TRIAL STATISTICAL ANALYSIS PLAN

c35106585-02

Trial No.:	Uni-Koeln-4370
BI Trial No.:	1487-0005
Title:	A Phase 1/2a Trial of the Inhaled Administration of the SARS-CoV-2-Neutralizing Monoclonal Antibody DZIF-10c in SARS-CoV-2-Infected and -Uninfected Individuals Including Protocol Amendment 3 [Version V04_0, 01-APR-2021]
Investigational Product:	DZIF-10c
BI product No.:	BI 767551
Sponsor Representative	[redacted]
Responsible trial statistician:	[redacted]

Statistician with Boehringer Ingelheim	[redacted]
Date of statistical analysis plan:	28 MAY 2021
Version:	2.0

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Term	Definition / description
ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BI	Boehringer Ingelheim
bpm	Beats Per Minute
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
COVID-19	Coronavirus SARS-CoV-2
CPE	Cytopathic Effect
CT	Cycle Threshold
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DLT	Dose Limiting Toxicity
DZIF	Deutsches Zentrum für Infektionsforschung / German Center for Infection Research
eCRF	electronic Case Report Form
ECG	Electrocardiogram
EMA	European Medicines Agency
FEV1	Forced expiratory volume within one second after maximal inspiration
FVC	Forced Viral Capacity
IC100	100% Inhibitory Concentrations
IC50	50% Inhibitory Concentrations
ICH	International Conference on Harmonisation
iDBL	interim Database Lock
IMSB	Institute of Medical Statistics and Computational Biology

Term	Definition / description
INT_END	Interval End
INT_START	Interval Start
iPD	Important Protocol Deviation
ITT	Intention-To-Treat
i.v.	intravenous
IVC	Inspiratory Vital Capacity
LLT	Lower Level Term
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mITT	modified Intention-To-Treat
mL	Millilitre
mmHg	Millimetres of Mercury
MMRM	Mixed effect Model Repeat Measurement
mRNA	messenger Ribonucleic Acid
mTS	modified Treated Set
N	Number
P10	10^{th} Percentile
P90	90^{th} Percentile
PCR	Polymerase Chain Reaction
PEF	Peak Expiratory Flow
PIF	Peak Inspiratory Flow
PK	Pharmacokinetic
PKS	Pharmacokinetic Set
PN	Preferred Name
PT	Preferred Term
Q1	1^{st} Quartile
Q3	3^{rd} Quartile
qRT-PCR	quantitative Real-Time PCR
REML	Restricted Maximum Likelihood
REP	Residual Effect Period
RNA	Ribonucleic Acid

Term	Definition / description
RS	Randomised Set
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus Type 2
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SIAE	Significant Adverse Event
SCS	Screened Set
SD	Standard deviation
SDTM	Study Data Tabulation Model
SDG	Standardised Drug Grouping
sgRNA	Subgenomic mRNA
SMQ	Standardized MedDRA Queries
SOC	System organ class
SpO2	Saturation of oxygen
TLF	Tables, Listing, Figures
TOC	Table of Content
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
UKK	Uniklinik Köln / University Hospital Cologne
ULN	Upper Limit of Normal
VC	Viral Capacity
VL	Viral Load
WHO-DD	World Health Organization Drug Dictionary
WHO	World Health Organization

3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Trial Statistical Analysis Plan (TSAP) will describe the analyses strategy of Trial Uni-Koeln-4370 / BI Trial 1487-0005 and assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 8 "Statistical Methods and Sample Size Considerations". Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size as well as randomisation. To support the reader with the understanding of this document, please find a brief summary of the trial setup below.

The sponsor of Uni-Koeln-4370 / BI Trial 1487-0005 is the University Cologne. The trial is a phase I/IIa first-in-human trial evaluating the safety, pharmacokinetics, immunogenicity, and preliminary antiviral activity of the monoclonal SARS-CoV-2-neutralizing antibody DZIF-10c (also denoted BI 767551) administered by inhalation using a nebulizer in both SARS-CoV-2-uninfected individuals (Groups 1A-1C) and SARS-CoV-2-infected individuals (Groups 2A-2D).

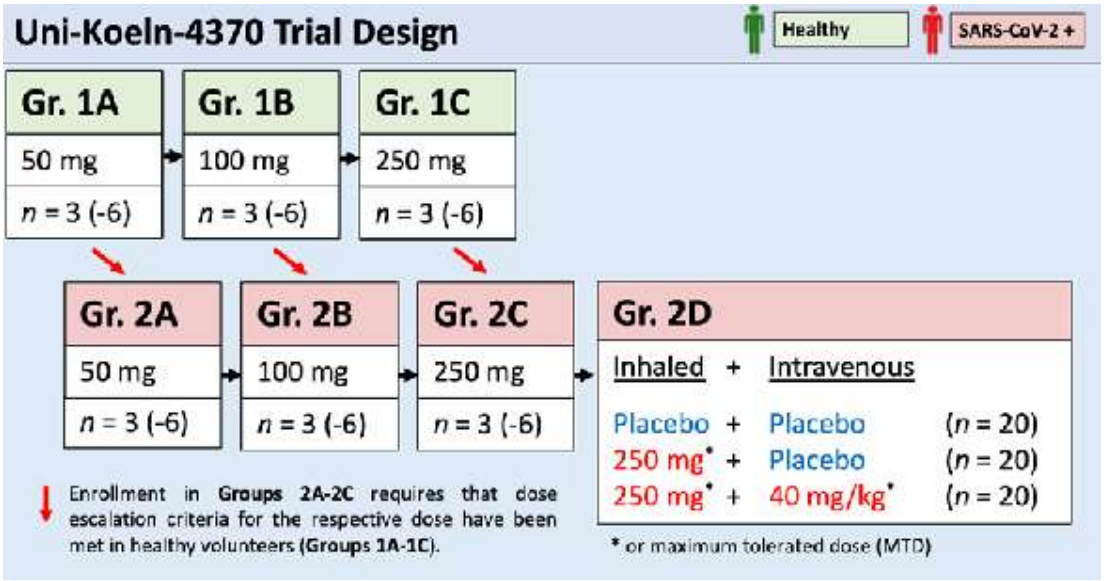


Figure 3: 1 Study design schematic of study Uni-Koeln-4370 / BI Trial 1487-0005.

Following a single-administration open-label dose-escalation phase (Groups 1A-1C and Groups 2A-2C, phase I component), the highest tested and tolerated dose will be administered to an expansion cohort of SARS-CoV-2-infected individuals in a randomised double-blind placebo-controlled manner (Group 2D, phase IIa component). In addition to the inhaled administration of DZIF-10c or placebo, participants in this expansion cohort will receive an intravenous infusion of DZIF-10c or placebo. Enrolment into Group 2D and intravenous dose selection must

be supported by the Safety Monitoring Committee based on data from the separate trial Uni-Koeln-4288 (EudraCT: 2020-003503-34) investigating the intravenous infusion of DZIF-10c.

Unless stated otherwise, SAS® Version 9.4 or later will be used for all analyses.

Pharmacokinetic parameters will be calculated using Phoenix WinNonlin®. Analyses will be done using SAS® Version 9.4 or later.

Please also note that Section 9.1 is dedicated to specifying evaluations to be done for envisaged interim analyses of the clinical data generated within the trial.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

4.1 ADDITIONS / NEW ANALYSES

In addition to the evaluations depicted in the CTP, the following evaluations will be added:

- Section 8.1.1 of the CTP states "Additional analysis populations can be defined in the SAP."
    - Section 6.3 in this TSAP shows additional analysis populations.
- Section 8.1.3 of the CTP states "Safety events will be evaluated in the time period until the day 7 visit after trial drug administration, after the day 7 visit until the end of study, and in aggregate."
    - Additional outputs will be created showing events occurring within 28 days of trial drug administration as well as during the whole trial.
- Section 8.1.4 of the CTP states "Endpoints can additionally be analysed by suitable multivariable models, including covariates."
    - Model based evaluations for the endpoint "SARS-CoV-2 RNA shedding in nasopharyngeal swabs determined by qRT-PCR in SARS-CoV-2-infected individuals" have been added to Section 7.5.2.2.3 of this TSAP.
- Section 8.1.5 of the CTP states "The definition of Subgroup categories and minimum number of participants for a subgroup analysis will be specified in the SAP."
    - In addition to the definitions, additional subgroups are added to Section 6.4 in this TSAP.

4.2 CHANGES

The following changes compared to the plans outlined in the CTP will be implemented:

- Section 8.1.5 of the CTP states "A subgroup analyses for sex will be performed for the primary endpoint."
    - This would be applicable for both the phase I dose finding part as well as the phase IIa expansion part of the trial. However, this is not feasible in the phase I part, as there are only 3 subjects in each cohort, and pooling of different cohorts is not possible due to participants receiving different dose levels of the substance. Therefore subgroup analyses will be limited to the phase IIa part of the trial.
- The CTP and previous versions of this TSAP denote the day of drug administration as day 0. However, in the interim reports as well as in the final clinical trial report (CTR), drug administration will be day 1 and each day label in this version of the TSAP has been increased by 1. This change aligns the timeline with BI standards for drug administration on day 1.

- The following further endpoint (for phase I and phase IIa) will not be included in the CTR: "The activity and frequency of SARS-CoV-2-reactive immune cells following DZIF-10c application". The analyses of this endpoint will be performed by UKK and might be reported elsewhere.

4.3 CLARIFICATIONS

The following points warrant further clarification:

- Please note that the substance description DZIF-10c and BI 767551 denote the same compound. Both are in use, but in the remainder of the TSAP only DZIF-10c is used.
- Please note that "Exploratory Endpoints" are referred to as "Further Endpoints" within this analysis plan.
- Within this document, "drug intake" refers to the intake of the trial medication – either placebo or DZIF-10c.
- The terms "trial drug", "trial medication", "study drug" and "study medication" will be used interchangeably throughout this document.
- This study is exploratory and hypothesis generating in nature. To avoid confusion and misinterpretation, the depiction of p-values in the outputs will be limited.
- An overview of the trial endpoints is shown in the CTP synopsis. Please note that all endpoints are applicable for both parts of the trial, but that the evaluation might differ according to the trial part (phase I vs. phase IIa). Additional information on endpoints can be found in Section 5.1, 5.2 and 5.3 and additional information on Analysis strategies will be part of Section 7.4, 7.5 and 7.6 of this TSAP.
- Please note that in some specifications there is a slight difference compared to flow charts with respect to the study day. This is deliberately done for alignment purposes and is not done in error.
- The following two further endpoints (for phase I and phase IIa) will be analysed by UKK and reported in a separate report which will be appended to the CTR: "Differences of viral spike gene sequences obtained before and after study drug administration and the investigation of the effect of observed mutations on viral sensitivity to DZIF-10 in neutralization assays" and "Subgenomic SARS-CoV-2 mRNA levels in respiratory samples in SARS-CoV-2-infected individuals".

