CLINICAL TRIAL PROTOCOL

Prevention of congenital CMV treated with valacyclovir during pregnancy: a prospective cohort study

"TreatCMV"

Version number: v3 **– Date** 31/07/2023

EU CT Nbr: 2022-500714-25-01

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Sponsor

University Hospitals Leuven (UZ Leuven)

Herestraat 49, B-3000 Leuven

Coordinating Investigator

Luc De Catte

Confidentiality Statement

The information in this document is strictly confidential and is available for review to Investigators, potential Investigators and appropriate Ethics Committees, Institutional Review Boards or Competent Authorities. No disclosure should take place without written authorization from the Sponsor.

LIST OF PARTICIPATING SITES

(as applicable)

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SIGNATURES

Title: Prevention of congenital CMV treated with valacyclovir during pregnancy: a prospective cohort study

Protocol: "TreatCMV"

The undersigned confirm that the above referenced protocol has been acknowledged and accepted, and agree to conduct the Trial in compliance with the approved protocol, and will adhere to: the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in the EU Clinical Trial Regulation 536/2014 (CTR) and any subsequent amendments thereto, the ICH guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of May 7th 2017 related to clinical trials on medicinal products for human use, the EU General Data Protection Regulation 2016/679 (GDPR), the Belgian law of July 30th 2018 on the protection of natural persons with regard to the processing of personal data, the Belgian Law of August 22nd 2002 on patient rights, and any other regulatory requirements and Standard Operating Procedures (SOPs), as applicable.

The undersigned agree not to disclose the confidential information contained in this document for any purpose other than the evaluation or conduct of the Trial, without prior written consent of the Sponsor.

The undersigned also commit to making the findings of the Trial publicly available through publication and/or other dissemination tools, in accordance with this protocol and applicable regulations, without any unnecessary delay and to provide an honest, accurate and transparent account of the Trial; and to explain any discrepancies or deviations from the approved Trial protocol.

Coordinating Investigator

Prof. Dr. Luc De Catte	……	……
Name & Title	Signature	Date

Principal Investigator (Participating Site) *(in case of monocentric Trial, the Principal Investigator is the same as the Coordinating Investigator)*

Dr. L. Van der Veeken	……	……
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Prof. Dr. Leonardo Gucciardo	……	……
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Dr. Ingrid Witters	……	……
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Dr. Joachim Van Keirsbilck	……	……
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Prof. Dr. Luc De Catte	……	……
Name & Title	Signature	Date

Principal Investigator (Participating Site) *(in case of monocentric Trial, the Principal Investigator is the same as the Coordinating Investigator)*

Dr. Ben De Becker	……	……
Name & Title	Signature	Date

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LIST OF ABBREVIATIONS

Abbreviation	Definition
(e)CRF	(electronic) Case Report Form
AE	Adverse Event
AESI	Adverse Event of Special Interest
AR	Adverse Reaction
CA	Competent Authority
cCMV	Congenital cytomegalovirus
CI	Coordinating Investigator
CM	Concomitant Medication
CMV	CytoMegalovirus
CSR	Clinical Study Report
CTP	Clinical Trial Protocol
CTIS	Clinical Trial Information System
CTR	EU Clinical Trial Regulation 536/2014
DMP	Data Management Plan
DPA	Data Processing Annex
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
EC	Ethics Committee
EU	European Union
ECG	Electrocardiogram
EoT	End of Trial
FPFV	First Patient First Visit
GCP	Good Clinical Practice (latest version of ICH E6)
GDPR	General Data Protection Regulation
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IVD	In Vitro Diagnostic
IMP	Investigational Medicinal Product
ISF	Investigator Site File
JCI	Joint Commission International
KCE	Federaal Kenniscentrum voor de Gezondheidszorg
LPLV	Last Patient Last Visit
MAH	Marketing Authorisation Holder
MD	Medical Device
MP	Monitoring Plan
MRI	Magnetic Resonance Imaging
PCR	Polymerase Chain Reaction

PI	Principal Investigator (Participating Site)
PRO	Patient Reported Outcome
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

FUNDING AND SUPPORT

Funder	Type of Financial or Non-Financial Support
FWO	TBM 01/10/2022 – 30/09/2026 ; 948.329€

No travel reimbursement or other compensation is foreseen for the Trial participants.

ROLES AND RESPONSIBILITIES

The Principle Investigator (PI) is responsible for the conduct of the Trial at his/her Participating Site, and for protecting the rights, safety and well-being of the Trial participants. As such the PI must ensure adequate supervision of the Trial conduct at the Participating Site. If any tasks are delegated, the PI will maintain a log of appropriately qualified persons to whom he/she has delegated specified Trial-related duties. The PI will ensure that adequate training is provided and documented for all Trial staff, prior to conducting assigned Trial-related activities.

It is the Coordinating Investigator's (CI's) responsibility to supervise the general conduct (e.g. Trial progress, communication, protocol training and support of the participating sites, annual reporting to the Ethics Committee (EC), end of Trial notification(s) and results reporting…) of the Trial. The CI fulfils both Investigator and Sponsor responsibilities, as outlined in International Council on Harmonisation – Good Clinical Practice (ICH-GCP) E6(R2) and applicable regulations.

PI and CI shall each be referred to as «Investigator(s)».

TRIAL SYNOPSIS

Title of clinical Trial («Trial»)	Prevention of congenital CMV treated with valacyclovir during pregnancy: a prospective cohort study
Protocol Short Title Acronym	"TreatCMV"
Trial Phase (I, II, III, IV)	Phase III
Sponsor name	University Hospitals Leuven (UZ Leuven)
Coordinating Investigator	Luc De Catte
Contact Address CI	Herestraat 49, 3000 Leuven
Contact Email CI	luc.decatte@uzleuven.be
EU CT number	2022-500714-25-01
Other public database nbr	NA
Principal Investigators and Participating Sites	UZ Leuven – Luc De Catte UZA – Lennart Van der Veeken UZ Brussel – Leonardo Gucciardo UZ Gent – Ellen Roets ZOL – Ingrid Witters AZ Brugge – Joachim Van Keirsbilck GZA – Ben De Becker
Medical condition or disease under investigation	Fetal CMV infection
Trial rationale	During pregnancy, maternal CMV infections can be transmitted to the fetus. Fetal infection, depending on the gestational age at infection can lead to severe neurodevelopmental delay and (unilateral) hearing loss. Currently there is no treatment available to prevent vertical transmission to the fetus or to prevent morbidity in affected foetuses.
Primary objective	To assess the effectivity of valacyclovir to prevent fetal infection in case of a proven maternal first trimester infection.
Secondary objective(s)	- Assess maternal and fetal safety - Evaluate long-term neurobehavioral outcomes - Evaluate long term hearing outcome - Assess the rate of imaging abnormalities as seen on fetal ultrasound and fetal MRI
Trial Design	Prospective cohort study
Endpoints	The rate of vertical transmission to the fetus assessed by amniocentesis at 20w gestational age
Sample Size	112 patients
IMP, dosage and route of administration	Valacyclovir 4x2g/d oral
Active comparator product(s)	N/A

Maximum duration of treatment and Follow Up of a Participant	treatment will be maximal 12 weeks. Mothers will be followed until the end of pregnancy. Children (treated foetuses) will be followed until the age of 5 years
Maximum duration of entire Trial	8 years
Date anticipated First Patient First Visit (FPFV)	01/07/2023
Date anticipated Last Patient Last Visit (LPLV)	01/07/2031
Third parties	We negotiated a reduction in price for valacyclovir with Sandoz NV.

TRIAL FLOWCHART

Schedule of Events – Trial specific Procedures / Assessments

Contact moments	Inclusion	Treatment phase	Amniocentesis	Post-treatment follow-up		Neonatal period (< 21 days)	Age 6mo	Age 1y	Age 2y	Age 3y	Age 4y	Age 5y
Timing (weeks)		Every 2 weeks	20 weeks GA	Every 2 weeks until delivery (only if CMV positive)	30 weeks GA							
Window (days)		±3 days	± 2 Weeks	± 3 Days	± 2 Weeks	± 5 Days	± 1 Month	± 1 Month	± 1 Month	± 1 Month	± 1 Month	± 1 Month
Eligibility and inclusion (with informed consent)	X[1]											
Anamnesis	O	X										
Clinical examination (with blood sampling)	O	X				O	OX					
12w ultrasound report	O											
Concomitant therapy	X											
Screening medication intake		X										
Urinalysis						O						
Amniocentesis			O									
Ultrasound			O	OX	O	OX						
MRI					OX	OX						
Eye examination						OX						
ENT test						OX	OX	OX	OX	OX	OX	
Ages and Stages Questionnaire								OX	OX			OX
PARCA-R Questionnaire									X			
Trial drug dispensation	X	X										
Trial drug accountability	X	X										
Reason for discontinuation		(X)	(X)	(X)	(X)							
(Serious) Adverse event assessment		X	X	X	X							

I : Informed Consent be obtained prior to performing any other Trial-related procedures

O **This is a standard visit during pregnancy follow-up**
X **This is a study specific visit**
OX **This is a standard visit if your child is CMV positive, however if your child is CMV negative, this is a study specific visit**

Visit 1: Patients refered with a proven 1st trimester CMV infection will be screened for inclusion/exclusion criteria. A full history will be taken, vitals measured and a fetal ultrasound will be performed to demonstrate viability. If patients consent to participate a base line blood analysis will be performed including hematology and chemistry. Patients will be given the first badge of medication. Between 11+6 and 13+6 weeks gestational age a more extended ultrasound will be performed including early anatomy, this can be combined with the viability scan depending on the gestational age at presentation.

