PROJECT FINAL REPORT

Grant Agreement number: 223614

Project acronym: TINN1

Project title: Treat Infections in Neonates 1

Funding Scheme: FP7-CP-FP

Period covered from 01/10/2008 to 31/10/2015

Name of the project co-ordinator: Prof. Evelyne Jacqz-Aigrain

Title and Organisation: Institut National de la Santé et de la Recherche Médicale (INSERM)

Tel: +33 1 4003 2150

Fax: +33 1 4003 4759

E-mail: evelyne.jacqz-aigrain@rdb.aphp.fr

Project website address: http://tinn-project.org/

FINAL PUBLISHABLE SUMMARY REPORT

EXECUTIVE SUMMARY

For a favourable benefit-risk balance it is essential to determine drug dosage to optimise efficacy and safety. In adults pharmacokinetic (PK), pharmacodynamic (PD) and safety studies are conducted to determine the appropriate dosing regimen. However, for many medicines, including anti-infective drugs, information about PK/PD and safety in children is insufficient and dosing varies widely. This may expose children to a considerable risk of lack of efficacy or overdose and insufficient information about the safety profile of these medicines.

Studying medicines in children requires considerable expertise. European experts in this field and paediatric patients are scattered throughout Europe. Therefore, European collaboration is key in bringing together relevant expertise of paediatric researchers and recruiting patients.

Given the above situation the TINN Consortium responded in 2008 to an EU-call, FP7-Health-2007-4.2.1 « Adapting off-patent drugs to the specific needs of paediatric populations ».

TINN1 aimed at evaluating PK and safety of ciprofloxacin, fluconazole and micafungin prescribed to critically ill neonates. Paediatric researchers from seven EU countries collaborated and divided research activities into seven Work Packages (WPs). The project was managed by INSERM Transfert:

- Project management (WP1)
- Preclinical studies (WP2)
- Pharmacokinetic and safety studies of ciprofloxacin (WP3) and fluconazole and micafungin (WP4)
- Ethics and safety (WP5)
- Set up and conduct of ciprofloxacin and fluconazole/ micafungin clinical trials (WP6)
- Distribution and publication of TINN1 results (WP7)

Pre-clinical studies were conducted using a stepwise approach starting with the review of the literature for PK and safety and conducting several surveys. Juvenile animal studies examined the PK of ciprofloxacin and fluconazole and developmental toxicity of ciprofloxacin. In silico modeling and simulation with PBPK models informed dose selection. Results of the literature reviews, surveys, animal studies, modelling and simulation studies for ciprofloxacin and fluconazole/ micafungin have been published. (see Section 6)

Clinical trials were conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practices Guideline and European Clinical Trial Regulations. The ciprofloxacin trial provided information on pharmacokinetics, efficacy and safety in neonates and will help to establish a consensus on ciprofloxacin use in neonates. Recruitment into the fluconazole versu micafungin randomized study has been completed and the data analysis is almost finalized. Results will be published after study completion.

To date Consortium members published a total of 34 **articles in peer reviewed journals** (15 open access) and shared their knowledge with the scientific community at a variety of conferences.

The TINN1 Consortium considers the conduct of paediatric research into medicines prescribed to children essential in order to fill relevant knowledge gaps. This will reduce harm and increase the benefit of drugs used for treating children in Europe and beyond. Filling this knowledge gap is considered a common responsibility of society and should be shared among all stakeholders including academia, industry, regulators and governments. Facilitating paediatric research with the aim of determining the correct dose and assessing drug safety will provide the necessary evidence to ensure consistent prescribing of drug doses that are efficacious and sufficiently safe for children.

Ensuring that children, as some of the most vulnerable members of society, have their right to access effective, safe and good quality medicines respected makes not only economic sense, as it saves resources and money in the long-term, but also ensures a more equitable society as a whole. The project has highlighted areas where additional support for academic researchers is needed to enable research into medicines prescribed to children; most of these being off-patent drugs.

The benefit of continuing to finance research into paediatric medicines in Europe will contribute "to the Union becoming the world's leading research area" and promote "world-class state-of-the art research" in Europe, as stated in the legislative basis for the Seventh Framework Programme.

1. PROJECT CONTEXT AND OBJECTIVES

It is essential to determine a suitable drug dosage optimising efficacy and safety thus providing a favourable benefit-risk balance. In adults pharmacokinetic (PK) and pharmacodynamic (PD) studies are conducted to determine the appropriate dosing regimen with an acceptable benefit-risk balance. However, for many drugs prescribed to children information about PK/PD is insufficient and dosing varies widely. (1)(2)(3) This may expose children to a considerable risk of lack of efficacy or overdose and insufficient information about the safety profile of these medicines.

The lack of appropriate information in the product label for the paediatric patient population has been recognised by many health authorities. Recent legislation in Europe has attempted to fill this information gap by obliging pharmaceutical companies applying for a marketing authorisation to submit a Paediatric Investigation Plan (PIP) or to apply for a waiver. (4)(5)

For medicines already on the market, companies have the opportunity to apply for a Paediatric Marketing Use Authorisation (PUMA). (5) However, a recent report by the EMA noted that this legislation did not appear to provide sufficient incentive for pharmaceutical companies to conduct paediatric studies on medicines where the patent has expired. (6) Notably, the majority of drugs prescribed to children are off-patent and sales of drugs for the treatment of paediatric conditions are usually lower than for adults.

It is therefore difficult to engage pharmaceutical industry to conduct paediatric research to fill the knowledge gap, notably concerning dosing and safety. This means in clinical practice dosing for the same condition in the same age and weight range varies considerably depending on local prescribing practices. (2)

Consequently children may receive a medicine which is not effective, because the dose is too low, thus exposing them to risks of side-effects without having sufficient benefit from the treatment. Alternatively they may be prescribed a dose that is too high and thus have a higher risk of experiencing dose-related toxicities. The prescription of off-label doses, i.e. a dose different to the one described in the product label, is common in children and particularly frequent in neonates. Off-label use in children has been associated with a higher risk of serious adverse drug reactions (ADRs) compared to licensed drug prescriptions.(7)

For paediatric patients, their families and paediatricians the current situation means that the large majority of drugs prescribed to children still do not have sufficient information in the product label to allow effective and safe prescribing for these young patients. This is reflected in the “Priority List” published by PDCO describing research priorities for off-patent drugs prescribed to children. (8)

Studying medicines in children requires considerable expertise and a thorough understanding of the differences between children of various age groups and adults. European experts in this field are scattered throughout Europe. Furthermore, paediatric patients with a specific condition in a given age category are distributed across Europe. Therefore, European collaboration is key in bringing together the relevant expertise of paediatric researchers and recruiting patients into studies evaluating drugs prescribed to children.

Neonates are a particularly vulnerable paediatric patient population in whom factors influencing PK, PD and safety are changing more rapidly compared to older children. (9–12) Furthermore, the drug metabolism maybe altered in neonates who are critically ill. (13) In contrast to older children and adults, neonatal systemic infections carry a considerable risk of spreading rapidly to the central nervous system and can have long-term sequelae. (14–17) Neonatal sepsis is one of the three most common causes of death in newborns world-wide. (18) Thus timely and effective treatment, with plasma

concentrations of anti-infective drugs sufficient to penetrate into the cerebrospinal fluid (CSF), is essential for these young patients.

Given the situation described above the TINN Consortium (Figure 1) responded in 2008 to an EU-call, FP7-Health-2007-4.2.1 « Adapting off-patent drugs to the specific needs of paediatric populations ».

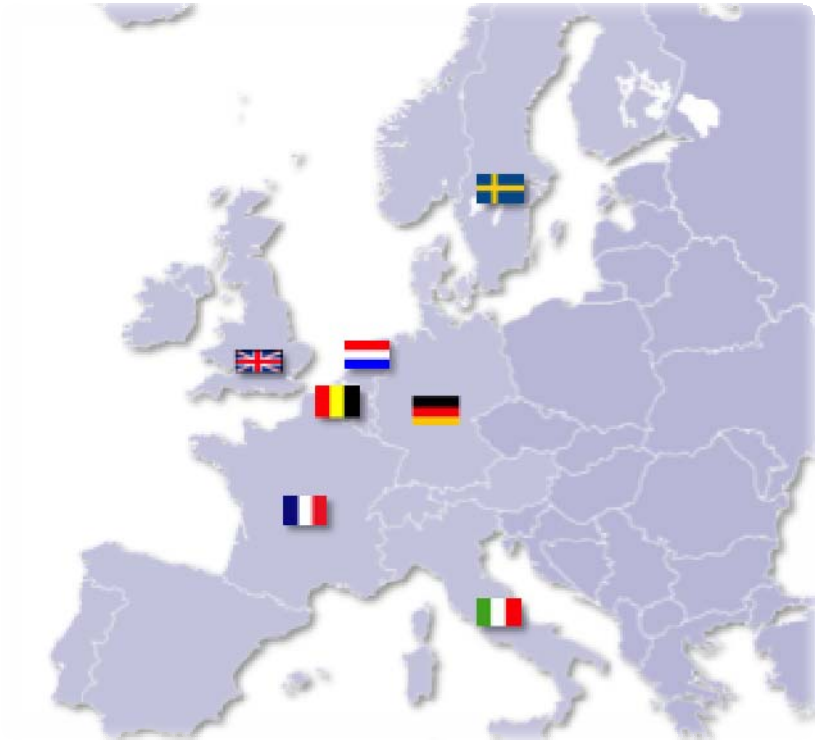


Figure 1 - EU COUNTRIES OF THE TINN1 CONSORTIUM

The TINN1 Consortium included 17 partners including initially two SMEs and a total of 74 participants from 7 EU countries. Experts included neonatologists and researchers trained in paediatric pharmacology and clinical trials.

The initial aim of the TINN1 project was to evaluate ciprofloxacin and fluconazole in neonates. In collaboration with two Small and Medium Enterprises (SMEs), a PIP was submitted for each drug with the aim to study PK and safety of these two anti-infectives, adapt formulations for neonatal administration and to obtain a PUMA for each. Both drugs are on the PDCO Priority List. (8) Ciprofloxacin is administered to treat neonates with sepsis caused by multi- resistant bacteria. Fluconazole is prescribed to neonates for the prevention or treatment of invasive candidiasis.

The initial PIPs for both projects were submitted but the PDCO asked for modifications on the studies planned for both drugs. After discussions within the consortium, all partners involved eventually decided that pursuing the PIPs to obtain PUMAs will not be feasible.

The TINN1 Consortium responded to feedback from health authorities, ethics committees and institutions concerning the PIP and the study protocols.

Ciprofloxacin.

