Study Title: A Phase 2/3 Study to Evaluate the Safety and Efficacy of Dociparstat Sodium for the Treatment of Severe COVID-19 in Adults at High Risk of Respiratory Failure

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Post-Cohort 1 or 2 Lock Analyses - Shells

Sponsor Name:	Chimerix, Inc
Protocol Number and Title:	CMX-DS-004 A Phase 2/3 Study to Evaluate the Safety and Efficacy of Dociparstat Sodium for Treatment of Severe COVID-19 in Adults at High Risk of Respiratory Failure
Final Protocol Date:	Protocol Amendment 3, dated 06 Nov 2020
Syneos Health Project Code:	7015085
Author(s):	Roland Wolf, PhD, Lead Biostatistician
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APPROVALS and ACKNOWLEDGEMENT OF REVIEW		
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Revision History

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
1.0	17 Sep 2020	Roland Wolf	Initial Release Version
2.0	12 Mar 2021	Roland Wolf	Updated for Protocol Amendment 3. Clarify analysis of subjects randomized but not treated.

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1. PURPOSE

This is a randomized, double-blind, placebo-controlled, Phase 2/3 study to determine the safety and efficacy of dociparstat in adults with acute lung injury associated with severe COVID-19 who are at high risk of respiratory failure.

An independent unblinded data monitoring committee (DMC) will review safety data from Cohort 1 to make a recommendation on dose escalation in Cohort 2 and review safety data from both Cohorts 1 and 2 to make a recommendation on dosing in Cohort 3. The sponsor will consider the DMC recommendation when determining the actual doses for Cohorts 2 and 3.

Due to the evolving standard of care for COVID-19, the sponsor may decide to unblind and review study data following Cohorts 1 and/or 2.

The purpose of this document is to describe the pre-defined post-Cohort 1 or 2 lock analysis. This document specifies the derivations and TFL package and is based on the study protocol amendment 3, dated 06 November 2020.

2. INTRODUCTION

Cohort 1 contains 6 participants randomized to dociparstat, 6 randomized to placebo. Dociparstat will be dosed as 4 mg/kg IV bolus followed by continuous infusion of 0.25 mg/kg/hr.

Cohort 2 includes 6 participants randomized to dociparstat, 6 randomized to placebo. Dociparstat will be dosed as 4 mg/kg IV bolus followed by continuous infusion of 0.325 mg/kg/hr (dose to be confirmed after review of data from Cohort 1).

Based on Protocol Amendment 3, dated 06 November 2020, the randomization ratio (dociparstat: placebo) changed from 1:1 in Cohort 1 to 2:1 in the following cohorts.

Both Cohorts 1 and 2 may be unblinded to the entire team following cleaning and database lock of Cohort 1/2 data. The full randomization code will remain blinded as is; in this event, only the Cohort 1/2 assignments will be unblinded.

The first part of the analysis defined in this document will be eqivalent to the statistical output delivered to the DMC-members for the 2nd Cohort (see Section 5.1), however with all data collected until End of Study (EOS).

3. DERIVATIONS AND DEFINITIONS

Kaplan-Meier estimates

Time to xxx (days): Days are calculated as (start date/time – first study drug date/time)/24h). Time will be censored at last individual date/time reported.

Worst-case results in 2 scenarios for missing time-values:

1. Missing time for negative events will be imputed with “00:01”, missing time for censored observations will be imputed with “23:59”.

   Negative events are:
   - Time to first invasive mechanical ventilation or ECMO
   - Time to first invasive mechanical ventilation, ECMO or all-cause mortality
   - Time to all-cause mortality

2. Missing time for positive events will be imputed with “23:59”, missing time for censored observations will be imputed with “00:01”.

   Positive events are:
   - Time to clinical improvement
   - Time to hospital discharge

   In addition, to avoid bias in the positive events, deaths occurring prior to the positive event being observed will censored at Day 28.

Ventilator-free days

Ventilator-free days are only counted from baseline through Day 28 or end of study, whichever comes first. They are derived based on the eCRF data collected on the Ventilator/Oxygen/Medical Care Status CRF page, Ventilator-free days are all days where Ventilator/Oxygen/Medical Care Status is not equal “Invasive Mechanical Ventilation or extracorporeal membrane oxygenation (ECMO)”.

Ventilator days are defined as cumulative rounded number of days with Ventilator/Oxygen/Medical Care Status = “Invasive Mechanical Ventilation or extracorporeal membrane oxygenation (ECMO)” devided by 24 h. Missing time for start will be imputed with “00:01”, missing time for stop will be imputed with “23:59”.

Study duration in days is defined as: Date of study completion (or date of early study discontinuation) – date of first study treatment + 1. For subjects randomized but not treated the date of randomization will be used instead of first study treatment date. The maximum study duration is set to 28 days, even if study completion or study discontinuation is after 28 days.

Ventilator-free days are defined as: study duration - number of ventilator days. For subjects who died during the course of the study, the number of ventilator-free days will be defined as 0.

Randomized, but not treated subjects:

The following rules will apply for randomized subjects without receiving study treatment, if not stated otherwise:

- Calculations referring to start of treatment or baseline will be performed with respect to randomization date/time.
- Study duration in days is calculated as study discontinuation date - randomization date +1.
- In Kaplan-Meier analysis the “time-to” will be censored at 0.

4. CONVENTIONS FOR SUMMARY TABLES AND LISTINGS

At the top of each table/listing/figure, the first three title lines should read:

```
Chimerix
CMX-DS-004
Post-Cohort 1/2 Lock Analysis - FINAL (Unblinded)
```

Following those titles, the next title should include the output number and a description of the table/listing content, including the Analysis Set used.

The next line is an optional sub-title with description of a subgroup, if applicable.

Horizontal lines will appear before and after the column heading of the table/listing. Footnotes will be put under the main body of text and each new footnote should start with a new line. Very long footnotes will be presented only on the very first page of the output.

At the bottom of each TFL, the following information should be printed: date of the data base cut off, date and time of the run of the TFL and name of the program.

```
Data Cut-off date: DDMMMYYYY;
Program name: M:\project-sas\chimerix\7015085\biostat\3-cohort\tables\production\xxxxx.sas
Run date: DDMMMYYYY HH:MM
                                                                    Page X of Y
```

Outputs will be prepared in landscape layout unless otherwise specified. Blank margins of all tables and listings will be a minimum of 1 inch. In general, Courier New 8 point font will be used.

