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Early View

Original research article

Early high antibody-titre convalescent plasma for hospitalised COVID-19 patients: DAWn-plasma

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Early high antibody-titre convalescent plasma for hospitalised COVID-19 patients: DAWn-plasma.

A Randomised Clinical Trial.

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TAKE HOME MESSAGE

Early transfusion of 4 units of high neutralising-antibody-titre convalescent plasma in hospitalised COVID-19 patients does not reduce mortality or the need for mechanical ventilation.

ABSTRACT

BACKGROUND Several randomised clinical trials have studied convalescent plasma (CP) for COVID-19 using different protocols, with different SARS-CoV-2 neutralising-antibody-titres, at different time-points and severities of illness.

METHODS In the prospective multicentre DAWN-plasma trial, adult patients hospitalised with COVID-19 were randomised to 4 units of open-label convalescent plasma combined with standard of care (intervention group) or standard of care alone (control group). Plasma from donors with neutralising-antibody-titres (NT50) ≥ 1/320 was the product of choice for the study.

RESULTS Between May 2nd, 2020 and January 26th, 2021, 320 patients were randomised to convalescent plasma and 163 patients to the control group according to a 2:1 allocation scheme. A median volume of 884 mL convalescent plasma (IQR 806-906 mL) was administered, and 80.68% of the units came from donors with neutralising-antibody-titres (NT50) ≥1/320. Median time from onset of symptoms to randomisation was 7 days. The proportion of patients alive and free of mechanical ventilation on Day 15 was not different between both groups (convalescent plasma: 83.74% (n=267) versus control: 84.05% (n=137) – Odds ratio 0.99 (0.59-1.66) – p-value=0.9772). The intervention did not change the natural course of antibody titres. The number of serious or severe adverse events was similar in both study arms, and transfusion-related side effects were reported in 19/320 patients in the intervention group (5.94%).

CONCLUSIONS Transfusion of 4 units of convalescent plasma with high neutralising-antibody-titres early in hospitalised COVID-19 patients did not result in a significant improvement of the clinical status, or a reduced mortality.

TRIAL REGISTRATION: Clinical Trials.gov Identifier: NCT04429854

MANUSCRIPT TEXT

Introduction

The toll of the COVID-19 pandemic remains high, with 188,655,968 confirmed cases and 4,067,517 attributed deaths worldwide as of the 16th of July [1]. Although only a minority of SARS-CoV-2 infected subjects requires hospitalisation, the absolute number of patients presenting with severe or critical illness is large enough to cause near or actual collapse of healthcare systems worldwide [2–4].

The management of hospitalised COVID-19 patients is mainly supportive. So far, two interventions have demonstrated a mortality benefit in hospitalised patients requiring oxygen, primarily targeting the hyperinflammatory phase: dexamethasone [5], tocilizumab [6, 7] and tofacitinib [8]. Therapeutic options in the viral replication phase remain limited. Remdesivir demonstrates little benefit [9] with no impact on mortality [10] and lacks evident antiviral activity in hospitalised patients [11].

The administration of convalescent plasma from donors who recently recovered from COVID-19 may offer passive immunisation to naïve patients. Randomised clinical trials have studied this therapy in different settings, with different SARS-CoV-2 neutralising-antibody-titres, at different time-points and severities of illness [12–15]. A recent meta-analysis [16]

found no mortality benefit, although heterogeneity between the studies was considered significant. Discrepant findings between different studies might be explained by differences in timing of administration [14, 15], volumes transfused, or plasma antibody-titres [17].

We hypothesised that giving a high volume of convalescent plasma with high neutralising-antibody-titres early in hospitalisation for COVID-19 would significantly reduce the proportion of patients who require mechanical ventilation.

Materials and methods

Study design

Donated Antibodies Working agaiNst COVID-19 (DAWn-plasma) is a prospective, randomised open-label, multicentre clinical trial to evaluate the efficacy and safety of convalescent plasma added to standard of care in adult patients hospitalised with COVID-19, conducted in 22 Belgian centres, and coordinated by the University Hospitals Leuven, Belgium, with public funding by the Belgian Health Care Knowledge Centre (KCE). The trial adhered to the Declaration of Helsinki and Good Clinical Practice principles, had institutional review board approval from the coordinating and participating sites and was supervised by an independent data and safety monitoring board. The protocol was publicly registered (ClinicalTrials.gov identifier: NCT04429854) and published [18, 19]. Statistical analysis was done by the principal investigator and the study statistician. The first draft of the manuscript was written by the first and last author, specific sections were written by the writing committee. All authors have read and approved the final manuscript and take responsibility for accuracy and completeness of the data as well as adherence to the protocol. Contributions of individual authors are listed in supplement S1.

Inclusion and exclusion criteria

Adult (≥18 years) hospitalised patients with laboratory or radiological confirmed COVID-19 were screened for eligibility. In view of the primary endpoint, patients receiving mechanical ventilation upon assessment or a therapy restriction code excluding mechanical ventilation and/or endotracheal intubation were excluded. Other exclusion criteria were pregnancy or lactation, a documented previous grade 3 allergic reaction to plasma transfusions, and treatment with rituximab or another anti-CD20 monoclonal antibody during the past year. Informed consent was obtained after confirmation of the availability of convalescent plasma prior to randomisation. When written informed consent was not possible due to restrictions for research staff to access the isolation ward, oral consent was documented in the medical file, and completed with a signed consent as soon as possible.

Intervention

Patients were randomised through a computerised system (RedCap®, Vanderbilt University, USA, Version 10.6.13) according to a 2:1 allocation scheme stratified by study site using randomly selected block sizes of 6 or 9, to open-label convalescent plasma combined with standard of care (intervention group) or standard of care alone (control group). In the intervention group, two units of convalescent plasma (approximately 200-250 mL) were administered within 12 hours after randomisation, with a second administration of two units 24-36 hours after the first administration. The study protocol did not specify the standard of care therapy.

Selection of donors

Plasma donations were exclusively obtained from voluntary unpaid donors after informed consent, in accordance with EU and Belgian legislation for personal data protection. Donors

who recovered from a documented SARS-CoV2 infection (RT-PCR or radiological confirmation) were recruited in the general population via a web-based interface.

Plasma collection and processing

Plasma was collected by apheresis using Autopheresis-CTM and Aurora (Fresenius®, Belgium) or NexSys (Haemonetics®, Switzerland) equipment. During collection, donor blood was anticoagulated with a citrate solution (sodium citrate dihydrate 4%) at a ratio of 1:16. The maximum donated volume allowed per session was 650 mL (anticoagulant excluded). Methylene blue was used for pathogen reduction of the plasma, and plasma was shock-frozen within 18 hours to -30°C, over 1 hour. Plasma from donors with neutralising-antibody-titres ≥ 1/320 (NT50) was the product of choice for the study, although titres ≥ 1/160 were allowed in case of non-availability. Donor titres were tested monthly.

Neutralising-antibody titres

Anti-SARS-CoV-2 virus-neutralisation-titres were determined by neutralisation assays, performed in BSL3 laboratories in a 96-well plate format, using heat-inactivated plasma or serum samples (30-60 minutes at 56°C), as described in supplement S2. Virus-neutralisation-titres were reported as NT50.

Viral load measurements

Nasopharyngeal swabs were placed in a viral transport medium, of which a sample (150 µL) was inactivated by adding 600 µL RAV1 lysis buffer and subsequent heating for 5 minutes at 70°C. Next, 600 µL ethanol was added and total RNA was extracted with the NucleoSpin kit (Macherey-Nagel®), according to the manufacturer's instructions. RT-qPCR for SARS-CoV-2 was performed on a LightCycler96 platform (Roche®) with iTaq Universal Probes One-Step RT-qPCR kit (BioRad®) with N2 primers and probes targeting nucleocapsid16. Standards of

known concentrations of SARS-CoV-2 cDNA (IDT) were used to extrapolate the total number of viral genome copies per sample.

Study outcomes

Our primary outcome was the number and proportion of patients alive without mechanical ventilation at Day 15. Secondary endpoints included the clinical status on Days 15 and 30, assessed with the WHO 11-point ordinal scale; the time to (whichever comes first) alive hospital discharge or sustained clinical improvement at day 30 (defined as an improvement of > 2 points vs. the highest value of Day 0 and 1 and sustained for at least 3 days); all-cause mortality at Days 15 and 30; the duration of hospital stay; the incidence and duration of intensive care unit (ICU) stay and mechanical ventilation; the incidence of transfusion-related side effects and severe adverse events; the quality of life at Day 30 (assessed with the EX-5D-5L-questionnaire).

As an exploratory endpoint, the correlation between the number of transfused convalescent plasma units from donors with neutralising antibody titres ≥ 1/320 (NT50) and the primary endpoint was analysed. Determination of viral load in a nasal PCR and neutralising-antibody titres (NT50) in serum samples of patients, both at baseline and Day 6 were optional according to protocol and were examined as additional exploratory outcomes when available.

Sample size calculation

In order to test the superiority hypothesis for a reduction in the proportion of mechanically ventilated patients at Day 15 from 16% in the control group to 7.5% in the intervention group (a delta of 8.5%) (with a two-sided type I error rate of 0.050 and a power of 0.8 using a Pearson Chi-square test for proportion difference), in a 2:1 randomisation scheme, 322

patients needed to be randomised to convalescent plasma and 161 patients to standard of care, yielding a total sample size of 483 patients.