5. ENDPOINTS

In this section, more details are given regarding endpoints. Note that for all endpoints and analyses, Section 6.7 should be consulted for baseline value definition. Analyses for the first interim analysis will be based on all data collected until the data snapshot for interim database lock 1 (iDBL1). Analyses for the second interim analysis will be based on all data collected until the data snapshot for iDBL2. Analyses for the final CTR reported after the final DBL will be based on all data collected within the trial. Information on the interim database locks and corresponding analyses can be found in Section 9.1 of this TSAP.

Handling of missing data points is described in Section 6.6.

For endpoints where the "date of last contact" is utilised, the following will apply:

- The last contact date when the subject was known to be alive is defined as the latest date recorded in the electronic Case Report Form (eCRF) from the dates listed below (in case a date is planned to be imputed for the analysis, the imputed date will also be used for the definition of "date of last contact"):
    - Date of last visit, data of last reported Adverse Event (AE) (excluding censored dates and end dates when outcome is fatal or unknown), date of last reported concomitant treatment, date of last laboratory sample, date of drug intake, last contact date (as documented on the end of study eCRF page if the reason for not completing the planned observation period is NOT "Death"), vital status date (from the end of study if the subject is known to be alive) and the latest of vital status date / last successful contact date (from the vital status eCRF page if the subject was lost to follow-up).

For endpoints where viral load is utilised, the following will apply:

- Viral load measurements below the limit of valid quantification (2116 copies/mL for the E gene and 1950 copies/mL for the ORF1a/b gene) will be set to half this limit on the log10 scale (46 and 44.16 copies/mL, respectively). This imputation will also be applied for negative swab test results.

5.1 PRIMARY ENDPOINT

The primary endpoints for the two trial parts, phase I and phase IIa are the:

- Rate of Adverse Events after study drug inhalation
- Rate of Adverse Events after combined inhalation and intravenous infusion of the study drug

This actually translates into the

- Proportion of patients with any adverse event occurring within 7 days of study drug inhalation
- Proportion of patients with any adverse event occurring within 7 days of study drug after combined inhalation and intravenous infusion of the study drug

As this study is exploratory and hypothesis generating in nature, no formal statistical testing will be implemented. The safety analysis will be descriptive and reported in total, by seriousness, relatedness, and severity. In addition, the safety events will be listed by participant. Handling of missing data points is described in Section 6.6.1.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

This section is not applicable as no key secondary endpoint has been specified in the CTP.

5.2.2 Secondary endpoints

5.2.2.1 $AUC_{0\text{-}672h}$ (the area under the concentration-time curve of DZIF-10c in serum over the time interval from 0 to 672 hours (i.e. post drug administration until Day 29))

Serum levels of DZIF-10c will be determined using a validated immunoassay. Non-compartmental analysis methods will be used to calculate pharmacokinetic parameters.

5.2.2.2 The frequency and magnitude of anti-drug antibodies targeting DZIF-10c

The following parameters will be assessed:

- The number and percentage of subjects with anti-drug antibodies (ADA) on Day 1, 15, 29, 57 and 91 by cohort and overall
- For subjects with ADA: the ADA titer on Day 1, 15, 29, 57 and 91

5.2.2.3 SARS-CoV-2 RNA shedding in nasopharyngeal swabs determined by qRT-PCR in SARS-CoV-2-infected individuals

Viral shedding is quantified as viral load (VL) in nasopharyngeal swabs by using a SARS-CoV2-RNA qPCR assay, and reported as PCR threshold cycle (CT) values. The transformation of CT into units of copies/mL is performed by using assay reference standards.

5.3 FURTHER ENDPOINTS

5.3.1 Successful virus isolation from nasopharyngeal swabs in SARS-CoV-2-infected individuals

Observance of a cytopathic effect (CPE) after inoculation of VeroE6 cells with virus transport medium and/or a decrease of the SARS-CoV-2-RNA-PCR CT value of cell culture supernatant by 3 or more within seven days of culture will be defined as successful virus isolation (i.e., presence of infectious virus in the respective sample).

5.3.2 SARS-CoV-2 RNA shedding in oropharyngeal swabs determined by qRT-PCR in SARS-CoV-2-infected individuals

Viral shedding is quantified as VL in oropharyngeal swabs by using a SARS-CoV2-RNA qPCR assay, and reported as PCR CT values. The transformation of CT into units of copies/mL is performed by using assay reference standards.

5.3.3 Successful virus isolation from oropharyngeal swabs in SARS-CoV-2-infected individuals

Observance of a CPE after inoculation of VeroE6 cells with virus transport medium and/or a decrease of the SARS-CoV-2-RNA-PCR CT value of cell culture supernatant by 3 or more within seven days of culture will be defined as successful virus isolation (i.e., presence of infectious virus in the respective sample).

5.3.4 Frequency of COVID19-related hospitalization and medically-attended health care contacts in SARS-CoV-2-infected individuals not previously hospitalized

For SARS-CoV-2-infected individuals, information is collected on hospitalization or medically-attended health care contacts (e.g., emergency room visit) and the relationship or association with SARS-CoV-2-infection is evaluated by the investigator.

5.3.5 Time to resolution of self-assessed SARS-CoV-2-related symptoms

Date of symptom assessment for an individual subject and symptom will be obtained from the subject diary for every symptom (namely: cough, feverishness, body ache, headache, sore throat, shortness of breath, change in/loss of taste and smell) separately. Symptom evaluation scoring will take place every day on a 4-point scale (0=absent; 1=mild; 2=moderate; 3=severe), and the results entered in a subject diary. Date of resolution on the 4-point scale will be defined as the first day after drug intake where a SARS-CoV-2-related symptom is recorded as “0”. Any subsequent reoccurrence will not be considered.

For subjects with known date of symptom resolution within the first 28 days after drug intake the derivation will be as follows:

- Time to resolution [days] = Date of resolution of symptom – date of drug intake + 1

Subjects who did not experience any resolution of their existing symptom by day 29, or who have missing evaluation data, or who did not show a particular symptom at baseline will be censored according to the mechanism for censoring as described in Table 5.3.5: 1 below. In particular, all subjects with no symptom at baseline will be censored at day 1, even if they later develop a symptom (after drug intake).

Table 5.3.5: 1 Censoring and Event Rules for Time to resolution of self-assessed SARS-CoV-2-related symptoms within the first 28 days after drug intake.

Rule #	Situation	Outcome (event or censored)	Date of event or censoring
1	Subject had a symptom at baseline and a resolution within the first 28 days and date of resolution is known	Event	Date of event
2	Subject had a symptom at baseline and a resolution within the first 28 days and date of resolution is unknown	Event	Imputed date of event
3	Subject had a symptom at baseline but no resolution within the first 28 days	Censored	Day 29 (28 days after first drug intake)
4	Subject had a symptom at baseline but resolution status within the first 28 days is unknown or a subject has missing assessment data	Censored	Date of last recorded consecutive follow-up entry of symptom status within the first 28 days after drug intake
5	Subject did not show a particular symptom at baseline	Censored	Day 1 (Date of drug intake)

5.3.6 Differences of viral spike gene sequences obtained before and after study drug administration and the investigation of the effect of observed mutations on viral sensitivity to DZIF-10 in neutralization assays

SARS-CoV-2 spike protein gene sequences will be determined from extracted viral RNA at baseline and after study drug administration, and analysed for the development or enrichment of non-synonymous mutations after study drug administration. Selected individual mutations, such as those within the antibody epitope or recurrent mutations, will be assessed for their impact on DZIF-10c sensitivity as determined by neutralization assays, e.g., after introducing these mutations into pseudoviruses by site-directed mutagenesis. Sensitivity results will be and reported as 50% inhibitory concentrations (IC50) and/or 100% inhibitory concentrations (IC100), if applicable, and compared to wild-type pseudovirus variants.

This further endpoint will be analysed by UKK and reported in a separate report which will be appended to the CTR.

5.3.7 The activity and frequency of SARS-CoV-2-reactive immune cells following DZIF-10c application

As described in Section 4, the analyses of this endpoint will be performed by UKK and will not be included in the CTR but might be reported elsewhere.

5.3.8 Subgenomic SARS-CoV-2 mRNA levels in respiratory samples in SARS-CoV-2-infected individuals

Viral subgenomic mRNA (sgRNA) is generated during viral replication, remains intracellularly, and indicates actively infected cells in the sample. sgRNA may therefore provide a more robust assessment of viral replication compared to overall levels of viral genomic RNA. Levels of SARS-CoV-2 sgRNA will be determined in swab (potentially NP and/or OP swabs) samples by qRT-PCR and assessed quantitatively.

This further endpoint will be analysed by UKK and reported in a separate report which will be appended to the CTR.

5.3.9 Pharmacokinetic profile of DZIF-10c, including elimination half-life, peak serum concentration, area under the curve, clearance, and volume of distribution

If data allows, the following parameters will be assessed:

- $AUC_{0\text{-}504h}$ (the area under the concentration-time curve of DZIF-10c in serum over the time interval from 0 to 504 hours (i.e., post drug administration until Day 22))
- $AUC_{0\text{-}inf}$ (the area under the concentration-time curve of DZIF-10c in serum over the time interval from 0 extrapolated to infinity)
- C_{max} (maximum measured concentration of DZIF-10c in serum)
- t_{max} (time from dosing to Cmax of DZIF-10c in serum)
- $t_{1/2}$ (the terminal elimination half-life of DZIF-10c in serum)
- CL/F (apparent clearance after extravascular administration) for individuals receiving DZIF-10c by inhalation only
- V_z/F (apparent volume of distribution during the terminal phase after extravascular administration) for individuals receiving DZIF-10c by inhalation only

Further parameters might be calculated, if appropriate.

