TRIAL STATISTICAL ANALYSIS PLAN c35105623-01

BI Trial No.:	1487-0001
Title:	A Phase II/III seamless, randomised, double-blind, placebo-controlled, parallel-group, group-sequential study to evaluate efficacy, safety and tolerability of BI 767551 for the treatment of symptomatic, non-hospitalized adults with mild to moderate COVID-19. Including Protocol Amendment 1 [c33563257-02]
Investigational Product(s):	BI 767551 (formerly EX 14870 or DZIF-10c)
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	19 OCT 2021 SIGNED
Version:	1
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1. TABLE OF CONTENTS

[redacted]

[redacted]

LIST OF TABLES

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
ADA	Anti-drug antibodies
COVID-19	Coronavirus disease 2019
nAb	Neutralizing antibody
LLOD	Lower limit of quantification
LOQ	Limit of detection
mL	Milliliter
NP	Nasopharyngeal
RNA	Ribonucleic acid
RT-qPCR	Quantitative reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDG	Standardised drug grouping

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 TSAP 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 7 “Statistical Methods and Determination of Sample Size”. 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, randomization.

This TSAP covers only Phase II of the study. As the study has been terminated early by BI, only a restricted set of analyses are planned.

SAS® Version 9.4 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Following BI's decision to terminate the development program for BI 767551 (anti-SARS-CoV-2 neutralizing antibody (nAb) under investigation for SARS-CoV-2-infected patients), study 1487-0001 has been discontinued as of 25 June 2021, with only a few patients screened (7), and randomized (5). Considering this low number of patients randomized in the study, the following changes to the planned analysis will be implemented:

- No model based statistical analysis will be performed. Descriptive statistics will be provided for primary and secondary endpoints. Further endpoints will not be analysed but data will be listed.
- No subgroup analyses will be performed.
- Unless described otherwise in Section 6.6, missing data will not be imputed.
- PK and ADA samples will not be analysed.

5. ENDPOINTS

In this section, more details are given regarding endpoints. Note that baseline value definitions for all endpoints and analyses are provided in Section 6.7.

Handling of missing data points is described in Section 6.6.

All analyses of viral load endpoints will be based on the N1 gene. The lower limit of quantification (LLOQ) of the assay is 3.348 Log10 copies/mL (2228 copies/mL). Viral load measurements below the LLOQ will be set to half this limit on the log10 scale (1.674 Log10 copies/mL). Undetectable viral load measurements will be set to 0. Inconclusive results will not be imputed but will be set to missing.

5.1 PRIMARY ENDPOINT

The primary endpoint in Phase II is the time-weighted change from baseline in viral shedding over 8 days in site-collected nasopharyngeal (NP) swabs by Quantitative Reverse Transcription Polymerase chain reaction (RT-qPCR), defined as a change from baseline in log10 viral load. Time-weighted average change in $\log_{10}$ viral load from baseline is defined as:

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

- Where
  - a = baseline assessment at Day 1
  - b = last assessment at or prior to the threshold day (Day 8 for the primary endpoint)
  - Y_i = change from baseline in $\log_{10}$ viral load at visit i (and where Y_a=0)
  - t = time at the specified time point (the actual study day)

The normalisation by the denominator assures comparability of the values if t_b is different between patients.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint(s)

This section is not applicable, as no key secondary endpoints have been specified in the protocol.

