NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG
getragen von:
Deutsches Krebsforschungszentrum
Universitätsklinikum Heidelberg
Thoraxklinik-Heidelberg
Deutsche Krebshilfe

Study Title:

A Randomized Open label Phase-II Clinical Trial with or without Infusion of Plasma from Subjects after Convalescence of SARS-CoV-2 Infection in High-Risk Patients with Confirmed Severe SARS-CoV-2 Disease

Short Title/ Acronym: RECOVER

This is a multicentre clinical trial designed to evaluate the clinical outcome of severe SARS-CoV-2 disease in high-risk patients (divided in 4 sub-groups) following treatment with anti-SARS-CoV-2 plasma from subjects after convalescence of SARS-CoV-2 infection and/or vaccination in comparison to standard of care. The primary endpoint of the trial is defined as time from randomization until an improvement (within 84 days) by two points on a seven point ordinal scale or live discharge from the hospital.

Final Study Report (Synopsis) according to §42b AMG and §13(9) GCP-V

Version Number/ Date:	Final 1.0, 30st March 2023
Investigational Product:	RECOVER CT SARS-CoV-2-ab Plasma COVID-19(HD)
EudraCT-Number:	2020-001632-10
Protocol-Number:	SARS-CoV-2CP-HD-001; Protocol V3.0 8th March 2021
Registry-Number:	NCT05200754

Sponsor:	**Coordinating / Principal Investigator:**
Ruprecht-Karls-University Heidelberg Medical Faculty represented in law by its Commercial Director Katrin Erk Im Neuenheimer Feld 672 69120 Heidelberg, Germany Phone +49 (0)6221 - 56 7000 Fax: +49 (0)6221 - 56 4888 E-Mail: Kaufmaennische-Direktion@med.uni-heidelberg.de	Prof. Dr. Carsten Müller-Tidow University Hospital Heidelberg Internal Medicine V Hematology, Oncology and Rheumatology Im Neuenheimer Feld 410 69120 Heidelberg Phone: +49 (0)6221 - 56 8001 Fax: +49 (0)6221 - 56 33639 E-Mail: Carsten.Mueller-Tidow@med.uni-heidelberg.de

Author of Trial Report:	**Study Initiation and Completion Dates:**
Prof. Dr. Richard F. Schlenk National Center for Tumor Diseases (NCT) Trial Center Im Neuenheimer Feld 130.3 69120 Heidelberg Phone: +49 6221 - 56 6228 Fax: +49 6221 - 56 5863 E-Mail: richard.schlenk@nct-heidelberg.de	First Patient In: 3rd Sep 2020 Last Patient In: 12th Jan 2022 Date of early termination: 20th Jan 2022 End of Study: 05th Apr 2022 Database Lock: 12th Apr 2022

Signatures

The present trial study report was subject to critical review and has been approved in the present version. The information contained is consistent with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (current version), the principles of ICH-GCP and all local regulatory requirements.

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of this study.

Coordinating Investigator / Designated Representative of Sponsor

[redacted] [redacted]

Prof. Dr. med. Carsten Müller-Tidow — Place, Date

Biostatistician

Prof. Dr. Richard F. Schlenk — Place, Date

Biostatistician

Baumann, Lukas — Place, Date

Signatures

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Biostatistician

Prof. Dr. Richard F. Schlenk — Place, Date

Biostatistician

[redacted] — [redacted]

Baumann, Lukas — Place, Date

Synopsis

Name of Sponsor/Company:

Ruprecht-Karls-University Heidelberg, Medical Faculty
Im Neuenheimer Feld 672
69120 Heidelberg, Germany

Name of Finished Product:

RECOVER CT SARS-CoV-2-ab Plasma COVID-19 (HD)

Name of Active Ingredient:

per 1 ml suspension:
0.85 – 0.89 ml human plasma with antibodies against the SARS-CoV-2-virus

Title of Study:

A Randomized Open label Phase-II Clinical Trial with or without Infusion of Plasma from Subjects after Convalescence of SARS-CoV-2 Infection in High-Risk Patients with Confirmed Severe SARS-CoV-2 Disease

Short Title/Acronym:

RECOVER

Protocol versions:

V 1.2 dated 9th July 2020 (First authorization)

V 2.0 dated 29th Oct 2020 (Substantial Amendment)

V 3.0 dated 8th Mar 2021 (Substantial Amendment)

Study center(s) and Principle Investigator(s):

For a detailed list of all study centers and principle investigators see appendix 1.

