Biostatistical report

A prospective, randomized, open-label Phase 2 clinical trial to evaluate superiority of anti-SARS-CoV-2 convalescent plasma versus standard-of-care in hospitalized patients with mild COVID-19

Prospective, randomized, open-label, multicenter Phase 2 clinical trial

Intervention: SOC anti-SARS-CoV-2 convalescent plasma
Control: SOC alone
Indication: hospitalized patients with mild COVID-19 infection

COMET
[EudraCT-No.: 2020-001936-86]

Study initiation date (first patient enrolled): 14.01.2021
Study completion date (last patient completed): 22.09.21

Protocol identification:
Development phase of study: II

Sponsor of the Clinical Trial:

Hannover Medical School
Carl-Neuberg-Straße 1
30625 Hannover, Germany

Study Chair:

Prof. Dr. med. Rainer Blasczyk
Hannover Medical School
Institute of Transfusion Medicine and Transplant Engineering

This study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents

Version / Date: [1.0 / 14.09.2022]

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Anti-SARS-CoV-2 convalescent plasma - Gefrorenes Apherese-COVID-19-RKP Leukozy-tendepletiert	Volume:	
Name of Active Ingredient: Anti-SARS-CoV-2 antibodies	Page:	

Title of study:

A prospective, randomized, open-label Phase 2 clinical trial to evaluate superiority of anti-SARS-CoV-2 convalescent plasma versus standard-of-care in hospitalized patients with mild COVID-19

EudraCT no.: 2020-001936-86

Protocol code no.: COMET

Information about study protocol version(s):

First submission:

Version 1.2 of 30.09.2020

Subsequent amendments:

1.3 – 02.12.2020

Investigator(s) and study centre(s): Name(s) and address(es):

Study center	**Principal Investigator**
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Publication (reference):
A publication of the study results is in preparation.

Studied period: 01/2021 – 11/2021 date of first enrolment: 14.01.2021 date of last completed: 22.09.21 **Information about temporary halt(s) and premature termination of the trial:** The study was terminated prematurely on 15.11.2021	**Phase of development:** Phase II

Objectives:

Primary objective:

To assess the efficacy of convalescent plasma for the treatment of hospitalized patients with mild COVID-19 infection

Secondary objective:

To evaluate the safety and tolerability of experimental regimen

Methodology:

This was a prospective, randomized, open-label, multicenter Phase 2 clinical trial to evaluate superiority of SARS-CoV-2 convalescent plasma on top of standard-of-care (SOC) versus SOC in hospitalized patients with mild COVID-19.

Number of patients (planned and analysed):

Planned:

Sample size was 170 patients per group; total sample size was 340 patients including a dropout rate of 5%

- To be allocated to trial: n = 340
- To be analyzed in trial: n = 340

Analysed:

- ITT/Safety: n=15
- Per Protocol: n= 14

Diagnosis and main criteria for inclusion:

Diagnosis:

Hospitalized patients with mild SARS-CoV-2 infection (WHO R&D Blueprint Ordinal Scale for Clinical Improvement = 3 and 4) were included in the clinical trial.

Inclusion criteria:

Patients infected with SARS-CoV-2 virus and

1. age ≥ 18 years and ≤ 75 years
2. fulfills RKI case definition including a positive verification of a SARS-CoV-2 infection from any specimen (e.g. respiratory, blood, other bodily fluid)*

   * confirmed by PCR (BAL, sputum, nasal and/or pharyngeal swap)
3. mild disease defined by the following criteria:
   - Hospitalized (score 3 or 4 of WHO R&D Blueprint ordinal scale for clinical improvement)
4. signed written informed consent and willingness to comply with treatment and followup procedures
5. ► men;

or

► women without childbearing potential defined as follows:

- at least 6 weeks after surgical sterilization by bilateral tubal ligation or bilateral oophorectomy,
- hysterectomy or uterine agenesis,
- ≥ 50 years and in postmenopausal state > 1 year, or
- < 50 years and in postmenopausal state > 1 year with serum FSH > 40 IU/l and serum estrogen < 30 ng/l or a negative estrogen test, both at screening;

or

► women with childbearing potential:

- who are practicing true abstinence from sexual intercourse (periodic abstinence and withdrawal are not acceptable),
- who have sexual relationship with female partners only and/or with sterile male partners, or
- who are sexually active with fertile male partner, have a negative pregnancy test during screening and agree to use reliable methods of contraception** from the time of screening until end of the clinical trial.

**The following methods of contraception are acceptable: combined oral contraceptives, oral progestogen-only hormonal contraceptives associated with inhibition of ovulation, implants of progestogen-only hormonal contraception associated with inhibition of ovulation, injectable progestogen-only hormonal contraception associated with inhibition of ovulation, transdermal patches, hormonal vaginal devices, and intrauterine devices/intrauterine hormone-releasing systems (IUD/IUS) with a failure rate of < 1% per year.

Exclusion criteria:

1. Accompanying diseases other than COVID-19 with an expected survival time of less than 12 months
2. In the opinion of the clinical team, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatment
3. Chronic obstructive lung disease (COPD), stage 4
4. Lung fibrosis with UIP pattern in CT and severe emphysema
5. Chronic heart failure NYHA >= 3 and/or pre-existing reduction of left ventricular ejection fraction to ≤ 30%
6. Liver cirrhosis Child C
7. Liver failure: Bilirubin > 5xULN and elevation of ALT /AST (at least one >10xULN).

8. End-stage renal failure requiring hemodialysis
9. Organ or bone marrow transplant in the three months prior to screening
10. History of adverse reactions to plasma proteins
11. Known deficiency of immunoglobulin A
12. Pregnancy and breastfeeding women
13. Volume overload until sufficiently treated
14. Pulmonary edema
15. Body mass index (BMI) > 40 kg/m2
16. Participation in another clinical trial, especially for treatment of COVID-19
17. Allergy or other contraindication to one of the investigational products
18. Previous treatment with SARS-CoV-2 convalescent plasma

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

Test product:

Anti-SARS-CoV-2 convalescent plasma (Gefrorenes Apherese-COVID-19-RKP Leukozytendepletiert)

Mode of administration:

Intravenous use (iv)

Batch number:

Batch number
2057706
205772
2057103-2
2057706-2
2054701
2057761-2
2054702
2056964-2
2056928-2
2054702-2
2055905-2
2054701-2
2055214-3
2054798-2

Duration of treatment:

Convalescent plasma was given iv twice at a dose of 1 plasma unit (230 ml – 270 ml) on day 1 and day 2.

Reference therapy, dose and mode of administration, batch number

n/a

Criteria for evaluation:

Efficacy:

Primary efficacy endpoint:
Proportion of patients with treatment failure on day 14. A treatment failure was defined as progression of COVID-19 disease. Progression was defined as a score 5, 6, 7 or 8 of WHO R&D Blueprint ordinal scale for clinical improvement.

Key secondary endpoints:

- Failure rates on day 7, day 21, day 28
- Time to clinical improvement (defined as time from randomization to an improvement of two points on the WHO R&D Blueprint ordinal scale for clinical improvement)
- Adverse events
- All-cause mortality (ACM) on day 7, day 14, day 21, day 28, 4 months

Assessment of safety:
All (serious) adverse events (AEs/SAEs) were collected during the study for the whole study population.

Safety:

The AE documentation period for this trial began with transfusion of the IMP and ended with the last study visit (at day 120). AEs that were still ongoing at the last visit should be followed up until a definite outcome was established. Documentation of adverse events had to be performed in a timely manner on the respective AE forms in the eCRF.

The same documentation responsibilities as described for AEs apply to SAEs. In addition, SAEs had to be documented on the respective SAE paper form and immediately reported to the Sponsor`s delegate for Pharmacovigilance. Documentation of SAEs had to be as complete and detailed as possible. In case of death, an autopsy should be aimed for and the results should be forwarded to the Sponsor`s delegate for Pharmacovigilance.

Statistical methods:

Patient population for primary and key secondary analysis:

The primary and key secondary analyses were conducted according to the intention-to-treat-principle (ITT). All randomized patients were analyzed in the group they were randomized to. Missing values were replaced conservatively (see the respective endpoint for details). Sensitivity analyses were conducted on the per-protocol population (PP). The PP-population was defined as those patients that received the treatment as randomized and defined in this protocol. Patients with early treatment discontinuation were excluded for the PP-analysis and missing values were not replaced.

Analysis of the primary endpoint
It was assumed that SOC and convalescent plasma reduce the number of treatment failures as compared to SOC alone. Hospitalized patients with mild COVID-19 infection (WHO scale 3 or 4) were included in this study. Patients were defined as failures if their COVID-19 infection progressed to WHO categories 5, 6, 7 or 8. The primary endpoint was assessed on day 14.

Logistic regression was used to demonstrate that treatment with SOC and convalescent plasma reduced the risk for treatment failure as compared to SOC alone. The type-1-error was set to 5% (two-sided). Missing values were counted as failures. Patients were randomized centrally to the two treatment groups and randomization were stratified by center and WHO scale. The analysis was adjusted for treatment, WHO scale

and center. Superiority of treatment with convalescent plasma was concluded if the upper boundary of the 95%-CI was below one for the odds-ratio for treatment divided by SOC failure rates.

Analysis of key secondary endpoints:

- Failure rates at different time points were analyzed in line with the primary analysis.
- Time to improvement were analyzed with Cox regression, where improvement by two categories was served as the dependent variable, treatment group, center and WHO scale as independent variables. Hazard ratios were displayed along with their 95%-CI. Kaplan-Meier curves were descriptively displayed. The ITT population was used and missing values were replaced as no improvement.
- All-cause mortality was analyzed in line with the primary analysis. The ITT population was used and missing values were replaced as dead.

Safety analysis:

All AEs/SAEs were reported with absolute and relative frequencies for all randomized patients.

Major changes in the conduct of the study and planned analyses:

Substantial Amendment:

One substantial amendments (SA) was made to the original study protocol (Version 1.0, 01.07.2020).

SA No.1.0 (resulting in protocol version 1.3 of 02.12.2020) covered the following changes:

- IMP volume specification
- Correction exclusion criteria 15. BMI
- Adjustment of the neutralizing anti-SARS-CoV-2 antibody titre
- Transfusion period of the IMP

Early Study Termination

The sponsor and the coordinating investigator of the study have terminated the study prematurely on 15.11.2021 because of a low recruitment rate and difficulties to achieve the planned numbers of study participants within a reasonable period. For the primary analysis a logistic regression using only therapy as an independent variable is used instead of the planned multivariate logistic regression. Additionally sensitivity and secondary analyses were not conducted.

1 Recruitment Overview / Study Population

Patients were screened in 5 study centers in Germany. Overall, 17 patients were screened for eligibility and signed the informed consent. 3 patients were screening failures (see Table 1).

One patient (01-003) was screening failure due to meeting exclusion criteria 5 (Chronic heart failure NYHA >= 3) but was still randomized although the patients did not receive any IMP. Therefore, the analysed ITT population consists of 15 patients.

According to the study protocol the primary analysis set for efficacy should be defined as Intention-To-Treat (ITT) population. All randomized patients will be analyzed in the group they were randomized to.

The Per Protocol (PP) population is defined as those patients that received the treatment as randomized and defined in this protocol. Patients with early treatment discontinuation will be excluded for the PP analysis. Patient 01-003 was identified as a screening failure after randomization but did not receive any IMP. Therefore this patient was excluded from the PP population, accordingly the PP population consists of 14 patients. Due to early study termination no per protocol analyses were conducted.

Table 1. Screening information of all patients. * Patient 01-003 was randomized but later identified as meeting the exclusion criteria 5.

		Screening					
Patient	**Therapy**	**Date of informed consent**	**Date of randomisation**	**Screening failure?**	**Reason for screening failure**	**ITT**	**PP**
01-001	Plasma	14/01/2021	14/01/2021	no		yes	yes
01-002	Control	21/01/2021	22/01/2021	no		yes	yes
01-003	Plasma	04/02/2021	04/02/2021	Yes *	NHYA ≥ 3 *	yes	no
01-004	Control	25/02/2021	25/02/2021	no		yes	yes
01-005	Control	19/03/2021	19/03/2021	no		yes	yes
01-006	Plasma	06/04/2021	07/04/2021	no		yes	yes
01-007	Control	23/04/2021	23/04/2021	no		yes	yes
02-001	Plasma	26/04/2021	26/04/2021	no		yes	yes
02-002	Plasma	27/05/2021	27/05/2021	no		yes	yes
04-001	Control	07/04/2021	08/04/2021	no		yes	yes
04-002	Control	13/04/2021	14/04/2021	no		yes	yes
05-001	Plasma	22/04/2021	22/04/2021	no		yes	yes
05-002	Plasma	04/05/2021	04/05/2021	no		yes	yes

		Screening					
Patient	**Therapy**	**Date of informed consent**	**Date of randomisation**	**Screening failure?**	**Reason for screening failure**	**ITT**	**PP**
07-001	Control	02/06/2021	02/06/2021	no		yes	yes
07-002	Plasma	21/06/2021	22/06/2021	no		yes	yes
07-003		27/09/2021	.	yes	Worsening of WHO Score, ICU treatment necessary	no	no
07-004		28/09/2021	.	yes	Lungemphysema	no	no

Table 2. Recruitment overview by center.

Center-ID	**Center Name**	**Total (N = 15)**
01	MHH, Hannover	7 (46.67%)
02	Krefeld	2 (13.33%)
04	Essen	2 (13.33%)
05	Dortmund Klinikum	2 (13.33%)
07	Siloah	2 (13.33%)

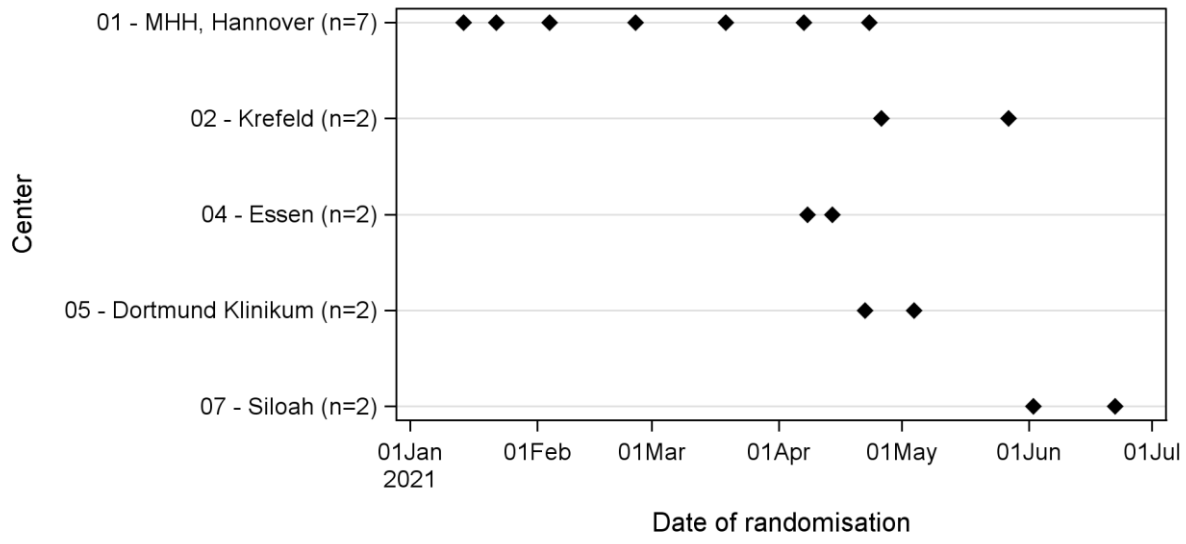

Figure 1. Overview of recruitment of patients over the study centres by date of randomisation.

1.1 Visit Overview

Table 3. Overview for visit completion.

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
Screening			
Visit carried out	7 (100.0%)	8 (100.0%)	15 (100.0%)
Treatment (Day 1)			
Study terminated before visit	0 (0.0%)	1 (12.5%)	1 (6.7%)
Visit carried out	7 (100.0%)	7 (87.5%)	14 (93.3%)
p-VALUE (CHI^2)			0.3329
Treatment (Day 2)			
Study terminated before visit	0 (0.0%)	1 (12.5%)	1 (6.7%)
Visit carried out	7 (100.0%)	7 (87.5%)	14 (93.3%)
p-VALUE (CHI^2)			0.3329
Follow Up (Day 3)			
Study terminated before visit	0 (0.0%)	1 (12.5%)	1 (6.7%)
Visit carried out	7 (100.0%)	7 (87.5%)	14 (93.3%)
p-VALUE (CHI^2)			0.3329
Follow Up (Day 4)			
Study terminated before visit	0 (0.0%)	1 (12.5%)	1 (6.7%)
Visit carried out	7 (100.0%)	7 (87.5%)	14 (93.3%)
p-VALUE (CHI^2)			0.3329
Follow Up (Day 5)			
Study terminated before visit	0 (0.0%)	1 (12.5%)	1 (6.7%)
Visit carried out	7 (100.0%)	7 (87.5%)	14 (93.3%)
p-VALUE (CHI^2)			0.3329

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
Follow Up (Day 6)			
Study terminated before visit	0 (0.0%)	1 (12.5%)	1 (6.7%)
Visit carried out	7 (100.0%)	7 (87.5%)	14 (93.3%)
p-VALUE (CHI^2)			0.3329
Follow Up (Day 7)			
Study terminated before visit	0 (0.0%)	1 (12.5%)	1 (6.7%)
Visit missing	0 (0.0%)	2 (25.0%)	2 (13.3%)
Visit carried out	7 (100.0%)	5 (62.5%)	12 (80.0%)
p-VALUE (CHI^2)			0.1939
Follow Up (Day 8)			
Study terminated before visit	0 (0.0%)	1 (12.5%)	1 (6.7%)
Visit carried out	6 (85.7%)	5 (62.5%)	11 (73.3%)
Visit not carried out (discharged from hospital)	1 (14.3%)	2 (25.0%)	3 (20.0%)
p-VALUE (CHI^2)			0.5057
Follow Up (Day 9)			
Study terminated before visit	0 (0.0%)	1 (12.5%)	1 (6.7%)
Visit carried out	6 (85.7%)	5 (62.5%)	11 (73.3%)
Visit not carried out (discharged from hospital)	1 (14.3%)	2 (25.0%)	3 (20.0%)
p-VALUE (CHI^2)			0.5057
Follow Up (Day 10)			
Study terminated before visit	0 (0.0%)	1 (12.5%)	1 (6.7%)
Visit carried out	6 (85.7%)	5 (62.5%)	11 (73.3%)
Visit not carried out (discharged from hospital)	1 (14.3%)	2 (25.0%)	3 (20.0%)
p-VALUE (CHI^2)			0.5057
Follow Up (Day 11)			
Study terminated before visit	0 (0.0%)	1 (12.5%)	1 (6.7%)

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
Visit carried out	6 (85.7%)	4 (50.0%)	10 (66.7%)
Visit not carried out (discharged from hospital)	1 (14.3%)	3 (37.5%)	4 (26.7%)
p-VALUE (CHI^2)			0.3098
Follow Up (Day 12)			
Study terminated before visit	0 (0.0%)	1 (12.5%)	1 (6.7%)
Visit carried out	5 (71.4%)	3 (37.5%)	8 (53.3%)
Visit not carried out (discharged from hospital)	2 (28.6%)	4 (50.0%)	6 (40.0%)
p-VALUE (CHI^2)			0.3483
Follow Up (Day 13)			
Study terminated before visit	1 (14.3%)	1 (12.5%)	2 (13.3%)
Visit carried out	1 (14.3%)	3 (37.5%)	4 (26.7%)
Visit not carried out (discharged from hospital)	5 (71.4%)	4 (50.0%)	9 (60.0%)
p-VALUE (CHI^2)			0.5918
Follow Up (Day 14)			
Study terminated before visit	1 (14.3%)	1 (12.5%)	2 (13.3%)
Visit missing	1 (14.3%)	0 (0.0%)	1 (6.7%)
Visit carried out	5 (71.4%)	7 (87.5%)	12 (80.0%)
p-VALUE (CHI^2)			0.5293
Follow Up (Day 21)			
Study terminated before visit	2 (28.6%)	1 (12.5%)	3 (20.0%)
Visit missing	1 (14.3%)	1 (12.5%)	2 (13.3%)
Visit carried out	4 (57.1%)	6 (75.0%)	10 (66.7%)
p-VALUE (CHI^2)			0.7155
Follow Up (Day 28)			
Study terminated before visit	2 (28.6%)	1 (12.5%)	3 (20.0%)
Visit missing	2 (28.6%)	0 (0.0%)	2 (13.3%)
Visit carried out	3 (42.9%)	7 (87.5%)	10 (66.7%)

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
p-VALUE (CHI^2)			0.1434
Follow Up (Day 120)			
Study terminated before visit	4 (57.1%)	4 (50.0%)	8 (53.3%)
Visit missing	1 (14.3%)	0 (0.0%)	1 (6.7%)
Visit carried out	2 (28.6%)	4 (50.0%)	6 (40.0%)
p-VALUE (CHI^2)			0.4477

After discharge from the hospital, follow-up examinations are carried out at the study center on day 14, day 21, day 28 and day 120 after randomization. If the patients have left the hospital before day 3 and/or day 7, patients are asked to come to the study center for a visit on these two days as well.

A listing of all visit dates for all patients in given in Supplement Table 2 and Supplement Table 3.

1.2 End of Study

Table 4. Study completed according to study protocol?

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
Study completed according to study protocol?			
Completed	2 (28.6%)	4 (50.0%)	6 (40.0%)
Terminated prematurely	5 (71.4%)	4 (50.0%)	9 (60.0%)
p-VALUE (CHI^2)			0.3980

One patient had the “End of Study” date one day after the scheduled Follow-Up Day 120 visit. He was set to “End of Study” because the patient did not show up for the appointment. Therefore he was counted as “Visit missing” in Table 3 and “Study not completed” in Table 4.

Table 5. Reasons for discontinuation of the study participation.