Statistical analysis

Statistical analysis was performed in accordance with the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines (ICH version E9). A detailed description of the analysis is provided in the Statistical Analysis Plan (SAP), which was finalised and filed before database lock. A brief summary is provided here.

Analysis sets were finalised during a Blind Review Meeting prior to database lock. The Full Analysis Set (FAS) included all randomised patients, except patients that were confirmed to be SARS-CoV-2 negative, and patients who withdrew consent to use any data immediately after randomisation and before treatment administration. The Per Protocol Set (PPS) included all FAS patients in the intervention group that received 4 units of convalescent plasma and all patients in the control group that did not receive any convalescent plasma within 30 days of randomisation.

Missing clinical status data were accounted for by means of multiple imputation, using a total of 100 imputations [20]. Treatment effects for all endpoints were estimated by an appropriate measure and presented with 95% confidence intervals and were adjusted for study site and period. The primary endpoint was compared using logistic regression to estimate the odds ratio. Pre-specified subgroup analyses were performed for the primary endpoint only, considering the following subgroups of interest: duration of symptoms prior to enrolment (according to observed median); age groups (according to observed median); study period; blood group; size and province of study site; primary admission to the ICU; blood institute that processed the convalescent plasma. All-cause mortality and survival

without mechanical ventilation up to 30 days were assessed using a Cox regression to obtain hazard ratios. Incidence rates were estimated using Kaplan-Meier methodology. Time to sustained improvement, incidence and duration of supplemental oxygen, mechanical ventilation, extracorporeal membrane oxygenation (ECMO) and ICU were analysed using competing-risk methodology, using cumulative incidence functions (CIF) to estimate event rates and a Fine & Grey regression model to obtain cause-specific hazard ratios. All tests were two-sided and assessed at a significance level of 5%. No correction was made for multiple secondary endpoints. All analyses were performed using SAS software version 9.4 for Windows 10.

Results

Patients

Between May 2nd, 2020 and January 26th, 2021, 499 patients were assessed for eligibility, of whom 489 were randomised to convalescent plasma (n=326) or control (n=163) (figure 1: consort flow diagram). The FAS consisted of 320 patients in the plasma group and 163 in the control group. Baseline and demographic data are summarised in Table 1, both groups were well matched. Concomitant therapy for COVID19 was similar between both groups (supplement S3). Median time from symptom onset to hospital admission was 6 days (IQR 3-8 days) and median time from admission to randomisation was 1 day (IQR 1-2 days) in both groups. In the convalescent plasma group, the median time from randomisation to the first plasma transfusion was 5 hours (IQR 4-7 hours), and a median volume of 884 mL convalescent plasma (IQR 807-906 mL) was administered. 80.7% of the administered plasma units (981/1215 units) came from donors with neutralising antibody titres of at least 1/320.

Six patients in the plasma group of the FAS never received convalescent plasma; 294 (91.9%) patients received all 4 units and were included in the PPS.

Primary outcome

The proportion of patients alive and free of mechanical ventilation on Day 15 was not different between both groups in the FAS (convalescent plasma: 83.7% (n=266) versus control: 84.1% (n=137) – Odds ratio 0.99 (0.59-1.68) – p-value=0.976) (table 2). Kaplan-Meier curves are depicted in figure 2. Results were similar for the PPS (supplement S4). Pre-specified subgroup analyses for the primary endpoint (figure 3) demonstrated a significant interaction with age (p-value= 0.023).

Secondary outcomes

Secondary endpoints are summarised in Table 2. No difference was detected in the proportion of patients alive and free of mechanical ventilation on Day 30 (figure 2), or any of the other secondary endpoints on day 15 or day 30.

Exploratory endpoints

There was no significant association between the number of units transfused with neutralising antibody titres of at least 1/320 and outcome (figure 4). At baseline, 30% (33/110) in the plasma group and 26% (14/53) of patients in the control group already had neutralising antibody serum titres of $\geqslant$ 1/320. Titres of neutralising antibodies against SARS-CoV-2 (NT50) increased between baseline and day 6 after randomisation, but this increase was not influenced by the intervention (estimated difference in $\log_2$ transformed Day 6 values between study groups, adjusted for baseline =0.08 (-0.43; 0.58), p = 0.766) (figure 5A). A better outcome was correlated with higher neutralising-antibody-titres at Day 0 (odds

ratio of good outcome for increase of 1 in log2-transformed NT50 at day 0=1.45 (1.11; 1.83), p = 0.005) and Day 6 (odds ratio=1.68 (1.30; 2.16), p < 0.001) (figure 5B), but not with the magnitude of increase in NT50 between Day 0 and Day 6. Viral load decreased in a similar manner in both treatment groups (estimated treatment difference of log10-transformed Day 6 values, adjusted for baseline=1.70 (0.40; 7.21), p= 0.466). (figure 6).

There were no significant interactions between the fraction of inhaled oxygen (FiO_2) at baseline (p-value=0.0906) or the time from symptoms to randomisation (p-value=0.9386) and randomised treatment in their effect on the primary outcome (supplement S5).

Safety

Numbers of serious or severe adverse events reported were similar in both study arms: 20.6% (66/320) in the plasma-arm and 22.1% (36/163) in the control group (supplement S6). Transfusion related side effects were reported in 19/320 patients in the intervention group (5.9%). (supplement S7).

Discussion

In the DAWn-plasma study, the administration of high-volume (median total volume 884 ml), high-titre convalescent plasma early in hospitalisation for COVID-19 disease did not succeed in reducing the need for mechanical ventilation at day 15 (primary endpoint) or had an impact on any of the secondary outcomes, including the need for and the duration of ICU stay, mortality, and quality of life at day 30. Administration of CP was safe as no major adverse events were registered and transfusion reactions were in the expected range of occurrence.

These results are in line with other trials on convalescent plasma for COVID19, as evident from a recent meta-analysis of published and unpublished trials [16], including the large

RECOVERY study [21]. Even while more than 80% of the units came from donors with ⩾ 1/320 neutralising antibody titres, and the volume of plasma transfused was higher than any other published trial, the intervention did not succeed in influencing the natural course of SARS-CoV-2 neutralising antibodies or viral load. The median time between onset of symptoms and randomisation was 7 days, which might have been too late to obtain a meaningful clinical effect. The finding that 28.8% of patients already showed significantly elevated (⩾ 1/320) serum neutralising antibodies at baseline supports this hypothesis. However, from a pragmatic point of view, the timing of presentation to the hospital is a clinical reality and the administration of blood products in the prehospital phase is no routine clinical practice in Belgium, like in many other countries. Given the short timeframe of 1 day between hospital admission and randomisation, it is unlikely that convalescent plasma could have been administered earlier in the Belgian setting. In addition, since the time from symptom onset to randomisation was not a significant interaction term, it seems unlikely that the results would have been different with earlier administration. The overall all-cause mortality in our trial (8.8% at 30 days), both in plasma and control group, is relatively low compared to the control group mortality of 12.7% in previously published peer-reviewed trials [16], 24% in the RECOVERY trial [21], or 24.6% in the control group of the O'Donnell trial [22]. As such, our findings might not translate to other settings, potentially representing a different case mix, hospital systems or a different degree of healthcare system overflow.

In our study, a significant interaction was found between plasma administration and age whereby plasma administration was associated with improved clinical outcome in younger patients. No such age interaction was observed in a placebo-controlled convalescent plasma trial [13] with exactly the same median age of patients as in our study. In view of the overall

lack of benefit of the intervention across several trials, it is debatable whether future studies should focus on the younger population based on this interaction analysis.

Our study has several limitations. The study was designed as an open label study, where the intervention was not blinded. No placebo treatment was given. Six study patients were excluded post-randomisation because of early withdrawal, all in the intervention group. Only 91% of patients received the intervention strictly per protocol, and almost 20% of convalescent plasma units did not contain the pre-specified $\geqslant$ 1/320 neutralising antibody titres.

Patients treated with B-lymphocyte depleting monoclonal antibodies during the year before admission were excluded from participation in the DAWn-plasma study. As such, the results of our study cannot be extrapolated to these patients, often not clearing the SARS-CoV-2 virus, where convalescent plasma could still be considered [23, 24]. Lastly, the study was largely conducted before the appearance of new variants of SARS-CoV-2 in Belgium.

In summary, transfusion of a high volume of 4 units of convalescent plasma with high neutralising antibody-titres early in hospitalised COVID-19 patients could not change the natural course of antibody titres and did not result in a significant improvement of the clinical status, nor did the intervention reduce mortality.

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The acknowledgements can be found in supplement S8.