5.4 OTHER VARIABLES

5.4.1 Demographics and baseline characteristics

5.4.1.1 Demographic data

- Gender
- Age [years] at time of informed consent
- Age in categories [years]

- Phase I: (<55; ≥55)
- Phase IIa: (<65; ≥65)

- Weight [kg] as continuous variable and in two different ways in classes (<45; ≥45 - <60; ≥60 - <90; ≥90 and <70; ≥70)
- Height [cm]
- Body mass index [kg/m^2]: Weight[kg] / (Height[m]*Height[m]), as a continuous variable and in classes (< 20; ≥20-<25; ≥25-<30; ≥30-<35; ≥35)

5.4.1.2 Trial indication

- SARS-CoV-2 test result
  - From nasopharyngeal / oropharyngeal swabs
- For subjects with positive SARS-CoV-2 test
  - Days since symptom onset
  - Days since positive SARS-CoV-2 test
  - Disease stage at baseline [WHO 11pt scale] (Scores 1-4)
  - Serum or plasma antibodies detected against SARS-CoV-2 (yes; no)

5.4.1.3 Baseline characteristics

- Baseline Conditions
- ECG (normal; abnormal; abnormal – clinically significant)
- Concomitant Therapies
- Oxygen Saturation on Pulse Oximetry (SpO2) [%]

5.4.1.4 Baseline characteristics on pulmonary function (for subjects in groups 1A-1C only)

- Vital capacity (VC) (L)
- Forced vital capacity (FVC) (L)
- Forced expiratory volume within one second after maximal inspiration (FEV1) (L)
- Inspiratory vital capacity (IVC) (L)
- FEV1/FVC
- Peak expiratory flow (PEF) (L/min)
- Peak inspiratory flow (PIF) (L/min)

5.4.1.5 Baseline characteristics on COVID-19 infection (for subjects in Group 2A-2D only)

- COVID-19 related symptoms (presence/absence)
- Nasopharyngeal / Oropharyngeal swab CT values as well as copies/ml

5.4.2 Compliance

Compliance will be evaluated by whether or not the medication was administered according to protocol.

5.4.3 Exposure

Total dose of specific trial medication [mg]:

Total dose of trial medication will be calculated separately for DZIF-10c, and the matching placebo. It will be based on the actual dose [mg] received. Total dose will be evaluated descriptively.

Dose intensity of specific trial medication [%]:

For each formulation (inhaled or i.v.) dose intensity of trial medication will be calculated separately for DZIF-10c, and the matching placebo.

$$\text{Dose intensity [\%]} = \frac{\text{Total dose of specific trial medication actually received by a subject}}{\text{Planned total dose of specific trial medication}} \times 100$$

The planned total dose is calculated as the total dose of the medication a subject should have received based on their baseline weight and the dose level of the treatment cohort they were assigned to. Dose intensity will be summarised in percent and in categories (≤50%, >50% - ≤90%, >90% - <100%, 100%) and evaluated descriptively.

Inhalation volume [ml]:

The total inhalation volume received by a subject during the complete inhalation duration. Inhalation volume will be evaluated descriptively.

Infusion volume [ml]:

The total infusion volume received by a subject during the complete infusion duration. Infusion volume will be evaluated descriptively.

Time to premature inhalation stoppage in classes:

The following classes will be used: ≤ 5min, > 5 − ≤10 min, > 10min

Time to premature inhalation stoppage will be evaluated descriptively.

Time to premature infusion stoppage in classes:

The following classes will be used: ≤ 5min, > 5 − ≤15 min, > 15 - ≤30 min, > 30min

Time to premature infusion stoppage will be evaluated descriptively.

5.4.4 Liver function tests

Time to initial onset of liver enzyme elevations and frequency of patients with liver function test abnormalities will be produced. A listing of all liver function tests will be provided for all subjects who meet the following criteria at any time:

- ALT or AST ≥3xULN and elevation of total bilirubin ≥2xULN at the same time

In addition, E-dish plots may be used for ALT and AST.

5.4.5 Marked changes in vital signs

A marked increase is defined as:

- Systolic Blood Pressure >150 mmHg and increase ≥ 25 mmHg above baseline
- Diastolic Blood Pressure >90 mmHg and increase ≥ 10 mmHg above baseline
- Pulse Rate >100 bpm and increase ≥ 10 bpm above baseline

A marked decrease is defined as:

- Systolic Blood Pressure <100 mmHg and decrease >10 mmHg below baseline
- Diastolic Blood Pressure <60 mmHg and decrease >10 mmHg below baseline
- Pulse Rate <60 bpm and decrease >10 bpm below baseline

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

Please see CTP Sections 5.9.1 and 5.9.2 for information on treatments as well as administration. Assignment of subjects to treatment groups can be found in CTP Section 5.9.4, and Section 5.9.5 contains information on the selection of doses.

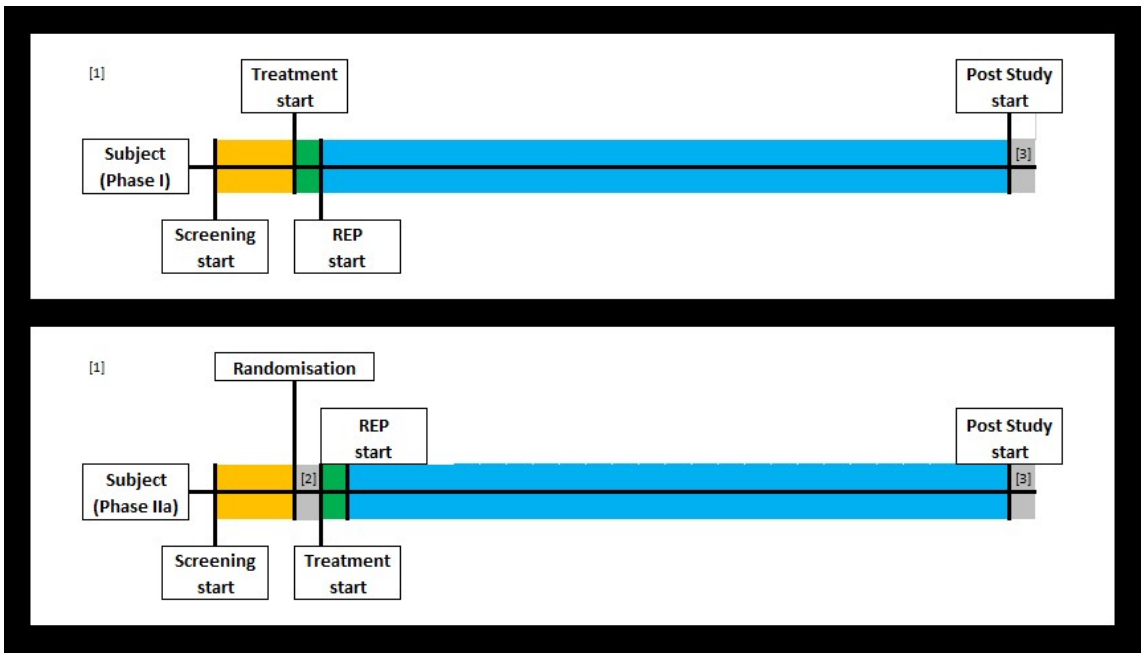
Note: the last day of each of the periods is excluded from the respective period. It defines the first day of the subsequent period.

- Screening:
  - Phase I part (Groups 1A-1C, 2A-2C): From informed consent to trial drug intake
  - Phase IIa part (Group 2D): From informed consent to randomisation
- Post-randomisation (if applicable[a][b]):
  - From randomisation to trial drug intake in treatment period
- Treatment period:
  - From date of trial drug intake to date of trial drug intake plus one day
- Residual effect period:
  - From the date of trial drug intake plus one day to 90 days plus one day after trial drug intake
- Post-study[a]:
  - From 90 days plus one day after trial drug intake or date of intake of other SARS-CoV-2 medication, whichever occurs earlier

[a] This period is optional insofar as it does not necessarily exist for all subjects.
[b] This period is only applicable for subjects in the phase IIa part of the trial.

Please see Figure 6.1: 1 below for a graphical depiction of the individual treatment periods. The grey highlighted areas are the optional periods that do not necessarily exist for all subjects.

All analyses will be based on the actual treatment the subjects received unless stated otherwise.



[1] The orange area represents the screening period, the green area the treatment period, and the blue area the residual effect period.
[2] This grey area represents the optional post-randomisation period. It is only applicable for subjects in the phase IIa part of the trial and, hence, does not necessarily exist for all subjects. Ideally, date of randomisation and date of treatment start are on the same day.
[3] This grey area represents the optional post-study period. It does not necessarily exist for all subjects.

Figure 6.1: 1 Period overview for a participant of study Uni-Koeln-4370 / BI Trial 1487-0005.

6.2 IMPORTANT PROTOCOL DEVIATIONS

No per protocol set analysis will be performed for this study; however, the following list in Table 6.2: 1 defines the different categories of potentially important protocol deviations (iPD), and it shows whether subjects will potentially be excluded from evaluations performed in this trial. The proportion of subjects with potential iPDs will be presented for completeness purposes and to demonstrate the adherence to the CTP.