Visit 2: After one week, patients will be seen again to screen for side effects. Vitals are measured and blood analysis will be performed. Further medication will be dispensed. Side effects will be actively questioned with a specific designed questionnaire.

Visit 3-8: Patients will be seen every two weeks. Normal pregnancy follow-up in the first trimester is approx. every 4 weeks. We will **double the frequency of visits** to screen for side effects by measuring vitals and blood analysis. Further mediation will be dispensed each visit.

Visit 9: Around 20w gestational age, (at least 8 weeks after starting the treatment) patients receive a full anatomy scan, including detailed neurosonography. At this moment an amniocentesis will be performed. This is **standard practice** in case of maternal CMV infection.

Two-weekly follow-up: Every two weeks a detailed anatomy and neurosonography will be performed if amniocentesis demonstrated the presence of CMV in amniotic fluid. This is **standard practice**. If the amniocentesis was negative, only the 30w visit will be part of the study.

Visit 30w gestational age: at 30 weeks gestational age, all patients will undergo a detailed anatomy scan and neurosonography. This is standard practice in pregnancy. All patients that received treatment will undergo a fetal MRI to investigate brain development. Fetal MRI is **standard practice** in case of fetal infection however in the study also CMV negative foetuses will be scanned.

Newborn visit: After birth, hematology and chemistry will be determined on umbilical cord blood. Children will be examined physically which is **standard practice** and have an eye exam which is standard for CMV positive neonates. This prevents the neonate to undergo blood sampling. A urine sample will be taken to confirm infection status and to measure kidney function. During the early postnatal period, a neonatal brain ultrasound and MRI will be performed to investigate brain development. Chemistry is an **extra analysis** in newborns. A neonatal ultrasound and MRI are **standard practice** in case of symptoms of CMV infection at birth, during the study, all fetuses will be subjected to an MRI.

Childhood follow-up: Children will undergo hearing test at 6 months, 2, 3 and 4 years. At age 1 en 2 children that tested CMV positive will undergo neurodevelopmental testing (Bailey Score for Infant Development) with an in dept interview. At age 1, 2 and 5 we will do an online assessment of neurologic development using the Ages and Stages Questionnaire and the Parent Report of Children's Abilities-Revised, this will be provided to all children, CMV positive or negative. This follow-up is less frequent than the advised **standard follow-up** for fetuses infected with CMV, CMV negative fetuses are normally not followed-up.

1 Background, Rationale and Risk Assessment

Cytomegalovirus (CMV) is a member of the 'Herpesviridae' family and a commonly acquired infection. In healthy individuals CMV infections most often causes no symptoms or a mild cold-like disease. During pregnancy maternal CMV infection might be transmitted to the fetus, known as congenital or cCMV infection. In industrialized countries cCMV has an estimated prevalence of 0.7% - 1.5% and can occur as a primary infection or a non-primary infection (reinfection or re-activation). This makes the disease more prevalent than Down's syndrome, spina bifida or fetal alcohol syndrome. Newborns with cCMV infection have 15-20% risk to develop long-term sequela such as sensorineural hearing loss or neurodevelopmental disabilities. cCMV is therefore the leading nongenetic cause of sensorineural hearing loss and neurodevelopmental sequela during childhood. The risk for long-term consequences depends on the timing of maternal infection during pregnancy. Severe neurodevelopmental problems result from first trimester infections, while second and third trimester infections usually only result in (unilateral) hearing impairment without severe long-term neurodevelopmental morbidity.

In 2005 Naessens et al. calculated seroconversion rate to be 1.4% in Flanders. Despite the high prevalence and disease burden, there is still no effective treatment for cCMV. Therefore, the best strategy is to prevent maternal and fetal infection. The corner stone of maternal infection prevention is education on hygienic measures: reducing direct mucosal contact with saliva, urine or nasal excretions of young children. Simple measures such as: not sharing food, drinks or cutlery; no kissing on the lips but rather kiss on the hands or cheeks and handwashing after diaper changing could effectively reduce maternal CMV infections. To achieve this, public awareness of cCMV should be raised in general, but more in particular in pregnant women and health care providers. Currently, awareness of CMV is less than that of fetal alcohol syndrome, Down's syndrome or spina bifida, despite the fact that it's prevalence is much higher. A recent study demonstrated that only 20% of (mainly educated) women in the US had previously heard of CMV. Despite the fact that this number is believed to be slightly higher in Europe, there is still an important lack of knowledge regarding CMV. Increased knowledge and understanding of the disease would enhance the efficacy of prevention of maternal infection by hygienic measures.

Since fetal infections occur as a consequence of vertical transmission, screening for a maternal CMV infection can identify those fetuses at risk. Screening is performed by blood analysis for maternal IgG and IgM antibodies. Screening is currently not advised in Belgium by the KCE. This was decided mainly because of the many uncertainties that are linked to a maternal infection. Firstly it is unknown if a maternal infection will lead to a fetal infection. Secondly, infected fetuses are not necessarily severely neurologically impaired. During the last decade however, these uncertainties have largely been overcome. First of all, it is now clear that only first trimester maternal infections lead to severe neurologic morbidity, second and third trimester infections (usually) may only lead to hearing impairment. Therefore the window of screening can be narrowed down to the first trimester. Currently, screening is already performed in five out of the eight tertiary obstetrical units in Flanders, albeit not in a uniform standardized manner.

Secondly, upon a first trimester infection, CMV can be detected in amniotic fluid after 16 weeks gestational age (GA) and at least 8 weeks after onset of maternal infection. Therefore amniocentesis at 20 weeks GA is a reliable measure to demonstrate fetal infection. Thirdly, by combining prenatal ultrasound with fetal Magnetic Resonance Imaging (MRI) and a known fetal infection status, positive and negative predictive values of severe neurologic morbidity are 88.9% and 93.3%, respectively. This means that severe morbidity can be predicted or ruled out with a high certainty. On top of the fact that screening has been calculated to be cost-effective, it does not burden patients anymore with large uncertainties as it did before. The majority of patients, if instructed correctly about the impact of CMV during pregnancy, opt for screening even at own expenses. As a consequence, currently, in five out of eight perinatal centers in Flanders, screening for CMV is already offered to pregnant patients. However since there are no official guidelines, screening is not uniformly organized hence timepoints and frequency of screening vary between centers and screening is often still offered after the first trimester.

Upon infection during early gestation, a second strategy to prevent cCMV is to prevent maternal-fetal transmission. A randomized controlled trial recently demonstrated that women with a primary CMV infection during the first trimester who received valacyclovir (8 g per day) had a significant lower risk for a fetal infection with CMV than women treated with placebo (11% vs 30%). Although this treatment could

lower significantly the transmission rate, a few limitations are holding universal valacyclovir treatment for first trimester CMV infection back at this time. Firstly, in order to recognize women with a first trimester primary infection, screening for CMV in pregnancy is necessary. Despite evidence suggesting that screening for CMV is cost effective, currently in Belgium screening for CMV during pregnancy is not advised by local guidelines. Secondly this study only included 40 women in each arm. Thirdly, data on the long-term outcome of children born from mothers who receive highdoses of valacyclovir during pregnancy are still lacking. Theoretically ganciclovir or valganciclovir are more potent drugs to treat a viral infection with CMV, however these drugs are believed to be embryotoxic. Therefore, although less potent, acyclovir and valacyclovir are preferred because of their higher safety profile. Because of its favorable safety profile, valacyclovir is a drug of choice to treat Herpes infections both early and late in pregnancy. Data however are still limited and safety of valacyclovir is mostly investigated upon in lower dose regimens or shorter treatment durations.

2 Trial Objectives and Design

2.1 Trial objectives

This study aims to investigate the effectivity of valacyclovir to prevent CMV transmission in primary first trimester maternal CMV infections in the Belgian population. Secondly we want to investigate the long-term safety of valacyclovir treatment during pregnancy.

To achieve this project, we aim to set the following goals:

- Increase patient awareness of CMV during pregnancy
- Standardize first trimester CMV screening for pregnant women
- Investigate the efficacy of valacyclovir-treatment to prevent CMV transmission in primary first trimester maternal CMV infections in the Belgian population
- Recalculate the cost-effectiveness of population screening for CMV during pregnancy in Flanders
- Investigate safety and long-term follow-up

Our hypothesis is that prenatal treatment with valacyclovir during pregnancy will reduce the rate of fetal infections.

2.2 Primary Endpoints

The rate of vertical transmission, assessed by CMV PCR on amniotic fluid collected during an amniocentesis at 20w. This result will be reconfirmed by PCR on a urine sample postnatally.

