PROJECT FINAL REPORT

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Project acronym: TINN2

Project title: Treat Infections in NeoNates 2 – Evaluation of an infective agent (azithromycin) for the treatment of infections in preterm and term neonates.

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FINAL PUBLISHABLE SUMMARY REPORT

1. Executive summary

The fact that health professionals are forced to use off-label medicines in order to ensure that children receive adequate treatment is an unsatisfactory state of affairs within the EU. The EMA-PDCO has identified azithromycin in neonates among the unmet medical needs in Paediatrics.

Azithromycin is an antibiotic with good activity against *Ureaplasma* which is well tolerated by neonates and has anti-inflammatory properties. Therefore, it is a drug of choice to reduce the rate of the condition in preterm babies at risk of bronchopulmonary dysplasia (BPD), a consequence of birth at extreme prematurity.

In this context, TINN2 collaborative project is a proposal to the EU-call FP7-Health-2010-4.2.1 « Off-patent medicines for children».
TiNN2 consortium was composed of 16 partners including 3 SMEs in 8 countries. The integrated TINN2 project brought together leading European developmental pharmacologists and clinicians with other research groups whose expertise in molecular biology development or conduct of clinical trials to help shorten the time lag from basic research to translational applications.

Although the TINN2 clinical trial did not go ahead the partners collectively produced new knowledge on the use of azithromycin in preterm neonates that will lead to benefits for the medical, scientific and patient communities as detailed below:

- Evidence of the implication of *Ureaplasma spps*. in BPD thus suggesting that azithromycin treatment of preterm babies could decrease rates of BPD by eradicating *Ureaplasma spps*
- A state-of-the-art on European NICUs practice and opinion regarding *Ureasplasma* as a risk factor in the development of BPD and the use of azithromycin to prevent BPD (published in 2013).
- The development of an HPLC-MS/MS technique to measure intracellular concentrations of azithromycin published in 2014 that will benefit other research groups
- A safe and ethically sound protocol for the investigation of azithromycin in neonates via a randomized clinical trial
- An approved Pediatric Investigation Plan by the PDCO at EMA
- A framework for a future Electronic Data Capture (EDC) system;

Moreover TINN2 consortium identified factors that hinder the research activities of all partners and stakeholders, at the regulatory, ethic and scientific levels.

To date, the TINN2 Consortium published 18 articles in peer-reviewed journals (10 open access) and shared their knowledge with the scientific community at a variety of conferences.

This advance in knowledge will have an impact in the appropriate use of a major drug in the neonatal population and this direct beneficial impact can be extended to positive impacts on harmonization of ethical practices, evaluation of safety in preterm and term neonates and in the paediatric population in general.

2. Summary description of project context and objectives

The fact that health professionals are forced to use off-label medicines in order to ensure that children receive adequate treatment is an unsatisfactory state of affairs within the EU. The Pediatric Committee (PDCO) of the European Medicine Agency (EMA) has identified azithromycin in neonates among the unmet medical needs in Paediatrics, as listed in the paediatric priority list of off-patent medicines to be developed in priority. Indeed, azithromycin is an off-patent drug prescribed for neonatal infections by various pathogens such as Chlamydia, Mycoplasma, Bordetella and *Ureaplasma*.

Bronchopulmonary dysplasia (BPD), also known as Chronic Lung Disease (CLD), is a consequence of birth at extreme prematurity. BPD is a multifactorial disease, observed in premature babies either *Ureaplasma*-negative or *ureaplasma*-positive. However, infants who develop BPD are more likely to be colonized with the microbe *Ureaplasma.* In addition lung inflammation early after birth is more common among premature babies who develop BPD. To date, there is no established treatment to prevent BPD.

Azithromycin is an antibiotic with good activity against *Ureaplasma* which is well tolerated by neonates and has anti-inflammatory properties. Therefore, it is a drug of choice to reduce the rate of the condition in preterm babies at risk of BPD. These anti-inflammatory properties reduce the incidence of surrogate end-points for BPD, even among neonates not colonised with *Ureaplasma.* Moreover, the efficacy of azithromycin for *Ureaplasma* in older age groups is *prime facie* evidence that azithromycin will have an effect on the development of BPD.

Collaboration across Europe is crucial in projects evaluating drugs in neonates, because of numerous difficulties:

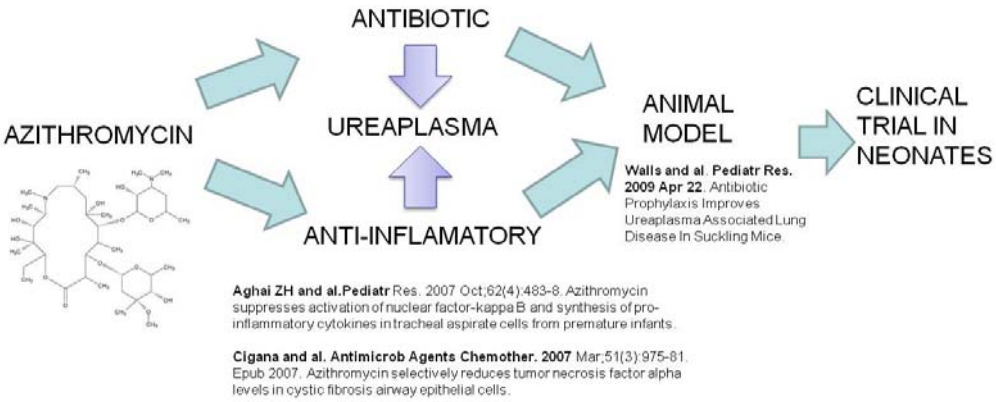
- Limited number of neonates with comparable diseases
- Lack of adapted formulations
- Need for adapted methodological approaches for clinical trials
- Need for trained investigators with expertise in neonatal clinical trials *(inadequate critical mass of investigators in any single European country)*
- Lack of organized structures and networks to optimize trial conduct
- Lack of adequate drug monitoring programs in this population
- Major ethical issues