	Therapy		
	Control N=5	**Plasma N=4**	**Total N=9**
Reason study participation was discontinued			
Death	1 (20.0%)	1 (25.0%)	2 (22.2%)
Consent withdrawal	1 (20.0%)	0 (0.0%)	1 (11.1%)
Other reason	3 (60.0%)	3 (75.0%)	6 (66.7%)
p-VALUE (CHI^2)			0.6376

Table 6. Other reasons for discontinuation of study participation.

	Therapy		
	Control N=3	**Plasma N=3**	**Total N=6**
Specifications of "Other reasons" why the study participation was discontinued			
Patient did not show for follow-up (Day 120)	0 (0.0%)	1 (33.3%)	1 (16.7%)
Patient did not show up for the appointment	1 (33.3%)	0 (0.0%)	1 (16.7%)
SCreen Failure, after Randomized	0 (0.0%)	1 (33.3%)	1 (16.7%)
The patient could not be contacted several times	0 (0.0%)	1 (33.3%)	1 (16.7%)
could not be reached several times	1 (33.3%)	0 (0.0%)	1 (16.7%)
lost to follow up	1 (33.3%)	0 (0.0%)	1 (16.7%)
p-VALUE (CHI^2)			0.3062

2 Baseline Data

Table 7. Demographic data and blood type.

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
Age			
MISSING	0	0	0
MEAN	62.86	55.13	58.73
STD	6.99	9.88	9.25
MIN	54	41	41
MEDIAN	63	58.50	62
MAX	74	67	74
p-VALUE (T-TEST)			0.1083
Gender			
male	5 (71.4%)	5 (62.5%)	10 (66.7%)
female	2 (28.6%)	3 (37.5%)	5 (33.3%)
p-VALUE (CHI^2)			0.7144
Ethnicity			
caucasian	7 (100.0%)	6 (75.0%)	13 (86.7%)
asian	0 (0.0%)	2 (25.0%)	2 (13.3%)
p-VALUE (CHI^2)			0.1553
Height			
MISSING	0	0	0
MEAN	174.71	168.88	171.60
STD	5.31	10.37	8.66
MIN	165	150	150
MEDIAN	176	174	176
MAX	180	178	180
p-VALUE (T-TEST)			0.2034

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
Weight			
MISSING	0	0	0
MEAN	90.43	79.75	84.73
STD	9.85	19.78	16.36
MIN	78	48	48
MEDIAN	90	79.50	83
MAX	104	110	110
p-VALUE (T-TEST)			0.2191
BMI			
MISSING	0	0	0
MEAN	29.67	27.64	28.59
STD	3.46	5.04	4.35
MIN	25.90	21.30	21.30
MEDIAN	28.70	25.80	27.80
MAX	36	36.80	36.80
p-VALUE (T-TEST)			0.3864
AB0 blood type			
A	3 (42.9%)	5 (62.5%)	8 (53.3%)
B	1 (14.3%)	0 (0.0%)	1 (6.7%)
0	3 (42.9%)	3 (37.5%)	6 (40.0%)
p-VALUE (CHI^2)			0.4868

Table 8. Vitals.

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
Body temperature			

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
MISSING	0	0	0
MEAN	36.40	37.34	36.90
STD	0.91	1.24	1.16
MIN	35.10	35.80	35.10
MEDIAN	36.60	36.85	36.80
MAX	37.60	39.10	39.10
p-VALUE (T-TEST)			0.1228
Systolic blood pressure			
MISSING	0	0	0
MEAN	122.71	128.38	125.73
STD	14.60	18.39	16.40
MIN	96	99	96
MEDIAN	126	132	128
MAX	138	159	159
p-VALUE (T-TEST)			0.5251
Diastolic blood pressure			
MISSING	0	0	0
MEAN	68.86	75.25	72.27
STD	9.72	11.85	11.03
MIN	55	52	52
MEDIAN	70	78	73
MAX	83	87	87
p-VALUE (T-TEST)			0.2785
Pulse			
MISSING	0	0	0
MEAN	74.29	81.38	78.07
STD	12.78	12.22	12.57
MIN	60	69	60

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
MEDIAN	71	79	79
MAX	94	108	108
p-VALUE (T-TEST)			0.2924

Table 9. COVID-19-related data.

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
COVID-19 test result			
positive	7 (100.0%)	8 (100.0%)	15 (100.0%)
Fever			
no	5 (71.4%)	5 (62.5%)	10 (66.7%)
yes	2 (28.6%)	3 (37.5%)	5 (33.3%)
p-VALUE (CHI^2)			0.7144
Cough			
no	2 (28.6%)	1 (12.5%)	3 (20.0%)
yes	5 (71.4%)	7 (87.5%)	12 (80.0%)
p-VALUE (CHI^2)			0.4376
Shortness of breath			
no	3 (42.9%)	2 (25.0%)	5 (33.3%)
yes	4 (57.1%)	6 (75.0%)	10 (66.7%)
p-VALUE (CHI^2)			0.4642
WHO R&D Blueprint Ordinal Scale			
3. Hospitalized mild disease (Hospitalized, no oxygen therapy)	4 (57.1%)	4 (50.0%)	8 (53.3%)

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
4. Hospitalized mild disease (Oxygen by mask or nasal prongs)	3 (42.9%)	4 (50.0%)	7 (46.7%)
p-VALUE (CHI^2)			0.7821

A listing of the whole WHO R&D Blueprint Ordinal Scale is given in Supplement Table 1.

Table 10. Chest imaging.

	Therapie		
	A N=7	**B N=8**	**Total N=15**
Chest X-ray performed?			
no	5 (71.4%)	7 (87.5%)	12 (80.0%)
yes	2 (28.6%)	1 (12.5%)	3 (20.0%)
p-VALUE (CHI^2)			0.4376
Category			
MISSING	5	7	12
normal	1 (50.0%)	0 (0.0%)	1 (33.3%)
abnormal	1 (50.0%)	1 (100.0%)	2 (66.7%)
p-VALUE (CHI^2)			0.3865
Extent			
MISSING	5	7	12
low-grade	1 (50.0%)	0 (0.0%)	1 (33.3%)
moderate	1 (50.0%)	1 (100.0%)	2 (66.7%)
p-VALUE (CHI^2)			0.3865
CT Scan performed?			
no	5 (71.4%)	4 (50.0%)	9 (60.0%)
yes	2 (28.6%)	4 (50.0%)	6 (40.0%)
p-VALUE (CHI^2)			0.3980

	Therapie		
	A N=7	**B N=8**	**Total N=15**
Category (DRG)			
MISSING	5	6	11
1	2 (100.0%)	2 (100.0%)	4 (100.0%)
Extent			
MISSING	5	4	9
low-grade	1 (50.0%)	1 (25.0%)	2 (33.3%)
moderate	1 (50.0%)	3 (75.0%)	4 (66.7%)
p-VALUE (CHI^2)			0.5403

Table 11. Oxygenation level / Respiratory rate.

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
Oxygenation level (PaO2/FiO2)			
MISSING	0	1	1
MEAN	150.06	298.37	224.21
STD	69.47	153.37	137.86
MIN	84.38	72.73	72.73
MEDIAN	157.14	328.57	176.43
MAX	276.19	456	456
p-VALUE (T-TEST)			0.0380
Respiratory rate			
MISSING	2	0	2
MEAN	18	17.75	17.85
STD	0	1.75	1.34
MIN	18	16	16
MEDIAN	18	17.50	18

	Therapy		
	Control N=7	Plasma N=8	Total N=15
MAX	18	20	20
p-VALUE (T-TEST)			0.7596

Table 12. Medical History

	Therapie		
	A N=7	B N=8	Total N=15
COPD			
no	7 (100.0%)	8 (100.0%)	15 (100.0%)
COPD Stages			
MISSING	7 (100.0%)	8 (100.0%)	15 (100.0%)
Chronic heart failure			
no	7 (100.0%)	7 (87.5%)	14 (93.3%)
yes	0 (0.0%)	1 (12.5%)	1 (6.7%)
p-VALUE (CHI^2)			0.3329
Lung fibrosis			
no	7 (100.0%)	8 (100.0%)	15 (100.0%)
Liver cirrhosis			
no	7 (100.0%)	8 (100.0%)	15 (100.0%)
Child-Pugh Score for Liver cirrhosis			
MISSING	7 (100.0%)	8 (100.0%)	15 (100.0%)
Diabetes mellitus			
no	4 (57.1%)	6 (75.0%)	10 (66.7%)
yes	3 (42.9%)	2 (25.0%)	5 (33.3%)
p-VALUE (CHI^2)			0.4642

	Therapie		
	A N=7	**B N=8**	**Total N=15**
Hypertension			
no	2 (28.6%)	3 (37.5%)	5 (33.3%)
yes	5 (71.4%)	5 (62.5%)	10 (66.7%)
p-VALUE (CHI^2)			0.7144
Secondary infections			
no	6 (85.7%)	8 (100.0%)	14 (93.3%)
yes	1 (14.3%)	0 (0.0%)	1 (6.7%)
p-VALUE (CHI^2)			0.2685
Cardiovascular disease			
no	6 (85.7%)	8 (100.0%)	14 (93.3%)
yes	1 (14.3%)	0 (0.0%)	1 (6.7%)
p-VALUE (CHI^2)			0.2685
Chronic renal disease			
no	7 (100.0%)	6 (75.0%)	13 (86.7%)
yes	0 (0.0%)	2 (25.0%)	2 (13.3%)
p-VALUE (CHI^2)			0.1553
Chronic neurological disease			
no	7 (100.0%)	7 (87.5%)	14 (93.3%)
yes	0 (0.0%)	1 (12.5%)	1 (6.7%)
p-VALUE (CHI^2)			0.3329
Chronic liver disease			
no	7 (100.0%)	8 (100.0%)	15 (100.0%)
Rheumatologic/immunologic disease			
no	6 (85.7%)	7 (87.5%)	13 (86.7%)
yes	1 (14.3%)	1 (12.5%)	2 (13.3%)
p-VALUE (CHI^2)			0.9192

	Therapie		
	A N=7	**B N=8**	**Total N=15**
Smoking History			
ex-smoker	0 (0.0%)	3 (37.5%)	3 (20.0%)
never smoked	1 (14.3%)	2 (25.0%)	3 (20.0%)
unknown	6 (85.7%)	3 (37.5%)	9 (60.0%)
p-VALUE (CHI^2)			0.1173
Chronic lung disease			
no	6 (85.7%)	8 (100.0%)	14 (93.3%)
yes	1 (14.3%)	0 (0.0%)	1 (6.7%)
p-VALUE (CHI^2)			0.2685
Organ transplantation			
no	6 (85.7%)	6 (75.0%)	12 (80.0%)
yes	1 (14.3%)	2 (25.0%)	3 (20.0%)
p-VALUE (CHI^2)			0.6048
Active tumor / cancer			
no	7 (100.0%)	8 (100.0%)	15 (100.0%)
Allergies			
MISSING	1 (14.3%)	0 (0.0%)	1 (6.7%)
no	5 (71.4%)	8 (100.0%)	13 (86.7%)
yes	1 (14.3%)	0 (0.0%)	1 (6.7%)
p-VALUE (CHI^2)			0.2308
Other diagnosis			
no	2 (28.6%)	1 (12.5%)	3 (20.0%)
yes	5 (71.4%)	7 (87.5%)	12 (80.0%)
p-VALUE (CHI^2)			0.4376

Table 13. ECG

	Therapie		
	A N=7	**B N=8**	**Total N=15**
Puls			
MISSING	0	0	0
MEAN	76.71	82	79.53
STD	20.36	18.08	18.67
MIN	52	55	52
MEDIAN	84	82	82
MAX	108	105	108
p-VALUE (T-TEST)			0.6031
Sinus rhythm			
yes	7 (100.0%)	8 (100.0%)	15 (100.0%)
Atrial fibrillation			
no	7 (100.0%)	8 (100.0%)	15 (100.0%)
Atrial flutter			
no	7 (100.0%)	8 (100.0%)	15 (100.0%)
Cardiac pacemaker			
no	7 (100.0%)	8 (100.0%)	15 (100.0%)
Other rhythm			
MISSING	1 (14.3%)	0 (0.0%)	1 (6.7%)
no	6 (85.7%)	8 (100.0%)	14 (93.3%)

3 Laboratory diagnostics

The laboratory values are displayed with mean values and standard error for each treatment group. Values for carbondioxide are not shown because different units were documented that could not be converted.

