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CDFV890

CDFV890D12201/NCT04282053

DFV890: Phase 2, randomized, controlled, open label multi-center study to assess efficacy and safety of DFV890 for the treatment of SARS-CoV-2 infected patients with COVID-19 pneumonia and impaired respiratory function

Statistical Analysis Plan (SAP) – Amendment 1

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CDFV890D12201".***

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol to be reported in the CSR. The data presentation and analyses for the DMC are not part of this analysis plan.

1.2 Study reference documentation

This SAP Amendment 1 is based on the protocol amendment 1 for study CDFV890D12201 dated 22-Jun-20.

1.3 Study objectives

Table 1-1 Study objectives

Objective(s)	Endpoint(s)
Primary Objective(s)	Endpoint(s) for primary objective(s)
• To evaluate the effect of DFV890 in addition to SoC, compared with SoC alone, on the Acute Physiology and Chronic Health Evaluation II (APACHE II) score	• APACHE II severity of disease score on Day 15 or on day of discharge (whichever is earlier) with worst case imputation for death
Secondary Objective(s)	Endpoint(s) for secondary objective(s)
• To evaluate the effect of DFV890 in addition to SoC, compared with SoC alone, on inflammatory status	• Serum C-reactive protein (CRP) levels
• To evaluate the effect of DFV890 in addition to SoC, compared with SoC alone, on clinical status	Endpoints based on the 9-point ordinal scale: • Survival without the need for invasive mechanical ventilation at Days 15 and 29 • At least one level improvement in clinical status at Days 15 and 29 • Clinical status over time
• To evaluate the safety of DFV890 in addition to SoC, compared with SoC alone	• Number of participants with Adverse Events (AE), Serious Adverse Events (SAE), clinically significant changes in laboratory measures, and vital signs

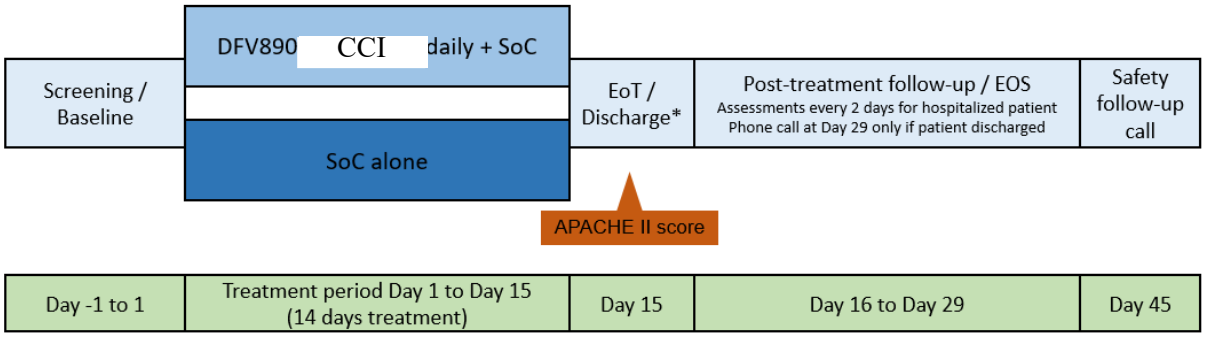
1.4 Study design and treatment

This is a Phase 2, randomized, controlled, open label multi-center study to assess the efficacy and safety of DFV890 for the treatment of SARS-CoV-2 infected patients with COVID-19 pneumonia and impaired respiratory function (Figure 1-1).

Written informed consent will be obtained from participants before any study related assessments or procedures are performed. Thereafter, medications and eligibility criteria will be reviewed by study personnel. All participants signing informed consent must be registered by study staff in the Interactive Response Technology (IRT).

Assessments during the study will occur per the schedule of study assessments as described in the protocol.

Figure 1-1 Study design



*If participant discharged from hospital prior to Day 15, investigational treatment should be taken at home to complete the 14-day treatment period.

The study consists of four parts:

1. **Screening / Baseline visit** (Day -1 to 1): lasts up to a maximum of 24 hours and comprises a screening / baseline assessment. This visit will be used to confirm that the study inclusion and exclusion criteria are met and serves as baseline assessment prior to randomization.

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   Baseline blood tests will be performed in all participants; those who screen fail because of study inclusion / exclusion criteria (e.g., serum CRP, liver function tests), will not undergo randomization.
2. **Treatment period** (Day 1-15): Participants in the investigational treatment arm will receive DFV890 CCI orally or via a nasogastric feeding tube administered for a total of 14 days CCI in addition to SoC. Study drug will be supplied in tablet form which can be crushed, allowing for both oral and nasogastric administration. Participants in the control arm will receive SoC alone.