In this context, TINN2 collaborative project is a proposal to the EU-call FP7-Health-2010-4.2.1 « Off-patent medicines for children».

The aim of TINN2 was to evaluate the antibiotic azithromycin, included in the EMA priority list of the therapeutic areas that need specific drug evaluation in preterm and term neonates by providing validated data to allow the administration of azithromycin in preterm and term neonates.

To ensure the success of the project, the TINN2 consortium requested Scientific Advice from the European Medicine Agency (EMA) ad-hoc committee for the validation of its development plan.
The EMA Scientific Advice made some specific and useful suggestions, which were all taken into

account in the final TINN2 protocol.



TINN2 Project

The two main objectives of TINN2 were the following:

Objective 1: To develop an adapted formulation of azithromycin for neonates

Objective 2: To assess the safety and efficacy of azithromycin for the treatment of *Ureaplasma* infection of neonates.

Based on the work towards these objectives, the ultimate aim was to obtain a Paediatric Use Marketing Authorization (PUMA) for the treatment of *Ureaplasma* infection in neonates.

3. Description of main S&T results/foregrounds

The TINN2 project was developed to allow the evaluation of azithromycin in preterm neonates and the overall strategy was presented and organized in 7 Work Packages (WP) that was worked on by complementary partners. The project was managed Inserm Transfert:

- Project management (WP1)
- Literature review on paediatric formulation - survey on the use of azithromycin in neonates (WP2)
- Development of azithromycin PIP (WP3)
- Organisation of azithromycin PK and pivotal trial (WP4)
- Coordination of the clinical work (WP5)
- Ethics and Safety (WP6)

TINN2 also involved an ethics advisory board, an independent safety monitoring Board and a scientific advisory board.

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Objective 2: To assess the safety and efficacy of azithromycin for the treatment of *ureaplasma* infection of neonates.

Based on the work towards these objectives, the ultimate aim was to obtain a Paediatric Use Marketing Authorization (PUMA) for the treatment of Ureaplasma infection in neonates.

For this purpose, TINN2 designed used a 2-step approach:

1) The first step consisted of the development of an **in silico PK/PD model** in order to model the dose regiment in the target population. This model was developed based on literature data and pharmacokinetic data in the targeted neonatal population (provided by Pr Rose Viscardi). The purpose was to confirm the dosage regimen for the pivotal trial and define key safety parameters.

2) The second step consisted in performing **a pivotal trial, placebo-controlled, randomized, double-blind trial** for assessing the efficacy and safety of azithromycin in the target population.

Formulation of azithromycin

The main objectives of WP2 were:
- To review all available data on azithromycin;
- To identify and list formulations/presentations of azithromycin used in neonates in Europe;
- To find the appropriate formulations/presentations of azithromycin for use in neonates.

To understand the potential impact and efficacy of azithromycin in the prevention of bronchopulmonary dysplasia in neonates, the WP2, jointly with WP4, reviewed all the data available on the association of *Ureaplasma* infection and bronchopulmonary dysplasia in neonates. This work resulted in a meta-analysis published in July 2014 (Lowe *et al*. 2014).

Facing some difficulties to find an appropriate source of azithromycin powder to develop its own azithromycin preparation, the TINN2 Consortium identified European suppliers of intravenous formulations of azithromycin and finally decided to conduct the trial using the marketed product of a supplier based in Germany. Using a marketed product also had its benefits as no additional animal studies were required.

Data on azithromycin pharmacokinetics and efficacy on *Ureaplasma* were also reviewed to develop in silico simulations and define the appropriate azithromycin regimen to be used in the clinical trial. A population pharmacokinetic model has been initially developed, based on limited available data from previous studies. Different daily dosing have been simulated (according to the pharmacokinetic-pharmacodynamic predictor for achieving azithromycin efficacy: AUC0-24(unbound) to MIC90 ratio), with or without a loading dose. A daily dosing at 10mg/kg for 10 days without a loading dose was

selected for the trial. This 10-day course of azithromycin reflects a balance between anti-infective treatment, anti-inflammatory treatment and the need to minimize antibiotic exposure.

The review of all available safety data on azithromycin, jointly with the WP6 – "Ethics and Safety", resulted in a systematic review of the safety of azithromycin in neonates that has been published in BMJ open in December 2015 (Smith *et al*. 2015).

While reviewing data on azithromycin, it appeared that azithromycin drug was predominantly concentrating on alveolar macrophages through an undefined mechanism resulting in major differences of its concentrations in cells versus blood.