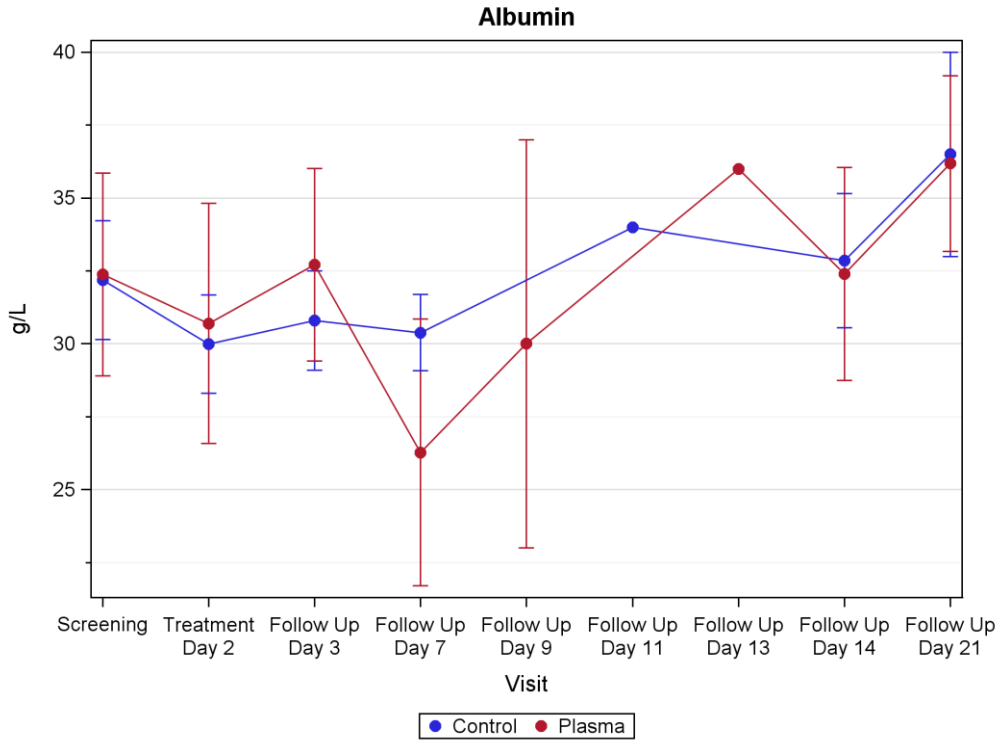

Figure 2. Albumin

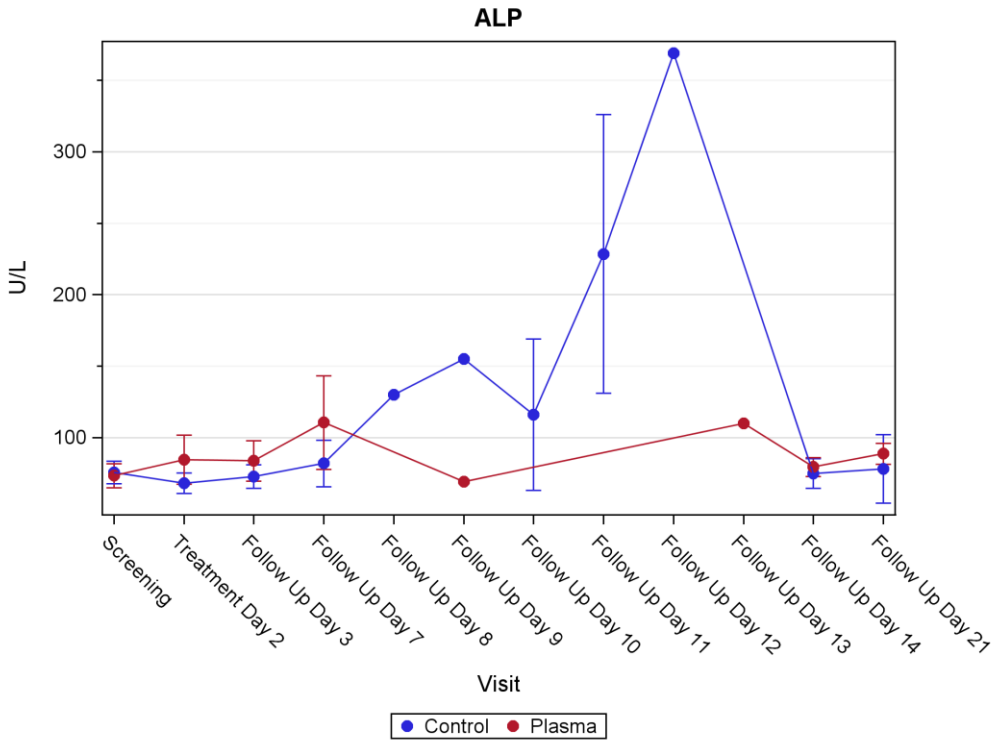

Figure 3. ALP

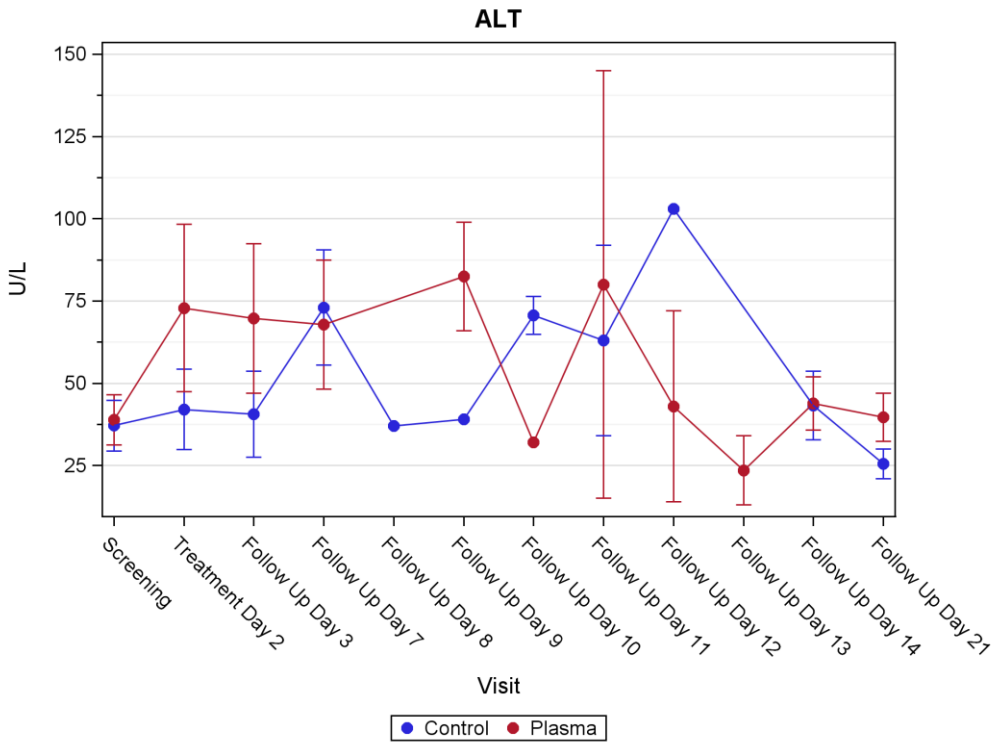

Figure 4. ALT

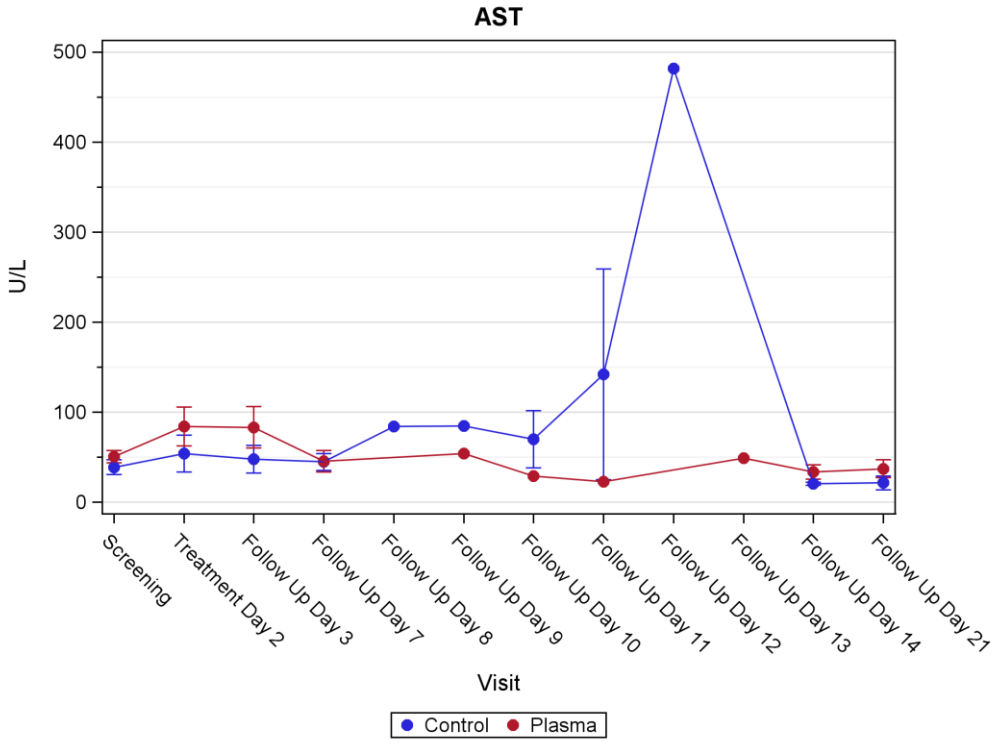

Figure 5. AST

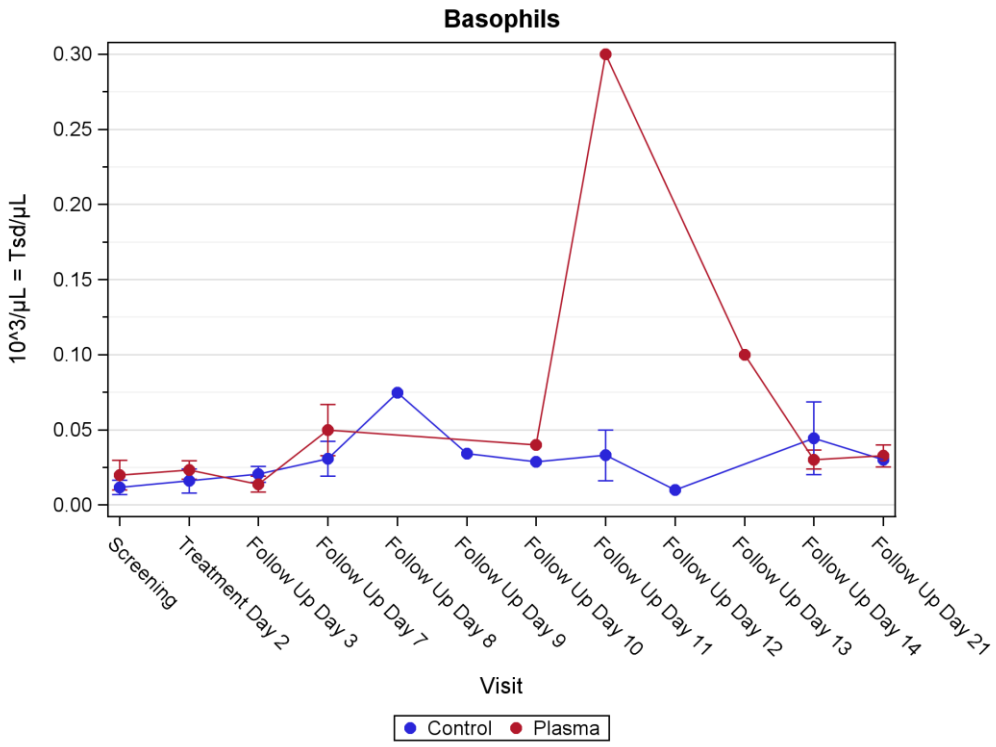

Figure 6. Basophils

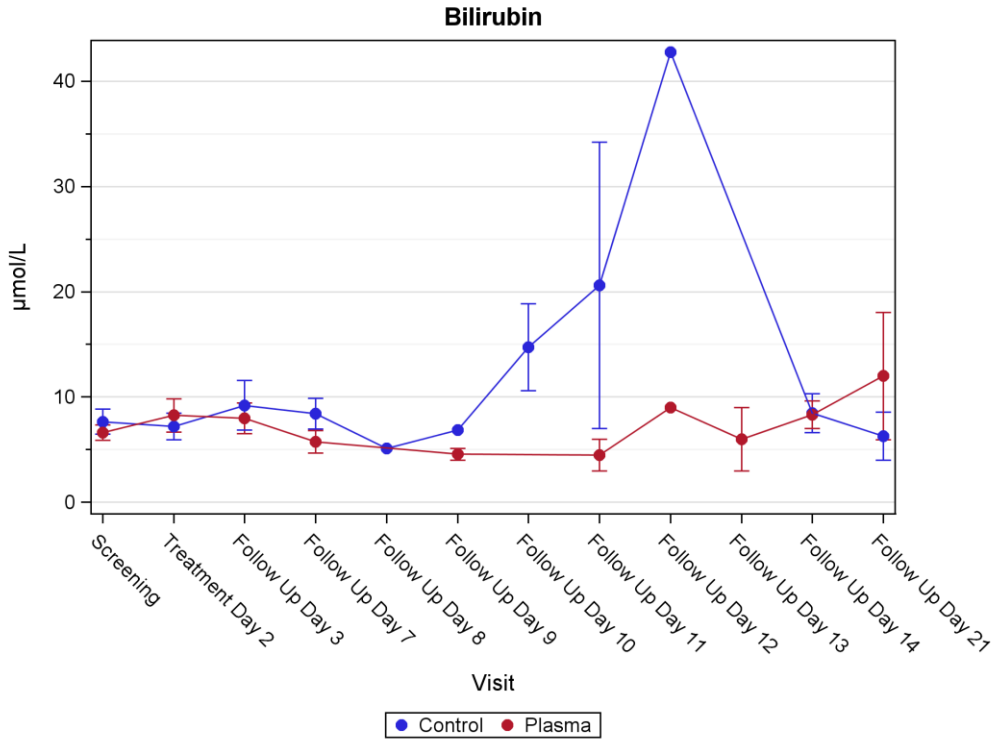

Figure 7. Bilirubin

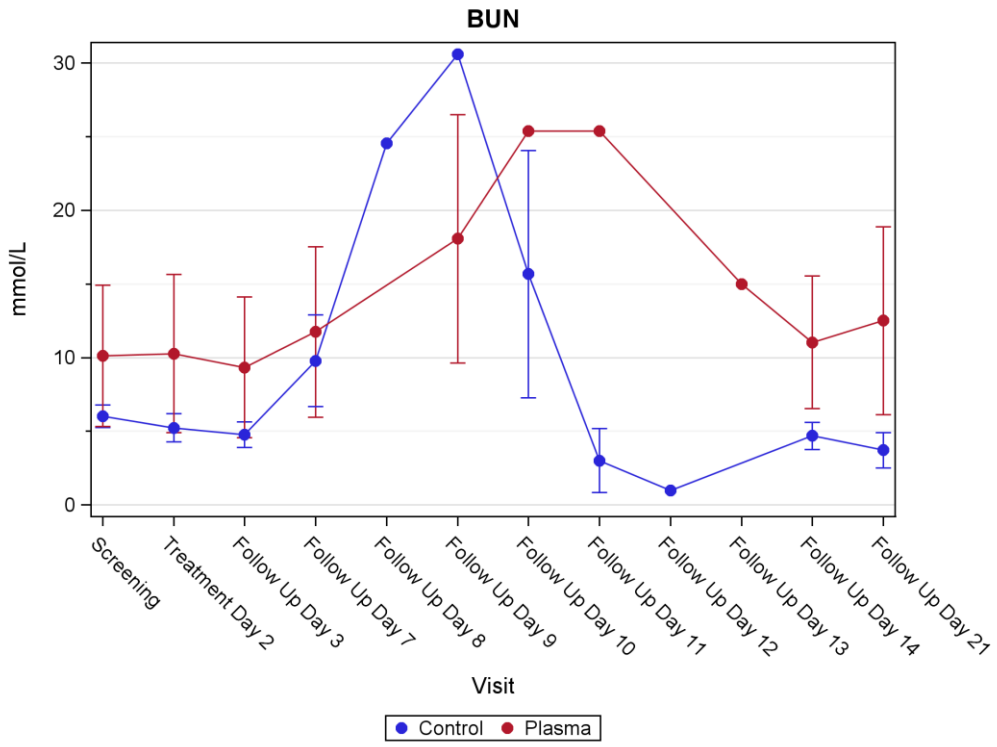

Figure 8. BUN

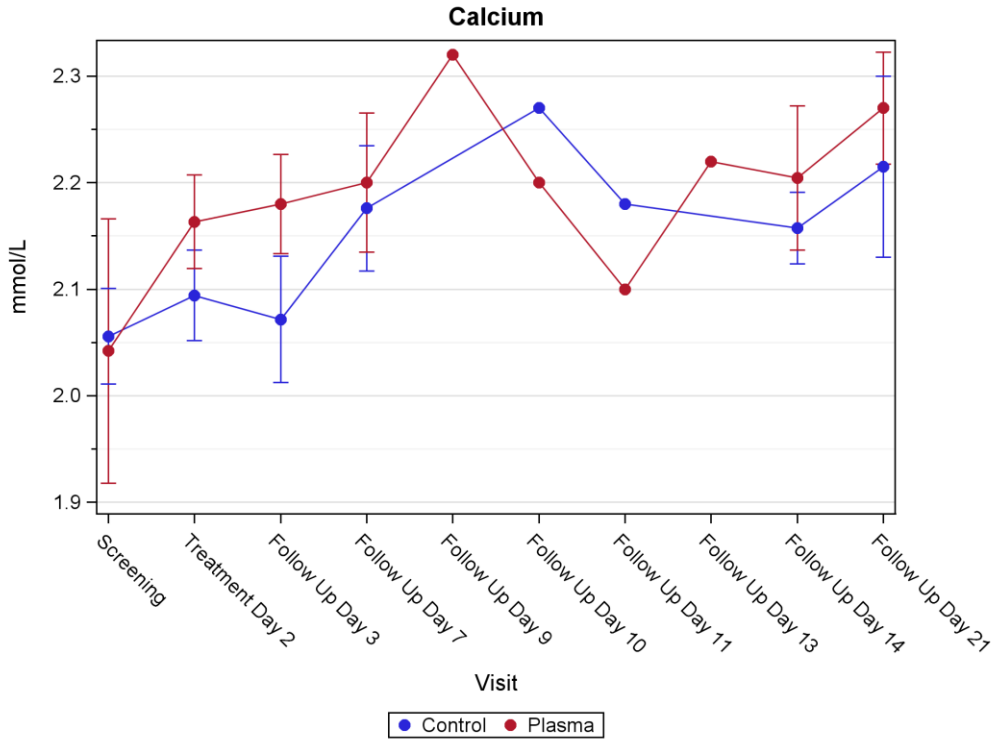

Figure 9. Calcium

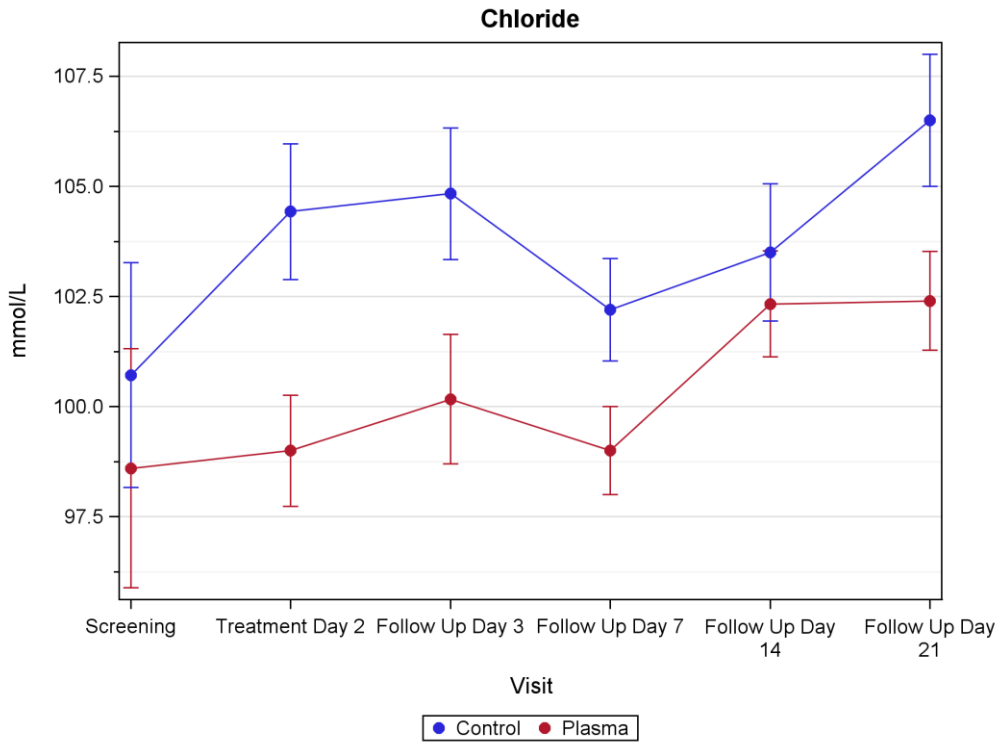

Figure 10. Chloride

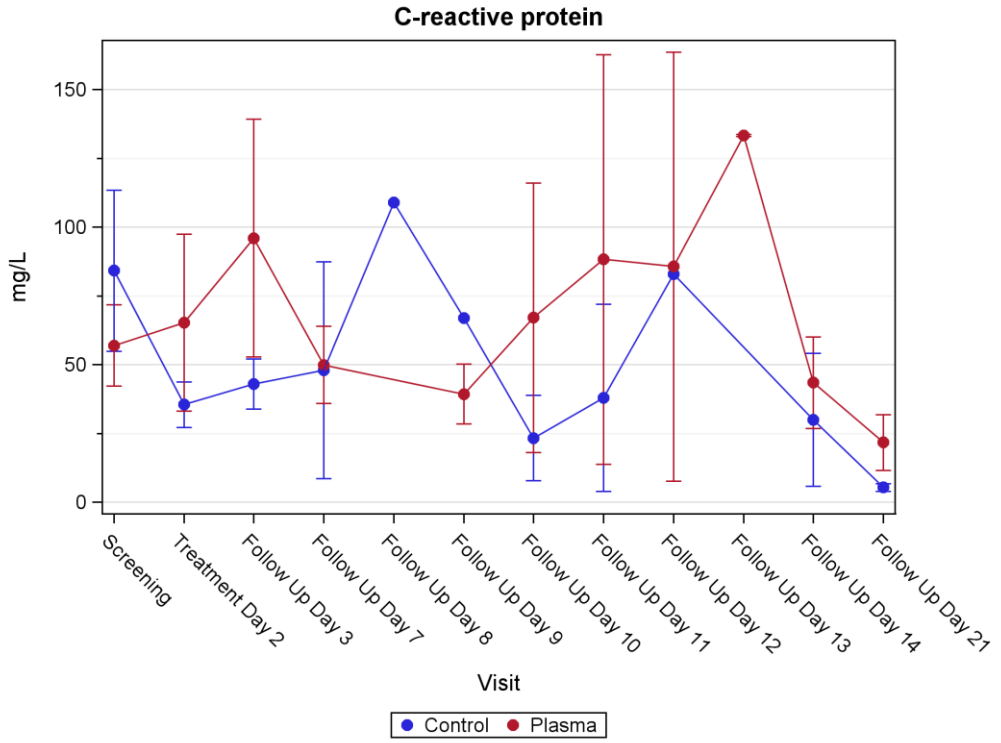

Figure 11. C-reactive protein

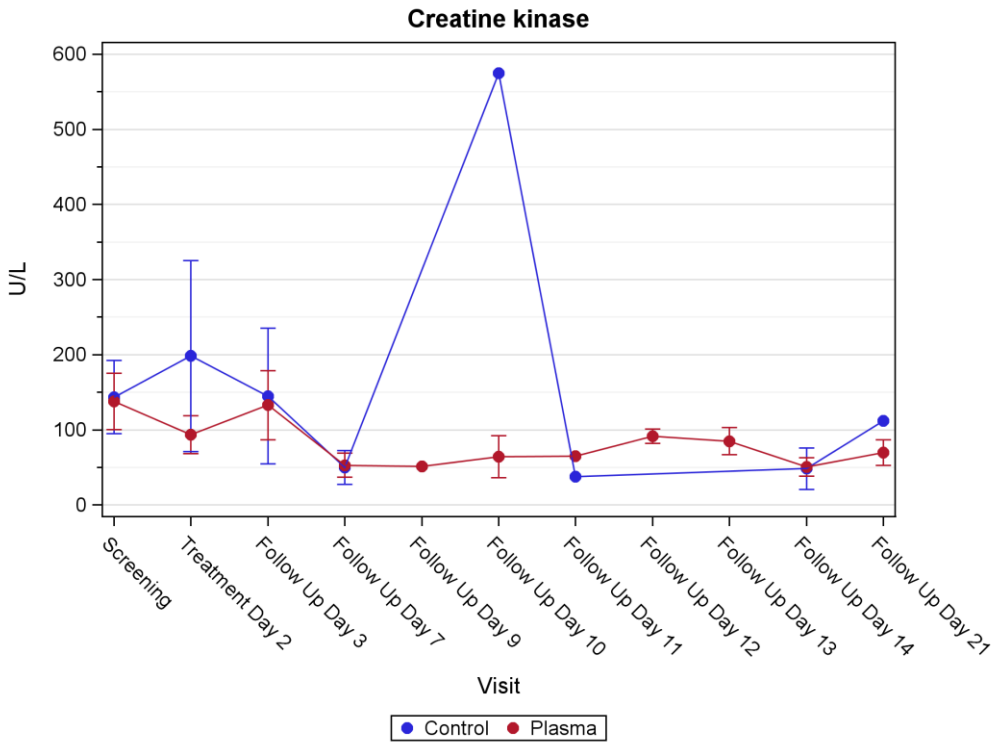

Figure 12- Creatine kinase

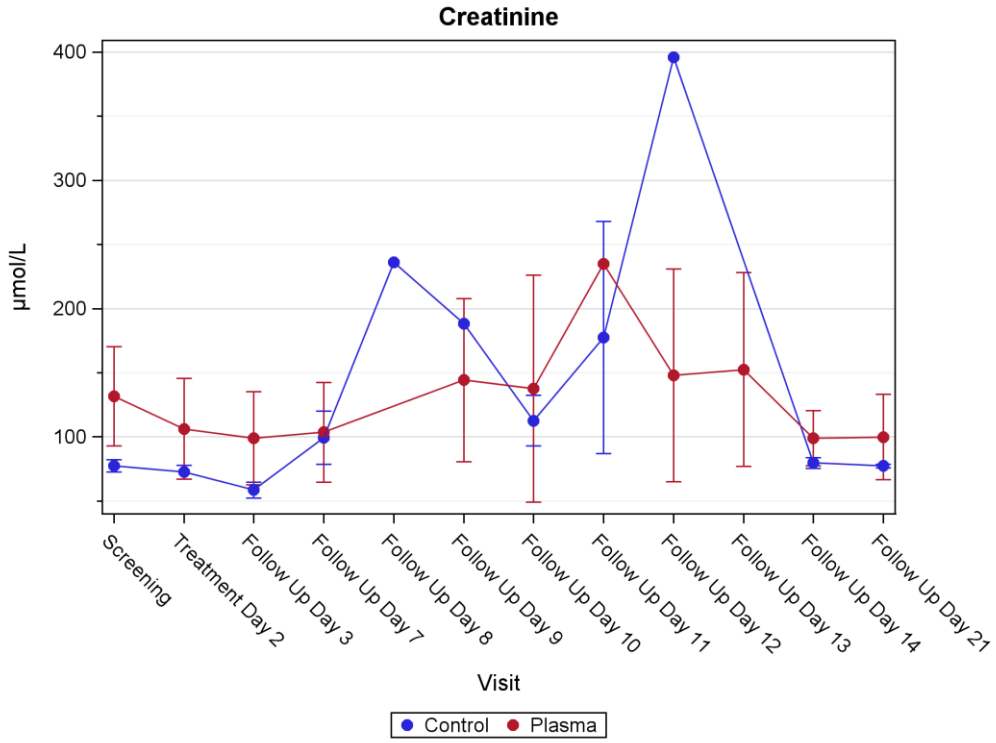

Figure 13. Creatinine

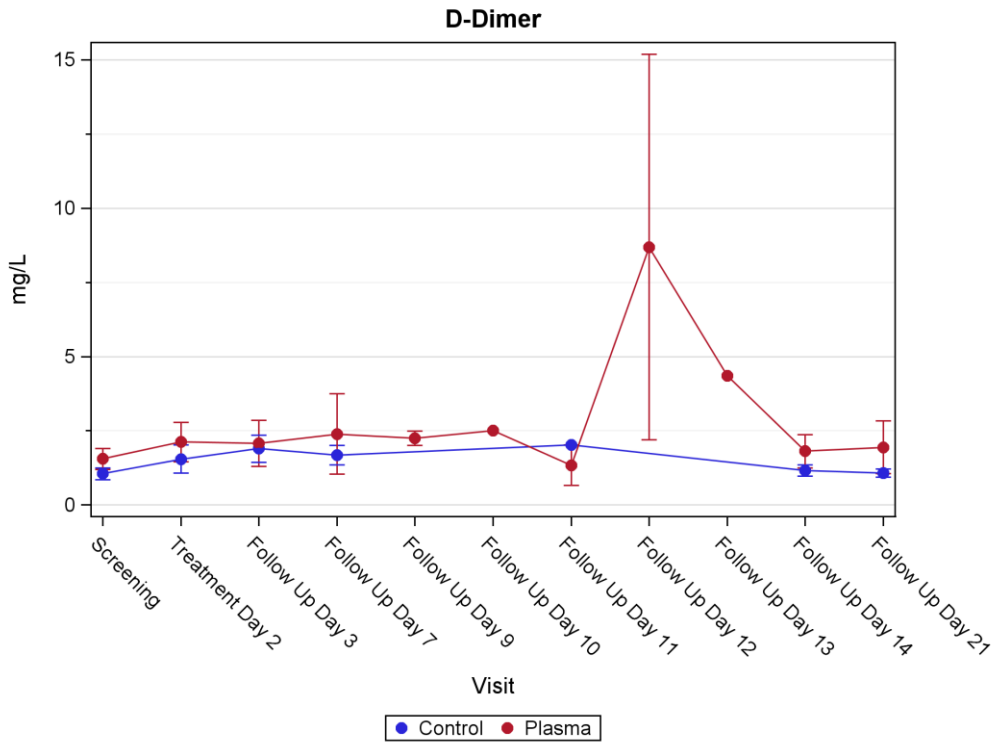

Figure 14. D-Dimer

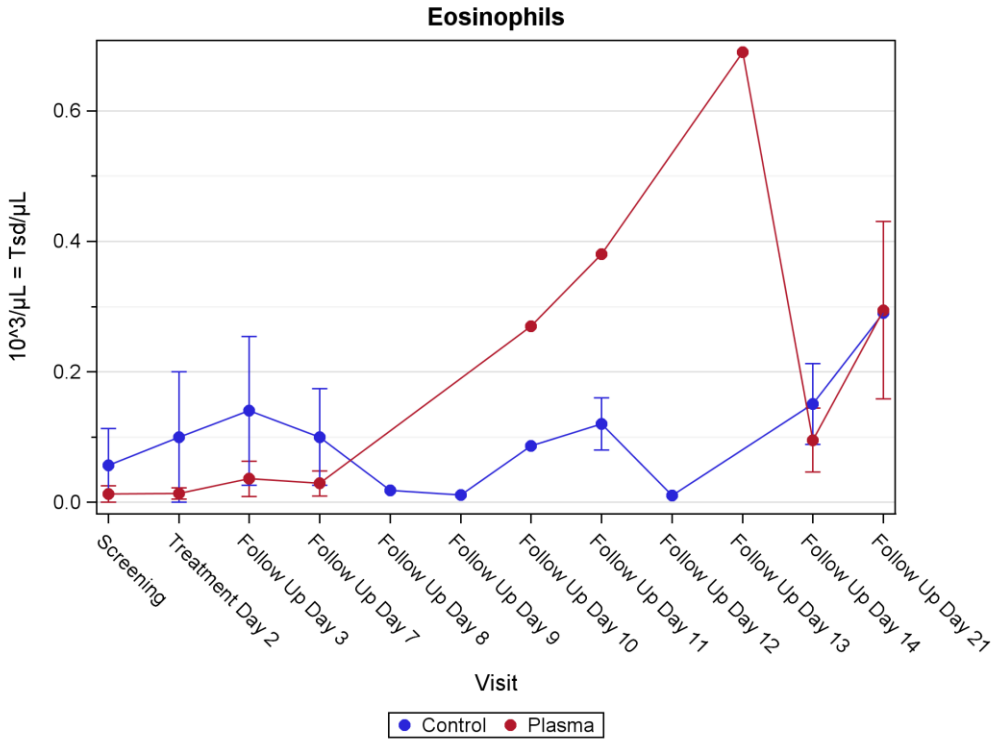

Figure 15. Eosinophils

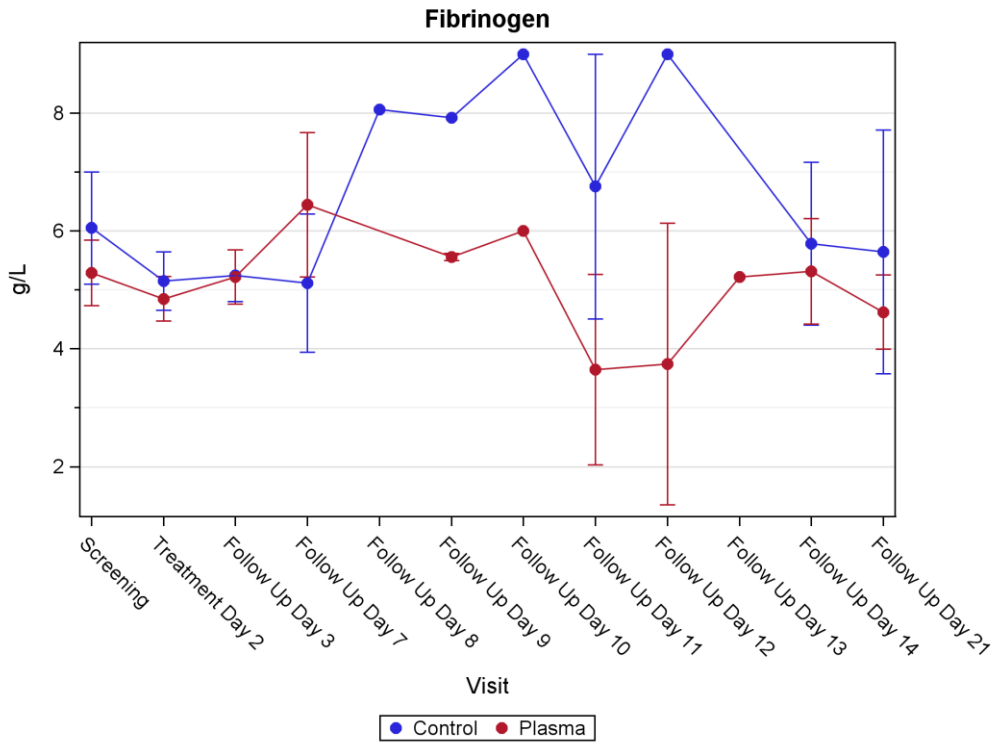

Figure 16. Fibrinogen

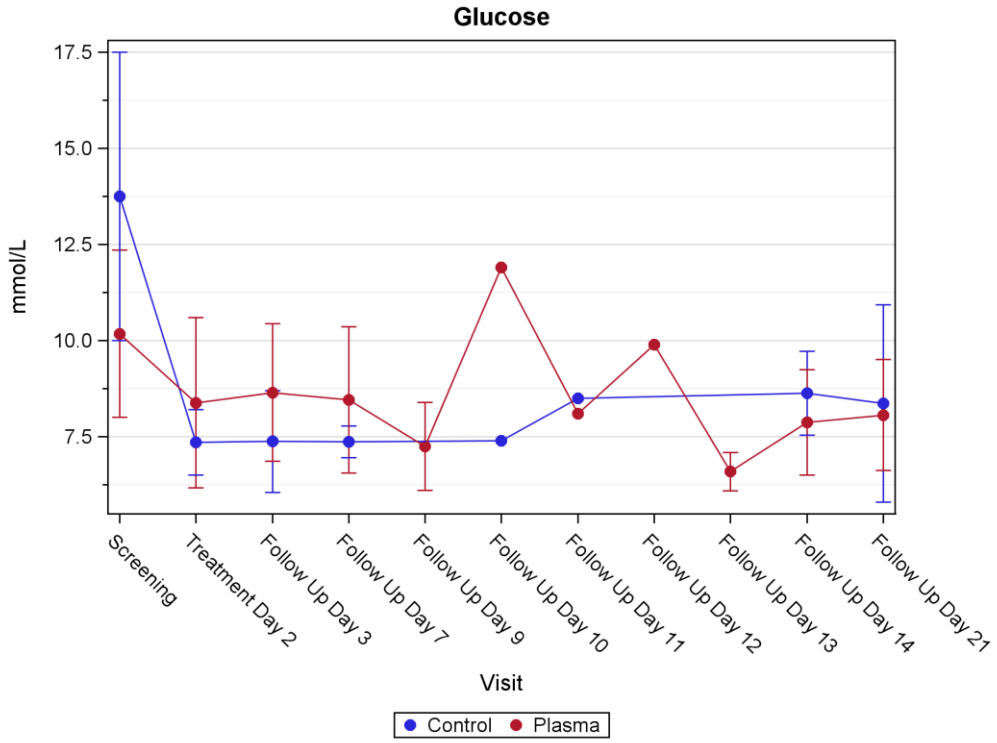

Figure 17. Glucose

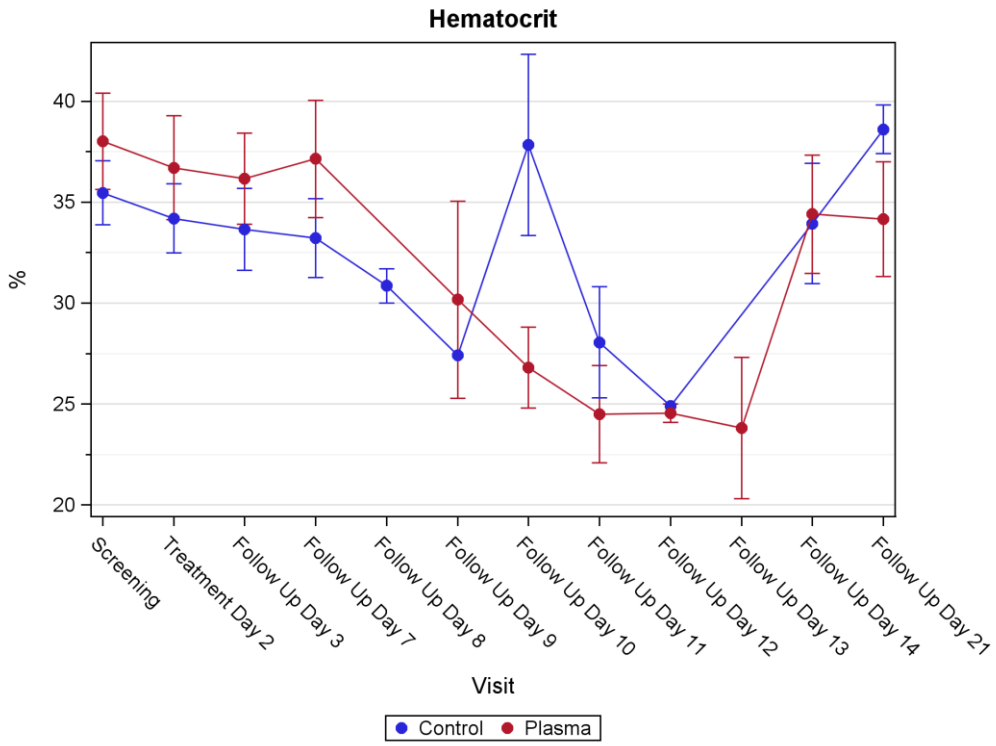

Figure 18. Hematocrit

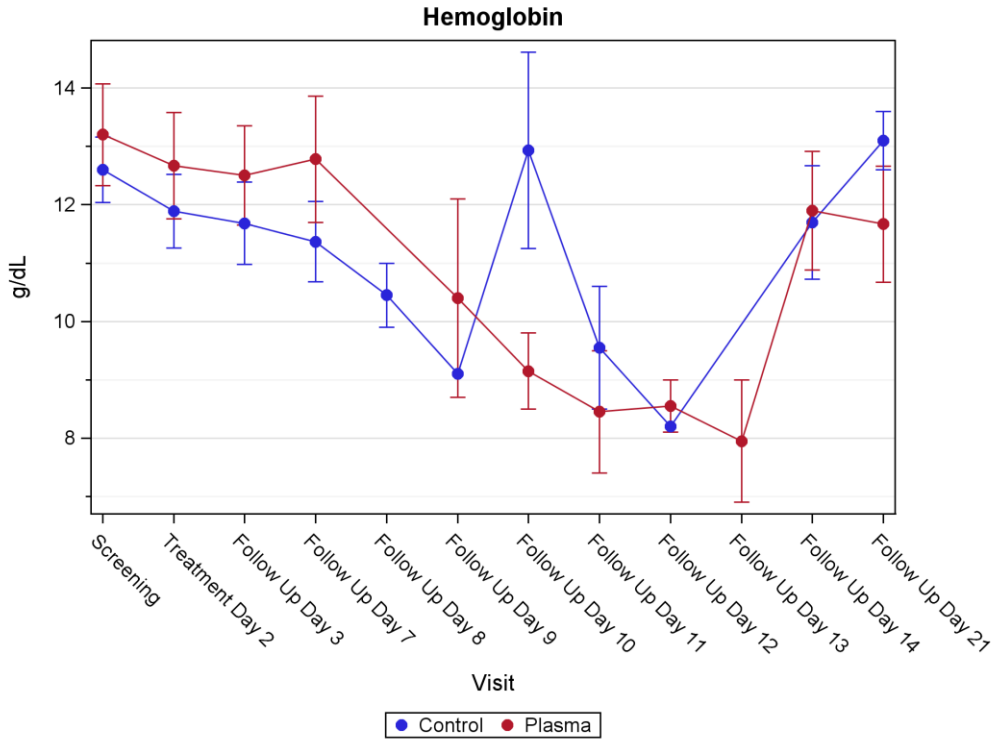

Figure 19. Hemoglobin

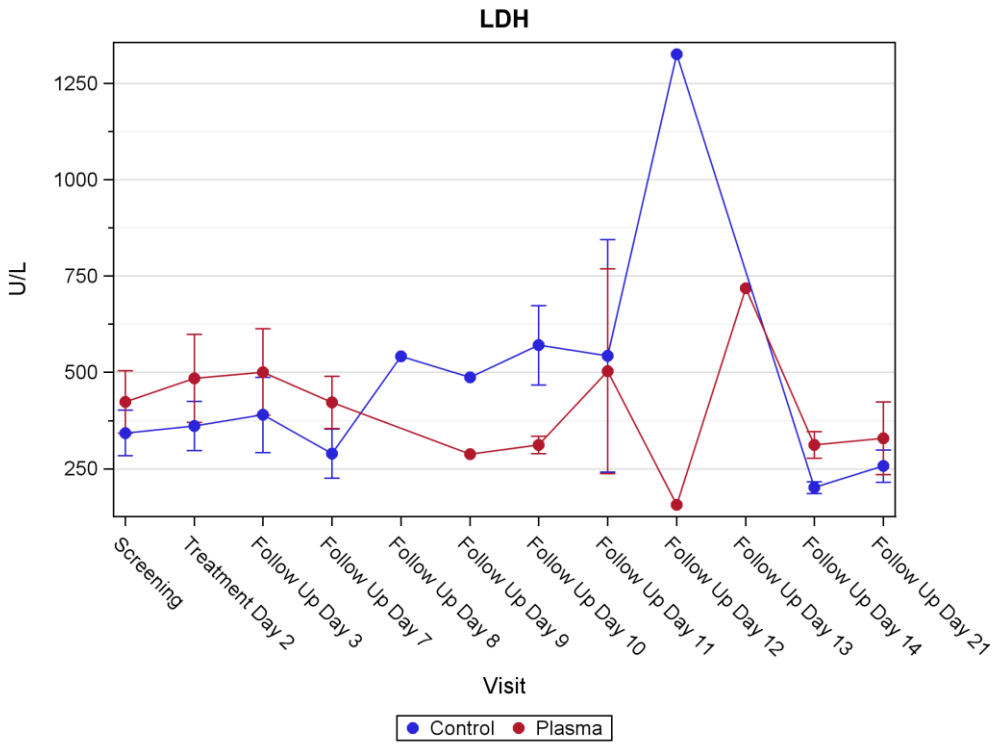

Figure 20. LDH

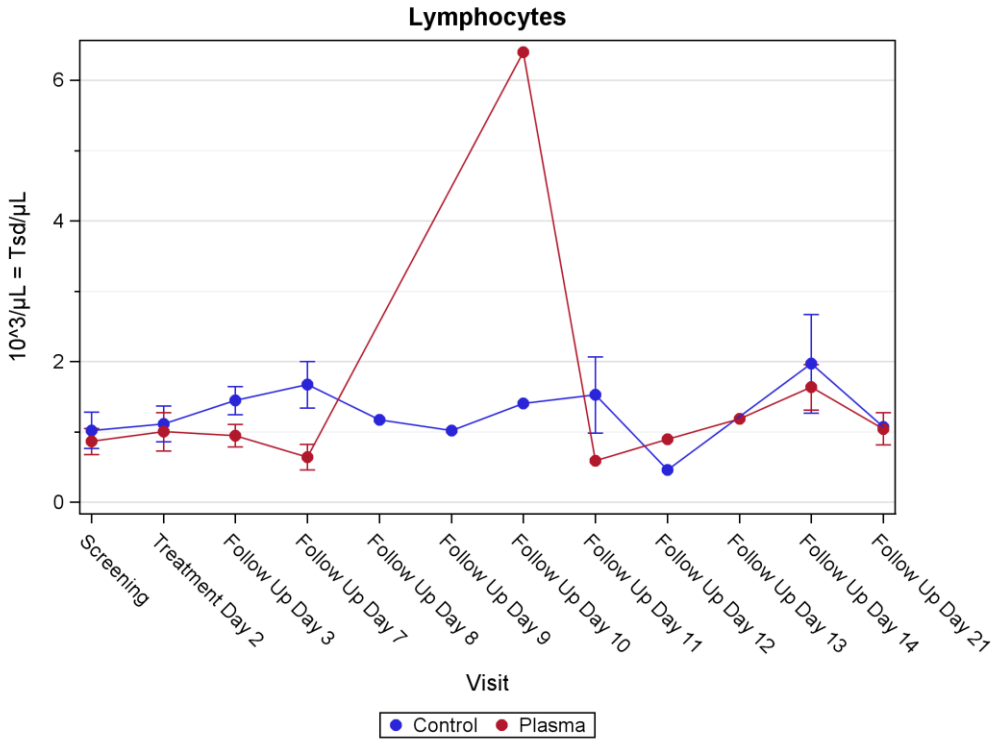

Figure 21. Lymphocytes

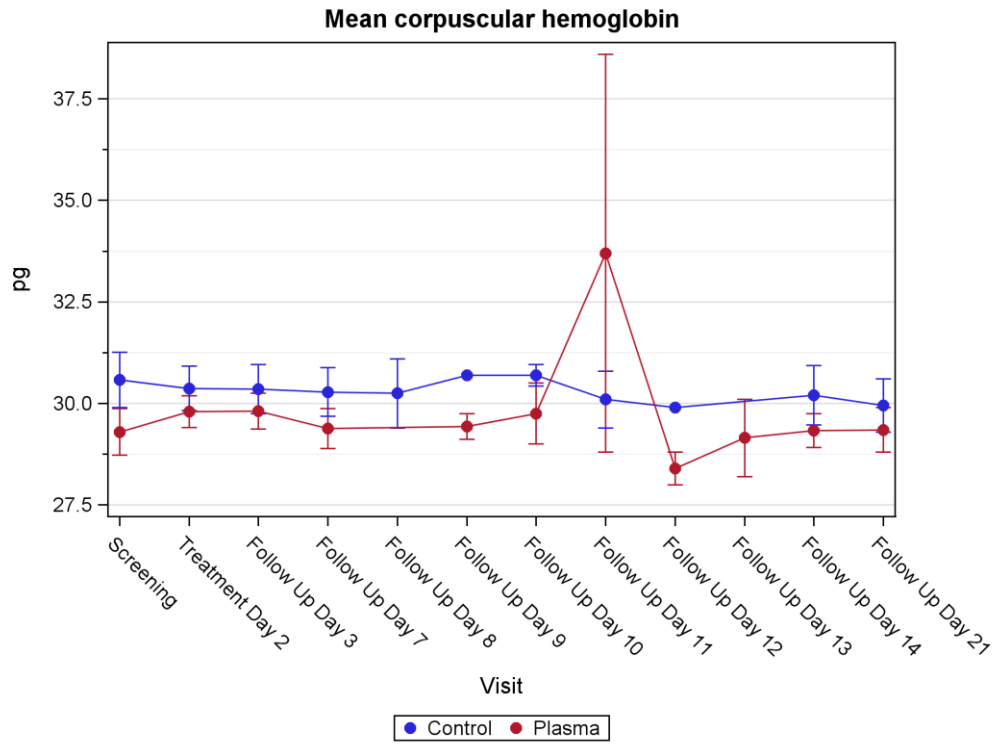

Figure 22. Mean corpuscular hemoglobin

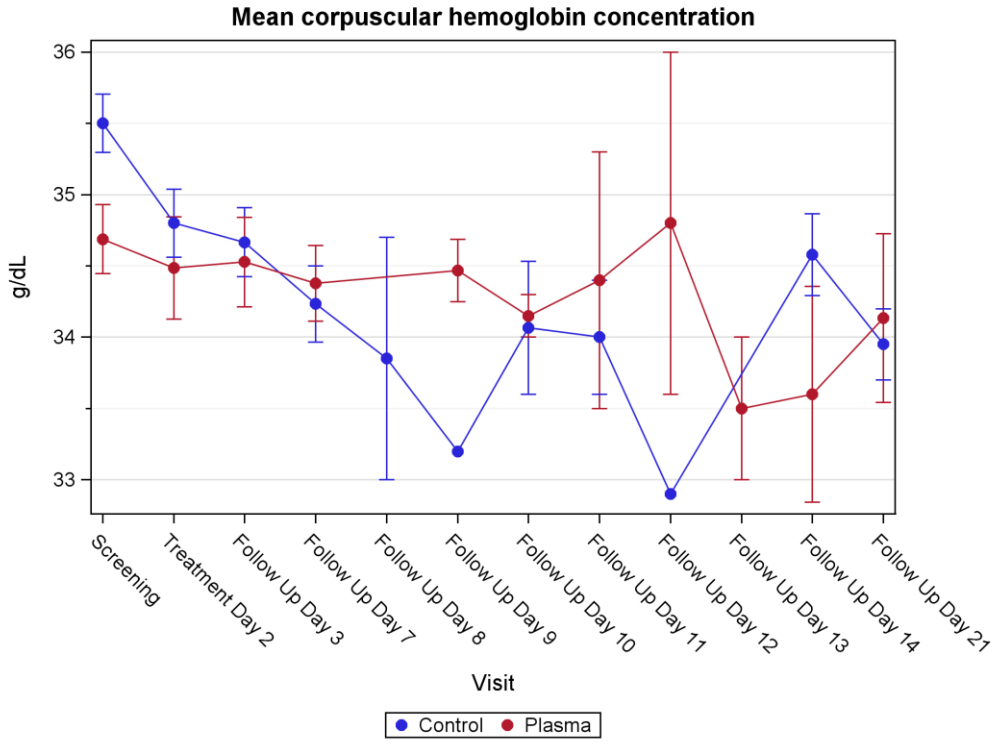

