**Meropenem vs standard of care for treatment of neonatal late onset sepsis**

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**Key words**

Carbapenem resistance, cefotaxime, gentamicin, sepsis diagnosis

# Abstract

**Background**

Meropenem is used for treatment of late onset sepsis (LOS) but is not licensed in neonates. We aimed to compare the efficacy and safety of meropenem to standard of care (SOC) in infants aged <90 days with LOS.

**Methods**

In an open-label, superiority trial we randomly assigned infants with clinical or culture proven LOS in a 1:1 ratio to receive meropenem or SOC (ampicillin+gentamicin or cefotaxime+gentamicin) for 8-14 days. The primary outcome was treatment success (survival, no modification of allocated therapy, resolution/improvement of clinical and laboratory markers, no need of additional antibiotics and presumed/confirmed eradication of pathogens) at test-of-cure visit (TOC) in full analysis set. Stool samples were tested at baseline and day 28 for carbapenem-resistant Gram-negative organisms (CRGNO).

**Results**

In total 136 patients in each arm were randomised; 140 (52%) were culture-positive. Success at TOC was achieved in 44/136 (32%) in the meropenem arm vs 31/135 (23%) in the SOC arm (p=0.087); 17/63 (27%) vs 10/77 (13%) in those with positive cultures (p=0.022). Adverse events occurred in 72% and serious adverse events in 17% of patients, the mortality rate was 6%. Cumulative acquisition of CRGNO by day 28 occurred in 4% in the meropenem and 12% in the SOC arm (p=0.052).

**Conclusions**

Meropenem was not superior to SOC in achieving the primary endpoint but resulted in improved outcomes in patients with culture-proven LOS. Meropenem did not select for CRGNO colonisation.

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# Introduction

Despite significant changes in neonatal care over the last several decades, late onset sepsis (LOS) is one of the leading causes of neonatal morbidity and mortality in developing and highly developed countries.1-3 The early use of broad-spectrum antibiotics remains the cornerstone for the treatment of LOS. However, which antibiotics should be used is still debatable, as relevant studies were conducted more than 20 years ago, were single centre or country, insufficiently powered, evaluated antibiotics not in clinical use anymore and had variable inclusion/exclusion criteria and outcome measures.4,5 As a result, most antibiotics are prescribed off-label in neonates6,7 and treatment guidelines are based on expert opinion rather than on evidence from randomised controlled trials (RCT).8 We recently showed that 49 different treatment regimens were used for the empiric treatment of LOS in 111 patients across Europe.9 The issue is now further complicated by the rise of antibiotic resistance in NICUs worldwide10 and the paucity of new antibiotics entering the market.11-13

Meropenem a broad-spectrum carbapenem has been used off-label in NICUs for more than a decade14 but firm dosing recommendations or efficay/safety has not been established. The advantage of meropenem over standard of care (SOC) might be its wider antibacterial coverage and the use of mono- instead of combination therapy, but there is a potential risk of selection of carbapenem-resistant Gram-negative organisms (CRGNO)15.

The safety and effectiveness of meropenem was recently demonstrated in a single-arm study including 200 infants <91 days with suspected or confirmed intraabdominal infections; only 11% received meropenem as monotherapy and 15% had positive blood cultures.16 Meropenem was included in the European Medicines Agency (EMA) priority list of off-patent drugs for which studies in neonates are requested (http://www.ema.europa.eu/docs/en\_GB/document\_library/Other/2013/05/WC500143379.pdf).

We compared the efficacy and safety of meropenem monotherapy with a predefined SOC regimen for the treatment of LOS. The distribution of causative microorganisms with their antibiotic susceptibility and mucosal colonisation with CRGNO were also evaluated.

# Methods

## Study design and participants

NeoMero-1 was an open-label RCT conducted in 18 NICUs in Estonia, Greece, Italy, Lithuania, Spain and Turkey17 and included infants with a postnatal age (PNA) of ≤90 days. Culture-confirmed bacterial LOS was defined as a positive culture from a normally sterile site together with at least one abnormal clinical or laboratory parameter within the 24 hours prior to randomisation (Appendix 1).17 Clinical LOS criteria were based on postmenstrual age (PMA). If PMA was >44 weeks the International Paediatric Sepsis Consensus Conference criteria had to be met.18 For patients with PMA ≤44 weeks the criteria defined by the EMA Expert Meeting on Neonatal and Paediatric Sepsis4,17 were used and the presence of at least two clinical and two laboratory parameters were required (Appendix 1). Main exclusion criteria were use of systemic antibiotics for more than 24 hours within the 7 days prior to randomisation (except treatment failures), meningitis and/or presence of microorganisms suspected or known to be resistant to study antibiotics.