Therefore, taking into account the challenges of drug measurements in the neonatal population and the specificities of azithromycin, the Consortium decided to develop an analytical method to measure azithromycin intracellular concentrations in collaboration with the French CEA (Commissariat à l'Energie Atomique) based on the literature review. This work resulted in a publication in Bioanalysis Journal in August 2014 (Legrand *et al*. 2014).

TINN2 Clinical trial

Paediatric Investigation Plan

The PIP (Paediatric Investigation Plan) is the basis for the development and authorisation of a medicinal product for paediatric population subgroups. It Includes details on the timing and the measures proposed to demonstrate the quality, safety and efficacy. It is to be agreed upon and/or amended by the Paediatric Committee (PDCO) from the European Medicine Agency (EMA).

To ensure the success of the project, the TINN2 consortium requested a Scientific Advice to EMA ad-hoc committee for the validation of its development plan, particularly the following key questions:

1) Formulation: What would be the best formulation for neonates?
2) Proof of concept: Are there sufficient data to support the concept of use of azithromycin for the treatment of pulmonary colonisation of *Ureaplasma* in preterm infants.
3) Toxicological study in animal model: What would be the appropriate animal model?
4) Clinical study: Which design for a feasibility study? Which design for an efficacy and safety study? Do we have to use placebo?

TINN2 PIP procedure was initiated in March 2012 with a Letter of Intent followed by the submission of the PIP and all related documents in April 2012. In order to efficiently address all the comments of the PDCO during the TINN2 PIP evaluation, the TINN2 Trial Management Group (TINN2 TMG), composed by partners actively involved in the coordination of the trial, has been established. The collective work of the TINN2 TMG analyzed the answers of the PDCO during each step (days 60 and 90) of TINN2 PIP evaluation.

The discussions with the PDCO and with different stakeholders (including sponsor, ethic boards ...) have been very positive allowing discussing very important issues related to drug evaluation in

neonates. Among them,

- the use of juvenile animal models (that was not included in the project funded by the EU but was initially a request of the PDCO
- the room to be given to modelling and simulation to select neonatal dose and dosage schedule as well as duration of treatment
- the need for confirmatory pharmacokinetic data when such methodology is used
- the need for agreement on common definitions of various neonatal diseases (BPD, Patent Ductus Arteriosus (PDA), Necrotizing Enterocolitis (NEC), etc.
- the way to adapt pharmacovigilance plans to the specificities of neonatal trials…

TINN2 PIP was approved in January 2013, (PIP reference: EMEA-001298-PIP01-12, Decision number: P/0037/2013), more information can be found on the EMA related page: *http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/pips/EMEA-001298-PIP01-12/pip_000990.jsp&mid=WC0b01ac058001d129*

Once the PIP was validated, it has been used to finalize TINN2 protocol before the regulatory submissions to obtain TINN2 clinical trial approval in all participating countries.

Design of the clinical trial protocol

WP4 of TINN2 centred around the design of the pivotal study and development of the clinical trial protocol to include all regulatory, ethical, technical and pharmacovigilance aspects. The content reflected the results of extensive collaborative effort by the consortium as a whole over the whole course of the grant.

Specifically, the scientific content of the protocol was based on the PIP developed in conjunction with WP3. The overall plan of the study was written for publication as a review article (Turner *et al. 2012*). The PIP was a requirement for future submission for a PUMA, thus the first main draft of the pivotal trial protocol was written over the duration of PIP development from the start of the project until the partners met with the EMA PDCO in January 2013. The PDCO requested that the consortium modify the PIP that was in agreement with the program granted by the EC and include several substantial additional cardiovascular and immunology sub-studies as a condition of their approval. These requests were complex (both scientifically and in terms of clinical implementation and feasibility, reflecting complexities of conducting trials in vulnerable group of premature babies); however, they were successfully incorporated to the trial design by distributing sub-studies amongst the most experienced countries and recalculating the budget for each infant to be recruited.

Concurrent work on establishing the safety of azithromycin was completed as part of WP2 and data from the recent report in BMJ Open fed in to these assessments and formed the basis of the pharmacovigilance strategy within the pivotal trial protocol and formed the content of the Investigator's Brochure required for regulatory submission (Smith *et al.* 2015). Unfortunately, approval of the pharmacovigilance plans by the Sponsor (reported in detail in WP5) was a significant contributor to the delays incurred by the project.

Furthermore, in order to supplement the evidence for the implication of *Ureaplasma* spps. in BPD, a systematic review and meta-analysis was performed. The results of this analysis confirmed the association of *Ureaplasma* Spps. with the development of CLD thus suggested that azithromycin treatment of preterm babies could decrease rates of CLD/BPD by eradicating *Ureaplasma* spps (Lowe *et al*. 2014). Microbiology protocol was developed throughout the course of the project. This included of refining sample acquisition, optimising sampling timepoints, arrangements for safe transport of samples, culture/qPCR analyses, and antibiotic resistance methodologies.

Individual patient data was obtained from US for modelling PK data establishing that a dose regimen of 10 mg/kg for 10 days would achieve therapeutic plasma levels required to exert both anti-inflammatory and anti-infective of azithromycin. Utilising these data negated the need to perform and independent PK study as originally planned; a confirmatory 'sparse sampling' sub-study was instead incorporated into the pivotal trial thus reducing the overall number of additional blood draws required.

