-NEOMERO-1 – END OF TRIAL REPORT

1. Report		
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	December 18, 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-US19	
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	NA	
2.7 EUDRACT No	2011-001515-31	
3. Publication, presentation and dissemination		
	Date	**Published Reference / Conference**
3.1 Published papers	2011	Irja Lutsar, Ursula MT Trafojer, Paul T Heath, Tuuli Metsvaht, 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
3.2 Abstracts/Presentations	May 28-June 1, 2013 May 12-16, 2015	**ESPID (Italy)** : Poster Irja Lutsar, CorineChazallon, 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 Saïdi, 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.** **ESPID (Germany)**: Short oral presentation. Irja Lutsar, NeoMero writing committee. **Feasibility of large randomised controlled trials (RCT) in European neonatal intensive care units (NICU): the NeoMero-1 trial.**
3.3 Feedback to participants	January 2016	Waiting for final results.
4. Trial design		

4.1 Objective	To compare the efficacy at Test Of Cure (TOC) visit of meropenem to the standard of care (SOC) in the treatment of clinical or confirmed late onset sepsis (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	**Inclusion criteria** • Informed consent form signed by the parents/carers. • Chronological age below 90 days inclusive. • Chronological age greater or equal to 72 hours of life at beginning of LOS. • Clinical or confirmed sepsis*. ***definition based on the Expert Meeting on Neonatal and Paediatric Sepsis (Report on the Expert Meeting on Neonatal and Paediatric Sepsis, 8 June 2010, EMA London) for subjects below 44 weeks of postmenstrual age, and defined according to the Goldstein criteria (Goldstein et al, 2005) for subjects above 44 weeks of postmenstrual age. **Exclusion criteria** • 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. • Severe congenital malformations if the subject is not expected to survive for more than 3 months. • Other situations where the treating physician considers a different antibiotic regimen necessary. • Known intolerance or contraindication to study medication. • Participation in any other clinical study of investigational drugs. • Renal failure (as defined by Akcan-Arikan et al., 2007) and requirement for haemofiltration or peritoneal dialysis. • Confirmed sepsis with microorganisms known to be resistant to study therapies.
4.4 Treatment/Intervention	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 based on SOC regimen and timing of initiation of antibiotics for LOS (having received any dose of antibiotic vs no antibiotics before randomisation). Duration of allocated therapy was 11 ± 3 days.
4.5 Primary outcome measure	The primary outcome was the outcome at the TOC visit performed 2±1 days after completion of an 11± 3 days' full course of antibiotic treatment. A favourable outcome was defined as subject is alive, has resolution or significant improvement of all abnormalities that defined LOS and no new clinical or laboratory abnormalities