Publications (reference):

Article, December 2020 Trials 21(1)

A Randomized Open label Phase-II Clinical Trial with or without Infusion of Plasma from Subjects after Convalescence of SARS-CoV-2 Infection in High-Risk Patients with Confirmed Severe SARS-CoV-2 Disease (RECOVER): A structured summary of a study protocol for a randomised controlled trial
DOI:10.1186/s13063-020-04735-y
Janssen et al. Trials (2020) 21:828

EHA, Abstract, June 2022 HemaSphere 6:183-184

Abstract: S282: A randomized controlled clinical trial demonstrates that plasma from convalescent and vaccinated donors improves outcome of COVID-19 in patients with hematological disease, cancer or immunosuppression

DOI: 10.1097/01.hs9.0000844020.02619.0f

MedRxiv Preprint, 13 October 2022

Anti-SARS-CoV-2 antibody containing plasma improves outcome in patients with hematologic or solid cancer and severe COVID-19 via increased neutralizing antibody activity – a randomized clinical trial
DOI:10.1101/2022.10.10.22280850

Abstract: 1142, 15 December 2022

Plasma with high titers of anti-SARS-Cov2 antibodies improves outcome of COVID-19 in patients with hematological malignancy and cancer in a randomized controlled trial Open Forum Infectious Diseases, Volume 9, Issue Supplement_2, December 2022, ofac492.980, https://doi.org/10.1093/ofid/ofac492.980

Article, 29 December 2022

Anti-SARS-CoV-2 antibody-containing plasma improves outcome in patients with hematologic or solid cancer and severe COVID-19: a randomized clinical trial
Denkinger et al Nat Cancer. 2023 Jan;4(1):96-107.
DOI: 10.1038/s43018-022-00503-w. Epub 2022 Dec 29.

Studied period (years):	**Phase of development**:
Date of first enrolment: 3rd Sep 2020 Date of last enrolment: 12th Jan 2022 Date of early termination: 20th Jan 2022 Date of last completed: 05th April 2022 Early termination after treatment of 134 patients as it could not be ensured at that time point that the collected plasma contains antibodies against the new omicron variant of the SARS-CoV-2 virus.	Phase II

Objectives

Primary Objective:

To assess the time from randomization until an improvement (within 84 days) defined as two points on a seven point ordinal scale or live discharge from the hospital in high-risk patients (group 1 to group 4) with a SARS-CoV-2 infection requiring hospital admission by infusion of plasma from subjects after convalescence of a SARS-CoV-2 infection or after vaccination or standard of care.

Secondary Objectives:

1. To assess overall survival, and the overall survival rate at 28, 56 and 84 days.
2. To assess SARS-CoV-2 viral clearance and load, cytokine changes over time as well as antiviral antibody titres.
3. To assess percentage of patients that required mechanical ventilation
4. To assess time from randomization until discharge

Methodology:

This trial was designed as a multicentre, randomized, open-label, phase II clinical trial to evaluate the clinical outcome in high-risk patients with SARS-CoV-2 infection by infusion of plasma from subjects after convalescence of SARS-CoV-2 infection and/or vaccination. High-risk was defined as SARS-CoV-2 positive infection with oxygen saturation at ≤ 94% at ambient air with additional risk features as categorized in 4 groups.

The duration of the trial for each patient was about 3 months, including two days of intervention (infusion of frozen convalescent and/or vaccinated plasma), followed by a

follow-up of 3 months. Patients randomized into the standard arm of the study had the possibility to cross over into the experimental arm of the study starting at day 10 (+ 2 days) in case of not improving or worsening clinical condition.

Treatment response was assessed daily until day 28, thereafter weekly until day 56, and finally at day 84.

