



PROJECT FINAL REPORT

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1 - Final Publishable Summary Report

1.1 - Executive Summary

Previous studies have demonstrated the high frequency of bacterial sepsis in neonates and infants admitted to neonatal intensive care unit (NICU), often associated with serious complications or death. Many pathogens capable of causing nosocomial bacterial sepsis in neonates and young infants have developed resistance to the antibiotics considered of choice for treatment. Meropenem is an antibiotic that can overcome antimicrobial resistance, generally being safe and well tolerated with very good pharmacokinetic (PK) and pharmacodynamic characteristics. However, it has not yet been registered in neonates and infants aged less than 3 months due to limited data on its PK characteristics, activity and safety.

The core objectives of NeoMero were to evaluate the PK, safety and efficacy of meropenem in comparison to standard care in neonates and infants aged less than 3 months suffering from late-onset sepsis and describe its PK and safety in bacterial meningitis (BM). To achieve these aims, clinical trials on meropenem use for late-onset sepsis and BM were performed. Using previously published PK models, a sampling scheme was designed and population PK analysis used to identify relevant PK parameters. Safety was evaluated through analysis of haematological and biochemical parameters and monitoring adverse events. Appearance of resistant bacteria was monitored through regular cultures during therapy. Clinical assessments including neurological and developmental evaluations (Bayley Scales) are being undertaken at two years of age. Immunologic and genetic studies were also performed to evaluate predictors of susceptibility to infections and response to therapy. In addition, resistant bacterial isolates were studied to elucidate the mechanism of resistance and sensitive PCR assays were used to test culture negative samples. A Paediatric Investigators Plan was developed and a new RfM will be submitted to the EMA in September 2015.

1.2 - Summary description of project context and objectives

Bacterial sepsis is a relatively common disease in the first days of life and poses a significant threat to neonates, particularly those who are born prematurely. Up to 30% of very low birth weight infants experience an early onset or late onset sepsis prior to discharge from the nursery, and bacterial meningitis (BM) is a possible complication of neonatal sepsis. Incidence of BM ranges from 0.25 to 1 per 1,000 live births and it occurs in approximately 25% of neonates with bacteremia. Group B beta- haemolytic streptococci (GBS), Gram negative enteric bacteria, and *Listeria monocytogenes* are the most common agents causing BM in the neonatal period. Gram negative rods account for 30%-40% of sepsis cases, with *Escherichia coli* being the most common organism isolated (50% of all Gram negative isolates), followed by *Klebsiella* spp., other organisms that have been implicated in sepsis and BM include *Enterobacter* spp., *Citrobacter* spp., *Pseudomonas* spp. and *Serratia* spp. Finally, sepsis with organisms such as coagulase negative *Staphylococci* appear common in neonates requiring prolonged hospitalization, central venous catheters, parenteral nutrition and ventilator support.

Neonatal sepsis and BM are serious diseases that can be followed by death in 10% to 30% of the cases. Moreover, both diseases can cause long-term disabilities in an additional 20% to 50% of patients. Long-term sequelae among survivors include hydrocephalus, developmental delay, cerebral palsy, seizures requiring anticonvulsant therapy, visual impairment and, above all, hearing loss. Antibiotic therapy remains the most effective treatment for bacterial sepsis and BM. It should be aggressive, based on antibiotics active against the possible infecting pathogen, and administered in doses able to achieve a bactericidal concentration in the blood and, when BM is diagnosed, also in the cerebrospinal fluid (CSF). Considering the large variability of the pathogens possibly involved in neonatal bacterial sepsis and BM, the initial choice of intravenous antibiotics for neonates with these diseases must cover both Gram positive and Gram negative organisms. Once a pathogen has been isolated, antibiotic therapy can be tailored to the pathogen. However, the initial therapy may be critical for the final prognosis of neonatal bacterial sepsis and BM because a delay in achieving blood and CSF sterilization has been shown to be associated with an increased risk of relapses and neurological sequelae, respectively.

In recent years, many pathogens capable of causing neonatal bacterial sepsis and BM have developed high resistance to the antibiotics considered of choice to treat these diseases. This is especially so in cases of late-onset and probable nosocomial origin, and most worrying in the context of Gram negative bacteria.

Gram negative bacteria have developed resistance through a number of advantageous mutations. One increasingly important method seen is acquisition of inactivating enzymes such as extended-spectrum β -lactamases (ESBLs), plasmid-encoded enzymes that have mutated from the more common β - lactamases. The pattern of ESBL prevalence within Europe has increased dramatically in recent years. The presence of ESBL-producing pathogens has considerable clinical significance, since they are associated with higher morbidity and mortality than non-ESBL producers (Siegel, R.E, 2008). Further, plasmids responsible for ESBL production frequently carry genes encoding resistance to other drug classes (for example, aminoglycosides and fluoroquinolones), leading to often complex multidrug resistant phenotypes. Antibiotic options in the treatment of ESBL-producing organisms are extremely limited. European surveillance in adults shows widespread rises in cephalosporin resistance in *E. coli*, along with dramatic increases in fluoroquinolone resistance. Treatment is usually restricted to the carbapenems, (imipenem, meropenem and ertapenem), and the glycylcycline, tigecycline. However, even carbapenem-resistant isolates, containing carbapenemases have recently been reported (Nordmann, P., Poirel, L., 2002). Further, the precise

mode of spread of ESBLS has not been defined, but it is clear that they are becoming more common in the community as well as in hospitals, making control even more difficult. Outbreaks of multi-resistant Gram-negative organisms are increasingly being reported from neonatal intensive care units (NICU's).