The local Ethics Committees approved the study and parents/guardians signed informed consent prior to randomisation.

## Interventions and study visits

Meropenem (Chiesi Farmaceutici S.P.A.) was given via 30-minute infusion at a dose of 20 mg/kg q8h with the exception of those with gestational age (GA) <32 weeks and PNA <2 weeks, who received the same dose q12h with the possibility to reduce dosing interval to q8h from a PNA of two weeks. Ampicillin, cefotaxime and gentamicin were administered according to the British National Formulary for Children (www.bnfc.org). The concomitant use of other systemic antibiotics except vancomycin, teicoplanin or linezolid if started pre-randomisation, was not allowed.

Patients were examined at Day 0 (screening and randomisation), Day 3, end of antibacterial therapy (EOT) and test of cure (TOC) visit performed 2±1 days after EOT for patients treated with antibiotics for the predefined duration. Short-term follow-up was performed on Day 28 by on-site visit or telephone call.

Microbiological samples were taken at baseline, on Day 3, on appearance of any new signs suggestive of LOS and repeated until the relevant microorganisms were no longer detected. Samples were processed at local laboratories according to their own guidelines. In a post-hoc analysis two experts (IL, JG) reviewed susceptibility data and categorised organisms as susceptible, non-susceptible to study antibiotics, or not possible to categorise. Perirectal swabs were collected within 72 hours of baseline, at EOT and at Day 28 visit or NICU discharge, and stored locally at -80°C. The samples were analysed in the Department of Medical Microbiology of St George’s Hospital, London for carbapenem resistant microorganisms using selective media. The isolate was considered CRGNO if phenotypic resistance according to EUCAST criteria was detected to meropenem or if *Stenotrophomonas maltophilia* was isolated, and considered to be highly CRGNO if meropenem MIC was ≥8 mg/L. Acquisition of CRGNO during the study was defined as not detected at baseline but found in subsequent colonisation cultures.

Hearing was assessed according to local protocol between EOT and Day 28 visit. Cerebral ultrasound (and if persistently abnormal, magnetic resonance imaging or computed tomography) was undertaken at any time between EOT and Day 28 visit.

## Outcomes

The composite primary endpoint was assessed at the TOC visit and defined as success if (1) the patient was alive, and (2) all baseline clinical and laboratory parameters that defined LOS were resolved or improved, (3) there was no need to continue antibiotics, and the baseline microorganisms were eradicated or presumably eradicated with no new microorganisms identified, and (4) allocated therapy (AT) was given for 8 to 14 days without any modification for more than 24 hours.

The secondary outcomes were safety, clinical and laboratory response on Day 3, and EOT, survival at Day 28, duration of NICU stay, presence of hearing disturbances and abnormalities in brain ultrasound, acquisition of CRGNO in rectal swabs and occurrence of relapses or new infections after successful outcome at TOC visit until Day 28. Clinical relapses were defined as recurrence of LOS together with initiation of a new course of antibiotic treatment, and microbiological relapse as an isolation of a phenotypically similar organism from a normally sterile site in a patient with signs of infection.

## Randomisation

Patients were centrally randomised using a computer generated list (1:1 ratio) to either meropenem or one of the SOC regimens (ampicillin + gentamicin or cefotaxime + gentamicin) chosen by each site prior to the start of the study. Patients were stratified by SOC regimen and use of systemic antibiotics for LOS in the 24 hours prior to randomisation.

## Statistical analysis

We estimated that failure rate in the control arm would be 36%.2 The required sample size to show a reduction of failure rate from 36% to 23% with 80% power in the meropenem arm using a 2-sided test at an alpha level of 0.05, was 220 patients per arm. An ineligibility rate of 15% to 20% was anticipated. The sample size was thus conservatively increased to 275 subjects per arm to compensate for the dilution effect. Recruitment was closed on November 30, 2014 with 272 patients randomised, due to expiration of funding by the European Commission. Considering the unexpected overall high rate of failures (70% instead of 36% due to frequent modifications of AT) and the very low percentage of ineligible subjects, we calculated that the study had already yielded 80% power to show a 20% reduction of the failure rate, well beyond the objective of the trial.