Table 6.2: 1 Handling of iPDs

iPD code	iPD Category & Brief Description	Excluded from which analysis set
A	**In/Exclusion Criteria not met**	
A1	**Inclusion Criteria not met**	
A1.1	SARS-CoV-2-RNA negative (SARS-CoV-2-uninfected subjects)/positive (SARS-CoV-2-infected subjects) naso- or oropharyngeal swab obtained within 3 calendar days before study drug administration by NAAT	None
A1.2	SARS-CoV-2-infected subjects only: Onset of COVID-19 symptoms not within 7 days prior to study drug administration *or* No non-reactivity of serum or plasma antibodies against SARS-CoV-2 by serological assay at screening	None
A2	**Exclusion Criteria not met**	
A2.1	Subjects with laboratory values that indicate additional risk	None
A2.2	Patient with other underlying diseases, conditions or risks which are excluded as per clinical trial protocol	None
A2.3	Forbidden previous therapy as per clinical trial protocol	None
B	**Informed Consent**	
B1	Informed consent not available/not done	All
B2	Informed consent too late	None
C	**Trial Medication and Randomisation**	
C1	Wrong dose level received compared to dose level subject was assigned (phase I) / randomised (phase IIa) to	None
C2	Medication taken that is not matching the treatment a subject was randomised to (phase IIa only)	None
E	**Missing data**	

E1	No negative pregnancy test result prior to / and the end of study participation	None
E2	Missing diary data for 7 consecutive days within the first 14 days	None
F	**Study Procedure Timing**	
F1	Time window violation for drug administration (drug administration ≤ 3 days after screening)	None
F2	Time window violation for procedures performed post baseline within the first 7 days (day 1 and day 2 without time window; day 4 within +/- 1 day; day 8 +/- 2 days)	None
G	**Other Trial Specific Important Violation**	
G1	Other protocol violations affecting patient rights or safety (manual PVs to be captured)	None

6.3 SUBJECT SETS ANALYSED

- Screened set (SCS):
  - This subject set includes all subjects having signed informed consent and would correspond to the intention-to-treat set (ITT) in the phase I part of the trial.
- Randomised set (RS):
  - This subject set includes all randomised subjects in the phase IIa part of the trial, whether treated or not. This would correspond to the intention-to-treat set (ITT) in the phase IIa part of the trial
- Treated set (TS):
  - This subject set includes all subjects who received any amount of study drug.
- Modified Treated set (mTS):
  - This subject set includes all subjects who received any amount of study drug and did not require replacement in the phase I part of the trial. Details about requirement for replacement can be found below.
- Modified Intention-To-Treat set (mITT):
  - This subject set includes all randomised subjects in the phase IIa part of the trial that received any amount of study drug and who have at least a baseline value and a second measurement in the first week (up to 7 days after drug intake) of viral RNA shedding in nasopharyngeal swabs by qRT-PCR.

- PK parameter analysis set (PKS):
    - This subject set includes those subjects in the TS with at least one valid serum concentration of DZIF-10c available

Participants who are withdrawn from the trial after DZIF-10c administration will not be replaced, except for participants during the dose-escalation phase of the trial that are not followed until at least the day 7 visit after drug administration for reasons not related to safety events. Subjects who were replaced will be excluded from the primary analysis of the primary endpoint. Replacement of subjects will be determined on a case-by-case basis; exclusion of these subjects from the primary analysis will be confirmed by the trial team at the report planning meeting prior to database lock.

Please see Table 6.3: 1 for a general overview which patient set will be used for which type of analyses. Additionally, biomarker analyses might be performed on subsets of the mITT set.

Table 6.3: 1 Subject sets used in the different types of analysis

	Subject set					
Type of analysis	SCS	RS	TS	mTS	mITT	PKS
Primary endpoints			X	X[1]		
Further endpoints			X			
Safety data, ADA & treatment exposure			X			
Demographic/baseline characteristics			X			
Disposition	X	X				
PK parameters						X
Viral Load			X[1][2]		X	

[1] Will be used for the phase I part of the trial.

[2] Will be used for analyses of OP swabs.

Note that the number of subjects with available data for an endpoint may differ. For details, see Section 6.6.

6.4 SUBGROUPS

In general, model-based subgroup analyses will not be performed for this trial. Only summary statistics will be created based on these subgroups for adverse events as well as viral load data for the phase IIa part of the trial:

- Time from symptom onset to first drug intake (<3, ≥3 days)
- Time from symptom onset to study randomisation (<3, ≥3 days)
- Baseline severity of COVID-19 (mild, moderate)
- Age group (<65, ≥65 years old)
- Gender (male, female)
- Serum or plasma antibodies against SARS-CoV-2 at baseline (present/absent)
- Baseline weight (<70, ≥70 kg)

- Baseline BMI (<35, ≥35kg/m^2)
- COVID-19 symptoms at baseline (present/absent)
- Disease stage at baseline [based on WHO 11pt scale] (Score 1-3, Score 4)
- Viral load (nasopharyngeal swabs) at baseline (<10^6, ≥10^6 copies/ml)
- Trial site[*]
- Viral variant[*]

[*] These subgroups will only be considered if applicable (e.g. if more than one trial cite, if viral variant data available at data base lock for the CTR).

If there are subgroups with expression levels that contain less than 5 patients, the subgroup evaluation will be omitted (if there are two subgroups) or expression levels may be pooled based on medical judgement (e.g. pooling of the smallest trial sites until all are larger or equal than 5) or modified as deemed appropriate based on the characteristics of the included subjects.

6.5 POOLING OF CENTRES

This section is not applicable because centre is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

In general, missing data will not be imputed. Exceptions are detailed in the subsequent subsections.

6.6.1 Safety data

Missing or incomplete AE dates will be imputed in order to determine if an AE belongs into the on-treatment period (covering the treatment and residual effect period). Please see Section 9.4 for an overview of the implemented procedures.

AEs with missing / incomplete onset dates are excluded from the time-to-event analyses (e.g. time to the onset of liver enzyme elevations). AEs with missing / incomplete onset or end dates are not included in the routine duration analyses (e.g. duration of an AE). If an AE is ongoing at the time of analysis, then the corresponding AE end date will be censored using the snapshot date and this AE will be included in the routine duration analysis if the onset date is complete.

6.6.2 Pharmacokinetic data

Missing data will not be imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

As a general rule, the last assessment / measurement observed prior to start of trial medication will be assigned to baseline. Note that for some trial procedures (e.g., body weight, vital signs, laboratory tests) this may be the value measured on the same day trial medication was started. In these cases, it will be assumed that the measurements were taken prior to the intake of any study medication (if the measurement time was not captured). If no further data available, this can also be the last screening assessment. For viral load and pulmonary function test related

data it is paramount that the sample is taken prior to drug administration, and for these procedures time of sampling will be taken into consideration and compared to the time of drug intake.

Furthermore, for assessments of viral load data for the first 7 days after drug administration which require grouping to timepoints (e.g., descriptive statistics by timepoint, MMRM), the following will be done. Measurements for baseline (day 1) and days 2, 4, 6 and 8 will be included, where the measurement for day 6 is optional. The following time windows are allowed.

- The measurements for baseline and for day 2 must be taken exactly on the respective day. There is no time window.

- If there is no measurement on day 4, it will be replaced by a measurement on day 3 or day 5 with a preference for day 3.

- If there is no measurement on day 8, it will be replaced by a measurement on day 7.

If the optional measurement on day 6 is missing, it will be replaced by the value on day 5 or day 7 if these values have not been assigned to days 4 and 8, respectively. The measurement for day 5 will be preferred over day 7 if both values are available.

Additionally, for assessments of viral load data for the first 14 or 28 days after drug administration which require grouping to timepoints (e.g., MMRM), the following time windows apply. These analyses windows are non-overlapping and cover the whole trial period by using the middle between each scheduled visit.

- If there are no measurement on days 7 and 8, the day 8 measurement will be replaced by the earliest measurement up to day 11.

- If there is no measurement on day 15, it will be replaced by the closest measurement taken between day 12 and day 18.

- If there is no measurement on day 22, it will be replaced by the closest measurement taken between day 19 and day 25.

- If there is no measurement on day 29, it will be replaced by the closest measurement taken between day 26 and day 43.

Additionally for descriptive statistics, the following non-overlapping time windows apply.

- If there is no measurement on day 57, it will be replaced by the closest measurement taken between day 44 and day 74.

- If there is no measurement on day 91, it will be replaced by the closest measurement taken between day 75 and day 107.

7. PLANNED ANALYSIS

Planned analyses can be categorized based on:

- The study period for which they are performed:
  - Phase I dose escalation and phase IIa expansion cohort.
- The study population for which they are performed:
  - Healthy volunteers or SARS-CoV-2-infected individuals.

Unless specified otherwise, analyses for the phase I dose escalation part and the phase IIa expansion cohort part will be identical. The same will hold true for evaluations including healthy volunteers and SARS-CoV-2-infected individuals.

For End-Of-Text tables, the set of summary statistics is: N / Mean / SD / Min / Q1 / Median / Q3 / Max. In descriptive statistics tables, mean, sd and median will be rounded to one additional digit than the raw data. In case extreme data outside of the expected range are observed, other percentiles may be presented additionally in the phase IIa outputs.

Tabulations of frequencies for categorical data will include all categories depicted in the eCRF and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all subjects in the respective subject set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

All evaluations are exploratory in nature and p-values will be presented where appropriate.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

A table in the CTR will present the number of subjects screened, entered (only applicable for subjects in the phase I part of the study)/randomised (only applicable for subjects in the phase IIa part of the study) and treated. The number of subjects prematurely discontinuing their study treatment / study participation will be shown with the reasons for discontinuation. The number and percent of subjects completing trial visits and the number of subjects ongoing will also be presented. Please note there will only be ongoing subjects at the time the interim analyses take place; at the time point when the final analysis will take place there will not be any more ongoing subjects in this trial. Where percentages are shown, the denominator will be the number of subjects treated in each cohort, separately for each study part.

Descriptive statistics, as well as frequency counts, will be provided for all demographic and baseline characteristics depicted in Section 5.4.1. The CTR tables will show the relevant descriptive statistics (number and percent within categories; other descriptive statistics for continuous variables) by cohort and study part.

Only descriptive statistics are planned for this section of the report.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report.

7.2.1 Baseline conditions and relevant medical history

The baseline conditions will be included as coded items using the current Medical Dictionary for Regulatory Activities (MedDRA) version in use at UKK at the time of database lock. They will be summarised by MedDRA primary system organ class (SOC) and Preferred Term. The CTR table will show the counts of subjects with a baseline condition in each SOC present (SOC sorted by standard European Medicines Agency (EMA) order) and then the conditions (preferred terms) under that SOC in descending order of overall prevalence. This summary will be produced on all subjects, separate for each study period.

The relevant medical history will be summarised. In SARS-CoV-2 infected subjects particular focus will be to baseline disease assessment and contributing factors to a potentially more severe course of SARS-CoV-2.

7.2.2 Concomitant therapies

The following categories of concomitant therapies have been created:

- Previous therapies
    - Defined as treatments with an end date before trial drug intake. As per eCRF, the last four weeks before drug intake are collected.
- Baseline therapies
    - Defined as treatments with a start date before trial drug intake and taken after or on the day of the trial drug intake.
- On-treatment concomitant therapies
    - Defined as treatments with a start date after or on the day of trial drug intake and before or on the last day of the residual effect period (for details, please see Section 6.1).
- Post-study drug discontinuation therapies
    - Defined as treatments with a start date after the end of the residual effect period (for details, please see Section 6.1).

