1 TITLE PAGE

CLINICAL STUDY REPORT

Study title:	**H**amburg **E**doxaban fo**R** anticoagulation in C**O**vid-19 study
Protocol number:	HERO-19
Regulatory Agency identifier(s):	EudraCT No.: 2020-002504-39 CTgov No.: NCT04542408
Development phase:	Phase 3
Test drug/ investigational product:	Edoxaban (on top of standard of care for anticoagulation)
Indication:	Anticoagulation therapy in COVID-19
Study design:	Prospective, randomized, placebo-controlled, assessor-blinded, multi-center, interventional trial (Investigator-Initiated Trial)
Study dates:	First patient's first visit was on: 12-Nov-2020 Last patient's last visit was on 06-Sep-2022 This study was prematurely terminated due to recruitment issues after the enrollment of 140 patients. Notably, no safety issues led to the decision to discontinue the study
Sponsor:	University Medical Center Hamburg-Eppendorf Martinistrasse 52 20246 Hamburg, Germany
Investigator(s):	The Coordinating Principal Investigator of this study was: Prof. Dr. med. Stefan Kluge University Medical Center Hamburg-Eppendorf Department of Intensive Care Medicine See Appendix 16.1.4.1 for names and addresses of further investigators
Date and version of this report:	Report Version: Final Version 1.0 Report date: 23-May-2024
Confidentiality statement:	This report is confidential. It may not be used for any purpose without the prior written permission of the Sponsor of this study.

This study was conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the archiving of essential documents.

SPONSOR SIGNATORY AND SIGNATURE PAGE

Study title: Hamburg Edoxaban foR anticoagulation in COvid-19 study (HERO-19)

I, the undersigned, have reviewed and approved the final version of the clinical study report with the date of 23-May-2024:

S. Kluge — 30.05.24

Prof. Dr. med. Stefan Kluge
Co-ordinating Investigator & Sponsor,
UKE Hamburg

Date

M. Karakas — 06-JUN-2024

Prof. Dr. Dr. med. Mahir Karakas
Trial Lead,
UKE Hamburg

Date

Prof. Dr. Antonia Zapf
Statistician,
UKE Hamburg

Date

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Prof. Dr. med. Stefan Kluge Co-ordinating Investigator & Sponsor, UKE Hamburg	Date
Prof. Dr. Dr. med. Mahir Karakas Trial Lead, UKE Hamburg	Date
A. Zapf Prof. Dr. Antonia Zapf Statistician, UKE Hamburg	28.5.2024 Date

2 SYNOPSIS

Name of Sponsor

University Medical Center Hamburg-Eppendorf
Martinistrasse 52
20246 Hamburg, Germany

Name of Active Ingredient Edoxaban (in addition to intensified SoC for anticoagulation)

TITLE OF STUDY: Hamburg Edoxaban for anticoagulation in COVID-19 study (HERO-19)

EudraCT No.: 2020-002504-39
CTgov No.: NCT04542408

PRINCIPAL/COORDINATING INVESTIGATOR NAME:

Prof. Dr. med. Stefan Kluge
University Medical Center Hamburg-Eppendorf
Department of Intensive Care Medicine

STUDY CENTRE(S): A total of 7 German sites (UKE Hamburg [No. 01], University Clinic Hannover [No. 03], University Clinic/Cardiac Center Freiburg [No. 04], Clinic TU Munich [No. 07], University Clinic Augsburg [No. 11], Asclepios Clinic Hamburg St. Georg [No. 14], and Asklepios Clinic Hamburg Altona [No. 15]) participated in the study and had randomized at least 1 patient.

PUBLICATION (REFERENCES): None so far.

STUDY PERIOD:	First patient's first visit (FPFV):	12-Nov-2020
	Last patient's last visit (LPLV):	06-Sep-2022

PHASE OF DEVELOPMENT: Phase 3

BACKGROUND AND RATIONALE FOR THE STUDY:

Coagulopathy in the context of COVID-19 is a major threat to affected patients due to deep vein thromboses and pulmonary embolisms. Actual data at the time of study start showed an unexpectedly high incidence of partially fatal complications without any prior clinical evidence in some cases. Therefore, the study investigated whether therapeutic anticoagulation on top of standard of care (SoC) compared to prophylactic anticoagulation as part of SoC can improve objective patient-relative endpoints, relevant for prognosis in patients with COVID-19.