1. Questions discussed included conducting double blind randomized-controlled trials (RCTs) rather than open label trials. The TINN Consortium considered that whilst it is recognised that double blind RCTs are considered the golden standard to establish efficacy, bacteria and fungi sensitive to anti-infective drugs will have the same AUC/MIC in adults as in neonates, thus bridging from adults to neonates was considered adequate. In addition, data from animal and in-vitro studies was available to successfully bridge using state-of the art modelling and simulation techniques. It was noted by the TINN Consortium that the EU guidance on paediatric clinical trials recognises that double blind RCTs do not need repeating in children, if the condition to be treated is the same as in adults. (19)

2. The potential chondrotoxicity of ciprofloxacin observed in animal studies was further point of discussion. As a consequence the TINN Consortium conducted a meta-analysis of safety data in the literature and found insufficient evidence for permanent chondrotoxicity of ciprofloxacin in neonates included in studies with limited follow-up. (20) In addition, a specific safety sub-study was added to the ciprofloxacin protocol using magnet resonance imagining (MRI) to assess the hip joint of neonates. The proposal by the TINN Consortium to evaluate potential skeletal effects of ciprofloxacin through a patient registry was rejected by PDCO.

3. A third point of discussion concerned the potential photo-tumorgenesis observed in mice exposed to UVA rays and whether there is a risk for neonates treated with phototherapy for hyperbilirubinaemia. (Klecak, 1997) The TINN1 Consortium noted that UVA radiation has a wave length of 320 to 400 nm, whereas phototherapy units use predominantly a wave length of 460-to-490 nm. (21) Therefore, phototherapy was not considered to pose a risk.

Considering that the use of ciprofloxacin is a rescue treatment for critically ill neonates where no other antibiotic is effective, and that health authorities have not contraindicated its use in these patients, the TINN Consortium considered it pertinent to examine PK and safety of ciprofloxacin prescribed during routine neonatal clinical practice, in order to determine the appropriate dose for this patient population. Thus providing evidence for effective and safe dosing.

Fluconazole

1. Reviewers noted that a considerable amount of data has been published about the use of fluconazole for the prevention of systemic candidiasis. The TINN Consortium noted that the proposed fluconazole study excluded this indication focusing on the assessment of PK and safety of fluconazole for the treatment of suspected or proven invasive candidiasis in neonates. Dosing requirements differ between prophylaxis of invasive candidiasis and treatment of acute systemic candidiasis and haematogenous Candida meningoencephalitis (HCME), where it is important that plasma levels are high enough to ensure penetration into the CSF.

2. Shortly after the project was accepted by the European Commission (EC) a new anti-fungal drug, micafungin obtained marketing authorisation in Europe. The micafungin label included the neonatal population. However, dose recommendations for the paediatric patient population was only stratified by body weight into two large groups, children with a weight below 40 kilogram and those equal to or above 40 kilogram. Considering that the former group will include pre-term neonates who may weigh only 500 gram to adolescents and recent publications suggesting that neonates may require higher doses per kilogram body weight than older children due to differences in drug clearance, micafungin was added to the fluconazole protocol as an active comparator.

Following feedback from PDCO, the death of the CEO of the sponsor company and the recent EU marketing authorisation of micafungin for the treatment of fungal infections, including in neonates (2008), the project plan was revised.

- INSERM was identified as a new sponsor
- Ciprofloxacin was to be studied in a single center in the UK
- The design of the fluconazole study protocol was modified to a randomised PK and safety trial of fluconazole and micafungin for treating invasive candidiasis in neonates

In conclusion, the TINN1 Consortium considers the conduct of paediatric research into medicines prescribed to children essential in order to fill relevant knowledge gaps. This will reduce harm and increase benefit of drugs used for treating children in Europe and beyond. Filling this knowledge gap is considered a common responsibility of society and should be shared among all stakeholders including academia, industry, regulators and governments. (Figure 2)

Given the importance of paediatric research it might be worthwhile discussing how European paediatric research can be better facilitated, ensuring solid financing of a complete research infrastructure with adequately trained administrative staff for sponsoring such research. National laws and regulations may need adapting to avoid duplication of processes.

Administrative burden should be reduced and input into planned paediatric protocols and consent forms by relevant and qualified stakeholders should be provided in a coordinated, pragmatic and consistent manner. A joint reflection by key stakeholders including EC, EMA and PDCO, SMEs, pharmaceutical industry, health care providers and paediatric researchers might be helpful in defining areas where the current European paediatric regulation can be improved. A training infrastructure should be financed on a permanent basis to ensure parties involved in paediatric research including regulatory authorities, sponsors of research, health care professionals and researchers are adequately qualified.

Consideration might be given to a close collaboration between academia, regulators and industry in laying out a training curriculum facilitating rotating internships of trainees between these stakeholders. Finally, it should be discussed at a European regulatory level whether a process can be developed to allow paediatricians to request an update of the SPC with paediatric data, if no PIP or PUMA is associated with the available data.

The benefit of financing and encouraging research into paediatric medicines and health care in Europe will be considerable. It will for example reduce health care costs in Europe by reducing mortality and long-term morbidity of children treated with ineffective or toxic drug doses. Furthermore, a European paediatric research infrastructure using a pragmatic approach to paediatric research and an accredited training program of staff involved in paediatric research will contribute "to the Union becoming the world's leading research area" and promoting "world-class state-of-the art research, based primarily upon the principle of excellence in research" as stated in the legislative basis for the Seventh Framework Programme.

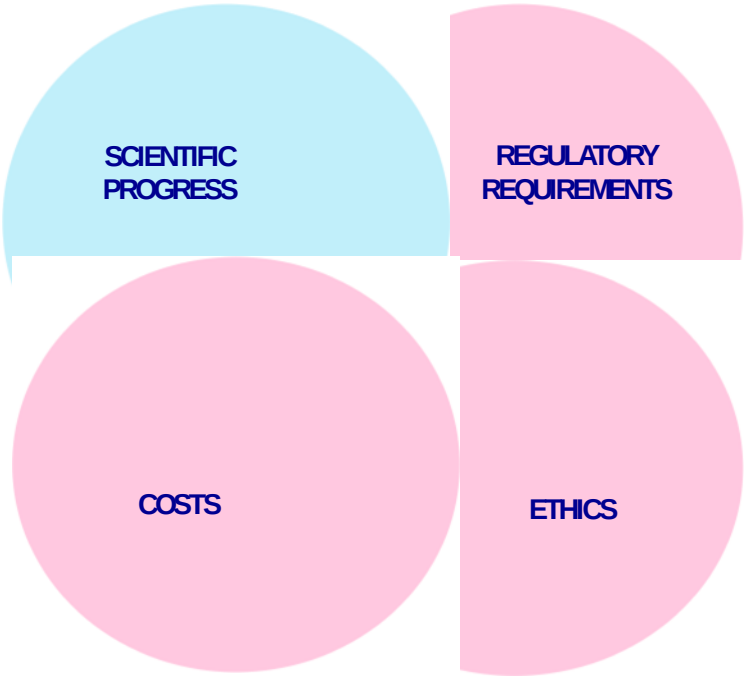


Figure 2 - CHALLENGES OF THE FP7 TINN PROJECT - CONCILING DIFFERENT OBJECTIVES

2. MAIN S&T RESULTS/FOREGROUNDS

TINN1 research activities were divided into seven Work Packages (WP) including project management (WP1), preclinical studies (WP2), pharmacokinetic study of ciprofloxacin (WP3), pharmacokinetic and safety study of fluconazole and micafungin (WP4), ethics and safety (WP5), organisation of clinical trials of ciprofloxacin and fluconazole/ micafungin (WP6) and distribution and publication of TINN1 results (WP7). (Figure 3)

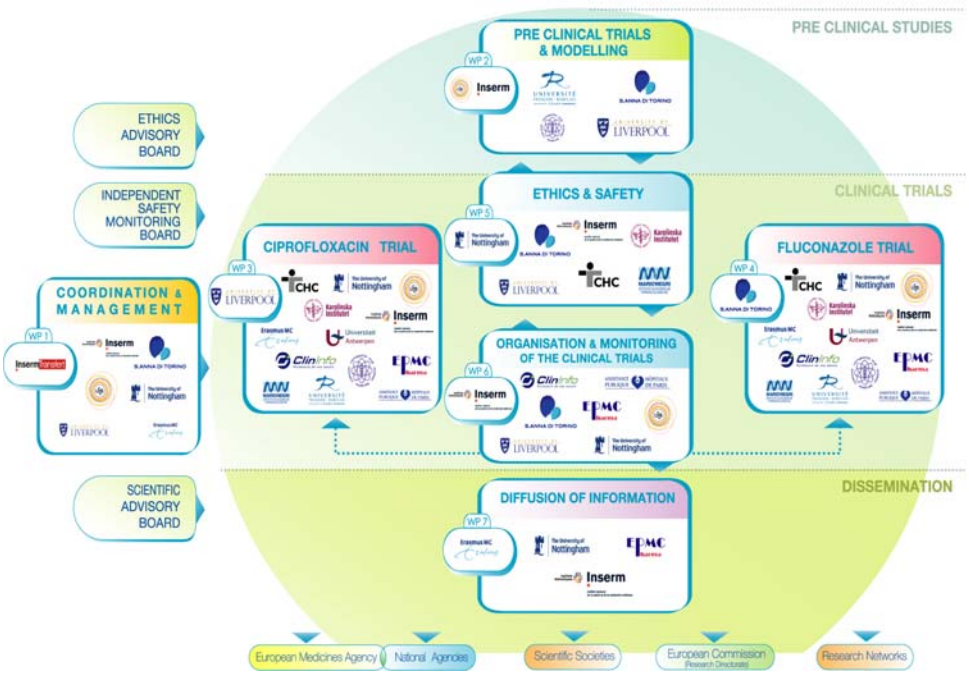


Figure 3 - TINN: WORK PACKAGE ORGANIZATION

WP1 - PROJECT MANAGEMENT

The project was managed by INSERM Transfert. WP1 consisted of managing the consortium activities in support of the coordinator. It involved contractual follow-up of the consortium and grant agreement and the overall legal, financial and administrative management of the consortium. It also included coordinating and completing project reporting.

WP2 - PRECLINICAL STUDIES

The literature was reviewed to identify all available animal studies, in silico studies and human PK data for ciprofloxacin and fluconazole. Juvenile animal studies examining developmental toxicity and PK of ciprofloxacin and fluconazole were conducted. This supported the development of a dosing rationale for ciprofloxacin and fluconazole, informed protocol writing and added to the understanding of the safety profile of these drugs prescribed to neonates (WP 3 and 4).

Pre-clinical studies, modeling and simulation were performed for both drugs.

Ciprofloxacin

We assessed the potential adverse effects of ciprofloxacin on neurodevelopment, liver and joints in mice. Newborn mice received subcutaneous ciprofloxacin at 10, 30 and 100 mg/kg/day from 2 to 12 postnatal days. Peak plasma levels of ciprofloxacin were in the range of levels measured in human neonates. We examined vital functions in vivo, including cardio-respiratory parameters and temperature, psychomotor development, exploratory behaviour and potential effects on joints, kidneys and liver. We found no effect of ciprofloxacin at 10 and 30 mg/kg/day. In contrast, administration at 100 mg/kg/day delayed weight gain, impaired cardio-respiratory and psychomotor development, caused inflammatory

infiltrates in connective tissues surrounding the knee joint and moderately increased extramedullary haematopoiesis. In summary, careful monitoring of cardio-respiratory, motor development and potential effects on joint development in neonates treated with ciprofloxacin is recommended. The results of the ciprofloxacin study have been submitted for publication.