Closely allied to this is work done to develop the assay methodology for assessment of azithromycin in small volumes of (ethically acceptable) blood obtained from neonates. Azithromycin becomes concentrated in leukocytes thus the amount of intracellular drug better reflects antimicrobial activity compared to plasma. The adapted methodology determined the intracellular concentration of azithromycin using 500µg of blood only (Legrand *et al*. 2014). Further complementary work on the pharmacogenomics of azithromycin cell transport has also been performed (partner 14) by identifying single nucleotide polymorphisms (SNPs) in candidate transporter genes (namely P-gp and MRP2) and assessing their response to azithromycin using lymphoblastoid cell lines. The work to measure intracellular concentrations is current ongoing at the time of writing the report and once completed will be submitted for publication.

Following approval of the TINN2 PIP, the protocol entered a period of extensive reiteration following many independent reviews on the behalf of the nominated Sponsor including important delays, linked to multiple consultations, to validate the pharmacovigilance and monitoring plans; **this lead to a significant delay of 18 months from PIP approval until submission for regulatory approvals** using the voluntary harmonisation procedure (VHP) in July 2014 again in collaboration with WP5 and WP6.

Ethics and safety

The aim of work package 6 was to review the ethics and safety of the project. A systematic review of the safety of azithromycin was initially undertaken. This has been published in 2015 (Smith *et al*. 2015).

This systematic review was used for the development of the protocol for the clinical trial. The protocol included pharmacovigilance for adverse drug reactions built into its design and pharmacovigilance from a long-term safety point of view was incorporated into the clinical trial design by incorporating potential long-term monitoring until the age of 5 years.
Once written the protocol was reviewed by the ethics review board. This was composed of Dr Martin

Ward Platt (Chair), Prof Karel Allegaert and Prof Henry Halliday. Their sign off for the protocol was given in October 2013.

An Independent Safety Monitoring Board (ISMB) was formed for the clinical trial. Final agreement of the ISMB charter and responsibilities of the ISMB within the protocol was agreed. The ISMB charter had been signed by all members and initial kick off meeting took place in London on the 13th March 2014. The members were Prof Peter Brocklehurst (Chair), Prof Umberto Simeoni, Dr Christèle Gras-Le Guen and Louise Linsell (Statistician).

Liaison with all work package partners within the consortium has been ongoing regarding their input into the safety and ethical aspects of the trial. The parent information leaflets had been reviewed and translation had taken place in the different European countries by the partners for submission. Full approval had been granted in Hungary. Submissions to the competent authorities and local ethics review boards were underway in the UK, France, Germany and the Netherlands. These were awaiting final sponsorship arrangements for the trial to be agreed for full approvals to have been issued.

Selection of clinical centres and regulatory procedure

WP5 aimed at organizing the TINN2 EU-trial and ensuring that it is conducted in high quality centres by appropriately trained investigators, performed through effective collaboration and ensuring high ethical standards, with the objective of providing the information required for adequate drug use in neonates. The concept of the study was published in 2012 (Turner *et al. 2012*).

As part of the TINN2 Project a European Survey was undertaken to evaluate:

- the practices and opinions of European neonatal intensive care units (NICUs) regarding *Ureaplasma* as a risk factor in the development of BPD;
- the use of azithromycin, which is currently used off-label throughout Europe for this indication, to prevent BPD;
- and the need for a randomized controlled trial to evaluate efficacy of azithromycin in reducing the rates of BPD.