2.3 Secondary Endpoints

- Imaging abnormalities indicative for vertical transmission assessed on ultrasound two weekly and on MRI at 30w GA.
- Maternal safety assessed by blood analysis (hematology, liver function, kidney function) and clinically.
- Fetal safety assessed by ultrasound prenatally, blood analysis at birth on umbilical cord blood (hematology, liver function), postnatal urine sample, MRI postnatally.
- Long term effects: hearing assessment yearly until year 4 and neurodevelopmental follow-up at 1,2 and 5 years of age.

2.4 Trial Design

This is a prospective longitudinal cohort study.

Given the evidence delivered by Nissan et al. on the efficacy of valacyclovir in prevention of vertical transmission, there is currently no need for a new randomized controlled trial to compare this drug with placebo. However, since there is no data on the long term safety of this drug for this indication, it is important to include the patients in an controlled setting of a trial. We will compare the current rate of vertical transmission to a cohort of historical controls and we will also follow, these patients per protocol, that decide not to take the drug but opt for expectant management.

2.5 Expected Duration of the Trial

The expectant duration of the trial in total will be 8 years.

We expect to include all patients needed to demonstrate efficacy of the drug within 2.5 years. This means we will have the result of our primary outcome after 3 years. Because we want to follow these patients until the age of 5, the trial will last eight years.

2.6 End of the Trial

The end of trial is defined as the last visit of the last included patient.

3 Trial Population / Eligibility Criteria

3.1 Inclusion criteria

Participants eligible for inclusion in this Trial must meet **all** of the following criteria:

1. Voluntary written informed consent of the participant or their legally authorized representative has been obtained prior to any screening procedures
2. 18 years or older
3. Proven first trimester primary CMV infection
    a. Seroconversion from IgG negative to IgG positive (independent of IgM)
    b. IgG with low avidity (<35) in the presence of specific IgM and a subsequent rise in IgG titer

3.2 Exclusion criteria

Participants eligible for this Trial must **not** meet any of the following criteria:

1. Participant has a history of kidney function problems, liver function problems, immunocompromised
2. Hypersensitivity to valaciclovir or aciclovir or any of it's excipients
3. Any disorder, which in the Investigator's opinion might jeopardise the participant's safety or compliance with the protocol
4. Any prior or concomitant treatment(s) that might jeopardise the participant's safety or that would compromise the integrity of the Trial
5. Participation in an interventional Trial with an investigational medicinal product (IMP) or device

4 Trial Procedures

4.1 Participant consent and withdrawal of consent

The Trial will be conducted only on the basis of prior informed consent by the Trial participants and/or their legally authorized representative(s). As such, no Trial-related procedures will be conducted prior to obtaining written informed consent from potential Trial participants.

The process for obtaining and documenting initial and continued informed consent from potential Trial participants will be conducted in accordance with ICH-GCP E6(R2), applicable regulatory requirements and internal Standard Operating Procedures (SOPs).

All originally signed obtained Informed Consent Forms (ICFs) must be retained/archived in the Investigator Site File (ISF) at the Participating Site and must not be destroyed (even when a scanned copy is available) before expiration of the legal archiving term as defined in the protocol section entitled "Archiving".

Participants may voluntarily withdraw consent to participate in the Trial for any reason at any time. The participant's request to withdraw from the Trial must always be respected without prejudice or consequence to further treatment. Consent withdrawal will be documented in the participant's medical record.

Trial data and samples collected before withdrawal can be used in the trial. No new trial data or samples will be collected after withdrawal of the participant.

4.2 Selection of Participants / Recruitment

This trial will be performed in the eight tertiairy obstetric centers in Flanders. All gynaecologists in these centers, as well as the referring physicians to these centers will be informed on this trial, which will be more than 90% of Flemish gynaecologists. Currently, we estimate that more than 50% of pregnant patients are screened for CMV in Flanders at different time points in pregnancy. Therefore, screening for CMV IgG and IgM at 7 and 13 weeks will not be a part of the trial. However, next to this trial we will try to introduce a uniform screening protocol in Flanders, i.e. at 7 and 13 weeks. In case of a proven first trimester seroconversion, or the assumption of a first trimester primo infection, patients are referred to one of this eight centers, which is currently standard practice in Flanders. In the reference center, the patient will be counselled and fully informed about this trial by the maternal-fetal-medicine specialist assessing the patient.

4.3 Randomization

Patients are not randomized. Given the existing evidence on the efficacy of valacyclovir to prevent vertical transmission of CMV, we will not randomize patients. We will inform patients about the current knowledge on this drug and the existing uncertainties and let the patient decide if she opts for prenatal treatment or not. We expect that most patients will opt for prenatal treatment. We will follow both groups until and after delivery in a similar way.

4.4 Premature discontinuation of Trial treatment

Participants may voluntarily discontinue from Trial treatment and/or prematurely end their participation in the Trial for any reason at any time. In such case the Investigator must make a reasonable effort to contact the participant (e.g. via telephone, e-mail, letter) in order to document the primary reason for this decision.

The Investigator may also decide at any time during the course of the Trial, to temporarily interrupt or permanently discontinue the Trial treatment if it is deemed that continuation would be detrimental to, or not in the best interest of the participant.

Similarly, the Sponsor, Ethics Committee or authorized regulatory authority can decide to halt or prematurely terminate the Trial when new information becomes available whereby the rights, safety and well-being of Trial participants can no longer be assured, when the integrity of the Trial has been compromised, or when the scientific value of the Trial becomes obsolete and/or unjustifiable.

Circumstances requiring premature treatment interruption or discontinuation of the Trial, include but are not limited to:

- Safety concerns related to IMP or unacceptable intolerability
- Trial participation while in violation of the inclusion and/or exclusion criteria

In any such case of early Trial termination and/or treatment interruption/discontinuation, the Investigator will continue to closely monitor the participant's condition and ensure adequate medical care and follow-up. It is recommended that follow-up information will be collected as follows:

similar to protocol within the trial.

For participants whose status is unclear because they fail to appear for Trial visits without stating an intention to discontinue or withdraw, the Investigator must make every effort to demonstrate "due diligence" by documenting in the source documents which steps have been taken to contact the participant to clarify their willingness and ability to continue their participation in the Trial (e.g. dates of telephone calls, registered letters, etc.).

A participant should not be considered lost to follow-up until due diligence has been completed.

4.5 Trial procedures

An overview of the assessments and visits is provided in the trial flowchart at page 16.
A detailed description of the trial can be found in a separate document: "Standard operating procedures".

Pregnancy follow-up

- Referral (<14 weeks)
  - Vitals (heart rate, blood pressure)
  - Repeat CMV IgG and IgM and avidity
  - Bloodwork
  - Intake
  - Informed consent
  - Start medication

-If patients participate in this study, they need to be followed in the perinatal centre and will need to deliver there.
-Return to clinic 1 week after start medication and from then onward two weekly
-After 8 weeks treatment AND after 18w GA

  - Ultrasound (US)
  - Amniocentesis
  - Stop treatment

- Subsequent follow-up
  - Amniocentesis PCR CMV negative
    - 30w extended US
    - 30w fetal MRI
  - Amniocentesis PCR CMV positive
    - 2 weekly extended US
    - 30w fetal MRI (earlier is possible in case of severe lesions)
    - Termination of pregnancy is possible if the infection is severe and after multidisciplinary meeting, according to the local guidelines
    - In case of termination, a cordocentesis will be done to perform the TOP, a blood fetal blood sample will be taken.
  - Counseling by pediatric neurology / neonatology in case of severe lesions

<u>Amniocentesis</u>
At 18-22 weeks (minimum 8w after treatment initiation)

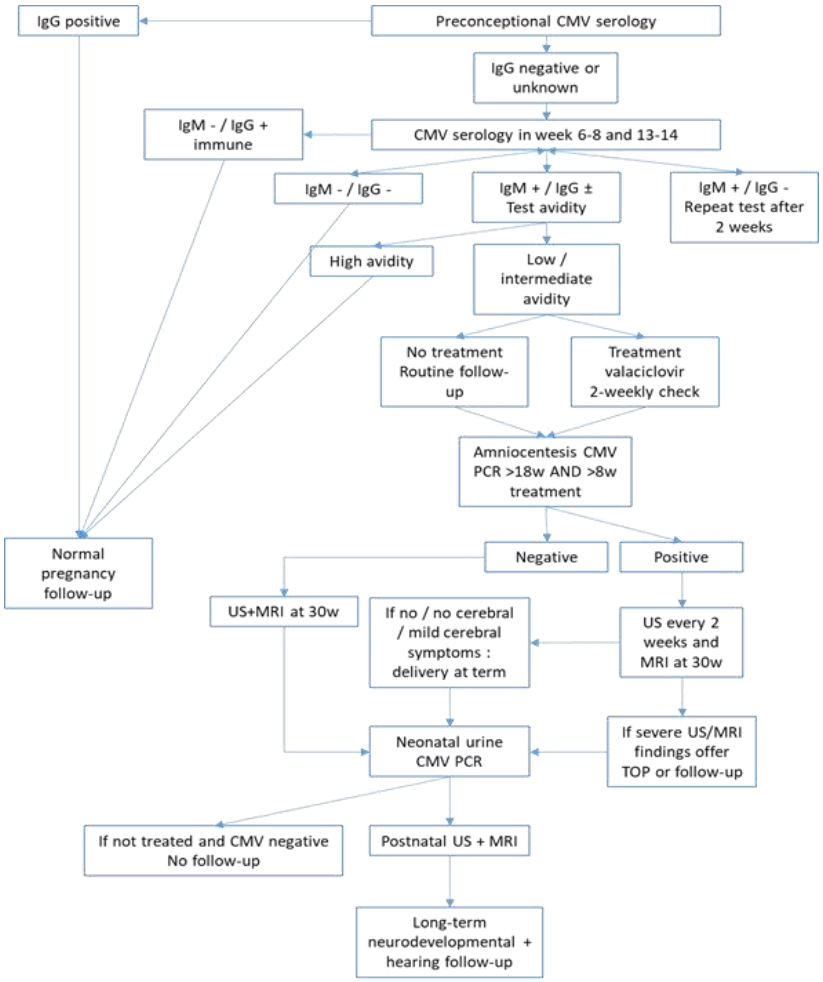
<u>Postnatal follow-up:</u>
Neonatal:

- Biometry
- Bloodwork
- Urine sample
- Eye fundus exam
- Brain US
- MRI
- Audiology exam

Child:

- Hearing and balance age 6m, 1y, 2y, 3y, 4y
- Neurodevelopment at 1y and 2y using BSID-3 in COS, only for CMV positive children
- Neurodevelopment online at 1y, 2y and 5y using ASQ and Parca-R at 2y for everyone

<u>Flow chart</u>



4.6 Personal information

In order to analyse the neurodevelopmental outcome of foetuses we will collect the following socio-economic information:

- Etnicity
- Education both parents
- Working situation both parents
- Family situation

To enable sending the online questionnaires to the parents for the neurodevelopmental follow-up, we will also collect a working email adres.

4.7 Use of In-Vitro Diagnostic (IVD) or Medical Device (MD)

This trial is not aiming at investigating any IVDs or MDs.

5 Trial Medication / Drug

Generic Drug Name (& company brand name)	IMP or non-IMP	Used within Indication? (Y or N)	Route of administration (po,sc,iv,…)	Dose/dosage and units
Valaciclovir Sandoz NV	IMP	N	PO	2g, 4x/d (500mg tablets)

5.1 Investigational Medicinal Product and Dosing Regimen

Patients that opt for valacyclovir treatment, will receive a bottle containing the right amount of tablets for the period until their next visit (i.e. two weeks). At the end of these two weeks, patients are re-evaluated, they have to return unused tablets and they receive the following dose of medication.

Study medication includes daily intake of 8g valacicloir. These will be taken in four gifts, morning-noon-afternoon-evening, e.g. 8.00-12.00-16.00-20.00h ±1h. Each time 4 tablets of 500mg valacyclovir will be taken.

5.2 Drug Accountability

Drugs will be deliverd to each hospital by Sandoz NV. In hospital, the pharmaceutical department will accept and repack the medication so each patients will only receive enough medication for two weeks. The medication is deliverd in tablets, which can be handled and stored at room temperature.

5.3 Concomitant / Prohibited Medication / Treatment

Prohibited medications are all medication that can lead to an altered neurodevelopment in the fetus or teratogenic medication. In this case, the baby cannot be included in the postnatal follow-up but can be included in the first part of the trial. Secondly valacyclovir should not be combined with nefrotoxic medication. Lastly, medication such as cimetidine, probenicide and mycofenolaat mofetil should be avoided.

5.4 Rescue Medication

In case of an overdose, hemodialysis can be performed to increase clearance of valacyclovir

6 Safety

6.1 Definitions

6.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or subject during a trial, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE.

6.1.2 Adverse Reaction (AR) or Adverse Drug Reaction (ADR)

An AR is any noxious and unintended responses to an investigational medicinal product or to a trial and, when an investigational product is concerned, related to any dose administered.

6.1.3 Serious Adverse Event (SAE)

A SAE is any untoward medical occurrence that at any dose, results in any of the following:

- Death
- A life-threatening[a] experience
- In-patient hospitalisation or prolongation of existing hospitalisation, except for routine obstetrical care (i.e. delivery)
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect

- Important medical events that may be considered an SAE when - based on appropriate medical judgement - they could jeopardise the participant's safety and may require medical or surgical intervention to prevent one of the above outcomes

[a] *The term "life threatening" in the definition of SAE refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.*

6.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is an AR, the nature or severity of which is not consistent with the information on the experiment, and, when a clinical Trial is concerned, with the applicable product information (e.g. Investigator's brochure (IB) for an unauthorised investigational product or the patient leaflet joined to the summary of product characteristics for an authorised product).

6.1.5 Adverse Events of Special Interest (AESI)

The following events should always be reported within the same timelines as SAEs:

- Overdose
- Misuse/abuse
- Medication error

6.1.6 Unexpected events that might influence the benefit-risk balance

The following unexpected events that might materially influence the benefit-risk balance, and which are not considered SUSARs, should be reported to the Member States:

- Increase in rate of occurrence of expected serious adverse events which may be clinically important
- Significant hazard to patient population

Unexpected events that are likely to seriously affect the benefit-risk balance and emergency safety measures which have been taken to protect the subjects are considered urgent safety measures.

6.2 Safety Events that do not require reporting

In general, the following should not be reported as AEs:

- Pre-existing conditions, including those found as a result of screening (these should be reported as medical history or concomitant illness), unless the condition worsens during Trial treatment
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first Trial-related activity after the participant has signed the informed consent
- Pregnancy

The following AEs are commonly observed and expected during pregnancy, and are therefore not considered adverse events for the purpose of the Trial unless these is a deterioration of these symptoms after onset of the medication:

- Nausea
- Vomiting
- Fatigue
- Headache
- Dizziness
- Polyuria
- Mood swings

Although these events should not be reported to the Sponsor, these should be recorded in the participant's medical notes according to routine practice.

The following events are not to be considered as SAEs:

- Pre-planned hospitalisations unless the condition for which the hospitalisation was planned has worsened from the first Trial-related activity after the participant has signed the informed consent.

- Hospitalisation as part of the standard procedure for protocol therapy administration However, hospitalisation or prolonged hospitalisation for a complication of therapy administration will be reported as an SAE
- Hospitalisation or prolongation of hospitalisation for technical, practical, or social reasons, in absence of an AE
- Hospitalisation in case of normal obstetrical events, i.e. delivery
- Delivery (i.e. vaginal birth, scheduled or unplanned caesarean birth, assisted vaginal delivery (vacuum or forceps) or VBAC (vaginal birth after cesarean)) in a full-term pregnancy. However, in case of an anomaly, an unexpected complication or a preterm delivery, this should be reported as an SAE.

6.3 Recording and Reporting of Safety Events

Investigators will seek information on the occurrence of safety events at each participant contact. All events, whether reported by the participant or noted by Trial staff, will be recorded in a timely manner in the participant's medical record and in the (e)CRF. If available, the *diagnosis* should be reported on the appropriate (S)AE page in the (e)CRF, rather than the individual signs or symptoms. If no diagnosis is available, the Investigator should record each sign and symptom as individual safety events.

The following minimum information should be recorded for each event:

- event description
- start and stop date of the event
- severity
- seriousness
- causality assessment to the IMP and/or Trial procedures
- outcome

6.3.1 Assessment

All safety events must be evaluated by an Investigator with regards to:

- **Seriousness:** determine whether the AE is an SAE. See above for the seriousness criteria.
- **Severity:**
  - Severity must be evaluated by the Investigator according to the following definitions:
    - *Mild* – no or transient symptoms, no interference with the participant's daily activities
    - *Moderate* – marked symptoms, moderate interference with the participant's daily activities
    - *Severe* – considerable interference with the participant's daily activities, unacceptable
- **Causality:**
  - *None* – The AE is not related to the IMP or participation in the experiment
  - *Unlikely* – It is unlikely that the AE is related to the IMP or participation in the experiment; an alternative explanation is more likely (e.g. concomitant medication(s), concomitant disease(s)), and/or the relationship in time suggests that a causal relationship is unlikely
  - *Possible* – The AE might be due to the use of the IMP or participation in the experiment. An alternative explanation is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be ruled out
  - *Probable* - The AE might be due to the use of the IMP or participation in the experiment. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely
  - *Definitely* – The AE is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation. The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge)

6.3.2 Timelines for reporting

After obtaining informed consent and prior to initiation of Trial treatment, only (serious) adverse events caused by a Trial specific procedure should be reported in the (e)CRF.