The analysis of concomitant therapies will be based on the following groupings of the aforementioned categories of concomitant therapies:

- Previous therapies
- Baseline therapies
- On-treatment concomitant therapies
- Baseline and on-treatment concomitant therapies
- All concomitant therapies (including baseline therapies, on-treatment concomitant therapies and post-study drug discontinuation therapies)
- Post-study drug discontinuation therapies

Concomitant therapies will be described separately for both the phase I and the phase IIa part of the trial.

Table 7.2.2: 1Table 7.2.2: 1 summarises the concomitant therapy outputs which will be provided for both trial phases. Summaries by WHO-DD ATC and preferred name (PN) will use the ATC3 code, and will be sorted by alphabetical ATC class and decreasing frequency of PN based on the overall number of subjects taking them within ATC class. Summaries by SDGs will be sorted by alphabetical SDG and decreasing frequency of PN based on the overall number of subjects taking them within SDG. SDGs can be found in Section 9.3.

Table 7.2.2: 1 Concomitant therapy outputs.

	By ATC and PN		**By SDGs and PN**	
	Phase I dose escalation	**Phase IIa expansion cohort**	**Phase I dose escalation**	**Phase IIa expansion cohort**
Previous therapies	Listing	Listing	Listing	Listing
Baseline therapies	Table + listing	Table + listing	Table + listing	Table + listing
On-treatment concomitant therapies	Table + listing	Table + listing	Table + listing	Table + listing
Post-study drug discontinuation therapies	Table + listing	Table + listing	Table + listing	Table + listing

7.3 TREATMENT COMPLIANCE

Treatment compliance will be computed for both parts of the trial and for both routes of administration separately. Subjects receiving the full dose, and those that – due to any reason – did not, will be assessed. The outputs will show the number of subjects who have received the trial medication in accordance to the CTP as well as those who did not, including the initial dose level computed for the subjects. Only descriptive statistics are planned for this section of the report.

7.4 PRIMARY ENDPOINTS

- To evaluate the primary objective of evaluating the safety and tolerability of a single inhalation of DZIF-10c in SARS-CoV-2-uninfected and SARS-CoV-2-infected individuals, a toxicity-guided approach is utilised in this study.
- To evaluate the primary objective of evaluating the safety and tolerability of a single combined treatment with inhalation and intravenous infusion of DZIF-10c in SARS-CoV-2-uninfected and SARS-CoV-2-infected individuals, a toxicity-guided approach is utilised in this study.

All evaluations for the primary endpoints will be done on the subject set mTS in phase I and on the subject set TS in phase IIa.

7.4.1 Primary analysis of the primary endpoint

The primary endpoint analysis, implemented separately for phase I and phase IIa, will evaluate the proportion of patients with any adverse event occurring within 7 days of study drug administration.

As this study is exploratory and hypothesis generating in nature, no formal statistical testing will be implemented. Handling of missing data points is described in Section 6.6.1. Please note that the number of events will also be provided in listings. All adverse events with onset during the first 7 days after drug administration will be taken into consideration for this endpoint analysis, and an overall summary of AE occurrences (N and %) will be created. In addition to the occurrence of adverse events the following AE attributes will be presented and evaluated:

- Severity / Maximum CTCAE grade
- Relatedness
- Outcome
- Time to first occurrence [days]

As one specific aim of the study is to determine a safe dose to be taken forward into subsequent development, the evaluation of dose-limiting toxicities (DLT) is of particular importance in the phase I part of the trial. A DLT for this trial will be defined as any grade 3 or higher adverse event that the investigators determine to be related to DZIF-10c. The following evaluations will therefore be implemented:

- Proportion of patients with DLTs after DZIF-10c inhalation occurring within 7 days of study drug administration.

Any AE meeting the criteria for DLT, regardless at which point in time after drug administration it occurred, will be considered a significant adverse event (SIAE). The analysis of non-serious SIAEs and serious adverse events (SAEs) is described in Section 7.8.1 of this document.

7.4.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the primary endpoint

The above analyses will be repeated on all adverse events, and adverse events meeting the criteria for DLT as shown in Section 7.4.1 (irrespective of relatedness to treatment) and adverse events of special interest (AESIs) with onset from the date of administration of trial medication and up to 28 days after drug intake and during follow-up from day 9 to day 91. It will also be repeated on all adverse events, and all related adverse events meeting the criteria for DLT regardless of onset date for the whole trial duration leading to the following additional evaluations.

- Rate of Adverse Events after DZIF-10c administration occurring within 28 days of trial drug administration
- Rate of Adverse Events after DZIF-10c administration occurring at any time during trial participation

7.5 SECONDARY ENDPOINTS

As this study is exploratory and hypothesis generating in nature, no formal statistical testing will be implemented. Please note that any p-values will be considered nominal in nature and no adjustment for multiplicity will be made.

7.5.1 Key secondary endpoints

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.1.1 Primary analysis of the key secondary endpoints

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.1.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the key secondary endpoints

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 Other Secondary endpoints

The same secondary endpoints have been defined for both parts of the trial. Due to the nature of the different trial parts, there may however be differences in the analysis of those endpoints.

7.5.2.1 Secondary endpoints phase I

7.5.2.1.1 $AUC_{0\text{-}672h}$ (the area under the concentration-time curve of DZIF-10c in serum over the time interval from 0 to 672 hours (i.e. post drug administration until Day 29))

$AUC_{0\text{-}672h}$ will be derived according to the relevant BI internal procedure. Descriptive statistics of PK parameters (a.o. Min, Median, Max) will be tabulated by cohort.

Please compare with Section 7.6.1.9. This endpoint will be evaluated on the subject set PKS.

7.5.2.1.2 The frequency and magnitude of anti-drug antibodies targeting DZIF-10c

The ADA status (positive/negative) and ADA titer will be listed by cohort and overall. Descriptive statistics of ADA status (n, %) and ADA titer (Min, Median, Max) will be provided by cohort and overall, if data allows. Further exploratory characterization of ADA responses may be performed if data allows.

This endpoint will be evaluated on the subject set TS.

7.5.2.1.3 SARS-CoV-2 RNA shedding in nasopharyngeal swabs determined by qRT-PCR in SARS-CoV-2-infected individuals

Summary statistics of CT values as well as copies/ml based on a reference standard will be shown for each assessment time point by cohort and overall. This will be done for absolute values as well as relative and absolute change from baseline. All statistics will be calculated separately for the assessed SARS-CoV-2 genes (E gene and the ORF1a/b gene).

This endpoint will be evaluated on the subject set subject set TS who have at least a baseline value and a second measurement in the respective time period of viral RNA shedding in NP swabs by qRT-PCR.

7.5.2.2 Secondary endpoints phase IIa

All summary statistics are provided by treatment arm.

7.5.2.2.1 $AUC_{0\text{-}672h}$ (the area under the concentration-time curve of DZIF-10c in serum over the time interval from 0 to 672 hours (i.e. post drug administration until Day 29))

The same analyses will be performed as described in Section 7.5.2.1.1.

This endpoint will be evaluated on the subject set PKS.

7.5.2.2.2 The frequency and magnitude of anti-drug antibodies targeting DZIF-10c

The same assessments will be performed as described in Section 7.5.2.1.2.

This endpoint will be evaluated on the subject set TS.

7.5.2.2.3 SARS-CoV-2 RNA shedding in nasopharyngeal swabs determined by qRT-PCR in SARS-CoV-2-infected individuals

All evaluations for the first 7 days after drug administration will be done on the mITT set and will take data into consideration based on the time window around the corresponding visit as defined in Section 6.7. The latest day to be taken into account is 7 days after drug administration. The evaluations for the later time points will be based on all subjects in the subject set TS who have at least a baseline value and a second measurement in the respective time period of viral RNA shedding in NP swabs by qRT-PCR.

Absolute viral load in SARS-CoV-2-infected individuals, as well as absolute and relative changes from baseline, will be summarised descriptively for each assessment time point and plotted by treatment arm and listed.

Time-weighted average change in viral load

The evaluation of viral load will be done by a time-weighted average change in $\log_{10}$ viral load from baseline, defined by:

$$\frac{\sum_{i=a}^{b-1}\{0.5 * (Y_i + Y_{i+1}) * (t_{i+1} - t_i)\}}{(t_b - t_a)}$$

where

- Y_i = change from baseline in $\log_{10}$ viral load at visit i
- t = time at the specified time point (the actual study day)
- a = baseline assessment at day 1
- b = last assessment at or prior to the threshold day (7 days after drug intake)

A parametric analysis of covariance (ANCOVA) model with corresponding baseline viral load and antibody status will be used. Adjusted means and 95% confidence intervals (CIs) will be provided. Missing values will not be imputed and since a linear trajectory on the log scale is expected, the normalisation by the denominator assures comparability of the values if t_b is different between patients.

Ratios between means (DZIF-10c vs placebo) will be calculated for each treatment arm separately for the respective time period. These calculations will be based on the mean time-weighted average change in viral load based on the ANCOVA model. CIs for the ratios will be reported for which the Delta method (Taylor method) will be used to calculate the variance of the ratios.

Mixed effect Model for Repeated Measures (MMRM)

In addition to a time-weighted average change, changes from baseline will also be evaluated using a restricted maximum likelihood (REML) based repeated measures approach. Analyses will include the fixed, categorical effects of antibody status, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. An unstructured (co)variance structure will be used to model the within-subject measurements. In

case the model does not converge, other covariance structures will be used sequentially until convergences is reached and the used covariance structure will be reported. The sequence of covariance structures to be used is as follows: unstructured, antedependence, heterogeneous Toeplitz, Toeplitz, heterogeneous AR(1). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

All model-based evaluations (time-weighted average change and MMRM) will be done for the following time periods:

- first 7 days after drug administration
- first 14 days after drug administration
- first 28 days after drug administration

Note that only data points within the analysis periods are considered. Data available after the cut-offs will not be considered for the model based evaluations.

All model-based evaluation will be done for the SARS-CoV-2 E gene. As sensitivity analyses, the evaluations will be repeated for the additionally assessed SARS-CoV-2 gene (ORF1a/b gene). This sensitivity analysis will be done on subjects from the subject set TS who have at least a baseline value and a second measurement in the respective time period of viral RNA shedding in OP swabs by qRT-PCR.