Number of patients (planned and analyzed):

Number of patients planned: 174

Number of patients analyzed: 134

Diagnosis and main criteria for inclusion:

1. PCR confirmed SARS-CoV-2 infection in a respiratory tract sample.
2. Oxygen saturation (SaO_2) of 94% or less while breathing ambient air or a ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) of less than 300 mm Hg.
3. High risk due to either

   pre-existing or concurrent hematological malignancy and/or active cancer therapy incl. chemotherapy, radiotherapy, surgery) within the last 24 months or less. (*group 1*)

and/or

chronic immunosuppression not meeting the criteria of group 1 (*group 2*)

and/or

Age ≥ 50 - 75 years meeting neither the criteria of group 1 nor group 2 (*group 3*) and at least one of these criteria: Lymphopenia < 0.8 x G/l and/or D-dimer > 1µg/mL

and/or

Age ≥ 75 years meeting neither the criteria of group 1 nor group 2 (*group 4*)

4. Blood hemoglobin concentration ≥ 8g/dl.

Investigational product, dose and mode of administration, batch number:

IMP: RECOVER CT SARS-CoV-2-ab Plasma COVID-19 (HD) obtained from subjects following recovery of a SARS-CoV-2 infection or after vaccination

Dose: 270 (238-337) ml suspension/bag

Composition of the drug product in 1ml suspension:

Component	Function	Amount
Plasma	antibodies in plasma	0.85 - 0.89 ml
Sodium citrate	stabilizer solution	0.11 - 0.15 ml
Maximum cellular contamination	part of the plasma	< 0,1 x 10^9 leucocytes / l < 6,0 x 10^9 erythrocytes / l < 50 x 10^9 platelets / l

Route of administration: intravenous (i.v.)

Reference therapy, dose and mode of administration, batch number:

Standard of care

Duration of treatment:

Two consecutive intravenous administration of human plasma containing SARS-CoV-2 abs (Day 1 + Day 2)

Criteria for evaluation:

Efficacy:

The *primary efficacy endpoint* was the time from randomization until an improvement within 84 days defined as two points on a seven point ordinal scale or live discharge from the hospital.

The *secondary efficacy endpoints* were defined as:

- Overall survival, defined as the time from randomization until death from any cause 28-day, 56-day and 84-day overall survival rates
- SARS-CoV-2 viral clearance and load as well as antibody titres.
- Requirement of mechanical ventilation at any time during hospital stay (yes/no)
- Time until discharge from randomization.
- Viral load, changes in antibody titers and cytokine profiles

Safety:

Safety endpoints included all AEs, their severity, SAEs, the relation of AEs to the study treatment, dose modifications for toxicity and discontinuation of study treatment during the trial phase (grading according to CTCAE V5.0).

Statistical methods:

The ***primary analysis*** assessed the null hypothesis 'the cumulative improvement curves for the primary endpoint in the experimental and control arm are equal', i.e. H0: SE = SC against the alternative hypothesis H1: SE ≠ SC at a two-sided significance level of a=5%. This was achieved by using the log-rank test stratified for the factor “patient group” as used in the randomization procedure. The event 'death from any cause' was handled by censoring those patients at day 84 (in analogy to the approach of Cao et al, NEJM 2020). Using this approach ensures that deceased patients are considered as 'not improved' over the whole observation period of 84 days.

The primary analysis was based on the full analysis set (FAS). The main estimate for the hazard ratio for treatment group was computed using a Cox regression model stratifying for the factor “patient group” together with a 95% profile-likelihood confidence interval. The cumulative improvement curves were calculated using the Kaplan-Meier method together with 95% log-log-type confidence bands, and were calculated separately for both treatment groups. In addition, cumulative improvement curves were also calculated separately for each patient group per treatment group, and descriptive log-rank tests were done to compare the cumulative improvement groups for each patient group. Patients who dropped out during the trial or were lost to follow-up were taken into account as censored observations.

Overall survival was assessed by means of a log-rank test and Cox regression, both stratified for each patient group.