After initiation of Trial treatment and Trial specific procedure, safety events will be reported as follows:

- All AEs, SAEs and AESIs occurring in all patients until the childhood follow-up (including the newborn period visit 1) will be reported for both the mother and the fetus/newborn.
- All SAEs and AESIs as defined in the protocol must be reported to the Sponsor within 24 hours of the Trial staff becoming aware of the event. The initial report shall be followed by detailed, written reports. Both the initial and follow-up reports shall identify participants only by their Trial-specific identification.
- SAE details will be reported by the Investigator to the Sponsor:
  - By completing the SAE form in the (e)CRF
- If an authorised Investigator from the reporting site is unavailable, initial reports without causality and expectedness assessment should be submitted to the Sponsor by a healthcare professional within 24 hours of becoming aware of the SAE, but must be followed-up by a medical assessment performed by an authorised Investigator, as soon as possible thereafter.

6.3.3 Follow-up

The Investigator must record follow-up information by updating the participant's medical records and the appropriate form(s) in the (e)CRF.

SAE follow-up information should only include new information (e.g. corrections or additions) and must be reported within 24 hours of the Investigator's first awareness of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- All **SAEs** must be followed until the outcome of the event is 'recovered', 'recovered with sequelae', 'not recovered' (in case of death due to another cause than the SAE) and until all related queries have been resolved, or until the end of the Trial (whichever occurs first)
- **Non-serious AEs** must be followed until the participant's last Trial visit, and until all related queries have been resolved

SAEs after the end of the Trial: If the Investigator or Trial team becomes aware of an SAE with suspected causal relationship to the IMP or experiment, after the participant has ended the Trial, then this SAE must be reported within the same timelines as for SAEs occurring during the Trial.

6.3.4 Technical Complaints

Technical complaints with the IMP or comparator treatment should be reported to the Sponsor and to the Marketing Authorisation Holder (MAH) (e.g. change in colour, unequal sizes, broken vials/pills, sedimentation, inconsistent packaging or labelling etc.).

6.3.5 Death

All deaths, both maternal and/or fetal will be reported without delay to the Sponsor (irrespective of whether the death is related to disease progression, the IMP, participation in the experiment or an unrelated event).

6.4 Reporting requirements to the Member states

The Investigator is responsible for ensuring that all safety events are recorded in the (e)CRF and reported to the Sponsor in accordance with instructions provided in the protocol.

The Sponsor will promptly evaluate all SAEs and AESIs against medical experience to identify and expeditiously communicate possible new safety findings to Investigators.

6.4.1 Sponsor's reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

After receiving the SAE report form from the Investigator, the Sponsor must perform a causality (relationship) assessment. The term Serious Adverse Drug Reaction (SADR) is to be used whenever either the Investigator or the Sponsor deems the SAE is possibly or probably related to the IMP.

The Sponsor must evaluate (and document the evaluation of) the expectedness for each SADR against the Reference Safety Information, e.g. the Investigator's Brochure or applicable product information. In case the event is Unexpected (i.e. a SUSAR) it must be reported by the Sponsor to the Member states (through the EudraVigilance database) and other participating Investigators using the Council for International Organizations of Medical Sciences (CIOMS) form within the following timelines:

- **7 calendar days** if the event is fatal or life-threatening (follow-up information to be provided within an additional 8 calendar days)
- **15 calendar days** if non-fatal or non-life-threatening event (follow-up information be provided as soon as possible)

Other participating investigators should be notified of safety profile changes via investigators' letters, not of individual SUSAR reports.

For reporting to the EudraVigilance database, all information related to the SUSAR should be provided by the Sponsor to the CTC of UZ Leuven as soon as possible. Contact details: CTC.safety@uzleuven.be and tel. 016 34 19 98.

6.4.2 Sponsor's reporting of unexpected events that might influence the benefit-risk balance

The sponsor has the obligation to notify the Member states through the EU portal (CTIS) for all unexpected events, that are not SUSARs, and which affect the benefit-risk balance within the following timelines:

- **7** calendar days for serious urgent safety measures
- **15** calendar days for other events

6.4.3 Temporary halt or early termination of the clinical Trial for reasons of subject safety

The sponsor has the obligation to notify the concerned Member States through the EU portal (CTIS) in case of early termination of the clinical Trial for safety reasons. The notification (containing information on the reasons for such action and follow-up measures) should be made immediately, but not later than 15 calendar days after the temporary halt or termination.

6.4.4 Annual reporting

The Sponsor has the obligation to, once a year throughout the clinical trial (or on request), submit a Development Safety Update Report (DSUR) through the EU portal (CTIS), taking into account all new available safety information received during the reporting period.

6.4.5 Overview reporting requirements

	WHAT	HOW	TO	TIMELINES
Investigator	AE	AE form	sponsor	as defined in protocol
	SAE	SAE form	sponsor	Immediately (within 24 hours of becoming aware of the event) Exceptions: as defined in protocol
	death	SAE form	sponsor	asap
	Unexpected events affecting the benefit-risk balance	ad hoc	sponsor	asap

Sponsor	SUSAR	EudraVigilance	**unblinded:** - Member states (via EudraVigilance) - MAH (if applicable) **Safety profile changes:** - PI's of participating sites	asap, but no later than - 7 calendar days (in case of fatal or life-threatening SUSAR) - 15 calendar days (other SUSAR)
	Unexpected events affecting the benefit-risk balance	EU portal (CTIS)	EU portal (CTIS)	asap, but not later than - 7 calendars days (serious urgent safety measures) - 15 calendar days (other unexpected events)
	Annual Progress/ Development Safety Update Report	DSUR template	EU portal (CTIS)	annually

6.5 Data Safety Monitoring Board (DSMB)

We composed a multi-disciplinary committee to evaluate the study. The committee is composed of different specialists: gynaecologists-neonatologists-otolaryngologists-radiologist-pediatrician. The committee evaluated the build-up of this study. The specific details on monitoring are described in the DSMB Charter.

6.6 Dissemination update safety information

Safety updates need to be reported yearly in the updated Investigator Brochure and/or Development Safety Update Report (DSUR) and in case of substantial safety changes these need to be reflected in an updated informed consent form and submitted to CTIS to be approved, prior to providing to the Trial participants.

7 Statistics and Data Analysis

Statistical analysis will be performed in accordance with ICH E9; a detailed description of the analysis is provided in the Trial-specific Statistical Analysis Plan (SAP). ICH E3 and E8 will guide the structure and content of the clinical trial report.

Data will be compared to historical controls that were assessed at UZLeuven before the start of this trial. Outcomes of the rate of maternal CMV and cCMV infections will be descriptive. Lastly the long-term outcome of neurodevelopmental outcomes will be compared to standardized outcomes for this tests that reflect the general population.

Known factors that can influence the vertical transmission risk as well as the chance of a positive PCR on amniocentesis are: type of infection (primary vs non primary), gestational age at infection and time of amniocentesis, treatment, indication for screening, type of screening. To minimize possible confounders, we will only include patients in the control arm that were screened in the first trimester and meet the inclusion criteria of this trial, i.e. either seroconversion from IgG negative to positive in the presence of IgM or positive IgM and IgG with low avidity, hence recent primary infections. Because they tested positive in the first trimester, this cannot be based upon ultrasound findings. Furthermore, we only include patients that underwent an amniocentesis in between week 18 and 22 and were tested by PCR for CMV. All these patients were followed in one center, that did not offer any treatment. Although we cannot exclude that

some of these patients were screened because of mononucleosis type infection, this is very rare and 90% will have been asymptomatic, similar to the patients in this study. Given these restrictions to our inclusion criteria in the control arm, we are confident we accounted for all possible confounding factors.

Because patients are only included if they had an amniocentesis, there are no missing data. The rate of positive postnatal PCR in case of a negative amniocentesis PCR (false positive amniocentesis is nearly impossible) will also be compared. We have a subgroup in the control arm of 70 patients on whom we have postnatal PCR data that tested negative during pregnancy.

Although we strongly feel that the presence or absence of an amniocentesis in the active or control arm is not a source of bias, we can never be certain. To overcome this, we will perform case-control matching based on gestational age at infection, age and parity. To further decrease the selection bias and to deal with possible missing data in the active arm, firstly, we will compare the active and the control arm if possible confounders are evenly distributed. Therafter we will perform an analysis of the postnatal infections and compare this with the prenatal collected data to calculate if rejecting an amniocentesis is creating missing data at random or not. If missing an amniocentesis is at random, a complete-case approach for the amniocentesis outcome will be performed. For the secondary outcomes we will us a multiple-imputation approach for any outcome variable with more than 5% missing data, with a complete-case approach in a sensitivity analysis. Otherwise, only a complete case analysis will be performed.

We don't think that there are patients factors that influence the choice of amniocentesis and influence the transmission risk. Patient factors influencing the pick-up rate of amniosentesis are anxiety and fear for complications and pain, in addition to the patient's attitude towards conservative management or termination of pregnancy. Therefore we feel that having an amniocentesis yes or no has no impact on the transmission risk. That said, with the changes in the statistical analysis, we believe we can correct for this in case we are wrong.

Other possible but unknown confounders could be parity or age at infection. These data have been and will be collected. We will use a binary multivariate logistic regression model, in which possible confounding factors will be included.

Differences between the cases and historical controls are assessed using Mann Whitney U-tests for continuous data, and Chi-square tests for categorical data. Inter- and intra-observer variability of ultrasound data will be analysed with intraclass correlation coefficients and Bland Altman test.