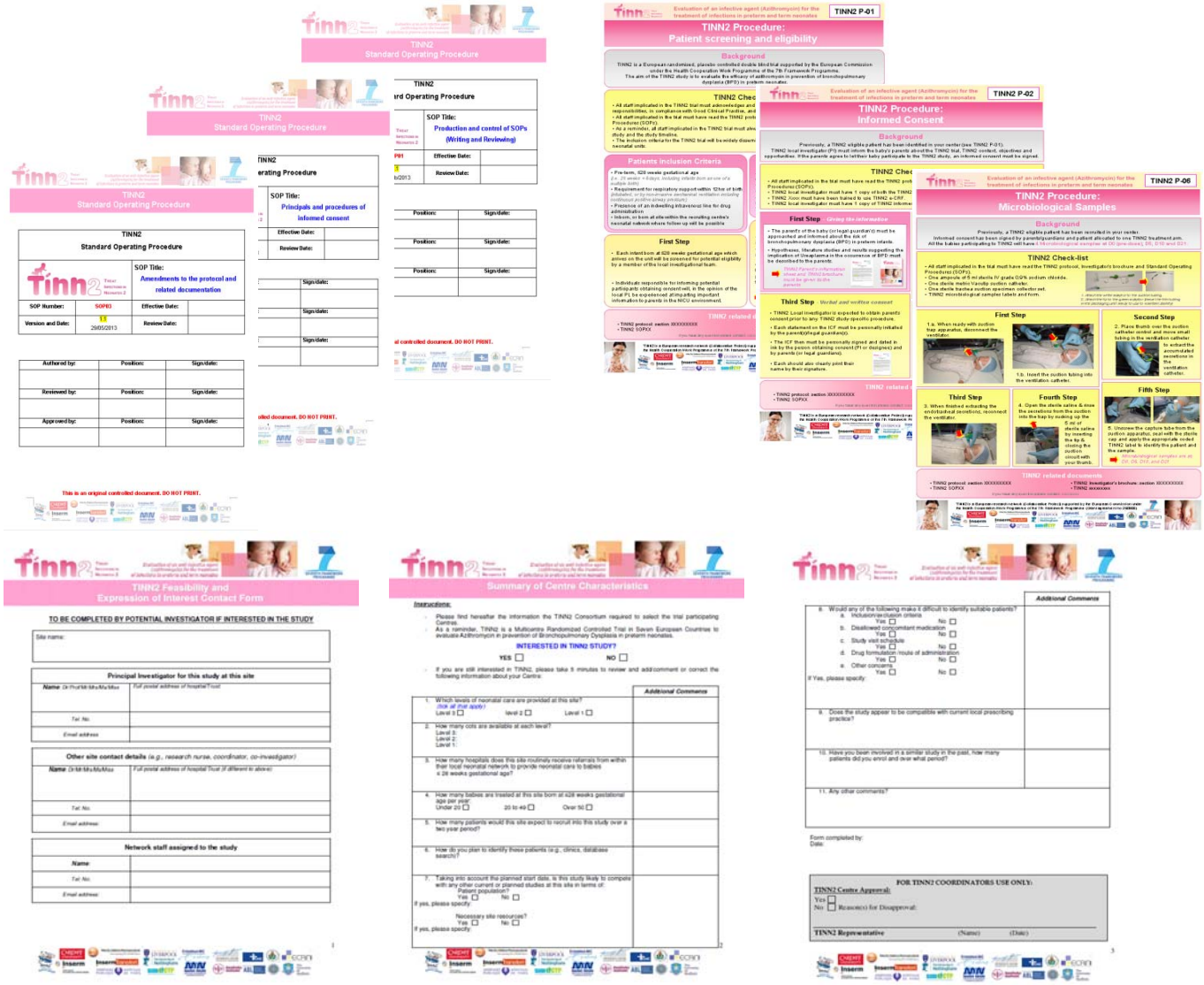
Practices were also compared taking into consideration size of the NICUs and the countries' BPD rates. A subsidiary goal was to underpin other clinical studies about prevention of BPD by summarizing clinical practice relevant to trial design in multiple European units.
167 NICUs participated in the survey, representing 28 European countries. For respondents, the two major perceived risk factors for BPD were prematurity of <28 weeks and high oxygen requirements. Only 38% of NICUs had a protocol for BPD prevention and 47% routinely tested for *Ureaplasma*. In cases of infection, macrolides were the first choice (Pansieri *et al*. 2014).

Opinions and clinical practice varied between European neonatal units, and differences in *Ureaplasma* treatment and prevention of BPD highlight the need for further azithromycin evaluation and for improved therapeutic knowledge in preterm infants.

The ultimate goal of TINN2 European Survey was to identify NICUs that would be interested in participating to the TINN2 trial**: most (78%) NICUs were interested in participating in a trial evaluating azithromycin safety and efficacy in reducing BPD rates.**
It was established there would be sufficient level 3 neonatal units (with >40 admissions per year of infants ≤28 weeks gestation). **Thanks to the Survey, 30 centres have been enrolled in TINN2 in seven countries: France, Germany, Hungary, Italy, the Netherlands, Sweden and UK.** Centres were asked to confirm their interest and provide additional details including their experience in neonatal trials, potential competing studies and recruitment capabilities over a 24-month period (in respect with TINN2 inclusion criteria). Due to the regulatory delay and competing clinical trials, several centres withdrew from the TINN2 study.

The VHP procedure was successful with only minor modifications required. However, not all of the nominated countries were able to participate in this harmonisation process due to database-related issues affecting several National Competent Authorities. Applications in France, Sweden, and Italy had to be submitted independently of the VHP, which required the completion of additional multiple applications. Following TINN2 VHP, regulatory evaluations by Ethics Committees were still ongoing and pending in Netherlands, Germany and France. Management of regulatory submissions was delegated to the European Clinical Research Infrastructure Network – ECRIN.

However, during this time further collaboration between WP4 and WP5 enabled the development of the trial quality system including a suite of standard operating procedures, monitoring plan and work instructions (for practical use by centres) based on the information in the protocol. Furthermore, all site-specific documentations for trial management (delegation and screening logs, pharmacy drug accountability records) were developed. Unfortunately, review and validation of these documents through multiple committees again delayed the initiation of the trial. Both project coordinators and project managers maintained close contact with interested centres during this time and provided email updates as well as presenting the study at national and international meetings. In parallel of the TINN2 protocol finalization, all TINN2 relative documents and procedures have been prepared: TINN2 Investigator's Brochure, TINN2 Standard Operating Procedures, TINN2 Informed Consent Form, TINN2 Parent Information Form, TINN2 nurses illustrated procedures, TINN2 e-Case Report Form content, etc.



Difficulties with sponsorship and with SMEs

Paediatric clinical trials are considered risky because of the elevated rate of adverse outcomes complicating prematurity. They are either short-term outcomes, including ventricular haemorrhages, necrotizing enterocolitis, septic shock and death in the first days – weeks of life. Adverse long-term outcomes also include prolonged hospitalization, disabilities and sequellae impacting neurodevelopment and growth.
For all these reasons, TINN2 project is a multicentre, multinational paediatric clinical trial that required a Sponsor with preferentially experience in multinational and paediatric clinical trials.