Listings Layout

Listings will contain the data of all subjects except when otherwise specified. The following visit labels will be used (shorthand in parentheses), but data will be sorted by assessment date (including the Unscheduled Visits):

- Screening (SCRN)
- Baseline (D1)
- Day 2 (D2)
- Day 3 (D3)
- Day 4 (D4)
- Day 5 (D5)
- Day 6 (D6)
- Day 7 (D7)
- Day 8 (D8)
- Day 14 (D14)
- Day 28 (D28)
- Early Tx DC (TXDC)
- Unscheduled (UNSCH)

5. TABLE SHELLS

5.1. DMC – TABLE SHELLS

Table 1: Demographics and Baseline Characteristics – Safety Set

	DSTAT 0.25 N=xxx	Cohort 1 PBO N=xxx	DSTAT 0.325 N=xxx	Cohort 2 PBO N=xxx	Total N=xxx
Gender, n(%)					
Male	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Female	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown/Not Answered	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Race, n(%)					
White	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown/Not Answered	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity, n(%)					
Hispanic or Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic or Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown/Not Answered	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Age (years)					
n	Xxx	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	Xx	xx	xx	xx	xx
Q1, Q3	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Age (years), n(%)					
< 60	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>=60	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Weight (kg)					
N	xxx	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx	xx	xx	xx	xx
Q1, Q3	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

	DSTAT 0.25 N=xxx	Cohort 1 PBO N=xxx	DSTAT 0.325 N=xxx	Cohort 2 PBO N=xxx	Total N=xxx
Height (cm)					
n	xxx	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx	xx	xx	xx	xx
Q1, Q3	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Body mass index (kg/m2)					
n	xxx	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx	xx	xx	xx	xx
Q1, Q3	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Temperature (°C)					
n	xxx	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx	xx	xx	xx	xx
Q1, Q3	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Fever, n(%)					
<= 37.2°C	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
> 37.2°C to 38.2°C	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
> 38.2°C	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
NIAID-Score (IRT), n(%)					
3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
NIAID-Score (actual), n(%)					
3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

N = Number of subjects in a specific group; n = Number of subjects with data available; Percentages are based on N;
SD: Standard deviation; Q1, Q3: First, third quartile; Min: minimum; Max: maximum.
Baseline is defined as last measurement prior to or on the date of first study treatment.
NIAID-Score (IRT): directly entered in RAVE by the investigator.
NIAID-Score (actual): calculated using hospitalization and ventilation status at time of randomization.

Table 2: Listing of demographics, baseline characteristics, study drug usage and disposition – Safety Set

Subject Age/Sex	Treatment Group	Race	Ethni-city	Weight (kg)	BMI (kg/m2)	Temp (°C)	NIAID (IRT / actual)	Bolus received / # infusion days	Treatment disposition	Study disposition	Death / Date
999-999 /70/F	DSTAT 0.25	Asian	HL	xx.x		xx.x	4 / 4	Yes / 3	Discontinued: AE	Discontinued: Progression	
999-999 xx/xx	Cohort 1 PBO	Other: xxxxxx	NHL	xx.x	xx.x		3 / 3	Yes / 7	Discontinued: Other: xxx	Discontinued: FUP	
999-999 xx/xx	Cohort 1 PBO	Other: xxxxxx	NHL	xx.x	xx.x		3 / 3	Yes / 7	Completed	Completed	Yes / ddMMMYYY
999-999 xx/xx	Cohort 1 PBO	Other: xxxxxx	NHL	xx.x	xx.x		3 / 4	Yes / 7	Unknown	Ongoing	

Ethnicity: HL=Hispanic or Latino, NHL=Not Hispanic or Latino
NIAID-Score (IRT): directly entered in RAVE by the investigator.
NIAID-Score (actual): calculated using hospitalization and ventilation status at time of randomization.

(Notes for programmer:
- Sorted by subject number
- Disposition: Progression=Progression of disease, AE=Adverse Event, Prohibited=Patient requires use of a prohibited therapy, Compliance=Non-compliance, FUP=Lost to follow-up, Consent=Patient withdrawal of consent, Physician=Physician decision, Sponsor=Sponsor decision, Improvement=Improvement of condition under study, UNK=Unknown/Not answered*)*

Table 3: Study drug usage – Safety Set

	DSTAT 0.25 N=xxx	Cohort 1 PBO N=xxx	DSTAT 0.325 N=xxx	Cohort 2 PBO N=xxx
Bolus received, n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Infusion (days received), n(%)				
1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
5	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
6	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
7	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

N = Number of subjects in a specific group; n = Number of subjects with data available; Percentages are based on N;
Infusion (days received): Study drug administered at any time during the corresponding study-day (cumulated).

Table 4: Listing of study drug interruptions / discontinuations – Safety Set

Subject Age/Sex/Race	Treatment Group	Visit	Start Date / Time	Stop Date / Time	Bolus / Infusion no	Total Voulume Given (mL)	Interrupted due to	Permanently discontinued due to
999-999 / 69/F/W	DSTAT 0.25	Baseline (D1)	ddMMMyy hh:mm	ddMMMyy hh:mm	Bolus	999.99	Adverse Event	
			ddMMMyy hh:mm	ddMMMyy hh:mm	1	999.99		
		Day 2 (D2)	ddMMMyy hh:mm	ddMMMyy hh:mm	2	999.99	Other:xxxxxx	
		Day 3 (D3)	ddMMMyy hh:mm	ddMMMyy hh:mm	3	999.99		Adverse Event
		Day 4 (D4)	ddMMMyy hh:mm	ddMMMyy hh:mm	4	999.99		Other: xxxxxx
999-999 / 35/M/B	Cohort 1 PBO	Baseline (D1)	ddMMMyy hh:mm	ddMMMyy hh:mm	Bolus	999.99	Adverse Event	
			ddMMMyy hh:mm	ddMMMyy hh:mm	1	999.99		
		Day 2 (D2)	ddMMMyy hh:mm	ddMMMyy hh:mm	2	999.99		

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(Note for programmer: Sorted by subject number, start date, start time)

Table 5: Treatment disposition – Safety Set

Treatment disposition Primary reason for treatment discontinuation	DSTAT 0.25 N=xxx	Cohort 1 PBO N=xxx	DSTAT 0.325 N=xxx	Cohort 2 PBO N=xxx
Completed treatment, n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treatment disposition unknown, n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued treatment, n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Primary reason for treatment discontinuation, n(%)				
Progression of disease	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adverse Event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Patient requires use of a prohibited therapy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Non-compliance	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Patient withdrawal of consent	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Physician decision	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sponsor decision	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Improvement of condition under study	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown/Not Answered	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death (during treatment period)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

N = Number of subjects in a specific group; n = Number of subjects with data available; Percentages are based on N;

(Note for programmer: Death (during treatment period) to be derived in case death date = date of last treatment start date or stop date)