Figure 23. Mean corpuscular hemoglobin concentration

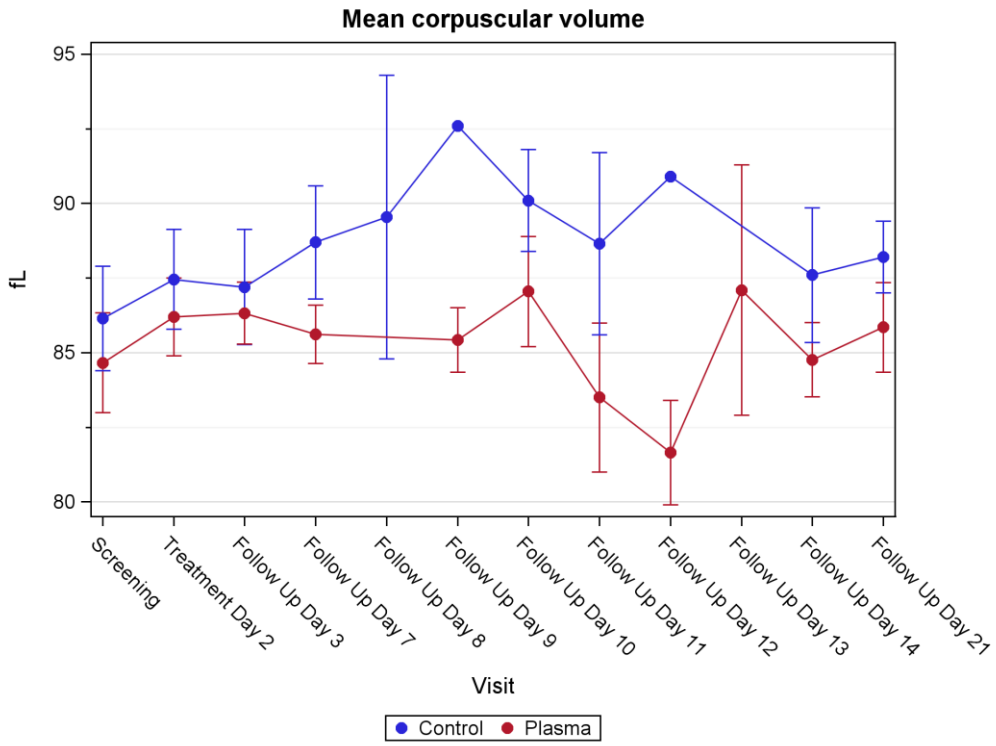

Figure 24. Mean corpuscular volume

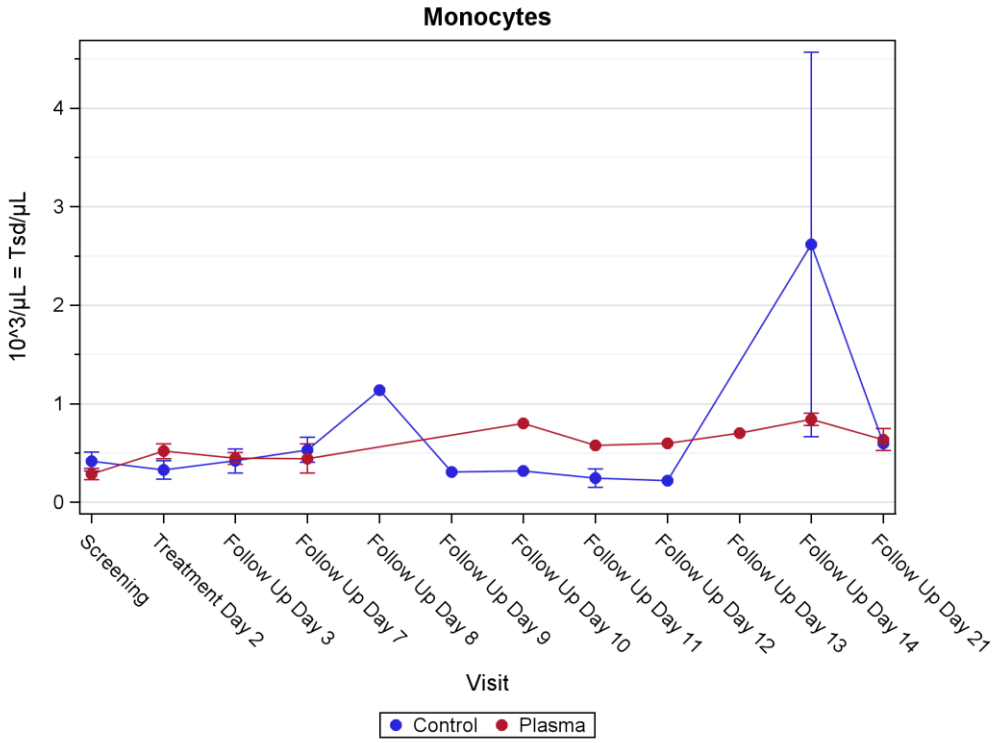

Figure 25. Monocytes

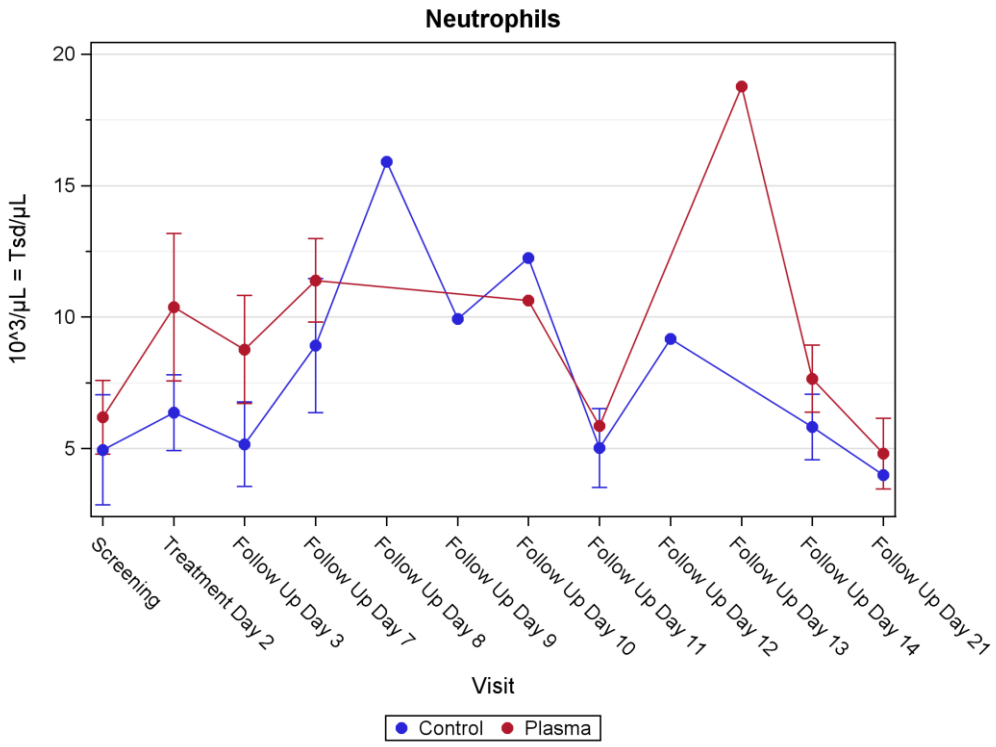

Figure 26. Neutrophils

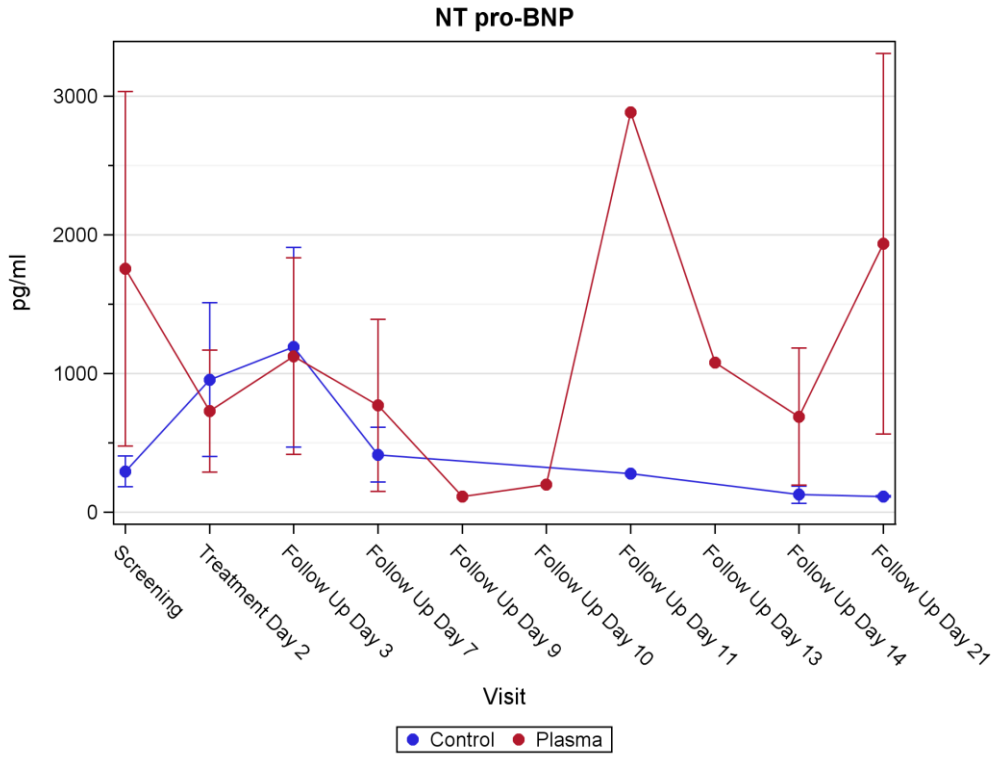

Figure 27. NT pro-BNP

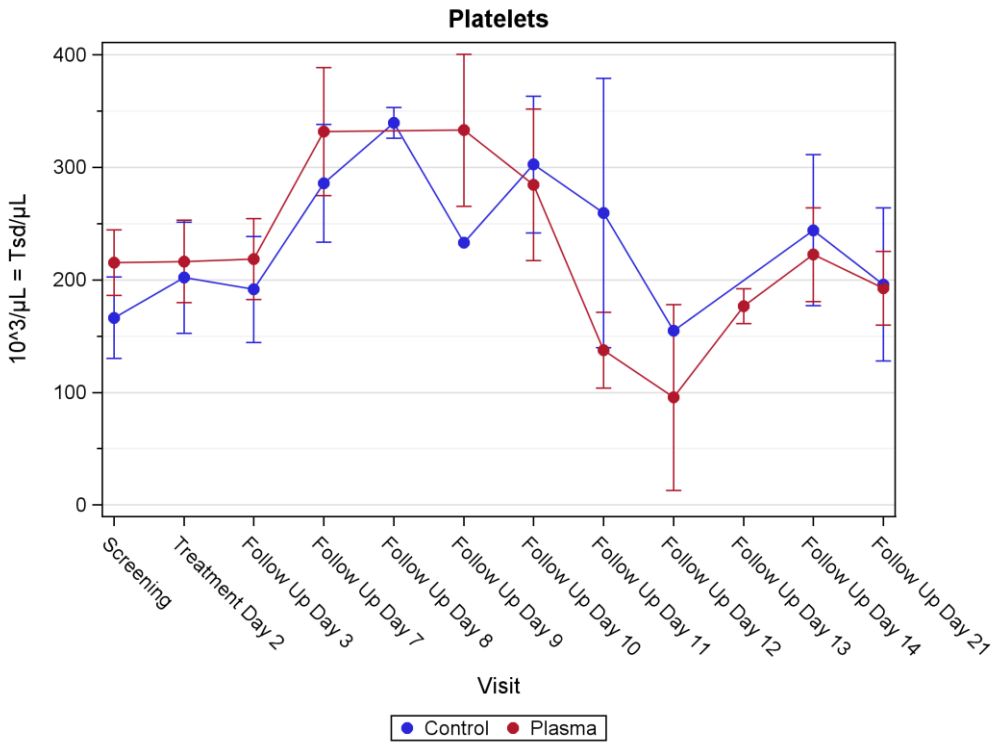

Figure 28. Platelets

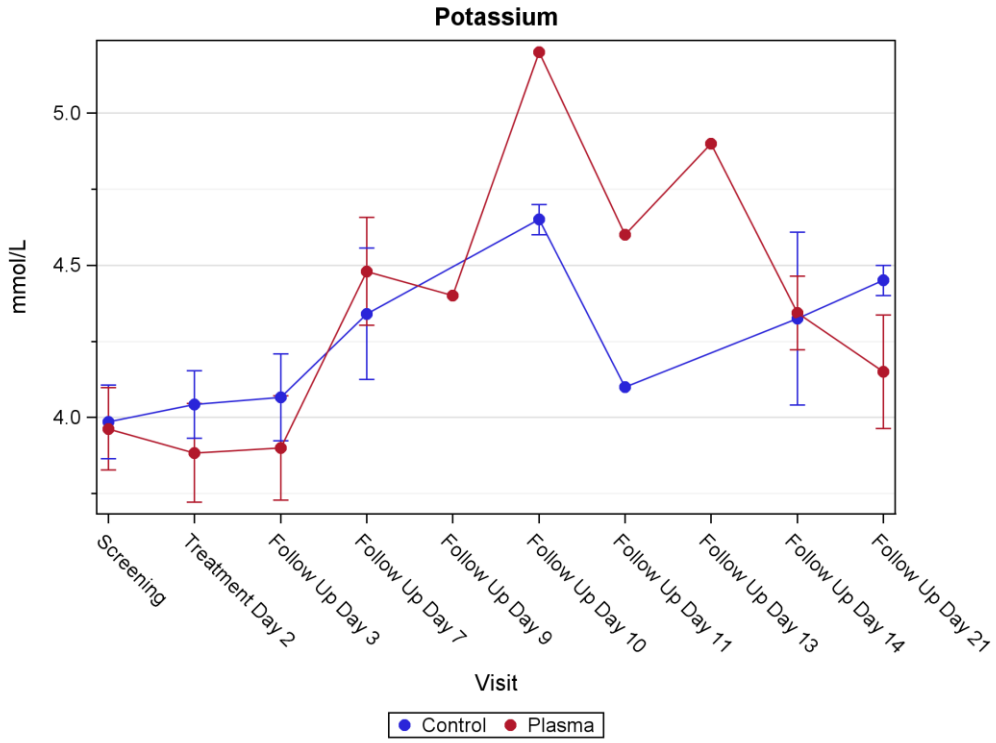

Figure 29. Potassium

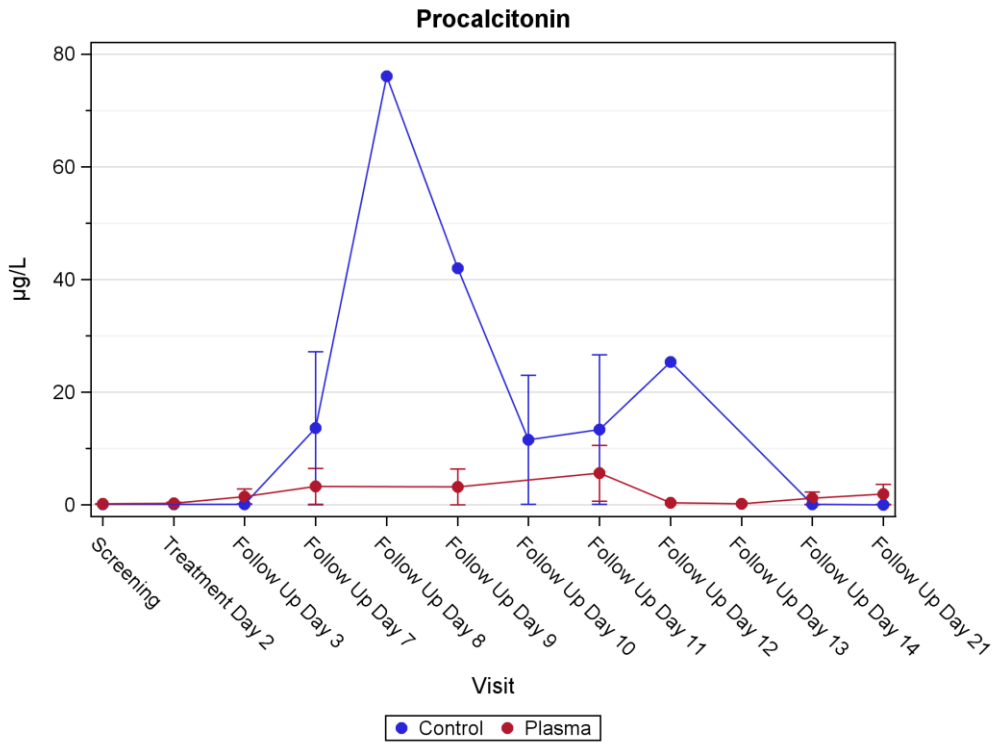

Figure 30. Procalcitonin

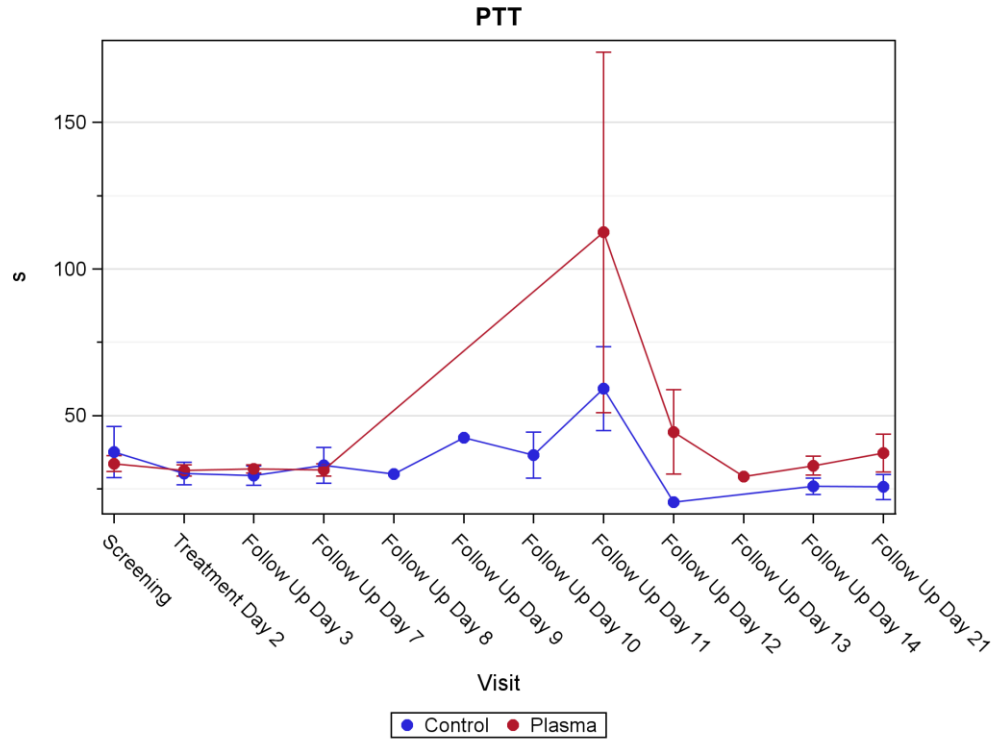

Figure 31. PTT

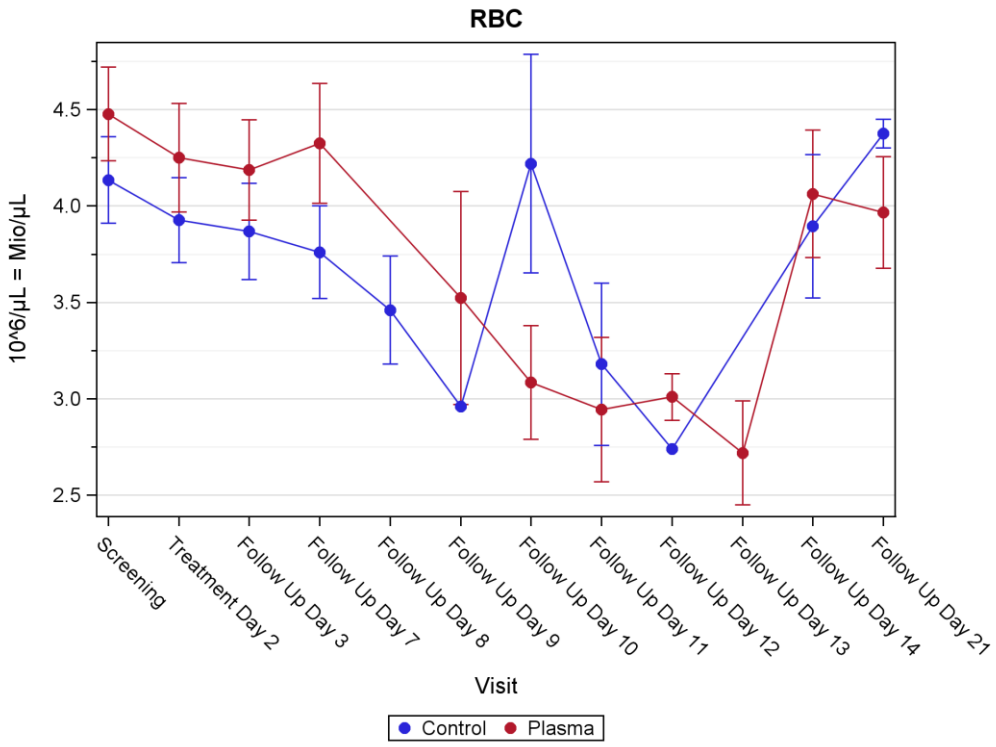

Figure 32. RBC

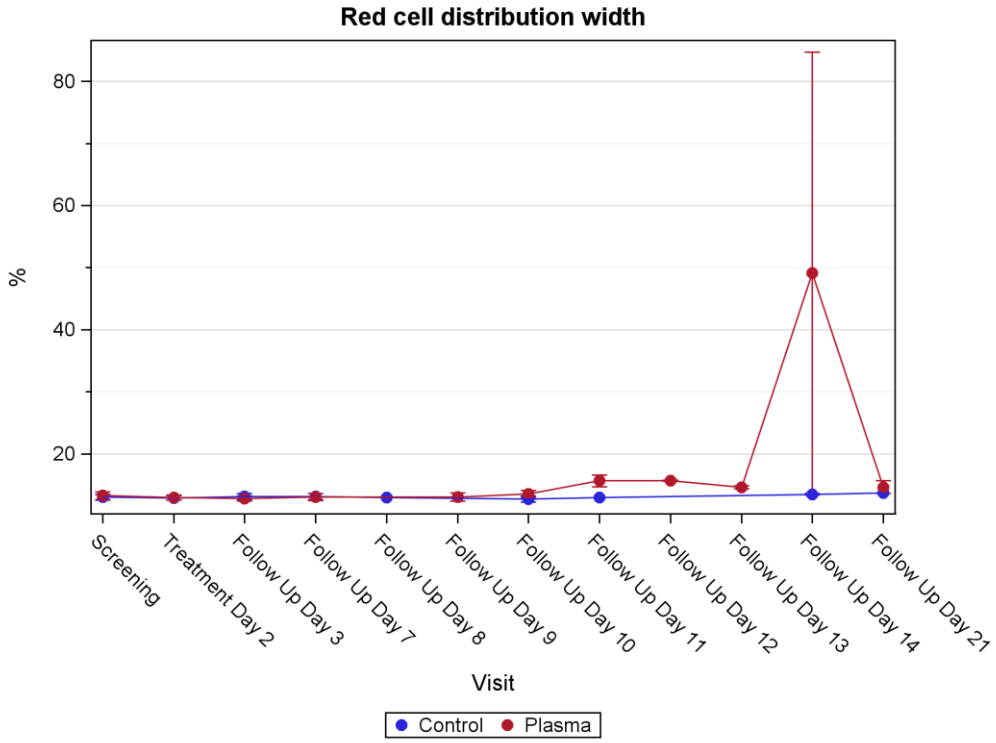

Figure 33. Red cell distribution width

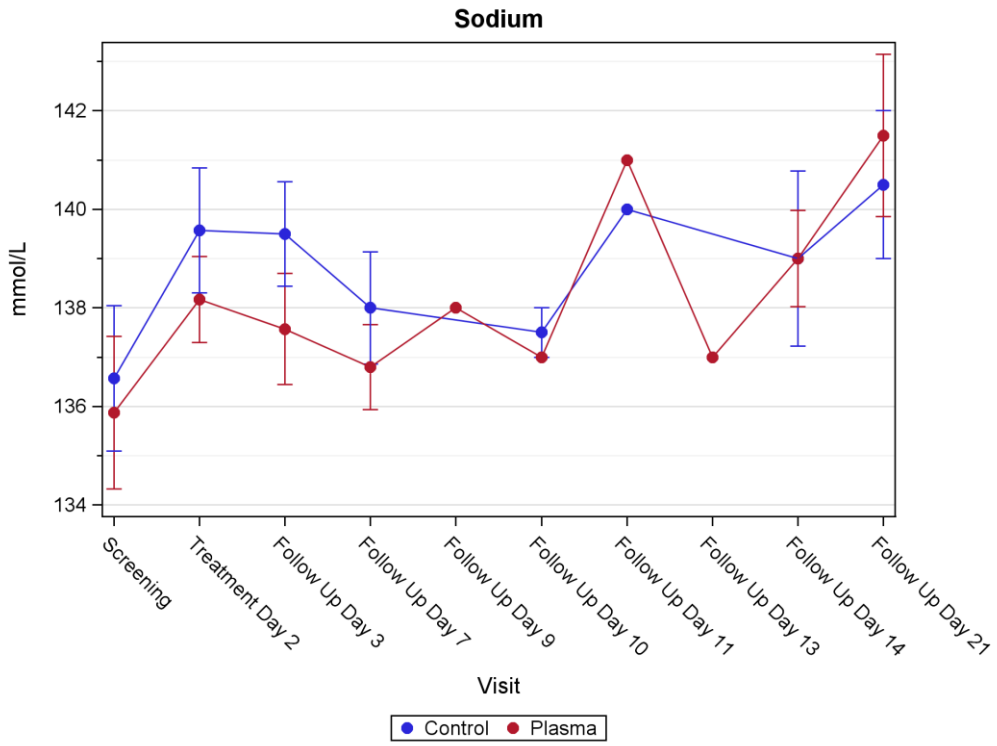

Figure 34. Sodium

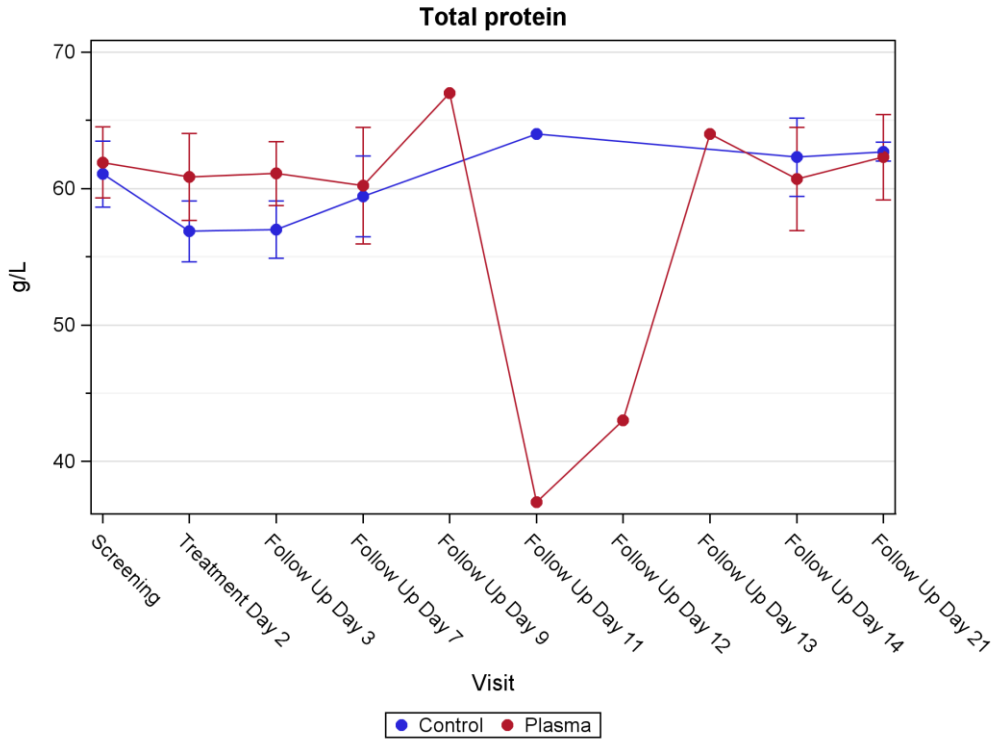

Figure 35. Total protein

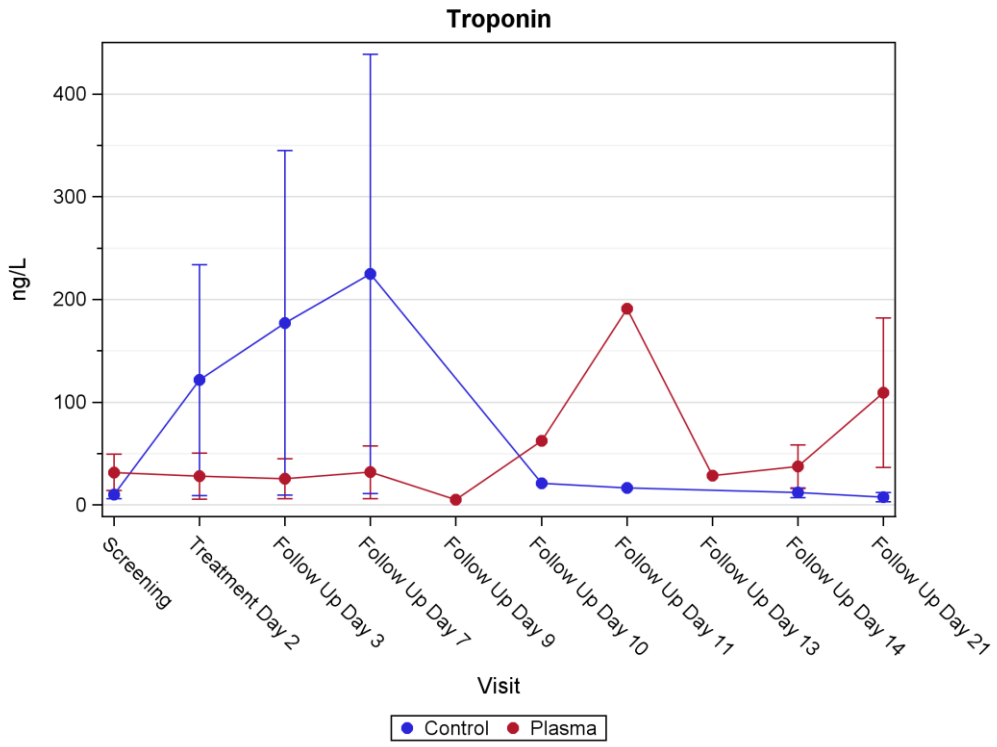

Figure 36. Troponin

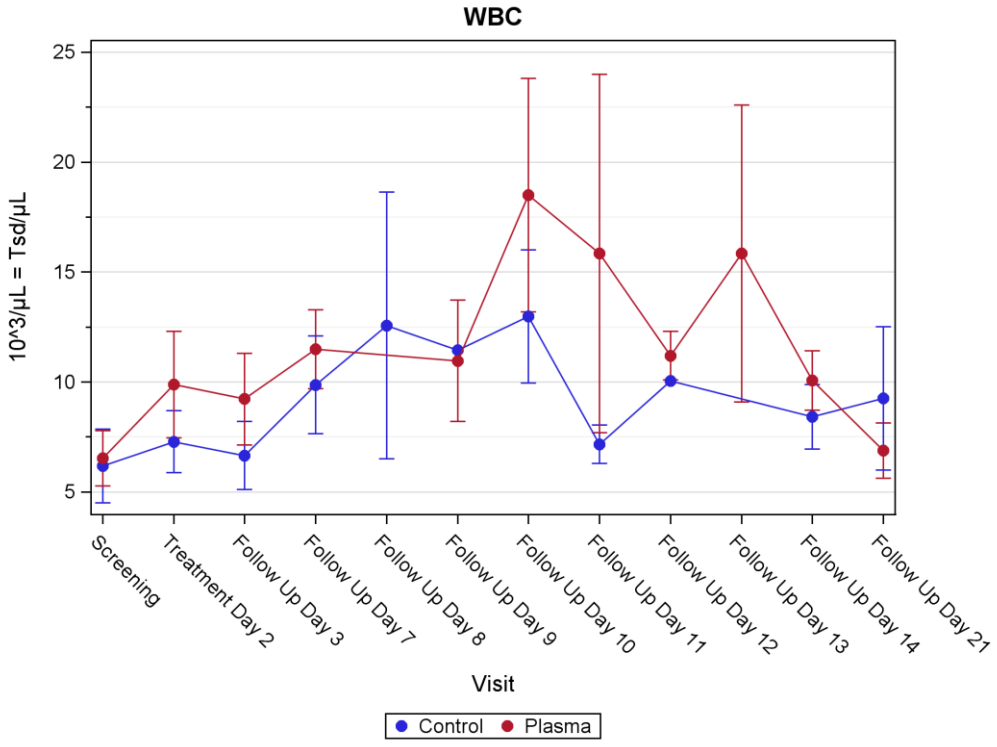

Figure 37. WBC

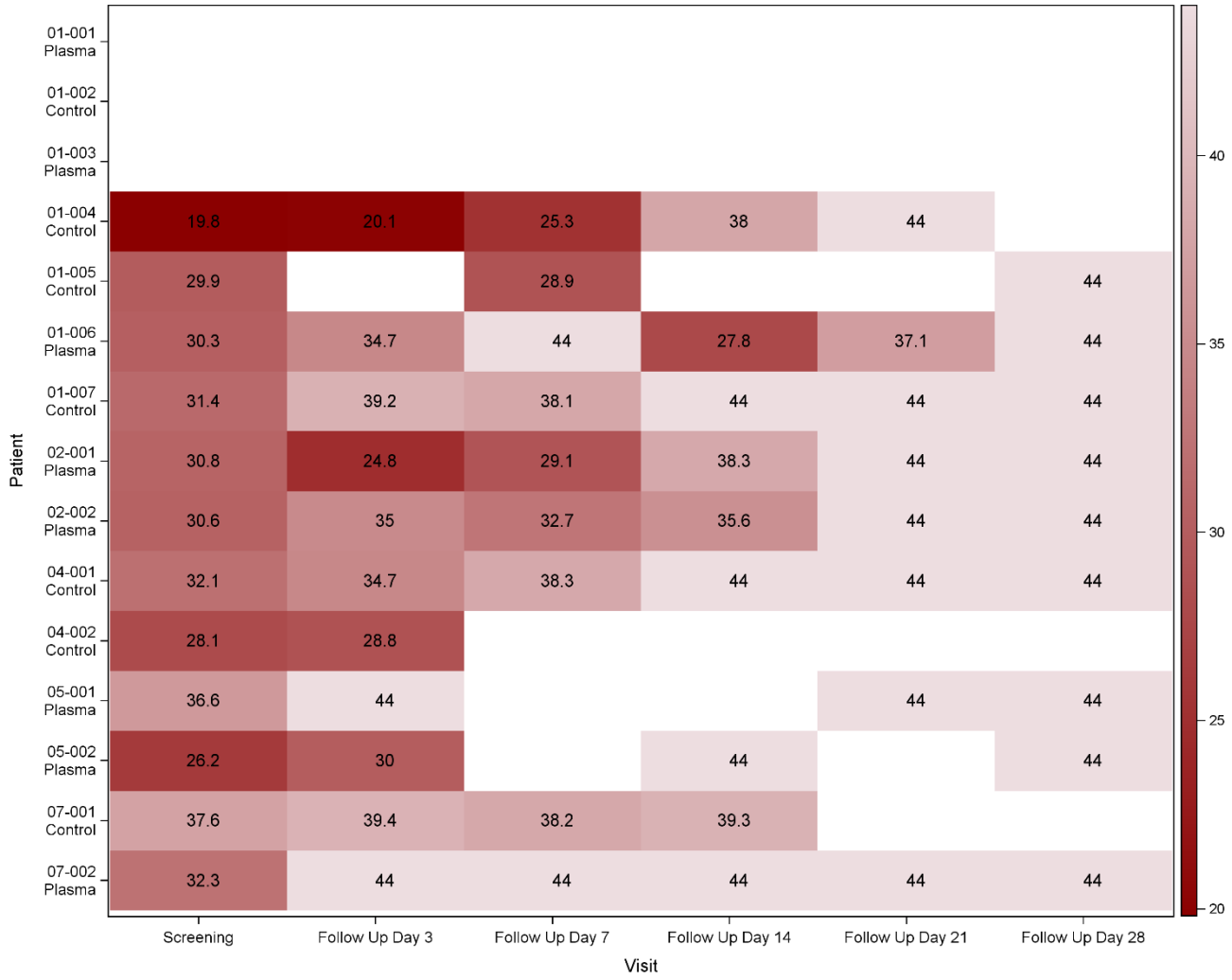

Figure 38. CT values for all patients over all visits. Patients 01-001, 01-002 and 01-003 had no available data. Missing values were not imputed. Negative PCR was imputed with 44 because higher CT values imply lower virus levels.

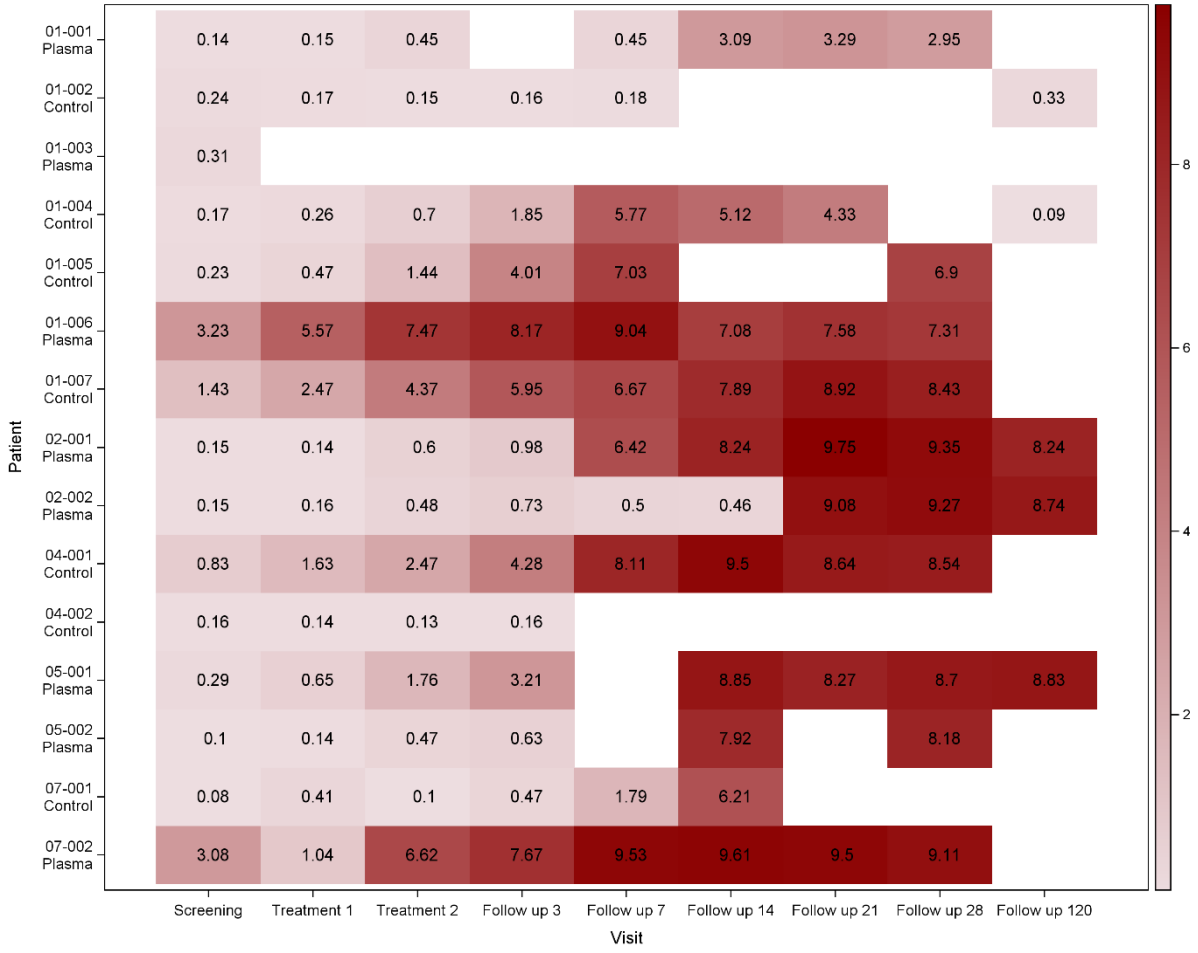

Figure 39. IgG values for all patients over all visits. Missing values were not imputed.