TINN2 project encountered difficulties finding such a Sponsor and several candidates were first contacted until INSERM agreed to participate as Sponsor. However, there have been many meetings and discussions with INSERM Research Unit (PRC) about pharmacovigilance and monitoring plans but no decisions were made. It was finally decided to delegate monitoring of the clinical trial to ECRIN and the pharmacovigilance to the French platform EUCLID. **However, thirty months were thus**

necessary to obtain the final agreement for the sponsorship.

Despite all the efforts that have been made by the consortium in five years, including meeting and teleconferences to validate pharmacovigilance plan with EUCLID, demonstration of feasibility, very good collaboration between partners in the consortium, **sponsor still doubted on the feasibility of TINN2 trial and abruptly decided unilaterally to withdraw its sponsorship for TINN2 clinical trial**.

Further attempts were made to secure sponsorship by legal entities competent in neonatal/paediatric trials: firstly PENTA-Foundation who declined due to current workload commitments, and latterly Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF), who accepted the position after unanimous approval by the consortium. Unfortunately, by then, it was not possible to conduct the clinical trial without an extension of the project, which was not granted.

Another event faced by TINN2 Consortium is the financial difficulties encountered by the SME in charge of the management of all TINN2 Investigational Medicinal Products (IMP) aspects (production, packaging, labelling, storage and distribution of placebo and drug). In agreement with the SME, the IMP management tasks were transferred to another partner, an institutional organisation, which required the launch of a call for tender and thus delayed the production of the drugs.

4. Potential impact and the main dissemination activities and exploitation of results

Potential impact

Although the TINN2 clinical trial did not go ahead the partners collectively produced new knowledge on the use of azithromycin in preterm neonates that will lead to benefits for the medical, scientific and patient communities as detailed below:

Key result 1: Implication of *Ureaplasma spps.* in BPD thus suggesting that azithromycin treatment of preterm babies could decrease rates of CLD/BPD by eradicating *Ureaplasma* spps.

> **Potential Impact**: Our literature reviews summarized all recent knowledge and evidenced that *Ureaplasma spps* has a role in BPD.

Key result 2: The development of an HPLC-MS/MS technique to measure intracellular concentrations of azithromycin published in 2014.

> **Potential Impact**: As azithromycin concentrated into cells reaching levels much higher than in plasma, this adapted technique will benefit other research groups wishing to measure azithromycin in cells rather than in plasma.

Key result 3: A state-of-the-art on European NICUs practice and opinion regarding *Ureasplasma* as a risk factor in the development of BPD and the use of azithromycin to prevent BPD.

Potential Impact: Neonatologists are now increasingly looking for *Ureaplasma spps* using different bacteriological techniques and PCR and treating colonization by different antibiotics (azithromycin, clarithromycin...). Our work will help supporting additional research aiming to evaluate:

1) the rate of maternal and neonatal colonization,
2) factors affecting variability in colonization and high risk neonatal groups,
3) optimal drug and treatment schedule

Key result 4: A safe and ethically sound protocol for the investigation of azithromycin in neonates via a randomized clinical trial

Potential Impact: This has significantly increased the scientific knowledge in this area and has been published in an open access journal for all in the field to access for their practice. This would allow evaluation of the current evidence for the use of Azithromycin in neonates and will help identify the future work that is needed in this area.

However, this protocol was not implemented due to the many technical and administrative delays encountered. The main dissemination activity will be to feed back our experiences on the significant challenges beyond the investigators' control of establishing a multinational clinical trial to the scientific community. Namely:

a) difficulties with appointing a sponsor with sufficient capacity and expertise to support the complexities of an essentially academic-lead project;
b) difficulties appointing a sponsor with experience in neonatal trials and the complexities of defining the appropriate pharmacovigilance and monitoring plans;
c) disparities between the initial plans for the project and adaption required to meet the conditions of a PIP (significant increase in complexity and costs of the clinical trial);
d) the need for serial reviews of the protocol by multiple agencies external to the consortium (often imposed by the sponsor);
e) the requirement for complex contractual negotiations when a clinical trial forms part of the consortium activities.

Key result 5: Approval of a Paediatric Investigation Plan in January 2013 by PDCO-EMA

Potential Impact: This has been a positive experience for the consortium as e partners had a positive face to face meeting with the PDCO to discuss the innovative aspects of the TINN project and in particular the modelling and simulation methodology used to select the dose and schedule, based on all available knowledge on the disease and pharmacological properties of azithromycin. All partners now understand the regulatory requirements for a Paediatric Use Marketing Authorization.

Key result 6: Framework for a future Electronic Data Capture (EDC) system

Potential Impact: Even if the trial didn't happen, the TINN2 team collaborates to define the TINN2 deliverables in terms of data but also what would be the general specifications for an eCRF. ABL developed a framework which could be the basis for a future Electronic Data

Capture (EDC) system. As of today, pharmaco-vigilance needs, business rules and reporting are not available. ABL is planning to continue the development of the eCRF if ABL is able to get financial support through an innovation grant (from EU or national) to cover the technical and regulatory accreditation (FDA, ISO) gaps to make it a commercial product.