Table 6: Study disposition – Randomized Subjects

Study Disposition Primary reason for early termination	DSTAT 0.25 N=xxx	Cohort 1 PBO N=xxx	DSTAT 0.325 N=xxx	Cohort 2 PBO N=xxx
Randomized subjects, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Randomized not treated subjects, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x
Treated subjects, n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed study, n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ongoing, n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued study	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Primary reason for study discontinuation, n(%)				
Patient withdrawal of consent	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adverse Event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Use of a prohibited therapy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Non-compliance	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Investigator decision	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sponsor decision	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown/Not Answered	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death, n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

N = Number of randomized subjects in a specific group; n = Number of subjects with data available; Percentages are based on N;

Table 7: Proportion of subjects who go on invasive mechanical ventilation or ECMO - Safety Set

	DSTAT 0.25 N=xxx	Cohort 1 PBO N=xxx	DSTAT 0.325 N=xxx	Cohort 2 PBO N=xxx
Number of subjects with any invasive mechanical ventilation, ECMO or early study discontinuation, n (%) (a)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any invasive mechanical ventilation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Early study discontinuation < Day 25	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Kaplan-Meier estimates (b)				
Number of censored subjects, n (%) (b)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Time to first invasive mechanical ventilation or ECMO (days) (b)				
25% Quartile (95% CI)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)
Median (95% CI)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)
75% Quartile (95% CI)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)
Number of subjects who stopped invasive mechanical ventilation or ECMO, n(%) (c)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Kaplan-Meier estimates (c)				
Number of censored subjects, n (%) (c)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Duration of first invasive mechanical ventilation or ECMO (days) (c)				
25% Quartile (95% CI)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)
Median (95% CI)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)
75% Quartile (95% CI)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)

N = Number of subjects in a specific group; n = Number of subjects with data available; Percentages are based on N;
ECMO: Extracorporeal membrane oxygenation.
(a) Subjects with any invasive mechanical ventilation, ECMO or early study discontinuation before Day 25 will be counted as event.
(b) Kaplan-Meier estimates: Subjects with any invasive mechanical ventilation or ECMO will be counted as event. All other subjects will be censored. Time to first invasive mechanical ventilation or ECMO (days): Days are calculated as (start date/time - first study drug date/time)/24h). Time will be censored at last individual date/time reported. If time is not available for events "00:01" will be imputed, for censored observations "23:59" will be imputed.
(c) Kaplan Meier estimates: Duration of first invasive mechanical ventilation or ECMO (days): Only calculated for subjects with an invasive mechanical ventilation or ECMO reported. Duration is calculated as (stop date/time - start date/time)/24h). If start time is not available "00:01" will be imputed, if end time is missing "23:59" will be imputed. Duration will be censored for subjects with ongoing ventilation at last individual date/time reported. Page X of Y

Figure 1: Time to first invasive mechanical ventilation or ECMO (KM-Plot) - Safety Set

Kaplan-Meier Plot:

y-axis:
range: 0% to 100% by 20%
label: Event-free Probability
reference-line: 50%

x-axis:
range: 0 to xxx (depending on data), by 7 days
label: Time to Event (Days)

Lines:
solid
different colors/line styles for the treatment-groups
starting at (100%/Baseline)
Censored values marked

Please use the following footnote for Figure 1 :

N = Number of subjects in a specific group; (+) = censored values;
Kaplan-Meier estimates: Subjects with any invasive mechanical ventilation or ECMO will be counted as event. All other subjects will be censored.
Time to first invasive mechanical ventilation or ECMO (days): Days are calculated as (start date/time – first study drug date/time)/24h). Time will be censored at last individual date/time reported. If time is not available for events “00:01” will be imputed, for censored observations “23:59” will be imputed.

Figure 2: Duration of first invasive mechanical ventilation or ECMO (KM-Plot) - Safety Set

Kaplan-Meier Plot:

y-axis:
- range: 0% to 100% by 20%
- label: Event Probability
- reference-line: 50%

x-axis:
- range: 0 to xxx (depending on data), by 7 days
- label: Duration (Days)

Lines:
- solid
- different colors/line styles for the treatment-groups
- starting at (0%/Baseline)
- Censored values marked

Please use the following footnote for Figure 2 :

N = Number of subjects in a specific group; (+) = censored values;
Kaplan Meier estimates: Duration of first invasive mechanical ventilation or ECMO (days): Only calculated for subjets with an invasive mechanical ventilation of ECMO reported. Duration is calculated as (stop date/time – start date/time)/24h. If start time is not available “00:01” will be imputed, if end time is missing, “23:59” will be imputed. Duration will be censored for subjects with ongoing ventilation at last individual date/time reported.

Table 8: Treatment-emergent Adverse Events (TEAEs) – Safety Set

Primary system organ class Preferred term	DSTAT 0.25 N=xxx n (%)	Cohort 1 PBO N=xxx n (%)	DSTAT 0.325 N=xxx n (%)	Cohort 2 PBO N=xxx n (%)
Number (%) of subjects with at least one such AE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
:	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
:	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

N = Number of subjects in a specific group; n = Number of subjects with at least one event in the category;
Percentages are based on N; Adverse events are coded using MedDRA version 23.0.
If a subject has multiple occurrences of an AE, the subject is presented only once in the respective subject count (n).

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(Note for programmer: AEs are sorted by decending patients' frequency of SOC and by decending frequency of PT within the SOC in the DSTAT 0.25*)*

Table 9: Severe, life-threatening or fatal treatment emergent Adverse Events – Safety Set

For the layout refer to Table 8

(Notes for programmer:
- Change first line in the table to "Number (%) of subjects with at least one such AE".
- TEAEs with the following AE severity grades are reported: Grade 3 (Severe), Grade 4 (Life-threatening), Grade 5 (Fatal).)

Table 10: Treatment emergent Adverse Events leading to study drug discontinuation – Safety Set

For the layout refer to Table 8
(Note for programmer: Change first line in the table to "Number (%) of subjects with at least one such AE".

Table 11: Serious treatment emergent Adverse Events – Safety Set

For the layout refer to Table 8
(Note for programmer: Change first line in the table to "Number (%) of subjects with at least one such TEAE".