Clearance rate

It will be shown how many patients fell below the limit of valid quantification. Finally, the proportions of participants with positive and negative PCR for each assessed SARS-CoV-2 gene assessed at every given visit will be described (clearance rate). Missing data will not be imputed. Consequently, the number of patients with non-missing data will be used as denominator for each proportion. CIs for the proportions will be derived as Clopper-Pearson intervals.

7.6 FURTHER ENDPOINTS

The same further endpoints have been defined for both parts of the trial. Due to the nature of the different trial parts, there will however be differences in the analysis of those endpoints.

7.6.1 Further endpoints phase I

7.6.1.1 Successful virus isolation from nasopharyngeal swabs in SARS-CoV-2-infected individuals

Information will be shown for each assessment time point on whether live virus could be isolated in participating subjects or not, for each cohort and overall. In addition, the relative frequency of positive samples will be shown per timepoint.

This endpoint will be evaluated on subjects from the subject set TS.

7.6.1.2 SARS-CoV-2 RNA shedding in oropharyngeal swabs determined by qRT-PCR in SARS-CoV-2-infected individuals

Summary statistics of CT values as well as copies/ml based on a reference standard will be shown for each assessment time point, by cohort and overall. This will be done for absolute values as well as relative and absolute change from baseline. All assessments will be calculated separately for the assessed SARS-CoV-2 genes (E gene and the ORF1a/b gene).

These evaluations will be based on all subjects in the subject set TS who have at least a baseline value and a second measurement in the respective time period of viral RNA shedding in OP swabs by qRT-PCR.

7.6.1.3 Successful virus isolation from oropharyngeal swabs in SARS-CoV-2-infected individuals

Information will be shown for each assessment time point on whether live virus could be isolated in participating subjects or not, for each cohort and overall. In addition, the relative frequency of positive samples will be shown per timepoint.

This endpoint will be evaluated on subjects from the subject set TS.

7.6.1.4 Frequency of COVID19-related hospitalization and medically-attended health care contacts in SARS-CoV-2-infected individuals not previously hospitalized

Summary statistics will be shown for each assessment time point and in total, by cohort and overall.

This endpoint will be evaluated on subjects from the subject set TS.

7.6.1.5 Time to resolution of self-assessed SARS-CoV-2-related symptoms

Summary statistics will be shown for each assessment time point, by cohort and overall.

This endpoint will be evaluated on subjects from the subject set TS.

7.6.1.6 Differences of viral spike gene sequences obtained before and after study drug administration and the investigation of the effect of observed mutations on viral sensitivity to DZIF-10 in neutralization assays

Differences in gene sequences will be reported descriptively for cohorts including SARS-CoV-2-infected individuals (i.e. cohorts 2A-2Ds). Summary statistics, i.e. absolute values as well as relative and absolute change from baseline of IC50 and IC100 values against selected viral variants will be reported by cohort and overall.

These analyses will be performed by UKK and reported in a separate report which will be appended to the CTR.

7.6.1.7 The activity and frequency of SARS-CoV-2-reactive immune cells following DZIF-10c administration

As described in Section 4, these analyses will be performed by UKK and will not be included in the CTR but might be reported elsewhere.

7.6.1.8 Subgenomic SARS-CoV-2 mRNA levels in respiratory samples in SARS-CoV-2-infected individuals

Summary statistics (absolute values as well as relative and absolute change from baseline) will be shown for each assessment time point and dose cohort.

These analyses will be performed by UKK and reported in a separate report which will be appended to the CTR.

7.6.1.9 The pharmacokinetic profile of DZIF-10c, including elimination half-life, peak serum concentration, area under the curve, clearance, and volume of distribution

The PK parameters listed as further endpoints in Section 5.3.9 will be derived according to the relevant BI internal procedure. Further PK parameters may be calculated, if considered reasonable (these parameters will be considered exploratory). Serum concentrations and PK parameters of DZIF-10c will be listed and analysed descriptively. If the number of subjects included allows, the following descriptive statistics will be calculated for analyte concentrations as well as for all pharmacokinetic parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, P10, Q1, Q3, P90, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation.

Descriptive statistics of PK parameters (a.o. Min, Median, Max) will be tabulated by cohort.

7.6.2 Further endpoints phase IIa

All summary statistics are provided by treatment arm.

7.6.2.1 Successful virus isolation from nasopharyngeal swabs in SARS-CoV-2-infected individuals

Information will be shown for each assessment time point on whether live virus could be isolated in participating subjects or not. In addition, the relative frequency of positive samples will be shown per timepoint.

This endpoint will be evaluated on subjects from the subject set TS.

7.6.2.2 SARS-CoV-2 RNA shedding in oropharyngeal swabs determined by qRT-PCR in SARS-CoV-2-infected individuals

The same evaluations as proposed to be done for the secondary endpoint of SARS-CoV-2 RNA shedding in nasopharyngeal swabs determined by qRT-PCR in SARS-CoV-2-infected individuals shown in Section 7.5.2.2.3 will be implemented for this endpoint. These evaluations will be based on all subjects in the subject set TS who have at least a baseline value and a second measurement in the respective time period of viral RNA shedding in OP swabs by qRT-PCR.

7.6.2.3 Successful virus isolation from oropharyngeal swabs in SARS-CoV-2-infected individuals

Information will be shown for each assessment time point on whether live virus could be isolated in participating subjects or not. In addition, the relative frequency of positive samples will be shown per timepoint.

This endpoint will be evaluated on subjects from the subject set TS.

7.6.2.4 Frequency of COVID19-related hospitalization and medically-attended health care contacts in SARS-CoV-2-infected individuals not previously hospitalized

Subjects will be categorised into having a hospitalisation or medically-attended health care contact over 29 days. Descriptive summary statistics by treatment group will be provided for this endpoint.

This endpoint will be evaluated on subjects from the subject set TS.

7.6.2.5 Time to resolution of self-assessed SARS-CoV-2-related symptoms

A log-rank test will be used to evaluate the effect of DZIF-10c on time to resolution of self-assessed SARS-CoV-2-related symptoms compared to Placebo over 29 days. A Cox proportional-hazards model will be used to derive the hazard ratio and 95 % CI between each of the two randomised treatment regimens that were assigned DZIF-10c and the placebo regimen (Hazard ratios <1 will favour DZIF-10c). This will be done for each symptom (cough, feverishness, body ache, headache, sore throat, shortness of breath, loss of taste or smell) separately as well as together for all symptoms. Breslow's method for handling ties will be used. Kaplan-Meier plots by treatment group will also be presented and the rates at day 29 compared.

This endpoint will be evaluated on subjects from the subject set TS.

7.6.2.6 Differences of viral spike gene sequences obtained before and after study drug administration and the investigation of the effect of observed mutations on viral sensitivity to DZIF-10c in neutralization assays

These analyses will be performed by UKK and reported in a separate report which will be appended to the CTR.

7.6.2.7 The activity and frequency of SARS-CoV-2-reactive immune cells following DZIF-10c administration

As described in Section 4, these analyses will be performed by UKK and will not be included in the CTR but might be reported elsewhere.

7.6.2.8 Subgenomic SARS-CoV-2 mRNA levels in respiratory samples in SARS-CoV-2-infected individuals

These analyses will be performed by UKK and reported in a separate report which will be appended to the CTR.

7.6.2.9 The pharmacokinetic profile of DZIF-10c, including elimination half-life, peak serum concentration, area under the curve, clearance, and volume of distribution

Same analysis will be performed as described in Section 7.6.1.9.

7.7 EXTENT OF EXPOSURE

Analyses of exposure will be based on the treated set and presented according to trial part and dose cohort. Reason for early stoppage of infusion/inhalation will be presented.

Only descriptive summary statistics are planned for this section of the report.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set unless specified otherwise.

7.8.1 Adverse Events

Unless otherwise specified, the analyses of adverse events (AEs) will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs.

For analysis multiple AE occurrence data on the eCRF will be collapsed into an AE provided that all of the following applies:

- All AE attributes are identical (LLT, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AESI and CTCAE grade (based on version 5)).
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all adverse events occurring after drug intake until the end of the residual effect period (+90 days thereafter) (+7 and +28 days as additional analysis) will be assigned to the treatment. In addition, AEs starting from day 9 until day 91 will be tabulated separately. All adverse events occurring before drug intake will be assigned either to ‘screening’ or ‘post-randomisation’ (phase IIa part and for listings only). All adverse events occurring after drug intake +90 days will be assigned to ‘post-study’ (for listings only). For details on the treatment definition, see Section 6.1.

Adverse events related to infusion-related reactions (AEs presenting as hypersensitivity/allergic reaction, anaphylaxis, or cytokine release syndrome) as well as inhalation-related reactions presenting as allergic reaction (e.g., bronchospasm that may manifest with wheezing and/or respiratory distress) will be considered as protocol-specified AESIs, and ticked as such in the eCRF. Further adverse event groupings by safety topic have been defined outside the trial protocol, which will be continuously updated at project level (2). These safety topics are deemed of particular importance, and these definitions can be based on selection of coded terms

based on MedDRA. The latest approved version of the project level overview archived prior to either DBL will be used in the corresponding CTR.

An overall summary of adverse events having occurred during trial participation will be presented, including all AEs occurring:

- Within the first 7 days after drug administration
- Within the first 28 days after drug administration (sensitivity analysis)
- At any time during trial participation after drug administration (sensitivity analysis)

The frequency of subjects with adverse events per cohort and trial part, will be summarised by treatment, primary system organ class and preferred term. Separate tables will be provided for subjects with protocol-specified adverse events of special interest (as ticked in the AE page of the eCRF). Displays will also be provided for subjects with any adverse events, non-serious SIAEs, severe adverse events and also serious adverse events, for subjects with adverse events occurring with an incidence in preferred term greater than 5% (in at least one treatment arm), for subjects with adverse events leading to treatment discontinuation, for subjects with investigator defined drug-related adverse events, for subjects with drug-related serious adverse events, and for subjects with adverse events leading to death.

In addition, there will be outputs showing the total number of adverse events, not the number of subjects with adverse events.

Additional outputs will be created for the subgroups depicted in Section 6.4 focusing on the overall summary of adverse events, subjects with serious adverse events and subjects with related adverse events.