Overall Impacts:

TINN2 has a potential socio-economic impact on a project specific level, i.e. the safe and effective use of azithromycin in an attempt to prevent BPD in preterm infants. In addition, this research with azithromycin is supported by the European Commission; the project may have more general implications for preterm neonates and their families, neonatologists, paediatricians, paediatric researchers, and the European economy…

FOR NEONATOLOGISTS AND PAEDIATRICIANS:

Access to information about BPD, recent knowledge on appropriate dosing based on modelling and simulation will assist neonatologists/paediatricians who are already using the drug in selecting the best available treatment for their patients. Furthermore, evidence based information will help physicians to discuss and further evaluate benefits and risk of various treatment options with the families of these premature infants.

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. Our combined expertise across Europe will facilitate scientific exchange and generate a collaborative environment where new hypotheses can be developed and discussed. This furthers scientific development and supports sharing best practices across the EU. In addition, conducting multicenter trials across the EU remain a difficult task but will shorten 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.

FOR EUROPEAN SOCIETY:

Ensuring that children, as one of the most vulnerable members of society, 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 equitable society as a whole. Furthermore, the project has highlighted areas where regulatory processes should be simplified, where additional support for academic researchers is needed to enable research into medicines, most of these being off-patent drugs, in preterm infants.

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 preterm infants. This will reduce health care expenses due to mortality and long-term morbidity in preterm infants 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.

TINN2 aimed to strengthen drug evaluation in neonatal patients across Europe and support initiatives from the European pharmaceutical industry. TINN2 build up a network of units with experience in evaluating anti-infective agents in neonates. This work will increase the capacity of evaluating drugs in neonates, increase the appropriate use of medicines in neonates which will be of direct benefit to them, their families and healthcare providers.

In summary, we have been able to disseminate important information including analysis of risk factors for bronchopulmonary dysplasia in neonates, "standard of care of these patients in the NICUs, efficacy safety and review of the use of azithromycin in the neonate. In addition a highly specific and sensitive method to quantify intracellular concentrations of the drug is not available for future use.

FOR EUROPEAN SOCIETY:

Ensuring that children, as one of the most vulnerable members of society, 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 equitable society as a whole. Furthermore, the project has highlighted areas where additional support for academic researchers is needed to enable research into medicines, most of these being off-patent drugs, in preterm infants.

FOR THE EUROPEAN ECONOMY:

Our project has shown that off-label drug use in neonates, both term and preterm is not the exception. Therefore, facilitating paediatric research with the aim of determining the correct dose and assessing drug safety is need to provide the necessary evidence to ensure consistent prescribing of drug doses that are efficacious and sufficiently safe in preterm infants. This will reduce health care expenses due to mortality and long-term morbidity in preterm infants 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. In this context, optimizing regulatory requirements, reducing multiple requirements, aligning EU projects and grants with EMA requirements to obtain a PUMA, analyzing the potential role of SMEs and burdens when it comes to develop new formulations are some of the areas where collaborative works between regulators and academics is urgently needed for positive economic benefits.

TINN2 has strengthened drug evaluation in neonatal patients across Europe. TINN2 build up a network of units with experience in evaluating anti-infective agents in neonates. This work will increase the appropriate use of medicines in neonates which will be of direct benefit to them, their families and healthcare providers.

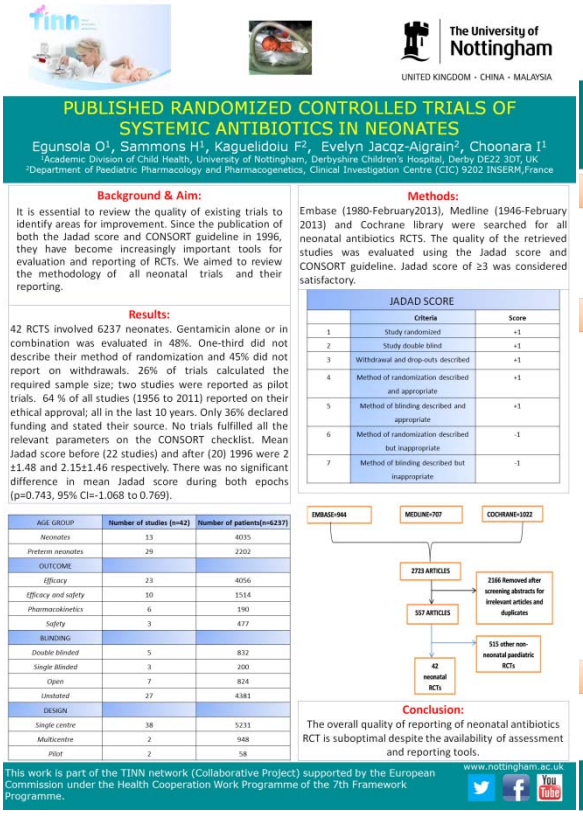
In summary, we have been able to disseminate important information about the use of azithromycin in the neonate.