The rise in resistance to conventional antibiotics is coupled with a reduction in the pharmaceutical development of novel antibiotics against Gram-negative bacteria, to replace those that are now less effective. This makes the choice of empiric therapy difficult and clinicians are now challenged to employ a combination of strategies for effective prevention and treatment of such infections.

Meropenem, a drug included in the class of carbapenems, is an attractive candidate for empiric therapy of late-onsets sepsis and BM in the first 3 months of life because it is active in vitro against a broad range of Gram-negative and Gram-positive aerobic and anaerobic bacteria including *Listeria* sp.. It appears to have significant efficacy and to be safe and well tolerated, with good pharmacokinetic (PK) and pharmacodynamic (PD) characteristics in older children and adults with sepsis or BM. Adequate CSF penetration has been noted for intravenous single doses of 20-40 mg per kg of body weight in humans with inflamed meninges. However, there are few data on its blood PK and PD characteristics, no data on its CSF penetration and little information on its activity and safety in the first months of life, and it is unlicensed for this indication.

Meropenem has been included in the revised EMEA “priority list for studies into off patent paediatric medicinal products” (Doc. Ref.EMEA/226983/2008), the list of off-patent drugs intended to address unmet therapeutic needs in children and to increase information on drug uses in paediatrics. Data on PK, efficacy and safety of meropenem in patients below 3 months of age are requested. This aspect is of relevance because, according to the Paediatric Regulation, ‘medicinal products no longer covered by a patent can be eligible for PUMA (Paediatric Use Marketing Authorisation), which will cover exclusively therapeutic indications which are relevant for use in paediatric populations.

Meropenem has been off patent for many years and largely used off label for the treatment of neonatal sepsis and meningitis without sufficient data on PK, safety and efficacy. To overcome these shortcomings, the NeoMero project aimed to evaluate the PK characteristics, efficacy and safety of meropenem in comparison to standard treatment in neonates and infants aged <3 months suffering from late-onset sepsis and BM. The results obtained will represent a decisive expansion of the available data on the subject, facilitating and expediting the development of the corresponding PUMA.

In order to reach these aims, a comprehensive work plan has been devised, which included both sepsis and meningitis trials, as well as PK, immunology, genetics and microbiology studies. Regulatory and dissemination activities are also encompassed in the project scope to ensure appropriate use of the results obtained. Two clinical studies (NeoMero1 and NeoMero2) were performed by the consortium.

The **primary objective of the NeoMero1 study project** was:

- To compare the efficacy of meropenem to the standard of care (SOC) in the treatment of clinical or confirmed LOS in infants \leq 90 days of postnatal age at TOC visit

The primary aim of NeoMero2 was:

- To describe the PK (plasma and cerebrospinal fluid) of meropenem in infants \leq 90 days of postnatal age with probable or confirmed BM and to characterize the safety profile of

meropenem in the treatment of infants \leq 90 days of postnatal age with probable or confirmed BM.

The **secondary objectives** were:

- To collect data relevant for clinical efficacy assessments of meningitis in patients aged <3 months in order to plan future studies on meropenem efficacy in this population.
- To identify pharmacogenetic and ontogenetic variabilities of various transporters involved in the elimination of meropenem in order to define potential biomarkers for the most appropriate dosing of meropenem in neonates.
- To identify pathogens causing culture negative infections in neonates.
- To characterise a Europe-wide knowledge base of patterns of antibiotic resistance in Gram negative bacteria.
- To provide a general framework for the management of the proposed study across different European countries. This framework will also serve as a model for future studies on other drugs for Paediatric infectious diseases.

Additionally, NeoMero was intended to serve as a test-bed for a permanent European network based on a partnership between two well established European PID networks, PENTA and ESPID, devoted to paediatric antimicrobial studies, which should provide a considerable added value in this area for the future.

1.3 - Description of the main S&T results/foregrounds

CAUTION: the results presented below are preliminary results. Final results will be available at the end of October.