For in silico experiments, the 'bottom- up' and 'top-down' approaches were considered. For the bottom-up approach, PBPK models were developed for ciprofloxacin. The population ciprofloxacin model allowed estimating PK Parameters and the influence of covariates. Simulations supported defining the dosing regimen according to age and bacterial strains.

For the validation of the PBPK model for ciprofloxacin in adults we compared data from simulations with observed data in plasma and tissues (liver, kidney, heart, spleen, lung and muscle) after adjusting for plasma clearance. Simulated AUC to observed AUC ratio was between 0.6 and 5.3. In children less than 5 years data from simulations over-predicted compared to observed data. However, the number of data samples was very small per study. We had two hypotheses to understand where the differences between simulated and observed data, in particular in tissues, came from: either from the structure of the model or the PK data measured by PET scan. Since simulations in animals with PK data and predictions were not accurate we considered that the structure of the model was not representative of reality. These findings were published in 2014. (22)

Fluconazole

We studied blood plasma levels of fluconazole following a single injection at 7 days of age or a chronic injection from 2 to 12 days of age in juvenile mice and analyzed pharmacokinetic samples.

Pharmacokinetic modeling and simulation approach was used to predict neonatal pharmacokinetics and dosing regimens for fluconazole (see Figure 4 below). As shown, three pharmacokinetic data sets were used. Extrapolated PK data from juvenile mice and adult healthy volunteers were used together with data from PB/PK modellling and estimated PK in neonates to simulate data for 100 clinical trials. Extrapolations were then compared with available PK data in neonates, showing that the extrapolated PK parameters were in close agreement with the references parameters available in neonates. Thus model-based extrapolations from juvenile mice, adults and in vitro-in silico data provided consistent predictions of pharmacokinetics of fluconazole in neonates. (Figure 4)

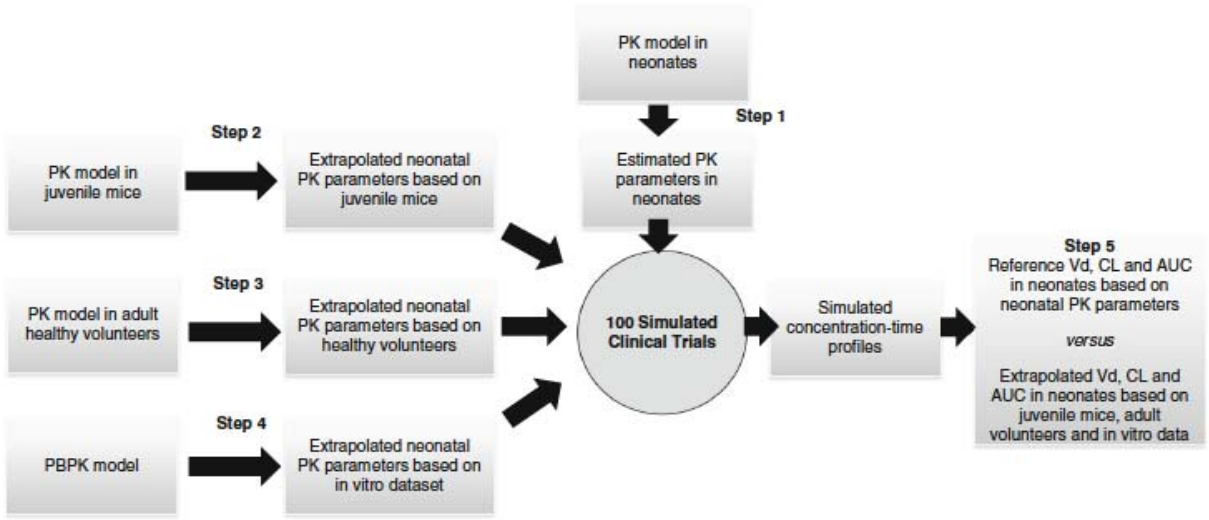


Figure 4 - MODELLING AND SIMULATION FOR NEONATES

For the 'top-down' approach, a mixed effect model published by Wade et al. was used to optimize the fluconazole dosing regimen. This model helped to define blood sample timing. Concerning the validation of the PBPK model for fluconazole in adults, we compared data from simulations with observed data in plasma and tissues (bone, heart, kidney, liver, spleen, muscle and lung). Simulated AUC to observed AUC ratios were between 0.3 and 4.7. In neonates we compared

simulations from the PBPK models with simulations from the population PK model published by Wade et al. (23) Results were accurate except at the peak of concentration. These results were published in 2014. (24) Finally, new data will be available once data from the fluconazole versus micafungine trial are available.

WP3 - CIPROFLOXACIN – PHARMACOKINETIC AND SAFETY STUDY

This WP successfully completed the design and conduct of clinical studies of pharmacokinetics, efficacy and safety of ciprofloxacin in neonates and young infants. This work provided evidence for a novel dosing regimen and enhanced the understqnding of the benefit risk balance of ciprofloxacin in this population.

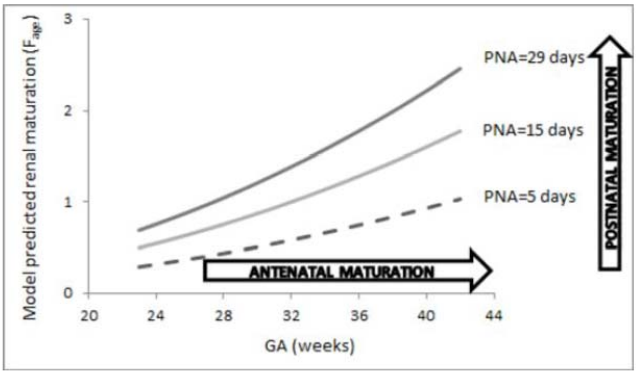
A clinical trial was conducted to assess pharmacokinetics, safety and efficacy of ciprofloxacin. This study recruited 64 neonates in two centres in the UK. All relevant ethical and regulatory approvals were in place.

PHARMACOKINETICS (PK)

The data from 60 newborn infants (postmenstrual age range: 24.9-47.9 weeks) were available for population pharmacokinetic analysis. A two-compartment model with first-order elimination showed the best fit with the data. A covariate analysis identified that gestational age, postnatal age, current weight, serum creatinine concentration and use of inotropes had a significant impact on ciprofloxacin pharmacokinetics. Monte Carlo simulation demonstrated that 90% of hypothetical newborns with PMA<34 weeks treated with 7.5 mg/kg twice daily and 84% of newborns with PMA≥34 weeks and young infants receiving 12.5 mg/kg twice daily would reach the AUC/MIC target of 125, using the standard EUCAST MIC susceptibility breakpoint of 0.5 mg/L. The associated risks of overdose for the proposed dosing regimen were less than 8%. The results expand our understanding of ontogeny during the neonatal period and the relationship between time since birth and maturity (Figure 5).

Figure 5 - Model-based predicted impact of renal maturation on clearance of ciprofloxacin in neonates

The population PK model contributes to our understanding of the ontogeny of drug disposition in premature neonates. This figure (taken from Zhou et al. 2014) illustrates the combined effects of the duration of pregnancy and the time since birth on renal maturation.



Influence of both gestational age (representing antenatal maturation) and postnatal age (representing postnatal maturation) on renal maturation

COMPARISON OF THE RESULTS OF PLANNED SAMPLING AND OPPORTUNISTIC SAMPLING

Pharmacokinetic data from 60 newborns were obtained with a total of 430 samples available for analysis; 265 collected at predetermined times and 165 that were scavenged from those obtained as part of clinical care (Figure 6). All datasets were fit using a two-compartment model with first order elimination. The model derived from opportunistic sampling could identify the most significant covariates and provided reasonable estimates of population pharmacokinetic parameters (clearance and steady-state volume of distribution) when compared with the model based on the planned samples and the model that included all the available time points. The predictive performance of all the models was confirmed in an external validation by Bayesian estimation, and all three models showed similar results. Monte Carlo simulation based on area under the concentration–time curve from zero to 24 h (AUC24)/minimum inhibitory concentration (MIC) using either the opportunistic or planned sampling model gave predicted similar doses ciprofloxacin (Figure 7). The conclusion of this

piece of work was that blood samples obtained opportunistically (scavenged) during clinical care of neonates can be used to estimate ciprofloxacin pharmacokinetic parameters and dose requirements.

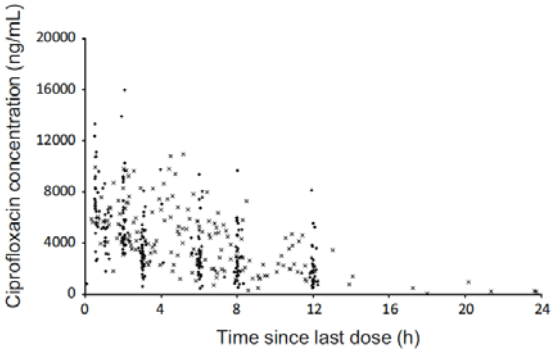


Figure 6 - Ciprofloxacin concentrations versus time. Diamonds represent special pharmacokinetic samples, and crosses represent opportunistic samples

The methodological work to compare the effects of timed samples and opportunistic samples started with an assessment of the times at which samples were taken.

The opportunistic samples covered all the relevant time points and may have provided a more complete coverage of the sampling times.

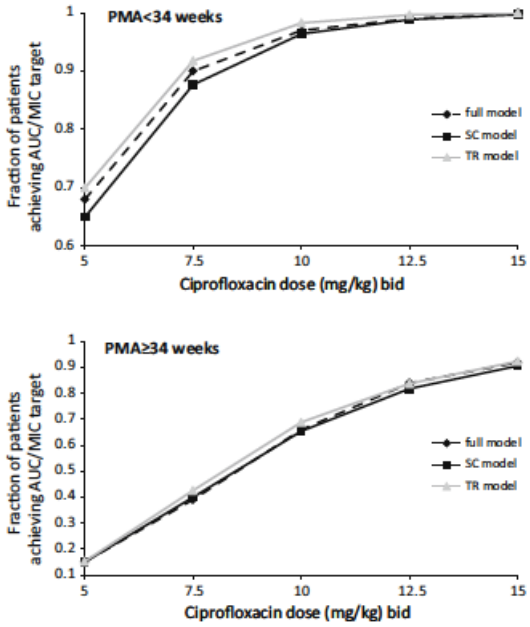


Figure 7 - Target attainment rates in neonates and young infants

Several comparisons were made of the models derived from samples at specified time points and samples obtained during clinically indicated sampling episodes. In mathematical terms the models were identical. This is illustrated in the figures where predictions of the success rate of different doses, and the risk of overdose, are superimposable.