   Participants will be randomized as soon as possible, but within a maximum of 24 hours after screening in a 1:1 ratio to receive either DFV890 in addition to SoC or SoC alone.

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   Study assessments will be conducted every 2 days for hospitalized participants.

   The End of Treatment (EOT) visit will take place on Day 15. If participants are discharged from the hospital prior to Day 15, assessments on the day of discharge should be performed according to the schedule listed under Day 15; participants will continue to take the investigational treatment at home to complete the 14-day treatment period and the participants should return to the site for the Day 15/EOT assessment (all other visits between discharge and Day 15 can be omitted). If a hospital visit is not possible at Day 15, then home nursing services may be used to support this last visit where these are available in

accordance with local guidelines and should include all possible assessments (e.g., oxygen saturation with portable monitors).

3. **Follow-up** (Day 16-29): After completion of the 14 day- treatment period, participants will be observed until Day 29 or discharged from hospital, whichever is sooner. Study assessments to be conducted every 2 days for hospitalized participants.
   If participants are discharged from hospital prior to Day 29, a study visit conducted by telephone will occur on Day 29 (all other visits between discharge and Day 29 can be omitted).
4. **30-day safety follow-up assessment** (Day 45): A follow-up visit for safety will be conducted by telephone.

2 First interpretable results (FIR)

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3 Interim analyses

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4 Statistical methods: Analysis sets

For all analysis sets, participants will be analyzed according to the study treatment(s) randomized.

The Safety analysis set will include all randomized participants.

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The PD analysis set will include all randomized participants with no protocol deviations with relevant impact on PD data.

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of protocol deviation	Additional condition	Data exclusion
Subjects are excluded from safety analysis in case of these conditions:			**Exclude subject from safety analysis set**
INCL02	Informed consent form not obtained		Yes

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Subjects are excluded from PD analysis in case of these conditions:			**Exclude subject from PD analysis set**
TRT02	Study treatment dose adjustments and/or interruptions	Study treatment dose interruptions resulting in exposure of **less** than 6 consecutive doses	Yes
TRT02	Study treatment dose adjustments and/or interruptions	Study treatment dose interruptions resulting in exposure of **at least** 6 consecutive doses	No
INCL06	Patient enrolled but APACHE II score is less than 10 at Screening Visit		Yes
INCL03	Patient randomized but no confirmed coronavirus (SARS-CoV)-2 infection		Yes
INCL02	Informed consent form not obtained		Yes

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

4.1 Baseline

The baseline value is defined as the last assessment performed on or prior to randomization.

4.2 Unscheduled visits

Data collected at unscheduled visits will be used to replace missing values if a Last observation carried forward (LOCF) approach is applied within the allowed LOCF period of maximum 4 days(i.e. for the mortality scores APACHE II, Commercially Confidential Information as described in Sections 6.1.6 and Section 6.3.1).

In addition for the screening/baseline visit unscheduled assessments within 24 hours prior to signing the Informed Consent Form (ICF) can be used.

For other type of analyses and other visits no unscheduled visits data will be considered.

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6 Statistical methods for Pharmacodynamic (PD) parameters

6.1 Primary objective

The primary aim of the study is to evaluate the effect of DFV890 in addition to SoC compared with SoC alone on the APACHE II score.

6.1.1 Variable

The primary clinical question of interest is: What is the effect of DFV890 in addition to SoC versus SoC alone in SARS-CoV-2 infected patients with COVID-19 pneumonia and impaired respiratory function on APACHE II severity of disease score taking into account early discharge from hospital or death but regardless of investigational treatment discontinuation?

The justification for the primary estimand is that it will capture the combined effect of investigational treatment in participants who remain in hospital for 14 days, the effect on early discharge within 14 days and the effect on death rate within 14 days, in a manner than reflects clinical practice. In this document the primary estimand will be referred to as the "**combined APACHE II score**".

The primary estimand is described by the following attributes:

- **Population:** SARS-CoV-2 infected patients with COVID-19 pneumonia and impaired respiratory function. Further details about the population are provided in the protocol (Section 5)
- **Endpoint**: APACHE II severity of disease score on Day 15 or on day of discharge (whichever is earlier) with worst case imputation for death. Participants who die on Day 15 or earlier will be assigned the highest observed APACHE II score of any of the participants at any time during the trial. Note this imputation for death takes precedence over the APACHE II score on day of discharge.
- **Treatment of interest:** the randomized treatment (the investigational treatment DFV890 in addition to SoC or control treatment of SoC alone).
- **Handling of remaining intercurrent events:** Treatment discontinuation for any reason will be ignored and thus follow a treatment policy strategy i.e. participants who discontinue treatment will be treated in the same manner as those that continue the treatment as planned.
- **Summary measure:** The difference in variable means between treatments.