ABBREVIATIONS

| Abbreviations | Expansions |
|---------------|---------------------------------|
| COAT | Completion Of Allocated Therapy |
| COT | Completion Of Therapy |
| EOAT | End Of Allocated Therapy |
| EOT | End Of Therapy |
| FU | Follow Up |
| IQR | Inter Quartile Range |
| LOS | Late Onset Sepsis |
| RCT | Randomized Controlled Trial |
| SAR | Serious Adverse Reactions |
| SOC | Standard Of Care |
| TOC | Test Of Cure |

NEOMERO-1 Study

| 1. Report | |
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| 1.1 Full name of trial | Efficacy, pharmacokinetics and safety of Meropenem in subjects below 90 days of age (inclusive) with clinical or confirmed late-onset sepsis: a European multicentre randomised phase III trial |
| 1.2 Acronym | NeoMero-1 |
| 1.3 Report date | August 2015 |
| 1.4 Report type | End of trial report |
| 2. Trial organisation and governance | |
| 2.1 Trial Unit | Institut National de la Santé et de la Recherche Médicale – INSERM SC10-US019 |
| 2.2 Sponsor | Fondazione PENTA |
| 2.3 Funding | European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no: 242146 - Call: FP7-HEALTH-2009-4.2-1 |
| 2.4 Chief Investigator | Irja LUTSAR, TARTU, ESTONIA Ursula TRAFOJER, PADOVA, ITALY |
| 2.5 IMP trial | Yes |
| 2.6 ISRCTN | N/A |

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| 2.7 EUDRACT No | 2011-001515-31 | |
| 3. Publication, presentation and dissemination | | |
| | Date | Published Reference / Conference |
| 3.1 Published papers | 2011 | <p>IrjaLutsar, Ursula MT Trafojer, Paul T Heath, TuuliMetsvaht, Joseph Standing, Susanna Esposito, Vincent Meiffrédy de Cabre, Clarissa Oeser and Jean-Pierre Aboulker, for The NeoMero Consortium. Meropenem vs standard of care for treatment of late onset sepsis in children of less than 90 days of age: study protocol for a randomised controlled trial. Trials 2011, 12:215;</p> <p>Lutsar I, Chazallon C, Carducci FI, Trafojer U, Abdelkader B, de Cabre VM, Esposito S, Giaquinto C, Heath PT, Ilmoja ML, Katragkou A, Lascoux C, Metsvaht T, Mitsiakos G, Netzer E, Pugni L, Roilides E, Saidi Y, Sarafidis K, Sharland M, Usonis V, Aboulker JP; NeoMero Consortium. Current management of late onset neonatal bacterial sepsis in five European countries. Eur J Pediatr. 2014 Feb 13</p> |
| 3.2 Abstracts/Presentations | <p>May 28-June 1, 2013</p> <p>May 12-16, 2015</p> | <p>ESPID (Italy) : Poster Irja Lutsar, Corine Chazallon, Ursula Trafojer, Ben Abdelkader, Jean-Pierre Aboulker, Vincent Meiffrédy de Cabre, Susanna Esposito, Isabelle Fournier, Paul T. Heath, Mari-Liis Ilmoja, Aspasia Katragkou, George Mitsiakos, Emmanuelle Netzer, Laura Picault, Lorenza Pugni, Emmanuel Roilides, Yacine Saidi, Kosmas Sarafidis, Vytautas Usonis and Tuuli Metsvaht. European multicentre network to evaluate pharmacokinetics, safety and efficacy of meropenem in neonatal late-onset sepsis and meningitis.</p> <p>ESPID (Germany): Short oral presentation. ILutsar, NeoMero writing committee.</p> <p>Feasibility of large randomised controlled trials (RCT) in European neonatal intensive care units (NICU): the NeoMero1 trial.</p> |
| 3.3 Feedback to participants | January 2016 | Waiting for final results. |
| 4. Trial design | | |
| 4.1 Objective | To compare the efficacy at TOC (Test Of Cure) visit of meropenem to the standard of care (SOC) in the treatment of clinical or confirmed LOS in subjects ≤ 90 days of postnatal age. | |
| 4.2 Summary of design | Open label, European multicentre active-comparator randomised controlled phase III superiority trial. | |
| 4.3 Main eligibility/ineligibility criteria | <p>Inclusion criteria</p> <p>Informed consent form signed by the parents/carers.</p> <p>Chronological age below 90 days inclusive.</p> | |