Fig. 4 Target attainment rates in neonates and young infants. The target attainment rates for the 100 simulated trials for an MIC value of 0.5 mg/L is presented as a function of dose and sampling strategy. AUC/MIC target is 125 h. *MIC* minimum inhibitory concentration, *AUC* area under the concentration–time curve, *PMA* postmenstrual age, *bid* twice daily, *SC* opportunistic blood samples model, *TR* predetermined (i.e. scheduled) samples model

EFFICACY

The primary outcome for the assessment of efficacy was survival with a normal value for C-reactive protein (CRP) 3 days after stopping ciprofloxacin. The survival status or CRP data (3 days after the cessation of ciprofloxacin) were available for 61 participants. Overall 47 were cured and 14 were not cured. Of those cured, 13 did not have a CRP > 10mg/L during the course of ciprofloxacin so did not have evidence of infection (this was not known at the time of recruitment). Among the 48 with a CRP > 10mg/L during the course of ciprofloxacin (i.e. with evidence of infection) 34 (71%) were cured. The three participants with proven Gram-negative infections (the target of ciprofloxacin) were cured.

SAFETY

A total of 22 AEs were reported by investigators in 19 of 62 included patients. 8 deaths were reported in the 42 days following the last dose of ciprofloxacin. All reported AEs were assessed as “probably not related” or “definitely not related to ciprofloxacin”. Seizures were reported in five participants before they were recruited and an exacerbation of seizures

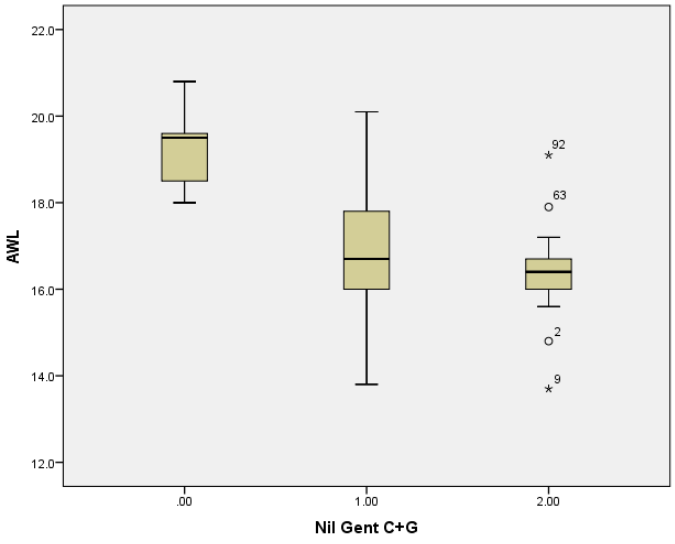
was reported as an adverse event after recruitment in one participant; no participants developed seizures after recruitment. Abnormal cranial ultrasound findings were present at recruitment in 16 participants. One developed periventricular leucomalacia on cranial ultrasound after recruitment but this was not confirmed on magnetic resonance imaging; the participant had surgery for panintestinal necrotizing enterocolitis just before recruitment.

Joint assessment did not show any problems relating to altered mobility, pain and/or redness. The incidence of inflammation at the site of infusion of ciprofloxacin (phlebitis) was no higher during infusion of ciprofloxacin than in routine clinical practice. A small number of changes in laboratory parameters were observed. None were clinically significant and all could be related to the underlying illness.

MRI

A separate cohort study was designed to investigate a specific concern about the use of ciprofloxacin in neonates, arthropathy. This study was designed to use magnetic resonance imaging (MRI) to study the relationship to between exposure to ciprofloxacin and measurements of the largest joint in neonates (the hip). A total of 119 neonates were recruited of whom 96 attended for scan. It was possible to complete the hip sequences in 68 cases. Of these 3 had no medication history. Accordingly, 65 neonates were evaluable for the relationship between medication and variables on hip MRI. Participants were classified according to whether they had received ciprofloxacin or not. Exposure to gentamicin was included as a control for exposure to infection. Neonates who received neither antibiotic had larger acetabular width and depth than other neonates. There were no differences between the group exposed to gentamicin and the group who were given gentamicin and ciprofloxacin. There was no relationship between exposure to ciprofloxacin and hip measurements. Although this study was small, the measurements of hip variables were precise and reproducible. This study does not raise a safety signal for effects of ciprofloxacin on the hips of neonates. (Figure 8)

Figure 8 - Comparison between groups defined by antibiotic exposure for acetabular width on the left (AWL)



The key result of the MRI study was the different measurements for the acetabulum among babies with different antibiotic exposures.

Group 0 is the group that did not receive any antibiotics before the MRI scan. Group 1 is the group that only received gentamicin. Group 2 is the group that received both gentamicin and ciprofloxacin. In line with the prescribing policy of the recruiting unit babies did not receive ciprofloxacin without receiving gentamicin. Group 0 has a statistically larger measurement of AWL than Groups 1 and 2. Groups 1 and 2 are not different. This suggests that exposure to ciprofloxacin is not associated with any changes in hip measurements on MRI

This WP provides an increased understanding of an antibiotic that is widely used in neonates globally. This is relevant to a vulnerable population that is at high risk from the emerging threat of antimicrobial resistance.

The increased understanding will allow individual clinicians to make more informed choices about the use ciprofloxacin in neonates. In the past the risks of ciprofloxacin have not been expressed precisely. The work in this WP provides more precise information than previous studies. In particular, there have been concerns about inflammation at the site of injection. We have shown that this is not a common problem. More importantly, the use of ciprofloxacin is limited because of concerns about damage to the joints. The lack of evidence for acute joint injury during the administration of ciprofloxacin during the clinical trial and the MRI study will help re-evaluating the potential risks of arthropathy in this age group and guide the clinical community if and when to use this medicine based on microbiological and clinical reasons.

This body of work will also inform guideline development groups nationally and internationally.

The population PK model contributes to our understanding of the ontogeny of drug disposition.

The methodological work to compare two approaches to the timing of blood samples during clinical trials is of general importance. One of the ethical imperatives during the conduct of clinical trials involving neonates is to minimize the burden of the trial on the participants. One common approach to PK studies is to collect study-specific blood samples at fixed time points. This often means that babies have venipuncture (when needles are inserted to do blood tests) that they wouldn't have as part of clinical practice. This has a greater impact on neonates than other groups, particularly extremely premature neonates. The demonstration that models for ciprofloxacin are similar for study-specific samples and for samples obtained during clinical practice will increase the readiness of clinicians to contribute to clinical studies of pharmacokinetics. In addition, it will be easier to design studies that validate population PK models by embedding PK studies in other trials and by embedding PK studies in clinical practice. Not every molecule will be suitable for this approach but for suitable molecules this is a useful advance.

WP4 - FLUCONAZOLE AND MICAFUNGIN FOR THE TREATMENT OF NEONATAL INVASIVE CANDIDIASIS - PHARMACOKINETIC AND SAFETY STUDY

The incidence of neonatal invasive fungal infection varies considerably by region and neonatal unit. (25–27) In neonates Candida is the most common fungal organism causing infection. (26) In preterm very low birth weight (VLBW; i.e. <1500 g at birth) neonates invasive candidiasis carries a high burden of long-term morbidity and mortality. Up to 41 % of VLBW neonates with invasive candidiasis and 43% of those with an extremely low birth weight (ELBW; <1000g) die. (15,26,28) Neurodevelopmental impairment has been observed in up to 56% of VLBW neonates surviving invasive candidiasis. (29)

Antifungal agents currently used in neonatal care for the treatment of invasive fungal infections are amphotericin B, fluconazole and micafungin. (30) Caspofungin, 5-Flucytosine, voriconazole and ABLC are additional antifungal drugs prescribed. (31) However, available pharmacokinetic, pharmacodynamic and safety data for these drugs for the indication of neonatal invasive candidiasis and HCME is limited. (31) Finally, limited information is available on the comparability of PK/PD, pharmacogenetics and benefit-risk of antifungal treatments in neonates with invasive candidasis.

Fluconazole is a triazole and is available as either oral or intravenous formulation. Fluconazole interferes with the synthesis of ergosterol in the fungal plasma membrane by inhibiting the cytochrome P450 (CYP) dependent lanosterol C-14α-demethylase, leading to a disruption of cell replication. (32) In neonates the volume of distribution of fluconazole is larger and has a higher variability, compared to older children and adults, due to the larger proportion of body water. Fluconazole is eliminated primarily unchanged through the kidneys and elimination is prolonged in patients with renal impairment. In neonates the elimination half-life is longer than in older children and adults. (23)

The US label of fluconazole notes that "in premature newborns (gestational age 26 to 29 weeks), the mean (%CV) clearance within 36 hours of birth was 0.180 (35%, N=7) mL/min/kg, which increased with time to a mean of 0.218 (31%, N=9) mL/min/kg six days later and 0.333 (56%, N=4) mL/min/kg 12 days later. Similarly, the half-life was 73.6 hours, which decreased with time to a mean of 53.2 hours six days later and 46.6 hours 12 days later." (33)

The Summary of Product Characteristics (SPC) of fluconazole currently recommends a dose of 6 to 12mg/kg every 72 hours for the treatment of invasive candidiasis in term neonates aged 0 to 14 days. For neonates aged 15 to 27 days the dosing frequency is changed to every 48 hours. No loading dose for the paediatric patient population and no dosing information for pre-term neonates is provided. However, a loading dose is proposed for children (28 days to 11 years old) with mucosal candidiasis and adults with oral or systemic candidiasis. (33)

In contrast, the literature suggests dosing neonates with a loading dose of 25mg/kg and a maintenance dose of 12mg/kg/day in order to reach the target $AUC_{0\text{-}24}$, because without loading dose drug therapeutic levels are only reached after several days in neonates. (34–37)

Limited data is available about the safety profile of intravenous fluconazole for the treatment of invasive candidiasis in newborns. Most data concerns the use of fluconazole for prophylaxis against fungal infections reporting transient elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). (38–43) In the SPC common undesirable effects include abnormal liver function tests and gastrointestinal effects (abdominal pain, vomiting, diarrhoea, nausea). Uncommon or rare undesirable effects include more severe hepatotoxicity, effects on the hematopoietic system, QT prolongation, seizures and severe skin reactions (including toxic epidermal necrolysis, Stevens-Johnson syndrome and angioedema).

Micafungin is an echinocandin and is available as intravenous formulation. Micafungin inhibits the synthesis of 1,3-β-D-glucan, an essential component of the fungal cell wall. (44) Micafungin has been shown to be metabolised to several compounds. Whilst in adults exposure to these metabolites is low, higher exposure levels have been observed in children. (45) These metabolites do not contribute to the overall efficacy and it is currently unclear whether there is any concern for safety. Micafungin is primarily eliminated via faeces. Mean clearance in premature infants is more rapid than in older children and adults. (46)

The SPC for micafungin currently recommends a daily dose of 2 to 4mg / kilogram / body weight for all children (including neonates) with a body weight $\leq$40kg for the treatment of invasive candidiasis. No more detailed, age adjusted dosing information for the treatment of systemic fungal infections in the paediatric patient population is provided. No loading dose is recommended for adults or children. (44)

In contrast, the literature suggests dosing neonates with a loading dose of 15mg/kg of micafungin and a maintenance dose of 10mg/kg/day in order to reach the target AUC_{0-24} for the treatment of invasive candidiasis. (27,46–50)

Limited data is available concerning the safety profile of micafungin in neonates. In the SPC clinical trial data in older children noted a higher frequency of thrombocytopenia, tachycardia, hypertension, hypotension, hyperbilirubinemia, raised ALT, AST and alkaline phosphatise (AP) and acute renal failure compared to adults. (44,51–53) Further, potential serious adverse drug reactions with an unknown frequency include haemolysis and severe skin reactions (such as toxic epidermal necrolysis and Steven-Johnson syndrome).

