# CONgenital Cytomegalovirus: Efficacy of antiviral treatment in a non-Randomized Trial with historical control group

Published: 05-09-2013
Last updated: 22-04-2024

Primary Objective: Investigate whether early valganciclovir treatment of children with SNHL of * 20 dB, unilateral or bilateral, and a confirmed congenital CMV infection can prevent deterioration of the hearing loss at follow-up (age 18 * 22 months...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Skin and subcutaneous tissue disorders NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON41461

**Source**
ToetsingOnline

**Brief title**
CONCERT study 2.0

### Condition

- Skin and subcutaneous tissue disorders NEC
- Hearing disorders
- Developmental disorders NEC

**Synonym**
congenital cytomegalovirus (CMV)

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Leids Universitair Medisch Centrum

**Source(s) of monetary or material Support:** Fonds NutsOhra

## Intervention

**Keyword:** cytomegalovirus, sensorineural hearing loss, valganciclovir

## Outcome measures

### Primary outcome

The primary endpoint is the status of the SNHL expressed in dB, in children

with congenital CMV at follow-up (age 18 * 22 months after birth).

### Secondary outcome

Treatment group and refusal & historical control group

The secondary endpoint is the development of the infants.

Viral load in urine at follow-up.

Treatment group and refusal control group

The viral load (in dried blood spots, blood and urine) will be monitored during

the 7 weeks after inclusion. Furthermore, possible resistance to the medication

will be analysed.

# Study description

### Background summary

Congenital cytomegalovirus (CMV) is a common infection leading to a wide range of clinical signs and symptoms. These include intrauterine growth retardation, microcephaly, cerebral involvement with developmental delay, sensorineural hearing loss (SNHL) and opthalmological disorders. Transient problems include hepatic damage and haematological disorders (leucopenia and thrombocytopenia). One of the most apparent, frequent and serious consequences of a congenital CMV infection is SNHL. Most children with a congenital CMV infection have no symptoms at birth. Of these 85-90% asymptomatic children, 13.5% will eventually

develop complaints, such as SNHL and possibly also mental retardation and visual defects.
Due to the wide variety in presenting signs and symptoms caused by a congenital CMV infection, a distinction is made between symptomatic and asymptomatic congenital CMV. Symptomatic CMV infection is defined as clinically apparent disease in the newborn period including microcephaly, intracranial calcifications, chorioretinitis and abnormal cerebrospinal fluid. Asymptomatic congenital CMV infection includes all children with no clinically apparent disease at birth, thus also including children with SNHL. This distinction has traditionally existed in literature because until the introduction of NHS, hearing impairment was usually not diagnosed until the child was much older.

CMV is the most common cause of congenital infections worldwide. To determine the birth-prevalence of congenital CMV in the Netherlands, a random sample of 6500 dried blood spots (DBS), obtained in 2007 from neonates from all regional screening areas, was tested for CMV. Results show a birth-prevalence of 0.54% (95% CI 0.3-0.7%). This means that yearly about 1000 neonates are born in The Netherlands with a congenital CMV infection. Of all children with congenital CMV infection 17-20% will have long-term permanent sequelae. Of those children, 2/3 will be asymptomatic at birth and 1/3 will be symptomatic. These permanent sequelae result in disabilities such as SNHL, visual impairment and mental retardation.
Moderate to severe bilateral SNHL affects about one per 1000 newborns in the Netherlands. Early detection of severe hearing loss and subsequent intervention before the age of 6 months has been shown to improve cognitive, social and learning abilities. This is the reason for the recent implementation of universal neonatal hearing screening in the Netherlands. Congenital CMV infection is an important cause of both early and late-onset SNHL, causing 20-30% of cases. Korver et al recently showed that the rate of congenital CMV among Dutch children with permanent bilateral hearing impairment was 8%, and 23% among children with profound hearing impairment. Only early-onset cases of SNHL with hearing impairment above the screening thresholds, will be detected by the NHS.
Several studies have shown the beneficial effect of intravenous ganciclovir and/or oral valganciclovir on hearing preservation in newborns diagnosed with congenital CMV. However, these studies concentrated on infants with symptomatic congenital CMV infections (clinically apparent disease in the newborn period) and treated, in most cases, with intravenous ganciclovir. The mentioned studies show a substantial effect of treatment. However, there is not sufficient data available on the treatment of congenital CMV infections whether being symptomatic or asymptomatic, or with the use of oral valganciclovir. Oral treatment should be explored for the obvious reasons of it being less invasive for the patient and without the necessity for hospital admission during the treatment.
An effective and easy to administer treatment for congenital CMV infections may prevent further deterioration of already existing SNHL and also prevent the development of SNHL in a group where this is not yet apparent (at risk for