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| | <p>Chronological age greater or equal to 72 hours of life at beginning of LOS.</p> <p>Clinical or confirmed sepsis.</p> <p>Exclusion criteria</p> <p>Administration of any systemic antibiotic regimen for more than 24 hours prior to the randomisation, unless the change is driven by the lack of efficacy of the former regimen.</p> <p>Severe congenital malformations if the subject is not expected to survive for more than 3 months.</p> <p>Other situations where the treating physician considers a different antibiotic regimen necessary.</p> <p>Known intolerance or contraindication to study medication.</p> <p>Participation in any other clinical study of investigational drugs.</p> <p>Renal failure (as defined by Akcan-Arikan et al., 2007) and requirement for hemofiltration or peritoneal dialysis.</p> <p>Confirmed sepsis with microorganisms known to be resistant to study therapies.</p> |
| 4.4 Treatment/Intervention | <p>Subjects were randomized 1:1 to either the experimental arm (meropenem) or the control arm (2 options available: ampicillin + gentamicin or cefotaxime + gentamicin) and stratified on SOC regimen and on received/not received previous treatment.</p> <p>Treatment duration is 11 ± 3 days.</p> |
| 4.5 Primary outcome measure | <p>Favourable outcome at the TOC visit performed 2 days after completion of allocated therapy (COAT), defined as subject alive, with resolution or significant improvement of all abnormalities that defined LOS so that there is no need to continue antibiotics, with microbiological eradication and no change in the treatment allocated at randomisation and patients had received allocated antibiotics for 11 ± 3 days.</p> |
| 4.6 Main Secondary outcome measures | <ul style="list-style-type: none"> • Description of all clinical and biological adverse events experienced by subjects receiving meropenem or comparator agents. • Clinical and biological response in all patients and also in patients with positive baseline cultures at Day 3, at COT, at EOT and EOAT. • Survival at Day 28. • New infections or relapses of LOS that occur between TOC and FU visit in participants with a favourable outcome at TOC visit. |
| 4.7 Sample size calculation and rational | <p>550 subjects (275 subjects per group).</p> <p>The primary analysis compares the percentages of favourable outcomes at the TOC visit in the meropenem group and the SOC group. We have estimated that, in the control arm, the proportion of neonates who will die before the TOC visit will be 15% and that, among the</p> |

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| | neonates who will survive, the proportion reaching the failure definition will be 25%. In this arm, the proportion of neonates who will die or fail therapy is thus expected to be 36.25%. The main hypothesis of the trial is that neonates treated with the experimental drug (meropenem) will have improved survival (90% instead of 85% at TOC visit) and a better response to therapy (15% failures instead of 25% in surviving babies). In the experimental arm, the expected proportion of neonates who will die or fail therapy should thus be reduced to 23.5%. Under these hypotheses, the required sample size to have a power of 80% to show the superiority of the experimental regimen over standard antibiotic therapy, using a continuity-corrected chi-square test with a two-sided 5% alpha level, is 220 subjects per arm that means a total of 440 neonates (NQuery software). As initiation of therapy for sepsis in neonates is a matter of great urgency and cannot be delayed until results of all diagnostic explorations become available, it is anticipated that 15 to 20% of neonates could be randomized in the trial and start empirical therapy when actually they did not need it because an alternative condition to bacterial sepsis, not amenable to trial drugs, becomes evident later on. |
| 4.8 Statistical methods | <p>This report includes preliminary results</p> <p>The preliminary results are based on the data taken from the NM1 clinical database extracted at the end of May 2015. The database was closed at the end of July 2015.</p> <p>The primary analysis is done by intention-to-treat and includes all randomised participants (full analysis set population). The primary endpoint is a favourable outcome of clinical or confirmed LOS at TOC visit as defined in section 4.5. According to the operational definition of the primary endpoint, the outcome of all randomised participants was categorised as success (favourable outcome) or failure, and no censoring was used. In case the primary endpoint or one of the components of the endpoint was missing, the methodologist decided during the data review (blind review) how to analyse the missing endpoint. Proportions of participants with a favourable outcome were calculated in the meropenem arm and in the SOC arm. They were then compared using a logistic regression model adjusting on the factors of stratification with a two-sided 5% alpha level.</p> |
| 5. Trial progress | |
| 2.1 CTA Approval date | 18 th August 2011 |
| 5.2 Recruitment start date | 3 rd September 2012 |
| 5.3 Recruitment completion date | 21 th November 2014 |
| 5.4 Participating Investigators/centres | A total of 22 sites participated of which 18 were active (recruiting patients) across 6 countries (Estonia, Greece, |

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| | Italy, Lithuania, Spain and Turkey). For full details see Table 1. |
| 5.5 No. participants recruited/analysed | 272 patients recruited /271 analysed |
| 5.6 Date of last clinical visit | 17 th December 2014. Subjects were followed for a maximum of 31 days. |
| 5.7 Data completeness | No TOC visit missing for the evaluation of the primary endpoint. |
| 5.8 Final protocol version | VERSION 3 – 31 MARCH 2014 |
| 6. Summary of results | |
| 6.1 Patient characteristics | <p>Of the 272 subjects randomized, one was excluded from the analyses due to a major consent violation (no consent given by the parents – no data were collected for this subject). A total of 271 children were evaluated: 136 in the meropenem and 135 in the SOC treatment group. Baseline demographics were comparable between arms. There were 72 (53%) males and chronological age was median (IQR) 17 days (9-29). The median gestational age at inclusion was 31 weeks [30% < 28 weeks, 25% (28-32) weeks, 18% (32-37) weeks, 26% > 37 weeks]. The median (IQR) weight at inclusion was 1.540 Kg (1.030-2.900) and the median (IQR) weight at birth was 1.385 Kg (0.845-2.664). For subjects below 44 weeks of postmenstrual age, the median (IQR) number of clinical criteria defining the sepsis was 3 (3 -4) and the median (IQR) number of laboratory criteria defining the sepsis was 2 (2 -3). Sixty two (46%) and 75 (56%) patients had proven sepsis in the meropenem arm and the SOC arm, respectively. The distribution of bacteria cultured across the two arms was comparable.</p> <p>Pre-trial antibiotic exposure was identical between arms; 199 (73%) of the subjects received antibiotics before randomization for a median (IQR) of 17 hours (9-22). Meropenem was given before randomization to 35 (26%) subjects in the meropenem arm and to 27 (20%) subjects in the SOC arm.</p> |
| 6.2 Treatment | <p>The allocated therapy was started for 136 (100%) of the subjects in the meropenem arm and for 130 (96%) in the SOC arm. 5 participants in the SOC arm did not start the treatment allocated by randomisation. The initial dose and frequency was according to protocol for 133 (98%) of the subjects in the meropenem arm and for 124 (92%) subjects in the SOC arm.</p> <p>131 (43%) of the subjects had the allocated therapy alone, 116 (43%) of the subjects had the allocated therapy plus Vancomycin (which was allowed by the protocol).</p> <p>The median (IQR) duration of allocated therapy was 8 (4 - 10) days for meropenem and 7 (3 -10) for SOC.</p> |
| 6.3 Efficacy | <p>Primary outcome</p> <p>Superiority of meropenem against SOC was not demonstrated when comparing the proportion of</p> |