	requiring a new course of antibiotic therapy, has presumed or confirmed microbiological eradication and has completed the 11 ± 3 days' course of the regimen allocated at randomisation with no modification.
4.6 Secondary outcome measures	• Description of all clinical and laboratory adverse events experienced by subjects receiving meropenem or comparator agents. • Clinical, biological and microbiological response at Day 3, and End Of Allocated Treatment (EOAT) and at End Of Treatment (EOT). • 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. • The organisms causing LOS in infants $\leq$ 90 days of age. • Gut colonisation with antibiotic resistant bacteria at enrolment, EOT and prior to NICU discharge following meropenem or SOC therapies • PK of meropenem. • Genetic parameters that can affect response to therapy. • Auditory and neurological evaluation (cerebral ultrasound) by Day 28. • Time to NICU discharge.
4.7 Sample size calculation and rationale	550 subjects (275 subjects per group). The primary analysis compares the percentages of favourable outcomes at the TOC visit in the meropenem group and the SOC group. In the original planning of the trial we estimated that, in the control arm, the proportion of neonates who will die before the TOC visit will be 15% and that, among the 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%. This represents a 12.75% absolute reduction in the proportions of failures across the 2 arms and a 35% relative reduction in the risk. 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, 440 neonates in total (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. They will therefore not contribute to demonstration of a difference in efficacy between the 2 regimens and will reduce its apparent size (dilution effect). Consequently, taking into account a maximum of 20% randomized subjects not contributing to testing efficacy (any cause), the sample will be conservatively increased by 25%, e.g. to 275 neonates per arm, 550 in total, to maintain the specified power in the efficacy comparison. During the trial, analysis of pooled data provided new and important information for future trials of antibiotics in LOS: 1) The 28-day mortality was lower than anticipated (6% instead of 10 to 15%) 2) The proportion of babies enrolled with suspected clinical sepsis later classified as having an alternative condition not amenable to study drugs and therefore not contributing to the efficacy comparison was minimal (2% instead of 15 to 20%) 3) The overall proportion of babies having an "unfavourable" outcome was dramatically greater than hypothesized (72% instead of 30%). This was mostly driven, by frequent modifications of allocated therapy for various reasons that accounted for about 60% of the failures. On the basis of this new information, a sample of 136 subjects per arm provides 80% power to demonstrate an absolute reduction of 16%, from 80% to 64%, in the proportion of failures together with a 20% relative reduction in the risk. It is thus concluded that NM1 with a total of 272 subjects was already adequately powered to address its main objective.
4.8 Statistical methods	The final results are based on the data extracted from the NM1 frozen database as of 28th of July 2015. The primary analysis is done in the intention-to-treat population that includes all randomised participants (full analysis set). 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 (blind) data 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 by using a logistic regression model adjusted for the factors of stratification with a two-sided 5% alpha level. Odd ratio (95% CI) are given for the treatment arms (meropenem vs SOC). Relative risks (95% CI) are shown for the treatment arms (meropenem vs SOC). To determine the relative risk, a log binomial model was used.
5. Trial progress	
5.1 CTA Approval date	18th August 2011
5.2 Recruitment start date	3rd September 2012
5.3 Recruitment completion date	21th 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, 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	17th December 2014. Subjects were followed for a maximum of 31 days.
5.7 Data completeness	Only one TOC visit was 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	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 subjects were evaluated: 136 in the meropenem and 135 in the SOC treatment arm. Baseline demographics were comparable between arms (Table 1). There were 144 (53%) males and median (IQR) chronological age was 17 days (9-29). The median gestational age was 31 weeks [30% < 28 weeks, 25% (28-32) weeks, 18% (32-37) weeks, 26% $\geq$ 37 weeks]. The median (IQR) weight at inclusion was 1.540 Kg (1.030-2.900) and the median (IQR) birth weight 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-three (46%) and 77 (57%) patients had culture proven sepsis in the meropenem arm and the SOC arm, respectively. The distribution of most common causative agents across the two arms was comparable for *Staphylococcus epidermidis* (14 (22%) in meropenem arm,

	25 (32%) in the SOC arm), *Enterobacter* spp (9 (14%) in meropenem arm, 11 (14%) in the SOC arm) and *Klebsiella pneumonia* (7 (11%) in meropenem arm, 4 (5%) in the SOC arm). Among the subjects with a culture proven sepsis, 24 (38%) in the meropenem arm and 25 (32%) in the SOC arm had a Gram negative bacterium (Table 2). Pre-trial antibiotic exposure was comparable between treatment arms; 100 (74%) of the subjects in the meropenem arm and 98 (73%) of the subjects in the SOC arm received antibiotics before randomization for a median (IQR) of 19 hours (9-22) in the meropenem arm and 16 hours (8-21) in the SOC arm. Meropenem was given before randomization to 35 (26%) subjects in the meropenem arm and to 29 (21%) subjects in the SOC arm.
6.2 Treatment	The allocated therapy was started in 136 (100%) subjects in the meropenem arm and 131 (97%) in the SOC arm. The initial dose and frequency were given according to the protocol recommendations to 134 (99%) in the meropenem arm and 127 (94%) in the SOC arm. 132 (49%) of the subjects received the allocated therapy alone, 116 (43%) of the subjects received the allocated therapy plus vancomycin (which was allowed by the protocol), 11 (4%) of the subjects received the allocated therapy plus teicoplanin (also allowed per protocol) and 8 (3%) subjects received the allocated therapy plus an antibiotic which was not allowed (2 (1%) in meropenem arm, 6 (4%) in the SOC arm). The protocol stipulated that the allocated therapy should be given for no less than 8 and for no more than 14 days with no modification of dose or duration for more than 24 hours. Considering this, the allocated therapy was given per protocol for 58 (43%) subjects in the meropenem arm and 46 (35%) in the SOC arm. The median (IQR) duration of allocated therapy was 8 (4-10) days for meropenem and 7 (3-10) for SOC.
6.3 Efficacy	Primary outcome Superiority of meropenem against SOC was not demonstrated when comparing the proportion of subjects with a favourable outcome at the TOC visit (44 (32%) in the meropenem arm, 31 (23%) in the SOC arm, logistic regression: p=0.087) (table 3). The OR (95% CI) of having a favourable outcome at TOC (meropenem vs SOC) is 1.6 (0.9-2.8) and the RR (95% CI) of having a favourable outcome at TOC (meropenem vs SOC) is 1.4 (0.9-2.0). The main reason for failure was the modification of the allocated therapy (see 6.2 Treatment) which occurred in 78 (57%) subjects in the meropenem arm and in 85 (63%) subjects in the SOC arm for reasons which differed across the two arms. The allocated therapy was stopped due to