Table 12: Listing of Serious Adverse Events and Adverse Events of Special Interest – Safety Set

Subject Age/Sex/Race	Treatment Group	Preferred term Verbatim	Start Date (Study Day)	Stop Date (Study Day)	Severity	Relation-ship	Outcome	Serious AE	AE of Special Interest	Action taken with study drug
999-999 / 70/F/W	DSTAT 0.25	PT1 xxxxxxxxx	DdMMMyy (xx)	DdMMMyy (xx)	Mild	Related	Fatal	Yes	Yes	Discontinued
999-999 / xx/xx/xx	Cohort 1 PBO	PT1 xxxxxxxxx	DdMMMyy (xx)	DdMMMyy (xx)	Mild	Related	Recovered	No	Yes	No Change

Note: Adverse events are coded using MedDRA version 23.0.
Study Days prior to first treatment date are calculated as (actual date – first treatment date), after first treatment date as (actual date – first treatment date) + 1.

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(Notes for programmer:
- *Sorted by subject number, start date, stop date, Preferred term and Verbatim*
- Outcome: Ongoing=Not recovered (Ongoing), Sequelae=Recovered with Sequelae, Unknown=Unknown/Lost to Follow-up
- Action taken with study drug: Interrupted=Study drug temporarily interrupted, Discontinued=Study drug permanently discontinued
)

Table 13: Overview CTCAE v5.0 Grades

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	<LLN - 10.0 g/dL <LLN - 6.2 mmol/L <LLN - 100 g/L	<10.0 - 8.0 g/dL <6.2 - 4.9 mmol/L <100 - 80g/L	<8.0 g/dL <4.9 mmol/L <80 g/L	NA
Platelets	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9/L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9/L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9/L	<25,000/mm3; <25.0 x 10e9/L
Activated Partial Thromboplasting Time (aPTT)	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	NA
Prothrombin Intl. Normalized Ratio (INR)	>1.2 - 1.5	>1.5 - 2.5	>2.5	NA
Aspartate Aminotransferase (AST)	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Alanine Aminotransferase (ALT)	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Total Bilirubin	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Creatinine	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN
Creatinine Clearance, Estimated	<LLN - 60 ml/min	<60 - 30 ml/min	<30 - 15 ml/min	<15 ml/min

NA = Not applicable, ULN = Uppler limit of normal, LLN = Lower limit of normal.
Grade 0 : Any result not graded 1, 2, 3, 4 or Unknown.
Grade Unkown : Missing result or missing upper limit of normal for parameters requiring ULN for grading.

(Notes for programmer:
- LLN for creatinine clearance is fixed 90 mL/min
- Calculation of creatinine clearance (CC) (Cockcroft-Gault):

$$CC\ (ml/min) = \frac{(140 - age\ (years))}{0.8143 * serum\ creatinine\ (\mu mol/L)} * baseline\ weight\ (kg) * (0.85\ if\ female)$$

)

Table 14: Distribution of laboratory grade by parameter and visit – Safety Set

Parameter: <Hemoglobin> <Platelets> <Activated partial thromboplastin time (aPTT)> <Prothrombin International Normalized Ratio (INR)> <Aspartate aminotransferase (AST)> <Alanine aminotransferase (ALT)> <Total bilirubin> <Creatinine> <Creatinine Clearance, Estimated >

Scheduled Visit Grades (a)	DSTAT 0.25 N=xxx	Cohort 1 PBO N=xxx	DSTAT 0.325 N=xxx	Cohort 2 PBO N=xxx
Baseline				
Grade 0	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Maximum Post-baseline Grade				
Grade 0	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

N = Number of subjects in a specific group; n = Number of subjects with data available; Percentages are based on N;
(a) CTCAE v5.0 grades using absolute thresholds without accounting for baseline.
Baseline value is defined as the last non-missing measurement prior to, or on the date/time of the first administration of study treatment.
NA = not applicable

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(Notes for programmer:
- CTCAE Grades: Unknown: missing result (or missing upper limit of normal for parameters requiring ULN for grading). Grade 0: any result not graded 1, 2, 3, 4 or Unknown.
- display only for visit Baseline and Maxiumum Grade per subject and all 6 categories (Grade 0 – Grade 4 and Unknown), if applicable.
- generate a post-baseline Maximum Grade per subject (incl. unscheduled measurements)
- for the generation of Maxiumum Grade use the following order: Unknown – Grade 0 – Grade 1,…. Grade 4)
- Calculation of creatinine clearance (CC) (Cockcroft-Gault):

$$CC\ (ml/min) = \frac{(140 - age\ (years))}{0.8143 * serum\ creatinine\ (\mu mol/L)} * baseline\ weight\ (kg) * (0.85\ if\ female)$$

)

Table 15: Listing of laboratory results – Safety Set

Subject Age/Sex/Race	Treatment Group	Parameter	Date/Time	Visit	Value	$		Unit	Lower Limit	Upper Limit	Grade (a)
999-999 70/F/W	DSTAT 0.25	Hemoglobin	Ddmmmyy/mm:hh	Screening	99999	H	NCS	Unit	LLL	UUU	1
			Ddmmmyy/mm:hh	Baseline	99999	L	CS	Unit	LLL	UUU	4

(a) CTCAE v5.0 grades using absolute thresholds without accounting for baseline. Grade=0 and Grade=Unknown are not displayed.
$: H = Above upper limit of normal; L = Below lower limit of normal, NCS = Not clinically significant, CS= Clinically significant.
Visit "Early Tx DC (TXDC)" denotes Early Treatment Discontinuation Visit.

(Notes for programmer:
- Sorted by subject number, Parameter, date and time
- The following parameter will be displayed: Hemoglobin, platelets, activated partial thromboplastin time (aPTT), prothrombin time (PT), prothrombin international normal ratio (INR), d-dimer, Anti-Xa, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, creatinine, Creatinine Clearance, Estimated.
- LLN for creatinine clearance is fixed 90 mL/min
- CTCAE Grades: reference Table 13.)

Table 16: Shift-table of laboratory results – Safety Set

Parameter: <Hemoglobin> <Platelets> <Activated partial thromboplastin time (aPTT)> <*prothrombin time (PT)*> <Prothrombin International Normalized Ratio (INR)> <d-dimer> <Anti-Xa> <Aspartate aminotransferase (AST)> <Alanine aminotransferase (ALT)> <Total bilirubin> <Creatinine> <Creatinine Clearance, Estimated>

	Baseline (D1)											
	DSTAT 0.25 N=xxx			Cohort 1 PBO N=xxx			DSTAT 0.325 N=xxx			Cohort 2 PBO N=xxx		
	<LLN	Normal	>ULN	<LLN	Normal	>ULN	<LLN	Normal	>ULN	<LLN	Normal	>ULN
Post-Baseline Minimum, n(%)												
<LLN	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Post-Baseline Maximum, n(%)												
<LLN	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

N = Number of subjects in a specific group; n = Number of subjects with data available; Percentages are based on N;
Normal: Within normal range, LLN: Lower limit of normal, ULN: Upper limit of normal.
Only subjects with baseline and at least one post-baseline value are considered.
Baseline value is defined as the last non-missing measurement prior to, or on the date/time of the first administration of study treatment. NA = not applicable.

