Conclusion of the reporting Member State as regards Part I of the assessment report (Art. 8(2))

1 ADMINISTRATIVE INFORMATION

EU CT number	2023-509703-33-00
Title of the study	Empirical Meropenem versus Piperacillin/Tazobactam for Adult Patients with Sepsis (EMPRESS) trial
Name of sponsor(s) *Note: if there is more than one sponsor the primary contact should be identified*	Rigshospitalet
Trial category *(as per EMA Appendix on disclosure rules: EMA/228383/2015 Endorsed)*	Category 1 ☐ Category 2 ☐ Category 3 ☒
Low intervention trial	Yes ☒ No ☐
First in human ☐ Phase I ☐ II ☐ III ☐ IV ☒	
Vulnerable population(s)	Yes ☒ No ☐ See Section 5.4.7
IMPs	Product name/EU MP number: Piperacillin/Tazobactam Fresenius Kabi/PRD767183 (Comparator) Substance (name/ code): PIPERACILLIN SODIUM, TAZOBACTAM SODIUM, PIPERACILLIN, TAZOBACTAM, PIPERACILLIN MONOHYDRATE/SUB03840MIG, SUB04682MIG, SUB09867MIG, SUB10849MIG, SUB237761 Strength: Tazobactam Sodium 536.6mg, Piperacillin Monohydrate 4g, Piperacillin Sodium 4.17g, Tazobactam 0.5g, Piperacillin 4g Pharmaceutical form: SOLUTION FOR INFUSION Route of administration: INTRAVENOUS USE Marketing authorisation status (MA number, MS where authorised etc): 40178 / DK Modified in relation to MA: No Max Dosage: g gram(s) Duration of use: Day Product name/EU MP number: Meropenem Fresenius Kabi/PRD2054440 (Test) Substance (name/ code): MEROPENEM TRIHYDRATE/SUB21617 Strength: Meropenem Trihydrate 1140mg Pharmaceutical form: SOLUTION FOR INJECTION/INFUSION Route of administration: INTRAVENOUS USE Marketing authorisation status (MA number, MS where authorised etc): 45320 / DK Modified in relation to MA: No Max Dosage: g gram(s) Duration of use: Day
Placebo	

AMP(s)	Yes ☐ No ☒ See Section 5.4.9.2	
Medical device(s)	Yes ☐ No ☒ See Section 5.4.9.3	
Date/version/number of the protocol(s)	Protocol(s) Document Name: D1_Protocol 2023-509703-33-00 - Submission date: 2024-03-23 - Manual version: 1.10 - System version: 3.00 Document Name: D4_Patient facing documents EQ-5D-5L - Submission date: 2024-01-12 - Manual version: 1 - System version: 1.00 Document Name: D4_Patient facing documents EQ-VAS - Submission date: 2024-02-29 - Manual version: 1 - System version: 1.00	
Date/version/number of IMPD(s) (subsection)	**Subsection**	**Date/version**
	Quality	
	Safety and Efficacy	
Date/version/number of the IB(s)	Investigator Brochure	
Date/version/number of the RSI	**SmPC** ☒ Role: Comparator - G2_SmPC Piperacillin-Tazobactam Role: Test - G2_SmPC Meropenem **Subsection of IB** ☐ -No Documents provided	**Date/version** Submission date: 2023-12-20 - Manual version: 1 - System version: 1.00 Submission date: 2023-12-20 - Manual version: 1 - System version: 1.00
Scientific Advice	Yes ☐ No ☒ If yes, CHMP ☐ NCA ☐ If yes, Date(s): -No Documents provided	
PIP	Yes ☐ No ☒ -No Documents provided	
Resubmission	Yes ☐ No ☒ If yes, provide details of previous submission(s):	
EudraCT number(s) of other CT application(s) by the sponsor for the IMP(s)		

2 INFORMATION ON THE PROCEDURE

Reporting Member State	Name of RMS and contact details: DK kf@dkma.dk
Other Member States concerned	List all:
Final AR ☒	Date: 09.04.2024

The Reporting Member State has assessed the application with regard to the following aspects (as per Art 6(1) of the Regulation):

a) Whether the clinical trial is a low-intervention clinical trial, where claimed by the sponsor;
b) Compliance with Chapter V with respect to the following:
   1. The anticipated therapeutic and public health benefits taking account of all of the following (sections 4, 5, 6 and 7):
      - the characteristics of and knowledge about the investigational medicinal products;
      - the relevance of the clinical trial, including whether the groups of subjects participating in the clinical trial represent the population to be treated, or if not, the explanation and justification provided in accordance with point (y) of paragraph 17 of Annex I to this Regulation; the current state of scientific knowledge; whether the clinical trial has been recommended or imposed by regulatory authorities in charge of the assessment and authorisation of the placing on the market of medicinal products; and, where applicable, any opinion formulated by the Paediatric Committee on a paediatric investigation plan in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council (1);
      - the reliability and robustness of the data generated in the clinical trial, taking account of statistical approaches, design of the clinical trial and methodology, including sample size and randomisation, comparator and endpoints;
   2. The risks and inconveniences for the subject, taking account of all of the following (sections 4, 5 and 7):
      - the characteristics of and knowledge about the investigational medicinal products and the auxiliary medicinal products;
      - the characteristics of the intervention compared to normal clinical practice;
      - the safety measures, including provisions for risk minimisation measures, monitoring, safety reporting, and the safety plan;
      - the risk to subject health posed by the medical condition for which the investigational medicinal product is being investigated;
      - the requirement for scientific grounds for a direct clinically relevant benefit for subjects in emergency situation trials, where the first trial-specific intervention is carried out before an informed consent is provided from the subject or from his/her legally designated representative

