for relative Change OI (all value irrespective of position)		
At day 5	-24.4 (-58.0; 9.3)	-26.2 (-60.6; 8.2)
At day 15	-14.5 (-102.5; 73.6)	-16.3 (-104.3; 71.7)
% Change LS Means Difference for eGFR		
At day 4	8.6 (-5.4; 22.5)	6.8 (-7.6; 21.2)
At day 15	17.3 (-8.2; 42.9)	15.6 (-9.8; 40.9)
% Change LS Means Difference for LDH		
At day 4	-11.1 (-26.2; 4.1)	-11.0 (-26.3; 4.3)
At day 15	-21.8 (-45.7; 2.0)	-21.7 (-45.7; 2.2)
% Change LS Means Difference for D-Dimer		
At day 4	213.8 (24.1; 403.5)	200.3 (2.6; 397.9)
At day 15	-26.7 (-420.6; 367.2)	-40.3 (-442.1; 361.6)
% Change LS Means Difference for Lymphocytes		
At day 4	28.8 (-2.3; 59.9)	29.1 (-2.3; 60.4)
At day 15	49.5 (-28.6; 127.6)	49.8 (-28.5; 128.0)
LS Means Difference for abs. change OI (all value irrespective of position) [mmHg]		
At day 5	-41.6 (-91.3; 8.1)	-43.6 (-94.5;7.3)
At day 15	-5.2 (-119.3;108.9)	-7.2 (-121.7;107.3)
Abs. Change LS Means Difference for eGFR [mL/min per 1.73m²]		
At day 4	6.2 (-5.3; 17.8)	4.6 (-7.4; 16.7)
At day 15	15.7 (-6.1; 37.5)	14.1 (-7.5;35.7)
Abs. Change LS Means Difference for LDH [U/L]		
At day 4	-58.3 (-124.9; 8.3)	-58.5 (-125.8; 8.9)

At day 15	-101.3 (-212.0; 9.4)	-101.5 (-212.6; 9.7)
Abs. Change LS Means Difference for D-Dimer [mg/L]		
At day 4	0.8 (-4.3; 5.9)	0.5 (-4.5;5.6)
At day 15	-3.2 (-7.7; 1.3)	-3.5 (-8.1;1.1))
Abs. Change LS Means Difference for Lymphocytes [10^9/L]		
At day 4	0.2 (0; 0.5)	0.2 (0;0.5)
At day 15	0.5 (0.1; 0.9)	0.5 (0.1;0.9)

Supplemental Table 4: Summary of all adverse events by treatment arm and MedDRA System Organ Class and Preferred Term.