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(Notes for programmer:
- generate a post-baseline Maximum Value and post-baseline Minimum Value per subject (incl. unscheduled measurements
- LLN for creatinine clearance is fixed 90 mL/min
- if ULN (eg CC) available, please display n/a
)

Figure 3: Selected laboratory parameters over time (Box-Whisker-Plot) - Safety Set

Box-Whisker-Plots: by <Parameter> (<*unit*>), Cohort X, Reference Ranges xxx – yyyy <unit>

y-axis:
range: depending on data
label: Value

x-axis:
range: Visits : Screening, D1 to D28 (depending on data) visit. Incl Early Tx DC at the end of the x-axis.
label: Visit
Box-Whisker Plots:
different styles/colors for the treatment-groups

Plots shifted to not overlap
Default SAS Box-Whisker-Plots – Min, 25%, Median, 75%, Max. Whiskers as 1.5 IQR. Mean included.

Footnotes to be used for the Box-Whisker-Plots :
Visit "Early Tx DC (TXDC)" denotes Early Treatment Discontinuation Visit. Reference Ranges do not necessarily present "values of concern" in this population but will give some context to the results relative to a normal population.

(Notes for programmer:
- replace <Parameter> <unit>, in label by actual parameter and unit used
- Adapt Visits as relevant for the different parameters. Not all parameters are reported for all visits, only scheduled visits to be included in the Figure
- display for: Hemoglobin, Platelets, Activated partial thromboplastin time (aPTT), prothrombin time (PT), Prothrombin International Normalized Ratio (INR), d-dimer, Anti-Xa, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Total bilirubin, Creatinine, Creatinine Clearance, Estimated)
- Include reference lines for each parameter in the Box-Whisker-Plot based on the table below. Use the last column "Proposed Reference Range for Boxplots".

Given that normal ranges for laboratory values vary from center to center, we propose standard reference lines be added to the boxplots based on ranges available from the American Board of Internal Medicine (January 2020). Specifically, we will implement this approach according to the ranges noted in the table below without objection. It should be noted that these ranges do not necessarily represent "values of concern" in this population but will give some context to the results relative to a normal population.

Test	**ABIM Reference Range**	**Proposed Reference Range for Boxplots**
Hemoglobin	Female: 120–160 g/L Male: 140–180 g/L	120–180 g/L
Platelets	150–450 10^9/L	150–450 10^9/L
aPTT	25–35 sec	25–35 sec
PT	11–13 sec	11–13 sec
PT-INR*	n/a	0.8–1.2
D-dimer	<0.5 mg/L	0–0.5 mg/L
Anti-Xa	0.3–0.7 IU/mL	0.3–0.7 IU/mL
AST	10–40 U/L	10–40 U/L
ALT	10–40 U/L	10–40 U/L
Total Bilirubin	5.13–17.10 umol/L	5.13–17.10 umol/L
Creatinine	Female: 44.21–97.26 umol/L Male: 61.89–114.95 umol/L	44.21–114.95 umol/L
Creatinine Clearance	90–140 mL/min/1.73m^2	90–140 mL/min

* Upper reference corresponds to lowest CTCAE Grade 1 result; lower reference from Medline

Table 17: Listing of Prior and Concomitant Medications (only Targeted Medications) – Safety Set

Subject Age/Sex/Race	Treatment Group	ATC Level 2/ Preferred Term/ Medication Name	Start Date (Study Day)	Stop Date (Study Day)	Dose [Unit]	Frequency	Route	Indication
999-999 / 70/F/W	DSTAT 0.25	ATC Level 2 Preferred Term Medication Name	DdMMMyy (xx)	DdMMMyy (xx)	40 [mg]	BID	IV	AE: xxxxxxxxxxx AE: xxxxxxxxxxxxx AE: xxxxxxxxxx
999-999 / xx/xx/xx	Cohort 1 PBO	ATC Level 2 Preferred Term Medication Name	DdMMMyy (xx)	Ongoing			PBO	MH: xxxxxxxxxxxx MH: xxxx
999-999 / xx/xx/xx	Cohort 1 PBO	ATC Level 2 Preferred Term Medication Name	DdMMMyy (xx)	Ongoing			PBO	PR: xxxxxxxx

Note: Medications are coded using WHO-DD Version March 2020.
Study Days prior to first treatment date are calculated as (actual date – first treatment date), after first treatment date as (actual date – first treatment date) + 1.
AE: Adverse Event, MH: Medical History, PR: Prophylaxis or Other

(Notes for programmer:
- Sorted by subject number, start date, stop date, ATC Level 2, preferred term and Medication Name
- Target Medications are:
Remdesvir (WHO-DC starting with "142690")
Dexamethasone (WHO-DC starting with "000160")
Anti-XA (enoxaparin) (WHO-DC starting with "017082" or "000277")
- Indication: If multiple, concatentate and wrap, drop the AE/MH-Numbers
)

5.2. ADDITIONAL POST-COHORT 2 LOCK ANALYSES – TABLE SHELLS

Figure 4: Biomarkers during the course of the study – Safety Set

Line-plots

Biomarker: <HMGB1 *(SI-unit)*> <IL-6 *(SI-unit)*> <TNF alpha *(SI-unit)*> <SAA *(SI-unit)*> *- see list of Biomarkers on the next page*

y-axis:
range: depending on data
label: Value (unit)

x-axis:
range: Baseline (D1), Day 3 (D3), Day 5 (D5), Day 7 (D7), Day 14 (D14), Day 28 (D28)
label: Visit
Line-Plots: different line styles/colors to differentiate cohort/group

Lines:
one line per subject
4 different line styles/colors to differentiate cohort/group

(Notes for programmer:
- *one figure per biomarker,*
- *additional Biomarkers might be added on short notice of sponsor*
- *"(SI-unit) » in sub-title to be replaced by actual SI-unit*
)