c) Compliance with the requirements concerning the manufacturing and import of investigational medicinal products and auxiliary medicinal products set out in Chapter IX (section 3);
d) Compliance with the labelling requirements set out in Chapter X (section 3);
e) The completeness and adequateness of the investigator's brochure (section 5).

3 QUALITY ASSESSMENT

The quality data are acceptable	☒
Overall comment/ conclusion on the quality assessment:	

4 NON-CLINICAL ASSESSMENT

The non-clinical data provided are acceptable	☒
Overall comment/ conclusion on the non-clinical assessment: ***Note***	

5 CLINICAL ASSESSMENT

The clinical aspects of the application are acceptable	☒
Overall comment/ conclusion on the clinical assessment:	

6 STATISTICAL/METHODOLOGICAL ASSESSMENT

The statistical aspects of the application are acceptable	☒
Overall comment/ conclusion on the statistical assessment:	

7 REGULATORY ASSESSMENT

The regulatory aspects of the application are acceptable	☒
Overall comment/ conclusion on the regulatory assessment:	

8 CONCLUSION OF THE RMS (as per Art 6(1) of the Regulation)

Is the overall benefit/risk ratio acceptable for approval and considered as positive for the individual subject participating in the clinical trial (**from quality, non-clinical, clinical, statistical and regulatory perspectives)?**	Yes ☒ No ☐

Assessor's comment on benefit/risk:

The EMPRESS trial is an investigator-initiated, parallel-group, randomised, open-label, adaptive clinical trial with an integrated feasibility phase. The EMPRESS trial will employ adaptive stopping rules (for superiority/inferiority/practical equivalence, and with a maximum pre-specified sample size) to increase the chance that the trial will be conclusive and response-adaptive randomisation to increase each participant's chance of being randomised to the superior intervention arm.

EMPRESS is a stand-alone clinical trial that is partially based on the methodology and core protocol for the upcoming adaptive platform trial INCEPT.

The hypothesis is that meropenem will lower mortality compared to piperacillin/tazobactam without any substantial effects on adverse outcomes. The objective of the *Empirical Meropenem vs. Piperacillin/Tazobactam for Adult Patients with Sepsis (EMPRESS) trial* is to assess the effects of empirical meropenem versus piperacillin/tazobactam on mortality and other patient-important outcomes in critically ill adults with sepsis.

The primary outcome is all-cause mortality at 30 days after randomisation.

Safety monitoring and risk minimization is considered acceptable. The trial has an iDSMB.

Design: the design is deemed acceptable and should be able to answer the proposed hypothesis by the Sponsor.

Clinical rationale: the clinical relevance for this trial has been justified by the sponsor in a sufficient manner.

Adaptive analyses will start after follow-up and data collection concludes for 400 participants and every subsequent 300 participants up to a maximum of 14,000 participants.

EMPRESS will use constant, symmetrical stopping rules for inferiority/superiority calibrated to keep the type 1 error rate at 5%. Benefit/risk: Overall the trial has an acceptable benefit risk. This clinical trial can be approved. **Danish National Medical Research Ethics Committee (VMK) has the following comment to the sponsor:** As part of the RFI response to RFI-CT-2023-509703-33-00-IN-006, the sponsor has made changes to the protocol which were not requested as a part of the RFI. These changes were considered "minor" by the sponsor; however, no specific list of the changes was provided. For the future submissions, the sponsor should be aware that only the changes specified in the considerations in the RFI may be carried out and changes not directly addressing considerations in the RFI should be submitted subsequently as a substantial or non-substantial modification depending on the changes to be implemented.

9 FINAL OVERALL CONCLUSION OF THE RMS (as per Art 6(3) of the Regulation)

The Investigator's brochure is complete and adequate	Yes ☐ No ☐
For low-interventional trials only: The clinical trial fulfils the conditions for a low-intervention trial	Yes ☒ No ☐
The conduct of the clinical trial is **acceptable** in view of the requirements set out in this Regulation	☒
The conduct of the clinical trial is acceptable in view of the requirements set out in the Regulation, but subject to compliance with **specific conditions** which shall be specifically listed in that conclusion	☐
The conduct of the clinical trial is **not acceptable** in view of the requirements set out in this Regulation	☐
The final agreed wording of conditions or rejects to be sent to sponsor:	

Final document versions approved:

<table>
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