Time to discharge was assessed analogously to the primary endpoint.

Requirement of mechanical ventilation (yes versus no) was analyzed by means of a logistic regression model adjusting for the factors treatment and patient group, including all patients with more than 1 day of follow-up. Patients who died were accounted for as having received mechanical ventilation.

For ***neutralizing antibodies***, the difference between baseline and the highest value on day 3/5 was assessed to compare the plasma versus control arm titers stratified by patient group (1–4), and a van Elteren test was performed.

The ***assessment of safety*** was based mainly on the frequency of adverse events and on the laboratory values. Safety analysis was based on the safety population. Adverse events were summarized by presenting the number and percentage of patients having any adverse events or serious adverse events, and having each individual adverse event, and by determining and summarizing the maximum individual toxicity grade (over all forms of toxicity). Furthermore, the most common AEs (those occurring in at least 10% of the treatment group) were determined. Event rates were summarized along with two-sided Clopper-Pearson 95% confidence intervals and analyzed by (descriptive) chi-squared tests. Any other information collected (e.g. severity or relatedness to study drug) were summarized using descriptive methods.

For the ***cytokine levels***, the ratio between the values at day 3/day 5 (whichever was available) and day 1 was calculated. These ratios were analyzed descriptively.

All ***exploratory endpoints*** were analyzed descriptively.

Descriptive analysis for continuous variables comprises the calculation of: number of observations, mean, standard deviation, median, Q1, Q3, minimum and maximum. For categorical variables, absolute and relative frequencies are given with missing values being reported as a separate category. Percentages for categorical variables are based on all non-missing values in the respective groups.

The descriptive methods described above were used separately for each treatment group. For endpoints that were assessed at multiple time points, each time point wasanalyzed separately.

Statistical analyses were performed using the software packages SAS version 9.4, R Base (version 4.0; https://r-project.org) and GraphPad Prism version 9.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

In this clinical trial hospitalized patients with severe COVID-19 ($n = 134$) within four risk groups ((1) cancer ($n = 56$); (2) immunosuppression ($n = 16$); (3) laboratory-based risk factors ($n = 36$); and (4) advanced age ($n = 26$)) were either randomized to standard of care (control arm) or standard of care plus convalescent/vaccinated anti-SARS-CoV-2 plasma (plasma arm). Clinical improvement as the primary outcome was assessed using a seven-point ordinal scale (7POS). Secondary outcomes were time to discharge and overall survival.

Results of the analysis of the primary endpoint:

In the full analysis set, the median time from randomization to **improvement of two points on the 7POS or live hospital discharge** was 12.5 d (95% confidence interval (CI) = 10–17) in the plasma arm and 18 d (95% CI = 11–28) in the control arm (hazard ratio (HR) = 1.29;

95% CI = 0.86–1.93; log-rank *P* = 0.205). This result shows that for the four groups combined, those receiving plasma did not improve clinically compared with those in the control arm.

However, pre-specified subgroup analyses revealed benefit in patients with cancer (group 1; *n* = 56). For these patients, the median time to improvement was 13 d (95% CI = 7–14) for the plasma arm and 31 d (95% CI = 15–not available (NA)) for the control arm (HR = 2.50; 95% CI = 1.34–4.79; log-rank *P* = 0.003). Given potential confounders in age and gender distributions between the plasma and control arms, we adjusted for these variables in a sensitivity analysis. This resulted in a similar HR in group 1 (HR = 2.79; 95% CI = 1.35–5.94), supporting the beneficial role of plasma for patients with cancer.

Results of the secondary endpoint analyses:

Overall, *n* = 27 patients died and no significant difference was seen for **overall survival** according to randomization (HR = 0.72; 95% CI = 0.33–1.55; log-rank *P* = 0.403). In the cancer group (group 1), improved overall survival was observed in the plasma arm compared with the control arm (HR = 0.28; 95% CI = 0.06–0.96; log-rank *P* = 0.042). The treatment arms of groups 2–4 did not differ in survival.