late-onset hearing loss) and which thus cannot be detected by NHS. It is possible that other manifestations of congenital CMV infection, such as psychomotor developmental delay, might also benefit from early treatment. The diagnosis of congenital CMV infection can be carried out using dried blood spots (DBS).
We hypothesize that this study will show that early treatment of congenital CMV infected children with hearing impairment will prevent deterioration of hearing loss in a considerable number of children.

**Study objective**

Primary Objective:
Investigate whether early valganciclovir treatment of children with SNHL of * 20 dB, unilateral or bilateral, and a confirmed congenital CMV infection can prevent deterioration of the hearing loss at follow-up (age 18 * 22 months after birth).

Secondary Objectives:
Investigate whether early valganciclovir treatment of children with SNHL of * 20 dB, unilateral or bilateral, and a confirmed congenital CMV infection can prevent communicative and speech developmental delay and cognitive and motor retardation.

Investigate whether early valganciclovir treatment of children with SNHL of * 20 dB, unilateral or bilateral. and a confirmed congenital CMV infection reduces the CMV viral load in urine and blood samples after 6 weeks treatment and one week after completion of treatment. At follow-up (18-22 months after birth) the viral load will be determined solely in urine.

Investigate whether drug resistance has evolved.

**Study design**

The design of the study is an efficacy trial with a combined refusal and historical control group. See the logistical flowcharts on pages 44 and 45 for a schematic depiction of the trial. Two separate phases constitute the study, also implying that parents will be asked for informed consent separately for each phase. Phase 1 encompasses the diagnostic phase, for which informed consent will be asked to test for congenital CMV. Phase 2 comprises inclusion in the study (treatment and / or follow-up) for infants diagnosed with congenital CMV and hearing loss of * 20 dB. Three groups of infants may participate in the CONCERT study 2.0, all infants who are eligible for inclusion will go through both phases. Infants in the treatment group and infants in the refusal control group come into contact with the CONCERT study 2.0 after referral to the Audiological Center (AC). Generally infants are aged approximately 4 weeks at referral. Inclusion of these infants (in the treatment

group or refusal control group) takes place before 13 weeks of age. Infants in the historical control group will be mostly older and receive a letter with information (including informed consent form for CMV diagnostics) when the infant is 14-21 months of age. Inclusion of infants in the historical control group occurs only after congenital CMV has been diagnosed and parents decide to participate in the follow-up. Depending on the age of the infant, the follow-up will take place shortly or several months after parents have provided consent. Infants in the historical control group participate only in the follow-up of phase 2.

### Intervention

Treatment consists of twice daily administration of 16 mg/kg valganciclovir (32 mg/kg daily) (Roche Pharmaceuticals) in an oral solution. The doses should be administered orally just before morning and evening feeding moments.
All treated infants will be treated for a total of 6 weeks.

### Study burden and risks

One of the main benefits of this trial is the chance of preventing deterioration of hearing loss in the treated infants. Another benefit will be extensive follow-up with laboratory tests, extra physical examinations, developmental tests and hearing evaluation. At follow-up all children will be physically examined, audiometric examinations will be carried out and cognitive and motor development will be investigated. Early habilitation of hearing loss is known to have a significant impact on the communicative, emotional, cognitive and social development as well as the quality of life. Besides hearing amplification, other adjustments (for example learning sign language and special education and family intervention programs) will benefit the infant.
Besides the above mentioned benefits, another benefit associated with participation is the possibility of early recognition of a cause of SNHL in children in whom otherwise the cause of the SNHL will most often remain unknown.