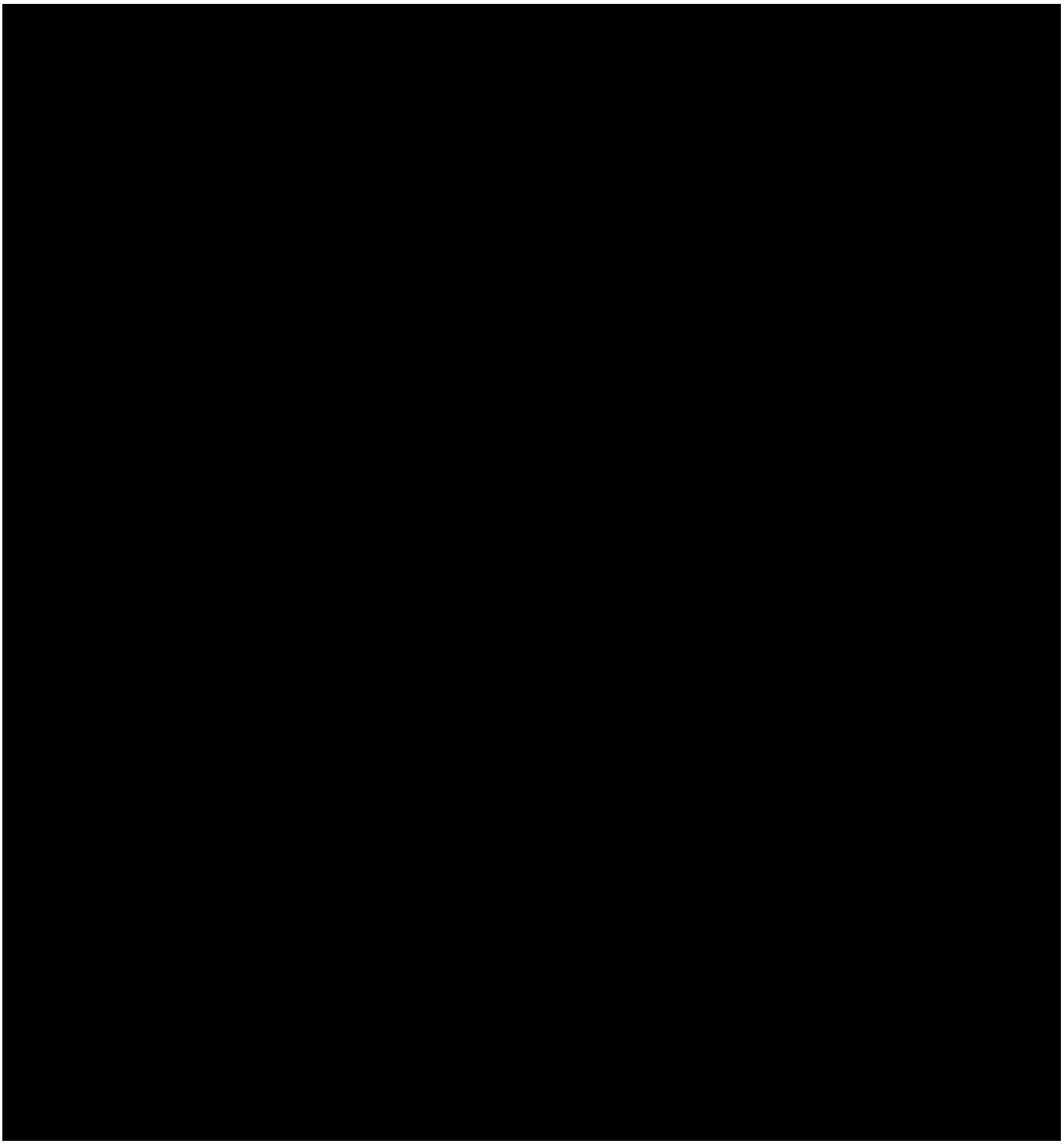
5.2.2 Secondary endpoints

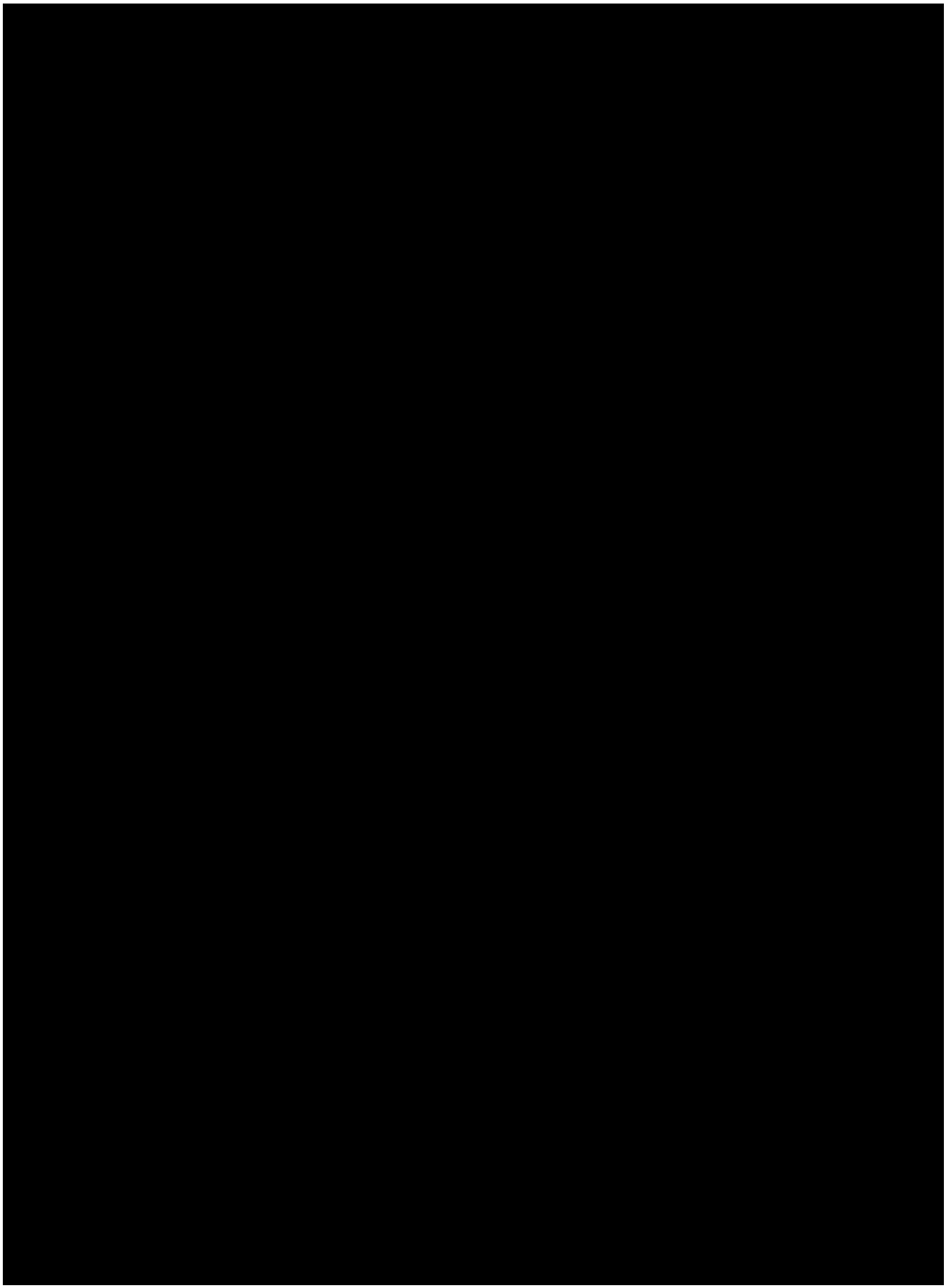
5.2.2.1 Time-weighted change from baseline in viral shedding over 29 days in site collected NP swabs by RT-qPCR

Time-weighted change from baseline in viral shedding over 29 days in site-collected NP swabs by RT-qPCR is defined as a change from baseline in $\log_{10}$ viral load. Time-weighted average change in $\log_{10}$ viral load from baseline is defined as described in Section 5.1, but using all measurements through Day 29 (b=Day29).

5.2.2.2 Loss of detection of SARS-CoV-2 RNA by site-collected NP swabs at Day 4, 8, 15, 22 and 29

Loss of detection of SARS-CoV-2 RNA will be evaluated by site-collected NP swabs at Day 4, 8, 15, 22 and 29. Detection of SARS-CoV-2 RNA will be considered as lost at a specific timepoint if the quantitative viral load assessment at this timepoint is below the LOD. Refer to Section 6.7 for the definition of time windows for the different assessment times.





[redacted]

5.4.3 Liver function tests

A listing of all liver function tests will be provided for all subjects who meet one of the following criteria at any time:

- ALT and/or AST ≥3xULN and elevation of total bilirubin ≥2xULN measured in the same blood sample, or in later samples drawn within 30 days after the ALT and/or AST increase
- ALT and/or AST ≥10xULN

5.4.4 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

For the definition of treatment administered during the trial, see Section 4 of CTP.

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: From informed consent to randomisation
- Post-randomisation (optional[a]): From randomisation to trial drug intake in treatment period
- Treatment period: From date and time 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

[a] This period is optional insofar as it does not necessarily exist for all subjects.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Handling of iPDs in analysis is included in the DV domain specifications and stored within the TMF in EDMS.

No per protocol set analysis will be performed for this study. The proportion of subjects with iPDs will be presented for completeness purposes and to demonstrate the adherence to the CTP.