CONFLICT OF INTEREST

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- Figure 3: prespecified subgroup analysis for the primary endpoint
- Figure 4: outcome according to antibody titre in donor plasma – FAS
- Figure 5A and 5B: neutralising antibodies in study patients and outcome
- Figure 6: evolution of viral load (baseline versus day 6 since randomisation) – FAS
- Table 1: baseline characteristics study patients
- Table 2: primary and secondary endpoints (ITT) - FAS

SUPPLEMENTS

- Supplement S1: list of DAWn-plasma investigators
- Supplement S2: method description VNA assay and NT50 titre detection
- Supplement S3: concomitant therapy
- Supplement S4: primary and secondary outcome – PPS
- Supplement S5: additional primary outcome analysis - FAS
- Supplement S6: SAE
- Supplement S7: Transfusion-related side effects
- Supplement S8: Acknowledgements

Table 1: Baseline Characteristics – Full Analysis Set (FAS)

		Randomised Treatment			
Demographics	Statistic	PLASMA + SOC	SOC	Total	P-value
Total Number of Patients	N	320	163	483	
Age [y]	Mean (SD)	62 (14)	62 (14)	62 (14)	0.772
Gender: Male	n/N (%)	219/320 (68.4%)	113/163 (69.3%)	332/483 (68.7%)	0.842
Ethnicity					0.253
Caucasian	n/N (%)	247/320 (77.2%)	135/163 (82.8%)	382/483 (79.1%)	
North African	n/N (%)	39/320 (12.2%)	20/163 (12.3%)	59/483 (12.2%)	
Middle east	n/N (%)	16/320 (5.0%)	2/163 (1.2%)	18/483 (3.7%)	
Black or sub-sahara (africa)	n/N (%)	10/320 (3.1%)	2/163 (1.2%)	12/483 (2.5%)	
Asian	n/N (%)	5/320 (1.6%)	2/163 (1.2%)	7/483 (1.5%)	
Latino or hispanic	n/N (%)	3/320 (0.9%)	2/163 (1.2%)	5/483 (1.0%)	
BMI [kg/m²]	[n] Mean (SD)	[264] 29 (5)	[140] 30 (6)	[404] 29 (6)	0.173
History of Diabetes Mellitus	n/N (%)	98/320 (30.6%)	45/163 (27.6%)	143/483 (29.6%)	0.528
Insulin Dependent	n/N (%)	29/ 320 (9.1%)	17/ 163 (10.4%)	46/483 (9.5%)	0.628
Oral Antidiabetics	n/N (%)	77/320 (24.1%)	23/161 (14.3%)	100/481 (20.8%)	0.013
Smoking Status					0.759
Active	n/N (%)	15/316 (4.8%)	10/159 (6.3%)	25/475 (5.3%)	
Former	n/N (%)	98/316 (31.0%)	47/159 (29.6%)	145/475 (30.5%)	
Never	n/N (%)	203/316 (64.2%)	102/159 (64.2%)	305/475 (64.2%)	
COPD	n/N (%)	29/317 (9.2%)	16/160 (10.0%)	45/477 (9.4%)	0.743
Asthma	n/N (%)	32/317 (10.1%)	16/160 (10.0%)	48/477 (10.1%)	1.000
Heart Failure	n/N (%)	26/318 (8.2%)	14/159 (8.8%)	40/477 (8.4%)	0.861

Ischaemic Heart Disease	n/N (%)	41/317 (12.9%)	26/158 (16.5%)	67/475 (14.1%)	0.328
Chronic Kidney Disease	n/N (%)	44/320 (13.8%)	20/159 (12.6%)	64/479 (13.4%)	0.777
Kidney Disease Requiring Dialysis	n/N (%)	3/ 318 (0.9%)	3/ 158 (1.9%)	6/ 476 (1.3%)	0.379
Active Cancer	n/N (%)	20/319 (6.3%)	9/162 (5.6%)	29/481 (6.0%)	0.841
HIV/AIDS	n/N (%)	3/308 (1.0%)	0/157 (0.0%)	3/465 (0.7%)	0.554
Chronic Systemic Corticosteroid Therapy	n/N (%)	27/317 (8.5%)	17/161 (10.6%)	44/478 (9.2%)	0.504
Other Immunosuppressive Therapy	n/N (%)	22/318 (6.9%)	17/161 (10.6%)	39/479 (8.1%)	0.215
Highest Body Temperature [°C]	[n] Mean (SD)	[316] 37.6 (1.0)	[162] 37.7 (1.0)	[478] 37.7 (1.0)	0.171
Lowest Oxygen Saturation [%] When Breathing Room Air	[n] Median (Q1; Q3)	[272] 91.0 (88.0; 93.0)	[127] 91.0 (86.0; 94.0)	[399] 91.0 (87.0; 93.0)	0.792
Oxygen Therapy					0.599
No	n/N (%)	36/320 (11.3%)	21/163 (12.9%)	57/483 (11.8%)	
Yes	n/N (%)	284/320 (88.8%)	142/163 (87.1%)	426/483 (88.2%)	
Consciousness Level					1.000
Alert	n/N (%)	310/320 (96.9%)	157/163 (96.3%)	467/483 (96.7%)	
Verbal	n/N (%)	9/320 (2.8%)	5/163 (3.1%)	14/483 (2.9%)	
Pain	n/N (%)	1/320 (0.3%)	1/163 (0.6%)	2/483 (0.4%)	
Disease Triage at Admission					0.698
Ward	n/N (%)	262/320 (81.9%)	135/161 (83.9%)	397/481 (82.5%)	
Intensive care unit	n/N (%)	48/320 (15.0%)	23/161 (14.3%)	71/481 (14.8%)	
Emergency Room	n/N (%)	10/320 (3.1%)	3/161 (1.9%)	13/481 (2.7%)	

Note: Continuous variables were compared using a 2-sample t-test. Categorical variables were compared using a chi-squared test.

Table 2: Trial Primary and Secondary Endpoints – Full Analysis Set (FAS)

Full Analysis Set (n=483)					
Primary and secondary endpoints	**Statistic**	**Estimate (95% Confidence Interval)**		**Treatment Effect**	**Estimate (95% CI)**
		Plasma	**SOC**		
Alive and free of MV at 15 Days	%	83.7 (79.3; 87.4)	84.1 (77.6; 88.9)	Odds Ratio	0.99 (0.59; 1.68)
Alive and free of MV at 30 Days	KM [%]	82.5 (78.1; 86.4)	82.2 (76.0; 87.6)	Hazard Ratio	0.94 (0.60; 1.48)
Sustained Improvement or Discharge within 30 Days	CIF [%]	82.6 (77.9; 86.3)	84.7 (78.1; 89.4)	Subdistribution HR	0.98 (0.81; 1.20)
Hospital Discharge (30 Days)	CIF [%]	80.5 (75.7; 84.4)	79.8 (72.8; 85.2)	Subdistribution HR	1.06 (0.87; 1.30)
All-Cause Mortality					
Day 15	KM [%]	3.1 (1.7; 5.8)	4.9 (2.5; 9.6)	Hazard Ratio	0.61 (0.24; 1.54)
Day 30	KM [%]	9.1 (6.3; 12.9)	8.7 (5.3; 14.3)	Hazard Ratio	0.99 (0.52; 1.88)
Supplemental Oxygen (30 Days)					
Incidence	CIF [%]	89.5 (85.5; 92.4)	89.0 (83.0; 92.9)	Subdistribution HR	1.01 (0.93; 1.09)
Life-Weaning from SO_2	CIF [%]	80.7 (75.6; 84.8)	82.3 (74.9; 87.7)	Subdistribution HR	1.05 (0.86; 1.29)
Mechanical Ventilation (30 Days)					
Incidence	CIF [%]	15.0 (11.3; 19.2)	13.5 (8.8; 19.2)	Subdistribution HR	1.08 (0.65; 1.80)
Life-Weaning from MV	CIF [%]	58.4 (42.1; 71.5)	68.2 (43.3; 83.9)	Subdistribution HR	0.49 (0.22; 1.08)
ICU (30 Days)					

Admission	CIF [%]	36.0 (30.8; 41.3)	34.4 (27.2; 41.7)	Subdistribution HR	1.00 (0.74; 1.34)
Life Discharge	CIF [%]	78.3 (69.5; 84.8)	82.1 (69.0; 90.1)	Subdistribution HR	0.95 (0.66; 1.35)
Clinical Status					
Day 0	Med. (IQR)	5 (5; 5)	5 (5; 5)		
Day 15	Med. (IQR)	2 (0; 5)	2 (0; 5)	Common OR	1.09 (0.78; 1.53)
Day 30	Med. (IQR)	2 (0; 2)	2 (0; 3)	Common OR	0.95 (0.67; 1.33)
EQ-5D-5L					
Baseline	Mean (SD)	54 (18)	54 (18)		
Day 30	Mean (SD)	73 (16)	72 (17)	Mean Difference	1.32 (-2.24; 4.88)
NT50 Values					
Day 0 - Log_2-transformed	Med. (IQR)	3 (1; 5)	3 (1; 5)		
Day 6 - Log_2-transformed	Med. (IQR)	6 (5; 6)	6 (5; 6)	Mean Difference	0.08 (-0.43; 0.58)
Ratio (D6/D0) - Log_2-transf'd	Med. (IQR)	2 (1; 3)	2 (0; 4)	Mean Difference	0.03 (-0.62; 0.68)

KM = incidence estimated using Kaplan-Meier methodology; 95% confidence interval calculated using log(-log)-transformation. CIF = incidence estimated using Cumulative Incidence Function accounting for competing risk; SD = standard deviation; Med. = Median; IQR = Interquartile range; HR = hazard ratio; OR = odds ratio.

All estimates of treatment effects were adjusted for study site and period.

Hazard ratios were obtained using a Cox regression including factors for randomised treatment, study period and site. Subdistribution hazard ratios were obtained using a Fine&Grey regression model (accounting for competing risk) including factors for randomised treatment, study period and site. Mean differences between treatments were obtained using a general linear model including the baseline value as a covariate and factors for randomised treatment, study period and site. Common odds ratios were obtained using a proportional odds logistic regression analysis including baseline clinical status as covariate and factors for randomised treatment, study period and site.

