TREAT INFECTIONS IN NEONATES

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To evaluate the pharmacokinetics, tolerability and short-term safety of ciprofloxacin in neonates with suspected (or proven) Gram Negative infection

Phase I, open-label pilot PK Study -TINN Treat Infections in Neonates Program

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PROTOCOL SYNOPSIS

Type of study	Pilot Population PK study - Clinical Trial
Study Design	Phase I, open-label study to evaluate the pharmacokinetics, tolerability and short-term safety of ciprofloxacin in neonates with suspected (or proven) Gram Negative infection.
Type of control	Nil
Location	Liverpool Women's NHS Foundation Trust (Neonates) Alder Hey Children's NHS Foundation Trust, Liverpool UK
Test products	Ciprofloxacin
Dosage regimen	10 mg / kg / dose, 12 hourly (adjusted if indicated by interim analysis)
Route of administration	Intravenous, 30 - 60 minutes infusion

Objective(s) of the study	To evaluate the multiple-dose pharmacokinetics of ciprofloxacin in neonates and young infants (24 – 52 weeks postmenstrual age) with suspected or proven Gram Negative infection. To evaluate the tolerability and describe short-term safety of ciprofloxacin in neonates and young infants with suspected (or proven) Gram Negative infection. To describe the clinical outcomes of neonates treated with ciprofloxacin
Sample size	50 patients between 24 -52 weeks postmenstrual age
M/F	not predetermined
Sample Size (Pro rata to the ICH EMEA age-groups for paediatric studies)	50 neonates stratified according to postmenstrual age (premature or not) to represent ages between 24 -52 weeks with 5- 8 patients in each 4 /5 week period. The target recruitment is 5-8 patients to represent each 4/5 week period in the range 24-27, 28-31, 32-35, 36-39, 40-43, 44-47 and 48-52 weeks postmenstrual age. In order to attain this number of samples on day 5- 7, we will need to recruit more participants than this as some participants will die, others will move to other centres and some parents will decline repeated sampling.
Study Interventions	Sparse blood samples (n=2 or 3 depending on weight) will be drawn on day 1 and day 5- 7 (or last day of treatment if the course is completed before day 7). Monitoring of adverse events DNA for pharmacogenetics (scavenged clinical samples or buccal) CSF (if required clinically) Faeces
Duration of ciprofloxacin treatment	At least 5 days
Duration of follow up	3 days after completion of ciprofloxacin treatment (plus stool sample 4 - 6weeks after completion of ciprofloxacin)
Inclusion criteria	Receiving ciprofloxacin following clinical decision by attending physician
Exclusion criteria	Likely not to survive 48 hours in the judgement of attending physician
Endpoints	
Primary	Ciprofloxacin plasma concentration and population pharmacokinetic (PK) parameters [maximum concentration, clearance, area under the curve (0-tau)], their relationship with selected covariates their inter-individual variability (CV%). Covariate analysis will include postmenstrual age, gestational age, postnatal age, weight, and serum creatinine
Secondary	1. PK variables, including apparent volume of distribution and half life. 2. Withdrawal due to lack of tolerability 3. Adverse events (AEs) and serious adverse events (SAEs). 4. Outcome of treatment episodes (clinical and microbiological)
Power calculation	This is not a hypothesis-testing study. The pharmacokinetic (PK) data generated from this study will assist in dose selection for use in neonates

	and infants. At this stage there is no data for this medicine in this age group. Accordingly, sample size calculations are not possible for this pilot study. Sample size and number in each age-range have been based on the experience of the PK scientists involved in the study.
Options	
Recruitment issues	If recruitment is poor, other sites will be approached.
Interim analyses	Blood levels will be monitored after every 10 patients recruited and interim pharmacokinetic analyses will be conducted, following which adjustments may be made to optimise the dose based on PK PD modelling.
Stopping rules	None anticipated
Statistical methods	
Primary analysis	Population pharmacokinetic analyses will be performed and the effect of covariates. This preliminary POP-PK model (PK parameters and their variability estimates in the 50 neonates and infants) will be used for simulations to determine the optimal dosing regimen in this population. The optimal dose will be defined based on the pharmacokinetic-pharmacodynamic break points extrapolated from adult patients: AUC_{0-24}/MIC (AUIC) >100 for gram-negative pathogens. The optimal dose will be evaluated in further clinical studies.
Secondary analyses	1. PK: to investigate the potential effects of other covariates. 2. Tolerability: proportion of participants who withdraw due to intolerance of ciprofloxacin as judged by attending clinicians 3. Safety: descriptive statistics of adverse events 4. Outcome of treatment episodes: proportion of participants who have recovered within 3 days of stopping ciprofloxacin. 5. Pharmacogenetic analyses will focus on ciprofloxacin transporters (OAT3, BCRP).

Action	Following admission to the neonatal unit	At time judged suitable by clinical staff	Clinicall suspicion of sepsis	Clinical decision to start cipro-floxacin	First dose of cipro-floxacin	Sampling		Final dose of cipro-floxacin	3 days after completion of cipro-floxacin	4 – 6 weeks after completion of antibiotics
						Day 1	Day 5-7			
Parents or legally appointed representative told about study	X									
Formal discussion with parents or legally appointed representative		X		X*						
Consent		X		X*						
Blood culture as per clinical practice			X							
Gram Negative (suspected or proven)				X						
Enrolment (when eligible)				X						
Ciprofloxacin administered					X					
Baseline safety blood sample#					X					
Repeat safety blood sample#								X	X	
PK blood sample and pharmacogenetics						X	X			
CSF sample if required clinically and if consented				X						
Safety data collection				X	X			X		
Safety evaluation								X	X	
Faeces sample		X								X
DNA sample – if consented		X								
DNA sample from blood required for clinical care if consent obtained				X						
Test-of-cure									X	

* Formal discussion about the study and consent will be undertaken before clinical suspicion of sepsis when possible but in some cases consent will be requested at the time the baby is assessed to be septic. # Safety blood samples will be clinically indicated sampling episodes that may be slightly before or after the start or finish of ciprofloxacin