	IFX-1 + BSC (N=15)			BSC (N=15)		
MedDRA System Organ Class MedDRA Preferred Term	Patient n	Patient %	Events	Patient n	Patient %	Events
Total	14	(93.3%)	140	14	(93.3%)	126
Metabolism and nutrition disorders	10	(66.7%)	20	11	(73.3%)	24
Hypokalaemia	5	(33.3%)	5	4	(26.7%)	4
Hypernatraemia	3	(20.0%)	3	5	(33.3%)	5
Hypophosphataemia	2	(13.3%)	3	5	(33.3%)	6
Hyperglycaemia	3	(20.0%)	3	3	(20.0%)	3
Hyponatraemia	2	(13.3%)	2	1	(6.7%)	1
Hyperkalaemia	1	(6.7%)	1	1	(6.7%)	1
Fluid overload	0	(0.0%)	0	1	(6.7%)	1
Hypercalcaemia	0	(0.0%)	0	1	(6.7%)	1
Hyperchloraemia	0	(0.0%)	0	1	(6.7%)	1
Hypermagnesaemia	0	(0.0%)	0	1	(6.7%)	1
Hypomagnesaemia	1	(6.7%)	1	0	(0.0%)	0
Metabolic alkalosis	1	(6.7%)	1	0	(0.0%)	0
Refeeding syndrome	1	(6.7%)	1	0	(0.0%)	0
Respiratory, thoracic and mediastinal disorders	10	(66.7%)	16	9	(60.0%)	14
Pulmonary embolism	6	(40.0%)	6	7	(46.7%)	7
Respiratory failure	3	(20.0%)	3	3	(20.0%)	4
Hypoxia	3	(20.0%)	3	1	(6.7%)	1
Bradypnoea	1	(6.7%)	1	0	(0.0%)	0
Dyspnoea	1	(6.7%)	1	0	(0.0%)	0
Hypoventilation	1	(6.7%)	2	0	(0.0%)	0
Pneumothorax	0	(0.0%)	0	1	(6.7%)	1
Sleep apnoea syndrome	0	(0.0%)	0	1	(6.7%)	1
Investigations	10	(66.7%)	19	7	(46.7%)	13
Hepatic enzyme increased	1	(6.7%)	1	3	(20.0%)	3
Blood bicarbonate increased	1	(6.7%)	1	1	(6.7%)	1
Blood potassium decreased	1	(6.7%)	1	1	(6.7%)	1
Electrocardiogram QT prolonged	1	(6.7%)	1	1	(6.7%)	1
Fluid balance positive	0	(0.0%)	0	2	(13.3%)	2
Oxygen saturation decreased	2	(13.3%)	2	0	(0.0%)	0
Staphylococcus test positive	1	(6.7%)	1	1	(6.7%)	1
Blood alkaline phosphatase increased	1	(6.7%)	1	0	(0.0%)	0
Blood culture positive	1	(6.7%)	1	0	(0.0%)	0
Blood fibrinogen increased	0	(0.0%)	0	1	(6.7%)	1
Blood phosphorus decreased	0	(0.0%)	0	1	(6.7%)	1
Culture negative	0	(0.0%)	0	1	(6.7%)	1
Culture urine	1	(6.7%)	1	0	(0.0%)	0
Cytomegalovirus test positive	1	(6.7%)	1	0	(0.0%)	0

MedDRA System Organ Class MedDRA Preferred Term	IFX-1 + BSC (N=15) Patient n	Patient %	Events	BSC (N=15) Patient n	Patient %	Events
End-tidal CO2 increased	1	(6.7%)	1	0	(0.0%)	0
Enterococcus test positive	1	(6.7%)	1	0	(0.0%)	0
Eosinophil count increased	1	(6.7%)	1	0	(0.0%)	0
Fibrin D dimer increased	0	(0.0%)	0	1	(6.7%)	1
Gamma-glutamyltransferase increased	1	(6.7%)	1	0	(0.0%)	0
Liver function test abnormal	1	(6.7%)	1	0	(0.0%)	0
Platelet count increased	1	(6.7%)	1	0	(0.0%)	0
Protein urine present	1	(6.7%)	1	0	(0.0%)	0
Sputum culture positive	1	(6.7%)	1	0	(0.0%)	0
Gastrointestinal disorders	5	(33.3%)	11	10	(66.7%)	19
Impaired gastric emptying	4	(26.7%)	4	7	(46.7%)	7
Constipation	2	(13.3%)	2	4	(26.7%)	4
Diarrhoea	1	(6.7%)	1	1	(6.7%)	1
Dysphagia	1	(6.7%)	1	1	(6.7%)	1
Frequent bowel movements	1	(6.7%)	1	0	(0.0%)	0
Gastric haemorrhage	0	(0.0%)	0	1	(6.7%)	1
Ileus	0	(0.0%)	0	1	(6.7%)	1
Ileus paralytic	0	(0.0%)	0	1	(6.7%)	1
Mouth ulceration	1	(6.7%)	1	0	(0.0%)	0
Nausea	0	(0.0%)	0	1	(6.7%)	1
Rectal haemorrhage	0	(0.0%)	0	1	(6.7%)	1
Salivary hypersecretion	1	(6.7%)	1	0	(0.0%)	0
Vomiting	0	(0.0%)	0	1	(6.7%)	1
Infections and infestations	9	(60.0%)	12	6	(40.0%)	7
Pneumonia	2	(13.3%)	2	5	(33.3%)	5
Staphylococcal infection	2	(13.3%)	2	0	(0.0%)	0
Aspergillus infection	1	(6.7%)	1	0	(0.0%)	0
Bronchopulmonary aspergillosis	1	(6.7%)	1	0	(0.0%)	0
Cellulitis	0	(0.0%)	0	1	(6.7%)	1
Device related sepsis	1	(6.7%)	1	0	(0.0%)	0
Enterococcal infection	1	(6.7%)	1	0	(0.0%)	0
Fungal infection	1	(6.7%)	1	0	(0.0%)	0
Pseudomonas infection	1	(6.7%)	1	0	(0.0%)	0
Sepsis	0	(0.0%)	0	1	(6.7%)	1
Urinary tract infection	1	(6.7%)	1	0	(0.0%)	0
Vascular device infection	1	(6.7%)	1	0	(0.0%)	0
Vascular disorders	10	(66.7%)	13	5	(33.3%)	6
Deep vein thrombosis	3	(20.0%)	3	3	(20.0%)	3
Hypertension	2	(13.3%)	2	2	(13.3%)	2
Phlebitis	1	(6.7%)	1	1	(6.7%)	1
Thrombophlebitis	2	(13.3%)	2	0	(0.0%)	0
Hypotension	1	(6.7%)	1	0	(0.0%)	0

