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Azithromycin therapy for chronic lung disease of prematurity

Submission date 23/07/2018	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [X] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 31/07/2018	**Overall study status** Completed	
Last Edited 22/05/2024	**Condition category** Respiratory	

Plain English summary of protocol

Background and study aims
Premature births account for a tenth of all worldwide births. Babies who survive are at risk of developing Chronic Lung Disease of Prematurity (CLD) as they have underdeveloped lungs, and also because the necessary treatment (breathing machines and oxygen therapy) in itself causes harm. CLD is defined as needing oxygen at 36 weeks “corrected” gestation. Most babies will come off their oxygen therapy by the end of their hospital stay, but some babies go home on oxygen placing an enormous burden on families. CLD babies also have a higher risk of childhood breathing problems. Inflammation (like redness or soreness) of the lungs is often seen in CLD babies, and a germ called Ureaplasma is often present. Some doctors think that Ureaplasma is a simple 'bystander', but others believe that it is actively causing harm. It has been shown that babies who have Ureaplasma have much greater chances of developing CLD than those who do not. Researchers have previously used antibiotics such as azithromycin to treat the Ureaplasma. Azithromycin decreases lung inflammation and is an effective antibiotic against Ureaplasma. A recent report noted that rates of CLD may improve with azithromycin therapy but the total number of babies included was small. A large study is needed to see if azithromycin therapy can indeed improve CLD rate. The aim of this study is to find out whether ten days of azithromycin improves survival without CLD in premature babies.

Who can participate?
Premature babies receiving respiratory support (breathing tube) and an intravenous line for drug administration

What does the study involve?
Babies are randomly allocated to be treated with either azithromycin or placebo (dummy drug) intravenously (into a vein). Lung fluid samples are collected via their breathing tube or from their nose/back of the mouth, and nappy stool samples are taken. These are used to see if lung Ureaplasma is successfully treated by azithromycin, and if common germs found in the gut and lungs develop antibiotic resistance. Studying resistance is important as azithromycin will be widely used if it is found to improve rates of CLD.

What are the possible benefits and risks of participating?
There are no certain benefits of taking part although it is hoped that the results might improve

the treatment of other babies in the future. Azithromycin has been used for a long time in children and has been used in other studies in premature babies, but like all medicines, antibiotics can cause side effects in some people. These are uncommon, but some babies may develop some soreness of the tummy or slightly looser stools. In older patients, azithromycin may affect the rhythm of the heart. There is no evidence that this happens in babies, but it is something that will be monitored closely.

Where is the study run from?
Cardiff University (UK)

When is the study starting and how long is it expected to run for?
January 2018 to December 2023

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Dr John Lowe
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Study website
https://www.aztec-trial.uk

Contact information

Type(s)
Scientific

Contact name
Dr John Lowe

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Additional identifiers

EudraCT/CTIS number
2018-001109-99

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
39385; 16/111/106

Study information

Scientific Title
A randomised, placebo controlled trial of azithromycin for the prevention of chronic lung disease of prematurity in preterm infants

