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

Summary

EudraCT number	2013-003068-30
Trial protocol	NL
Global end of trial date	17 May 2018

Results information

Result version number	v1 (current)
This version publication date	22 October 2022
First version publication date	22 October 2022

Trial information

Trial identification

Sponsor protocol code	CMV-MM-2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02005822
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Leiden University Medical Center
Sponsor organisation address	Albinusdreef 2, Leiden, Netherlands, 2333 ZA
Public contact	Aloysius Cornelis Maria Kroes, MD PhD, Leiden University Medical Center, 0031 71526 3931, A.C.M.Kroes@lumc.nl
Scientific contact	Aloysius Cornelis Maria Kroes, MD PhD, Leiden University Medical Center, 0031 71526 3931, A.C.M.Kroes@lumc.nl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 January 2017
Global end of trial reached?	Yes
Global end of trial date	17 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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 18-22 months follow--up.

Protection of trial subjects:

- By participating in the study, parents learned their child had cCMV while this might otherwise have been undetected. This knowledge could have posed a possible extra burden. We have tried to diminish stress by providing clear information before consent, providing time to consider and ask questions. The advantages of the awareness of the presence of the congenital CMV infection were explained, for instance additional hearing evaluations. We provided contact information of the lead investigator and an independent pediatrician to answer any questions at any time.
- Potential side effects of the study drug were monitored by regular blood tests
- Regular blood tests were performed at the home of the study subject to minimise burden burden of travel and stress for the child
- Blood tests in control subjects were only performed at baseline and 7 weeks after inclusion
- Urine samples were collected on filter paper by parents at home and sent via postal service to minimise burden of travel
- Parents of historic controles approached for the study might have experienced distress from realising their child could have been treated in the CONCERT 2.0 trial if the trial were started earlier. We stressed the advantages of the possibility of follow-up with the extra physical examination, extra developmental tests and extra hearing evaluation for the children in the historical control group.

Background therapy:

no medicinal treatment, regular care and follow-up by pediatrician, audiologist and possible other specialists such as ophthalmologists.

Evidence for comparator:

Current views on treatment are based on two seminal randomized controlled trials (Kimberlin 2003, Kimberlin 2015), which show that antiviral treatment has a favorable effect on long-term neurodevelopmental and audiologic outcome, the latter more notably in those with evidence of CNS disease. While there is widespread consensus on the treatment of infants with cCMV and clinically detectable symptoms and CNS involvement (Luck 2017), evidence from prospective controlled trials for antiviral treatment of cCMV infants with isolated hearing loss was long lacking. An observational study reported favorable long term hearing outcome in infants with cCMV and isolated hearing loss, after treatment with (val)ganciclovir (Pasternak 2018)

Actual start date of recruitment	02 September 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 37
Worldwide total number of subjects	37
EEA total number of subjects	37

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	37
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between September 1 2013 and 19 December 2016, subjects were recruited through a nationwide targeted screening approach using the national Newborn Hearing Screening (NHS) program. Parents or legal guardians of infants who failed three subsequent rounds of the NHS were informed about the trial and offered CMV testing.

Pre-assignment

Screening details:

1381 infants tested for CMV, of which 1374 (99%) were successfully tested; 59 (4.3%) CMV positive, of which 35 were included in the prospective trial; 24 were not: 19 were ineligible due to exclusion criteria and 5 due to procedural(1) or logistical reasons(2) or no interest(2).

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

A blinded audiologist reassessed all raw data from baseline and follow-up audiological tests.
Blinded psychologists assessed (performed and interpreted) the developmental tests at follow-up.
Data was subsequently analysed by non-blinded investigator.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment group

Arm description:

Infants in the treatment group received valgancivlovir 16mg/kg bid during six weeks. Per protocol, dosages were fixed for the entire treatment period. Initial home visit at inclusion: medical history taking, physical examination, child development test (van Wiechen), blood sampling (complete blood count with differential, liver function tests and viral load). Hereafter, weekly visits until one week after treatment for blood and urine filter paper sampling. Parents were asked keep diaries with abnormalities or signs during treatment and instructed to contact investigators in case of possible adverse events. Follow-up visit ate age 18-22 months: physical examination, developmental examination (BSID-III) and BERA.

Arm type	Experimental
Investigational medicinal product name	Valcyte
Investigational medicinal product code	SUB16471MIG
Other name	Valganciclovir
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

16mg/kg twice daily (32 mg/kg daily) during six weeks. The specific dosage was determined at inclusion according to the weight of the infant, registered at inclusion. The dosage remained unchanged during the 6 weeks treatment. Suspension was prepared by pharmacy and supplied to parents, along with (needleless) syringes for administration, which were marked to ensure that the correct dosage is administered by the parents.