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| | subjects with a favourable outcome at the TOC visit. The final analysis is on-going and will be completed by the end of October. |
| 6.4 Toxicity | The final analysis is on going and will be completed by the end of October. |
| 6.5 Conclusion | This is one of the largest RCT carried out in neonates with sepsis. Results will be very informative not just on the primary study outcome, but on the management of infants with LOS. |

NEOMERO-2 Study

| 1. Report | | |
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| 1.1 Full name of trial | Pharmacokinetics and safety of Meropenem in infant below 90 days of age (inclusive) with probable and confirmed meningitis: a European multicentre phase I-II trial. | |
| 1.2 Acronym | NeoMero-2 | |
| 1.3 Report date | August 2015 | |
| 1.4 Report type | End of trial report | |
| 2. Trial organisation and governance | | |
| 2.1 Trial Unit | Institut National de la Santé et de la Recherche Médicale – INSERM SC10-US019 | |
| 2.2 Sponsor | Fondazione PENTA | |
| Co-Sponsor | St George's University of London | |
| 2.3 Funding | European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no: 242146 - Call: FP7-HEALTH-2009-4.2-1 | |
| 2.4 Chief Investigator | Paul HEATH, LONDON, UK | |
| 2.5 IMP trial | Yes | |
| 2.6 ISRCTN | N/A | |
| 2.7 EUDRACT No | 2011-001521-25 | |
| 3. Publication, presentation and dissemination | | |
| | Date | Published Reference / Conference |
| 3.1 Published papers | - | - |
| 3.2 Abstracts/Presentations | May 28-June 1, 2013 | ESPID (Italy): Poster Irja Lutsar, Corine Chazallon, Ursula Trafojer, Ben Abdelkader, Jean-Pierre Aboulker, Vincent Meiffredy de Cabre, Susanna Esposito, Isabelle Fournier, Paul T. Heath, Mari-Liis Ilmoja, Aspasia Katragkou, George Mitsiakos, |

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| | | Emmanuelle Netzer, Laura Picault, Lorenza Pugni, Emmanuel Roilides, Yacine Saidi, Kosmas Sarafidis, Vytautas Usonis and Tuuli Metsvaht. European multicentre network to evaluate pharmacokinetics, safety and efficacy of meropenem in neonatal late-onset sepsis and meningitis. |
| 3.3 Feedback to participants | January 2016 | Waiting for final results. |
| 4. Trial design | | |
| 4.1 Objective | | To study the pharmacokinetics (plasma and cerebrospinal fluid) of meropenem in infants ≤ 90 days of postnatal age with probable or confirmed bacterial meningitis and to characterize the safety profile of meropenem in the treatment of infants ≤ 90 days of postnatal age with probable or confirmed bacterial meningitis. |
| 4.2 Summary of design | | A European multicentre open label single arm phase I-II trial |
| 4.3 Main eligibility/ ineligibility criteria | | <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Informed consent form signed by the parents/carers • Chronological age below 90 days inclusive • The presence of: <ul style="list-style-type: none"> • clinical signs consistent with bacterial meningitis: fever or hypothermia or temperature instability PLUS 1 or more neurological findings from among; coma, seizures, neck stiffness, apnoea, bulging fontanelle) • OR CSF pleocytosis (≥ 20 cells / mm³) • OR a positive Gram stain of CSF. • For infants included in NeoMero-1: diagnosis of meningitis in the first 3 days after randomization, whatever the arm of randomisation <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Presence of a CSF device • Proven viral or fungal meningitis • Severe congenital malformations if the infant is not to expect to survive for more than 3 months • Other situations where the treating physician considers a different empiric antibiotic regimen necessary • Known intolerance or contraindication to the study medication |