OBJECTIVES: The following study objectives were stipulated:

- To evaluate if an intensive anticoagulation strategy using edoxaban on top of SoC of COVID-19 therapy is superior to SoC (either in-hospital moderate anticoagulation strategy (=low-dose low-molecular weight heparin [LMWH] / fondaparinux or ambulatory no anticoagulation, i.e., placebo within this trial) in reduction of morbidity and mortality endpoints in patients with COVID-19.

- To assess safety and tolerability of edoxaban and high-dose LMWH / fondaparinux on top of SoC in patients with COVID-19.
- Furthermore, secondary objectives intended to evaluate the effect of both treatment regimens with respect to all-cause mortality, mortality related to venous and arterial thromboembolism, rate of arterial/venous thromboembolism, rate and length of mechanical ventilation, length of initial stay at intensive care unit (ICU), rehospitalization, rate and length of renal replacement therapy, cardiac arrest, and cardiopulmonary reanimation (CPR).

METHODOLOGY:

This study was a prospective, multicenter, open-label, assessor-blinded, randomized, placebo-controlled, interventional trial with an observation period of 42 days. A total of 172 eligible patients were planned to be randomized 1:1 to the intervention group or control group. Patients allocated to the intervention group received therapeutic (intensified) anticoagulation using LMWH/fondaparinux during the course of hospital stay and oral anticoagulation using edoxaban according to SmPC (60 mg once a day) after being discharged from hospital/outpatient course. Patients allocated to the control group received prophylactic anticoagulation using LMWH/fondaparinux as part of SoC whilst inpatient course, and edoxaban-matching placebo after discharge/outpatient course. Patients were informed of their treatment allocation to the placebo group (as it had been shown that the effect of placebo is still detectable), whereas endpoint assessors remained blinded to study treatment. Two interim analyses were planned in the course of the study after the enrollment of 50% and 75% of patients, respectively, in order to allow for sample size re-assessment.

NUMBER OF SUBJECTS:

The original sample size estimation required 172 patients to be enrolled. After the first interim analysis based on 88 enrolled patients, it turned out that clearly more patients would be needed to fulfil the statistical power requirements on the estimation model. Nevertheless, it was decided to still proceed with the originally planned sample size of 172, and the study was eventually terminated after the enrollment of 140 patients, because the recruitment rate remained too slow to complete the study in an appropriate time.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION AND EXCLUSION:

Patients suffering from COVID-19 were to be enrolled in the study. Key inclusion criteria were:

- Diagnosis of COVID-19 and hospitalization on ICU, or
- Diagnosis of COVID-19 and hospitalization on normal ward, or
- Diagnosis of COVID-19 (within 10 days) and troponin ≥ULN and/or D-dimer ≥0.5 mg/L
- Legally effective declaration of informed consent

Key exclusion criteria were:

- Age below 18 years

- Life expectancy less than 3 months before COVID-19
- Resuscitation duration >30 minutes
- Contraindications to the use of each of the standard LMWH/fondaparinux according to the respective Summary of Product Characteristics (SmPC)
- Hypersensitivity to the active substance, to edoxaban or any of its excipients
- Significantly increased bleeding risk
- Other indication for anticoagulation beyond COVID-19
- Glomerular filtration rate (GFR) <15 mL/min
- Planned transfer of the patient to another clinic within the next 42 days

TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, BATCH NUMBER(S):

The experimental treatment of the study consisted of intensified (therapeutic, high-dose) treatment with subcutaneous LMWH/fondaparinux (on top of SoC) during the hospital stay (ICU or normal ward) followed by oral edoxaban up to Day 42 during the ambulant phase (off-label). Ambulatory patients were directly to be treated with edoxaban. This treatment group is referred to as "intervention group".

Only marketed drugs were used; drug doses and application intervals were to be chosen according to the respective SmPC (e.g., for edoxaban, the standard dose was 60 mg once daily (od) or 30 mg od in the case of GFR between 15-30 mL/min or body weight ≤60 kg). Edoxaban was labelled in accordance with local study site regulations for Investigational Medicinal Products (IMPs) and provided by the Sponsor. LMWH/fondaparinux was taken from the routine supply at the study sites.

Experimental treatment was open labelled for study sites and patients, while assessors were blinded.

DURATION OF TREATMENT: Study treatment was administered during the entire duration of follow-up until Day 42.

REFERENCE THERAPY, DOSE, MODE OF ADMINISTRATION, BATCH NUMBER(S):

Reference treatment consisted of prophylactic (SoC) treatment with LMWH/fondaparinux during the hospital stay (ICU or normal ward) and oral edoxaban-matching placebo up to Day 42 during the ambulant phase. Ambulatory patients were directly treated with edoxaban-matching placebo. This treatment group is referred to as "control group".

Only marketed drugs were used; drug doses and application intervals were to be chosen according to the respective SmPCs. Edoxaban-matching placebo was labelled in accordance with local study site regulations for IMPs and provided by the Sponsor. LMWH/fondaparinux was taken from the routine supply at the study sites.

Reference treatment was open-labelled for study sites and patients, while assessors were blinded.

CRITERIA FOR EVALUATION:

The primary efficacy endpoint was the composite of all-cause mortality and/or venous thromboembolism (VTE) and/or arterial thromboembolism (ATE) occurring within 42 days.

Primary safety endpoints were:

- Rate of serious adverse events (SAEs) / adverse events (AEs) / suspected unexpected serious adverse reactions (SUSARs) in both arms occurring within 42 days
- Major and clinically relevant non-major bleeding according to International Society on Thrombosis and Haemostasis (ISTH) criteria
- Interruption of therapy due to intolerability to edoxaban
- New treatment-emergent AEs (TEAEs) (and changes in severity and frequency in these) related to edoxaban

Secondary study endpoints were:

- All-cause mortality within 42 days
- Mortality related to VTE
- Mortality related to ATE
- Rate of VTE and/or ATE
- Rate and length of mechanical ventilation (MV) until Day 42
- Length of initial stay at ICU after application of IMP up to a total of 42 days
- Re-hospitalization within 42 days
- Rate and length of renal replacement therapy (RRT) until Day 42
- Cardiac arrest/ cardiopulmonary reanimation (CPR) until Day 42

Moreover, an expanded safety composite endpoint including death, myocardial infarction (MI), stroke, recurrent hospitalization, acute kidney injury, and gastrointestinal disorders was to be analyzed (actually analyzed as separate variables).

STATISTICAL METHODS:

General considerations: All applicable statistical tests were two-sided and performed using a 5%-significance level. Thus, all presented confidence intervals (CIs) encompassed 95% and were two-sided. Analyses of secondary and safety outcomes were performed exploratory without adjustment for multiple testing. Categorical data were summarized by absolute and relative frequencies. Continuous data were summarized by mean, standard deviation (SD), median, interquartile range (IQR), and range. Histograms and boxplots were used where applicable to check the distribution and possible outliers for continuous variables. The numbers of available observations and numbers of missing observations were presented for the treatment groups separately.

Primary efficacy endpoint: The primary efficacy analysis was a test for difference performed in the FAS (full analysis set), which is as close as possible to the ITT (intention-to–treat) population, applying a mixed Cox proportional hazards model with random effect/frailty for

centers and fixed effects for the stratification factors "ICU status", "sex", and "treatment group". Hence, an adjusted estimated hazard ratio (HR) was provided for the comparison of the intervention group vs. control group along with the corresponding 95%-CI and corresponding p-value. All patients who did not reach the primary endpoint by study end were censored at that time point; dropouts were handled as independent right censoring. Aalen-Johansen plot was used for visualization. The analysis for the primary endpoint was repeated in the per protocol (PP) population.

Secondary efficacy endpoints: Single components of the composed primary efficacy endpoint (ATE/VTE) were analyzed similar to the primary endpoint but accounting for death as a competing risk, i.e., cause-specific Cox proportional hazards models were used with random effect/frailty for centers and fixed effects for ICU status, sex, and treatment group. Cumulative incidence plots (Kaplan-Meier for all-cause death and Aalen-Johansen plots for the other time-to-event endpoints) were used for visualization. For the dichotomous secondary efficacy endpoints (i.e., rates), a mixed logistic regression model (fixed effects: ICU status, sex, and treatment group; random effect: center) was used for analysis. Effect estimates were presented as Odds Ratios (ORs) together with 95%-CIs. and corresponding p-values. Continuous secondary efficacy endpoints were to be analyzed using a mixed linear model or a mixed negative binomial model with a random effect for center and time in follow-up as an offset. However, models were only estimated when there were enough observations, otherwise data were analyzed descriptively.

Safety outcomes: Safety endpoints for both treatment groups were analyzed descriptively, i.e., event rates with percentages on patient level (absolute and relative frequencies) and event numbers on event level were given.

Subgroup analysis: Subgroup analyses for the primary endpoint were conducted in the same manner as the primary endpoint analysis but with an additional interaction term between random group and the variable for the subgroups of interest.

SUMMARY OF RESULTS AND CONCLUSIONS:

Subject Disposition:

A total of 140 patients were randomized and 139 patients were allocated to treatment with either reference treatment (control group, N=71) or experimental treatment (intervention group, N=68). This population (N=139) constituted the ITT population, which was used for the analyses of most of the secondary endpoints. For two patients (one in each treatment group) primary endpoint assessment was missing and hence the primary endpoint analysis was based on this FAS population (N=137). Safety was analyzed in the "evaluable for safety" (EFS) set (N=132) based on patients exposed at least once to study drug treatment (68 patients in the control group and 64 patients in the intervention group). The PP population (N=121) included 58 patients in the control group and 63 patients in the intervention group.

Similar proportions of patients had completed the study (59 patients each in the control group and intervention group) or discontinued the study prematurely (12 patients in the control group and 9 patients in the intervention group).

Demography and Baseline Characteristics:

About two-third of study patients were men (93 patients, 66.9%) and one-third were women (46 patients, 33.1%). The mean age in the ITT population was 58.4 ± 13.7 years (median: 59.0

years) and ranged from 24 years to 84 years. Overall, there were no clinically meaningful differences between the 2 treatment groups in terms of sex, mean age, mean body weight, and mean body height.

Actually, no outpatients were enrolled in the study, while the majority of patients in either treatment group (43 patients [60.6%] in the control group and 41 patients [60.3%] in the intervention group) were randomized on a normal ward. Enrolment while on intensive care occurred in 28 patients (39.4%) in the control group and in 27 patients (39.5%) in the intervention group.

Efficacy Results:

The outcome of the primary efficacy analysis (first occurrence of the composite of all-cause mortality, VTE, or ATE in the FAS) is summarized in Synopsis Table A. A total of 14 endpoint-relevant events occurred in the intervention group vs. 20 events in the control group, and the resulting incidence per patient year was slightly lower in the intervention group than in the control group (2.311 events/year vs. 3.365 events/year). Consistently, the HR was <1.0 (0.74, thereby indicating a smaller incidence rate in the intervention group compared with the control group), but the upper bound of the 95%-CI for the HR was 1.48 and thus did not exclude the "1" value, and the p-value was greater than α=0.05 with p=0.3986. In conclusion, the HR was descriptively in favor of the intervention treatment but failed to reach statistical significance. Of note, the observed effect was smaller than expected with the initial sample size estimation, where an HR of 0.4812 was assumed. Similar results were seen with the sensitivity analysis in the PPS and the subgroup analyses by sex (male vs. female) and hospitalization status at enrollment (normal ward vs. ICU).

Synopsis Table A also includes the analysis of the single components of the composite primary endpoint; i.e., all-cause mortality, VTE or ATE separately (based on number of events), and the proportion of patients with VTA and/or ATE. These analyses, which were performed in a similar way as the primary efficacy analysis, showed a consistent outcome pattern: Apart from ATE (HR=1.05), HRs and OR were <1 and thus in favor of the intervention group. Of note, no deaths related to ATE or VTE were reported.

Synopsis Table A: Primary endpoint (composite in FAS) and single component analyses

	Control group	Intervention group	Estimate / (95%-CI)	p-value
Composite in FAS [a]	20 (3.365) [b]	14 (2.311) [b]	HR=0.74 / [0.38; 1.48]	0.3986
Composite in PPS	17 (3.241) [b]	13 (2.425) [b]	HR=0.66 / [0.32, 1.37]	0.2623
All-cause mortality [c]	8 (1.297) [b]	7 (1.099) [b]	HR=0.89 / [0.32; 2.45]	0.8200
ATE in FAS [a]	7 (1.177) [b]	7 (1.155) [b]	HR=1.05 / [0.37; 3.00]	0.9304
VTE in FAS [a]	5 (0.841) [b]	3 (0.484) [b]	HR=0.60 / [0.14; 2.53]	0.4904
ATE/VTE rate [a, d]	12 (17.14) [e]	9 (13.43) [e]	OR=0.76 / [0.29; 1.96]	0.5645

ATE=Arterial thromboembolic event; CI=Confidence interval, FAS=Full analysis set; HR=Hazard ratio, OR=Odds ratio; PPS=Per-protocol set; VTE=Venous thromboembolic event
Note: An HR/OR estimate of <1.0 indicates better outcome (less events/patients with event) in the intervention group. No deaths considered related to ATE and/or VTE were reported.
a: ITT patients with non-missing primary endpoint data (70 patients in control group and 67 patients in intervention group).
b: No. of events (incidence per patient year).
c: Analyzed in ITT, N=139 (71 patients in control group and 68 patients in intervention group).
d: Number of patients experiencing ATE and/or VTE within 42 days.
e: No. of patients (percentage).

Synopsis Table B summarizes the outcomes in the remaining secondary efficacy endpoints over 42 days. The re-hospitalization rate was lower in the intervention group than in the control group (OR=0.16, p=0.0942). Proportions of patients requiring MV were similar (OR=1.13), while the mean and median time of MV were slightly longer in the control group compared with the intervention group. Likewise, the proportions of patients with RRT were similar (OR=1.07) and mean and median time of RRT slightly longer in the control group than in the intervention group. Also, the median length of stay on the ICU was slightly longer in the control group than in the intervention group (8.0 days vs. 5.5 days). The incidence of cardiac arrest/cardiopulmonary reanimation was low; just 2 patients in the intervention group experienced such events, and an OR could thus not be calculated. Overall, the results of these endpoint analyses were consistent with those seen in the analyses of the primary composite endpoint and its components and mostly showed slightly more favorable outcomes in the intervention group compared with the control group.

Synopsis Table B: Analysis of other secondary efficacy endpoints (ITT)

	Control group	Intervention group	Estimate / (95%-CI)	p-value
Re-hospitalization				
Rate, n (%) [a]	6 (8.45)	1 (1.47)	OR=0.16 / [0.02; 1.37]	0.0942
MV				
Rate, n (%) [a]	25 (35.21)	25 (36.76)	OR=1.13 / [0.42; 3.03]	0.8147
Mean time (hrs.) [b]	281.1 ± 215.8	249.7 ± 251.6	---	---
Median time (hrs.)	230.3	201.9	---	---
RRT				
Rate, n (%) [a]	4 (5.63)	4 (5.88)	OR=1.07 / [0.25; 4.53]	0.9256
Mean time (days) [b]	20.8 ± 14.9	14.0 ± 14.1	---	---
Median time (days)	15.5	12.0	---	---
Length of stay on ICU				
N obs.	43 (60.6)	42 (61.8)	---	---
Mean time (days) [b]	10.1 ± 10.9	10.7 ± 11.9	---	---
Median time (days)	8.0	5.5	---	---
Cardiac arrest/CPR				
Rate, n (%) [a]	0 (0.0)	2 (2.9)	nc	nc

CI=Confidence interval, CPR=Cardiopulmonary reanimation; ICU=Intensive care unit; MV=Mechanical ventilation; nc=Not calculable; n obs.=Number of patients with observation; OR=Odds ratio, RRT=Renal replacement therapy
Note: An OR estimate of <1.0 indicates better outcome (less patients with event) in the intervention group.
a: Number of patients with event (percentage).
b: Arithmetic mean ± standard deviation.

Safety Results:

Synopsis Table C summarizes AE experience in HERO-19 over 42 days. The frequency of patients with AEs (61.8% vs. 50.0%) and SAEs (36.8% vs. 23.4%) was descriptively higher in the control group than in the intervention group. At the preferred term (PT) level, the 3 most common AEs in the total population occurred more frequently in the control group than in the intervention group: "respiratory failure" (13 patients [19.1%] in the control group and 8 patients [12.5%] in the intervention group), "pyrexia" (7 patients [10.3%] in the control group and 3 patients [4.7%] in the intervention group), and "pulmonary embolism (PE)" (6 patients [8.8%] in the control group and 3 patients [4.7%] in the intervention group). The group differences in respiratory failure and PE were also visible in the analysis of SAEs (respiratory failure: 13 patients [19.1%] in the control group vs. 7 patients [10.9%] in the intervention group; PE: 6 patients [8.8%] in the control group vs. 2 patients [3.1%] in the intervention

group). AEs considered related to study treatment were more frequent in the intervention group than in the control group, where all 5 related AEs reported in 5 patients in the intervention group were related to (expectable) bleeding events (thereof 2 SAEs with "cerebral hemorrhage"). The only related event reported in the control group was a mild and non-serious pruritus related to LMWH. Thus, no SUSARs were reported in the study. The 2 non-serious, mild, and resolved events considered related to edoxaban reflected bleeds and thus were expected. Mortality within 42 days was widely similar in the 2 treatment groups (HR=0.89). Frequently reported death causes were associated with sepsis, multi-organ failure, and respiratory decompensation. Fatal bleeding events were explicitly reported for 2 patients in the control group (intracerebral bleeding and intracranial bleeding) and for 1 patient in the intervention group (cerebral bleeding).

Synopsis Table C: Adverse event experience (EFS)

Event	Control group (N=68) n (%)	Intervention group (N=64) n (%)	Total (N=132) n (%)
Patients with any AEs	42 (61.8)	32 (50.0)	74 (65.1)
No. of AEs	*101*	*90*	*191*
Patients with SAEs	25 (36.8)	15 (23.4)	40 (30.3)
No. of SAEs	*32*	*21*	*53*
Patients with any related AEs	1 (1.5)	5 (7.8)	6 (4.5)
Patients with related SAEs	0 (0.0)	2 (3.1)	2 (1.5)
Patients with any AEs related to edoxaban	0 (0.0)	2 (3.1)	2 (1.5)
Patients with SAEs related to edoxaban	0 (0.0)	0 (0.0)	0 (0.0)
Patients with SUSARs	0 (0.0)	0 (0.0)	0 (0.0)
Deaths occurring within 42 days	8 (11.8)	7 (10.9)	15 (11.4)
All documented deaths	10 (14.7)	8 (12.5)	18 (13.6)

Synopsis Table D summarizes the protocol-defined safety endpoints of interest. Major bleeding and other clinically relevant, non-major bleedings according to ISTH classification were the primary safety endpoint and occurred in 4 patients (5.9%) in the control group vs. 7 patients (10.9%) in the intervention group. Thus, the rate of ISTH bleeding was descriptively higher in the intervention group than in the control group (and explainable by the applied intensified anticoagulation regimen), but the absolute number of events was too small to allow robust comparisons between the 2 treatment groups. Moreover, this finding has to be balanced against the observation that less patients in the intervention group experienced any AEs, SAEs, re-hospitalization (OR=0.16), and primary efficacy events (HR=0.74; see Synopsis Table A). No treatment interruptions of edoxaban due to safety issues were reported, and no unexpected AEs considered related to edoxaban were seen. Myocardial infarction, ischemic stroke, acute kidney injury, and gastrointestinal disorders occurred infrequently in either treatment group, and no clinically meaningful differences were observed between the treatment groups in these events.

Synopsis Table D: Protocol-specified safety endpoints (EFS)

Event	Control group (N=68) n (%)	Intervention group (N=64) n (%)	Total (N=132) n (%)
ISTH bleeding (major and clinically relevant non-major) [a]	4 (5.9)	7 (10.9)	11 (8.3)
Interruption of therapy due to intolerability to edoxaban	0 (0.0)	0 (0.0)	0 (0.0)
New TEAEs related to edoxaban	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	1 (1.5)	0 (0.0)	1 (0.8)
Ischemic stroke	1 (1.5)	0 (0.0)	1 (0.8)
Acute kidney injury	2 (2.9)	3 (4.7)	5 (3.8)
Gastrointestinal disorders	3 (4.4)	4 (6.2)	7 (5.3)

TEAE=Treatment-emergent adverse event
a: Primary safety endpoint

Conclusions:

Possibly also promoted by a smaller therapeutic effect than expected and recruitment issues with less enrolled patients than needed as per sample size estimation, this study failed to demonstrate statistically significant superiority of the intensified anticoagulation (intervention) regimen with therapeutic LMWH/fondaparinux and edoxaban compared with the anticoagulation SoC (control) regimen applying prophylactic LMWH/fondaparinux in terms of the prevention of the composite endpoint all-cause mortality, ATE, and VTE. Many of the descriptive efficacy results were in favor of the intervention regimen and thus suggested at least a trend towards potential beneficial effects of the intervention regimen compared with the control regimen. ISTH major and clinically relevant non-major bleedings occurred slightly more frequently in the intervention group than in the control group, but absolute event numbers were small in either treatment group. AEs and SAEs were reported more frequently in the control group than in the intervention group. Generally, the safety analyses did not reveal any unexpected or alarming safety issues with either treatment regimen. Overall, additional studies are required to determine the clinical value of an intensified anticoagulation strategy for the prevention of thromboembolic events in hospitalized COVID-19 patients.

DATE AND VERSION OF THIS REPORT: Final Version 1.0; dated 23-May-2024