A possible disadvantage of participation are potential side effects of valganciclovir, most importantly reversible neutropenia. In the treatment group the potential side effects are carefully monitored by means of weekly blood tests during the treatment period of six weeks. The blood samples will be taken by a study group member at the infant*s home. Neutropenia may also arise as a consequence of a congenital CMV infection itself. Hence the infants in the refusal control group will also be monitored for neutropenia.
Another disadvantage for the treated infants and the infants in the refusal control group are the blood samples that will be taken during the first 7 weeks after inclusion. A study group member will visit the infant*s home to reduce the strain on parents of traveling to a nearby hospital. The person responsible for taking the blood samples is a well-trained physician assistant with

experience in taking blood samples from young infants. The blood sampling is necessary to ensure the safety of the treated infants.
From inclusion until the follow-up at the age 18 * 22 months after birth, the following data will be collected: history, physical examination, parental questionnaire, blood tests (treatment group: at inclusion, weekly for 6 weeks during treatment and 1 week after completion of treatment; refusal control group: two blood samples, one at inclusion and one 6 weeks post inclusion), urine tests with filter paper in the diaper (weekly during 7 weeks after inclusion). At follow-up the following data will be collected at the home of the infant (for treatment group, refusal and historical control groups): urine test with filter paper in the diaper, hearing evaluation, developmental scores and a developmental questionnaire.
Infants in the historical control group are expected to be around the age of 15 - 22 months at the moment that they are contacted by the study group to participate in the historical control group. A possible disadvantage is that parents may realize that their child might have been treated in the CONCERT 2.0 trial if the trial were started earlier. At this stage these infants are too old to consider treatment. The possibility of follow-up with the extra physical examination, extra developmental tests and extra hearing evaluation are evident advantages for the children in the historical control group.

# Contacts

**Public**
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2300 RC
NL
**Scientific**
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2300 RC
NL

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Children (2-11 years)

## Inclusion criteria

Treatment group and refusal control group
- Infants with congenital CMV infection, and hearing loss (* 20 dB, in one or both ears).
- Age at time of inclusion is * 12 weeks after birth.
- Born at * 37 weeks gestational age.
- Birth weight > -2 SD corrected for duration of pregnancy and ethnic origin.
- Parental signed informed consent.;Historical control group
- Infants with congenital CMV infection, and hearing loss (* 20 dB, in one or both ears).
- Age at time of inclusion is > 13 weeks after birth.
- Born at * 37 weeks gestational age.
- Birth weight > -2 SD corrected for duration of pregnancy and ethnic origin.
- Parental signed informed consent.

## Exclusion criteria

Treatment group and refusal control group
- Previously noted (* 12 weeks after birth) symptoms possibly related to congenital CMV, for which medical attention was requested. For
example: intra uterine growth retardation, petechiae, hepatosplenomegaly, jaundice, microcephaly, thrombocytopenia, elevated transaminases, elevated bilirubin.
- Treatment with other antiviral agents or immunoglobulins.
- Solely applicable for treatment group: leucopenia < 0,5 x 10*9/L (blood sample tested at t=0).;Historical control group
- Previously encountered (* 12 weeks after birth) symptoms possibly related to congenital CMV, for which medical attention was requested For example: intra uterine growth retardation, petechiae, hepatosplenomegaly, jaundice, microcephaly, thrombocytopenia, elevated transaminases, elevated bilirubin.
- Treatment with (val)ganciclovir.
- Treatment with other antiviral agents or immunoglobulins.

# Study design

## Design

| | |
|---|---|
| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Other |
| Allocation: | Non-randomized controlled trial |
| Masking: | Open (masking not used) |

**Primary purpose:** Treatment

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 22-10-2013 |
| Enrollment: | 50 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Valcyte |
| Generic name: | Valganciclovir |
| Registration: | Yes - NL outside intended use |

# Ethics review

Approved WMO

| | |
|---|---|
| Date: | 05-09-2013 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 30-09-2013 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO
Date: 20-12-2013

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 24-02-2014

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 10-04-2014

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 04-07-2014

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 17-07-2014

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 28-05-2015

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

| | |
|---|---|
| Approved WMO Date: | 24-07-2015 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |

| | |
|---|---|
| Approved WMO Date: | 01-10-2015 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2013-003068-30-NL |
| CCMO | NL45593.058.13 |