An overview over the PRNT50 values is given in the appendix in Supplement Table 6.

4 Endpoints

4.1. WHO R&D Blueprint Ordinal Scale for Clinical Improvement

Table 14. WHO R&D Blueprint Ordinal Scale for Clinical Improvement for all visits. Missing values were not imputed.

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
Screening			
3	4 (57.1%)	4 (50.0%)	8 (53.3%)
4	3 (42.9%)	4 (50.0%)	7 (46.7%)
p-VALUE (CHI^2)			0.7821
Treatment (Day 1)			
MISSING	0 (0.0%)	1 (12.5%)	1 (6.7%)
3	3 (42.9%)	3 (37.5%)	6 (40.0%)
4	4 (57.1%)	4 (50.0%)	8 (53.3%)
p-VALUE (CHI^2)			1.0000
Treatment (Day 2)			
MISSING	0 (0.0%)	1 (12.5%)	1 (6.7%)
3	2 (28.6%)	2 (25.0%)	4 (26.7%)
4	5 (71.4%)	5 (62.5%)	10 (66.7%)
p-VALUE (CHI^2)			1.0000
Follow Up (Day 3)			
MISSING	0 (0.0%)	1 (12.5%)	1 (6.7%)
3	2 (28.6%)	1 (12.5%)	3 (20.0%)
4	5 (71.4%)	4 (50.0%)	9 (60.0%)
5	0 (0.0%)	2 (25.0%)	2 (13.3%)
p-VALUE (CHI^2)			0.2946
Follow Up (Day 4)			
MISSING	0 (0.0%)	1 (12.5%)	1 (6.7%)

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
3	3 (42.9%)	1 (12.5%)	4 (26.7%)
4	3 (42.9%)	3 (37.5%)	6 (40.0%)
5	1 (14.3%)	3 (37.5%)	4 (26.7%)
p-VALUE (CHI^2)			0.3679
Follow Up (Day 5)			
MISSING	0 (0.0%)	1 (12.5%)	1 (6.7%)
3	4 (57.1%)	2 (25.0%)	6 (40.0%)
4	2 (28.6%)	2 (25.0%)	4 (26.7%)
5	0 (0.0%)	3 (37.5%)	3 (20.0%)
6	1 (14.3%)	0 (0.0%)	1 (6.7%)
p-VALUE (CHI^2)			0.1979
Follow Up (Day 6)			