The system organ classes will be sorted according to the standard sort order specified by EMA, preferred terms will be sorted by frequency in the DZIF-10c arm (within SOC). In the phase I part, sorting will take place by overall frequency, as every subject receives DZIF-10c. In the phase IIa part of the trial combined safety outputs might be produced if deemed helpful.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and based on SI units. All analyses will be performed on the treated set, separately for the different trial parts. Clinically relevant abnormalities will be added as adverse events, but also shown as summary statistics as well as lab shift tables based on CTCAE grades (based on version 5) of standardised values. In addition descriptive visit-by-visit and baseline-last values statistics based on normalised values will be created.

A descriptive evaluation of liver enzymes and bilirubin elevations covering the complete time of trial participation will be given as well. E-dish plots may be created for ALT and AST as well. Please also see Section 5.4.4.

7.8.3 Vital signs

Only descriptive summary statistics will be presented for observed values and change from baseline by treatment and visit. The frequency of subjects with marked changes in vital signs

will also be summarised by treatment according to the parameters defined in Section 5.4.5 of this document.

7.8.4 ECG

Not applicable.

7.8.5 Others

To support the clinical trials disclosure process special safety displays may be necessary, e.g. the number of non-serious adverse events. All required outputs (including the following information) will be included in Appendix 16.1.13.1 of the CTR:

- Number of subjects included by country
- Number of subjects inside (member states) and outside the EU (third countries)
- Frequency of serious drug-related AEs by treatment, primary system organ class and preferred term.

8. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	Specifications for adverse event groupings by safety topic for BI 767551: BI 767551 / Clinical / covid-19 / Project Data Management and Statistics / Project-Section 2 PSAP / psap-sap-project-specific-aesis, current version; BIRDS.

9. ADDITIONAL SECTIONS

9.1 INTERIM ANALYSES

There will be two interim analyses in study Uni Koeln 4370 / BI Trial 1487-0005. The following sections will provide a detailed overview of which analyses of the ones described previously are going to be implemented. Due to the nature of the analyses additional rules, only pertaining to the interim analyses, will also be described. For the purpose of the interim analyses, database snapshots will be performed. These snapshots will follow processes as applicable at the UKK for interim database lock snapshots. Unblinding will also occur based on processes applicable at the UKK.

Evaluations for these interim analyses will be performed on data structures as provided by UKK.

An initial version of the TSAP will be archived before the snapshot for the first interim analysis is performed. The final version of the TSAP will be signed and archived before the snapshot for the second interim analysis is performed.

9.1.1 Interim analysis 1

9.1.1.1 Time point and general content

This interim analysis will commence when the last treated subject in the phase I part of the trial (Cohort 1C or 2C) has been followed up for safety for 7 days after drug intake. The analysis will evaluate data regarding the safety of subjects in the phase I part of the trial, and the main focus of this assessment will be the determination of the treatment dose to be taken forward into subsequent development stages. Only descriptive statistics of viral load will be calculated and no efficacy analyses will be performed. Preliminary PK data may be added if available by the time this interim analysis occurs.

Only a subset of data points is taken into consideration for this analysis.

9.1.1.2 Datapoints to be cleaned

Selected tables, listings and figures (TLFs) will be created and an overview of the specific TLFs will be available in a separate Table of Contents (TOC) document. The database should be as clean as possible before the snapshot is taken, and 7 days will be allocated to cleaning and reconciliation tasks after the last treated subject in the phase I part of the trial has been followed up for safety for 7 days after drug intake. The data generated at the UKK will then be transitioned to BI via SAS transport files for analysis. Despite all reasonable cleaning efforts, it is perceivable that data points might still not be completely clean at the time point the data snapshot is performed as the trial is ongoing. Please note that all data are taken as they are, and no hard coding will be implemented.

The cleaning and reconciliation efforts will particularly focus on, but are not limited to, the following eCRF pages:

- Pages related to AEs

- Pages related to laboratory data
- Pages related to the administration of trial drug
- Pages related to subject disposition
- Pages related to baseline characteristics including concomitant medications
- Data sources related to nasopharyngeal or oropharyngeal viral load data (central testing)
- Data sources related to PK data (central testing)
- Data sources related to ADA data (central testing)

9.1.1.3 Analyses

The following entities will be evaluated at this interim analysis:

- Trial Subjects
  - Disposition of subjects
  - Demographic characteristics
  - Baseline Conditions
  - Concomitant Therapies
  - Exposure to study medication including compliance
- Safety
  - AE overall summary covering AEs with onset during the first 7 days after drug administration
  - Subjects with DLTs within 7 days of trial drug administration
  - Subjects with AEs within 7 days of trial drug administration
  - Subjects with drug-related AEs within 7 days of trial drug administration
  - Subjects with AEs leading to trial drug administration discontinuation
  - Subjects with SAEs within 7 days of trial drug administration
  - Subjects with AESIs within 7 days of trial drug administration
  - Subjects with transitions of CTCAE grades at baseline and worst grade within 7 days of trial drug administration
  - Subjects with clinically relevant lab abnormalities within 7 days of trial drug administration
- Preliminary Efficacy
  - Descriptive summary outputs of absolute viral load (based on nasopharyngeal swabs) in SARS-CoV-2-infected individuals, as well as absolute and relative changes from baseline, for each assessment time point.
- Preliminary PK/ADA (if data allows)

- The same endpoints and assessments as listed in Sections 5.2.2.1 and 5.2.2.2 will be performed.

The safety outputs will be repeated covering the first 28 days after drug administration as well as the whole trial duration and from day 9 until day 91. Any table created will be accompanied by a corresponding listing.

Please note that all these outputs will also be included in the final CTR.

9.1.2 Interim analysis 2

9.1.2.1 Time point and general content

This interim analysis will commence when the last randomised subject in the phase IIa part of the trial has been followed up for safety and viral load data for 7 days after drug intake. The analysis will evaluate data regarding the safety and efficacy in subjects in the phase IIa part of the trial, and the main focus of this assessment will be the determination of additional relevant safety information, but also preliminary efficacy comparing subjects on DZIF-10c inhaled, DZIF-10c inhaled plus intravenous and Placebo with the focus on viral load changes to inform subsequent development stages.

Only a subset of data points are taken into consideration for this analysis.

9.1.2.2 Datapoints to be cleaned

Selected TLFs will be created and an overview of the specific TLFs will be available in a separate TOC document. The database should be as clean as possible before the snapshot is taken, and 7 days will be allocated to cleaning and reconciliation tasks after the last treated subject in the phase IIa part of the trial has been followed up for safety and viral load data for 7 days after drug intake. The data generated at the UKK will then be transitioned to BI via SAS transport files for analysis. Despite all reasonable cleaning efforts, it is perceivable that data points might still not be completely clean at the time point the data snapshot is performed as the trial is ongoing. Please note that all data are taken as they are, and no hard coding will be implemented.

The cleaning and reconciliation efforts will particularly focus on, but are not limited to, the following eCRF pages or data sources:

- Pages related to AEs
- Pages related to laboratory data
- Pages related to the administration of trial drug
- Pages related to subject disposition
- Pages related to baseline characteristics including concomitant medications
- Data sources related to nasopharyngeal or oropharyngeal viral load data (central testing)
- Data sources related to PK data (central testing)
- Data sources related to ADA data (central testing)

9.1.2.3 Analyses

The following entities will be evaluated at this interim analysis:

- Trial Subjects
  - Disposition of subjects
  - Demographic characteristics
  - Baseline Conditions
  - Concomitant Therapies
  - Exposure to study medication including compliance
- Safety
  - AE overall summary covering AEs with onset during the first 7 days after drug administration
  - Subjects with DLTs within 7 days of trial drug administration
  - Subjects with AEs within 7 days of trial drug administration
  - Subjects with drug-related AEs within 7 days of trial drug administration
  - Subjects with AEs leading to trial drug administration discontinuation
  - Subjects with SAEs within 7 days of trial drug administration
  - Subjects with AESIs within 7 days of trial drug administration
  - Subjects with transitions of CTCAE grades at baseline and worst grade within 7 days of trial drug administration
  - Subjects with clinically relevant lab abnormalities within 7 days of trial drug administration
- Preliminary Efficacy
  - Descriptive summary outputs of absolute viral load (based on nasopharyngeal swabs) in SARS-CoV-2-infected individuals, as well as absolute and relative changes from baseline, for each assessment time point.
  - Outputs for phase IIa part only:
    - Plots of absolute change from baseline in viral load by treatment arm
    - Time-weighted average change in viral load
    - Mixed effect Model for Repeated Measures (MMRM) of absolute change from baseline in viral load
- Preliminary PK/ADA (by trial part)
  - The same endpoints and assessments as listed in Sections 5.2.2.1 and 5.2.2.2 will be performed, if data allows.

The safety outputs will be repeated covering the first 28 days after drug administration as well as the whole trial duration and from day 9 until day 91. Any table created will be accompanied by a corresponding listing.

In addition to these outputs based on the expansion part, a complete re-run of the analyses of the escalation part (and covered during interim analysis 1 already) will be performed.

Please note that all these outputs will also be included in the final CTR.

9.2 EXAMPLE CODE

The provided sample code will have to be modified to suit the needs of the corresponding analysis.