Arm title	Combined control group

Arm description:

2 groups:
Refusal control group: Subjects of which parents/guardians refused medicinal treatment. Subjects received regular care after cCMV diagnosis. Referral to pediatrician was advised. Initial home visit at inclusion: medical history taking, physical examination, child development test, blood sampling (complete blood count with differential, liver function tests and viral load). Urine filter papers were collected by parents and mailed, at baseline and during 7 weeks hereafter. Parents were asked to keep diaries. Follow-up visit at age 18-22 months: physical examination, developmental examination (BSID-

III) and BERA.

Historical control group: Children with hearing loss born between November 2011 and July 2012 were informed by audiologists about CONCERT trial and retrospective dried blood spot (DBS) testing was offered. After retrospective diagnosis, children were included for follow-up visit at age 18-22 months.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Treatment group	Combined control group
Started	25	12
Completed	25	12

Baseline characteristics

Reporting groups

Reporting group title	Treatment group

Reporting group description:

Infants in the treatment group received valgancivlovir 16mg/kg bid during six weeks. Per protocol, dosages were fixed for the entire treatment period. Initial home visit at inclusion: medical history taking, physical examination, child development test (van Wiechen), blood sampling (complete blood count with differential, liver function tests and viral load). Hereafter, weekly visits until one week after treatment for blood and urine filter paper sampling. Parents were asked keep diaries with abnormalities or signs during treatment and instructed to contact investigators in case of possible adverse events. Follow-up visit ate age 18-22 months: physical examination, developmental examination (BSID-III) and BERA.

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Historical control group: Children with hearing loss born between November 2011 and July 2012 were informed by audiologists about CONCERT trial and retrospective dried blood spot (DBS) testing was offered. After retrospective diagnosis, children were included for follow-up visit at age 18-22 months.

Reporting group values	Treatment group	Combined control group	Total
Number of subjects	25	12	37
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	25	12	37
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Age at treatment for treatment group, age at inclusion for control group (excepting the 2 historic controls which were purposefully retrospectively included before at any age before follow-up of 18-22 months).			
Units: weeks			
arithmetic mean	8	7.7	
standard deviation	± 2.6	± 2.7	-
Gender categorical Units: Subjects			
Female	13	7	20
Male	12	5	17

Hearing loss Units: Subjects			
Unilateral hearing loss	13	4	17
Bilateral hearing loss	12	8	20
Best ear hearing loss			
Hearing loss in best ear			
Units: Subjects			
Normal	13	4	17
Mild hearing loss	3	3	6
Moderate hearing loss	4	4	8
Severe hearing loss	2	0	2
Profound hearing loss	3	1	4
Head circumference Units: SD			
arithmetic mean	-0.41	-1.05	
standard deviation	± 1.1	± 1	-
Birth weight Units: gram(s)			
arithmetic mean	3220	3107	
standard deviation	± 470	± 530	-
Gestational age Units: week			
arithmetic mean	39.5	38.9	
standard deviation	± 1.3	± 1.1	-

End points

End points reporting groups

Reporting group title	Treatment group

Reporting group description:

Infants in the treatment group received valgancivlovir 16mg/kg bid during six weeks. Per protocol, dosages were fixed for the entire treatment period. Initial home visit at inclusion: medical history taking, physical examination, child development test (van Wiechen), blood sampling (complete blood count with differential, liver function tests and viral load). Hereafter, weekly visits until one week after treatment for blood and urine filter paper sampling. Parents were asked keep diaries with abnormalities or signs during treatment and instructed to contact investigators in case of possible adverse events. Follow-up visit ate age 18-22 months: physical examination, developmental examination (BSID-III) and BERA.

Reporting group title	Combined control group

Reporting group description:

2 groups:
Refusal control group: Subjects of which parents/guardians refused medicinal treatment. Subjects received regular care after cCMV diagnosis. Referral to pediatrician was advised. Initial home visit at inclusion: medical history taking, physical examination, child development test, blood sampling (complete blood count with differential, liver function tests and viral load). Urine filter papers were collected by parents and mailed, at baseline and during 7 weeks hereafter. Parents were asked to keep diaries. Follow-up visit at age 18-22 months: physical examination, developmental examination (BSID-III) and BERA.

Historical control group: Children with hearing loss born between November 2011 and July 2012 were informed by audiologists about CONCERT trial and retrospective dried blood spot (DBS) testing was offered. After retrospective diagnosis, children were included for follow-up visit at age 18-22 months.