MISSING	0 (0.0%)	1 (12.5%)	1 (6.7%)
3	3 (42.9%)	3 (37.5%)	6 (40.0%)
4	3 (42.9%)	1 (12.5%)	4 (26.7%)
5	0 (0.0%)	3 (37.5%)	3 (20.0%)
6	1 (14.3%)	0 (0.0%)	1 (6.7%)
p-VALUE (CHI^2)			0.1718
Follow Up (Day 7)			
MISSING	0 (0.0%)	3 (37.5%)	3 (20.0%)
3	3 (42.9%)	1 (12.5%)	4 (26.7%)
4	3 (42.9%)	1 (12.5%)	4 (26.7%)
5	0 (0.0%)	3 (37.5%)	3 (20.0%)
6	1 (14.3%)	0 (0.0%)	1 (6.7%)
p-VALUE (CHI^2)			0.1203
Follow Up (Day 8)			
MISSING	1 (14.3%)	3 (37.5%)	4 (26.7%)
3	2 (28.6%)	0 (0.0%)	2 (13.3%)

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
4	3 (42.9%)	2 (25.0%)	5 (33.3%)
5	0 (0.0%)	3 (37.5%)	3 (20.0%)
6	1 (14.3%)	0 (0.0%)	1 (6.7%)
p-VALUE (CHI^2)			0.1041
Follow Up (Day 9)			
MISSING	1 (14.3%)	3 (37.5%)	4 (26.7%)
3	2 (28.6%)	1 (12.5%)	3 (20.0%)
4	3 (42.9%)	1 (12.5%)	4 (26.7%)
5	0 (0.0%)	3 (37.5%)	3 (20.0%)
6	1 (14.3%)	0 (0.0%)	1 (6.7%)
p-VALUE (CHI^2)			0.1520
Follow Up (Day 10)			
MISSING	1 (14.3%)	3 (37.5%)	4 (26.7%)
3	4 (57.1%)	2 (25.0%)	6 (40.0%)
4	1 (14.3%)	0 (0.0%)	1 (6.7%)
5	0 (0.0%)	1 (12.5%)	1 (6.7%)
6	1 (14.3%)	0 (0.0%)	1 (6.7%)
7	0 (0.0%)	2 (25.0%)	2 (13.3%)
p-VALUE (CHI^2)			0.2292
Follow Up (Day 11)			
MISSING	1 (14.3%)	4 (50.0%)	5 (33.3%)
3	5 (71.4%)	1 (12.5%)	6 (40.0%)
5	0 (0.0%)	1 (12.5%)	1 (6.7%)
6	1 (14.3%)	0 (0.0%)	1 (6.7%)
7	0 (0.0%)	2 (25.0%)	2 (13.3%)
p-VALUE (CHI^2)			0.0886
Follow Up (Day 12)			
MISSING	2 (28.6%)	5 (62.5%)	7 (46.7%)