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| | <ul style="list-style-type: none"> Participation in any other clinical study of an investigational medicinal product Renal failure and requirement of haemofiltration or peritoneal dialysis Meningitis with an organism known to be resistant to meropenem |
| 4.4 Treatment/Intervention | <ul style="list-style-type: none"> Infants will be treated with meropenem at a dose of 40mg/kg every 8 hours. For infants who are < 32 weeks GA and < 2 weeks post-natal age the dose is 40mg/kg every 12 hours. Treatment duration is 21 ± 7 days The PK study will be realized at steady state (as soon as possible after the 4th dose of meropenem) and will consist of collection of 3 specimens of blood at T1 (pre-dose), T2 (post-infusion), T3 (5-6h for q8h; 7-9h for q12h); and one specimen of CSF. |
| 4.5 Primary outcome measure | <ul style="list-style-type: none"> The PK of meropenem (plasma and CSF) in infants ≤ 90 days of age diagnosed with probable and confirmed BM. Adverse events experienced by infants receiving meropenem. Clinical and biological adverse events will be recorded until FU visit. |
| 4.6 Secondary outcome measures | <ul style="list-style-type: none"> A favourable outcome defined at Test of Cure visit (TOC), 2 days after EOAT as an infant fulfilling the following criteria: Alive with clinical and bacteriological resolution (see Appendix A of the abnormalities that defined BM at entry and no occurrence of any new clinical or laboratory abnormalities requiring a new course of antibiotic therapy and no modification of the initial meropenem therapy (for more than 24 hours). Clinical, biological and microbiological response at Day 3, at EOAT, at TOC and at FU; Survival at FU visit; Auditory test between EOAT and FU visits; Neurological evaluation as assessed by cerebral ultrasound (and if persistently abnormal, by MRI or CT) at any time up until the FU visit; The organisms causing BM; The antibiotic susceptibility of bacteria causing BM; Mucosal colonisation with antibiotic resistant bacteria or fungi at enrolment, EOAT and FU / discharge (whichever is earlier); Genetic parameters that can affect response to therapy. |
| 4.7 Sample size calculation and rational | <p>Sample size:</p> <p>Sample size is not based on statistical computation, but on accrual estimation. 60 infants will be enrolled in the study.</p> |

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| 4.8 Statistical methods | <p>Preliminary results are presented in this report. They are derived from a database extracted at the end of May 2015. The database was closed at the end of July 2015.</p> <p>Analysis of the primary endpoint:</p> <p>Pharmacokinetics: The final model will be used for dosing simulations to give final dose recommendation.</p> <p>Safety of meropenem: The nature, frequency and numbers of all adverse events will be described.</p> <p>Safety and pharmacokinetic analyses will be carried out on the infants who received at least one dose of meropenem after inclusion in NeoMero-2.</p> |
| 5. Trial progress | |
| 2.1 CTA Approval date | 18 th August 2011 |
| 5.2 Recruitment start date | 13 th February 2013 |
| 5.3 Recruitment completion date | 27 th October 2014 |
| 5.4 Participating Investigators/centres | A total of 29 sites participated of which 21 were active (recruiting patients) across 7 countries (United Kingdom, Netherlands, Estonia, Greece, Italy, Lithuania and Spain). |
| 5.5 No. participants recruited/analysed | 51 infants recruited / 51 analyzed |
| 5.6 Date of last clinical visit | 10 th December 2014. Infants were followed for a maximum of 48 days. |
| 5.7 Data completeness | Only one visit was missing in 3 out of 51 enrolled infants. |
| 5.8 Final protocol version | Version 4 – 31 March 2014 |
| 6. Summary of results | |
| 6.1 Patient characteristics | <p>Of the 51 infants included, 28 (55%) were male and chronological age was median (IQR) 11 days (4 -22). The median gestational age at inclusion was 37 weeks (18% < 28 weeks, 4% [28 -32] weeks, 20% [32 -37] weeks, 59% ≥ 37 weeks). The median (IQR) weight at inclusion was 2.960 Kg (1.700 -4.016) and the median (IQR) weight at birth was 2.925 Kg (1.450 -3.540).</p> <p>Infants recruited directly into NeoMero2 had different demographic characteristics to those recruited from</p> |