The **time to discharge** did not differ (HR = 1.28; 95% CI = 0.86–1.91; log-rank *P* = 0.217) in the overall study population (12.5 d (95% CI = 10–17) for the plasma arm versus 18 d (95% CI = 11–28) for the control arm). Discharge occurred earlier in group 1 for the plasma arm (median = 13 d; 95% CI = 8–14) versus the control arm (median = 31 d; 95% CI = 15–NA) (HR = 2.50; 95% CI = 1.34–4.78; log-rank *P* = 0.003).

Mechanical ventilation was applied in 28.5% of patients. No significant difference was observed between the treatment groups (27.9% (95% CI = 18.7–39.6) for the plasma arm versus 29% (95% CI = 19.2–41.3) for the control arm; odds ratio (OR) = 0.95 (95% CI = 0.44–2.06); *P* = 0.892) or within the subgroups. The outcome for patients who crossed over was not substantially different from that for other patients in the control arm.

At the time of randomization, the average percentage inhibition of SARS-CoV-2 virus measured with the surrogate neutralizing enzyme-linked immunosorbent assay was 9.3% (IQR = 4.8–26.2; 10.2% (IQR = 5.5–28.8) for the plasma arm versus 8.5% (IQR = 4.0–20.3) for the control arm). **Neutralizing activity** increased over time in both arms. The highest levels at day 3/5 were overall higher in the plasma cohort (51.1% (IQR = 14.7–92.5) for the plasma cohort compared with 21.6% (IQR = 7.2–87.3) for the control cohort). In patients with cancer, the neutralizing activity did not increase over time in the absence of plasma therapy. In contrast, plasma therapy increased the neutralizing activity in patients with cancer who had higher levels on day 3/5 (group 1; 30.9% (IQR = 15.4–98.0) for the plasma arm compared with 8.8% (IQR = 3.5–46.3) for the control arm. Accordingly, for group 1, the median difference from day 3/5 to baseline differed significantly in the plasma arm (9.1% (IQR = 3.8–24.9)) compared with the control arm (1.6% (IQR = −1.5–4.7) (*P* = 0.001). In groups 3 and 4, neutralizing antibodies were already present at the time of study inclusion and titers further increased over time regardless of the therapy arm. Thus, there was no benefit in neutralizing antibody titers for group 3 and 4 patients treated with plasma. Of note, in the few patients included in group 2 (immunosuppression), titers of neutralizing antibodies were low at the time of inclusion and remained low regardless of therapy arm.

Cytokine profiles were measured for a total of 81 patients (42 patients in the plasma arm and 39 patients in the control arm). Thereby the ratio between the values at day 3/day 5 (whichever was available) and day 1 was calculated. The evaluation of these data is ongoing.

SAFETY RESULTS:

Adverse events observed after plasma administration were in accordance with published data. No serious adverse events were observed related to plasma therapy.

Summary of Adverse events

	Experimental intervention[#]	Control intervention	Total
Intensity CTCAE V5* grade			
- Grade 1 - mild	118	94	212
- Grade 2 - moderate	135	151	286
- Grade 3 - severe	51	39	90
- Grade 4 - life-threatening	23	8	31
- Grade 5 - death	16	14	30
Maximal Intensity Grade for individual patients			
- no AEs experienced	19 (24.4%)	9 (16.1%)	28 (20.9%)
- Grade 1 - mild	7 (9.0%)	6 (10.7%)	13 (9.7%)
- Grade 2 - moderate	21 (26.9%)	18 (32.1%)	39 (29.1%)
- Grade 3 - severe	11 (14.1%)	10 (17.9%)	21 (15.7%)
- Grade 4 - life-threatening	5 (6.4%)	4 (7.1%)	9 (6.7%)
- Grade 5 – death	15 (19.2%)	9 (16.1%)	24 (17.9%)
Relation to IMP			
- Related	9	1	10
- Unrelated	334	305	639

* according to the common Terminology Criteria for Adverse Events (CTCAE vs5)
# classification according to actual treatment (experimental includes cross-over patients)
AE=adverse events; IMP=Investigational Medicinal Product