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
3	4 (57.1%)	0 (0.0%)	4 (26.7%)
5	0 (0.0%)	1 (12.5%)	1 (6.7%)
7	0 (0.0%)	2 (25.0%)	2 (13.3%)
8	1 (14.3%)	0 (0.0%)	1 (6.7%)
p-VALUE (CHI^2)			0.0460
Follow Up (Day 13)			
MISSING	6 (85.7%)	5 (62.5%)	11 (73.3%)
3	1 (14.3%)	0 (0.0%)	1 (6.7%)
5	0 (0.0%)	1 (12.5%)	1 (6.7%)
7	0 (0.0%)	2 (25.0%)	2 (13.3%)
p-VALUE (CHI^2)			0.1353
Follow Up (Day 14)			
MISSING	2 (28.6%)	1 (12.5%)	3 (20.0%)
0	1 (14.3%)	0 (0.0%)	1 (6.7%)
2	0 (0.0%)	4 (50.0%)	4 (26.7%)
3	4 (57.1%)	0 (0.0%)	4 (26.7%)
5	0 (0.0%)	2 (25.0%)	2 (13.3%)
7	0 (0.0%)	1 (12.5%)	1 (6.7%)
p-VALUE (CHI^2)			0.0174
Follow Up (Day 21)			
MISSING	3 (42.9%)	2 (25.0%)	5 (33.3%)
0	2 (28.6%)	1 (12.5%)	3 (20.0%)
1	1 (14.3%)	0 (0.0%)	1 (6.7%)
2	0 (0.0%)	2 (25.0%)	2 (13.3%)
3	1 (14.3%)	0 (0.0%)	1 (6.7%)
4	0 (0.0%)	1 (12.5%)	1 (6.7%)
5	0 (0.0%)	1 (12.5%)	1 (6.7%)
7	0 (0.0%)	1 (12.5%)	1 (6.7%)

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
p-VALUE (CHI^2)			0.3008
Follow Up (Day 28)			
MISSING	4 (57.1%)	1 (12.5%)	5 (33.3%)
0	1 (14.3%)	1 (12.5%)	2 (13.3%)
1	2 (28.6%)	0 (0.0%)	2 (13.3%)
2	0 (0.0%)	3 (37.5%)	3 (20.0%)
4	0 (0.0%)	2 (25.0%)	2 (13.3%)
7	0 (0.0%)	1 (12.5%)	1 (6.7%)
p-VALUE (CHI^2)			0.1066
Follow Up (Day 120)			
MISSING	5 (71.4%)	4 (50.0%)	9 (60.0%)
0	1 (14.3%)	4 (50.0%)	5 (33.3%)
1	1 (14.3%)	0 (0.0%)	1 (6.7%)
p-VALUE (CHI^2)			0.1213

A listing of the WHO R&D Blueprint Ordinal Scale for Clinical Improvement for all patients and visits is given in Supplement Table 4 and Supplement Table 5.

4.2. Primary and secondary endpoints

The primary endpoint is defined as the proportion of patients with treatment failures on day 14. Patients are defined as failures if their COVID-19 infection progressed to WHO categories 5, 6, 7 or 8. Missing values will be counted as failures.

The secondary endpoints are defined as the proportion of patients with treatment failures on day 7, day 21 and day 28.

Table 15. Primary and secondary endpoints for proportion of treatment failures. * Missing values that were imputed as “Treatment Failure” in a separate category.

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
Treatment (Day 7)			
No Treatment Failure	6 (85.7%)	2 (25.0%)	8 (53.3%)
Treatment Failure	1 (14.3%)	3 (37.5%)	4 (26.7%)
Imputed as Treatment Failure *	0 (0.0%)	3 (37.5%)	3 (20.0%)
p-VALUE (CHI^2)			0.0508
Treatment (Day 14)			
No Treatment Failure	5 (71.4%)	4 (50.0%)	9 (60.0%)
Treatment Failure	0 (0.0%)	3 (37.5%)	3 (20.0%)
Imputed as Treatment Failure *	2 (28.6%)	1 (12.5%)	3 (20.0%)
p-VALUE (CHI^2)			0.1833
Treatment (Day 21)			
No Treatment Failure	4 (57.1%)	4 (50.0%)	8 (53.3%)
Treatment Failure	0 (0.0%)	2 (25.0%)	2 (13.3%)
Imputed as Treatment Failure *	3 (42.9%)	2 (25.0%)	5 (33.3%)
p-VALUE (CHI^2)			0.3425
Treatment (Day 28)			
No Treatment Failure	3 (42.9%)	6 (75.0%)	9 (60.0%)
Treatment Failure	0 (0.0%)	1 (12.5%)	1 (6.7%)
Imputed as Treatment Failure *	4 (57.1%)	1 (12.5%)	5 (33.3%)
p-VALUE (CHI^2)			0.1534

Table 16. Primary and secondary endpoints for proportion of treatment failures. Missing values that were imputed as “Treatment Failure”. * Primary Endpoint

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
Treatment (Day 7)			
No Treatment Failure	6 (85.7%)	2 (25.0%)	8 (53.3%)
Treatment Failure	1 (14.3%)	6 (75.0%)	7 (46.7%)
p-VALUE (CHI^2)			0.0187
Treatment (Day 14) *			
No Treatment Failure	5 (71.4%)	4 (50.0%)	9 (60.0%)
Treatment Failure	2 (28.6%)	4 (50.0%)	6 (40.0%)
p-VALUE (CHI^2)			0.3980
Treatment (Day 21)			
No Treatment Failure	4 (57.1%)	4 (50.0%)	8 (53.3%)
Treatment Failure	3 (42.9%)	4 (50.0%)	7 (46.7%)
p-VALUE (CHI^2)			0.7821
Treatment (Day 28)			
No Treatment Failure	3 (42.9%)	6 (75.0%)	9 (60.0%)
Treatment Failure	4 (57.1%)	2 (25.0%)	6 (40.0%)
p-VALUE (CHI^2)			0.2049

The significant difference in treatment failures at day 7 can be contributed to an unequal number of imputations between both groups (0 in the control group and 3 in the plasma group, for more information see Table 15).

The primary endpoint was evaluated on day 14. At this point, two patients (28.6%) in the control group and four patients (50%) in the plasma group were treatment failures, including imputations of missing values.

The primary analysis was planned as a logistic regression adjusted for treatment, WHO scale at baseline and center to demonstrate that treatment with SOC and convalescent plasma reduces the risk for treatment failure as compared to SOC alone. The type-1-error is set to 5% (two-sided). Missing values will be counted as failures.

Due to the early study termination, the number of recruited patients (n=15) and the number of documented events (n=6) was small. Combined with the proposed number of covariates this led to numerical instability in the originally planned primary analysis model. A logistic regression using only therapy as an independent variable was performed instead. SOC and convalescent plasma was compared with SOC alone. Due to the inadequate number of observations and events the confidence interval was wide and non-informative. No statistical significant differences were found between treatment with SOC and convalescent plasma and SOC alone at day 14 (Odds Ratio 2.50, 95% Wald CI [0.292;21.392], p-value = 0.40).

One secondary endpoint was all-cause mortality. The number of death did not differ between both groups. In each group one patient died.

Table 17. Overview of patients that died during the study.

Therapy	Patient ID	Date of Death	Reason
Plasma	01-006	07MAY21	multiple organ failure
Control	04-002	25APR21	Covid-19 Pneumonia, multiple organ failure, severe Acute Respiratory Distress Syndrome

A more detailed description of the patients who died is given in 5.2. Serious Adverse Events (Pharmacovigilance).

5 Safety/Adverse Events

Table 18. Total number of adverse events.

	Therapy		
	Control N=24	Plasma N=34	Total N=58
Total Number of Adverse Events			
Total number of AEs	19 (79.2%)	32 (94.1%)	51 (87.9%)
Total number of SAEs	5 (20.8%)	2 (5.9%)	7 (12.1%)

A total number of 51 adverse events and 7 serious adverse events were reported. No SUSARs were documented.

Table 19. Overview of adverse events.

	Therapy		
	Control N=7	**Plasma N=8**	**Total N=15**
At least one Adverse Event			
Yes	6 (85.7%)	7 (87.5%)	13 (86.7%)
No	1 (14.3%)	1 (12.5%)	2 (13.3%)
p-VALUE (CHI^2)			0.9192
At least one Serious Adverse Event			
Yes	3 (42.9%)	2 (25.0%)	5 (33.3%)
No	4 (57.1%)	6 (75.0%)	10 (66.7%)
p-VALUE (CHI^2)			0.4642
At least one AE with Outcome: Fatal			
Yes	1 (14.3%)	1 (12.5%)	2 (13.3%)
No	6 (85.7%)	7 (87.5%)	13 (86.7%)
p-VALUE (CHI^2)			0.9192
At least one AE with potential causality to the study drug			
Yes	0 (0.0%)	4 (50.0%)	4 (26.7%)
No	7 (100.0%)	4 (50.0%)	11 (73.3%)
p-VALUE (CHI^2)			0.0289

The significant difference in adverse events with potential causality to the study drug is expected because the study was open-label.

5.1. Serious Adverse Events

Table 20. Serious adverse events - This table includes all serious adverse events. Percentages are calculated using total number of events per treatment arm as the denominator.

	Therapy		
System Organ Class Preferred Term	**Control (N=7)**	**Plasma (N=8)**	**Total (N=15)**
Total number of serious adverse events	5 (100.0%)	2 (100.0%)	7 (100.0%)
Cardiac disorders	1 (20.0%)	-	1 (14.3%)
Myocardial infarction	1 (20.0%)	-	1 (14.3%)
Infections and infestations	4 (80.0%)	2 (100.0%)	6 (85.7%)
Bronchopulmonary aspergillosis	1 (20.0%)	-	1 (14.3%)
COVID-19 pneumonia	1 (20.0%)	-	1 (14.3%)
Pneumonia staphylococcal	1 (20.0%)	-	1 (14.3%)
Septic shock	-	1 (50.0%)	1 (14.3%)
Superinfection bacterial	-	1 (50.0%)	1 (14.3%)
Urinary tract infection	1 (20.0%)	-	1 (14.3%)

Table 21. Serious adverse events - This table includes adverse events only once per patient. Percentages are calculated using total number of patients per treatment arm as the denominator.

	Therapy		
System Organ Class Preferred Term	**Control (N=7)**	**Plasma (N=8)**	**Total (N=15)**
Number of patients with at least one serious adverse event	3 (42.9%)	2 (25.0%)	5 (33.3%)
Cardiac disorders	1 (14.3%)	-	1 (6.7%)
Myocardial infarction	1 (14.3%)	-	1 (6.7%)
Infections and infestations	2 (28.6%)	2 (25.0%)	4 (26.7%)
Bronchopulmonary aspergillosis	1 (14.3%)	-	1 (6.7%)
COVID-19 pneumonia	1 (14.3%)	-	1 (6.7%)
Pneumonia staphylococcal	1 (14.3%)	-	1 (6.7%)
Septic shock	-	1 (12.5%)	1 (6.7%)
Superinfection bacterial	-	1 (12.5%)	1 (6.7%)
Urinary tract infection	1 (14.3%)	-	1 (6.7%)

5.2. Serious Adverse Events (Pharmacovigilance)

Therapy	Patient ID	SAE onset	SOC	PT	Outcome	Related?	Expected?
Plasma	01-001	18JAN21	Infections and infestations	Superinfection bacterial	completely recovered/back to baseline conditions	no	.
Narrative							
This is a SAE case report of 'bacterial superinfection' in a 63 year-old female participant in the COMET trial (A prospective, randomized, open label Phase 2 clinical trial to evaluate superiority of anti-SARS-CoV-2 convalescent plasma versus standard-of-care in hospitalized patients with mild COVID-19, COMET). The patient was already hospitalized since 01JAN2021 for acute renal transplant failure when she was diagnosed with mild COVID-19 (WHO score 3) on 13JAN2021 for which she was treated with antibiotic medication (piperacillin/tazobactam i.v.) since the same day. In the following she received IMP convalescent plasma (1x250 ml/d i.v.) on 15 and 16JAN2021 as per the COMET protocol. CRP and procalcitonin serum concentrations were elevated on 17JAN2021 and CRP further increased on 18JAN2021. On the same day grade 3 bacterial superinfection was diagnosed and antibiotic treatment was changed to meropenem i.v. (2x 1000mg/d).Lab values improved, antibiotic treatment was stopped on 01FEB2021 and the patient was reported as completely recovered.The patient's medical history was noteworthy for kidney transplant and type I diabetes (no start date provided), for which she was under concomitant medication with sirolimus (1x 2.5 mg/d p.o.) and insulin (no start date provided), among others.Both, investigator and the sponsor's delegate for pharmacovigilance assessed the event 'bacterial superinfection' as not related to the IMP convalescent plasma. It seems more likely that the event is a complication of the underlying disease (COVID-19) in a immunocompromised setting (concomitant immunosuppressive medication and diabetes type I).							

Therapy	Patient ID	SAE onset	SOC	PT	Outcome	Related?	Expected?
Control	01-004	11MAR21	Renal and urinary disorders	Urinary tract infection	completely recovered/back to baseline conditions	no	.
Narrative							

Therapy	Patient ID	SAE onset	SOC	PT	Outcome	Related?	Expected?
This is an SAE report of 'urinary tract infection' in a 55-year-old male study participant in the COMET trial (A prospective, randomized, open label Phase 2 clinical trial to evaluate superiority of anti-SARS-CoV-2 convalescent plasma versus standard-of-care in hospitalized patients with mild COVID-19, COMET). Of note, the patient had been randomized to standard-care therapy and therefore did not receive the study IMP.On 11MAR2021, the patient was admitted to hospital due to fever (39.5 °C), pain, nausea, and decreased appetite. Laboratory investigations revealed increased CRP and ferritin values as well as leukocyturia and bacteriuria. A urinary tract infection was suspected and treated empirically with piperacillin-tazobactam (3x 4.5 g/d i.v. from 11-17MAR2021) and infusions of metamizole and dimenhydrinate. The patient was discharged on 17MAR2021 as recovered into domestic isolation (due to ongoing COVID-19).The patient's medical history is noteworthy for transplantation of both lungs (JAN2019), post-transplant diabetes mellitus (DEC2020), and an ongoing mild (WHO score 3) COVID-19 infection (start date: 24FEB2021). Relevant concomitant medication for this case consisted of immunosuppressive agents tacrolimus and prednisolone. Further concomitant medication comprised trimethoprim-sulfamethoxazole, itraconazole, pravastatin, calcium carbonate, magnesium, colecalciferole, paracetamol, tinzaparin, and human insulin.As the patient was randomized to standard care (and thus did not receive the IMP convalescent plasma), there is no causal relationship between the event 'urinary tract infection' and the IMP.							

Therapy	Patient ID	SAE onset	SOC	PT	Outcome	Related?	Expected?
Control	01-005	21MAR21	Cardiac disorders	Myocardial infarction	completely recovered/back to baseline conditions	no	.
Narrative							
This is an SAE report of 'myocardial infarction' in a 75-year-old male study participant in the COMET trial (A prospective, randomized, open label Phase 2 clinical trial to evaluate superiority of anti-SARS-CoV-2 convalescent plasma versus standard-of-care in hospitalized patients with mild COVID-19, COMET).Of note, the patient had been randomized to standard-care therapy and therefore did not receive the study IMP.While being hospitalized due to an ongoing mild (WHO score 4) COVID-19 infection (start date: 18MAR2021), the patient complained about bad sleep and back pain on 21MAR2021. Increased values of troponin, NT-proBNP, CK, and CK-MB as well as echocardiographic findings were suggestive of an acute myocardial infarction that was confirmed and treated by emergency coronary catheterization with right coronary artery stent implantation. In addition, acetylsalicylic acid 500 mg i.v., was administered once on 21MAR2021. With regard to the event 'myocardial infarction', the patient recovered on 21MAR2021 but remains hospitalized for COVID-19.As the patient was randomized to standard care (and thus did not receive the IMP convalescent plasma), there is no causal relationship between the event 'myocardial infarction' and the IMP.							

Therapy	Patient ID	SAE onset	SOC	PT	Outcome	Related?	Expected?
Plasma	01-006	29APR21	Infections and infestations	Septic shock	fatal	no	.

Therapy	Patient ID	SAE onset	SOC	PT	Outcome	Related?	Expected?
Narrative							
This SAE refers to a case of 'septic shock' in a 68 year-old female participant in the COMET trial (A prospective, randomized, open label Phase 2 clinical trial to evaluate superiority of anti-SARS-CoV-2 convalescent plasma versus standard-of-care in hospitalized patients with mild COVID-19) who had been diagnosed with mild COVID-19 infection (WHO score 4) on 27MAR2021, progressing to COVID-19 pneumonia on 03APR2021. The patient had received IMP convalescent plasma (1x 250ml i.v.) as per the COMET protocol on 07 and 08APR2021.COVID-19 pneumonia aggravated and mechanical ventilation and extracorporeal membrane oxygenation (ECMO) became necessary since 15APR2021. On 29APR2021 the patient developed septic shock which was treated with antibiotics, plasma exchange, dialysis, and anti-infective medications (no details provided). Despite these efforts, the patient died due to multiple organ failure on 07MAY2021. No autopsy was performed.Both, investigator and sponsor's delegate for pharmacovigilance assessed the event 'septic shock' as not causally related to the IMP. Rather, the event is caused by a complication of the underlying disease.							

Therapy	Patient ID	SAE onset	SOC	PT	Outcome	Related?	Expected?
Control	04-002	22APR21	Infections and infestations	Bronchopulmonary aspergillosis	fatal	no	.
Narrative							
This SAE refers to a 56 year-old female participant in the COMET trial (A prospective, randomized, open label Phase 2 clinical trial to evaluate superiority of anti-SARS-CoV-2 convalescent plasma versus standard-of-care in hospitalized patients with mild COVID-19) who had been diagnosed with a mild COVID-19 infection (WHO score 3) on 08APR2021 and who had been randomized to standard care treatment on 13APR2021.While the patient was still hospitalized in intensive care for COVID-19 pneumonia since 16APR2021 (reported previously as a separate SAE) , an aspergillus pneumonia was diagnosed in a bronchoalveolar lavage specimen and treated with voriconazole (2x 400mg/d i.v.) since 22APR2021. In the course of the event the patient's situation aggravated and she died on 25APR2021 due to multiple organ failure and acute respiratory distress syndrome. No autopsy was done.Of note, the event was complicated by COVID-19 pneumonia and bacterial (staphylococcus) pulmonary infection (reported as separate SAEs).As the patient was randomized to standard care (and did not receive the IMP), there is no causal relationship between the event 'aspergillus pneumonia' and the IMP.							

Therapy	Patient ID	SAE onset	SOC	PT	Outcome	Related?	Expected?
Control	04-002	21APR21	Infections and infestations	Staphylococcal infection	fatal	no	.

Narrative

This SAE refers to a 56 year-old female participant in the COMET trial (A prospective, randomized, open label Phase 2 clinical trial to evaluate superiority of anti-SARS-CoV-2 convalescent plasma versus standard-of-care in hospitalized patients with mild COVID-19) who had been diagnosed with a mild COVID-19 infection (WHO score 3) on 08APR2021 and who had been randomized to standard care treatment on 13APR2021.While the patient was still hospitalized in intensive care for COVID-19 pneumonia (reported previously as a separate SAE) since 16APR2021, a staphylococcus aureus infection was diagnosed on 21APR2021 by bronchioalveolar lavage. Treatment was started with i.v. cefazolin 3x2g/d. In the course of the event the patient's situation aggravated and she died on 25APR2021 due to multiple organ failure and acute respiratory distress syndrome. No autopsy was done.Of note, the event was complicated by COVID-19 pneumonia and fungal (aspergillus) pulmonary infection (reported as separate SAEs). As the patient was randomized to standard care (and did not receive the IMP), there is no causal relationship between the event 'staphylococcal infection' and the IMP.

Therapy	Patient ID	SAE onset	SOC	PT	Outcome	Related?	Expected?
Control	04-002	16APR21	Infections and infestations	COVID-19 pneumonia	fatal	no	.

Narrative

This case reports on a 56 year-old female participant in the COMET trial (A prospective, randomized, open label Phase 2 clinical trial to evaluate superiority of anti-SARS-CoV-2 convalescent plasma versus standard-of-care in hospitalized patients with mild COVID-19) who had been diagnosed with a mild COVID-19 infection (WHO score 3) on 08APR2021 and who had been randomized to standard care (no IMP applied) on 13APR2021.On 16APR2021 she developed grade 4 COVID-19 pneumonia with respiratory insufficiency that led to prolonged hospitalization. CT thorax performed on 11APR2021 had shown multiple subpleural patchy milk glass opacities in all lobes of the lung typical for COVID-19 which were progredient on 19APR2021. The event was treated with i.v.dexamethasone 6mg/d from 15 till 24APR2021. The patient developed acute respiratory distress syndrome (ARDS) and was mechanically ventilated since 18APR2021. The event was complicated by multiple organ failure and ended fatally on 25APR2021. No autopsy was done.Of note, the event was complicated by bacterial (staphylococcus) and fungal (aspergillus) pulmonary infections (reported as separate SAEs).As the patient was randomized to standard care (and did not receive the IMP), there is no causal relationship between the event 'COVID-19 pneumonia' and the IMP.