APACHE II scores are on a range between 0 and 71 points, however, in practice it is rare for any patient to accumulate more than 55 points. A decrease in the APACHE II score is considered a favorable outcome.

The APACHE II scores are derived from a number of different clinical endpoints according to the scoring table as outlined in (Knaus et al., 1985) and listed in the Appendix. The handling of missing data is described in Section 6.1.6.

6.1.2 Descriptive analyses

To assess the impact of the replacement with score values at early discharge and the worst case imputation for death on the combined APACHE II score the following summary statistics will be provided:

- only for the participants with an early discharge (i.e. prior to day 15): if APACHE II score values at the early discharge visit and the actual Day 15 visit are available these will be summarized separately by visit ("early discharge", "Day 15").
- In addition the frequency of worst case imputation for deaths per treatment group will be provided.

Panels of individual spaghetti plots over time for APACHE II scores and their change from baseline will be provided by treatment group. The profiles of all participants in the respective treatment group will be included in these graphs as grey lines in the background and the respective individual participants profile will be plotted with darker color in the foreground. It will be indicated by a symbol when a patient was discharged or died (see data handling rules below in Section 6.1.7).

6.1.3 Statistical model, assumptions and hypotheses

The combined APACHE II endpoint as described in the estimand above is assumed to follow a normal distribution.

The primary endpoint will be analyzed by an analysis of covariance model including treatment group and the three stratification factors as factors and baseline APACHE II score as a covariate. The analysis will be performed on the safety analysis set. The mean differences of DFV890 in addition to SoC vs SoC alone will be reported with 90% confidence intervals (CIs). The 1-sided p-value for the overall treatment factor will be reported.

The primary objective will be achieved if the null hypothesis that DFV890 in addition to SoC is not different to SoC alone is rejected using a one side alpha of 10%.

6.1.4 Model checking procedures

The appropriateness of the normality assumption of the combined APACHE II score will be assessed by graphical means e.g. residual plots.

6.1.5 Intercurrent events

As described in the primary estimand discontinuation of study treatment for any reason will be ignored.

6.1.6 Missing data

Missing data for the APACHE II score will be handled as follows:

- Missing values for age at screening will be replaced by using the stratification information assigning 3 points to participants up to 65 years (<=65 years) and 5 points to participants above 65 years.
- Missing information on acute renal failure status: use Serum Creatinine values without renal status information.
- Subscores of the Glasgow Coma Score (i.e. responses to Best Eye Response, Motor Response, Verbal Response) scored as “untestable”, “unknown” or missing will be replaced by the last available actual score. The response “untestable” is selected if the patient is unconcious (e.g. through sedation in case of mechanical ventilation).
- Missing values in any of the other parameters required for the derivation of the APACHE II score will be replaced by the last available assessment, as long as data is not carried forward by more than 4 days.

For a given visit, these missing data rules will only be applied if for at least one of the parameters contributing to the APACHE II score a value was reported for this specific visit.

6.1.7 Handling of discharge and death

For the APACHE II score,

- in case a participant is discharged before Day 29 it will not be derived for any visits after the discharge visit (i.e. the last APACHE II score will be derived on the day of discharge).
- In case a participant dies no APACHE II score will be derived starting from the day of death.

6.1.8 Derivation of the primary estimand

The primary estimand, referred to as the "**combined APACHE II score**", will be derived as follows from the APACHE II scores after application of the missing data as well as discharge and death handling approaches described above:

- For participants hospitalized at Day 15: APACHE II score at Day 15
- For participants discharged prior to Day 15: APACHE II score at the discharge visit is used
- For participants that died on Day 15 or earlier: highest observed APACHE II score of any of the participants at any time during the trial
- Imputation for death takes precedence over the imputation of the APACHE II score on day of early discharge.