9.2.1 Change from baseline

9.2.1.1 Time-weighted average change in viral load

Change from Baseline in Viral load:

```
#####################################################
%MACRO auc (idvar =, dsname =, timevar =, yvar =, resultds =);
    %LOCAL lastid;
    %* All data mapulations are to be made outside of the macro;
    %* Sort dataset -> 1st data point is the starting point;
    PROC SORT DATA = &dsname OUT = _tmp;
        BY &idvar &timevar;
    RUN;

    %* Get last idvar;
    DATA _null_;
        y = COMPBL ("&idvar");
        y1 = COMPRESS (y);
        n = LENGTH (y) - LENGTH (y1);
        CALL SYMPUT ('lastid', COMPRESS (PUT (n+1, 5.)));
    RUN;

    %PUT lastid = &lastid;
    %LET lastvar = %SCAN (&idvar, &lastid, %STR ( ));

    DATA _tmp1;
        SET _tmp;
        RETAIN _ltime _lyvar _difftime _mintime;
        BY &idvar;
```

```
        IF FIRST.&lastvar THEN DO;
            _ltime = &timevar;
            _lyvar = &yvar;
            _difftime = .;
            _mintime = &timevar;
        END;
        IF NOT FIRST.&lastvar THEN DO;
            auccomp = 0.5 * (&yvar + _lyvar) * (&timevar - _ltime);
            diff = (&yvar - _lyvar);
            difft = (&timevar - _ltime);
            _ltime = &timevar;
            _lyvar = &yvar;
            IF last.&lastvar THEN _difftime = &timevar - _mintime;
            OUTPUT;
        END;
    RUN;

    PROC SUMMARY DATA = _tmp1;
        BY &idvar;
        VAR auccomp;
        OUTPUT OUT = &resultds._pre SUM = auc;
    RUN;

    DATA &resultds;
        MERGE &resultds._pre _tmp1 (WHERE = (_difftime NE .) KEEP = &idvar
_difftime);
        BY &idvar;
        auc = auc / _difftime;
    RUN;
%MEND;

%auc (idvar = subject swab_type gene, dsname = rawdata3, timevar = day, yvar = log_cp_ml_d,
resultds = auc_result);;
```

##

9.2.1.2 Mixed effect Model for Repeated Measures (MMRM) of absolute change from baseline in viral load

Change from Baseline in Viral load via MMRM approach:

##

```
ods exclude all;
ods output Diffs=diff0 classlevels=cl ConvergenceStatus=cs;
proc mixed data=viral_small_sim cl order=internal covtest;
  class usubjid trt01pn ady;
  model chg = antibs base base*ady trt01pn*ady  / solution ddfm=Kenwardroger outpred=outpred1;
  repeated ady / type=un subject=usubjid;
  lsmeans trt01pn*ady / pdiff=control ("100" "&cutoffdays") obsmargins cl alpha=0.05 slice=ady;
run;
ods exclude none;
```

##

Where:

- usubjid = subject
- trt01pn = treatment arm (here numeric)
- ady = analysis day
- antibs = antibody status
- base = baseline viral load
- chg = change from baseline in viral load
- cutoffdays = day for analysis ➔ 7 (primary analysis) or 28 (sensitivity analysis)

Note that the reference level in the code above ("100") has to be adapted to the level used in the study.

9.2.1.3 Mixed effect Model for Repeated Measures (MMRM) of viral load over time for mean viral load trajectories based on MMRM over time

Mean absolute viral load over time via MMRM approach:

##

```
ods exclude all;
ods output Diffs=diff0 classlevels=cl ConvergenceStatus=cs;
proc mixed data=viral_small_sim cl order=internal covtest;
  class usubjid trt01pn ady;
  model vl = antibs  trt01pn*ady  / solution ddfm=Kenwardroger outpred=outpred1;
  repeated ady / type=un subject=usubjid;
  lsmeans trt01pn*ady / pdiff=control ("100" "&cutoffdays") obsmargins cl alpha=0.05 slice=ady;
run;
```

```
ods exclude none;
```

```
#####################################################
```

Where:

- usubjid = subject
- trt01pn = treatment arm (here numeric)
- ady = analysis day
- antibs = antibody status
- vl = viral load at day for analysis
- cutoffdays = day for analysis ➔ 7 (primary analysis) or 28 (sensitivity analysis)

Note that the reference level in the code above ("100") has to be adapted to the level used in the study.

9.2.2 Time-To-Event

9.2.2.1 Log-rank test

Time to resolution of self-assessed SARS-CoV-2-related symptoms:

```
#####################################################
ods output Quartiles = quartiles_raw HOMTESTS = logrkp_raw;
title  "Unstratified log rank test";
PROC LIFETEST data=tte_analysis_allpat METHOD = km plots = (s, lls) ;
   TIME ady * cnsr(1);
   STRATA trt01p / TEST = logrank;
   SURVIVAL CONFTYPE = linear;
RUN;
ods output close;
#####################################################
```

Where:

- cnsr = censoring variable (1=censored)
- trt01p = treatment arm
- ady = analysis day

Note that this has to be implemented for each symptom separately.

9.2.2.2 Cox proportional-hazards model

Time to resolution of self-assessed SARS-CoV-2-related symptoms:

```
####################################################

ods output ParameterEstimates = param_est_raw GlobalTests = global_test_raw;
title  "Unstratified cox model";
PROC PHREG  DATA= tte_analysis_allpat ;
   CLASS trt01p (REF =  "Placebo") ;
   MODEL ady * cnsr(1) = trt01p  /TIES = BRESLOW;
   HAZARDRATIO trt01p /CL = WALD ALPHA = 0.05;
   ODS OUTPUT HAZARDRATIOS = hazard_raw;
RUN;
ods output close;
####################################################
```

Where:

- cnsr = censoring variable (1=censored)
- trt01p = treatment arm
- ady = analysis day

Note that the reference level in the code above ("Placebo") has to be adapted to the level used in the study, and that the evaluation has to be implemented for each symptom separately.

9.2.3 Evaluation of Proportions

9.2.3.1 Overall frequencies and proportions

Frequency of COVID19-related hospitalization and medically-attended health care contacts in SARS-CoV-2-infected individuals not previously hospitalized:

```
####################################################

PROC FREQ DATA= <dataset>;
        TABLES binaryvar;
        EXACT binomial;
        ODS OUTPUT binomialprop=bin(where=(name1 in ('XL_BIN', 'XU_BIN')));
RUN;
####################################################
```

Where:

- <dataset> = data set for COVID19-related hospitalization and medically-attended health care contacts in SARS-CoV-2-infected individuals not previously hospitalized
- binaryvar = hospitalisation (yes/no) or medically-attended health care contacts (yes/no)

9.2.3.1 Frequencies and proportions by visit

Frequency and proportions of participants with positive and negative PCR for each assessed SARS-CoV-2 gene (clearance rate) and frequency and proportion of patients who fell below the limit of valid quantification assessed at every given visit:

```
#######################################################

PROC FREQ DATA= <dataset>;
        BY visit;
        TABLES binaryvar;
        EXACT binomial;
        ODS OUTPUT binomialprop=bin(where=(name1 in ('XL_BIN', 'XU_BIN')));
RUN;
#######################################################
```

Where:

- <dataset> = viral load data set
- visit = visit assigned to viral load sample

binaryvar = below limit of valid quantification (yes/no) or negative swab test (yes/no)

9.3 OVERVIEW OF STANDARDISED DRUG GROUPINGS

Standardised drug groupings of interest for this trial are shown in Table 9.3: 1.

Table 9.3: 1 Concomitant Therapy groupings

CT grouping name	Type of grouping
Antihistamines	SDG
Antihypertensives	SDG
Antiarrhythmics	SDG
Antiemetics and antinauseants	SDG
Corticosteroids	SDG
Drugs for obstructive airway diseases	SDG
Immunomodulators	SDG
Monoclonal antibodies	SDG
NSAIDs	SDG
Systemic anti-infectives	SDG
Vaccines	SDG
Blood and related drugs (NB: for plasma use)	SDG

9.4 HANDLING OF MISSING AND INCOMPLETE ADVERSE EVENT DATES

The evaluation of AEs requires complete onset dates in order to determine if an AE is treatment-emergent or not. Hence imputations are needed to obtain complete AE onset dates. The employed algorithm is based on a worst-case approach, i.e. the imputed AE dates will maximize the possibility for the AE to be counted as treatment emergent AE.

The imputation of missing / incomplete AE onset date/time is performed according to the following steps:

Step 1: For each missing / incomplete AE onset date, an interval (INT_START, INT_END) is defined. The true unknown analysis start date of the AE is assumed to be within this interval.

Table 9.4: 1 Scenarios of AE onset dates and interval start / end points

Scenario of AE onset date	INT_START	INT_END
Completely missing AE onset date	Min(AE end date, Date of informed consent)	Min(AE end date, Date of last visit)
Only year of AE onset date is non-missing	Min(AE end date, 01 JAN of the reported year)	Min(AE end date, 31 DEC of the reported year)
Only year and month of AE onset date are non-missing	Min(AE end date, 01 of the reported month)	Min(AE end date, Last date of the reported month)

Note: Completely missing AE end date will not be considered in this derivation step. Partially missing AE end date (i.e., year and month are non-missing or only year is non-missing) will be

temporarily assigned the largest possible date in the observed year or month and year in this derivation step.

Step 2: Derive an imputed AE onset date based on the interval from step 1.

Table 9.4: 2 Scenarios and imputed AE onset dates

Scenarios	Treatment emergent	Imputed AE onset date
Date of first drug administration is within the interval [INT_START, INT_END]	YES	Date of first drug administration
Date of first drug administration is before INT_START*	YES	INT_START from step 1
Date of first drug administration is after INT_END or missing	NO	INT_END from step 1

* Note if the INT_START is after the date of the last drug administration plus residual effect period, then the AE is not treatment emergent.

Step 3: The AE onset date / time imputation flag(s) are set according to the level of imputation performed and the standard CDISC rules for imputation or the legacy data imputation rules.

If AE onset and end times are also collected, then the start and end times of the treatment record are also to be considered in the above imputation algorithm.

In trials where the date of randomization is different from the date of first drug administration, the date of first drug administration should be considered for imputing missing / incomplete AE onset dates because date of first drug administration corresponds to the start of trial treatment rather than the start of trial procedure and hence ensures the treatment emergent principle for the algorithm.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	25-FEB-21	[redacted]	None	This is the first version of the TSAP with special focus on interim analyses to be performed after relevant data from the phase I and phase IIa part are available
2.0	28-MAY-21	[redacted]	4.2, 5.2, 6.2, 6.3, 6.4, 6.6, 6.7, 7.2, 7.5, 7.6, 7.8, 9.2	This is the final version of the TSAP in which mainly sections relevant to interim analysis 2 and the final analysis have been changed. The day of drug administration has been changed to be denoted as day 1 and inconsistencies with day labels have been corrected.

11. SIGNATURE PAGE

Statistical Analysis Plan Version 2.0 (Dated 28-MAY-2021) for protocol Uni-Koeln-4370.

Author

Author: [redacted]
Position: [redacted]
Company: [redacted]

_____ _____

Signature Date

Reviewer / Approver

Statistical Analysis Plan Version 2.0 (Dated 28-MAY-2021) for protocol Uni-Koeln-4370.

Upon review of this document, the undersigned approves this version of the Trial Statistical Analysis Plan, authorising that the content is acceptable for the reporting of this study.

Approved by: [redacted]
Position: [redacted]
Company: [redacted]

_____ _____
Signature Date

Approved by: [redacted]
Position: [redacted]
Company: [redacted]

_____ _____
Signature Date

Approved by: [redacted]
Position: [redacted]
Company: [redacted]

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Signature Date