The primary analysis was performed in all randomised patients (full analysis set - FAS) and in patients with culture confirmed LOS. Proportions of participants with successful outcome were compared by using a logistic regression model adjusted for the stratification factors. Additional efficacy analyses were performed by ignoring the changes in AT due to safety reasons or all changes of AT. Post-hoc analyses (decided before un-blinding) were performed by allowing a duration of AT between 7 and 14 days. Two-sided P-values <0.05 were considered to indicate statistical significance.

All analyses were performed with the use of SAS software, version 9.3 (SAS institute).

The study was overseen by an independent data safety monitoring board and registered in EudraCT (2011-001515-31) and in clinicaltrials.gov (NCT01551394).

# Results

## Study patients and treatment

A total of 277 infants were consented and 136 in each arm were randomised from September 3, 2012 to November 30, 2014 as shown in Figure 1. Of 271 patients analysed for efficacy, 140 (52%) had culture-proven LOS.

**Figure 1.** Flowchart of the study NeoMero-1. EOS – early onset sepsis; SOC – standard of care; FAS – full analysis set; AT – allocated therapy; LOS – late onset sepsis; FU – follow-up

277 patients assessed for eligibility

5 were ineligible:

1 had EOS

2 had <2 laboratory criteria

1 had no clinical criteria/no consent

1 was data management failure

272 randomised

136 assigned to meropenem

136 received meropenem

136 assigned to SOC

-48 assigned to ampicillin+gentamicin

-88 assigned to cefotaxime+gentamicin

131 received SOC

5 did not receive SOC

1 consent violation

3 did not receive AT

1 received gentamicin 3 days after randomisation

135 included in the FAS

77 with culture confirmed LOS

132 included in the safety set

136 included in the FAS

63 with culture confirmed LOS

136 included in the safety set

13 discontinued study

10 died

2 withdraw consent

1 no short term FU visit

123 evaluated short term FU visit

75 had on-site visit

48 had telephone interview

7 discontinued study

7 died

128 evaluated short term FU visit

91 had on-site visit

38 had telephone interview

As shown in Table 1 the baseline characteristics of patients were well balanced between study groups. They were also similar when patients were sub-grouped according to prior antibiotic treatment, culture proven LOS or presence of Gram-positive or Gram-negative LOS (data not shown). In total 200 (74%) patients were premature.

**Table 1**. Characteristics of study population in meropenem and SOC arm at baseline (FAS population). Data are presented as numbers (%) if not stated otherwise