6.1.9 Supportive analysis

6.2 Secondary objectives

6.2.1 Variables

The following variables and corresponding objectives are classified as secondary pharmacodynamic endpoints and will be evaluated for their effect of DFV890 in addition to SoC compared with SoC alone:

- On inflammatory status: Serum C-reactive protein (CRP) levels

- On clinical status: Endpoints based on the 9-point ordinal scale:
  - Survival without the need for invasive mechanical ventilation at Days 15 and 29: defined by a 9-point ordinal scale score of < 6 points at all time points
  - At least one level improvement in clinical status at Days 15 and 29: defined as improvement of ≥1 in the 9-point ordinal scale score of the screening value – Day 15 or Day 29 score respectively.
  - Clinical status over time

Missing data

For the clinical status 9-point ordinal scale missing values will be handled as follows:

- For participants who died prior to Day 29: The score for death will be imputed for all visits following the death up to and including Day 29.
- For all other participants: LOCF will be applied up to and including Day 29. Following discharge or early discharge LOCF will be applied to all intermediate visits. In case the value reported for the (early) discharge visit does not reflect that the patient is ambulatory from now on (i.e. score ≥ 3), it will be set to the highest ambulatory score i.e. a value of 2 starting from the next scheduled visit.

6.2.2 Descriptive analyses

CRP

Panels of individual spaghetti plots over time for CRP will be provided using a logscale. The profiles of all participants in the respective treatment group will be included in these graphs as grey lines in the background and the respective individual participants profile will be plotted with darker color in the foreground. The respective applicable normal ranges will be added and it will be indicated by a symbol if a patient died.

Survival without the need for invasive mechanical ventilation

The numbers and percentages of responders will be calculated up to Day 15 and up to Day 29 respectively. It will be presented by treatment group together with the difference in response rates.

Improvement in clinical status

The numbers and percentages of responders will be calculated up to Day 15 and up to Day 29 respectively. It will be presented by treatment group together with the difference in response rates.

Clinical status over time

The 9-point ordinal scale will be summarized (mean, median, standard deviation, minimum, maximum, frequencies and percentages in each category) will be summarized by visit (including a time point for data from early discharge) and treatment group.

A stagged barchart illustrating the percentage of participants in each category of the 9-point ordinal scale will be provided. Treatment groups will be presented next to each other. This will be provided for Day 15 and Day 29.

The 9-point ordinal scale will also be plotted using a heat map with one row representing one patient and the score from baseline up to Day 29 visit will be shown by time using one unique color for each level of scale. The heat map will be plotted for each treatment group, within which patients will be sorted by the 9-point ordinal scale from high to low and by visit. The time when discharged from hospital will also be flagged on the plot. Values imputed by LOCF will be indicated by a different pattern (e.g. stripes) but the same color.

6.2.3 Statistical model, assumptions and hypotheses

CRP

CRP levels are assumed to follow a log-normal distribution. Thus the log-transformed CRP data will be analyzed by fitting an MMRM model. Treatment, visit and their interaction as well as the three stratification factors will be included as fixed factors and log-transformed baseline CRP as a covariate. Interactions between visit and each of the terms in the model will also be included. To model the dependency of observations an unstructured variance-covariance matrix will be fitted.

The analysis will be performed on the PD analysis set. All available values at all scheduled visits (excluding discharge or early discharge visits) up to Day 29 will be included in this analysis. The back-transformed geometric means for both treatment groups as well as the geometric mean ratios (DFV890 in addition to SoC vs SoC alone) will be reported together with 90% confidence intervals (CIs) for each visit. The 1-sided p-value for the overall treatment factor will be reported.

6.2.4 Model checking procedures

CRP

The appropriateness of the log-normality assumption of CRP values will be assessed by graphical mean e.g. residual plots.

6.2.5 Graphical presentation of results

CRP

Estimated geometric mean CRP +/- SE will be plotted over time by treatment group. The estimated geometric mean ratio to baseline in CRP +/- SE will also be presented.

Survival without the need for invasive mechanical ventilation

Kaplan-Meier graphs with separate lines by treatment group will be provided for a graphical presentation. Censoring events will be death and discontinuation from the study.

6.3 Exploratory objectives

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7 Statistical methods for safety and tolerability data

All safety presentations and analyses will be based on the Safety Analysis Set.

7.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, respiratory rate, body temperature, peripheral oxygen saturation, oxygen flow rate and/or FiO2), ECG intervals, safety laboratory measurements, as well as subject demographics, baseline characteristics, and treatment information.

7.2 Descriptive analyses

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data, which will also be summarized where appropriate (e.g. change from baseline summaries).

The on-treatment period lasts from the date of randomization to Day 29.

7.2.1 Subject demographics and other baseline characteristics

Screen failures with SAEs

For screen failed participants in case the participant experienced a serious adverse event during the screening phase the following information is captured and listed: demographic information, informed consent, as well as information on SAEs. Inclusion/Exclusion criteria will be summarized.