6.3 SUBJECT SETS ANALYSED

- Screened set (SCS):
  This subject set includes all subjects having signed informed consent

- Randomised set (RS):
  This subject set includes all randomised subjects, whether treated or not. This would correspond to the intention-to-treat set (ITT).

- Treated set (TS):
  This subject set includes all subjects who received any amount of study drug.

- Modified Intention-To-Treat set (mITT):
  This subject set includes all randomised subjects that received any amount of study drug and who have at least a measurable baseline value (above LLOQ) and a second measurement in the first week (up to 7 days after drug intake) of SARS-CoV-2 RNA by site collected NP swab.

Please see Table 6.3: 1 for a general overview which patient set will be used for which type of analyses.

Table 6.3: 1 Subject sets analysed

	Subject set			
Type of analysis	SCS	RS	TS	mITT
Primary endpoint				X
Secondary endpoints			X	X
Safety data, ADA & treatment exposure			X	
Demographic/baseline characteristics			X	
Disposition	X	X		

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

[redacted]

6.5 POOLING OF CENTRES

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

In general, missing data will not be imputed. Missing or incomplete AE dates will be imputed according to BI standards (2).

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 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.

Visit windowing will be performed as described in Table 6.7: 1, in order to assign data to the relevant study visit based on the actual day of the assessment. For some endpoints, data will be analysed using the re-calculated visits in the statistical tables. However, in the listings, all visits performed will be displayed (even if outside time-window), along with the re-calculated visit.

Table 6.7: 1 Time windowing rules for site collected viral load related data

Time window of actual day [1]			Allocated to		
Start (S_n) day	End (included) (E_n) day	Length of the time-window [days]	Visit number (n)	Visit name	Planned day of the visit (V_n)
-4	-2	3	1	Screening	-2
-1	-1	1	2	Baseline	-1
3	5	3	4	Day 4	4
7	9	3	5	Day 8	8
10	17	8	7	Day 15	15
18	24	7	8	Day 22	22
25	33	9	9	Day 29	29
34	105	72	EOS	Day 91	91

[1] First trial drug intake date is taken into account as a reference to calculate time windows

If after windowing of visits at baseline, two or more values fall within the same baseline interval, then the last value prior to first drug intake will be taken into account. If after windowing of post-baseline visits, two visits fall in the same interval, then the measurement closest to the planned visit will be taken into account. In case two measurements are equidistant from the planned visit, then the last one will be picked.

7. PLANNED ANALYSIS

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

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.

In Phase II, all analyses will be based on the treatment group as treated. If not specified otherwise, all analyses will be based on all randomised patients that have been treated.

Only descriptive analyses or listings will be provided due to the low patient numbers.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases and medication will be listed. No summary tables are planned.

7.2.1 Baseline conditions and targeted risk factors

The baseline conditions will be included as coded items using the current Medical Dictionary for Regulatory Activities (MedDRA) version in use at BI at the time of database lock. They will be listed by MedDRA system organ class (SOC) and Preferred Term. No summary tables are planned.

Targeted risk factors for progression to severe COVID-19 infection as collected on the corresponding eCRF page will be listed.

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.
- 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 therapies
    - Defined as treatments with a start date after the end of the residual effect period (for details, please see Section 6.1).

Concomitant therapies will be listed. No summary tables are planned.

7.3 TREATMENT COMPLIANCE

This section is not applicable as no analyses on treatment compliance are planned.

7.4 PRIMARY ENDPOINT

The primary endpoint in Phase II is the time-weighted change from baseline in viral shedding over 8 days in site collected NP swabs by RT-qPCR. Please refer to Section 7.1, 7.2.2 and 7.2.3 of the CTP for additional information on the underlying hypotheses and assessment strategy.

7.4.1 Primary analysis of the primary endpoint

Only descriptive analyses will be performed.

Evaluation will be performed on the mITT set and will take into account all data up to and including Day 8.

Missing values will not be imputed and since a linear trajectory on the log scale is expected.

[redacted]

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

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

7.5.2 (Other) Secondary endpoints

7.5.2.1 Time-weighted change from baseline in viral shedding over 29 days in site collected NP swabs by RT-qPCR

Only descriptive analyses will be performed.

Evaluation will be performed on all patients included in the randomised set that received any amount of study drug and who have at least a measurable baseline value (above LLOQ) of SARS-CoV-2 RNA by site collected NP swab and a second measurement after baseline.

All SARS-CoV-2 RNA measurements by site collected NP swab up to and including Day 29 will be used in the analysis.