In summary, evidence from the literature suggests that dosing instructions provided in the SPCs of fluconazole and micafungin may not be appropriate for the treatment of systemic neonatal candidiasis and HCME. Furthermore, very limited comparative PK, clinical outcome and safety data of fluconazole and micafungin is currently available for neonates. Furthermore, pharmacogenetic aspects of drug metabolism in neonates, which might be different compared to adults, have not been studied for these drugs. Consequently it is difficult for treating physicians to select a treatment with the most favourable benefit-risk profile for each patient, because there is insufficient information about the most appropriate dosing and safety in this vulnerable population.

Therefore, a study was conducted examining fluconazole and micafungin in neonates with suspected or culture proven systemic candidiasis treated with a loading dose and followed by a maintenance dose for at least five days.

The study was planned in collaboration with the TINN1 Consortium using a stepwise approach starting with the review of the available literature for PK and safety. This was followed by several surveys and a modelling and simulation study for fluconazole to support dosing and PK sampling times in the planned trial. WP2 informed dosing of fluconazole (figure 9), WP4 conducted the fluconazole / micafungin trial and WP 6 set up the trial.

CLINICAL TRIAL: Fluconazole versus micafungin in neonates with suspected or proven candidiasis : a randomized pharmacokinetic and safety study.

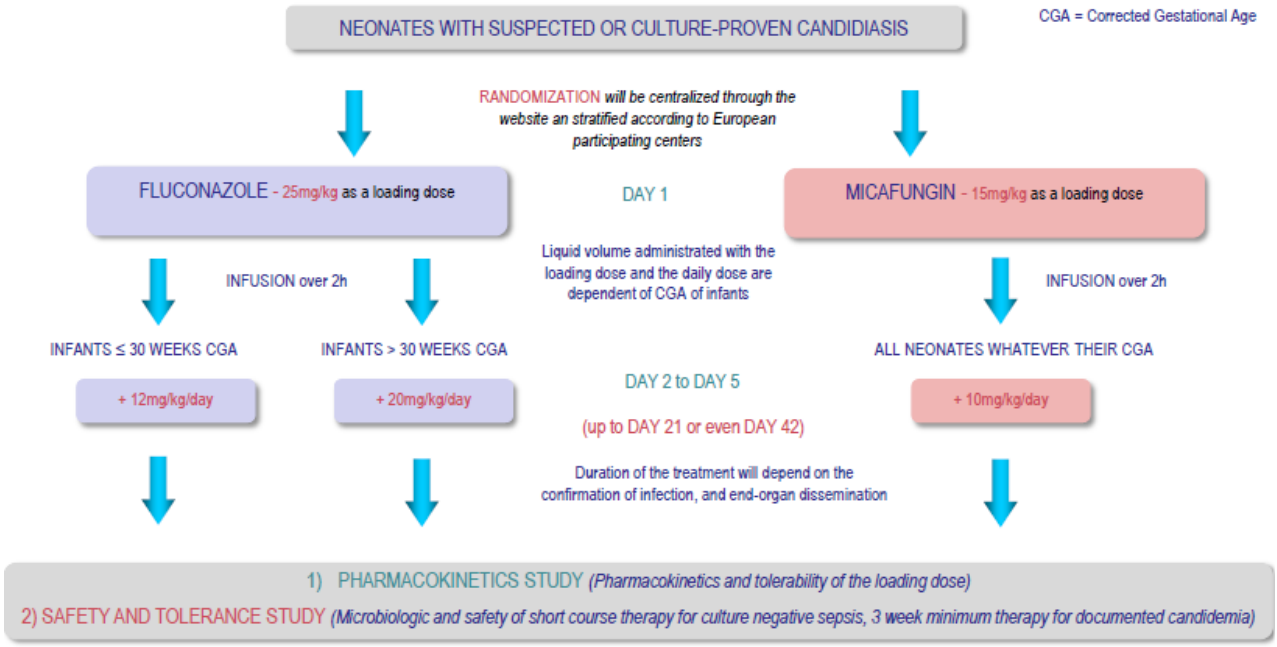


Figure 9 - OVERALL TRIAL PLAN FOR FLUCONAZOLE / MICAFUNGIN STUDY

1. Aims and Objectives

The aims were to determine optimal dosing and identify covariates that may influence pharmacokinetics, including drug interactions and pharmacogenetic factors. In addition, the time to reach the target $AUC_{0\text{-}24}$ was examined.

Primary objectives of this study were to evaluate the pharmacokinetics of fluconazole and micafungin in neonates with suspected or culture-proven candidiasis.

Secondary objectives were to evaluate safety, tolerability and short-term outcome of fluconazole and micafungin treatment in neonates.

The trial has been conducted in accordance with the principles of Declaration of Helsinki, Good Clinical Practice Guidelines and European Clinical Trial Regulations.(54–56) Ethics approval was granted by the Ethics board of the TINN Consortium and National Research Ethics Committees. Informed consent was sought from the parents or legal guardians of each child prior to inclusion.

Recruitment into the study has been completed and the data analysis is almost finalised. Results will be published after study completion.

2. Methods

Fourteen EU neonatal intensive care units participated and are listed in Annex 1. Inclusion and exclusion criteria are presented in Table 1.

TABLE 1: INCLUSION AND EXCLUSION CRITERIA for Fluconazole / Micafungin study

INCLUSION CRITERIA	EXCLUSION CRITERIA
- Neonates and infants between 24 and 42 weeks gestational age with a post-natal age of 48 hours of life up to 120 days of life at the time of culture acquisition - Requiring antifungal therapy for microbiologically documented or clinically suspected Candida infection - Written informed consent by the parents or the legally	- Prior exposure to any antifungal treatment (prophylaxis or treatment of systemic fungal infection) - Concomitant medical condition, which in the opinion of the investigator may create an unacceptable additional risk - Infant previously enrolled in the study

authorized representative - Sufficient venous access to permit administration of study medication and monitoring of safety variables - Specifically for the French participants: the infant had to be insured	- Co-infection with a non-candida fungal organism - Isolated candiduria - History of hypersensitivity or severe vasomotor reaction to echinocandins or fluconazole - Pre-existing hepatic or renal disease - Infants with baseline Candida spp. isolate resistant to fluconazole or micafungin according to EUCAST/CLSI clinical breakpoints - Infants with a baseline isolate where there is insufficient evidence that the species in question is sensitive to fluconazole or micafungin

3. Neonates were randomised 1:1 to fluconazole or micafungin treatment by a central randomisation procedure using a website. The initial aim was to recruit 50 patients into each treatment arm and to include between 20 and 40 preterm infants into each treatment arm.

4. Dosing and treatment

According to modelisation and simulation data, neonates randomized to the fluconazole treatment arm were given a loading dose of 25mg/kg regardless of corrected gestational age (CGA). (24) The next day a maintenance dose of 12mg/kg/day was administered to neonates with a CGA below 30 week. Neonates with a CGA of 30 weeks or older were treated with a maintenance dose of 20mg/kg/day. Doses were adjusted, during treatment once the newborn was 30 weeks CGA. (Figure 9 above)

Dosing of micafungin was based on data from the literature. (27,47,50) Neonates assigned to the micafungin treatment arm were given a loading dose of 15mg/kg and a maintenance dose of 10mg/kg/day regardless of corrected gestational age.

In both treatment arms intravenous treatment was given for up to five days. Following the first 5 days of study drug treatment, the protocol permitted changing the dose and/ or antifungal treatment depending on clinical judgment by the treating physician.

Clinical and biological safety monitoring was continued until discharge or death according to the protocol and using local routine neonatal care practices. Safety monitoring was continued until discharge from hospital or death. After discharge data from routine follow up is being collected from medical records up to 24 months after the last dose of study drug. (Figure 10)

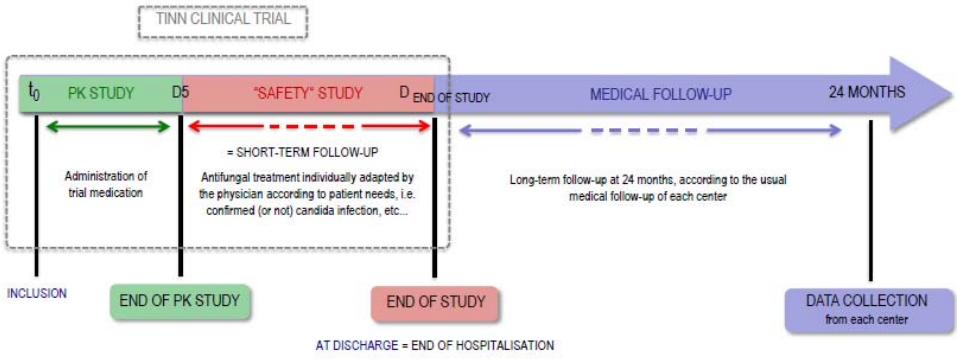


Figure 10 - PK AND SAFETY OF FLUCONAZOLE / MICAFUNGIN STUDY

5. PK study and samples

Blood samples for PK analyses were taken on day 1 and day 5 of treatment. (Figure 11) Two PK samples were taken from infants with a CGA below 32 weeks and three samples from those CGA 32 weeks or above. Infusion times and

sample times were recorded, and each age strata had two sampling schedules assigned according to wishes of the investigators and local usual practices.