Figure 1: Patient enrolment and treatment assignment

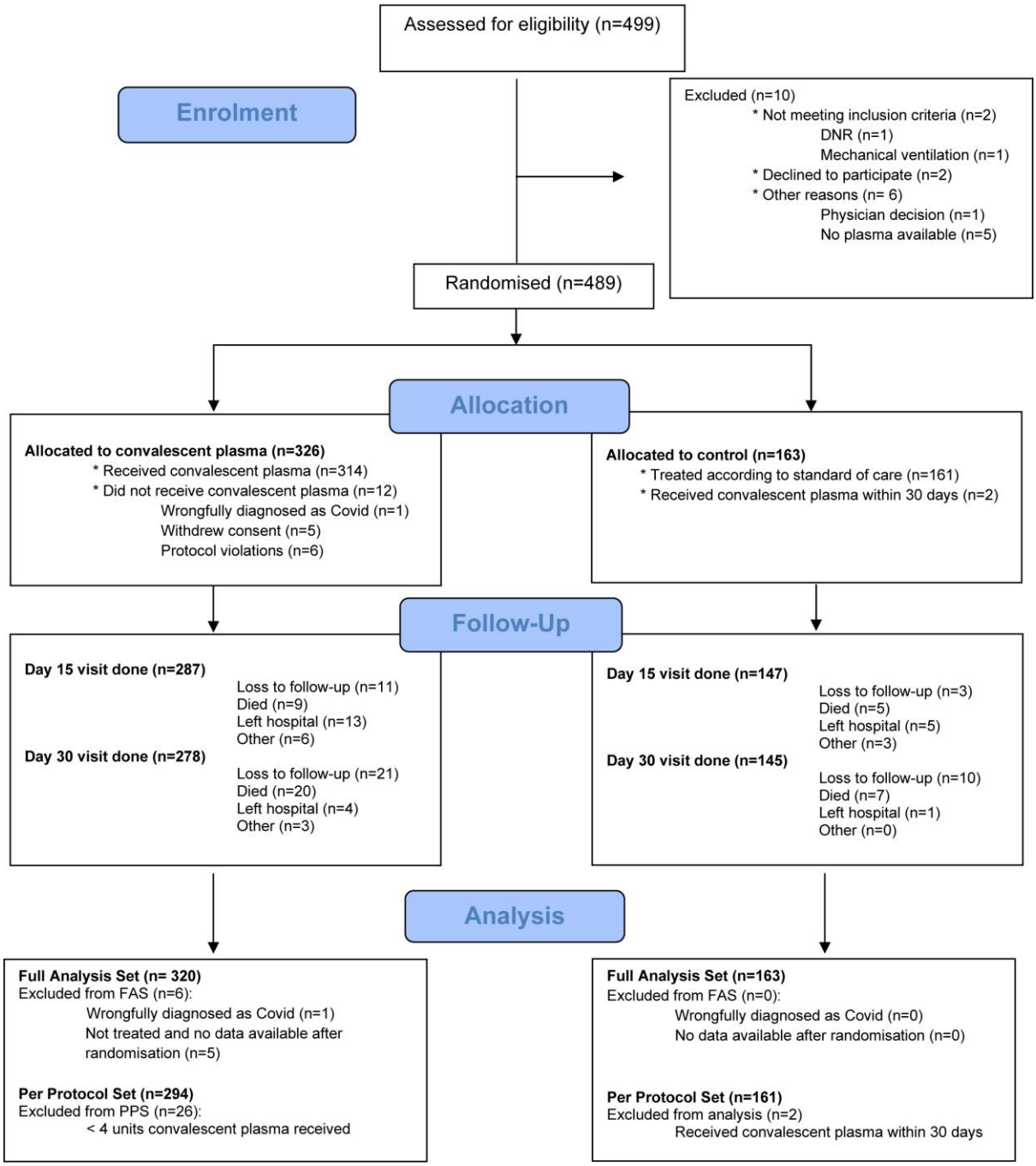
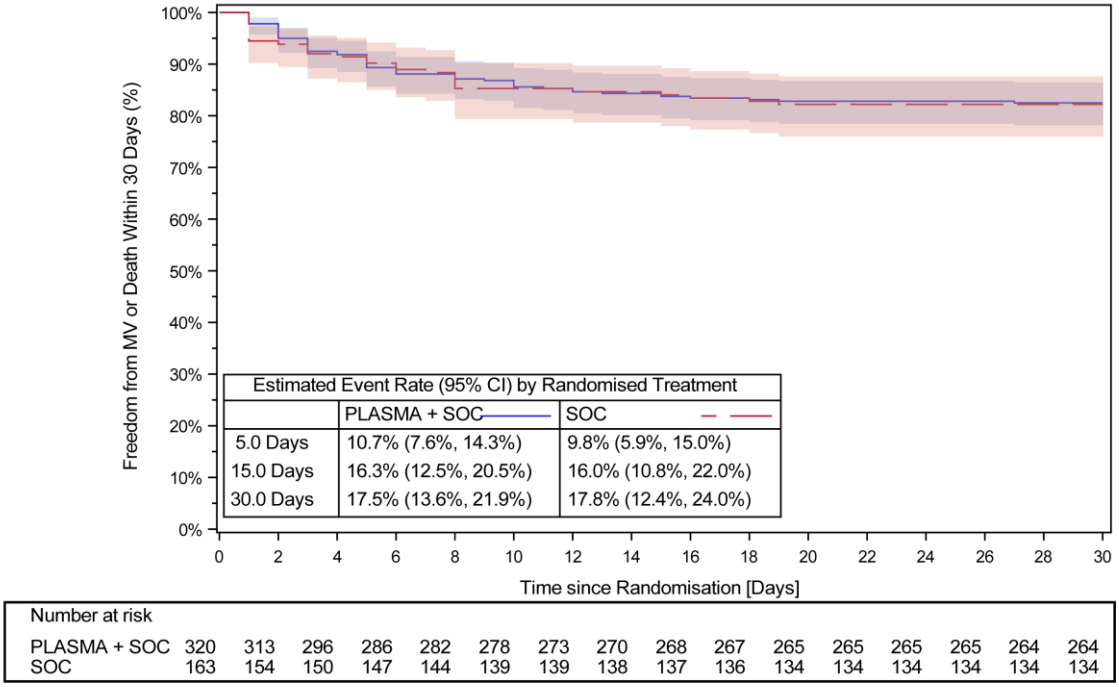


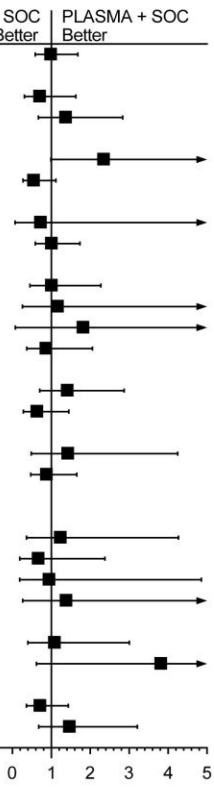
Figure 2: Proportion of patients remaining free of mechanical ventilation or death (FAS)



Number at risk																
PLASMA + SOC	320	313	296	286	282	278	273	270	268	267	265	265	265	265	264	264
SOC	163	154	150	147	144	139	139	138	137	136	134	134	134	134	134	134

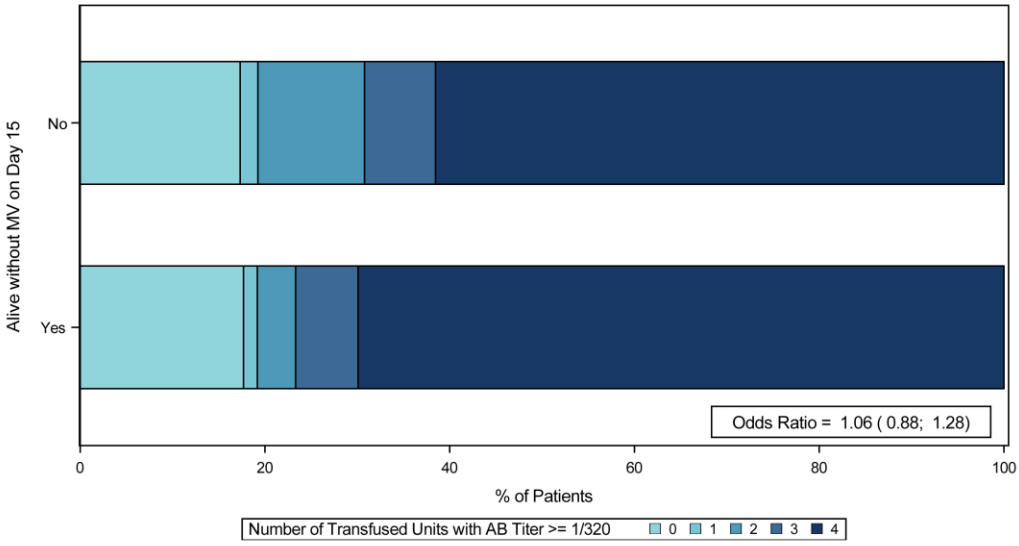
Figure 3: Pre-specified subgroup analyses for the primary endpoint - FAS