Transfusion Reactions

	Experimental intervention N=78 (incl. Cross-Over)
Transfusion reaction	
- No	74 (94.9%)
- Transfusion associated circulatory overload (TACO)	1 (1.3%)
- Allergic reaction	2 (2.6%)
- Other	1 (1.3%)
Discontinuation of plasma infusion	
- No	75 (96.2%)
- Yes	3 (3.8%)

CONCLUSION:

The results of this trial provide evidence that patients with cancer (group 1) who develop severe COVID-19 benefit from anti-SARS-CoV-2 plasma from convalescent/vaccinated donors and experience improved overall recovery. Although the size of group 1 was relatively small, with 56 patients, differences in the primary endpoint were substantial (median time-to-event 13 versus 31 days) and are supported by earlier discharge and improved overall survival. The likelihood of improved outcomes upon plasma therapy was substantial for patients with cancer, with shortened time to the primary endpoint, time to discharge and also survival. In contrast, no benefits were observed in groups 2–4, pointing toward a specific benefit of vaccinated/convalescent plasma in patients with cancer.

Furthermore, the results of the clinical trial shows that in patients with cancer an increase in neutralizing antibodies was observed after plasma infusion, which further supports the restriction of the beneficial effects of plasma to patients with limited ability to react to the antigen with a humoral response. While the subgroup analysis was exploratory, the effect sizes were substantial. Given the limited available effective treatment options for patients with cancer and the favorable safety profile, convalescent/vaccinated plasma should be considered.

Potential limitations of the study:

Compared with studies with nonselected patients, the overall cohort was relatively small. Also, while the overall cohort was well balanced, we observed imbalances between enrollment arms (for example, with respect to age, sex, comorbidities and therapy) in the subgroups. Therefore, we adjusted for the two variables (that is, age and sex) most likely to be associated with outcomes in a sensitivity analysis, which did not impact on the primary outcome in group 1. Another limitation could be the open-label design of our trial. However, the primary endpoint results for subgroups are supported by the secondary endpoint results for overall survival and neutralizing activity, showing the unique effectivity of plasma therapy in patients with cancer.

The group of patients with cancer was diverse, with most patients suffering from hematological malignancies. Thus, the conclusions might not be applicable to all types of cancer. Lastly, recruitment occurred over an extended time span with different virus variants and evolving standards of care. Nonetheless, randomization was in place and plasma was obtained during the respective waves of the pandemic. Our conclusions cannot formally be extended to novel variants not covered within the trial (starting with Omicron).

Strength of the study:

Plasma was obtained from donors with confirmed high titers of neutralizing antibodies, as indicated by the fact that <20% of patients in the donor pool met the criteria (≥1:80 titer and corresponding high saturation in the NeutraLISA). The relevant subgroups were predefined in the protocol. HRs and CIs indicated large effect sizes in group 1. Plasma therapy effects on neutralizing antibody levels matched clinical benefit, although causality cannot be proven. The inclusion of patient groups now known not to benefit from plasma (for example, groups 3 and 4) suggests that underlying disease characteristics determine the benefit of plasma therapy in patients with cancer.

Taken together, these data suggest that plasma therapy may improve outcomes in patients with cancer with severe COVID-19.

Substantial amendments / interruptions or early termination:

Substantial amendments:

IEC Independent Ethics Committee(s)

Amendment No.	Content	Approval Date
01	Protocol Version 1.1	04th May 2020
02	Protocol Version 1.2	20th July 2020
03	Protocol Version 2.0	10th Nov 2020
04	Change Deputy PI Darmstadt	7th Dec 2020
	Additional Site Chemnitz	9th Dec 2020
05	Additional Sites Hochsauerland, Frankfurt (Oder), Leverkusen	26th Jan 2021
06	Protocol Version 3.0	30st Mar 2021
07	Change PI Münster	24th Sep 2021
	Change Deputy PI Leverkusen	28th Sep 2021

Paul-Ehrlich-Institut (PEI)

Amendment No.	Content	Approval Date
01	Protocol Version 1.2	14th July 2020
02	Protocol Version 2.0	9th Nov 2020
03	Protocol Version 3.0	22nd Mar 2021

Early Termination of the Study:

After treatment of 134 patients, recruitment was stopped on 20th Jan 2022 as it could not be ensured at that time point that the collected plasma contains antibodies against the new omicron variant of the SARS-CoV-2 virus.

