DOSE CONFIRMATION OF FOSFOMYCIN AND FLOMOXEF FOR EMPIRIC TREATMENT OF NEONATAL SEPSIS

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BACKGROUND

- Rising antimicrobial resistance contributes to high morbidity and mortality associated with neonatal sepsis.[1]
- Off-patent fosfomycin and flomoxef antibiotics offer good coverage against ESBL-producing organisms, however recommended neonatal doses are based on limited data.
- NeoSep1 trial is an open-label RCT comparing novel combination and currently used antibiotic regimens for the empiric treatment of neonatal sepsis (ISRCTN48721236).

Aim: A run-in pharmacokinetic (PK) and safety study of fosfomycin and flomoxef was performed to confirm proposed doses before starting the main NeoSep1-trial

METHODS

Neonates with suspected sepsis were sequentially enrolled into 3 treatment cohorts:

1) fosfomycin and amikacin,
2) flomoxef and amikacin, and
3) flomoxef and fosfomycin

Fosfomycin Dose: Preterm infants: 100 mg/kg Q12 if postnatal age (PNA) ≤7 days (day of birth=day 1) or <1.5 kg, and 150 mg/kg Q12 if PNA ≥8 days and ≥1.5 kg. Term infants: 150 mg/kg Q12.
Flomoxef Dose: Preterm and Term infants: 40 mg/kg Q8 if PNA ≤7 days, and 50 mg/kg Q8 if PNA ≥8 days.

Day of birth = day 1 for PNA calculations
After the 1st dose, 3 blood samples were drawn for PK assessment. An additional pre-dose sample was drawn 5 days later if on antibiotics.

METHODS (cont.)

Plasma drug concentrations were quantified using validated LC-MS/MS methods. Fosfomycin concentrations were compared to the NeoFosfo study[2], and flomoxef to published studies from Japan.[3-7] Neonates were followed for 28 days for safety evaluations.

RESULTS

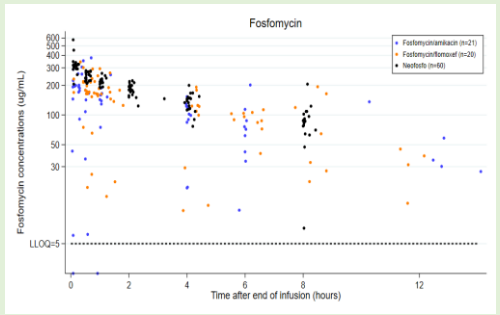
Sixty-five neonates (52 from South Africa; 13 from Kenya) were enrolled March-November 2023; 62 received trial antibiotics. At baseline, 48/62 (77%) were preterm, and 48 (77%) were ≤7 days PNA.

Table 1. Baseline characteristics of neonates administered fosfomycin and flomoxef

	Cohort 1 fosfomycin/amikacin N=21	Cohort 2 flomoxef/amikacin N=21	Cohort 3 fosfomycin/flomoxef N=20	Total N=62
Sex: Female	8 (38%)	12 (57%)	14 (70%)	34 (55%)
GA at birth (wks)	31 [27, 38]	34 [26, 40]	32 [30, 42]	32 [26,42]
Birth weight (g)	1285 [875, 3105]	1670 [870, 3310]	1682 [1180,2970]	1478 [870, 3310]

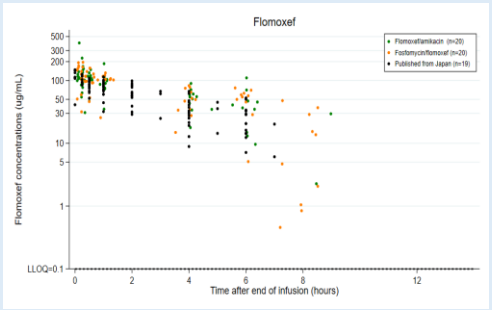
GA=gestational age; wks=weeks; g=grams; Numbers are N (%) or median [min, max]

Figure 1. Fosfomycin concentrations (µg/mL) in NeoSep1-trial overlayed with the NeoFosfo study [2]



Day	Time Point	N	Median (Q1; Q3)
Day 1	5-15 min	41	195 (164; 223)
	30-60 min	41	164 (137; 189)
	4-6 hours	40	98 (67; 117)
Day 5	Pre-dose	16	37 (29; 92)

Figure 2. Flomoxef concentrations (µg/mL) in NeoSep1-trial overlayed with Japanese studies [3-7]



Day	Time Point	N	Median (Q1; Q3)
Day 1	5-15 min	40	117 (97; 150)
	30-60 min	40	103 (88; 118)
	4-6 hours	40	50 (35; 64)
Day 5	Pre-dose	14	12 (2; 30)

RESULTS (cont.)

- 48 (77%) neonates had adverse events

Table 2. Adverse Events of neonates in the NeoSep1-trial

	Cohort 1 Fosfomycin/ amikacin N=21	Cohort 2 Flomoxef/ amikacin N=21	Cohort 3 Fosfomycin/ flomoxef N=20
None	5 (24%)	7 (33%)	2 (10%)
Grade 1	2 (10%)	3 (14%)	1 (5%)
Grade 2	7 (33%)	6 (29%)	9 (45%)
Grade 3	3 (14%)	0 (0%)	5 (25%)
Grade 4	1 (5%)	2 (10%)	2 (10%)
Grade 5	3 (14%)	3 (14%)	1 (5%)

- 18 (29%) neonates had 22 SAEs, all unrelated to study drug.
- Prolonged jaundice occurred in 1 neonate, possibly related to fosfomycin and flomoxef, and spontaneously resolved.
- Seven neonates (11.6%; 95%CI: 5.7–22.8) died by day 28.

Discussion

- In this run-in PK phase, neonates (mostly preterm infants) had fosfomycin and flomoxef plasma concentrations similar to published literature.
- Although variability was observed shortly after birth, drug exposures support these doses for the larger randomised NeoSEP1 trial.

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References: 1. Antimicrobial Resistance Collaborators. *Lancet.* 2022; 2. Kane Z, et al. *J Antimicrob Chemother.* 2021; 3. Motohiro T et al. *Jpn J Antibiot.* 1993; 4. Ihara T, et al. *Jpn J Antibiot* 1991; 5. Tomimasu K, et al. *Jpn J Antibiot* 1991; 6. Azagami S, et al. *Jpn J Antibiot* 1991; 7. Sato H, et al. *Jpn J Antibiot* 1991