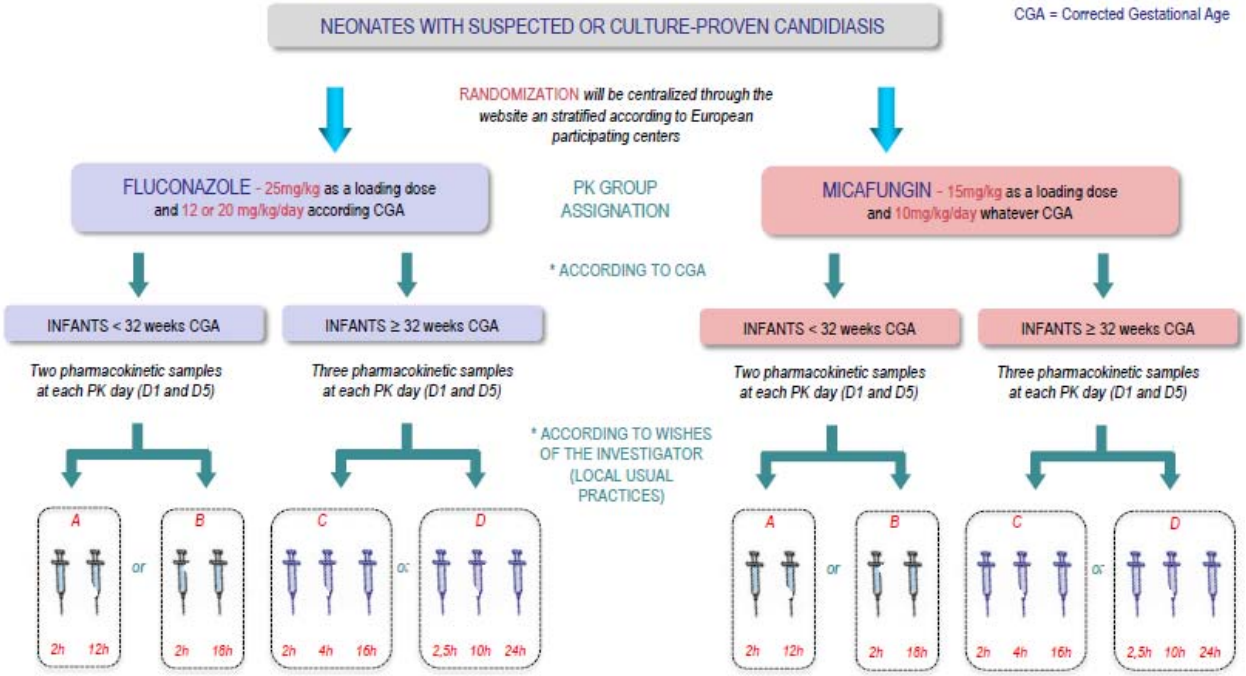


Figure 11 - PK SAMPLES OF FLUCONAZOLE / MICAFUNGIN STUDY

To increase the number of PK samples scavenged blood samples were obtained from the French neonatal network and an Italian center partner of the TINN Consortium. (Figure 12)

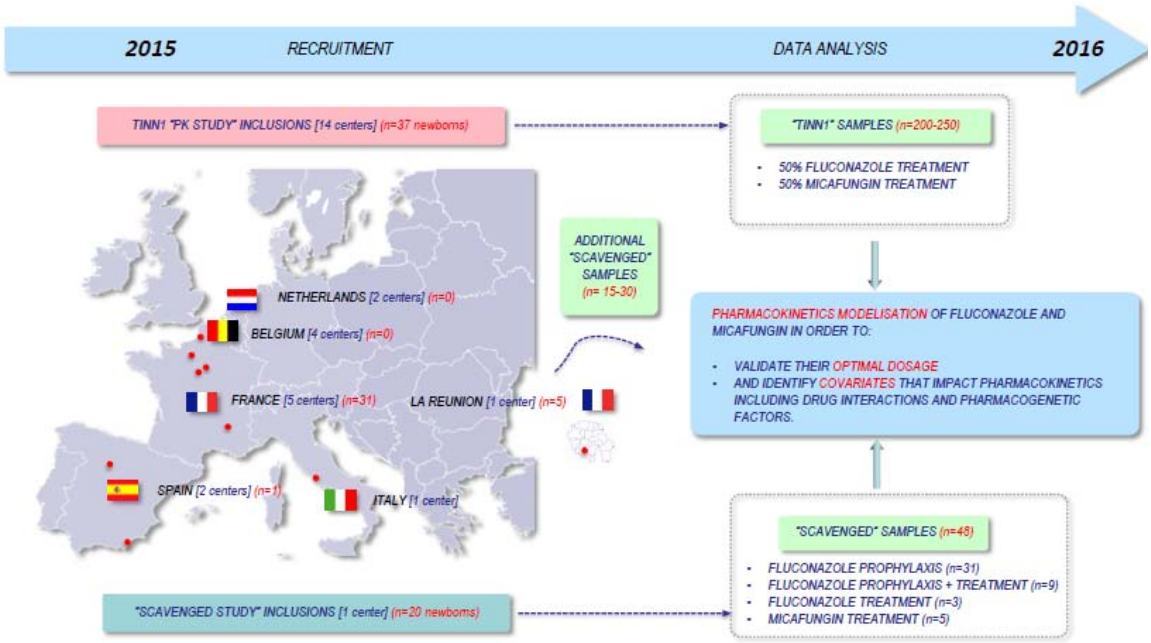


Figure 12 - SAMPLES FOR PHARMACOKINETICS MODELISATION OF FLUCONAZOLE AND MICAFUNGIN

DATA ANALYSIS

Characteristics of the study population will be summarised using descriptive statistics including demographic data, disease history and baseline characteristics describing the study population and comparing treatment groups.

Pharmacokinetic analysis out using the nonlinear mixed effects modeling program NONMEM (Globomax, USA) is ongoing

After model selection and internal validation, the impact of continuous and categorical covariates will be tested. The relationship between individual PK parameters and covariates will be explored and all significant covariates kept in the model. The validation of the final model will be based on graphical and statistical methods. The optimal dosing regimen to be used in neonates and infants will take into account the PK-PD relationship published for adults, i.e. an AUC/MIC ≥ 50 for fluconazole and ≥ 1332 for micafungin. (50) This approach is consistent with CHMP guidelines. (6,57–59)

The AUC/MIC ratio of fluconazole and micafungin will be used to examine efficacy. Outcome will be summarised using descriptive statistics.

Data of the safety analysis population will be examined using descriptive statistics and will include the analysis of adverse events, vital signs, laboratory data and comedication.

WP 5 - ETHICS AND SAFETY

Systematic reviews were conducted for the safety of ciprofloxacin and fluconazole in neonates and children (listed in Section 6) in partnership with colleagues from INSERM and the Mario Negri Institute (IRFMN). These reviews and surveys of practice were able to inform the writing and reviewing of both of the clinical protocols. They contributed to the writing of the safety monitoring and pharmacovigilance sections especially, and added to the evidence base available in the literature for their safe use in neonates and children.

WP 5 has ensured that the clinical trials carried out by the TINN consortium on ciprofloxacin and fluconazole/ micafungin have been to the highest ethical standards.

This has been achieved by the formation of an Ethics board for the project with Prof N Modi as the chair. They reviewed both protocols at a development stage and gave their comments. The patient information sheets were reviewed by both neonatal nurses and parents. Both projects underwent local and national ethical review, as were appropriate for their conduct.

An ISMB was convened for both projects chaired by Prof D Field. Data was provided for the ISMB by the partners recruiting for both trials; UOL and INSERM / APHP. The ISMB reviewed the serious adverse events for the ciprofloxacin PK study and were satisfied they were not related to the study drug. They convened to review the data for the fluconzole/ micafungin study. Due to the shortened recruitment period in most EU centers and the limited number of patients included, the Chair (Prof Fields) proposed to review the data at the end of the trial.

WP 6 - ORGANIZATION OF THE TRIALS

1. Ciprofloxacin trial : a national trial conducted in the UK

The ciprofloxacin trial was set up in the UK by the Work Package Leader of WP 03. It was noted that the set up of the ciprofloxacin trial has been easier than the organisation of the EU trial for fluconazole/ micafungin. It was considered that setting up a national trial involved less administrative burden, compared to the setting up of an EU trial with multiple centers in several EU countries.

2. Fluconazole / micafungin trial: an EU trial involving six EU countries

Work Package Leaders WP04 and WP06 developed the fluconazole / micafungin study.

Setting up the fluconazole / micafungin trial was difficult and time consuming. Due to complicated administrative processes at EU and country level it took more than six years from multi-national approval of the project (Figure 13). Twenty-five centers in six EU countries were selected for participating in the fluconazole/ micafungin study, with the initial plan to recruit 100 patients over a period of 2 to 3 years, because invasive neonatal candidiasis is a very infrequent disease. (27)

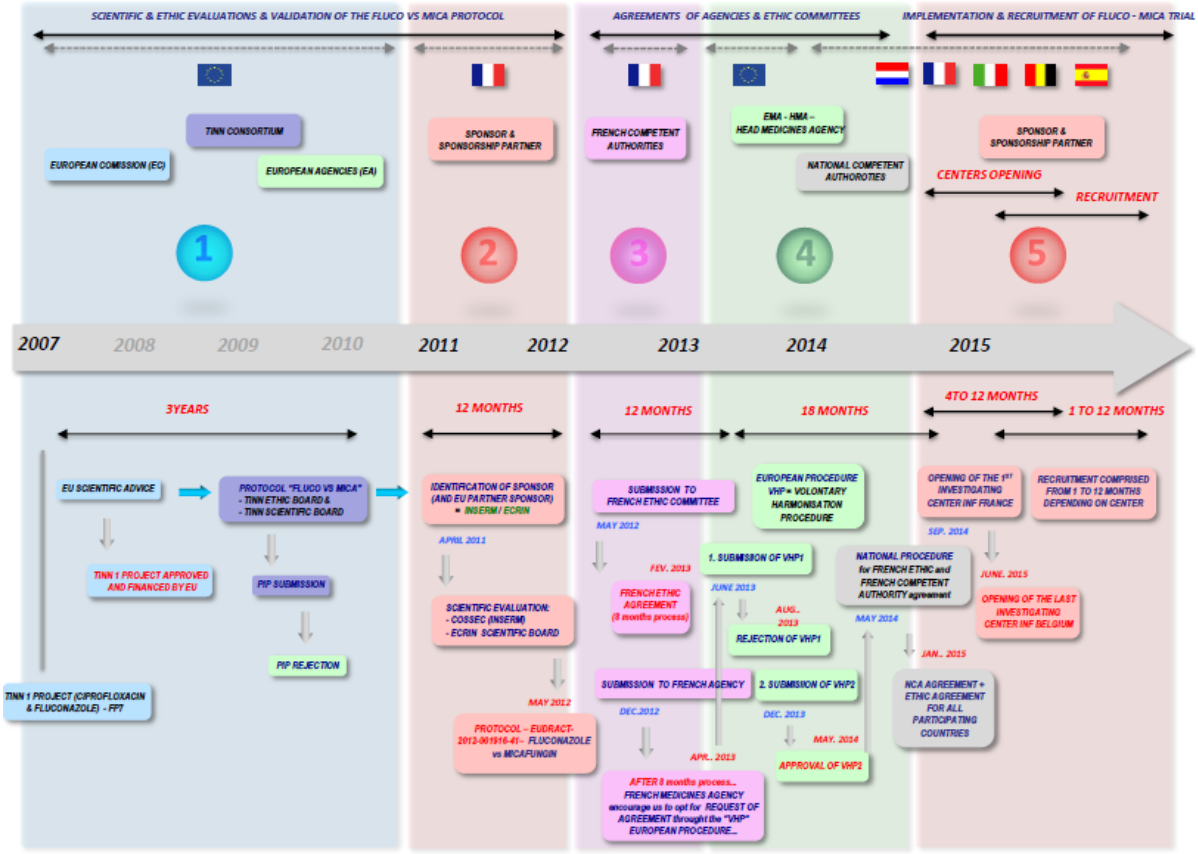


Figure 13 - APPROVAL PROCESS AND IMPLEMENTATION OF THE FLUCONAZOLE / MICAFUNGIN STUDY

After approval by the EU in 2007, scientific and ethic aspects of the research program were reviewed prior to the submission to all national Ethics Committees in the six EU countries participating in the trial:

- PDCO at the EMA (PIP),
- INSERM (3 sessions of the scientific board),
- ECRIN (input prior to acceptance and prior to the Voluntary Harmonisation Procedure (VHP)),
- Patient associations (INSERM, French Ethics Committee),
- TINN Ethics board and ISMB

The Consortium noted difficulties in the administrative coordination and harmonisation of processes between EC requirements, sponsor responsibilities, tasks and procedures laid out by the Clinical Research Units Network (ECRIN) and Ethics Committees. A considerable effort of duplication of processes reviewing scientific and ethical aspects of the trial was noted:

- EC: Ethics Board required to be established to review the protocol and informed consent forms
- Sponsor - INSERM: responsibility to approve the project and the consent forms; with additional input from their patient associations
- ECRIN: Scientific and ethical evaluation of the project
- VHP (2 procedures): Scientific questions and evaluation
- National and local Ethics committees

All these overlapping steps complicated the process of evaluation as questions and/or requests for modifications were made by all the parties in an uncoordinated manner. This was considered as not following the standard process of protocol and informed consent review, which is routinely conducted by the sponsor and ethics committees. It was mainly

left to the coordination team to manage this multitude of inputs. In addition, the setting up of the ISMB by the sponsor was delayed.