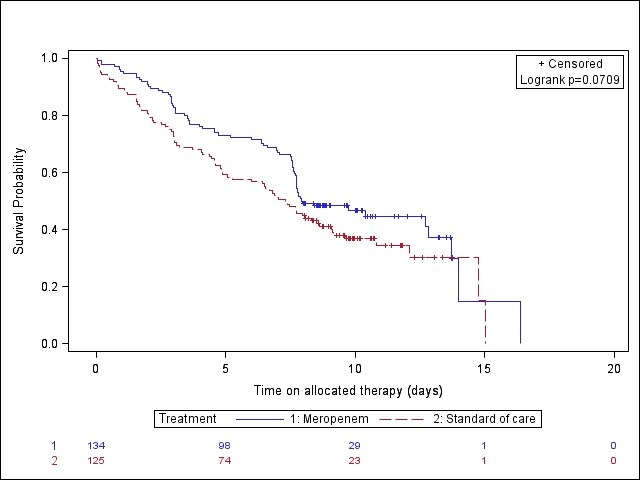
|  |  |  |
| --- | --- | --- |
| Characteristic | Meropenem  N = 136 (%) | SOC  N = 135 (%) |
| **Demographics** | | |
| Median GA weeks (IQR) | 31.6 (26.4 - 37.3) | 30.6 (27.0 - 36.3) |
| <28 weeks | 41 (30%) | 41 (30%) |
| 28-32 weeks | 31 (23%) | 38 (28%) |
| 32-37 weeks | 26 (19%) | 23 (17%) |
| >37 weeks | 38 (28%) | 33 (24%) |
| Median PNA days (IQR) | 16 (8 - 30) | 16 (8 - 30) |
| Median PMA days (IQR) | 34.5 (30.5 - 40.7) | 33.8 (29.9 - 40.1) |
| PMA > 44 weeks n (%) | 5 (3.7%) | 6 (4.4%) |
| Male n (%) | 72 (53%) | 72 (53%) |
| Median (IQR) birth weight (g) | 1540 (840 - 2830) | 1340 (850 - 2530) |
| -BW <1000 g (n) | 45 (33%) | 51 (38%) |
| -BW <1500 g (n) | 67 (49%) | 80 (59%) |
| -BW >2500 g (n) | 43 (32%) | 37 (27%) |
| SGA \*n (%) | 33 (24%) | 34 (25%) |
| **Peri- or neonatal conditions** | | |
| Multiple births | 29 (21%) | 32 (24%) |
| Medically assisted fertilisation | 21 (16%) | 15 (11%) |
| Antenatal steroids | 65 (48%) | 71 (53%) |
| Congenital conditions: | | |
| -Respiratory | 18 (13%) | 17 (13%) |
| -Cardiovascular | 13 (10%) | 11 (8%) |
| -Gastrointestinal | 8 (6%) | 10 (7%) |
| -Neurological | 8 (6%) | 4 (3%) |
| -Other | 6 | 6 |
| Surgery | 23 (17%) | 29 (21%) |
| Arterial catheters | 27 (20%) | 32 (24%) |
| Central Venous Catheter | 64 (47%) | 69 (51%) |
| Mechanically ventilated | 75 (56%) | 74 (55%) |
| Received antibiotics prior to randomisation | 100 (74%) | 98 (73%) |
| Median duration of prior antibiotic therapy (h) | 18.5 (9.0 - 22.1) | 16.0 (8.3 - 21.2) |
| Received meropenem prior to randomisation | 35 (26%) | 29 (21%) |

\* defined by birth weight ≤ 10 th percentile

Patients of PMA ≤44 weeks had a median (IQR) of 3 (3-4) clinical and 2 (2-3) laboratory signs at baseline, in each arm. Clinical or laboratory signs observed in more than 50% of patients were impaired peripheral perfusion, mottled skin, CRP >15 mg/L and lactate >2 mmol/L (Appendix 2).

AT was given according to protocol in 134 (99%) patients in the meropenem and 127 (94%) in SOC arm. Of these, 65 (48%) and 67 (50%) received AT alone and 69 (51%) and 58 (43%) received concomitantly glycopeptides in the meropenem and SOC arms, respectively. The median duration of AT was comparable in both arms (7.9 [IQR 4.0-9.7] days in the meropenem vs 7.0 [IQR 2.5-9.6] days in the SOC arm; p=0.09) but the duration of any antibiotic therapy was shorter in the meropenem than in the SOC arm (9.0 [IQR 7.8-12.0] vs 10.4 [IQR 8.5-13.3] days, respectively; p=0.009) (Figure 2).

**Figure 2.** Time to modification of allocated therapy (p = 0.0712; log-rank test). Blue indicates meropenem and red SOC



## Causative microorganisms

Baseline blood cultures were positive for 63/132 (46%) patients in the meropenem and 77/135 (57%) in the SOC and are listed in Table 2. Of all Gram-negative microorganisms a total of 46 (94%) were susceptible to meropenem, 17 (59%) to cefotaxime, 2 (4%) to ampicillin and 32 (65%) to gentamicin.