We will include the most recent 200 cases (this will only include patients in the past 10 years) who meet these inclusion criteria in the control arm. To achieve optimal power in a 1:1 controlled setting, we will need to include 69 patients. Power calculation done by a two tailed Fisher exact test with a transmission probability of 31.7% in the control arm (own data) and 11% in the treated arm (Nissan et al.); α=0.05; β=0.2.

In order to demonstrate the safety of valacyclovir treatment on neurodevelopmental outcome we will compare the score on the PARCA-R test to normative values. The average score on a PARCA-R is 100, with a 15 point standard deviation. We calculated the sample size in a non-inferiority test for continuous outcomes, with a non-inferiority limit of 5 points. We would need to include 112 patients (α=0.05; β=0.2). This was calculated using a Continuous outcome non-inferiority trial sample size calculator (Sealed Envelope Ltd. 2012. Power calculator for continuous outcome non-inferiority trial. [Online] Available from: https://www.sealedenvelope.com/power/continuous-noninferior/ [Accessed Mon Jun 26 2023].)

The prevalence of cCMV is estimated to be 0.7%1. As there were 62.862 births in Flanders in 2019, annually there should be approximately 440 cCMV infections, half of these will be due to non-primary infections. Of the remaining 220 primary infections, approximately 1/3 will occur in the first trimester. This means that annually about 70 pregnant women will be eligible to participate in this study. By including all tertiary centers in Flanders, we aim to include at least 25 women each year. To reach the primary outcome, the study will need to be continued for at least two years. To demonstrate safety, this study will need to be continued for at least five years. Based on Belgian data by Naessens et al. the estimated number of primary infections would be slightly higher at 381 per year which would make prospects more positive and allow inclusion of 70 patients within 1.5 year.

Because we calculated two different sample sizes, 1 based on efficacy, 1 based upon safety, we will aim to include 112 patients to demonstrate safety. We will perform an interim analysis after inclusion of the first 69 patients to investigate the efficacy.

7.1 Sample Size Determination

Approximately 100 participants will be screened to achieve 80 assigned to Trial treatment.

A maximum of 160 participants will be assigned to Trial treatment such that approximately 120 evaluable participants complete the Trial.

7.2 Statistical Analysis

7.2.1 Efficacy Analysis

Endpoint	Statistical Analysis Methods
Primary	A Fisher-exact test will be used to compare the rate of fetal infection measured post partum in our treated cohort to a historical untreated cohort. We will need **38 patients in the treated arm and 200 patients in the control arm** to demonstrated efficacy with an expected prevalence of 11% cCMV in the treated group versus 31.7% in the untreated group, α=0.05; β=0.2
Secondary	In order to demonstrate the safety of valacyclovir treatment on neurodevelopmental outcome using the PARCA-R test, in a non-inferiority test for continuous outcomes, with a non-inferiority limit of 5 points, average 100 points, SD 15 points we would need to include 112 patients (α=0.05; β=0.2)
Exploratory	< >

7.2.2 Other Analysis

The presence and frequency of side effects will be mainly descriptive. Analysis of blood sample values will be compared to normative data using a two-sample t-test. The rate of imaging abnormalities will be compared to historical controls using a Fisher-Exact test. Neonatal kidney function will be compared to normative controls using a two-sample t-test. Biometry (fetal and neonatal and child) will be expressed as Z-scores and compared to normatives using a one-sample t-test. Hearing abnormalities will be compared to normatives and to non-treated foetuses using a Fisher-exact test.

In a second phase, we will analyse the concentration of acyclovir in amniotic liquid. This can help us in the future exploring lower dosing regimens.

7.3 Interim Analysis and Final Database Lock

No interim analysis will be performed

7.4 Central Reading

All images will be reevaluated by 2 blinded central readers.

- fetal ultrasound: prof. L De Catte (UZ Leuven) and dr. L. Van der Veeken (UZ Antwerpen – UZ Leuven).
- Fetal MRI: dr. M. Aertsen (UZ Leuven) and dr. M. Walgraeve (AZ Sint-Jan Brugge)
- Neonatal ultrasound: dr. M. Aertsen (UZ Leuven) and dr. L. Breysem (UZ Leuven)
- Neonatal MRI: dr. S. Dekeyzer (UZ Gent – UZ Antwerpen) and prof. P. Demaerel (UZ Leuven)

Images will be transfered by Liquid Files anonymously, only provided of studynumber.

8 Data handling

Data handling and data flows for the Trial are summarized below and will be described in more detail in the Trial-specific Data Management Plan (DMP).

Patient data will be pseudonymised. All data will be stored in a REDCap database from UZLeuven. Investigators from other centers will be given access to this database to enter data. For data analyses we will use SPSS (SPSS release 25 for Windows, IBM, USA).

8.1 Data Collection Tools and Source Document Identification

8.1.1 Operational aspects

Data collection, handling, processing and transfer for the purpose of this Trial will be performed in compliance with applicable regulations, guidelines for clinical trials and internal procedures, as follows:

8.1.1.1 Data collection

Source Data will be collected and recorded in the Trial participant's files/medical records.

If applicable, worksheets may be used for capturing some specific data in order to facilitate completion of the (e)CRF. Any such worksheets will become part of the Trial participant's source documentation and will be filed together with or as part of the medical records (during but also following completion of the Trial).

It remains the responsibility of the Investigator to check that all data relating to the Trial, as specified in the Trial protocol, are entered into the (e)CRF in accordance with the instructions provided and that the forms are filled out accurately, completely and in a timely manner.

(e)CRFs are provided by the Sponsor for each participant. The Trial data will be transcribed from the source records (i.e. participant's medical file or Trial-specific source data worksheets) into an (e)CRF by Trial Staff. Transcription to the (e)CRF will be done as soon as possible after a participant visit and in a pseudonymized manner using a unique identifier assigned by the Sponsor.

The (e)CRFs will be available for review at the next scheduled monitoring visit (as applicable) and shall under no circumstances capture personal data such as but not limited to the participant or their relative(s) name, home address, contact details, full date of birth medical record number (e.g. UZ Leuven EAD number), social security number etc.

8.1.1.2 Data Validation

All data relating to the Trial must be prepared and validated by the Investigator. Any (e)CRF entries, corrections and alterations must be made by the Investigator or other authorized Trial staff.

Proper audit trails must be available to demonstrate the validity of the Trial data collected. This includes historical records of original data entries, by whom and when the data was entered, as well as detailed records of any corrections or additions made to the original data entry (i.e. who made the correction/addition, when and why), without obliterating the original data entry information.

8.1.1.3 Data Management

The Trial Data Manager will perform extensive consistency checks on the received data. Queries will be issued in case of inconsistencies in accordance with internal procedures. A Data Management Plan (DMP) will be developed to map data flows, data validation measures that will be taken, how (interim) database lock(s) will be managed and, as applicable, the role and responsibilities of the Data Safety Monitoring Committee (DSMB)

8.1.1.4 Data Transfer

Any participant records or datasets that are transferred to the Sponsor or any partners of the Sponsor will contain the Trial-specific participant identifier only; participant names or any information which would make the participant identifiable will not be transferred. All pseudonymized data relating to the Trial must be transmitted in a secure manner to the Sponsor or any partners of the Sponsor(see 8.1.2. legal requirements).

8.1.2 Legal requirements

All source data will be kept at a secured location with restricted access at all times. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data protection laws and regulations and more in particular the EU General Data Protection Regulation 2016/679 (GDPR) and relevant national laws implementing the GDPR. Appropriate technical and

organizational measures to protect the data against unauthorized disclosure or access, accidental or unlawful destruction, or accidental loss or alteration must be established. Trial staff whose responsibilities require access to personal data agree to keep the data confidential.

The Investigator and the Participating Site(s) (as applicable) shall treat all information and data relating to the Trial disclosed to them as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the objectives of the Trial as described in this protocol. The collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with applicable laws and regulations regarding personal data protection and the processing of personal data.

The Investigator will maintain all source documents and completed (e)CRFs that support the data collected from each Trial participant, and will maintain a Trial Master File (TMF)/Investigator Site File (ISF) containing all Trial documents as specified in ICH-GCP E6(R2) Chapter 8 entitled "Essential Documents for the Conduct of a Clinical Trial", and as specified by applicable regulatory requirement(s). The Investigator will take appropriate measures to prevent accidental or premature destruction of these documents.

Transfer of the pseudonymized data will be performed via a secured method of transfer taking into account all applicable security arrangements and regulations (such as GDPR).

8.2 Audits and Inspections

The Investigator will permit direct access to Trial data and documents for the purpose of monitoring, audits and/or inspections by authorized entities such as but not limited to: the Sponsor or its designees and competent regulatory or health authorities. As such (e)CRFs, source records and other Trial related documentation (e.g. Investigator Site File, the Trial Master File, pharmacy records, etc.) must be kept current, complete and accurate at all times.