Acronym
AZTEC

Study objectives
Premature births account for a tenth of all world-wide births. Babies who survive are at risk of developing Chronic Lung Disease of Prematurity (CLD) as they have underdeveloped lungs, and also because the necessary treatment (breathing machines and oxygen therapy) in itself causes harm. CLD is defined as needing oxygen at 36 weeks “corrected” gestation. Most babies will come off their oxygen therapy by the end of their hospital stay, however, some babies go home on oxygen placing enormous burden on families. CLD babies also have a higher risk of childhood breathing problems. Inflammation (like redness or soreness) of the lungs is often seen in CLD babies, and a germ called Ureaplasma is often present. Some doctors’ think that Ureaplasma is a simple 'bystander', but others believe
that it is actively causing harm - it has been shown that babies who have Ureaplasma have much greater chances of developing CLD than those who do not. Researchers have previously used antibiotics, such as azithromycin, to treat the Ureaplasma. Azithromycin decreases lung inflammation and is an effective antibiotic against Ureaplasma. A recent report combining 3 studies noted that rates of CLD may improve with azithromycin therapy but the total number of babies included were small. A large study is needed to see if azithromycin therapy can indeed improve CLD rate. This study will investigate if ten days of intravenous azithromycin improves survival without CLD in premature babies. Lung fluid samples will be collected via their breathing tube or from their nose/back of the mouth, and nappy stool samples. These will be used to see if lung Ureaplasma is successfully treated by azithromycin, and if common germs found in the gut and lungs develop antibiotic resistance. Studying resistance is important as azithromycin will be widely used if it is shown that the therapy improves rates of CLD.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 26/06/2018, Wales REC 2 (15-19 Cowbridge Road East, Cardiff, CF11 9AB, United Kingdom; +44 (0)29 2078 5738; Wales.REC2@wales.nhs.uk), ref: 18/WA/0199

Study design
Randomized; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See study outputs table

Health condition(s) or problem(s) studied
Chronic lung disease of prematurity

Interventions
The method of randomisation will be web-based. Azithromycin or placebo will be commenced within 72 hours (20 mg/kg once daily iv for 3 days then 10 mg/kg once daily iv for 7 days). The dosage and duration are based on achieving therapeutic levels of the drug to eradicate Ureaplasma colonisation and to utilise the drug's anti-inflammatory activities on pulmonary inflammation that is frequently observed in babies who develop CLD.

Oxygen dependency at 36 weeks' postmenstrual age will be physiologically assessed to define CLD. Secondary outcomes will be based on safety parameters (survival rates, adverse reactions, complications of prematurity including NEC, ROP); rates of Ureaplasma colonisation, and on development of antibiotic resistance in commensal microbes. Routinely collected data including duration/type of ventilation, overall length of respiratory support and hospital stay will be recorded. Additional resources will be sought to obtain respiratory and neurodevelopmental data at two years of corrected age, which most units now routinely collect and feed into national databases. Given the early antibiotic exposure and potential for development of antibiotic resistance, the trialists shall also assess the carriage of resistant organisms in the gut and respiratory tract.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Azithromycin

Primary outcome measure
Survival without physiologically defined CLD at 36 weeks postmenstrual age

Secondary outcome measures
1. Death at or before 36 weeks postmenstrual age
2. Number of days of respiratory support required, assessed from birth to 36 weeks postmenstrual age or discharge or death (whichever occurs earlier):
2.1. Conventional mechanical ventilation/HFOV
2.2. Continuous positive airway pressure

2.3. High flow nasal cannula
2.4. Number of days of oxygen dependency
3. Development of complications of prematurity, assessed from birth to 36 weeks postmenstrual age or discharge or death (whichever occurs earlier):
3.1. Nosocomial infection (line- sepsis, meningitis, pneumonia); confirmed microbiologically or antibiotic treatment for 5 days or more
3.2. Severe intraventricular haemorrhage (grade III/IV)
3.3. Necrotising enterocolitis (Bell stage II and above)
3.4. Treatment for retinopathy of prematurity
3.5. Treatment for patent ductus arteriosus
3.6. Serious adverse events/reactions
4. Resistance to macrolides among microbes isolated from respiratory and stool samples at baseline and day 14-21
5. Presence of ureaplasma identified through qPCR analysis of endotracheal and nasopharyngeal aspirate samples at baseline
6. Respiratory symptoms, measured using modified Liverpool questionnaire at 2 years corrected age
7. Neurodevelopmental symptoms, measured using modified Liverpool questionnaire at 2 years corrected age
8. Neurodevelopmental score (e.g. Bayley assessment) obtained from recruiting hospital or national databases at 2 years corrected age