	resistance for 3 (4%) of the subjects in the meropenem arm, and 16 (19%) of the subjects in the SOC arm (Table 4). The allocated therapy was completed earlier for 30 (38%) of the subjects in the meropenem arm and for 10 (12%) of the subjects in the SOC arm. At the TOC visit, no improvement and/or new signs of LOS were reported in 18 (13%) and 24 (18%) of the subjects in the meropenem and the SOC arms, respectively. Sixteen (6%) of the subjects had died before the TOC visit (10 (7%) in the meropenem arm, 6 (4%) in the SOC arm). Among 30 subjects who had a blood culture obtained up to 48 hrs before the TOC visit, 5 had a positive blood culture (3 in the meropenem arm, 2 in the SOC arm). The response was better for infants with a Gram positive bacterial infection; 10 (13%) of the subjects with a Gram positive and 17 (28%) of the subjects with a Gram negative bacterial infection had a favourable outcome (logistic regression: p=0.046). Secondary outcomes By day 28, 17 (6%) subjects died (10 (7%) in the meropenem arm, 7 (5%) in the SOC arm, log-rank test: p=0.465). Among the 75 subjects (44 in the meropenem arm, 31 in the SOC arm) with a favourable outcome at TOC, a clinical relapse and/or new infection occurred in 8 (18%) of the subjects in the meropenem arm, 5 (17%) of the subjects in the SOC arm. At day 3, 84 (67%) of the subjects in the meropenem arm and 91 (73%) of the subjects in the SOC arm had no resolution of abnormalities defining LOS at entry or had new sign of LOS or had died. At EOAT, 52 (41%) of the subjects in the meropenem arm and 67 (53%) of the subjects in the SOC arm had no resolution of abnormalities defining LOS at entry or had new sign of LOS or had died. At EOT, 39 (32%) of the subjects in the meropenem arm and 49 (39%) of the subjects in the SOC arm had no resolution of abnormalities defining LOS at entry or had new sign of LOS or had died. Auditory tests were performed up to day 28 in 61 (48%) of subjects in the meropenem arm and 70 (53%) of the subjects in the SOC arm. Abnormal tests were recorded in 9 (15%) of the subjects in the meropenem arm and 20 (29%) of the subjects in the SOC arm (Wilcoxon test: p 0.057). CNS imaging was performed up to day 28 in 108 (84%) of subjects in the meropenem arm and 110 (84%) of the subjects in the SOC arm. Abnormal tests were recorded in 27 (25%) of the subjects in the meropenem arm and 30 (27%) of the subjects in the SOC arm.