Subgroup	PLASMA + SOC Proportion [%] [n] Est. (95% CI)	SOC Proportion [%] [n] Est. (95% CI)	Odds Ratio versus SOC (95% CI)	P
Total Population	[320] 83.7 (79.3; 87.4)	[163] 84.0 (77.6; 88.9)	0.99 (0.59; 1.68)	0.976
Time from Symptoms to Randomisation (Interaction: p = 0.4850)				
< 7 Days	[129] 80.6 (72.9; 86.5)	[65] 84.6 (73.7; 91.5)	0.71 (0.31; 1.63)	0.418
>= 7 Days	[181] 86.7 (81.0; 91.0)	[92] 83.7 (74.7; 89.9)	1.37 (0.67; 2.83)	0.391
Age (Interaction: p = 0.0231)				
< 62 Years	[157] 91.7 (86.2; 95.1)	[78] 84.6 (74.8; 91.1)	2.35 (0.99; 5.60)	0.053
>= 62 Years	[163] 76.1 (68.9; 82.0)	[85] 83.5 (74.1; 90.0)	0.55 (0.27; 1.12)	0.099
Study Period (Interaction: p = 0.4322)				
02MAY20-09AUG20	[29] 86.2 (68.5; 94.7)	[10] 90.0 (53.3; 98.6)	0.73 (0.07; 7.92)	0.795
10AUG20-26JAN21	[291] 83.5 (78.8; 87.3)	[153] 83.7 (76.9; 88.7)	1.01 (0.59; 1.74)	0.974
Blood Type (Interaction: p = 0.0766)				
A	[139] 85.6 (78.7; 90.5)	[77] 84.4 (74.5; 90.9)	1.01 (0.45; 2.27)	0.981
B	[28] 78.6 (59.8; 90.0)	[18] 77.8 (53.5; 91.4)	1.17 (0.26; 5.31)	0.842
AB	[7] 85.7 (41.9; 98.0)	[5] 80.0 (30.9; 97.3)	1.82 (0.07; 45.18)	0.714
O	[146] 82.9 (75.9; 88.2)	[63] 85.7 (74.8; 92.4)	0.87 (0.37; 2.06)	0.752
Size of Study Site (Interaction: p = 0.2865)				
< 26 Patients	[161] 83.8 (77.3; 88.8)	[81] 79.0 (68.8; 86.5)	1.42 (0.70; 2.87)	0.332
>= 26 Patients	[159] 83.6 (77.1; 88.6)	[82] 89.0 (80.2; 94.2)	0.64 (0.28; 1.45)	0.283
Hospital Admission (Interaction: p = 0.9170)				
At ICU	[48] 70.8 (56.6; 81.9)	[23] 60.9 (40.2; 78.2)	1.43 (0.48; 4.25)	0.518
At Ward or ER	[272] 86.0 (81.4; 89.7)	[138] 87.7 (81.1; 92.2)	0.88 (0.47; 1.65)	0.696
Study Site Province (Interaction: p = 0.1469)				
Flemish Brabant	[38] 89.5 (75.1; 96.0)	[20] 100 (NC; NC)	NC (NC; NC)	NC
Brussels	[71] 90.1 (80.7; 95.2)	[41] 87.8 (73.9; 94.8)	1.24 (0.36; 4.27)	0.733
W. Flanders	[53] 79.2 (66.3; 88.1)	[26] 84.6 (65.5; 94.1)	0.67 (0.19; 2.38)	0.536
E. Flanders	[29] 75.9 (57.3; 88.0)	[13] 76.9 (47.8; 92.4)	0.95 (0.19; 4.85)	0.949
Antwerp	[24] 79.1 (58.5; 91.0)	[11] 72.7 (41.4; 91.0)	1.39 (0.26; 7.30)	0.700
Limburg	[8] 75.0 (37.7; 93.7)	[3] 100 (NC; NC)	NC (NC; NC)	NC
Liège	[80] 83.7 (74.0; 90.3)	[40] 82.5 (67.6; 91.4)	1.09 (0.39; 3.00)	0.869
Hainaut	[17] 82.4 (57.3; 94.2)	[9] 55.6 (25.1; 82.3)	3.82 (0.62; 23.60)	0.149
Blood Institute (Interaction: p = 0.3467)				
Rode Kruis	[185] 81.6 (75.4; 86.6)	[93] 86.0 (77.4; 91.7)	0.72 (0.36; 1.43)	0.346
Croix Rouge	[135] 86.7 (79.8; 91.4)	[70] 81.4 (70.6; 88.9)	1.47 (0.67; 3.21)	0.333



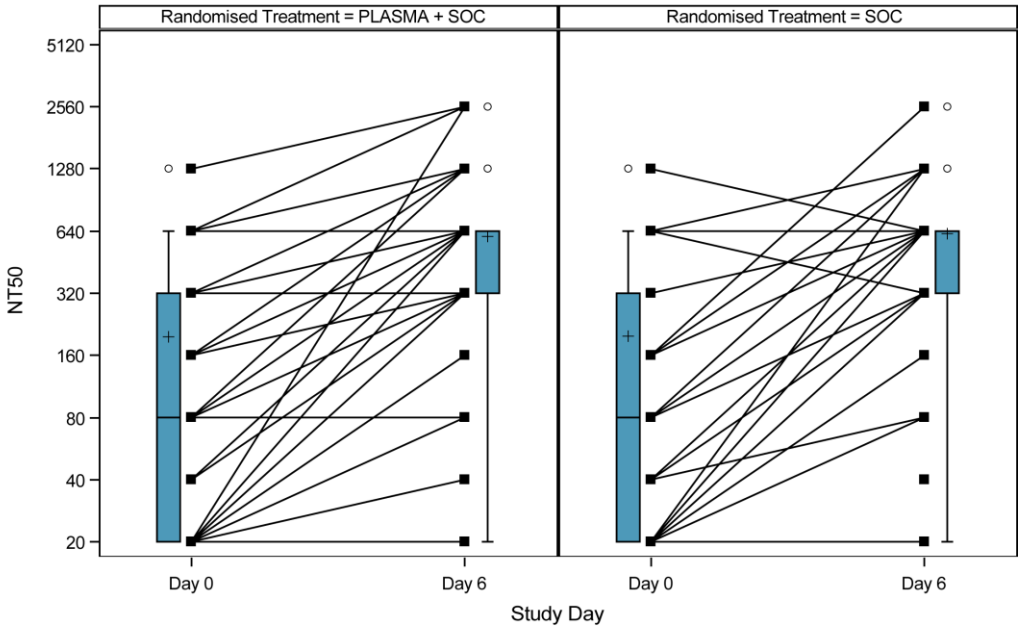
The odds ratios were obtained by means of a logistic regression that included factors for treatment, study site, study period, subgroup and the interaction between treatment and subgroup. For Blood Institute, study site was not included in the model due to problems with fitting the model.

Figure 4: Correlation between number of transfused CP units from donors with neutralising antibody titers ≥ 1/320 and outcome - Full Analysis Set (FAS)



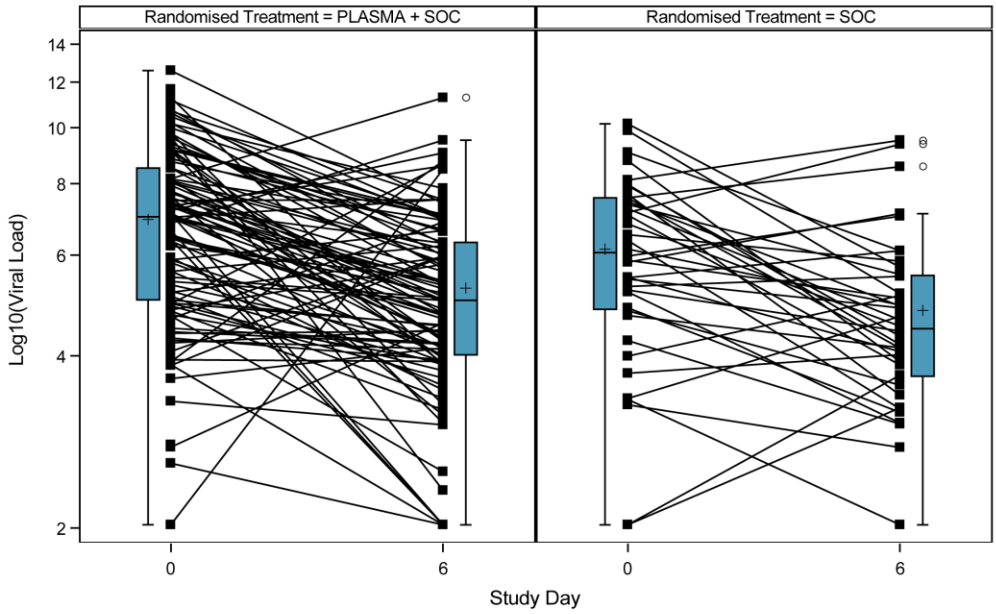
Association between the number of plasma units with antibody titer ≥ 1/320 given to patient and outcome, alive without MV at Day 15. The odds ratio reflects the change in odds for being alive with no MV on Day 15 when the number of units ≥ 1/320 increases by 1.

Figure 5A: Evolution of neutralising antibody titers in patient sera



Box plot shows median and interquartile range. Whiskers are drawn at (Q3+1.5*IQR, Q1-1.5*IQR).
Q1, Q3 = 1st and 3rd quartile, IQR = Q3 - Q1. +-sign indicates mean value. Circles indicate outlying values.
Lines connect individual patient values between Day 0 and 6.

Figure 6: Evolution of Viral Load (Baseline versus Day 6) - Full Analysis Set (FAS)



Box plot shows median and interquartile range. Whiskers are drawn at (Q3+1.5*IQR, Q1-1.5*IQR). Q1, Q3 = 1st and 3rd quartile, IQR = Q3 - Q1. +-sign indicates mean value. Circles indicate outlying values. BLQ values were imputed with half of the minimum observed value.
Log10-transformed viral load values at Day 6 were compared between group using a general linear model with factors for treatment, study site and period and including the baseline value as a covariate. The resulting estimate of the treatment difference was 0.23 (-0.40; 0.86).