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| | <p>Neomero1. The median (IQR) postmenstrual age at inclusion was 40 weeks for the infants recruited directly vs 33 weeks for the infants recruited from NeoMero1; 3.500 Kg vs 1.505 Kg for the weight at inclusion respectively.</p> <p>At inclusion, 18 (35%) of the infants had the criteria of temperature not controlled plus at least one neurological finding (coma, seizures, episodes of apnoea, bulging fontanelle), 42 (82%) had CSF pleocytosis (WBC count \geq 20 cells/mm³), and 12 (24%) had a positive Gram stain of CSF.</p> <p>Based on clinical examination and microbiological results, meningitis was classified as confirmed, probable or excluded case by the investigators, and the endpoint review committee. The meningitis was classified as confirmed for 28 (55%) of the infants, probable for 4 (8%) of the infants and excluded for 19 (37%) of the infants; 14 (50%) had Gram positive bacteria, 13 (46%) had Gram negative bacteria.</p> <p>Thirty nine (76%) of the infants were on antibiotics before inclusion for a median (IQR) of 31 hours (18 -78). Meropenem was given before inclusion for 9 (18%) of the infants. 94% (48) and 63% (32) patients had PK samples taken from blood and CSF respectively.</p> |
| 6.2 Treatment | <p>All the infants started the meropenem and respected the initial dose and frequency.</p> <p>Among the 32 infants with confirmed or probable meningitis, the allocated therapy was completed for 19 (59%) of the infants. The completion of the meropenem therapy means that meropenem was taken between 13 and 28 days with no modification (stop, addition or dose modification not per protocol) of more than 24 hours.</p> <p>The median (IQR) duration on meropenem was 14 (14 - 17) days.</p> <p>38 (75%) of the infants were on meropenem alone.</p> |
| 6.3 Efficacy | <p>PK study: data not available</p> <p>Among the 32 infants with confirmed or probable meningitis, 19 (59%) had a favourable outcome at TOC.</p> <p>The final analysis is on going and will be completed by the</p> |

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| | end of October. |
| 6.4 Toxicity | The final analysis is on going and will be completed by the end of October. |
| 6.5 Conclusions | <p>This study demonstrates that recruitment of neonates with a rare infection to a drug trial across multiple European countries is achievable. Regarding the primary objectives, the CSF and blood PK data are awaited.</p> |

1.4 - The potential impact and the main dissemination activities and exploitation of results

Theme Health within the Seventh Framework programme aimed at stimulating and sustaining multidisciplinary biomedical research while addressing global health issues, providing scientific validation of experimental results aimed to identify new therapies or methods for health promotion and prevention including promotion of child health. In line with the Regulation on medicinal products for paediatric use, the Health Theme had included in its Work Programme a specific topic:

HEALTH-2009-4.2-1: Adapting off-patent medicines to the specific needs of paediatric populations. FP7-HEALTH-2009-single-stage.

Proposals should provide **evidence for specific paediatric use of off-patent medicinal products currently used off-label**. Studies include the assessment of non-clinical safety, pharmacokinetics (as well as data analysis and extrapolation by means of in silico models), clinical efficacy and safety, and/or the development of appropriate formulations. With a view to benefit from the broadest possible expertise, the participation of research centres from Third countries already active in this field is also strongly encouraged. **Project proposals must take account of the priority list** of Off-Patent Medicinal Products of the Paediatric Committee of the European Medicines Agency (EMEA), and of the Regulation of the European Parliament and of the Council on Medicinal Products for paediatric use and amending Regulation (EEC) N° 1768/92, Directive 2001/83/EC and Regulation (EC) N°726/2004, Brussels, 29.9.2004, COM (2004) 599 final, 2004/0217 (COD).

Which expected impact is to provide evidence for a better use of off-patent medicinal products in paediatric populations.

Studies for ‘off-patent’ medicines and included in the priority list

Meropenem had been included in the revised EMA “priority list for studies into off patent paediatric medicinal products” (Doc. Ref.EMEA/226983/2008), the list of off-patent drugs intended to address unmet therapeutic needs in children and to increase information on drug uses in paediatrics. The objective of the revised priority list is to provide the basis for the work programme for the 3rd call of FP7 of the European Commission, ensuring that funding will be directed into research of medicinal products with the highest need in the paediatric population.

Meropenem had been off patent for many years and largely used off label for the treatment of neonatal sepsis and meningitis without sufficient data on pharmacokinetics, safety and efficacy.

Proposed studies could compensate the lack of existing information.

Meropenem, a carbapenem structurally related to imipenem, bears the potential to have the best qualities to treat bacterial infections in the neonatal period as well as in the first 3 months of life. So far, meropenem had been largely used with very good results for the treatment of severe infections including bacterial sepsis and BM of infants \geq 90 days and children. However, it has not been already registered in neonates and infants $<$ 90 days of age for the paucity of data on its pharmacokinetic characteristics, activity and safety in the first months of life. Despite that, there is a frequent use off label of these antibiotics with a high risk to develop bacterial resistance.

The need to carry out studies in age groups not covered by the existing indication, in which a widespread off-label use is demonstrated, has been also underlined by the EMA-PDCO, leading to inclusion of this compound in the priority list.

Contribution of the project

The present project was aimed at facilitating that meropenem can be used in infants and neonates with sepsis and meningitis more safely, assuring proper dosage. Data on dosing, efficacy and safety were included in the SPCs and PLs.

To achieve this aim the following was provided:

- a Paediatric Investigation Plan (PIP) submitted to the EMA- Paediatric Committee for approval
- studies included in the PIP were performed

It is worth mentioning that AstraZeneca and Chiesi SpA have been collaborating with this project and have provided the IMP that was used for NeoMero 1 and NeoMero 2 study purposes. Improvement of neonatal health was expected by the project. At the end of the project off-label use of meropenem in neonates could be fostered by including updated dosages and information in the product documentation leading to an extension of the paediatric indication in infants < 90 days of age.