	By day 28, 49 (36%) subjects in the meropenem arm and 38 (30%) in the SOC arm had been discharged from the NICU (log-rank test: p=0.104). At day 28 or NICU discharge, there were 10 highly carbapenem resistant microorganisms isolated from rectal swabs of subjects - (3/94 (3%) in meropenem and 7/100 (7%) in the SOC arm, p=0.3332). PK results are presented in a separate report. Genetic study is ongoing.
6.4 Toxicity	339 grade 1 or 2 clinical or laboratory adverse events and 280 grade 3 or 4 (defined as need for significant medical intervention) clinical or laboratory adverse events have been reported in 268 infants. The most common system organ class for these adverse events was blood and lymphatic system disorders (23.5% meropenem arm versus 24.2% SOC arm). There were no significant differences between the trial arms of the safety set analyses, but an excess of gastrointestinal disorders was noticed in the SOC group (24.2% versus 13.2%). 95 serious adverse events (SAE) in 46 infants occurred during the follow up (to Day 28) of the trial: 47 (28) in the meropenem arm and 48 (18) in the SOC arm. Only one SAE, a second episode of late-onset of sepsis occurring at Day 14, was considered possibly related to the SOC (SAR). Seventeen deaths have been reported (10 in the meropenem arm and 7 in the SOC arm), most of them related to sepsis or to intercurrent diseases.
6.5 Conclusion	NeoMero-1 is the largest international, multicentre Randomised Control Trial of antibiotics in LOS to be conducted predominantly in a preterm infant population. Around half of subjects had culture proven infection. Superiority of meropenem over SOC was not demonstrated using protocol defined assessment criteria including predefined fixed treatment duration. However, in the secondary analysis among patients treated with meropenem more patients completed therapy earlier and less discontinued treatment due to resistant microorganisms than in SOC arm. These data suggest that meropenem may result in a better outcome than commonly used antibiotics for the treatment of late onset sepsis, although this comparison did not reach statistical significance (RR 1.4 (0.9-2.0)). Meropenem treatment does not outselect carbapenem resistant microorganisms. These data also suggest that meropenem monotherapy is as safe as commonly used antibiotic combinations in infants with LOS.

7. Signatures		
Reviewed by :	Irja Lutsar, Ursula Maria Theresia Trafojer, Corine Chazallon	
Authorised by :	Carlo Giaquinto	

Table 1. Demographic characteristics

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	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 <1000g (n)	45 (33%)	51 (38%)
-BW <1500g (n)	67 (49%)	80 (59%)
-BW >2500g (n)	43 (32%)	37 (27%)
SGA *n (%)	33 (24%)	34 (25%)
Medical history		
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%)
CVC	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%)

Table 2. Microorganisms confirming the sepsis and susceptibility to the AT

Microorganism	Meropenem N = 63 (%)	Susceptible to the meropenem	SOC n = 77 (%)	Susceptible to one antibiotic in SOC
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.	9 (14)	7 (78%)	11 (14)	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 G-negative	0	-	2 (3)	1 (50%)
Mixed	8 (13)	2 (25%)	8 (10)	2 (25%)

Table 3. Primary endpoint and reasons for failure

	Meropenem	SOC	
	n=136	n=135	
Primary endpoint			
Success at TOC	**44 (32%)**	**31 (23%)**	
Failure	**92 (68%)**	**104 (77%)**	**p=0.087#**
Reasons for failures			
Clinical or microbiological failure	**29 (21%)**	**31 (23%)**	
Death	**10 (7%)**	**6 (4%)**	
Persistent or new pathogen*	***n=14***	***n=16***	
	3 (2%)	**2 (1%)**	
No improvement and/or new signs**	***n=74***	***n=76***	
	18 (13%)	**24 (18%)**	
Modification of allocated therapy	**78 (57%)**	**85 (63%)**	
Not allowed antibiotic taken in first line	**2 (1%)**	**6 (4%)**	
Allocated therapy not started	**0**	**4 (3%)**	

* Specimen drawn up to 48 hours before the TOC visit

** Infants assessed if antibiotic therapy taken 8-14 days

Table 4. Reasons for modification of allocated therapy

	Meropenem N = 78	SOC N = 85	Median duration of AT (days; IQR)
Treatment completed before Day 8	30 (38)	10 (12)	7.6 (7.0-7.7)
Meningitis diagnosed	10 (13)	7 (8)	1.1 (0.2-1.7)
Lack of response	8 (10)	15 (18)	3.1 (0.8-4.6)
Introduction of new and/or continuation antibiotics after EOAT	8 (10)	5 (6)	9.7 (8.6-12.7)
Study antibiotics not appropriate based on culture results	5 (6)	15 (18)	3.0 (2.4-4.4)
Death	4 (5)	3 (4)	1.5 (0.2-5.0)
Adverse event	4 (5)	4 (5)	1.9 (1.3-2.7)
Resistant microorganism isolated	3 (4)	16 (19)	2.9 (2.2-4.9)
Treatment completed after Day 14	1 (1)	2 (2)	15.0 (14.8-16.4)
Other	5 (6)	8 (9)	4.1 (1.9-5.2)