Protocol Synopsis

EUCT Trial number: 2023-509703-33-00. Title: Empirical Meropenem versus Piperacillin/Tazobactam for Adult Patients with Sepsis (EMPRESS) trial

Rationale
Piperacillin/tazobactam and meropenem are commonly used as empirical agents for patients with sepsis or septic shock. In a recent systematic review comparing empirical and/or definitive treatment with piperacillin/tazobactam versus meropenem for patients with severe bacterial infections, including sepsis and septic shock, it was shown that piperacillin/tazobactam may be associated with less favourable outcomes based on low or very low certainty of evidence. At present, it is unclear if piperacillin/tazobactam and meropenem are equally effective and safe for adults with sepsis.

Objective
To assess the effects of empirical meropenem vs. piperacillin/tazobactam on mortality and other patient-important outcomes in critically ill adults with sepsis.

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

Secondary trial endpoints
The secondary outcomes are the occurrence at least one serious adverse reaction (i.e., anaphylactic reaction to intravenous (IV) piperacillin/tazobactam or meropenem, invasive fungal infection, pseudomembranous colitis, or toxic epidermal necrolysis) within 30 days of randomisation; the occurrence of new isolation precautions due to resistant bacteria within 30 days of randomisation; days alive without life support (i.e., invasive mechanical ventilation, circulatory support, or renal replacement therapy) from randomisation to day 30 and 90; days alive and out of hospital from randomisation to day 30 and 90; all-cause mortality at day 90 and 180; and health-related quality of life at day 180 using EQ-5D-5L index values and EQ VAS. The feasibility outcomes are time to completion of feasibility phase (i.e., 200 participants randomised), recruitment proportion, proportion of participants without consent to the use of data, protocol adherence, and retention proportion.

Trial design
Investigator-initiated, international, parallel-group, randomised, open-label, adaptive clinical trial with an integrated feasibility phase. The EMPRESS trial will employ adaptive stopping rules 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.

Trial population
We will screen all adult patients who are critically ill with sepsis and who have indication for empirical treatment with meropenem or piperacillin/tazobactam. We will exclude patients with preceding intravenous treatment with meropenem or piperacillin/tazobactam for 24 hours or more; known pregnancy; known hypersensitivity or allergy to beta-lactam antibiotics; suspected or documented central nervous system infection; known infection or colonialisation with microorganism with acquired resistance to meropenem or piperacillin/tazobactam; current use of valproate; co-enrolment in other interventional trial where protocols collide; previous randomisation in EMPRESS; informed consent following inclusion expected to be unobtainable; and patients who are under coercive measures.

Experimental intervention

IV meropenem 1 g three times daily for up to 30 days.

Control intervention

IV piperacillin/tazobactam 4/0.5 g four times daily for up to 30 days.

Statistics and stopping rules

The trial will be analysed using Bayesian statistical methods with the primary analyses conducted in the intention-to-treat population. Outcomes will be analysed using logistic and linear regression models adjusted for relevant baseline characteristics and neutral and weakly informative to somewhat sceptical priors. Results will be presented as adjusted sample average treatment effects using both absolute (risk and mean differences) and relative (risk ratios and ratios of means) differences with 95% credible intervals and probabilities of benefit/harm. 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. Adaptations will be based on data for the primary outcome. EMPRESS will use constant, symmetrical stopping rules for inferiority/superiority calibrated to keep the type 1 error rate at 5%. Further, the trial will be stopped for practical equivalence if there is >90% probability that the absolute risk difference between arms is less than 2.5%-points. Restricted response-adaptive randomisation will be used to ensure minimum allocation probabilities of 40% to both groups.

Missing data will be imputed, and relevant secondary analyses, sensitivity analyses, and analyses of heterogeneity in treatment effects according to pre-defined baseline characteristics will be undertaken once the trial has been stopped.

Trial design performance metrics

Performance characteristics were evaluated assuming a 25% event probability for the primary outcome in the piperacillin/tazobactam arm and scenarios with no, small, and large differences corresponding to event probabilities of 25%, 22.5%, and 20% in the meropenem arm, respectively. The expected (mean) sample sizes under these scenarios are 5189, 5859, and 2570, respectively. The probabilities of conclusiveness (i.e., superiority or equivalence) are >99% in all scenarios, and the probabilities of superiority (power) are 72% and >99% in the small and large difference scenarios, respectively.

Estimated timeline

- Primo 2024: authority approvals and first participant randomised
- Primo 2025: feasibility phase analysis concluded
- Medio 2028: expected inclusion of the last participant if trial continues to the expected sample size in the small-difference scenario (i.e., the largest expected sample size under the three different scenarios assessed) (section 19.9)
- Medio 2032: expected inclusion of the last participant if the trial continues to the maximum sample size (n=14,000) (section 19.9)
- Approximately 3 months after inclusion of the last participant: primary report on 30-day outcomes submitted
- Approximately 6 months after inclusion of the last participant: report on 90-day outcomes submitted
- Approximately 9 months after inclusion of the last participant: report on 180-day outcomes submitted