Last patient last visit was on 5th April 2022.

Date of the report:

30st March 2023

Appendices

Appendix 1: List of Study centers

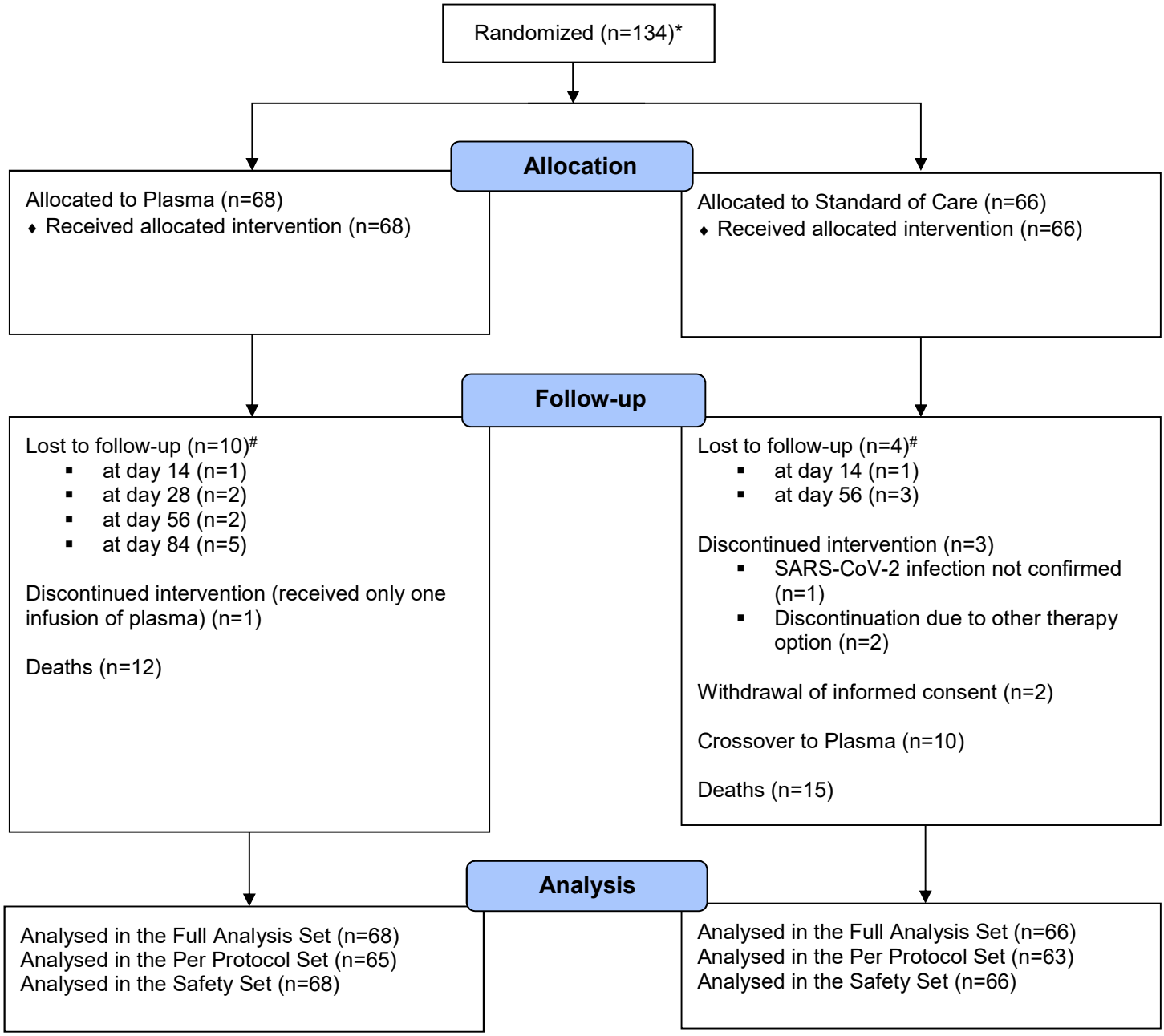
Appendix 2: CONSORT Flow Diagram

Appendix 1: List of study centers and Principle Investigators

No.	Name of Principle Investigator	Study center
001	Prof. Dr. med. Carsten Müller-Tidow	Universitätsklinikum Heidelberg Zentrum für Innere Medizin V Hämatologie, Onkologie, Rheumatologie Im Neuenheimer Feld 410 69120 Heidelberg
002	Prof. Dr. med. Lars Bullinger	Charité Universitätsmedizin Berlin Medizinischen Klinik m. S. Hämatologie, Onkologie und Tumorimmunologie Augustenburger Platz 1 13353 Berlin
003	Dr. med. Nael Alakel	Universitätsklinikum Dresden Medizinische Klinik und Poliklinik I Fetscherstraße 74 01307 Dresden
004	Prof. Dr. med. Oliver Witzke	Universitätsklinikum Essen Klinik für Infektiologie Hufelandstr. 55 45147 Essen
005	PD Dr. med. Timo Wolf	Universitätsklinikum Frankfurt/Main Medizinische Klinik II, Schwerpunkt Infektiologie Theodor-Stern-Kai 7 60590 Frankfurt/Main
006	Dr. med. Stefan Schmiedel	Universitätsklinikum Hamburg-Eppendorf Medizinische Klinik und Poliklinik (Gastroenterologie mit Sektionen Infektiologie und Tropenmedizin) Martinistraße 52 20246 Hamburg
007	Prof. Dr. med. Felix Herth	Thoraxklinik-Heidelberg gGmbH Studienzentrum Pneumologie Röntgenstraße 1 69126 Heidelberg
008	Prof. Dr. med. Carl Schimanski	Klinikum Darmstadt GmbH Medizinische Klinik II Grafenstraße 9 64283 Darmstadt