5.3. Adverse Events

Table 22. Adverse events - This table includes all adverse events. Percentages are calculated using total number of events per treatment arm as the denominator.

	Therapy		
System Organ Class Preferred Term	**Control (N=7)**	**Plasma (N=8)**	**Total (N=15)**
Total number of adverse events	19 (100.0%)	32 (100.0%)	51 (100.0%)
Blood and lymphatic system disorders	2 (10.5%)	4 (12.5%)	6 (11.8%)
Anaemia	1 (5.3%)	2 (6.3%)	3 (5.9%)
Lymphopenia	1 (5.3%)	1 (3.1%)	2 (3.9%)
Neutrophilia	-	1 (3.1%)	1 (2.0%)
Cardiac disorders	1 (5.3%)	1 (3.1%)	2 (3.9%)
Myocardial infarction	1 (5.3%)	-	1 (2.0%)
Tachycardia	-	1 (3.1%)	1 (2.0%)
Eye disorders	1 (5.3%)	1 (3.1%)	2 (3.9%)
Eye pruritus	-	1 (3.1%)	1 (2.0%)
Ocular hyperaemia	1 (5.3%)	-	1 (2.0%)
Gastrointestinal disorders	1 (5.3%)	2 (6.3%)	3 (5.9%)
Abdominal pain upper	-	1 (3.1%)	1 (2.0%)
Diarrhoea	-	1 (3.1%)	1 (2.0%)
Nausea	1 (5.3%)	-	1 (2.0%)
General disorders and administration site conditions	-	3 (9.4%)	3 (5.9%)
Fatigue	-	2 (6.3%)	2 (3.9%)
General physical health deterioration	-	1 (3.1%)	1 (2.0%)
Infections and infestations	5 (26.3%)	3 (9.4%)	8 (15.7%)
Bronchopulmonary aspergillosis	1 (5.3%)	-	1 (2.0%)
COVID-19	-	1 (3.1%)	1 (2.0%)
COVID-19 pneumonia	1 (5.3%)	-	1 (2.0%)
Pneumonia staphylococcal	1 (5.3%)	-	1 (2.0%)
Septic shock	-	1 (3.1%)	1 (2.0%)
Superinfection	1 (5.3%)	-	1 (2.0%)
Superinfection bacterial	-	1 (3.1%)	1 (2.0%)
Urinary tract infection	1 (5.3%)	-	1 (2.0%)
Injury, poisoning and procedural complications	1 (5.3%)	1 (3.1%)	2 (3.9%)

	Therapy		
System Organ Class Preferred Term	**Control (N=7)**	**Plasma (N=8)**	**Total (N=15)**
Arthropod bite	-	1 (3.1%)	1 (2.0%)
Fall	1 (5.3%)	-	1 (2.0%)
Investigations	2 (10.5%)	7 (21.9%)	9 (17.6%)
C-reactive protein increased	-	2 (6.3%)	2 (3.9%)
Fibrin D dimer increased	1 (5.3%)	2 (6.3%)	3 (5.9%)
Haemoglobin decreased	-	1 (3.1%)	1 (2.0%)
N-terminal prohormone brain natriuretic peptide increased	1 (5.3%)	-	1 (2.0%)
Procalcitonin increased	-	1 (3.1%)	1 (2.0%)
White blood cell count decreased	-	1 (3.1%)	1 (2.0%)
Metabolism and nutrition disorders	2 (10.5%)	1 (3.1%)	3 (5.9%)
Decreased appetite	1 (5.3%)	1 (3.1%)	2 (3.9%)
Hyperglycaemia	1 (5.3%)	-	1 (2.0%)
Musculoskeletal and connective tissue disorders	3 (15.8%)	1 (3.1%)	4 (7.8%)
Back pain	2 (10.5%)	1 (3.1%)	3 (5.9%)
Pain in extremity	1 (5.3%)	-	1 (2.0%)
Nervous system disorders	-	3 (9.4%)	3 (5.9%)
Cerebral disorder	-	1 (3.1%)	1 (2.0%)
Headache	-	1 (3.1%)	1 (2.0%)
Hypotonia	-	1 (3.1%)	1 (2.0%)
Psychiatric disorders	1 (5.3%)	1 (3.1%)	2 (3.9%)
Panic attack	-	1 (3.1%)	1 (2.0%)
Restlessness	1 (5.3%)	-	1 (2.0%)
Respiratory, thoracic and mediastinal disorders	-	3 (9.4%)	3 (5.9%)
Haemothorax	-	1 (3.1%)	1 (2.0%)
Hypoxia	-	1 (3.1%)	1 (2.0%)
Oropharyngeal pain	-	1 (3.1%)	1 (2.0%)
Skin and subcutaneous tissue disorders	-	1 (3.1%)	1 (2.0%)
Night sweats	-	1 (3.1%)	1 (2.0%)

Table 23. Adverse events - This table includes adverse events only once per patient. Percentages are calculated using total number of patients per treatment arm as the denominator.

	Therapy		
System Organ Class Preferred Term	**Control (N=7)**	**Plasma (N=8)**	**Total (N=15)**
Number of patients with at least one adverse event	6 (85.7%)	7 (87.5%)	13 (86.7%)
Blood and lymphatic system disorders	1 (14.3%)	2 (25.0%)	3 (20.0%)
Anaemia	1 (14.3%)	2 (25.0%)	3 (20.0%)
Lymphopenia	1 (14.3%)	1 (12.5%)	2 (13.3%)
Neutrophilia	-	1 (12.5%)	1 (6.7%)
Cardiac disorders	1 (14.3%)	1 (12.5%)	2 (13.3%)
Myocardial infarction	1 (14.3%)	-	1 (6.7%)
Tachycardia	-	1 (12.5%)	1 (6.7%)
Eye disorders	1 (14.3%)	1 (12.5%)	2 (13.3%)
Eye pruritus	-	1 (12.5%)	1 (6.7%)
Ocular hyperaemia	1 (14.3%)	-	1 (6.7%)
Gastrointestinal disorders	1 (14.3%)	2 (25.0%)	3 (20.0%)
Abdominal pain upper	-	1 (12.5%)	1 (6.7%)
Diarrhoea	-	1 (12.5%)	1 (6.7%)
Nausea	1 (14.3%)	-	1 (6.7%)
General disorders and administration site conditions	-	3 (37.5%)	3 (20.0%)
Fatigue	-	2 (25.0%)	2 (13.3%)
General physical health deterioration	-	1 (12.5%)	1 (6.7%)
Infections and infestations	2 (28.6%)	2 (25.0%)	4 (26.7%)
Bronchopulmonary aspergillosis	1 (14.3%)	-	1 (6.7%)
COVID-19	-	1 (12.5%)	1 (6.7%)
COVID-19 pneumonia	1 (14.3%)	-	1 (6.7%)
Pneumonia staphylococcal	1 (14.3%)	-	1 (6.7%)
Septic shock	-	1 (12.5%)	1 (6.7%)
Superinfection	1 (14.3%)	-	1 (6.7%)
Superinfection bacterial	-	1 (12.5%)	1 (6.7%)
Urinary tract infection	1 (14.3%)	-	1 (6.7%)
Injury, poisoning and procedural complications	1 (14.3%)	1 (12.5%)	2 (13.3%)

	Therapy		
System Organ Class Preferred Term	**Control (N=7)**	**Plasma (N=8)**	**Total (N=15)**
Arthropod bite	-	1 (12.5%)	1 (6.7%)
Fall	1 (14.3%)	-	1 (6.7%)
Investigations	2 (28.6%)	3 (37.5%)	5 (33.3%)
C-reactive protein increased	-	2 (25.0%)	2 (13.3%)
Fibrin D dimer increased	1 (14.3%)	2 (25.0%)	3 (20.0%)
Haemoglobin decreased	-	1 (12.5%)	1 (6.7%)
N-terminal prohormone brain natriuretic peptide increased	1 (14.3%)	-	1 (6.7%)
Procalcitonin increased	-	1 (12.5%)	1 (6.7%)
White blood cell count decreased	-	1 (12.5%)	1 (6.7%)
Metabolism and nutrition disorders	2 (28.6%)	1 (12.5%)	3 (20.0%)
Decreased appetite	1 (14.3%)	1 (12.5%)	2 (13.3%)
Hyperglycaemia	1 (14.3%)	-	1 (6.7%)
Musculoskeletal and connective tissue disorders	2 (28.6%)	1 (12.5%)	3 (20.0%)
Back pain	2 (28.6%)	1 (12.5%)	3 (20.0%)
Pain in extremity	1 (14.3%)	-	1 (6.7%)
Nervous system disorders	-	3 (37.5%)	3 (20.0%)
Cerebral disorder	-	1 (12.5%)	1 (6.7%)
Headache	-	1 (12.5%)	1 (6.7%)
Hypotonia	-	1 (12.5%)	1 (6.7%)
Psychiatric disorders	1 (14.3%)	1 (12.5%)	2 (13.3%)
Panic attack	-	1 (12.5%)	1 (6.7%)
Restlessness	1 (14.3%)	-	1 (6.7%)
Respiratory, thoracic and mediastinal disorders	-	3 (37.5%)	3 (20.0%)
Haemothorax	-	1 (12.5%)	1 (6.7%)
Hypoxia	-	1 (12.5%)	1 (6.7%)
Oropharyngeal pain	-	1 (12.5%)	1 (6.7%)
Skin and subcutaneous tissue disorders	-	1 (12.5%)	1 (6.7%)
Night sweats	-	1 (12.5%)	1 (6.7%)

6 Conclusion

The primary objectives of the COMET study were to evaluate the efficacy of convalescent plasma for the treatment of hospitalized patients with moderate COVID-19 (WHO grade 3 or 4) and to assess safety and tolerability.

The study was terminated prematurely on 15.11.2021 because of a low recruitment rate and difficulties to achieve the planned numbers of study participants with-in a reasonable period. The number of included patients was 15/340=4.4% of the planned sample size. One patient was randomized and included in the ITT analysis but did not receive any study medication.

The primary endpoint was defined as the proportion of patients with treatment failure on day 14. Two patients (28.6%) in the control group and four patients (50%) in the plasma group were treatment failures. No statistical significant differences were found between both treatment groups using a logistic regression.

In terms of safety, treatment with anti-SARS-CoV-2 convalescent plasma was generally well-tolerated. No treatment-related SAEs were observed. A total number of 51 adverse events and 7 serious adverse events were reported. No Suspected Unexpected Serious Adverse Reactions (SUSARs) were documented. Numerically, the incidence of SAEs was higher in the control arm (standard-of-care, 5 cases in 7 patients) than with the active treatment (2 cases in 8 Patients) (see Table 18).

Based on the small number of analyzed patients we did not find relevant differences for the primary endpoint as well as for safety parameters between anti-SARS-CoV-2 convalescent plasma and standard-of-care in patients with mild COVID-19. Furthermore, due to the low recruitment rate of patients and the high number of study discontinuations, no conclusions can be drawn regarding the efficacy and effectiveness of convalescent plasma in the study population.

Reasons for the low recruitment rate are manifold, for example, a high percentage (80%) of infected individuals had a mild to moderate form of SARS-CoV-2 disease. Due to the low incidences of new SARS-COV-2 infections and related to this, the number of hospitalized patients who could be included in the clinical trial (meeting the inclusion criteria) decreased sharply after a sharp increase in March/April 2021 due to contact reduction measures. The proportion of hospitalized patients was 10% of referred cases in Germany (3). Competing therapeutic options such as monoclonal antibody therapy also significantly influenced recruitment progression. Recommendations by professional societies (1) such as the COVRIIN working group at the Robert Koch Institute (2) guide the choice of therapeutic modality. Based on these recommendations, monoclonal antibody therapy has been used in more clinical settings as standard therapy for early stage COVID-19 disease.

The majority of theoretically eligible patients in COVID-19 normal wards could not be recruited due to the reasons mentioned above. In addition, potential study patients refused to participate in the study due to lack of language skills, fulfillment of exclusion criteria such as an elevated body mass index > 40 kg/m2 or patients with an age of >75 years and a general study fatigue in the population.
Furthermore, a high number of early study discontinuations were recorded during the course of the clinical trial, which further biased the study data. A high proportion of study patients did not show up for further study visits after the end of the inpatient stay despite all efforts.

Reference

1. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (AWMF). S3-Leitlinie - Empfehlungen zur stationären Therapie von Patienten mit CO-VID-19. AWMF online, 05.10.2021
2. Fachgruppe COVRIIN am Robert Koch-Institut. Medikamentöse Therapie bei COVID-19 mit Bewertung durch die Fachgruppe COVRIIN am Robert Koch-Institut. 20.10.2021; DOI 10.25646/7743.14
3. Robert-Koch-Institut. Epidemiologisches Bulletin 18/2021, Aktuelle Daten und Informationen zu Infektionskrankheiten und Public Health, 2021

Date of report: 14.09.2022

Disclaimer: ZKS has been responsible for data management and monitoring. The validated data transfer of the final data was performed on 22.08.2022. A careful assessment of plausibility has been conducted by the members of the department of Biostatistics and findings were discussed jointly.

Signatures

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

_____

[Prof. Dr. med. Rainer Blasczyk, Study Chair]

[Institute of Transfusion Medicine and Transplant Engineering]

_____ _____

[Maria von Karpowitz] [Prof. Dr. Armin Koch]

[Institute of Biostatistics, Study Statistician] [Institute of Biostatistics]

Appendices

Supplement Table 1. WHO R&D Blueprint Ordinal Scale

Patient State	**Descriptor**	**Score**
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
Ambulatory	Limitation of activities	2
Hospitalized mild disease	Hospitalized, no oxygen therapy	3
Hospitalized mild disease	Oxygen by mask or nasal prongs	4
Hospitalized severe disease	Non-invasive ventilation or high-flow oxygen	5
Hospitalized severe disease	Intubation and mechanical ventilation	6
Hospitalized severe disease	Ventilation + additional organ support – pressors, renal re-placement therapy, ECMO	7
Dead	Death	8

Supplement Table 2. Visit overview (part 1)

Patient	Screening	Treatment Day 1	Treatment Day 2	Follow Up Day 3	Follow Up Day 4	Follow Up Day 5	Follow Up Day 6	Follow Up Day 7	Follow Up Day 8	Follow Up Day 9
01-001	14/01/21	15/01/21	16/01/21	17/01/21	18/01/21	19/01/21	20/01/21	21/01/21	22/01/21	23/01/21
01-002	21/01/21	22/01/21	23/01/21	24/01/21	25/01/21	26/01/21	27/01/21	28/01/21	29/01/21	30/01/21
01-003	04/02/21	.	.	.	.	.	.	.	.	.
01-004	25/02/21	26/02/21	27/02/21	28/02/21	01/03/21	02/03/21	03/03/21	04/03/21	.	.
01-005	19/03/21	20/03/21	21/03/21	22/03/21	23/03/21	24/03/21	25/03/21	26/03/21	27/03/21	28/03/21
01-006	06/04/21	07/04/21	08/04/21	09/04/21	10/04/21	11/04/21	12/04/21	13/04/21	14/04/21	15/04/21
01-007	23/04/21	24/04/21	25/04/21	26/04/21	27/04/21	28/04/21	29/04/21	30/04/21	01/05/21	02/05/21
02-001	26/04/21	27/04/21	28/04/21	29/04/21	30/04/21	01/05/21	02/05/21	03/05/21	04/05/21	05/05/21
02-002	27/05/21	28/05/21	29/05/21	30/05/21	31/05/21	01/06/21	02/06/21	03/06/21	04/06/21	05/06/21
04-001	07/04/21	08/04/21	09/04/21	10/04/21	11/04/21	12/04/21	13/04/21	14/04/21	15/04/21	16/04/21
04-002	13/04/21	14/04/21	15/04/21	16/04/21	17/04/21	18/04/21	19/04/21	20/04/21	21/04/21	22/04/21
05-001	22/04/21	23/04/21	24/04/21	25/04/21	26/04/21	27/04/21	28/04/21	.	.	.
05-002	04/05/21	05/05/21	06/05/21	07/05/21	08/05/21	09/05/21	10/05/21	.	.	.
07-001	02/06/21	03/06/21	04/06/21	05/06/21	06/06/21	07/06/21	08/06/21	09/06/21	10/06/21	11/06/21
07-002	22/06/21	23/06/21	24/06/21	25/06/21	26/06/21	27/06/21	28/06/21	29/06/21	30/06/21	01/07/21

Supplement Table 3. Visit overview (part 2)

Patient	Follow Up Day 10	Follow Up Day 11	Follow Up Day 12	Follow Up Day 13	Follow Up Day 14	Follow Up Day 21	Follow Up Day 28	Follow Up Day 120
01-001	24/01/21	25/01/21	26/01/21	27/01/21	28/01/21	04/02/21	11/02/21	.
01-002	31/01/21	01/02/21	02/02/21	.	03/02/21	11/02/21	.	19/05/21
01-003	.	.	.	.	.	.	.	.
01-004	.	.	.	.	11/03/21	17/03/21	.	25/06/21
01-005	29/03/21	30/03/21	31/03/21	.	.	.	16/04/21	.
01-006	16/04/21	17/04/21	18/04/21	19/04/21	20/04/21	27/04/21	04/05/21	.
01-007	03/05/21	04/05/21	.	.	07/05/21	14/05/21	21/05/21	.
02-001	06/05/21	.	.	.	10/05/21	17/05/21	25/05/21	13/08/21
02-002	06/06/21	07/06/21	.	.	10/06/21	17/06/21	24/06/21	22/09/21
04-001	17/04/21	18/04/21	19/04/21	.	20/04/21	28/04/21	05/05/21	.
04-002	23/04/21	24/04/21	25/04/21	.	.	.	.	.
05-001	.	.	.	.	06/05/21	13/05/21	19/05/21	19/08/21
05-002	.	.	.	.	19/05/21	.	01/06/21	01/09/21
07-001	12/06/21	13/06/21	14/06/21	15/06/21	16/06/21	.	.	.
07-002	02/07/21	03/07/21	04/07/21	05/07/21	06/07/21	14/07/21	20/07/21	.

Supplement Table 4. Overview for the WHO R&D Blueprint Ordinal Scale for Clinical Improvement (part 1)

Patient	Screening	Treatment Day 1	Treatment Day 2	Follow Up Day 3	Follow Up Day 4	Follow Up Day 5	Follow Up Day 6	Follow Up Day 7	Follow Up Day 8	Follow Up Day 9
01-001	3	3	4	5	5	5	5	5	5	5
01-002	3	3	3	3	3	3	3	3	3	3
01-003	3									
01-004	3	3	3	3	3	3	3	3		
01-005	4	4	4	4	4	4	4	4	4	4
01-006	4	4	4	4	5	5	5	5	5	5
01-007	4	4	4	4	3	3	3	3	3	3
02-001	4	4	4	4	4	4	4	4	4	4
02-002	3	3	3	4	4	4	3	3	4	3
04-001	4	4	4	4	4	3	4	4	4	4
04-002	3	3	4	4	5	6	6	6	6	6
05-001	4	4	4	4	4	3	3			
05-002	3	3	3	3	3	3	3			
07-001	3	4	4	4	4	4	4	4	4	4
07-002	4	4	4	5	5	5	5	5	5	5

Supplement Table 5. Overview for the WHO R&D Blueprint Ordinal Scale for Clinical Improvement (part 2)

Patient	Follow Up Day 10	Follow Up Day 11	Follow Up Day 12	Follow Up Day 13	Follow Up Day 14	Follow Up Day 21	Follow Up Day 28	Follow Up Day 120
01-001	7	7	7	7	5	5	4	
01-002	3	3	3		3	0		1
01-003								
01-004					3	3		0
01-005	4	3	3				1	
01-006	7	7	7	7	7	7	7	
01-007	3	3			0	0	1	
02-001	3				2	2	2	0
02-002	3	3			2	0	0	0
04-001	3	3	3		3	1	0	
04-002	6	6	8					
05-001					2	2	2	0
05-002					2		2	0
07-001	3	3	3	3	3			
07-002	5	5	5	5	5	4	4	

Supplement Table 6. PRNT50 values for all patients and visits.

Patient	Screening	Treatment Day 1	Treatment Day 2	Follow Up Day 3	Follow Up Day 7	Follow Up Day 14	Follow Up Day 21	Follow Up Day 28	Follow Up Day 120
01-001	.	.	.	.	.	.	>1:1600	>1:600	.
01-002	.	.	.	.	.	.	.	.	.
01-003	1:25 - 1:100	.	.	.	.	.	.	.	.
01-004	1:25 - 1:100	1:100 - 1:400	1:100 - 1:400	1:400 - 1:1600	>1:1600	>1:1600	>1:1600	.	1:25 - 1:100
01-005	.	1:100 - 1:400	1:100 - 1:400	1:400 - 1:1600	1:400 - 1:1600	.	.	>1:1600	.
01-006	>1:1600	>1:1600	>1:1600	>1:1600	>1:1600	1:400 - 1:1600	>1:1600	1:400 - 1:1600	.
01-007	1:400 - 1:1600	1:400 - 1:1600	1:400 - 1:1600	1:400 - 1:1600	>1:1600	1:400 - 1:1600	1:400 - 1:1600	1:100 - 1:400	.
02-001	.	.	.	.	1:100 - 1:400	>1:1600	>1:1600	>1:1600	>1:1600
02-002	.	.	1:25 - 1:100	1:25 - 1:100	>1:1600	>1:1600	>1:1600	>1:1600	>1:1600
04-001	1:400 - 1:1600	>1:1600	1:400 - 1:1600	1:400 - 1:1600	>1:1600	>1:1600	>1:1600	>1:1600	.
04-002	.	.	.	.	.	.	.	.	.
05-001	1:100 - 1:400	1:25 - 1:100	1:400 - 1:1600	>1:1600	.	>1:1600	>1:1600	>1:1600	1:400 - 1:1600
05-002	.	.	1:25 - 1:100	1:400 - 1:1600	.	>1:1600	.	>1:1600	.
07-001	.	.	.	1:25 - 1:100	1:25 - 1:100	1:400 - 1:1600	.	.	.
07-002	>1:1600	>1:1600	>1:1600	>1:1600	>1:1600	>1:1600	>1:1600	>1:1600	.