8.3 Monitoring

In accordance with ICH-GCP E6(R2) the Sponsor is responsible for monitoring the Trial to ensure compliance with GCP and current legislation, and to verify, among other requirements, that proper written informed consent has been obtained and documented, that the Trial procedures have been followed as shown in the approved protocol, and that relevant Trial data have been collected and reported in a manner that assures data integrity. To this end Source Data will be compared with the data recorded in the (e)CRF. A risk-based approach will be applied to determine the extent of monitoring activities and monitoring of the Trial will be performed by qualified individuals (independent from the site Trial staff), as applicable.

Monitoring will be performed by the CTC Leuven. Each site will be visited once for the initiation (SIV), 4 monitoring visits (MV) and 1 Close-out visit at the end of the trial (COV).

The Sponsor and Investigator/Participating Site will permit direct access to the Trial data and corresponding Source Data, and to any other Trial related documents or materials to verify the accuracy and completeness of the data collected. More details about the monitoring strategy are described in the Trial specific Monitoring Plan (MP).

8.4 Archiving

As specified in ICH-GCP E6(R2) section 8.1 Addendum, the Sponsor and Investigator/Participating Site will maintain a record of the location(s) of all respective Essential Trial Documents (including but not limited to Source Documents, completed and final (e)CRF and ISF/TMF). The Sponsor should ensure that the Investigator has control of and continuous access to the (e)CRF data reported to the Sponsor during the Trial.

The Investigator/Participating Site should have control of all Essential Documents and records generated by the Investigator/Participating Site before, during and following termination of the Trial.

The Sponsor is responsible for archiving Trial specific documentation (such as but not limited to the Trial protocol, any modifications thereto, the final Clinical Study Report (CSR) and the Trial database) according

to ICH-GCP E6(R2). Source data and site-specific Trial documents (such as but not limited to the original signed ICFs) will be archived by the participating site(s) according to local practice, and for at least 25 years following termination of the Trial. Archived data may be held on electronic record, provided that media back-up exists, hard copies can be obtained, if required and measures are taken to prevent accidental or premature loss or destruction of data. Destruction of Essential Documents prior to, during or upon completion of the required archival period, will require written authorisation from the Sponsor.

9 Ethical and Regulatory Considerations

9.1 CA/EC review & reports

Before the start of the Trial, this protocol and other related documents (e.g. ICF, advertisements, IB, etc.) will be submitted through the CTIS portal for review to the CA/EC for Trial authorization. The Trial shall not commence until such approvals have been obtained and until other relevant essential Trial documents, such as duly signed contract agreements, evidence of adequate Trial financing etc. are in place.

It is the responsibility of the CI to produce the Development Safety Update Report (DSUR) and submit to CTIS within 30 days of the anniversary date on which favourable opinion to start the Trial was given, and annually until the Trial is declared ended.

The CI shall notify the EC/CA of the end of the Trial. Should the Trial be temporarily suspended or, ended prematurely, the CI will notify the EC/CA and include the reasons for suspension/premature termination within 15 days of the decision. The CI will submit a final report with the results of the study, including any publications/abstracts, to the EC/CA within 1 year of trial termination or within 6 months for paediatric Trials. The CTIS portal will be used for communication with the CA/EC of all participating Member States.

9.2 Peer review

This protocol was created after carefull discussion with over 20 specialist in the different domains involved. Furthermore, the study is overseen by 7 independent experts from different specialities (ENT, radiology, neonatology, pediatricians in neurologic development), who act as a supervising committee. Each year, the progress of this study will be presented and discussed with this committee.

9.3 Regulatory Compliance

The Trial will be conducted in compliance with the principles outlined in the requirements for the conduct of clinical Trials in the EU as provided for in the CTR and any subsequent amendments, as well as in compliance with ICH-GCP E6(R2) guidelines, other GxP guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of May 7th 2017 on clinical Trials with medicinal products for human use and with the EU General Data Protection Regulation 2016/679 (GDPR), the relevant Belgian laws implementing the GDPR, including the Belgian Law of July 30th 2018 on the protection of natural persons with regards to the processing of personal data and the Belgian Law of August 22nd 2002 on patient rights and all other applicable legal and regulatory requirements.

9.4 Protocol / GCP compliance

The Trial must be performed in accordance with the protocol, current ICH and ICH-GCP guidelines, and applicable regulatory and country-specific requirements. ICH guidelines are an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of Trial participants are protected, consistent with the principles that originated in the most recent version of the Declaration of Helsinki, and that the Trial data are credible, reliable and reproducible.

The Investigator and Trial team acknowledge and agree that prospective, planned deviations or waivers to the protocol are not permitted under applicable regulations on clinical studies. However, should there be an accidental protocol deviation, such deviation shall be adequately documented in the source documents and on the relevant forms and reported to the CI and Sponsor. Deviations should also be reported to the EC as part of the EC's continued review of the Trial (e.g. through the DSUR). Protocol deviations which are found to frequently recur, will require (immediate) action. The Investigator acknowledges that such

recurring protocol deviations could potentially be classified as a serious violation of ICH and/or the protocol.

It is understood that "a serious violation" is likely to affect to a significant degree:

- the safety or physical or mental integrity of the Trial participants; or
- the scientific validity of the Trial

The Investigator is expected to take any immediate action required to protect the safety of any participant included in the Trial, even if this action represents a deviation from the protocol. In such cases, the Sponsor should be notified of this action and the EC at the Trial site should be informed according to local procedures and regulations.

9.5 Data protection and participant confidentiality

The Trial will be conducted in compliance with the requirements of the GDPR, the relevant Belgian laws implementing the GDPR including the Belgian Law of July 30th 2018 on the protection of of natural persons with regards to the processing of personal data. Any collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with the aforementioned personal data protection laws (cfr. Data Processing Annex (DPA) in Appendix). In case personal data is transferred outside the European Economic Area, safeguards will be taken to ensure that appropriate protection travels with the data in accordance with the GDPR. (https://ec.europa.eu/info/law/law-topic/data-protection/international-dimension-data-protection/rules-international-data-transfers_en#documents)

Any personal data shall be treated as confidential at all times including during collection, handling and use or processing, and the personal data (including in any electronic format) shall be stored securely at all times and with all technical and organizational security measures that would be necessary for compliance with EU and national data protection legislation (whichever is more stringent). The Sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access thereto or disclosure thereof or loss or destruction while in its custody.

9.6 Insurance

The Participating Site, the Investigator and Sponsor shall have and maintain in full force and effect during the term of this Trial, and for a reasonable period following termination of the Trial, adequate insurance coverage for: (i) medical professional and/or medical malpractice liability, and (ii) general liability.

For Belgian Participating Sites

Art 12 of the Belgian Law of May 7th 2017 on clinical Trials with medicinal products for human use applies. Prior to the start of the Trial, the Sponsor shall enter into an insurance contract in order to adequately cover Trial participants from Belgian sites in accordance with art. 12 of the said law.

9.7 Modifications

During the Trial the Sponsor may modify the Trial. It is the Sponsor's responsibility to assess whether a modification is substantial or non-substantial, a change relevant to the the supervision of the Trial, or whether a substantial modification leads to changes in the Trial to an extent that it has to be considered as a completely new clinical trial.

A "substantial modification" is defined as any change of the Trial which is made after a decision is issued on a previously submitted application and that is likely to substantially impact the subjects' safety or rights or the reliability and robustness of the data generated in the Trial. A non exhaustive list of examples of substantial and non-substantial modifications is available in Annex III of the CTR Q&A document in Eudralex volume 10. Sponsor shall submit the substantial modifications in CTIS which will be evaluated by the CA/EC. A substantial modification may only be implemented if it has been approved by the CA/EC with no prejudice to the right of Sponsor and the Principal Investigator to take urgent safety measures without awaiting prior authorisation. In that case, the event and the measures taken should be reported in CTIS without undue delay but no later than 7 days from the date the measures have been taken.

A "change which is not a substantial modification but relevant to the supervision of the Trial by the CA/EC" shall be permanently updated in CTIS by the Sponsor, in line with article 81(9) of the CTR. An example of such change is an update of sponsor or CRO contact details.

A "non-substantial modification" is any change outside the scope of a substantial modification and irrelevant to the supervision of the Trial. A non-substantial modification should not be notified as such. These changes should be implemented during the next substantial modification. Non-substantial modifications need to be listed and identified as such in the cover letter of the substantial modification application.

9.8 Post-Trial activities

Participants will be able to contact the responsible gynaecology department that they visited during the trial.

10 Research Registration, Dissemination of Results and Publication Policy

The Declaration of Helsinki (latest version) and European and Belgian regulations require that every research Trial involving human participants be registered in a publicly accessible database before recruitment of the first participant. The CI is responsible for registering the Trial.

In addition, the CI will fulfil their ethical obligation to disseminate and make the research results publicly available. As such the CI is accountable for the timeliness, completeness and accuracy of the reports. Researchers, authors, Sponsors, editors and publishers must adhere to accepted guidelines for ethical reporting. Negative and inconclusive, as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in publication.