Supplement S1: Supplementary Appendix

Author contributions:

Drs Devos and Meyfroidt had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Devos, Liesenborghs, Meyfroidt, Schauwvlieghe, Verhamme.

Acquisition, analysis, or interpretation of data: Belmans, Devos, Meyfroidt, Romano, Dauby.

Drafting of the manuscript: Devos, Compernolle, Najdovski, Romano, Dauby, Belmans, Verhamme, Meyfroidt.

Critical revision of the manuscript for important intellectual content: all authors.

Writing and remodeling of the manuscript: Devos, Van Thillo, Meyfroidt.

Statistical analysis: Belmans.

Administrative, technical, or material support: Compernolle, Najdovski, Romano, Devos, Meyfroidt.

Supervision: Meyfroidt, Devos.

Other - site PI for study; recruitment and management of study participants; participation in investigator meetings: Jadot, Leys, Maillart, Loof, Seyler, Moonen, Moutschen, Van Regenmortel, Dauby, Devos.

Other - responsible for recruitment of patients at my institution: Van Thillo, Betrains, Engelen, Gyselinck.

Other - laboratory directors (VNA testing): Ariën, Barbezange, Gargigliany, Maes.

DAWN-plasma investigators

In addition to the individual authors, the following DAWN-plasma Investigators (listed in alphabetical order) participated in the study and are considered as co-authors (full authorship and pubmed-citation requested):

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Supplement S2:

Supplementary Material & Methods – Virus Neutralisation Assay - DAWn PLASMA TRIAL

Anti-SARS-CoV-2 virus neutralisation titers (NT50) were determined on plasma or serum samples in four Belgian laboratories (Liège University, Institute of Tropical Medicine, Rega Institute Leuven, Sciensano). NT50 titers were determined on donor plasma samples to select COVID-19 convalescent donors eligible for CCP donation for the DAWn plasma trial. NT50 titers were also determined on serum samples of study patients at Day 0 and Day 6 after randomisation. All the virus neutralisation assays (VNA) conducted in this study were performed in BSL3 laboratories in a 96-well plate format, using heat-inactivated plasma or serum samples (30-60 minutes at 56°C).

Methodological details of the protocols applied in the four laboratories are described hereafter.

Liège University (D. Desmecht/ M. Garigliany - Department of Animal Pathology, Liège University, Liège, Belgium)

Two-fold serial dilutions (1/10 to 1/1280) of heat-inactivated serum or plasma samples were mixed vol/vol with 100 TCID50/reaction of SARS-CoV-2 (strain BetaCov/Belgium/Sart-Tilman/2020/1, passage 5), corresponding to final testing dilutions of 1/20 to 1/2560 in DMEM supplemented with 2% foetal bovine serum, 1% antibiotic and 1% antimycotic. Following incubation for 1 h at 37 °C, triplicates of sample plus virus mixtures were transferred in 96-well plates containing confluent monolayer of Vero E6 cells (ATCC CRL-1586) (Wu H-S et al. Taiwan Emerg Inf Dis. 2004; 10: 304–310). Two samples, a negative control and a strong positive control (provided by the Croix-Rouge de Belgique) were tested per plate. This VNA relies on direct cytopathic effect (CPE) observation under light microscopy at day 5 post infection. Dilutions of samples/controls associated with CPE were considered as negative, while the absence of CPE indicated a complete neutralisation of SARS-CoV-2 inoculum and were considered positive for neutralisation. Virus neutralisation titers are reported as the highest dilution of serum that neutralised CPE in 50% of the wells. Serum/plasma specimens with a NT50 titer ≥ 40 are considered to neutralise the virus. *Method as described in Misset et al. BMC Pulm Med. 2020 Dec 7;20(1):317.*

Institute of Tropical Medicine (K.K. Ariën - Virology Unit, Department of Biomedical Sciences, Institute of Tropical Medicine, Antwerp, Belgium; University of Antwerp, Antwerp, Belgium)

Serial dilutions (1/33 to 1/1048) of heat-inactivated serum were incubated with 3xTCID100 of SARS-CoV-2 (strain 2019-nCoV-Italy-INMI1, reference 008V-03893, passage 5), corresponding to final testing dilutions of 1/50 to 1/1600 in EMEM supplemented with 2 mM L-glutamine, 100 U/ml - 100 µg/ml of Penicillin-Streptomycin and 2 % foetal bovine serum. Following incubation for 1 h (37 °C / 7 % CO2), 8 replicates of sample/virus mixtures and virus/cell controls were added to Vero cells (18.000 cells/well) in a 96-well plate and incubated for 5 days (37 °C / 7 % CO2). The cytopathic effect (CPE) caused by viral growth was scored microscopically. The Reed-Muench method was used to calculate the neutralising antibody titer that reduced the number of infected wells by 50 % (NT50) (Reed and Muench. Am J Hyg 1938; 27: 493-497), these values were used as a proxy for the neutralising antibody concentration in each sample. *Method as described in Mariën et al. J Virol Methods. 2021 Feb;288:114025. Epub 2020 Nov 20.*

Katholieke Universiteit Leuven (P. Maes - Department of Microbiology, Immunology and Transplantation, Laboratory of Clinical and Epidemiological Virology, KU Leuven, Leuven, Belgium)

Serial dilutions of heat-inactivated serum were incubated with 400 plaque-forming units (pfu) of SARS-CoV-2 (strain SARS-2-CoV/Belgium/GHB-03021/2020, GISAID accession number EPI_ISL_407976, passage 5) in 96-well plates seeded with Vero E6 wells (1 h, 37°C, humidified 5% CO2 atmosphere). Following incubation, a 1% agarose (SeaKem LE agarose, Lonza, Belgium) overlay was added and plates were incubated for 4 days (37°C, humidified 5% CO2 atmosphere). Following overlay with 1% neutral red/1% agarose (24 h, 37°C), plaques were counted. Virus neutralisation titers were reported as a 50% reduction (NT50) in the number of plaques in comparison to a non-neutralising antibody control. *Method as described in Betrains et al. Br J Haematol 2021; 192(6):1100-1105.*

Sciensano (C. Barbezange – Unit Respiratory viruses, Directorate Infectious diseases in humans)

Two-fold serial dilutions (1/40 to 1/5120) of heat-inactivated serum samples were mixed vol/vol with 100 TCID50/reaction of SARS-CoV-2 (hCoV-19/Belgium/S1871/2020, passage 3), corresponding to final testing dilutions of 1/80 to 1/10240 in DMEM supplemented with 2% foetal bovine serum, 100 U/ml - 100 µg/ml of Penicillin-Streptomycin. Following incubation for 1 h at 37 °C (5% CO_2), triplicates of sample plus virus mixtures were transferred in 96-well plates containing a confluent monolayer of Vero E6 cells (ATCC CRL-1586) seeded the day before at 20,000 per well. A negative control (serum from 2017) and a strong positive control (provided by Croix-Rouge de Belgique) were tested in parallel in each experimental run. This VNA relies on the staining of infected cells using SARS-CoV-2 specific antibodies and was adapted from Okba et al. (Emerg Infect Dis 2020; 26(7):1478-1488) and from Amanat et al. (Curr Protoc Microbiol. 2020; 58(1):e108). More specifically, two days post-infection, cells are fixed with 4% paraformaldehyde, permeabilised with PBS supplemented with 0.2% Triton X-100, incubated with diluted mouse monoclonal anti-SARS-CoV/SARS-CoV-2 Nucleocapsid antibody (Bio-Connect, 40143-MM08), incubated with diluted goat anti-mouse IgG HRP conjugated secondary antibody (Biorad, 172-1011) and revealed with a precipitate forming 3,3',5,5'-tetramethylbenzidine substrate (True Blue; VWR, KPLI50-78-02). Visual evaluation of individual wells is performed and wells with >50% of blue area are scored as positive for the virus. The Reed-Muench method was used to calculate the neutralising antibody titer that reduced the number of infected wells by 50 % (NT50). Samples with a NT50 titer ≥ 80 are considered as positive for neutralising antibodies against the virus.

Supplement S3: Supplementary Table: Concomitant Therapy – Full Analysis Set (FAS)

	Randomised Treatment			
Concomitant Therapy	PLASMA + SOC	SOC	Total	P-value
Total Number of Patients	320	163	483	
Specific Treatment for Covid-19 Used	130/320 (40.6%)	74/163 (45.4%)	204/483 (42.2%)	0.331
Chloroquine	0/320 (0.0%)	0/163 (0.0%)	0/483 (0.0%)	
Hydroxychloroquine	4/320 (1.3%)	3/163 (1.8%)	7/483 (1.4%)	0.693
Favipiravir	0/320 (0.0%)	0/163 (0.0%)	0/483 (0.0%)	
Remdesivir	46/319 (14.4%)	25/160 (15.6%)	71/479 (14.8%)	0.785
Tocilizumab	1/320 (0.3%)	2/163 (1.2%)	3/483 (0.6%)	0.264
Lopinavir/Ritonavir	1/320 (0.3%)	1/163 (0.6%)	2/483 (0.4%)	1.000
Other	78/320 (24.4%)	46/163 (28.2%)	124/483 (25.7%)	0.379
Other Antiviral Drugs	18/320 (5.6%)	8/163 (4.9%)	26/483 (5.4%)	0.833
Antibiotics	174/320 (54.4%)	94/163 (57.7%)	268/483 (55.5%)	0.500
Antifungal Treatment	30/320 (9.4%)	15/163 (9.2%)	45/483 (9.3%)	1.000
Systemic Corticosteroids	208/320 (65.0%)	112/162 (69.1%)	320/482 (66.4%)	0.414
Hydrocortisone	0/320 (0.0%)	1/162 (0.6%)	1/482 (0.2%)	0.336
Methylprednisolone	35/320 (10.9%)	25/162 (15.4%)	60/482 (12.5%)	0.188
Prednisolone	3/320 (0.9%)	0/162 (0.0%)	3/482 (0.6%)	0.554
Dexamethasone	179/320 (55.9%)	88/162 (54.3%)	267/482 (55.4%)	0.771
Other	1/320 (0.3%)	2/162 (1.2%)	3/482 (0.6%)	0.262
Anticoagulation	306/319 (95.9%)	153/160 (95.6%)	459/479 (95.8%)	1.000

Results are presented as n/N (%) whereby N=total number of patients with data available, n=number of patients with medication during hospital stay up to Day 30 and %=n*100/N. Differences between randomised groups were assessed using Fisher's exact test.