MedDRA System Organ Class MedDRA Preferred Term	IFX-1 + BSC (N=15) Patient n	Patient %	Events	BSC (N=15) Patient n	Patient %	Events
Jugular vein thrombosis	1	(6.7%)	1	0	(0.0%)	0
Peripheral artery thrombosis	1	(6.7%)	1	0	(0.0%)	0
Shock	1	(6.7%)	1	0	(0.0%)	0
Systolic hypertension	1	(6.7%)	1	0	(0.0%)	0
General disorders and administration site conditions	5	(33.3%)	10	9	(60.0%)	13
Multiple organ dysfunction syndrome	0	(0.0%)	0	4	(26.7%)	4
Oedema peripheral	0	(0.0%)	0	4	(26.7%)	4
Pyrexia	3	(20.0%)	4	1	(6.7%)	1
Catheter site extravasation	1	(6.7%)	1	0	(0.0%)	0
Chest discomfort	0	(0.0%)	0	1	(6.7%)	1
Chills	0	(0.0%)	0	1	(6.7%)	1
Face oedema	0	(0.0%)	0	1	(6.7%)	1
Hypothermia	0	(0.0%)	0	1	(6.7%)	1
Infusion site discolouration	1	(6.7%)	1	0	(0.0%)	0
Infusion site extravasation	1	(6.7%)	1	0	(0.0%)	0
Infusion site vesicles	1	(6.7%)	1	0	(0.0%)	0
Medical device site haemorrhage	1	(6.7%)	2	0	(0.0%)	0
Psychiatric disorders	7	(46.7%)	8	4	(26.7%)	4
Delirium	5	(33.3%)	6	3	(20.0%)	3
Anxiety	0	(0.0%)	0	1	(6.7%)	1
Hallucination	1	(6.7%)	1	0	(0.0%)	0
Nightmare	1	(6.7%)	1	0	(0.0%)	0
Skin and subcutaneous tissue disorders	4	(26.7%)	6	7	(46.7%)	7
Decubitus ulcer	2	(13.3%)	3	5	(33.3%)	5
Actinic keratosis	0	(0.0%)	0	1	(6.7%)	1
Alopecia	0	(0.0%)	0	1	(6.7%)	1
Angioedema	1	(6.7%)	1	0	(0.0%)	0
Urticaria	1	(6.7%)	2	0	(0.0%)	0
Cardiac disorders	3	(20.0%)	3	6	(40.0%)	7
Supraventricular tachycardia	1	(6.7%)	1	2	(13.3%)	2
Atrial fibrillation	1	(6.7%)	1	1	(6.7%)	1
Atrioventricular block second degree	0	(0.0%)	0	1	(6.7%)	1
Cardiac failure	0	(0.0%)	0	1	(6.7%)	1
Defect conduction intraventricular	0	(0.0%)	0	1	(6.7%)	1
Sinus tachycardia	1	(6.7%)	1	0	(0.0%)	0
Tachycardia	0	(0.0%)	0	1	(6.7%)	1
Renal and urinary disorders	5	(33.3%)	6	4	(26.7%)	5
Acute kidney injury	2	(13.3%)	2	4	(26.7%)	4
Oliguria	2	(13.3%)	2	0	(0.0%)	0
Glycosuria	1	(6.7%)	1	0	(0.0%)	0
Renal failure	0	(0.0%)	0	1	(6.7%)	1