Disposition

The following disposition status will be summarized as the number and percentage of participants

- who were screened but not randomized (percentage based on all screened participants)
- who were randomized (percentage based on all screened participants)
- who were discharged prior to day 15 and day 29 respectively
- who completed the study until day 15 and day 29 respectively
- who discontinued from study (overall and by the primary reason for discontinuation).

The number and percentage of participants included in each analysis set will be tabulated by treatment group. Participants excluded from an analysis sets will be listed with reasons for exclusion (i.e. including both protocol and non-protocol deviations).

Unless otherwise stated any percentages are based on the respective number of randomized participants.

Demographic and Baseline characteristics

Demographic characteristics, including gender, race, ethnicity, age, age categories (<65 and ≥ 65 years), height, body weight at screening, body categories (40 to <60 kg, 60 to <80 kg, 80 to <100 kg, 100 to <120 kg, >=120 kg), body mass index (BMI) at screening, BMI categories (≤ 30.0 kg/m^2 and > 30.0 kg/ m^2), country will be summarized with descriptive statistics by treatment and overall.Body mass index (BMI) will be calculated using the following formula:

- BMI = Body weight (kg) / [Height (m)]^2

The Screening visit height measurement will be used for BMI calculations throughout the study.

The number of days between the onset of symptoms to start of treatment will be listed.

The summary of the following baseline disease characteristics will be provided by treatment group:

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- Chest X-ray or CT scan interpretation (Normal/Abnormal/not available)
- Clinical status based on the 9-point ordinal scale (Score=0, 1, ..., 8)
- Use of corticosteroid at the time of randomization (based on prednisone equivalent dose see Section 10.7)
- Use of anti-viral treatment at the time of randomization (Yes, No) and by type of anti-viral treatment (e.g. hydroxychloroquine, chloroquine, remdesivir, faripivavir, ritonavir, lopinavir, convalescent plasma)
- Number and presence of the following comorbidities: diabetes, hypertension, cardiovascular disease (i.e. chronic heart disease), chronic lung disease (e.g. COPD, asthma)
- Baseline Oxygen use based on the type of pulmonary/ventilatory support (defined in Table 6-1)

- Marker for inflammation as continuous variables: CRP,

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- The distribution of the three stratification parameters will be summarized separately by treatment group.

For oxygen requirement at baseline the type of support required prior but closest to the day of randomization will be reported.

Protocol deviations will be listed and summarized by treatment group.

All medical history including the comorbidities will be listed.

7.2.2 Treatment

The duration of exposure to DFV890 in days will be summarized as well as the number and percentage of participants with treatment compliance of <80% and >=80% respectively.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system by treatment group. For corticosteroids ATC-Subclasses will be added. Convalescent plasma treatment will included in the anti-viral treatment presentations.

For any of the below mentioned three treatment categories, if it started prior to randomization and continued during the study, it will be reported under baseline as well as part of SoC during study participation.

Corticosteroids use

The number and percentage of patients will be summarized by treatment group for the following parameters:

- receiving any corticosteroids after randomization
- receiving corticosteroid for treatment of Covid-19 after randomization
- receiving Dexamethasone after randomization reporting the highest total daily dose observed during the study using the following ranges:
  <6 mg, 6-<12 mg, >= 12 mg

The following presentations will be based on the prednisone equivalent dose (see Appendix for details):

- with a change in their corticosteroids dose after randomization (increased/reduced/stable dose)
- receiving corticosteroids after randomization reporting the highest total daily dose observed during the study using the following ranges:
  <7.5 mg, 7.5-<20 mg, >= 20 mg

Anti-viral medication use

The number and percentage of patients will be summarized by treatment group for the following parameters:

- receiving any anti-viral medication after randomization

- receiving anti-viral medication for treatment of Covid-19 after randomization
- receiving hydroxychloroquine/chloroquine/remdesivir/faripivavir/ritonavir/lopinavir/ convalescent plasma after randomization receiving a combination of the above anti-viral medications after randomization tabulated by all combinations actually occurring.

Anti-coagulation therapy

The number and percentage of patients will be summarized by treatment group for the following parameters:

- receiving any anti-coagulation medication after randomization
- receiving anti-coagulation medication for treatment of Covid-19 after randomization

Combination of SoC medications

The number and percentage of patients receiving any combination of steroids, anti-viral and/or anti-coagulants treatments after randomization will be summarized by treatment group.