See list of Biomarkers provided by Chimerix on 9Dec2020

'25964	SAA,EDTApl(-70)RUO387PNL	ng/mL	ng/mL	Biomarkers
'25965	IL-6,EDTApl(-70)RUO387PNL	pg/mL	pg/mL	Biomarkers
'25966	TNF-alpha,EDTApl(-70)RUO387PNL	pg/mL	pg/mL	Biomarkers
'26776	AT-III,EDTApl(-80)RUO387	ug/mL	ug/mL	Biomarkers
'26777	Ficolin-3,EDTApl(-80)RUO387	ug/mL	ug/mL	Biomarkers
'5592	GM-CSF, EDTApl(-80)RUO-387	pg/mL	pg/mL	Biomarkers
'5593	IFN-gamma,EDTApl(-80)RUO-387	pg/mL	pg/mL	Biomarkers
'5594	IL-10, EDTApl(-80)RUO-387	pg/mL	pg/mL	Biomarkers
'5615	IL-18, EDTApl(-80)RUO-387	pg/mL	pg/mL	Biomarkers
'5597	IL-2, EDTApl(-80)RUO-387	pg/mL	pg/mL	Biomarkers
'5632	IL-3, EDTApl(-80)RUO-387	ng/mL	ng/mL	Biomarkers
'5627	IL-4, EDTApl(-80)RUO-387	pg/mL	pg/mL	Biomarkers
'5598	IL-5, EDTApl(-80)RUO-387	pg/mL	pg/mL	Biomarkers
'5617	IL-7, EDTApl(-80)RUO-387	pg/mL	pg/mL	Biomarkers
'5600	IL-8, EDTApl(-80)RUO-387	pg/mL	pg/mL	Biomarkers
'26778	LRG1,EDTApl(-80)RUO387	ug/mL	ug/mL	Biomarkers
'5623	MIP1 alpha, EDTApl(-80)RUO-387	pg/mL	pg/mL	Biomarkers
'5624	MIP-1b, EDTApl(-80)RUO-387	pg/mL	pg/mL	Biomarkers
'5619	MCP-1, EDTApl(-80)RUO-387	pg/mL	pg/mL	Biomarkers
'26779	Nr-CAM,EDTApl(-80)RUO387	ng/mL	ng/mL	Biomarkers
'26780	Neuropilin-1,EDTApl(-80)RUO387	ng/mL	ng/mL	Biomarkers
'26781	NAP-2,EDTApl(-80)RUO387	ng/mL	ng/mL	Biomarkers
'26782	PEDF,EDTApl(-80)RUO387	ng/mL	ng/mL	Biomarkers
'26783	RAGE,EDTApl(-80)RUO387	ng/mL	ng/mL	Biomarkers
'26784	SHBG,EDTApl(-80)RUO387	nmol/L	nmol/L	Biomarkers
'26785	Sortilin,EDTApl(-80)RUO387	ng/mL	ng/mL	Biomarkers
'26786	SOD-1,EDTApl(-80)RUO387	ng/mL	ng/mL	Biomarkers
'26787	TAFI,EDTApl(-80)RUO387	ug/mL	ug/mL	Biomarkers
'5626	TNF beta, EDTApl(-80)RUO-387	pg/mL	pg/mL	Biomarkers
8966	HMGB1,K3EDTApl(-70)RUO639	pg/mL	pg/mL	Biomarkers

Table 18: Proportion of and time to invasive mechanical ventilation or all-cause mortality – ITT Set

	DSTAT 0.25 N=xxx	Cohort 1 PBO N=xxx	DSTAT 0.325 N=xxx	Cohort 2 PBO N=xxx
Number of subjects who are alive and free of invasive mechanical ventilation or ECMO through Day 28 (a)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of subjects with any invasive mechanical ventilation, ECMO, all-cause mortality or early study discontinuation, whatever comes first, n (%) (b)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any invasive mechanical ventilation, ECMO	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Early study discontinuation < Day 25	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Kaplan-Meier estimates (c)				
Number of censored subjects, n (%) (c)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Time to first invasive mechanical ventilation, ECMO or all-cause mortality (days) (c)				
25% Quartile (95% CI)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)
Median (95% CI)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)
75% Quartile (95% CI)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)

N = Number of subjects in a specific group; n = Number of subjects with data available; Percentages are based on N;
ECMO: Extracorporeal membrane oxygenation.
(a) Early study discontinuation before Day 25 are not included.
(b) Subjects with any invasive mechanical ventilation, ECMO, all-cause mortality or early study discontinuation before Day 25 will be counted as event.
(c) Kaplan-Meier estimates: Subjects with any invasive mechanical ventilation, ECMO or all-cause mortality will be counted as event. All other subjects will be censored. Time to first invasive mechanical ventilation, ECMO or all-cause mortality, whatever comes first (days): Days are calculated as (start date/time – first study drug date/time)/24h). Time will be censored at last individual date/time reported. If time is not available for events "00:01" will be imputed, for censored observations "23:59" will be imputed. Randomized untreated subjects will be censored at time = 0.

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(Notes for programmer: Subjects randomized not treated will be counted in
a) as failure, and therefore not included in (a)
b) as event (in the line "Early study discontinuation < Day 25") in case of early study discontinuation < Day 25
c) as censored observation (censor time = 0)
)

Figure 5: Time to invasive mechanical ventilation, ECMO or all-cause mortality (KM-Plot) – ITT Set

Kaplan-Meier Plot:

y-axis:
range: 0% to 100% by 20%
label: Event-free Probability
reference-line: 50%

x-axis:
range: 0 to xxx (depending on data), by 7 days
label: Time to Event (Days)

Lines:
solid
different colors/line styles for the treatment-groups
starting at (100%/Baseline)
Censored values marked

Footnote:

N = Number of subjects in a specific group; (+) = censored values;
Kaplan-Meier estimates: Subjects with any invasive mechanical ventilation, ECMO or all-cause mortality will be counted as event. All other subjects will be censored.
Time to first invasive mechanical ventilation, ECMO or all-cause mortality, whatever comes first (days): Days are calculated as (start date/time – first study drug date/time)/24h). Time will be censored at last individual date/time reported. If time is not available for events "00:01" will be imputed, for censored observations "23:59" will be imputed. Randomized untreated subjects will be censored at time = 0.

(Notes for programmer: Subjects randomized not treated will be counted as censored observation (censor time = 0)
)

Table 19: Proportion of and time to all-cause mortality – ITT Set

	DSTAT 0.25 N=xxx	Cohort 1 PBO N=xxx	DSTAT 0.325 N=xxx	Cohort 2 PBO N=xxx
Number of subjects with all-cause mortality or early study discontinuation, n (%) (a)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Early study discontinuation < Day 25	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Kaplan-Meier estimates (b)				
Number of censored subjects, n (%) (b)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Time to all-cause mortality (days) (b)				
25% Quartile (95% CI)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)
Median (95% CI)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)
75% Quartile (95% CI)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)

N = Number of subjects in a specific group; n = Number of subjects with data available; Percentages are based on N;
(a) Subjects with all-cause mortality or early study discontinuation before Day 25 will be counted as event.
(b) Kaplan-Meier estimates: Subjects who died will be counted as events. All other subjects will be censored. Time to all-cause mortality (days): Days are calculated as (start date/time – first study drug date/time)/24h). Time will be censored at last individual date/time reported. If time is not available for events "00:01" will be imputed, for censored observations "23:59" will be imputed. Randomized untreated subjects will be censored at time = 0.