It is also important to underline the importance of a European approach.

There are three main reasons for carrying out the research at a European level as opposed to at a national, regional or local level:

1. Necessity of combining resources and knowledge: the scale and scope of the problem addressed requires the joining of different multidisciplinary areas of expertise, knowledge and research capacities on a European scale. The Consortium could count on members with different expertise and resources mainly with a scientific profile. Neonatologists, paediatricians, paediatric infectious disease clinicians, microbiologists, statisticians were involved in the trial design, the CTU staff was responsible for the study setup, monitoring and data analysis before, during and after the trials end. Specialized CROs were involved to carry out specific trial-related activities and the NICUs personnel – paediatricians, physicians, nurses, laboratory staff – to carry out enrolments as per the project objectives.

2. Cross-border problems need cross-border solutions: off-label use of meropenem for treating neonatal and infant sepsis and meningitis without specific PK, safety and efficacy information is a problem affecting all countries worldwide. Different pattern of antimicrobial resistance of pathogens causing neonatal sepsis/meningitis varies in different European countries. To be able to evaluate the efficacy of meropenem against a large spectrum of bacteria it was essential to perform the corresponding studies on across Europe. Therefore, the involvement of many NICUs in several European countries – from the north to the south and east to west – and research institutions with specific skills on PK and immunogenetic studies was key to obtain the needed data and properly study the problem of neonatal sepsis.

3. Necessity for multinational endorsement of results: this collaborative project addresses a public health problem concerning all European Member States. New knowledge and treatment was compliant with the PIP as released by the EMA and involved all interested parties (scientists, clinicians, patients, policy makers, scientific societies, etc.). All combined, the partners in the Consortium have access to a wide audience of colleague scientists, industry and patients, thus creating a natural platform for the further uptake of the project results that would not exist without this European level approach.

Account taken of other national or international research activities

The composition of the Consortium as a whole and the dissemination and collaboration activities undertaken by NeoMero ensures the creation of synergy with existing efforts and the prevention of unnecessary overlaps with relevant activities outside the Consortium. The inclusion of several partners involved in PDCO activities (PENTA, OPBG, UTARTU, CVBF) and of the coordination of the TEDDY (Task Force in Europe for Drug Development for Young) Network of Excellence was a key element to facilitate coordination of European research activities in the field of Paediatric Infectious Disease and neonatology.

Dissemination activities have consequences in terms of both financial and time expenditure. The dissemination agenda included the design of a **communication plan**, the development of **communication tools**, and the execution of **dissemination activities** in order to raise awareness of the project as a whole, and specifically of its results, among different stakeholders. WP8 contributors focused initially on developing a communication plan for publicizing the project and its results, thereby establishing a consistent strategy for maximizing the impact and efficiency of the communication efforts.

This fully defined and formalised the four basic pillars of the NeoMero communication strategy:

- i) Definition of the communication objectives;
- ii) Identification of the target audiences;
- iii) Description of the dissemination actions to be tackled;
- iv) Specific tools to be developed in order to support effective communication.

Subsequently, the communication tools identified by the communication plan were developed as needed, keeping in mind the actions, audiences and objectives to which these tools should serve as supporting materials. The bulk of these dissemination undertakings entailed primarily, though not exclusively, scientific interactions that included:

- **Publication of scientific papers.** Preference was given to the generation of publications related with the project activities and results, which will be mainly submitted for publication in international scientific journals with as high impact as possible.
- **Presentations at relevant events (congresses, meetings, workshops, etc.).** An important dissemination activity comprised participation in organisation of relevant events where the presentation of the project, its approaches and results, took place. Presentations took the form of oral communications, participation in poster sessions and other formats.
- **Individual presentations and meetings with key stakeholders.** To raise the interest and gain support of key actors in the field, such as regulatory authorities and pharmaceutical companies, individual contacts have been established as needed.

Some tools considered essential were developed in order to support and make the most of the dissemination activities planned. A brochure was produced, as well as a generic poster, with the intention to reflect the status of the project and to support the presentations at events and the individual meetings carried out. A website was set up, which intended to support and reinforce the rest of the above-mentioned dissemination activities. The website initially included general information, for example: description, objectives, participants, activities, contact links, etc. Nevertheless, as the project evolved, the site was updated with project news, and downloadable versions of all public documents generated by the project. A password-protected Intranet was

reserved for project participants, in order to facilitate co-operation and management tasks. Knowledge protection is an important issue in a project with these characteristics, in which patient data will be used. Therefore, IPR handling was tackled from the beginning of the project and it was specifically supported by management activities in WP9. Confidentiality among participants during the project development and confidentiality towards external participants, access rights, ownership and protection of results, just to mention a few aspects related to IPR handling, were covered in detail within the Consortium Agreement that was enforced before the official project start.