**Table 2.** Causative agents of LOS and their susceptibility to study antibiotics

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Microorganism | **Meropenem** | | **SOC** | |
| Total  N = 63 (%) | Susceptible to meropenem  N (%) | Total  N = 77 (%) | Susceptible to ≥1 antibiotic of SOC N (%) |
| **Gram-positive organisms** | **31 (49)** | **8 (26)** | **44 (57)** | **12 (27)** |
| CONS | 22 (35) | 3 (14) | 35 (45) | 4 (11) |
| -*S. epidermidis* | 14 (22) | 2 (14) | 25 (32) | 4 (16) |
| -Other CoNS | 8 (13) | 1 (13) | 10 (13%) | 0 |
| *S. aureus* | 5 (8) | 3 (60) | 5 (6) | 5 (100) |
| -MRSA | 2 (3) | 0 | 1 (1) | 1 (100) |
| GBS | 2 (3) | 2 (100) | 3 (4) | 3 (100) |
| *Enterococcus* | 1 (2) | 0 | 1 (1) | 0 |
| Other Gram positives | 1 (2) | 0 | 0 | - |
| **Gram-negative organisms** | **24 (38)** | **22 (92)** | **25 (32)** | **18 (72)** |
| *Enterobacteriaceae* | 22 (35) | 20 (91) | 21 (27) | 16 (76) |
| -          -*Enterobacter* spp. | 8 (13) | 7 (78) | 10 (13) | 6 (55) |
| -          -*K. pneumoniae* | 7 (11) | 6 (86) | 4 (5) | 3 (75) |
| -          -*K. oxytoca* | 4 (6) | 4 (100) | 3 (4) | 3 (100) |
| -          -*Serratia* spp. | 0 | - | 1 (1) | 1 (100) |
| Non-fermentative | 2 (3) | 2 (100) | 2 (3) | 1 (50) |
| -          -*Pseudomonas* spp. | 2 (3) | 2 (100) | 2 (3) | 1 (50) |
| Other Gram-negative | 0 | - | 2 (3) | 1 (50) |
| **Mixed** | **8 (13)** | **2 (25)** | **8 (10)** | **2 (25)** |

## Primary outcome

In the FAS the proportion of patients with a successful outcome at TOC as well as each component of composite endpoint was comparable in both study groups. In the culture-confirmed LOS the success rate of meropenem was greater than that of SOC (Table 3).

**Table 3.** Outcome at the TOC in FAS and culture-confirmed LOS. Data are presented as numbers (%) if not stated otherwise

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Primary endpoint (FAS)** | | **Culture-confirmed LOS** | |
| Meropenem  N = 136 | SOC  N = 135 | Meropenem  N = 63 | SOC  N = 77 |
| Treatment success at TOC | 44 (32)\* | 31 (23) | 17 (27)\*\* | 10 (13) |
| **Reasons for failure** | | | | |
| Modification of allocated therapy | 78 (57) | 85 (63) | 43 (68) | 59 (77) |
| Clinical signs not resolved and/or microbiological failure | 29 (21) | 31 (23) | 12 (19) | 18 (23) |
| Death before TOC | 10 (7) | 6 (4) | 3 (5) | 4 (5) |
| Antibiotics not started or not-allowed antibiotics given | 2 (1) | 10 (7) | 2 (3) | 4 (5) |

\*p=0.09, OR 95%CI: 1.6 (0.9 – 2.8); \*\*p=0.02, OR 95% CI: 3.0 (1.2 – 7.5) (logistic model including factors of stratification)

The main reason for failure at TOC was modification of AT, which was more frequent in the SOC than in the meropenem arm (Table 3). The main reason for modification/discontinuation was completion of AT before Day 8 (38%) (Appendix 3).

In a post-hoc analysis of the FAS population, by permitting a duration of AT between 7 and 14 days, a successful outcome was more frequent in the meropenem than in the SOC arm (65/135, 48% vs 37/135, 27%; p=0.001). There were no differences in success rate between meropenem and SOC arms if changes in the AT for safety reasons were ignored (32% vs 23%) or if all changes of AT were ignored (41% vs 37%, respectively).

### Secondary outcome

The groups did not differ in terms of secondary outcome (Appendix 4). At Day 28 9/61 (15%) in the meropenem arm and 20/70 (29%) in the SOC arm did not pass auditory tests (p=0.06). No differences were observed in abnormalities on cerebral ultrasound - 27/108 (25%) vs 30/110 (27%), respectively.

Rectal swabs were available for 130, 101 and 95 patients in the meropenem and for 127, 94, 103 patients in the SOC arm at baseline, EOT and Day 28/NICU discharge visit, respectively. Cumulative acquisition of CRGNO by Day 28 was observed in 4/94 (4%) in the meropenem and in 12/101 (12%) in the SOC arm (p=0.05) and highly CRGNO in 3/94 (3%) and 7/100 (7%), respectively. When comparing patients who received at least one dose of meropenem (n=170), regardless of study arm, with those not receiving meropenem, the acquisition of CRGNO in general or highly-resistant strains was similar (8/124 (6%) vs 8/71 (11%) for CRGNO and 5/124 (4%) vs 5/70 (7%) for highly CRGNO.