MedDRA System Organ Class MedDRA Preferred Term	IFX-1 + BSC (N=15) Patient n	Patient %	Events	BSC (N=15) Patient n	Patient %	Events
Urinary retention	1	(6.7%)	1	0	(0.0%)	0
Nervous system disorders	6	(40.0%)	7	1	(6.7%)	1
Epilepsy	1	(6.7%)	1	0	(0.0%)	0
Headache	1	(6.7%)	1	0	(0.0%)	0
Hemiparesis	1	(6.7%)	1	0	(0.0%)	0
Hypoaesthesia	1	(6.7%)	1	0	(0.0%)	0
Intensive care unit acquired weakness	1	(6.7%)	1	0	(0.0%)	0
Ischaemic cerebral infarction	1	(6.7%)	1	0	(0.0%)	0
Peripheral nerve lesion	0	(0.0%)	0	1	(6.7%)	1
Somnolence	1	(6.7%)	1	0	(0.0%)	0
Eye disorders	1	(6.7%)	2	3	(20.0%)	3
Ocular hyperaemia	1	(6.7%)	1	1	(6.7%)	1
Eye irritation	1	(6.7%)	1	0	(0.0%)	0
Miosis	0	(0.0%)	0	1	(6.7%)	1
Pupils unequal	0	(0.0%)	0	1	(6.7%)	1
Injury, poisoning and procedural complications	1	(6.7%)	1	2	(13.3%)	2
Infusion related reaction	1	(6.7%)	1	0	(0.0%)	0
Limb injury	0	(0.0%)	0	1	(6.7%)	1
Post procedural haematoma	0	(0.0%)	0	1	(6.7%)	1
Blood and lymphatic system disorders	2	(13.3%)	2	0	(0.0%)	0
Anaemia	2	(13.3%)	2	0	(0.0%)	0
Musculoskeletal and connective tissue disorders	2	(13.3%)	2	0	(0.0%)	0
Arthralgia	1	(6.7%)	1	0	(0.0%)	0
Muscular weakness	1	(6.7%)	1	0	(0.0%)	0
Ear and labyrinth disorders	1	(6.7%)	1	0	(0.0%)	0
Vertigo	1	(6.7%)	1	0	(0.0%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.0%)	0	1	(6.7%)	1
Meningioma	0	(0.0%)	0	1	(6.7%)	1
Product issues	1	(6.7%)	1	0	(0.0%)	0
Device leakage	1	(6.7%)	1	0	(0.0%)	0

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1,3
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6-9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	8
Sample size	7a	How sample size was determined	6-9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	NA

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10
	13b	For each group, losses and exclusions after randomisation, together with reasons	NA
Recruitment	14a	Dates defining the periods of recruitment and follow-up	10
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	22 and supplement
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	figure 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10-13
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	10-13
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	10-13 and supplement
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	10
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13-16
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13-16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13-16
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	supplement
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.