7.2.3 Vital signs

Vital sign measurements include respiratory rate, pulse rate (PR), systolic and diastolic blood pressure, mean arterial pressure body temperature, weight and BMI. Peripheral oxygen saturation on room air or on supplemental oxygen is also measured at the same time as the vitals. In case oxygen saturation is reported for both room air and under supplemental oxygen, the value for room air is included in summary presentations and analysis. For participants requiring supplemental oxygen, the oxygen flow rate (L/min) and/or FiO2 is also recorded.

Summary statistics will be provided by treatment group and visit/time.

7.2.4 ECG evaluations

Heart rate, PR, QRS, QT, QTcF, and RR intervals will be obtained from ECGs (12-lead or 5-lead) for each participant during the study. ECG data will be read and interpreted locally.

Categorical analysis of QT/QTcF interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTcF intervals or changes from baseline will be presented.

Summary statistics will be provided by treatment group and visit/time.

7.2.5 Clinical laboratory evaluations

Summary statistics will be provided by treatment group and visit/time.

In case for one parameter multiple types of assessments were reported for the same visit/assessment the following rules are applied for any analysis e.g. summarizing the results:

- In case both absolute counts and percentages (e.g. “bands” or ratios) are provided, absolute counts are used.
- In case both Urea and BUN parameters are provided, Urea is used.

7.2.6 Adverse events

All information obtained on adverse events will be listed by treatment and subject.

Summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. Separate summaries will be provided for study medication related adverse events and other significant adverse events leading to discontinuation.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

A subject with multiple adverse events within a body system is only counted once towards the total of this body system and treatment.

For the legal requirements of ClinicalTrials.gov and EudraCT, two tables are required:
on treatment emergent adverse events which are not serious adverse events and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety analysis set.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

7.2.7 Graphical presentation

For all vital signs, ECGs and laboratory parameters the following graphical presentations will be provided:

Panels of individual spaghetti plots over time for each parameter and their change from baseline will be drawn. The profiles of all participants in the respective treatment group will be included in these graphs as grey lines in the background and the respective individual participants profile will be plotted with darker color in the foreground. The respective applicable normal ranges will be added and it will be indicated by a symbol if a patient died.

Means (+/- SE) will be plotted over time by treatment group.

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9 Reference list

Knaus WA, Draper EA, Wagner DP, et al (1985) APACHE II: a severity of disease classification system. Crit Care Med; 13(10):818-29.

10 Appendix

10.1 Units and conversions

Special care must be taken with respect to converting lab parameters prior to applying the scoring described below to avoid propagation of rounding errors. The following principles will be applied:

- If the unit of the original lab assessment from the local lab is equal to the unit used in the scoring table, this original value is used.
- In case the SI unit which is available within the SDTM data sets is equal to the unit used in the scoring table, the value converted to SI units is used.
- If neither the original nor the SI unit are matching the unit used in the scoring table then convert the original value from the local lab to the unit required by the scoring table. Note that for some parameters there are scoring tables available for different units.
- Do convert the value in SI units further.
- Do apply rounding to the precision required in the scoring table only after conversion to the unit used in the scoring table has been done.

10.1.1 Conversion for absolute differential blood counts

If not reported, the absolute differential blood counts can be derived if

- % of blood count (on 0-1 scale) (e.g. for Neutrophils, Eosinophils, Lymphocytes, Monocytes, Basophils)
- Total WBC

is available via the following formula:

absolute differential blood count = total WBC * % of blood count.

10.2 APACHE II

The APACHE II score is derived from a number of different clinical endpoints according to the scoring table as outlined in ([Knaus et al., 1985]):

1. Body temperature (°C)
   Depending on the collection method selected apply the following correction factors before scoring:
   - Core: no correction needed
   - Axillary: + 1.0 °C
   - Oral: + 0.5 °C
   - No method selected: no correction.
2. Mean Arterial Pressure (mmHg)
   In case the "method" is reported as "calculated" confirm the calculation by applying the following formula: MAP = [SBP + (2x DBP)] / 3. If the reported and recalculated numbers differ by more than 10% use the recalculated value (i.e. if reported value < 0.9* recalculated value or reported value >1.1* recalculated value)
3. Heart Rate (beats per minute)
   If the participant has a pacemaker any HR <= 109 bpm will be scored to 0.
4. Respiratory Rate (breaths per minute)
5. Oxygenation: depending on the Fraction of inspired Oxygen (FiO2, where FiO2 is a value between 0 and 1 (i.e. not on % scale)):
   - If FiO2 < 0.5: use PaO2 (mmHg)
   - If FiO2 >= 0.5: use A-aDO2 (mmHg): where A-aDO2 is calculated as A-aDO2 = (FiO2 × 713 - PaCO2/0.8) – PaO2)