Supplement S4: Supplementary table: Trial Primary and Secondary Endpoints – Per Protocol Set (PPS)

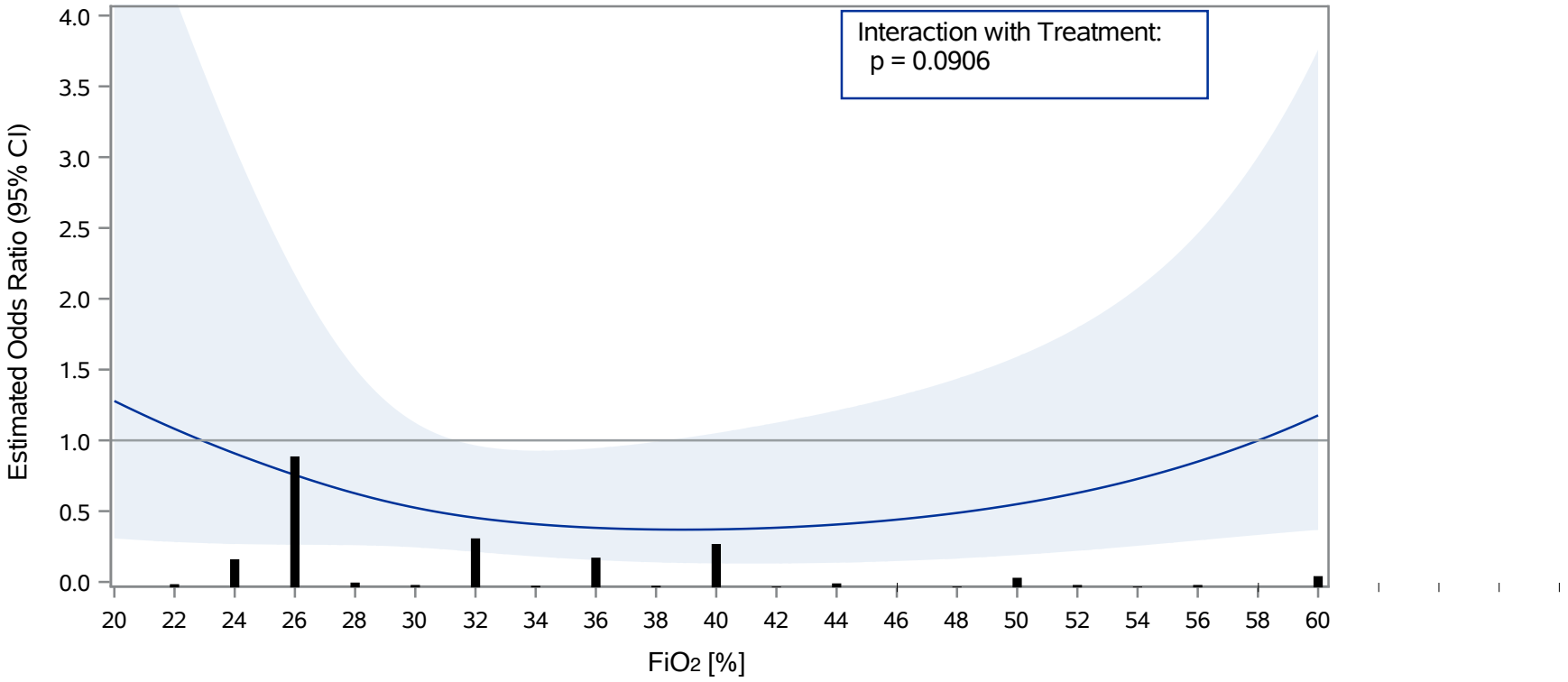
Per Protocol Set					
Primary and secondary endpoints	**Statistic**	**Estimate (95% Confidence Interval)**		**Treatment Effect**	**Estimate (95% CI)**
		Plasma	**SOC**		
Alive and free of MV at 15 Days	%	85.0 (80.5; 88.7)	84.5 (78.0; 89.3)		1.05 (0.59; 1.86)
Alive and free of MV at 30 Days	KM [%]	83.7 (79.2; 87.6)	82.6 (76.4; 88.0)		0.900 (0.56; 1.44)
Sustained Improvement or Discharge within 30 Days	CIF [%]	83.0 (78.2; 86.9)	85.7 (79.2; 90.3)		0.970 (0.796; 1.182)
Hospital Discharge (30 Days)	CIF [%]	81.2 (76.3; 85.2)	80.8 (73.8; 86.1)		1.050 (0.855; 1.291)
All-Cause Mortality					
Day 15	KM [%]	3.4 (1.9; 6.2)	5.0 (2.5; 9.7)		0.638 (0.251; 1.620)
Day 30	KM [%]	9.1 (6.3; 13.1)	8.2 (4.8; 13.7)		1.070 (0.545; 2.102)
Supplemental Oxygen (30 Days)					
Incidence	CIF [%]	89.6 (85.4; 92.6)	88.8 (82.8; 92.8)		1.011 (0.935; 1.094)
Life-Weaning from SO_2	CIF [%]	82.0 (76.7; 86.1)	82.7 (75.3; 88.1)		1.068 (0.867; 1.316)
Mechanical Ventilation (30 Days)					
Incidence	CIF [%]	13.6 (10.0; 17.8)	13.0 (8.4; 18.8)		1.030 (0.600; 1.766)
Life-Weaning from MV	CIF [%]	54.9 (37.5; 69.3)	71.4 (45.8; 86.5)		0.363 (0.149; 0.885)
ICU (30 Days)					
Admission	CIF [%]	34.7 (29.3; 40.1)	33.6 (26.4; 40.9)		0.992 (0.728; 1.353)
Life Discharge	CIF [%]	77.5 (68.0; 84.4)	83.3 (70.0; 91.1)		0.937 (0.649; 1.354)
Clinical Status					
Day 0	Med. (IQR)	5 (5; 5)	5 (5; 5)		
Day 15	Med. (IQR)	2 (0; 5)	2 (0; 5)		1.12 (0.80; 1.58)
Day 30	Med. (IQR)	2 (0; 2)	2 (0; 3)		0.97 (0.68; 1.38)
NT50 Values					
Day 0 - Log_2-transformed	Med. (IQR)	3 (1; 5)	3 (1; 5)		
Day 6 - Log_2-transformed	Med. (IQR)	6 (5; 6)	6 (5; 6)		-0.14 (-0.65; 0.37)
Ratio (D6/D0) - Log_2-transf'd	Med. (IQR)	2 (1; 3)	2 (0; 4)		-0.20 (-0.86; 0.45)

KM = incidence estimated using Kaplan-Meier methodology; 95% confidence interval calculated using log(-log)-transformation. CIF = incidence estimated using Cumulative Incidence Function accounting for competing risk; SD = standard deviation; Med. = Median; IQR = Interquartile range; HR = hazard ratio; OR = odds ratio.

All estimates of treatment effects were adjusted for study site and period.