In the absence of a single contact point at the sponsor, coordinating communication among all stakeholders and ensuring a timely workflow of interdependent tasks for setting up the trial has been challenging. For example, local contracts with investigators in the different countries were organised in sequence rather than in parallel with ethics committee reviews.

Furthermore, the conduct of a clinical trial in neonates by a network of academic centers is very challenging. It is of utmost importance that all stakeholders and most importantly sponsors are suitably trained and staffed to support the conduct of paediatric multicenter studies in Europe. It is particularly important for the sponsor to understand the importance of adhering to time lines to avoid failure of research in this vulnerable patient population. A thorough understanding of the multiples aspects of paediatric research such as sample size of the study, informed consent, blood sampling, pharmacovigilance and monitoring are considered key skills to facilitate paediatric research in Europe

Figure 14 illustrates the dates of opening and closing recruitment into the fluconazole/ micafungin trial, showing a significant delay in opening centers and early closing of these resulting in a shorter recruitment period than planned.

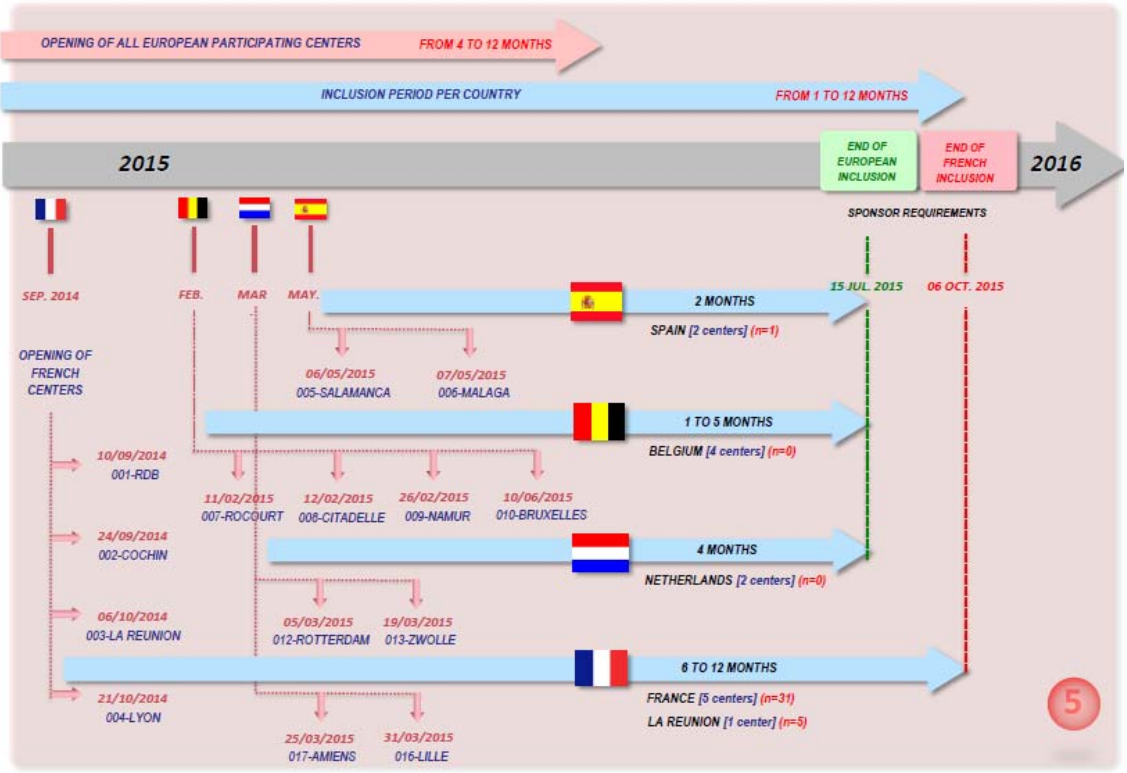


Figure 14 - IMPLEMENTATION & RECRUITMENT OF THE "FLUCO VS MICA" TRIAL

In the present case, all administrative challenges including late opening and early closing of recruitment by the sponsor (only two months in some centers) resulted in a smaller than planned patient population included (37 instead of 100 patients) from fewer centers (6 instead of 14 centers), this despite a 24 months extention thanks to the DG Research and dedication of investigators. It appears the decision to close the centers early was at least partly due to ensure adherence to strict timelines laid out by the EC.

Multiple contacts with the pharmaceutical industry were required to try to obtain the IMP for micafungin which still has patent protection. Discussions have been long and difficult because the fluconazole/ micafungin study was felt to be a competitor for inclusions into clinical trials conducted by pharmaceutical industry.

In conclusion, key challenges included EU regulations which appeared more suited to industry than academic research networks (in particular concerning the PIP and PUMA), multiple steps requiring a considerable amount of coordination at administrative level to review the protocol and informed consent forms, and to obtain ethics approval.

However, within the Consortium researchers succeeded in conducting the fluconazole/ micafungin trial and collecting data to inform suitable dosing of the two drugs.

All partners also learned about the general and specific EU processes, the challenges of such EU projects and are available to provide feedback to interested stakeholders.

WP 7 - PUBLICATIONS AND DISTRIBUTION OF RESULTS

WP7 was responsible for the dissemination of information. This information related to the main aspects of several substudies with ciprofloxacin and fluconazole / micafungin in this FP7-project. A total of 34 articles in peer reviewed journals (15 open access) were published as a result of this project. In addition, consortium members shared their knowledge with the scientific community at a variety of conferences. The results of the systematic literature reviews, various surveys, animal studies, modelling and simulation studies for ciprofloxacin and fluconazole and the ciprofloxacin clinical trial have been published. (see Section 6).

3. POTENTIAL IMPACT (INCLUDING THE SOCIO-ECONOMIC IMPACT AND THE WIDER SOCIETIAL IMPLICATION OF THE PROJECT SO FAR) AND THE MAIN DISSEMINATION ACTIVITIES AND EXPLOITATION OF RESULTS

POTENTIAL IMPACT

TINN1 has a potential socio-economic impact on a project specific level, i.e. the treatment of neonates with ciprofloxacin, fluconazole and micafungin. It provided data on pharmacokinetics efficacy and safety of these three drugs in neonates, allowing a safer use. The final aim being to possibly update the Summaries of Product Characteristics of all three drugs with relevant new information for the paediatric patient population; even in the absence of a PIP or PUMA.

FOR CHILDREN AND THEIR FAMILIES:

Being treated with the right dose of anti-infective drug ensures that critically ill neonates are treated with an age-appropriate dose of ciprofloxacin, fluconazole and micafungin. This will reduce risk of death or long-term sequelae due to inefficacious or toxic drug doses in the neonatal period; which in turn does have an additional major impact on the families of these neonates and as a consequence on society as a whole Finally, expanding research into other drugs prescribed to children will provide the paediatric population with access to effective and safe medicines.

FOR NEONATOLOGISTS AND PAEDIATRICIANS:

Access to information about appropriate dosing and benefit-risk of drugs will support physicians in selecting a suitable treatment for their patients. Furthermore, evidence based information will help doctors to discuss benefits and risk of various treatment options. Evidence based information is of particular importance for neonates since research in this paediatric subpopulation has been neglected. This has resulted in considerable variability of dosage regimens between neonatologists, centers and countries.

FOR PAEDIATRIC RESEARCHERS:

Studying medicines in children is a joint effort requiring input from a large variety of researchers with paediatric expertise scattered across Europe. Joining this expertise facilitates scientific exchange and generates a collaborative environment where new hypotheses can be developed and discussed. This furthers scientific development in Europe and supports sharing best practices across the EU. In addition, conducting multicenter trials across the EU shortens the time needed to recruit sufficient patients into clinical trials, because there are usually insufficient numbers of paediatric patients in any given centre or country. Finally, the TINN Consortium will share their learnings about general and specific EU processes, and challenges of such EU projects. Consortium members are available to provide feedback to interested stakeholders.

FOR EUROPEAN SOCIETY:

Ensuring that neonates, as one of the most vulnerable members of society and children in general, have access to effective, safe and good quality medicines makes not only economic sense, as it saves resources and money in the long-term, but also ensures a more fair society as a whole. Furthermore, the project has highlighted areas where additional support for academic researchers is needed to enable research into medicines prescribed to children; most of these being off-patent drugs.

FOR THE EUROPEAN ECONOMY:

Facilitating paediatric research with the aim of determining the correct dose and assessing drug safety will provide the necessary evidence to ensure consistent prescribing of drug doses that are efficacious and sufficiently safe in children. This will reduce health care expenses due to mortality and long-term morbidity in children arising from the prescription of inefficacious or toxic drug doses. Furthermore, providing a state-of-the art paediatric research environment may create investment opportunities for pharmaceutical industry and related business activities.

MAIN DISSEMINATION ACTIVITIES

Results of TINN1 have been published on an ongoing basis. To date a total of 34 articles have been published in per-reviewed journals and a number are available through Open Access. Consortium members shared knowledge with the scientific community at a variety of conferences. The TINN web site provides project information to the general public. Further details are provided in Section 6 below.

EXPLOITATION OF RESULTS

The TINN consortium expects that PK and safety data for ciprofloxacin, fluconazole and micafungin will be discussed with experts in the field and will allow consensus guidelines or even update of the respective Summaries of Product Characteristics for these products. This will ensure the prescription of appropriate and consistent doses for neonates in the EU. It will furthermore, reduce the administration of inefficacious or toxic doses and provide useful additional information to prescribers about the benefit-risk of these anti-infective drugs prescribed to critically ill neonates.