Overall study start date
01/01/2018

Completion date
06/12/2023

Eligibility

Key inclusion criteria
1. Gestational age ≤29w+6d (including infants born as one of a multiple birth)
2. Neonates who have had respiratory support for at least 2 continuous hours duration during the first 72 hours of life (intubated, or by non-invasive mechanical ventilation including continuous positive airway pressure and high flow nasal cannula or a combination thereof)
3. Presence of an indwelling intravenous line for drug administration
4. Written informed consent within 72 hours of birth
5. Anticipating administration of first dose within 72 hours
6. Reasonable to expect completion of 10 days of trial treatment whilst resident at the recruiting site
7. Inborn, or born at site within the recruiting site’s neonatal network where follow up will be possible

Participant type(s)
Patient

Age group
Neonate

Sex
Both

Target number of participants
Planned Sample Size: 796; UK Sample Size: 796

Key exclusion criteria
1. In the opinion of the Principal Investigator (PI), babies unlikely to survive until 48 hours after birth
2. Exposure to another systemic macrolide antibiotic (not maternal)
3. Presence of major surgical or congenital abnormalities (not including patent ductus arteriosus or patent foramen ovale)
4. Known contraindication of azithromycin as specified in the summary of characteristics of the product
5. Participation in other interventional trials that precludes participation in AZTEC

Date of first enrolment
19/09/2019

Date of final enrolment
31/07/2022

Locations

Countries of recruitment
England

Scotland

United Kingdom

Wales

Study participating centre
University Hospital Wales (lead site)
Heath Park
Cardiff
United Kingdom
CF14 4XW

Study participating centre
Southmead Hospital
Westbury-on-Trym
United Kingdom
BS10 5NB

Study participating centre

Queen Alexandra Hospital
Southwick Hill Road
United Kingdom
PO6 3LY

Study participating centre
Bradford Royal Infirmary
Duckworth Lane
United Kingdom
BD9 6RJ

Study participating centre
Leicester Royal Infirmary
Infirmary Square
United Kingdom
LE1 5WW

Study participating centre
Southampton General Hospital
Tremona Road
United Kingdom
SO16 6YD

Study participating centre
Queens Medical Centre
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
City Hospital
Hucknall Road
Nottingham
United Kingdom
NG5 1PB

Study participating centre

Hull Royal Infirmary
Anlaby Road
Hull
United Kingdom
HU3 2JZ

Study participating centre
Royal Victoria Hospital
Queen Victoria Road
Newcastle upon Tyne
United Kingdom
NE1 4LP

Study participating centre
The Royal Oldham Hospital
Rochdale Road
Oldham
United Kingdom
OL1 2JH

Study participating centre
Evelina London Children's Hospital
Westminster Bridge Road
London
United Kingdom
SE1 7EH

Study participating centre
Royal Sussex and County Hospital
Eastern Road
Brighton
United Kingdom
BN2 5BE

Study participating centre
Princess Royal Maternity Hospital
16 Alexandra Parade
Glasgow
United Kingdom
G31 2ER

Study participating centre
Royal Preston Hospital
Sharoe Green Lane
Preston
United Kingdom
PR2 9HT

Study participating centre
Medway Maritime Hospital
Windmill Road
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ME7 5NY

Sponsor information

Organisation
Cardiff University

Sponsor details
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CF24 0DE
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Sponsor type
Hospital/treatment centre

ROR
https://ror.org/03kk7td41

Funder(s)

Funder type
Government

Funder Name

NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: 16/111/106

Results and Publications

Publication and dissemination plan

Current publication and dissemination plan as of 22/05/2024:
Main trial results published in Lancet Respiratory Medicine

Previous publication and dissemination plan:
Planned publication in a high-impact peer-reviewed journal.

Intention to publish date

31/12/2024

Individual participant data (IPD) sharing plan

The data is currently unavailable since blinded follow-up is still active

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version v3	25/06/2018	31/07/2018	No	Yes
Protocol article		06/10/2020	13/08/2021	Yes	No
Statistical Analysis Plan		23/08/2022	24/08/2022	Yes	No
HRA research summary			28/06/2023	No	No
Results article		25/04/2024	22/05/2024	Yes	No