Viral load will be plotted individually for each patient over time.

7.5.2.2 Loss of detection of SARS-CoV-2 RNA by site collected NP swab at Day 4, 8, 15, 22 and 29

The number and proportion of patients with loss of detection of SARS-CoV-2 RNA by site collected NP swab will be calculated on Day 4, 8, 15, 22 and 29. Please refer to Section 6.7 for the definition of time-windowing rules.

Evaluation will be performed on all patients included in the randomised set that received any amount of study drug and, who have at least a measurable baseline value (above LLOQ) of SARS-CoV-2 RNA by site collected NP swab and a second measurement after baseline.

[redacted]

7.7 EXTENT OF EXPOSURE

Exposure data will be listed for all patients treated.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

7.8.1 Adverse Events

Unless otherwise specified, the analyses of 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.

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) will be assigned to the treatment. All adverse events occurring before drug intake will be assigned either to ‘screening’ or ‘post-randomisation’ (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.

All AEs that occur at any time during trial participation after drug administration, including all AEs occurring between drug intake (included) and up to the end of the residual effect period analyses will be included in the analysis.

An overall summary of adverse events will be presented.

The frequency of subjects with any adverse events will be summarised by treatment group, primary system organ class and preferred term. The system organ classes will be sorted according to the standard sort order specified by EMA, preferred terms will be sorted by decreasing frequency in the BI 767551 arm (within SOC).

In addition, infusion related reactions and inhalation related reactions will be listed based on the data reported on the dedicated eCRF pages.

7.8.2 Laboratory data

Laboratory data will be listed. No summary tables are planned.

The analyses of laboratory data will be based on BI standards. It will be based on SI units. All analyses will be performed on the treated set. E-dish plots will be provided for ALT and AST.

7.8.3 Vital signs

Vital signs will be listed. No summary tables are planned.

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.
- Frequency of serious AEs
- Frequency of non-serious AEs with incidence >5% in any treatment arm

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

In phase II, it was planned to release the treatment information for interim analysis to the sponsor. Following the decision to terminate the study early, the database was unblinded on 7th July 2021, while patients were still followed in the study.

9. 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.	*KMED-BDS-HTG-0035:* "Handling of Missing and Incomplete AE Dates", current version KMED.

10. ADDITIONAL SECTIONS

10.1 EXAMPLE CODE

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

10.1.1 Time-weighted average change 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);
```

10.2 DEFINITION OF HIGH RISK OF PROGRESSION TO SEVERE COVID-19 AS PER NIH TREATMENT GUIDELINE

According to the NIH COVID-19 Treatment Guidelines, version dated April 8, 2021, high risk of progression to severe COVID-19 is defined as patients who meet at least one of the following criteria:

- Have a BMI ≥35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥65 years of age
- Are ≥55 years and <65 years of age AND have
  - cardiovascular disease, OR
  - hypertension, OR
  - chronic obstructive pulmonary disease/other chronic respiratory disease.

[redacted]

Table 10.2: 1 Dictionary codes for risk factors based on comorbidities or concomitant medications – Risk factor definition as per NIH treatment guidelines

Risk factor	**Dictionary (level)**	**Code (label)**
Chronic kidney disease	MedDRA (PT)	10064848 (Chronic kidney disease)
Diabetes type 1 and type 2	MedDRA (PT)	10067584 (Type 1 diabetes mellitus) 10067585 (Type 2 diabetes mellitus)
Immunosuppressive disease	MedDRA (PT)	10061598 (Immunodeficiency) 10080575 (Solid organ transplant)
Cardiovascular disease	MedDRA (PT)	10007649 (Cardiovascular disorder)
Hypertension	MedDRA (PT)	10020772 (Hypertension)
Chronic obstructive pulmonary disease	MedDRA (PT)	10009033 (Chronic obstructive pulmonary disease)
Other chronic respiratory disease	MedDRA (PT)	10038683 (Respiratory disorder) 10011762 (Cystic fibrosis) 10037383 (Pulmonary fibrosis) 10003553 (Asthma) From baseline conditions page: 10022611 (Interstitial lung disease) 10037400 (Pulmonary hypertension)
Immunosuppressive treatment	WHODrug (SDG)	0000000186 (Immunosuppressant drugs) For prednisone, doses below 20mg will not be considered as risk factor.

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**19-10-2021**	[redacted]	None	This is the final TSAP