A total of 193 patients (72%) had at least one adverse event (AE). All-cause AEs totalled 304 and 317, with 47 and 48 serious AEs (SAEs) in the meropenem and SOC arms, respectively. The AEs seen in ≥3% of patients are listed in Appendix 5. Seizures, a recognised side effect of carbapenems, were seen in four (3%) patients in the meropenem arm and one (<1%) in the SOC arm.

Ten patients in the meropenem and seven in the SOC arm died with an overall mortality rate of 6%. All but three patients who died had a BW <1200g.

# Discussion (733)

We report the results of the largest RCT in LOS, undertaken in critically ill predominantly premature neonates in Europe. We show an overall low mortality and a similar efficacy of meropenem to commonly used SOC combinations based on a complex composite primary endpoint in the FAS population. If only patients with culture-proven LOS were analysed, the efficacy of meropenem was significantly greater than that of SOC. Allowing a minimal duration of AT of 7 days, (instead of 8 days) favourable outcome was significantly more frequent in the meropenem than in SOC arm. Patients in the meropenem group had a shorter duration of antibacterial therapy than those in the SOC. The two study arms were similar in terms of AEs and acquiring colonisation by CRGNO.

NeoMero1 differed from previous studies in LOS. First, it was a multicentre study in contrast to previous single center and/or national studies.4,16 Second, the demanding inclusion criteria resulted in selection of a very sick patient population (e.g. 55% mechanically ventilated, 35% with BW of <1000g) compared to previous studies.4 Third, only 2% of patients did not have LOS and altogether 52% had culture-proven LOS as opposed to 15% in a recent study of cIAI.16 Fourth, NeoMero1 had an ambitious primary endpoint that in addition to resolution or significant improvement of clinical and laboratory criteria, did not allow any changes of AT including deviations from fixed treatment duration, dosing and/or addition of another antibiotic, in contrast to more liberal or less specific endpoints in previous studies.4,16

The most intriguing finding of this study, in comparison to others, was a relatively low success rate in terms of the composite primary endpoint in both study arms while mortality rates were similarly low to those reported in a previous meropenem study in cIAI.16 The low efficacy rate was mainly driven by modification of AT and most of all by its fixed duration of between 8 and 14 days. The effect of the latter was clearly demonstrated in the post-hoc analysis in which reducing the allowed treatment duration by just one day (from 8 to 7 days) improved the success rate from 32% to 48% in the meropenem and from 23% to 27% in the SOC arms. The optimal duration of antibiotic therapy in LOS is not known.19

In contrast to previous studies, we did not find an association between carbapenem use and CRGNO colonization. Of note, NeoMero1 was a RCT with strict inclusion criteria, in contrast to previous retrospective and/or observational studies which included all patients without restriction 20-22. We should emphasize though, that the relatively short duration of meropenem treatment in the NeoMero1 study may be relevant. Clock *et al*. recently showed in an observational study that meropenem treatment >10 days but not >5 days was associated with increased colonisation with Gram negative multi-drug resistant bacteria.15

The study has some limitations. First, it was an open label study with the risk of investigator-induced bias when evaluating the primary endpoint or changing AT. An open label design was selected because a dummy infusion in critically ill, premature baby cannot be justified. We also note that the most appropriate targets for meropenem are Gram-negative microorganisms while only about half of the recruited patients had Gram-positive infections. We believe that until rapid and reliable methods, which allow early differentiation between Gram-negative and Gram-positive infections become available, recruitment of mixed populations into similar studies is unavoidable.

NeoMero1 is the first adequately powered RCT for LOS since the 1970s4,5 but several outstanding issues require further studies to be done. The question of best treatments for LOS in developing countries and/or in areas with high antibiotic resistance rates was not addressed as 92% of microorganisms were susceptible to meropenem and 72% at least to one component of SOC. Furthermore RCTs in LOS are challenging due to a vulnerable population and lack of validated disease criteria and endpoints.4,5,23 There is an urgent need for cooperation between academia, pharmaceutical industry and regulators in innovating clinical research in neonatology, including defining alternative and more feasible study designs (e.g. PK/PD, rather than solely clinical endpoint based designs, enabling modelling/simulation and extrapolation from studies in adults).5,23

**Conclusion:** In predominantly premature critically ill infants with LOS, meropenem treatment was not superior to SOC in terms of primary endpoint at TOC. Meropenem mono-therapy was more efficacious than SOC in patients with culture-proven LOS, resulted in slightly shorter treatment duration and did not select for CRGNO.

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