Primary: Best ear hearing analysis

End point title	Best ear hearing analysis

End point description:

End point type	Primary

End point timeframe:

Baseline to Follow-Up (18-22 months)

End point values	Treatment group	Combined control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: Subjects				
Improved at follow-up	3	0		
Normal hearing at baseline and Follow-up	12	2		
Same hearing loss at baseline and Follow-up	7	4		
Deteriorated hearing at follow-up	2	6		

Statistical analyses

Statistical analysis title	Best ear hearing analysis
Statistical analysis description: proportional odds model	
Comparison groups	Treatment group v Combined control group
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.003
Method	Regression, Logistic

Primary: Best ear hearing analysis, numerical

End point title	Best ear hearing analysis, numerical
End point description:	
End point type	Primary
End point timeframe: Baseline to Follow-Up (18-22 months)	

End point values	Treatment group	Combined control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: decibel				
number (not applicable)	-3.3	13.7		

Statistical analyses

Statistical analysis title	Best ear hearing, numerical
Comparison groups	Treatment group v Combined control group
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.02
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	17
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.6
upper limit	31.4

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to Follow-Up (18-22 months)

Assessment type	Systematic

Dictionary used

Dictionary name	none
Dictionary version	1

Reporting groups

Reporting group title	Treatment group

Reporting group description:

Infants in the treatment group received valgancivlovir 16mg/kg bid during six weeks. Per protocol, dosages were fixed for the entire treatment period. Initial home visit at inclusion: medical history taking, physical examination, child development test (van Wiechen), blood sampling (complete blood count with differential, liver function tests and viral load). Hereafter, weekly visits until one week after treatment for blood and urine filter paper sampling. Parents were asked keep diaries with abnormalities or signs during treatment and instructed to contact investigators in case of possible adverse events. Follow-up visit ate age 18-22 months: physical examination, developmental examination (BSID-III) and BERA.

Serious adverse events	Treatment group		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 25 (4.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
BRUE	Additional description: Admitted for observation due to a brief resolved unexplained event (BRUE), consisting of apnea and color change, which had resolved upon arrival of the ambulance. Independent pediatrician assessed the SAE as unlikely to be related to the test product		
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Treatment group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 25 (20.00%)		
Blood and lymphatic system disorders			
Anemia	Additional description: One subject temporarily halted valganciclovir because of anemia (Hb 4.4 mmol/L) and mild leucopenia (4.14 x 10^9/L) and neutropenia (0.82 x 10^9/L), which resolved three days after cessation of the drug.		

subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
neutropenia	Additional description: There were three occurrences of neutropenia in the treatment group: one resolved spontaneously without altering the dosage, one necessitated temporary suspension of the drug, and in one subject the dose was halved.		
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Gastrointestinal disorders			
reflux	Additional description: One subject temporarily halted the study drug because of gastrointestinal complaints which were later not ascribed to valganciclovir after restarting the drug.		
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2013	Changes in letter for parents to further explain the home visit. The letter to physicians regarding the participation of a child in the follow-up study has been added to further inform practitioners previously informed in CONCERT 1.0 about the follow-up in CONCERT 2.0
24 February 2014	Adjustment in the inclusion criterion regarding birth weight. The new criterion is: > -2 SD for gestational age and parentage. Previously, the criterion was ≥ 2500 grams. The new criterion is more accurate and more representative as birth weight is related to parentage and gestational age.
17 July 2014	- Recruitment method: Parents of children with hearing loss can also hear about the CONCERT study through another route (internet, friends/family or magazine article). Children who come into contact with the CONCERT study via these routes could also participate in CMV diagnostics. So not just with information from an audiologist. - Intention to treat for 6 weeks: In case of side effects, the treatment can be temporarily stopped. As soon as the blood values allow, treatment will be resumed with the intention of completing the 6 weeks of treatment. - Blood collection for neutropenia: after the detection of neutropenia, another blood sample is taken within 5 days. - The change in the letter concerns a textual change that the CMV diagnosis is offered to children older than 3 months.
28 May 2015	- Flyer 'Medical Scientific Research': This folder will in future be given by regional coordinators and audiologists who hand over the first information package (CMV diagnostics) to parents in the event of a referral in the hearing screening (region coordinator) or who are diagnosed with hearing loss (audiologist). - Inclusion of children of minor parents (<18 years): Excluding a child of minor parents is not in the best interests of the child itself. If the guardian(s) have been assigned and known to the researcher, the child can be included. - Change in letter information CMV diagnostics: In the letter it is added that parents have also received the flyer 'Medical Scientific Research' together with the letter. This is referred to in the consent form. - Change of consent forms: Two things have been added to the forms. Firstly, having the doctor (researcher) sign it for providing information to parents. Secondly, a textual addition that by signing the form parents / guardians also give permission for access to the research data by persons named in the folder 'Medical Scientific Research'.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Non-randomised trial; this summary is written by another person than the lead researcher who initiated and coordinated the trial.

Notes: