PLACE IN SITE FILE #4.2

Protocol change log

Protocol-version		Date for approval in CTIS part I	Date for approval in CTIS part II	Participant information	eCRF	
Start version: 1.8 Date: 19-12-2023	First version submitted for approval.			Start version: 1.0 Date: 28-11-2023		
Protocol-version	**Short description of protocol changes**	**Date for approval in CTIS part I**	**Date for approval in CTIS part II**	**Changes in participant information**	**Changes in the eCRF**	**What changes have been made in the eCRF**
New version: 1.9 Date: 28-02-2024	• Added ClinicalTrials.gov registration number to the first page. • Updated estimated timelines (sections 1 and 16). • Incorporated Danish Society of Infectious Diseases guidelines for meropenem dosing (section 4.3). • Provided additional justification for sample sizes and feasibility phase (sections 6.1, 6.3, and 9.2). • Clarified HRQoL data collection from next of kin (section 6.5). • Noted that dose adjustments are at the treating clinician's discretion (sections 8.4 and 8.5). • Clarified protocol deviations by the clinical team (section 8.8).	09-04-2024	08-04-2024	Yes ☒ No ☐ New version: 2.0 Date: 01-03-2024	Yes ☐ No ☒	

	• Corrected definitions and reporting details for SARs and SUSARs, including EudraVigilance reporting (sections 10.1–10.3). • Specified that the assessed drugs aren't subject to stricter Danish reporting requirements (section 10.2). • Enabled immediate SAE reporting by investigators and inclusion in annual safety reports (sections 10.2 and 10.3). • Clarified causality assessments for SUSARs and expected SARs (section 10.3). • Added a dedicated summary of the risk-benefit assessment (section 10.5). • Updated screening procedures regarding trial investigators and treating clinicians (section 11.1). • Added chronic renal replacement therapy to baseline variables (section 11.4 and relevant appendices). • Expanded justification for emergency enrolment prior to informed consent (section 11.2 and appendix 6). • Included additional details on handling partially missing data (section 12.9). • Updated conflicts of interest (section 15.7). • Made minor corrections and semantic edits throughout without altering meaning.					

Protocol-version	Short description of protocol changes	Date for approval in CTIS part I	Date for approval in CTIS part II	Changes in participant information	Changes in the eCRF	What changes have been made in the eCRF
New version: 1.10 Date: 22-03-2024	• Clarified that enrolment and informed consent follow applicable emergency trial legislation in multiple sections (section 4.4; section 8.2; section 11.2; and appendix 6, section 19.5, renamed). The Danish procedure has been removed from the main protocol, with country-specific procedures to be submitted separately and published on the trial website. • Specified that de-escalation to another antibiotic due to clinical improvement is permitted, will be recorded, and is not considered a protocol violation (section 4.3; section 6.5; section 8.3; section 8.4; section 8.5; section 8.9; section 11.4; and appendix 4, section 19.4). • Noted in section 6.5 that HRQoL data will be obtained via proxies only when participants cannot respond. • Corrected an error in the mock inclusion flowchart regarding participant counts (appendix 3, section 19.3). • Added references to two studies previously cited as “unpublished data from our group.” • Made minor corrections and semantic edits throughout.	10-04-2024	10-04-2024	Yes ☐ No ☒	Yes ☐ No ☒	

Protocol-version	Short description of protocol changes	Date for approval in CTIS part I	Date for approval in CTIS part II	Changes in participant information	Changes in the eCRF	What changes have been made in the eCRF
New version: 1.11 Date: 06-11-2024	• Corrected “anaphylactic reaction” to “anaphylactic shock” (abstract; section 10.2; appendix 4, section 19.4). • Updated the description of sequence generation for stratified block randomisation in the initial trial phase (section 6.2; section 12.5). • Corrected the reporting of SUSARs (section 10.3). • Added the dosing regimen (first dose) to the list of variables collected (section 11.4; appendix 4, section 19.4). • Provided a summary of the key attributes of the primary estimand in a single section (section 12.2). • Stated that a formal analysis of participants with one or more SARs will be conducted and presented to the IDMSC at the annual safety meetings, with corresponding updates to the missing data handling (section 12.9; appendix 1, section 19.1). • Updated the IDMSC charter to clarify the planned meetings, responsibilities, and structure of meetings and reports (appendix 1, section 19.1). • Clarified which proxy EQ-5D version is to be used when participants are unable to report on their health-related quality of life (appendix 4; section 19.4). • Made minor corrections and semantic edits in several areas.	13-01-2025		Yes ☐ No ☒	Yes ☐ No ☒	

Protocol-version	Short description of protocol changes	Date for approval in CTIS part I	Date for approval in CTIS part II	Changes in participant information	Changes in the eCRF	What changes have been made in the eCRF
New version: 1.12 Date: 01-10-2025	• Updated the estimated timeline (abstract and section 16) • Updated statement according to revised SPIRIT 2025 guideline concerning patient and public involvement (section 6.1). • Added elaboration on protocol violations (section 8.9). • Clarification regarding the procedure for submission of annual safety reports (section 10.3). • Added a paragraph to the benefit–risk assessment clarifying that exclusion due to pregnancy will be based on known pregnancy from clinical examination, history, or hCG testing. A routinely negative hCG-status will not be demanded in all fertile women, as pregnancy is very rare in ICU patients with shock and such a requirement would delay screening and limit enrolment. This approach is harmonized with the INCEPT domain-specific appendix, consistent with previous trials, and supported by the 2024 update of the Declaration of Helsinki (section 10.5). • Updated procedure for screening and included hCG screening status, to align with the new procedure as explained in section 10.5 (section 11.1). • Revised the variable "New isolation precautions due to resistant bacteria". The list of predefined resistant bacteria was expanded and updated (e.g., Acinetobacter baumannii, Citrobacter spp., Enterococcus faecium, Escherichia coli, Klebsiella spp., etc.), and the response options were harmonized to species level where relevant (section 11.4 and appendix 4, section 19.4). • Moved two variables from the Screening variables section to the Baseline variables section (section 11.4): - Latest fraction of inspired oxygen (FiO2) prior to randomisation (only for participants on invasive mechanical ventilation, non-invasive ventilation, or continuous use of CPAP).	01-10-2025		Yes ☒ No ☐ New version: 2.1 Date: 25-09-2025	Yes ☒ No ☐	• Moved two variables from screening form to baseline form • Elaborated on how resistant bacteria is defined and recorded in the eCRF

	- Maximum oxygen flow at randomisation (+/– 1 hour, only for participants receiving supplementary oxygen on an open system). • Expanded trial reporting procedure (section 15.2). • Updated the SPIRIT guideline from the 2013 version to the current 2025 version. For both checklists (SPIRIT and CONSORT-ACE), section numbers rather than page numbers are now reported to facilitate protocol navigation and future updating (appendix 2, section 19.2). • Corrected exclusion criteria definition to harmonize with the new procedure (appendix 4, section 19.4).					

Protocol-version	Short description of protocol changes	Date for approval in CTIS part I	Date for approval in CTIS part II	Changes in participant information	Changes in the eCRF	What changes have been made in the eCRF
New version: 1.13 Date: 25-11-2025	• Updated timespan in which HRQoL will be assessed and broadened description of consenting party (appendix 4, section 19.4). • Added 'Chronic liver disease' as variable in table S1 (appendix 7, section 19.7). • Minor corrections and semantic edits in a few places.	25-11-2025		Yes ☐ No ☒ New version: Date:	Yes ☐ No ☒	Added a variable already described in the protocol but was missing in the eCRF: 'Use of systemic corticosteroids at randomisation'.

Overview of substantial modficiations:

Type	ID	Parts	Content	Submission Date	Decision Date
Initial	IN	Part I & Part II	First version submitted to the authorities.	20/12/2023	10/04/2024
Non-substantial modification	NSM-1	Part II	This modification involved minor administrative updates to the participant information document. Corrections were made to ensure consistency with previously approved investigator information for RH, 4131.	10/04/2024	10/04/2024
Substantial modification	SM-1	Part II	This modification involved the addition of **Esbjerg ICU, Nykøbing Falster ICU, Køge ICU, Hvidovre Infectious Disease department, Odense Infectious Disease department and Rigshospitalet Infectious Disease department** as trial sites to the trial.	05/06/2024	30/07/2024
Substantial modification	SM-2	Part I	This modification comprised multiple clarifications and corrections to the protocol, including safety terminology, randomisation procedures, adverse event reporting, and statistical analysis descriptions. Additional updates were made to improve clarity around data collection, oversight processes, quality-of-life assessments, and overall document consistency.	26/11/2024	13/01/2025
Substantial modification	SM-4	Part I & Part II	This modification included updates to the protocol and CTIS submission to clarify procedures related to oversight, screening, consent processes, and site organisation, including the addition and removal of trial sites and investigators. It also incorporated several non-substantial updates to improve alignment with current guidelines, refine data collection variables, update product descriptions, and enhance overall clarity and consistency of trial documentation.	28/08/2025	06/10/2025
Substantial modification	SM-5	Part II	This modification involved change of a site investigator from **Klaus Marcussen to Anne Grønborg Vedel at the trial site Slagelse ICU**.	10/10/2025	31/10/2025
Non-substantial modification	NSM-7	Part I	This modification involved minor updates to trial documentation affecting health-related quality-of-life assessments, consent descriptions, and data collection variables. Additional editorial and semantic corrections were made to improve clarity and consistency.	28/11/2025	28/11/2025

Substantial modification	SM-6	Part II	This modification concerned updates to site investigator staffing at the **Bispebjerg ICU trial site**. Changes were made to replace a site investigator, without affecting site infrastructure, staffing levels, or trial conduct.	28/11/2025	22/12/2025