   In case PaO2 is not available for a certain visit it can be derived from SPO2 if available instead using the following conversion table:

Table 10-1 Conversion of SpO2 to PaO2

SpO2 (%)	PaO2 (mmHg)
80	44
81	45
82	46
83	47
84	49
85	50
86	52
87	53
88	55
89	57
90	60
91	62
92	65
93	69
94	73
95	79
96	86
97	96
98	112
99	145

6. Arterial pH: if Arterial pH is not available use Serum HCO3 (venous mMol/L) instead
7. Serum Sodium (mmol/L)
8. Serum Potassium (mmol/L)
9. Serum Creatinine (mg/dL=mg/100mL)
10. Hematocrit (%)
11. White Blood Count (10^9/L = 1000/mm^3 = 10^3/mm^3)
12. Age at Screening (years)
13. Chronic Health Points at Screening:
    Points are assigned only if for this patient “Did the subject experience Severe organ system insufficiency or is immunocompromised ?” is selected as “yes”.
    - If “Did the subject experience Severe organ system insufficiency or is immunocompromised ?” = “no”, no points are assigned and a record should not be created for this question in the SDTM data set.
    - If “Did the subject experience Severe organ system insufficiency or is immunocompromised ?” is selected as “yes” Chronic Health points will be derived from “Admission Classification”:
        - Medical(non-operative)
        - Emergency post-operative
        - Elective post-operative

If in this scenario none of these conditions is selected the Chronic Health points will be set to 0.

14. Glasgow Coma Score: First each sub-score is scored according to the scoring table below
    - Best Eye Response
    - Motor Response
    - Verbal Response

    Then these three subscores are added up to obtain the scoring of the "Total Glasgow Coma Score". The value included in the APACHE II for Glasgow-Coma-Score is then = 15 – "Total Glasgow Coma Score".

SDTM Mapping strategy

APACHE II specific mapping strategy: It provides guidance on how the result variables (RSORRES, RSSTRESC, and RSSTRESN) should be populated for the measure. All original results are represented with preferred terminology in RSORRES. This result is then transformed into a standard numeric score in RSSTRESN and a character representation of the standard numeric score in RSSTRESC.

To obtain the total APACHE II score all 14 derived values of RSSTRESN are then added up. If one item is missing the APACHE II score at STDM level for this visit is missing. Missing data imputation will be implemented at ADAM level.

10.2.1 APACHE II Scoring

Temperature (°C)

RSORRES	RSSTRESC	RSSTRESN
>=41	4	4
39-40.9	3	3
38.5-38.9	1	1
36-38.4	0	0
34-35.9	1	1
32-33.9	2	2
30-31.9	3	3
≤29.9	4	4

Mean Arterial Pressure (mmHg)

RSORRES	RSSTRESC	RSSTRESN
>=160	4	4
130-159	3	3
110-129	2	2
70-109	0	0
50-69	2	2
<=49	4	4

Heart rate (beats/min)

Does the participant have a pacemaker?	RSORRES	RSSTRESC	RSSTRESN
Irrespective	>=180	4	4
Irrespective	140-179	3	3
Irrespective	110-139	2	2
No/unknown	70-109	0	0
No/unknown	55-69	2	2
No/unknown	40-54	3	3
No/unknown	<=39	4	4
Yes	<=109	0	0

Respiratory rate (BREATHS/MIN)
Note: Ventilated or non-ventilated patient scores will be the same as per table below

RSORRES	RSSTRESC	RSSTRESN
>=50	4	4
35-49	3	3
25-34	1	1
12-24	0	0
10-11	1	1
6-9	2	2
<=5	4	4

Oxygenation:

- If FiO2 >= 0.5 the use A-aDO2 (mmHg)

RSORRES	RSSTRESC	RSSTRESN
>=500	4	4
350-499	3	3
200-349	2	2
<200	0	0

- If FiO2 < 0.5 then use PaO2 (mmHg)

RSORRES	RSSTRESC	RSSTRESN
>70	0	0
61-70	1	1
55-60	3	3
<55	4	4

Arterial pH

- Use arterial pH if reported

RSORRES	RSSTRESC	RSSTRESN
>=7.7	4	4
7.6-7.69	3	3
7.5-7.59	1	1
7.33-7.49	0	0

7.25-7.32	2	2
7.15-7.24	3	3
<7.15	4	4

- Alternatively use Serum HCO3 (mmol/L)

RSORRES	RSSTRESC	RSSTRESN
>=52	4	4
41-51.9	3	3
32-40.9	1	1
22-31.9	0	0
18-21.9	2	2
15-17.9	3	3
<15	4	4

Serum sodium (mmol/L)