009	Prof. Dr. med. Winfried Kern	Universitätsklinikum Freiburg Allgemeine Infektion-Ambulanz Klinik für Innere Medizin II Hugstetter Straße 55 79106 Freiburg

No.	Name of Principle Investigator	Study center
010	Dr. med. Phil-Robin Tepasse (former PI: Prof. Dr. med. Hartmut Schmidt)	Universitätsklinikum Münster Medizinische Klinik B (Gastroenterologie, Hepatologie, Endokrinologie, Klinische Infektiologie) Albert-Schweitzer-Campus 1 48149 Münster
012	Prof. Dr. med. B. Hertenstein	Klinikum Bremen-Mitte Klinik für Innere Medizin I St.-Jürgen-Str. 1 28205 Bremen
019	Dr. med. Matthias Ruhe	Klinikum Herford Medizinischen Klinik I Schwarzenmoorstr. 70 32049 Herford
021	Prof. Dr. Mathias Hänel	Klinikum Chemnitz gGmbH Medizinische Klinik III Flemmingstr. 2 09116 Chemnitz
022	Dr. med. Olaf Hopfer	Klinikum Frankfurt/Oder GmbH Medizinische Klinik I Müllroser Chaussee 7 15236 Frankfurt (Oder)
023	Dr. med. Mohammad-Amen Wattad	Klinikum Hochsauerland GmbH Klinik für Innere Medizin und Klinik für Hämatologie, Onkologie, Palliativmedizin und Stammzelltransplantation Schederweg 12 59872 Meschede
024	Prof. Dr. Utz Krug	Klinikum Leverkusen gGmbH Medizinische Klinik 3 Am Gesundheitspark 11 51375 Leverkusen

Appendix 2: CONSORT Flow Diagram



*Two more patients were initially randomized but were later deleted from the online randomization tool and the database. For one patient the informed consent form was lost and one patient withdrew consent and requested the deletion of all data.

#All patients lost to follow-up reached the primary endpoint, as lost-to-follow-up occurred after discharge.