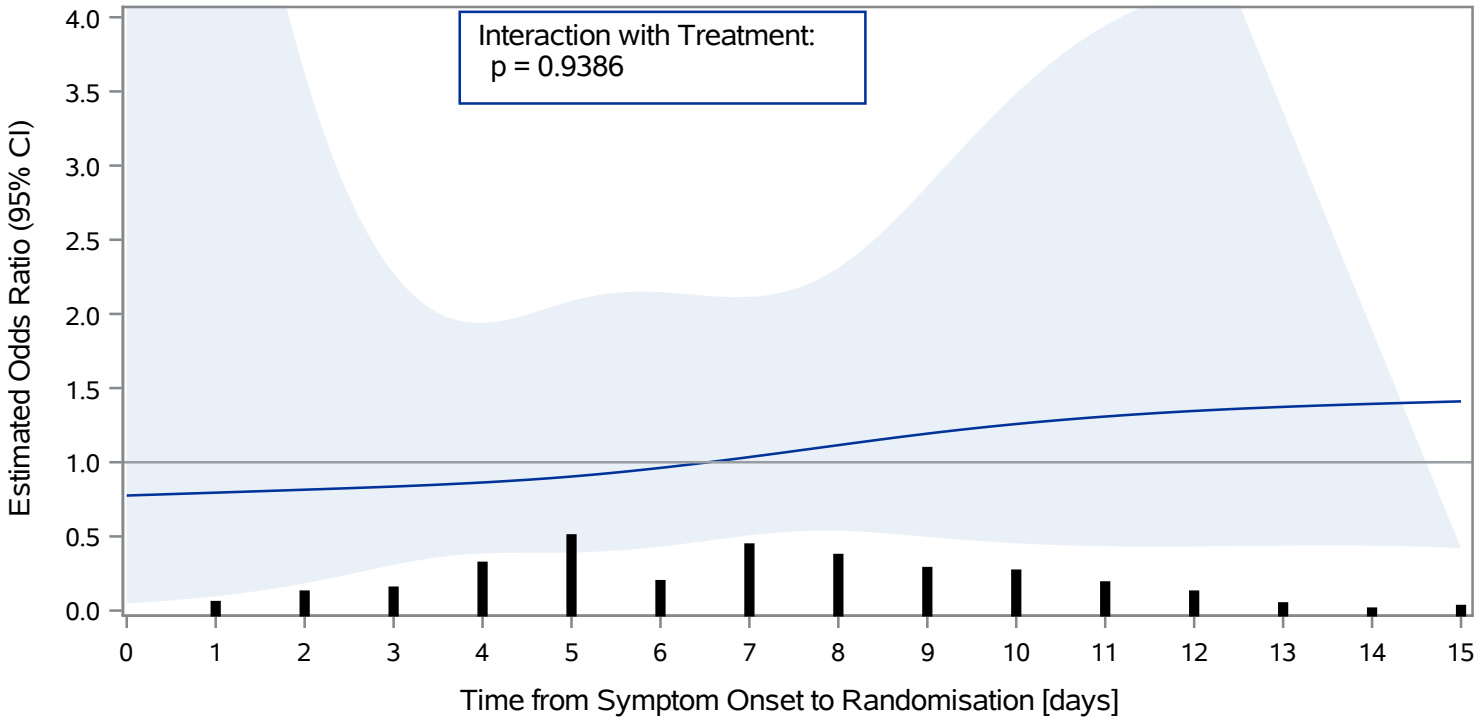
Hazard ratios were obtained using a Cox regression including factors for randomised treatment, study period and site. Subdistribution hazard ratios were obtained using a Fine&Grey regression model (accounting for competing risk) including factors for randomised treatment, study period and site. Mean differences between treatments were obtained using a general linear model including the baseline value as a covariate and factors for randomised treatment, study period and site. Common odds ratios were obtained using a proportional odds logistic regression analysis including baseline clinical status as covariate and factors for randomised treatment, study period and site.

Supplement S5A: Interaction between treatment and baseline FiO2



Odds ratios were obtained from a logistic regression model, including treatment (as factor), FiO_2 (as restricted cubic spline) and their interaction, and further adjusted for Study Site and Period. A histogram for the distribution of patients across the covariate values is included at the bottom of the graph.

Supplement S5B: Interaction between treatment and time from symptoms to randomisation



Odds ratios were obtained from a logistic regression model, including treatment (as factor), Time from Symptom Onset to Randomisation (as restricted cubic spline) and their interaction, and further adjusted for Study Site and Period.
A histogram for the distribution of patients across the covariate values is included at the bottom of the graph.

Supplement S6: Supplementary Table: Venous Thromboembolisms and Serious Adverse Events – Full Analysis Set (FAS)

	Randomised Treatment	
Adverse Events up to End of Study: SYSTEM ORGAN CLASS Preferred Term	PLASMA + SOC	SOC
Total Number of Subjects	320	163
DEEP VENOUS THROMBOEMBOLISMS		
Any Venous Thromboembolisms	1 (0.3%)	1 (0.6%)
Deep Vein Thrombosis	0 (0.0%)	0 (0.0%)
Pulmonary Embolism	1 (0.3%)	1 (0.6%)
SERIOUS ADVERSE EVENTS BY MEDDRA SYSTEM ORGAN CLASS AND PREFERRED TERM		
Number of subjects with Serious Adverse Events	66 (20.6%)	34 (20.9%)
Number of Serious Adverse Events	78	40
INFECTIONS AND INFESTATIONS	33 (10.3%)	17 (10.4%)
COVID-19	20 (6.3%)	13 (8.0%)
Septic shock	2 (0.6%)	1 (0.6%)
Bronchopulmonary aspergillosis	1 (0.3%)	1 (0.6%)
COVID-19 pneumonia	2 (0.6%)	0 (0.0%)
Pneumonia	0 (0.0%)	2 (1.2%)
Sepsis	2 (0.6%)	0 (0.0%)
Aspergillus infection	1 (0.3%)	0 (0.0%)

Bacterial infection	1 (0.3%)	0 (0.0%)
Enterobacter pneumonia	1 (0.3%)	0 (0.0%)
Enterococcal sepsis	1 (0.3%)	0 (0.0%)
Pneumonia legionella	1 (0.3%)	0 (0.0%)
Pulmonary sepsis	0 (0.0%)	1 (0.6%)
Urinary tract infection bacterial	0 (0.0%)	1 (0.6%)
Viral infection	1 (0.3%)	0 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	12 (3.8%)	8 (4.9%)
Hypoxia	3 (0.9%)	1 (0.6%)
Respiratory failure	3 (0.9%)	1 (0.6%)
Dyspnoea	3 (0.9%)	0 (0.0%)
Dyspnoea exertional	2 (0.6%)	1 (0.6%)
Acute respiratory distress syndrome	0 (0.0%)	1 (0.6%)
Bronchopneumopathy	0 (0.0%)	1 (0.6%)
Dyspnoea at rest	1 (0.3%)	0 (0.0%)
Interstitial lung disease	0 (0.0%)	1 (0.6%)
Pulmonary alveolar haemorrhage	0 (0.0%)	1 (0.6%)
Pulmonary embolism	0 (0.0%)	1 (0.6%)
Pulmonary oedema	1 (0.3%)	0 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	12 (3.8%)	1 (0.6%)
Multiple organ dysfunction syndrome	4 (1.3%)	0 (0.0%)
Pyrexia	4 (1.3%)	0 (0.0%)
General physical health deterioration	3 (0.9%)	0 (0.0%)
Death	0 (0.0%)	1 (0.6%)
Disease progression	1 (0.3%)	0 (0.0%)

CARDIAC DISORDERS	2 (0.6%)	5 (3.1%)
Cardiac failure	2 (0.6%)	0 (0.0%)
Arrhythmia	0 (0.0%)	1 (0.6%)
Atrial fibrillation	0 (0.0%)	1 (0.6%)
Cardiac arrest	0 (0.0%)	1 (0.6%)
Cardio-respiratory arrest	0 (0.0%)	1 (0.6%)
Mitral valve incompetence	0 (0.0%)	1 (0.6%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	5 (1.6%)	0 (0.0%)
Transfusion reaction	3 (0.9%)	0 (0.0%)
Febrile non-hemolytic transfusion reaction	1 (0.3%)	0 (0.0%)
Transfusion related complication	1 (0.3%)	0 (0.0%)
GASTROINTESTINAL DISORDERS	2 (0.6%)	2 (1.2%)
Abdominal pain	1 (0.3%)	0 (0.0%)
Gastrointestinal haemorrhage	1 (0.3%)	0 (0.0%)
Intestinal obstruction	0 (0.0%)	1 (0.6%)
Melaena	0 (0.0%)	1 (0.6%)
INVESTIGATIONS	3 (0.9%)	1 (0.6%)
Oxygen saturation decreased	2 (0.6%)	0 (0.0%)
Pseudomonas test positive	1 (0.3%)	0 (0.0%)
SARS-CoV-2 test positive	0 (0.0%)	1 (0.6%)
NERVOUS SYSTEM DISORDERS	3 (0.9%)	1 (0.6%)
Ischaemic stroke	1 (0.3%)	1 (0.6%)
Guillain-Barre syndrome	1 (0.3%)	0 (0.0%)
Transient ischaemic attack	1 (0.3%)	0 (0.0%)
RENAL AND URINARY DISORDERS	2 (0.6%)	1 (0.6%)

Acute kidney injury	2 (0.6%)	0 (0.0%)
Urinary retention	0 (0.0%)	1 (0.6%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.3%)	0 (0.0%)
Anaemia	1 (0.3%)	0 (0.0%)
METABOLISM AND NUTRITION DISORDERS	0 (0.0%)	1 (0.6%)
Fluid overload	0 (0.0%)	1 (0.6%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0%)	1 (0.6%)
Metastatic neoplasm	0 (0.0%)	1 (0.6%)
SURGICAL AND MEDICAL PROCEDURES	1 (0.3%)	0 (0.0%)
Lung assist device therapy	1 (0.3%)	0 (0.0%)
VASCULAR DISORDERS	1 (0.3%)	0 (0.0%)
Internal haemorrhage	1 (0.3%)	0 (0.0%)

Supplement S7: Supplementary Table: Transfusion-Related Side Effects – Full Analysis Set (FAS)

		Randomised Treatment
	Statistic	PLASMA + SOC
Total Number of Subjects	N	320
Any Transfusion Related Side Effects	n/N (%)	19 (6.0%)
Acute Lung Injury (TRALI)	n/N (%)	0 (0.0%)
Serious Allergic Transfusion Reaction	n/N (%)	2 (0.6%)
Transfusion Associated Circulatory Overload (TACO)	n/N (%)	3 (0.9%)
Non-Haemolytic Febrile Reaction	n/N (%)	5 (1.6%)
Other Related Side Effect	n/N (%)	9 (2.8%)

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