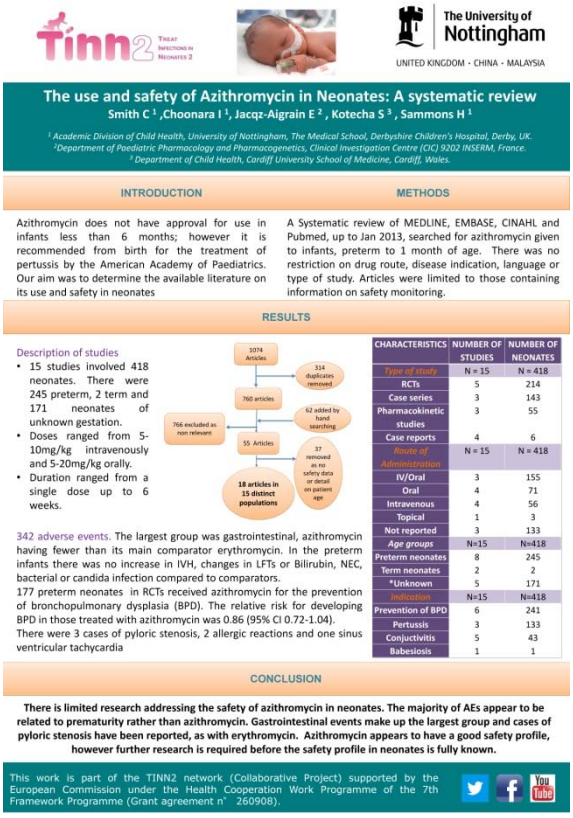
Dissemination

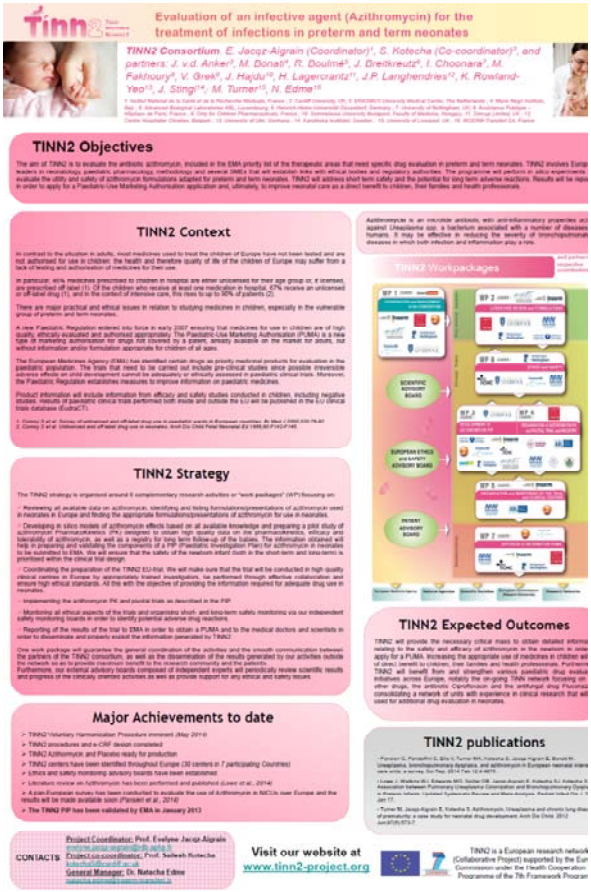
WP7 was responsible for the dissemination of information. The TINN2 website provides project information to the general public.

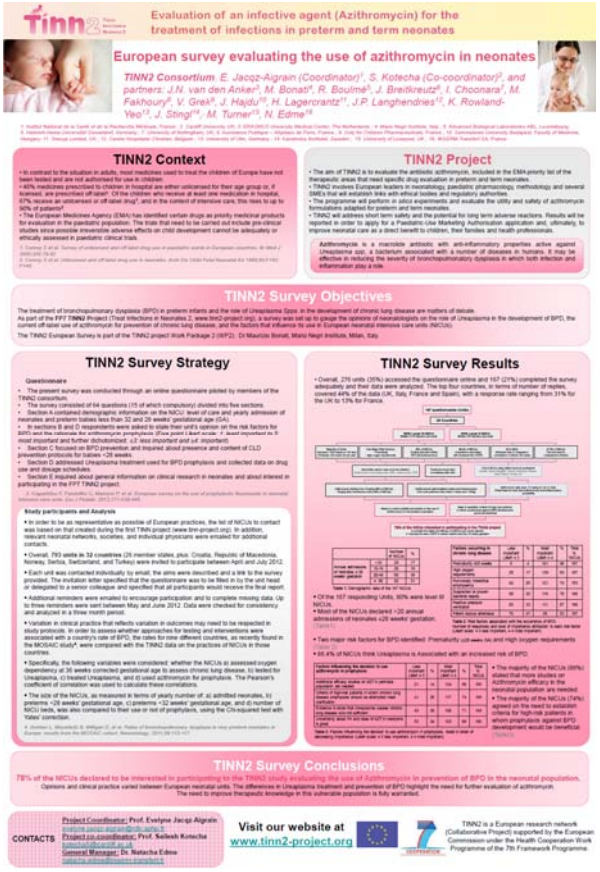
A total of 18 articles in peer-reviewed journals (10 open access) were published as a result of this project. Further details are available in Section 5 below.

In addition, consortium members shared their knowledge with the scientific community through 15 oral presentations or poster presentation at a variety of conferences in Europe. These presentations allowed to diffuse information to specialists and experts in the fields of neonatology, pharmacology, infectious diseases, trial management and trial conduct.









5. Address of the project public website and relevant contact details

Website: http://tinn2-project.org/

6. References

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