11 Intellectual Property

Any know how, inventions, methods, developments, innovations, discoveries and therapies, whether patentable or not, arising from the Trial or made in the performance of the Trial protocol ("Inventions") shall vest in the Sponsor. The Participating Site, its employees and Investigator(s) shall promptly disclose to the Sponsor any such Inventions. Parties have expressly agreed that any and all Trial data as collected and prepared in the performance of the Trial protocol shall be the sole property of Sponsor unless otherwise agreed in the clinical trial agreement.

12 Joint Commission International (JCI)

In order to ensure the same quality and safety standards in patient care for clinical research as commonly applied by the Sponsor in its regular activities, and in accordance with JCI standards, the Sponsor shall comply with the following obligations: (a) the Sponsor will use trained and qualified employees or contractors to manage and coordinate the Trial; (b) the Sponsor will ensure that multi-center Trial reporting is reliable and valid, statistically accurate, ethical, and unbiased. (c) the Sponsor will not grant incentives, other than standard compensations and reimbursement of costs, to Trial participants or to participating site's staff that would compromise the integrity of the research; (d) the Sponsor is responsible for monitoring and evaluating the quality, safety, and ethics of the Trial and will respect the participating site's policies and processes when performing such monitoring and evaluation activities; (e) the Sponsor will protect the privacy and confidentiality of the Trial participants in accordance with all applicable laws.

13 References

<insert>

APPENDICES

14 Appendix 1: Clinical trial protocol history

Original CTP version:	1.0 dated 31/07/2023

Amendment #1:	<CTP version nbr> dated 31/07/2023
Modifications made / Reason for amendment:	
<protocol section reference>	<describe modifications made>
<protocol section reference>	<describe modifications made>
<protocol section reference>	<describe modifications made>
<protocol section reference>	<describe modifications made>

Amendment #2:	<CTP version nbr> dated 31/07/2023
Modifications made / Reason for amendment:	
<protocol section reference>	<describe modifications made>
<protocol section reference>	<describe modifications made>
<protocol section reference>	<describe modifications made>
<protocol section reference>	<describe modifications made>

15 Appendix 2: Data Processing Annex (DPA) between Sponsor and Participating Site(s)

Definitions:

- "Protocol" means the document entitled Prevention of congenital CMV treated with valacyclovir during pregnancy: a prospective cohort study containing the details of the academic Trial as developed by the Sponsor and approved by the relevant CA/EC.
- "Sponsor" means University Hospitals Leuven (UZ Leuven).
- Participating site acts as a data processor as defined under article 4, 8) of the Regulation (EU) 2016/679 ("Data Processor") for the Sponsor who acts as data controller as defined under article 4, 7) of the Regulation (EU) 2016/679 ("Data Controller").
- "Applicable Law" means any applicable data protection or privacy laws, including:
    a) the Regulation (EU) 2016/679 also referred as the General Data Protection Regulation ("GDPR");
    b) other applicable laws that are similar or equivalent to or that are intended to or implement the laws that are identified in (a) of this definition;
- "Personal Data" means any information relating to an identified or identifiable natural person ("Data Participant"), including without limitation pseudonymized information, as defined in Applicable Law and described in the Protocol.

Rights and obligations:

1. The Data Processor is instructed to process the Personal Data for the term of the Trial and only for the purposes of providing the data processing tasks set out in the Protocol. The Data Processor may not process or use Personal Data for any purpose other than a Data Participant's medical records, or other than provided in the instructions of the Trial protocol, including with regard to transfers of personal data to a third country or an international organization, unless the Data Processor is required to do so according to Union or Member State law.
2. Data Processor shall at all times maintain a record of processing of Personal Data in accordance with Applicable Law and if the Data Processor considers an instruction from the Data Controller to be in violation of the Applicable Law, the Data Processor shall promptly inform the Data Controller in writing about this.
3. The Data Processor must ensure that persons authorized to process the Personal Data have committed themselves to confidentiality or are under an appropriate statutory obligation of confidentiality.
4. The Data Processor shall implement appropriate technical and organizational measures to prevent that the Personal Data processed is:
    (i) accidentally or unlawfully destroyed, lost or altered,
    (ii) disclosed or made available without authorization, or
    (iii) otherwise processed in violation of Applicable Law.
5. The appropriate technical and organizational security measures must be determined with due regard for:
    (i) the current state of the art,
    (ii) the cost of their implementation, and
    (iii) the nature, scope, context and purposes of processing as well as the risk of varying likelihood and severity for the rights and freedoms of natural persons.
6. Taking into account the nature of the processing, the Data Processor shall assist the Data Controller, by means of appropriate technical and organizational measures, insofar as this is

possible, in fulfilling its obligation to respond to requests from Data Participants pursuant to laws and regulations in the area of privacy and data protection (such as, the right of access, the right to rectification, the right to erasure, the right to restrict the processing, the right to data portability and the right to object)

7. The Data Processor shall upon request provide the Data Controller with sufficient information to enable the Data Controller to ensure that the Data Processor's obligations under this DPA are complied with, including ensuring that the appropriate technical and organizational security measures have been implemented.

8. The Data Controller is entitled to appoint at its own cost an independent expert, reasonably acceptable to the Data Processor, who shall have access to the Data Processor's data processing facilities and receive the necessary information for the sole purpose of auditing whether the Data Processor has implemented and maintained said technical and organizational security measures. The expert shall upon the Data Processor's request sign a non-disclosure agreement provided by the Data Processor, and treat all information obtained or received from the Data Processor confidentially, and may only pass on, after conferral with the Data Processor, the findings as described under 10) (ii) below to the Data Controller.

9. The Data Processor must give authorities who by Union or Member State law have a right to enter the Data Controller's or the Data Controller's processors' facilities, or representatives of the authorities, access to the Data Processor's physical facilities against proper proof of identity and mandate, during normal business hours and upon reasonable prior written notice.

10. The Data Processor must without undue delay in writing notify the Data Controller about:

    (i) any request for disclosure of Personal Data processed under the Protocol by authorities, unless expressly prohibited under Union or Member State law,

    (ii) any finding of (a) breach of security that results in accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, Personal Data transmitted, stored or otherwise processed by the Data Processor under the Protocol, or (b) other failure to comply with the Data Processor's obligations, or

    (iii) any request for access to the Personal Data (with the exception of medical records for which the Data Processor is considered data controller) received directly from the Data Participants or from third parties.

11. Such a notification from the Data Processor to the Data Controller with regard to a breach of security as meant in 10) (ii)(a) above will contain at least the following information:

    (i) the nature of the Personal Data breach, stating the categories and (by approximation) the number of Data Participants concerned, and stating the categories and (by approximation) the number of the personal data registers affected (datasets);

    (ii) the likely consequences of the Personal Data breach;

    (iii) a proposal for measures to be taken to address the Personal Data breach, including (where appropriate) measures to mitigate any possible adverse effects of such breach.

12. The Data Processor shall document (and shall keep such documentation available for the Data Controller) any Personal Data breaches, including the facts related to the Personal Data breach, its effects and the corrective measures taken. After consulting with the Data Controller, the Data Processor shall take any measures needed to limit the (possible) adverse effects of Personal Data breaches (unless such consultation cannot be awaited due to the nature of the Personal Data breach).

13. The Data Processor must promptly and reasonably assist the Data Controller (with the handling of (a) responses to any breach of security as described in 10) (ii) above and (b) any requests from Data Participants under Chapter III of the GDPR, including requests for access, rectification, blocking or deletion. The Data Processor must also reasonably assist the Data Controller by implementing appropriate technical and organizational measures for the fulfilment of the Data Controller's obligation to respond to such requests.

14. The Data Processor must reasonably assist the Data Controller with meeting the other obligations that may be incumbent on the Data Controller according to Union or Member State law where the assistance of the Data Processor is implied, and where the assistance of the Data Processor is necessary for the Data Controller to comply with its obligations. This includes, but is not limited to, at the request to provide the Data Controller with all necessary information about an incident under 10) (ii), and all necessary information for an impact assessment in accordance with Article 35 and Article 36 of the GDPR.

Subprocessor:

15. The Data Processor may only engage a subprocessor, with prior specific or general written consent from the Data Controller. The Data Processor undertakes to inform the Data Controller of any intended changes concerning the addition or replacement of a subprocessor by providing a reasonable prior written notice to the Data Controller. The Data Controller may reasonably and in a duly substantiated manner object to the use of a subprocessor. The Data Processor must inform the Data Controller in writing of the discontinued use of a subprocessor.
16. Prior to the engagement of a subprocessor, the Data Processor shall conclude a written agreement with the subprocessor, in which at least the same data protection obligations as set out in this DPA shall be imposed on the subprocessor, including obligations to implement appropriate technical and organizational measures and to ensure that the transfer of Personal Data is done in such a manner that the processing will meet the requirements of the Applicable Law.
17. The Data Controller has the right to receive a copy of the relevant provisions of Data Processor's agreement with the subprocessor related to data protection obligations. The Data Processor shall remain fully liable to the Data Controller for the performance of the subprocessor obligations under this DPA. The fact that the Data Controller has given consent to the Data Processor's use of a subprocessor is without prejudice for the Data Processor's duty to comply with this DPA.

16 Appendix 3: [Title]