RSORRES	RSSTRESC	RSSTRESN
>=180	4	4
160-179	3	3
155-159	2	2
150-154	1	1
130-149	0	0
120-129	2	2
111-119	3	3
<=110	4	4

Serum potassium (mmol/L)

RSORRES	RSSTRESC	RSSTRESN
>=7	4	4
6-6.9	3	3
5.5-5.9	1	1
3.5-5.4	0	0
3-3.4	1	1
2.5-2.9	2	2
<2.5	4	4

Serum creatinine (mg/dL)

RSORRES	RSSTRESC	RSSTRESN
>=3.5 and acute renal failure =”yes”	8	8
2-3.4 and acute renal failure =”yes”	6	6
1.5-1.9 and acute renal failure=”yes”	4	4
>=3.5	4	4

2-3.4	3	3
1.5-1.9	2	2
0.6-1.4	0	0
<0.6	2	2

Hematocrit (%)

RSORRES	RSSTRESC	RSSTRESN
>=60	4	4
50-59.9	2	2
46-49.9	1	1
30-45.9	0	0
20-29.9	2	2
<20	4	4

White Blood Count (10^9/L)

RSORRES	RSSTRESC	RSSTRESN
>=40	4	4
20-39.9	2	2
15-19.9	1	1
3-14.9	0	0
1-2.9	2	2
<1	4	4

Age points (years)

RSORRES	RSSTRESC	RSSTRESN
<=44	0	0
45-54	2	2
55-64	3	3
65-74	5	5
>=75	6	6

Chronic health points

RSORRES	RSSTRESC	RSSTRESN
For non-operative or emergency post-operative patients	5	5
For elective post-operative patients	2	2
None selected	0	0

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10.5 Glasgow Coma Score

10.5.1 Glasgow Coma Scoring

- Best eye response

Result	Score (Char)	Score (Num)
No eye opening	1	1
Eye opening to pain	2	2
Eye opening to verbal command	3	3
Eyes open spontaneously	4	4
Untestable	Untestable	
Unknown	Unknown	

- Motor response

Result	Score (Char)	Score (Num)
No motor response	1	1
Abnormal extension	2	2
Abnormal flexion	3	3
Flexion withdrawal	4	4
Localizes pain	5	5
Obeys command	6	6
Untestable	Untestable	
Unknown	Unknown	

- Verbal response

Result	Score (Char)	Score (Num)
No verbal response	1	1
Incomprehensible sound	2	2
Inappropriate words	3	3

Confused	4	4
Oriented	5	5
Untestable	Untestable	
Unknown	Unknown	

10.6 9-point ordinal scale

Patient State	Descriptor	Score	Abbreviated description
Uninfected	No Clinical or virological evidence of infection	0	Uninfected
Ambulatory	No limitation of activities	1	Amb: No limitations
	Limitation of activities	2	Amb: Limitations
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3	Hosp: No Oxygen
	Oxygen by mask or nasal prongs	4	Hosp: Oxy Mask
Hospitalized Severe disease	Non-invasive ventilation or high-flow oxygen	5	Hosp: Non-Inv Vent
	Intubation and mechanical ventilation	6	Hosp: Intub + Mech Vent
	Ventilation + additional organ support - pressors, RRT, ECMO	7	Hosp: Vent + pressors
Dead	Death	8	Dead

10.7 Steroid conversion factors

Steroids will be displayed using prednisone equivalent doses. The doses displayed in the following table are considered equivalent. To determine prednisone equivalent doses, doses (in unit mg) will be multiplied by the conversion factor shown in Table 10-2. In case multiple corticosteriods are used at a certain visit the prednisone equivalent doses will be added up to obtain the total prednisone equivalent dose.

Table 10-2 Steroids conversion factors

WHO drug code	Preferred Term Corticosteroid	Equivalent Dose [mg]	Conversion Factor
000447xx	Prednisone	5	1
000162xx	Prednisolone	5	1
000496xx	Methylprednisolone	4	1.25
012428xx	Meprednisone	4	1.25
001867xx	Prednylidene	5 5/7	0.875
000319xx	Triamcinolone	4	1.25
000146xx	Cortisone	25	0.2
000286xx	Hydrocortisone	20	0.25
002131xx	Fludrocortisone	2	2.5
000085xx	Betamethasone	0.75	20/3
000664xx	Paramethasone	2	2.5
000160xx	Dexamethasone	0.75	20/3
008827xx	Deflazacort	6	5/6