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(Notes for programmer: Subjects randomized not treated will be counted in
a) as event (in the line "Early study discontinuation < Day 25") in case of early study discontinuation < Day 25
b) as censored observation (censor time = 0)
)

Figure 6: Time to all-cause mortality (KM-Plot) – ITT Set

Kaplan-Meier Plot:

y-axis:
range: 0% to 100% by 20%
label: Event-free Probability
reference-line: 50%

x-axis:
range: 0 to xxx (depending on data), by 7 days
label: Time to Event (Days)

Lines:
solid
different colors/line styles for the treatment-groups
starting at (100%/Baseline)
Censored values marked

Footnote:

N = Number of subjects in a specific group; (+) = censored values;
Kaplan-Meier estimates: Subjects who died will be counted as event. All other subjects will be censored.
Time to all-cause mortality (days): Days are calculated as (start date/time – first study drug date/time)/24h). Time will be censored at last individual date/time reported. If time is not available for events "00:01" will be imputed, for censored observations "23:59" will be imputed. Randomized untreated subjects will be censored at time = 0.

(Notes for programmer: Subjects randomized not treated will be counted as censored observation (censor time = 0)
)

Table 20: Proportion of participants who are alive, discharged from the hospital, and not using home oxygen – ITT Set

Visit	DSTAT 0.25 N=xxx n (%)	Cohort 1 PBO N=xxx n (%)	DSTAT 0.325 N=xxx n (%)	Cohort 2 PBO N=xxx n (%)
Day 8 (D8)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Day 14 (D14)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Day 28 (D28)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

N = Number of subjects in a specific group; n = Number of subjects with data available;
Subjects who discontinued study early prior to start of time window (-3 days to -1 day for each visit) will be considered as failures even if alive and last records indicate no oxygen and out of hospital.
If the discontinuation is within the time window for the respective visit the last available status to be considered.

(Notes for programmer:

Number of subjects who are alive, discharged from the hospital and not using home oxygen are defined based on the Ventilator/Oxygen/Medical Care Status and the Hospitalization/Activity Status eCRF pages:

All subjects who are

- *not hospitalized (either with limited activities or not) AND*
- *do not require oxygen (no matter whether ongoing medical care is required or not)*

at the specific time points will meet this endpoint.

Use the CDISC study day – for corresponding start and stop date (e.g. hospitalization stop date, or start date of not require oxygen) and assign the relevant study days to the corresponding visit (Day 8, Day 14 and Day 28).

- *Determine status on particular day with respect to death, hospitalization, and oxygen use. For example, if a subject starts oxygen (e.g. Nasal Supplemental Oxygen) on Day -1 and stops on Day 10, subject is using oxygen at Visit Day 8, subject is not using oxygen at Day 14 and Day 28.*
- *If can't determine one, pick the **worst status** on that day. For example oxygen stops on Day 8, subject will be considered to be on oxygen for Day 8 analysis and subject is not using oxygen at Day 14 and Day 28.*
  Subject discharge from the hospital on Day 8, subject will be considered to be in the hospital for Day 8 analysis and to be discharged from the hospital on Day 14 and Day 28.
- *Subjects who discontinued study early **PRIOR** to start of time window (-3 days to -1 day for each visit) will be failures even if alive and last records indicate no oxygen and out of hospital. Subjects who discontinued study early but within the time window of the respective visit, e.g. on Day 7, discharged from hospital earlier and not using home oxygen will be* considered with the last available status at Day 8 (= no failure), and as failure at Day 14 and Day 28. Subjects who discontinued study early on Day 10 will be considered as failure at Day 14 and Day 28.)
- *Subjects randomized not treated will be counted as failure at the respective visit in case of early study discontinuation prior to start of the time window (-3 days to -1 day for each visit).*

Table 21: Clinical status assessed by the NIAID ordinal scale at fixed time points – ITT Set

Visit NIAID Score	DSTAT 0.25 N=xxx n (%)	Cohort 1 PBO N=xxx n (%)	DSTAT 0.325 N=xxx n %)	Cohort 2 PBO N=xxx n (%)
Day 8 (D8)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
5	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
6	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
7	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
8	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Day 14 (D14)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
5	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
6	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
7	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
8	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Day 28 (D28)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
5	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
6	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
7	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
8	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

N = Number of subjects in a specific group; n = Number of subjects with data available; Percentages are based on N;
NIAID scores are derived according to Appendix 4 of the study protocol. Higher values indicates a better outcome.
For subjects who discontinued study early within the time window (-3 days to – 1 day for each visit), the last available NIAID scale will be used at the corresponding visit and a NIAID score = missing to be assigned to all visits after early study discontinuation date.

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(Notes for programmer:

Use a skeleton and include all 8 NIAID scores in the table for each visit and include Missing category)

The NIAID ordinal score at the predefined time points will be derived based on the eCRF data collected on the Ventilator/Oxygen/Medical Care Status, the Hospitalizations/Activities Status pages and the death date. In the event subjects transition from one score to another on a particular Day, the worse score will be used.

Use the CDISC study day – for corresponding start and stop date (e.g. hospitalization stop date, or start date of nasal suppplemental oxygen) and assign the relevant study days to the corresponding visit (Day 8, Day 14 and Day 28).

- *Determine status on particular day with respect to death, hospitalization, and ventilatory care status. For example, if a subject starts nasal supplemental oxygen on Day -1 and stops on Day 10, and if the subject is still in hospital at Day 8, a NIAID score = 4 to be assigned at Day 8.*

- *If can't determine one, pick the worst status on that day.*
  For example nasal supplemental oxygen stops on Day 8, and subject does not require oxygen but requires ongoing medical are starting on Day 8, and the subject is in hospital at Visit Day 8, a NIAID score = 4 to be assigned at Day 8.

- *For subjects who discontinued study early within the time window (-3 days to – 1 day for each visit), the last available NIAID score will be used at the corresponding visit and a NIAID score = missing will be assigned to all visits after early study discontinuation date.*
  E.g. if a subject withdraw from study on Day 7, his or her last NIAID score will be assigned to Day 8, and NIAID scores at Day 14 and Day 28 are considered as missing. If subject withdrawal on Day 8, his or her Day 8 NIAID score will be assigned to Day 8, and NIAID scores at Day 14 and Day 28 are considered as missing.