TINN1 helped constructing a network of experts experienced in conducting research on drugs prescribed to neonates. This could be a first step in building a permanent EU research infrastructure conducting paediatric research. However, this would require reliable and independent financing by the EC

4. ADDRESS OF THE PROJECT PUBLIC WEBSITE AND CONTACT DETAILS

Website: http://tinn-project.org/

Contact details of project coordinator: evelyne.jacqz-aigrain@rdb.aphp.fr; Tel: +33 1 4003 2150

Beneficiaries: A list of all beneficiaries and corresponding contact names is provided in Annex 2

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6. USE AND DISSEMINATION OF FOREGROUND

TINN1 research has not resulted in any applications for patents or other commercially exploitable activity. Up to 31 October 2015 a total of 34 articles in peer reviewed journals (15 open access) have been published by the TINN 1 Consortium:

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ABSTRACTS / COMMUNICATIONS / POSTERS

- 2010 France, 16 January, 24 March and 15 November, Journée néonatale Rhône-Alpes, journée scientifique de l'EDISS and JFRN, L'utilisation du fluconazole en néonatologie. Nguyen KA, C.Castellan, Claris O, Kassai B.
- E. Jacqz-Aigrain. Challenges of drug development for neonates. IX International symposium and III Neonatal Nursing Conference - Bilbao - Spain. 27 November 2010
- 2011 Melbourne, Australia, November 2011, The 7th Congress of the World Society of Paediatric Infectious Disease and P2T 2011, A systematic review of the use of fluconazole in neonate. Nguyen KA, C Castellan, Claris O, Kassai B.
- 2011 Le Hague, Netherlands, 7 - 11 June, Congress of the European Society for Paediatric Infectious Disease , Epidemiology of invasive candida infection in a neonatal intensive care unit in France. Nguyen KA, Zmeter G, Claris O, Kassai B.
- 2011, France 22 - 24 March, P2T Congress, Evaluation of a generic physiological based pharmacokinetic model for fluconazole in term and preterm neonates.
- Kaguelidou F, Manzoni P, Choonara I, Jacqz-Aigrain E. European survey on the use of antifungal prophylaxis in neonatal intensive care units. Fundamental and Clinical Pharmacology 2011, 25 (Suppl. 1), 1–111. (Abstract)

- Bonati M, Pandolfini C, Kaguelidou F, Jacqz-Aigrain E, Turner M, Choonara I, TINN (Treat Infections in Neonates) FP7 EU Project. Safety of ciprofloxacin in neonates with sepsis. ESPID meeting 7 June 2011 - The Hague, the Netherlands. (Abstract & poster)
- Jacqz-Aigrain E, Pandolfini C, Kaguelidou F, Manzoni P, Rugner M, Choonara I, van den Anker J for the TINN consortium. TINN - Evaluation of the anti-infective agents ciprofloxacin and fluconazole for the Treatment of Infections in preterm and term NeoNates (TINN). ESDPPP - 13th Biennial Congress, Oslo, Norway. 15-17 June 2011. Topic: Drug therapy in neonates and children - Recent advances.
- Kaguelidou F, Pandolfini C, Manzoni P, Choonara I, Bonati M, Jacqz-Aigrain E. European survey on the use of prophylactic fluconazole in Neonatal Care Units FP7 Project TINN – WP3 Fluconazole. 13th biannual ESDPP Congress – Oslo –Norway, 14 June 2011
- E. Jacqz-Aigrain. Challenges of drug development for neonates - The example of antibiotics. 13th biannual ESDPP Congress. Oslo, Norway, 24 June 2011
- E. Jacqz-Aigrain. Clinical Trials in Neonates - The FP7 TINN experience. 13th biannual ESDPP Congress, Oslo, Norway, 25 June 2011
- E. Jacqz-Aigrain. TINN oveview. 29th Annual ESPID meeting La Hague, The Nederlands, 7 June 2011
- 2012, San Francisco, United States of America, 11 - 15 March, Society of Toxicology, Non invasive and automated acquistion of physiological and developmental parameters in rat neonates. Durand E., Spezia F., Gallego J., Barrow P., Forster R., Legrand JJ., Matrot B.
- E . Jacqz-Aigrain. Drug trials in neonates - Implementing clinical trials across a network ; the example of the EU TINN project. Beijing China, June 2012.
- 2013 Milan, Italy, May 28 - June 1, ESPID (European Society for Paediatrics Infectious Diseases), Pharmacokinetics and safety of Ciprofloxacin in Neonates, Hill H, Zhao W, Neal T, Paulus S, Mahoney S, Le Guellec C, Choonara I, Jacqz-Aigrain E, Turner MA. (Poster)
- 2013 Milan, Italy, 28 May - 1 June, ESPID (European Society for Paediatrics Infectious Diseases), Population Pharmacokinetics of Ciprofloxacin in Neonates and Young Infants less than 3 months of age, Zhao W, Hill H, Le Guellec C, Jacqz-Aigrain E. (Poster)
- 2013 Salzburg, Austria, 4-7 June, ESDPPP (European Congress on Developmental Perinatal and Pediatric Pharmacology), Randomised controlled trials of antibiotics for neonatal infections: a systematic review, Kaguelidou F, Turner MA, Choonara I, van Anker J, Manzoni P, Alberti C, Langhendries JP, Jacqz-Aigrain E. (Presentation)
- 2013 Salzburg, Austria, 4-7 June, ESDPPP (European Congress on Developmental Perinatal and Pediatric Pharmacology), Population Pharmacokinetics of Ciprofloxacin in Neonates and Young Infants less than 3 months of age, Zhao W, Hill H, Le Guellec C, Jacqz-Aigrain E. (Poster)
- 2013 Salzburg, Austria, 4-7 June, ESDPPP (European Congress on Developmental Perinatal and Pediatric Pharmacology), European Network on Evaluation of Anti-infective agents for the treatment of preterm and term neonates, Jacqz-Aigrain E, Matrot B, Weinbach J, Choonara I, Kassai B, Manzoni B, Turner M, van Anker J, Kirchheiner J, Langhendries JP, Le Guellec C, Jarreau PH, Chevarier P, Soetemont A, Bonatii M, Rane A. (Poster)
- 2013 Salzburg, Austria, 4-7 June, ESDPPP (European Congress on Developmental Perinatal and Pediatric Pharmacology), Published randomized controlled trials of systemic antibiotics in neonates, Egunsola O, Sammons H, Kaguelidou F, Jacqz-Aigrain E, Choonara I. (Presentation)
- 2013 Paris, France, Conference - Third General Consortium meeting, French Institute of Health and Medical Research and the University of Nottingham, European Conference on Nanotechnologies, 28 September - 1 October.

- 2013 Torino, Italy, Conference, Paolo Manzoni, 4th ICCN, June 2013.
- E. Jacqz-Aigrain. Challenges In Drug Evaluation in Neonates : the TINN FP7 project. EACPT, Geneva – Switzerland, 28 August 2013
- E. Jacqz-Aigrain. Challenges for dosage recommandations : a case study in neonates. Principes of population pharmacokinetics ; 1st International Workshop on Clinical Pharmacology of the Antifungal Drugs and Fungal Diseases. Berlin, Germany, 26 April 2013.
- E. Jacqz-Aigrain. Hot Topics in neonatology. 14th biannual ESDPPP Congres, Salzburg, Austria, 7 June 2013.
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- 2014 Paris, France 27 - 28 March, Societé française de Néonatologie, Analyse des protocols d'administration des antibiotiques dans les services de réanimation néonatale en France, Leroux S, Zhao W, Jacqz-Aigrain E. (Presentation)
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- 2015 Caen, France, 21-23 April, SFPT (Société Française de Pharmacologie et de Thérapeutique), Pharmacokinetic studies in neonates: Is an opportunistic sampling strategy sufficient for population pharmacokinetic modelling and dose prediction?, Leroux S, Zhao W, Jacqz-Aigrain E. (Presentation)
- 2015 Caen, France, 21-23 April, SFPT (Société Française de Pharmacologie et de Thérapeutique), Population pharmacokinetics of ciprofloxacin in neonates and young infants less than three months of age?, Leroux S, Zhao W, Jacqz-Aigrain E. (Presentation)
- E. Jacqz-Aigrain. TINN : Treat Infections in Neonates. China International Forum on Pediatric Development. 10 October 2015.

SECTION A (PUBLIC)

TABLE A1: LIST OF SCIENTIFIC (PEER REVIEWED) PUBLICATIONS, STARTING WITH THE OLDEST										
NO.	Title	Main author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Year of publication	Relevant pages	Permanent identifiers (if available)	Is/Will open access provided to this publication?
See list of scientific publications reported in the participant portal										

TABLE A2: LIST OF DISSEMINATION ACTIVITIES (CONFERENCES ABSTRACTS, POSTERS, FLYERS ETC)								
NO.	Type of activities	Main leader	Title	Date/ Period	Place	Type of audience	Size of audience (Estimated)	Countries addressed
See list of dissemination activities reported in the participant portal								

SECTION B

The TINN 1 project has not resulted in any applications for patents, trademarks or registered designs.

7. ANNEX 1 - TINN 1 - EU PARTICIPATING CENTERS

Location	Center	TINN Study participation
Liverpool	Liverpool Women's Hospital	ciprofloxacin
Rocourt	CHC St Vincent	fluconazole vs micafungin
Liège	CHR Citadelle	fluconazole vs micafungin
Bruxelles	Louvain Cliniques Universitaires Saint Luc - UCL	fluconazole vs micafungin
Namur	Service NIC - CHR (Centre Hospitalier Régional) de Namur	fluconazole vs micafungin
Paris	Hôpital Robert Debré	fluconazole vs micafungin
Lyon	Hôpital Femme Mère Enfant Bron	fluconazole vs micafungin
St Pierre (La Réunion)	GHSR - CHR Réunion	fluconazole vs micafungin
Paris	Cochin - Port Royal	fluconazole vs micafungin
Amiens	CHU Amiens	fluconazole vs micafungin
Lille	Clinique de Néonatologie, Hôpital Jeanne de Flandre	fluconazole vs micafungin
Rotterdam	Erasmus MC-Sophia, Rotterdam	fluconazole vs micafungin
Isala (Zwolle)	Sophia Hospital	fluconazole vs micafungin
Malaga	Hospital Materno-Infantil	fluconazole vs micafungin
Salamanca	Hospital universitario de Salamanca	fluconazole vs micafungin

8. ANNEX 2 – TINN 1 - BENEFICIARIES AND CONTACT NAMES

Beneficiary	Contact name
1. Institut National de la Santé et de la Recherche Médicale (INSERM)	Evelyne Jacqz-Aigrain
2. INSERM - Transfert S.A.	Natacha Edme
3. The University of Nottingham	Helen Sammons, Imti Choonara
4. Université Lyon 1 Claude Bernard	Berhouz Kassai
5. Azienda Ospedaliera, Ospedale Infantile Regina Margherita-Sant Anna di Torino	Paolo Manzoni
6. The University of Liverpool	Mark Turner
7. Erasmus Medical Center Rotterdam	John Van Der Anker, René Kornelisse
8. Universitaet Ulm	Julia Kirchheiner
9. Centre Hospitalier Chrétien ASBL	Jean Paul Langhendries
10. Université François Rabelais de Tours	Chantal Leguelec
11. Assistance Publique - Hôpitaux de Paris	Pierre Henri Jarreau
12. Clininfo S.A.	Patrick Chevarier
13. European Paediatric Medicine Company	Anne Soetemont
14. Istituto de Ricerche Farmacologiche Mario Negri	Chiara Gandolfini, Maurizio Bonati
15. Karolinska Institutet	Anders Rane