- *For subjects who died e.g. prior to or on Day 8 a NIAID score = 1 will be assigned for the visits on and after Day 8*

- *Subjects randomized not treated will be counted as missing at the respective visit in case of early study discontinuation prior to start of the time window (-3 days to -1 day for each visit).*

)

Table 22: Time to clinical improvement – ITT Set

	DSTAT 0.25 N=xxx	Cohort 1 PBO N=xxx	DSTAT 0.325 N=xxx	Cohort 2 PBO N=xxx
Number of participants with clinical improvement, n (%) (a)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Kaplan-Meier estimates (b)				
Number of censored subjects, n (%) (b)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of subjects without improvement	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Time to clinical improvement (days) (b)				
25% Quartile (95% CI)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)
Median (95% CI)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)
75% Quartile (95% CI)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)

N = Number of subjects in a specific group; n = Number of subjects with data available; Percentages are based on N;
Clinical improvement is defined as at least a 2-grade improvement from baseline on the NIAID ordinal score.
(a) Subjects with a clinical improvement will be counted as event.
(b) Kaplan-Meier estimates: Subjects with a clinical improvement will be counted as event. Subjects without a clinical improvement or deaths occurring prior to the positive event will be censored. Time to clinical improvement: Days are calculated as (start date/time – first study drug date/time)/24h). Time will be censored at last individual date/time reported. If time is not available for events "23:59" will be imputed, for censored observations "00:01" will be imputed. Participants who died prior to Day 28 without clinical improvement will be censored at Day 28. Randomized untreated subjects will be censored at time = 0.

(Notes for programmer: Subjects randomized not treated will be counted as censored observation (censor time = 0)
)

Figure 7: Time to clinical improvement (KM-Plot) – ITT Set

Kaplan-Meier Plot:

y-axis:
range: 0% to 100% by 20%
label: Event Probability
reference-line: 50%

x-axis:
range: 0 to xxx (depending on data), by 7 days
label: Time to Event (Days)

Lines:

solid
different colors/line styles for the treatment-groups
starting at (0%/Baseline)
Censored values marked

Footnote:

N = Number of subjects in a specific group; (+) = censored values;
Clinical improvement is defined as at least a 2-grade improvement from baseline on the NIAID ordinal score.
Kaplan-Meier estimates: Subjects with a clinical improvement will be counted as event. Subjects without a clinical improvement or deaths occurring prior to the positive event will be censored.
Time to clinical improvement (days): Days are calculated as (start date/time – first study drug date/time)/24h). Time will be censored at last individual date/time reported. If time is not available for events "23:59" will be imputed, for censored observations "00:01" will be imputed. Participants who died prior to Day 28 without clinical improvement will be censored at Day 28. Randomized untreated subjects will be censored at time = 0.

(Notes for programmer: Subjects randomized not treated will be counted as censored observation (censor time = 0)
)

Table 23: Number of ventilator-free days from baseline through Day 28 – ITT Set

	DSTAT 0.25 N=xxx	Cohort 1 PBO N=xxx	DSTAT 0.325 N=xxx	Cohort 2 PBO N=xxx
Number of ventilator-free days, n(%)				
0	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
5	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
6	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
7	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
8	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…				
28	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
n	xxx	Xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x
Median	xx	Xx	xx	xx
Q1, Q3	xx, xx	xx, xx	xx, xx	xx, xx
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx

N = Number of subjects in a specific group; n = Number of subjects with data available; Percentages are based on N;
SD: Standard deviation; Q1, Q3: First, third quartile; Min: minimum; Max: maximum.
Ventilator-free days are only counted through the date of early study discontinuation, study completion date or Day 28, whichever comes first. For subjects who die during the course of the study, number of ventilator-free days is defined as 0.

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(Notes for programmer:
Include only the categories of Days (0-28) in the table which are available in the data
)

Table 24: Time to last hospital discharge – ITT Set

	DSTAT 0.25 N=xxx	Cohort 1 PBO N=xxx	DSTAT 0.325 N=xxx	Cohort 2 PBO N=xxx
Number of subjects discharged from hospital, n (%) (a)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Kaplan-Meier estimates (b)				
Number of censored subjects, n (%) (b)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of subjects alive and still in hospital	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Time to hospital discharge (days) (b)				
25% Quartile (95% CI)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)
Median (95% CI)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)
75% Quartile (95% CI)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)	x.x (x.xx,x.xx)

N = Number of subjects in a specific group; n = Number of subjects with data available; Percentages are based on N;
(a) Subjects discharged from hospital will be counted as event.
(b) Kaplan-Meier estimates: Subjects discharged from hospital will be counted as event. Subjects who are still in the hospital or died in the hospital will be censored.
Time to hospital discharge (days): Days are calculated as (last hospital discharged date/time – first study drug date/time)/24h). Time will be censored at last individual date/time reported. If time is not available for events “23:59” will be imputed, for censored observations “00:01” will be imputed. Participants who died prior to hospital discharge will be censored at Day 28. Randomized untreated subjects will be censored with time to hospital discharge = 0.

(Notes for programmer: Subjects randomized not treated will be counted as censored observation (censor time = 0)
)

Figure 8: Time to last hospital discharge (KM-Plot) – ITT Set

Kaplan-Meier Plot:

y-axis:
range: 0% to 100% by 20%
label: Event Probability
reference-line: 50%

x-axis:
range: 0 to xxx (depending on data), by 7 days
label: Time to Event (Days)

Lines:

solid
different colors/line styles for the treatment-groups
starting at (0%/Baseline)
Censored values marked

Footnote:

N = Number of subjects in a specific group; (+) = censored values;
Kaplan-Meier estimates: Subjects discharged from hospital will be counted as event. Subjects who are still in the hospital or died in the hospital will be censored.
Time to hospital discharge (days): Days are calculated as (last hospital dischared date/time – first study drug date/time)/24h). Time will be censored at last individual date/time reported. If time is not available for events "23:59" will be imputed, for censored observations "00:01" will be imputed. Participants who died prior to hospital discharge will be censored at Day 28. Randomized untreated subjects will be censored with time to hospital discharge = 0.

(Notes for programmer: Subjects randomized not treated will be counted as censored observation (censor time = 0)
)

Table 25: Time to first hospital discharge – ITT Set

For the layout refer to Table 24

Adapt footnote:

… Time to hospital discharge (days): Days are calculated as (first hospital discharged date/time – first study drug date/time)/24h)...

Figure 9: Time to first hospital discharge (KM-Plot) – ITT Set

For the layout refer to Figure 8

Adapt footnote:

… Time to hospital discharge (days): Days are calculated as (first hospital discharged date/time – first study drug date/time)/24h)...