Clinical trial results:
Multicenter, randomized study comparing oral valganciclovir versus intravenous ganciclovir in patients following allogeneic stem cell transplantation

Summary

EudraCT number	2009-015965-29
Trial protocol	DE AT ES
Global end of trial date	09 March 2012

Results information

Result version number	v1 (current)
This version publication date	16 September 2017
First version publication date	16 September 2017

Trial information

Trial identification

Sponsor protocol code	ML 22371

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	THERAMetrics GmbH (formerly Pierrel Research Europe GmbH)
Sponsor organisation address	Zeche Katharina 6, Essen, Germany, 45307
Public contact	Coordinating Investigator, Prof. Dr. med. Hermann Einsele Medizinische Klinik und Poliklinik II, Zentrum für Innere Medizin, 0049 931 201 400 01, einsele_h@medizin.uni-wuerzburg.de
Scientific contact	Coordinating Investigator, Prof. Dr. med. Hermann Einsele Medizinische Klinik und Poliklinik II, Zentrum für Innere Medizin, 0049 931 201 400 01, einsele_h@medizin.uni-wuerzburg.de

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	14 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 March 2012
Global end of trial reached?	Yes
Global end of trial date	09 March 2012
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to assess the efficacy and safety of oral valganciclovir versus intravenous ganciclovir in patients following allogeneic stem cell transplantation (SCT).

- The event-free survival (patients without cytomegalovirus (CMV) disease or death from any cause) within 180 days after SCT.
- The proportion of patients with severe neutropenia (absolute neutrophil count (ANC) <500 cells/µL) until 7 days after discontinuation of antiviral therapy with the Study Drug.

Protection of trial subjects:

No specific measures had to be put in place because the study drug was well tolerated and safe in previous studies.

Background therapy:

Immunosuppressive graft-versus-host-disease (GVHD) prophylaxis according to center practice.

Evidence for comparator: -

Actual start date of recruitment	12 January 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Germany: 8
Worldwide total number of subjects	13
EEA total number of subjects	13

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)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	12
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was enrolled on 12-JAN-2011. The sponsor terminated the study prematurely on 16-DEC-2011 after the randomization of 13 patients. The main factor for this decision was the slow patient recruitment with less than 2 patients per month resulting in a considerable timely delay of the study conduct.

Pre-assignment

Screening details:

In the Screening Phase, the following assessments were performed CMV-Polymerase chain reaction (PCR) or pp65 antigenemia assay, assessment of CMV infection, safety laboratory (incl. hematology and serum chemistry). In total, 8 subjects in Germany, 2 subjects in Austria and 3 subjects in Spain were screened.

Pre-assignment period milestones

Number of subjects started	13
Number of subjects completed	13

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Valganciclovir

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Valganciclovir
Investigational medicinal product code	
Other name	Valcyte
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 x 900 mg valganciclovir p.o./d for at least 14 days

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

Dosage and administration details:

Valganciclovir powder for oral solution 50 mg/mL for at least 14 days.

Arm title	Ganciclovir

Arm description: -

Arm type	Active comparator

Investigational medicinal product name	Ganciclovir
Investigational medicinal product code	
Other name	Cymeven
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

2 x 5 mg/kg/d intravenous ganciclovir for at least 14 days

Number of subjects in period 1	Valganciclovir	Ganciclovir
Started	7	6
Completed	5	3
Not completed	2	3
Adverse event, serious fatal	2	-
Screening failure	-	1
Death occurred more than 180 days post SCT; no SAE	-	1
was discharged home, living too far from hospital	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Valganciclovir
Reporting group description: -	
Reporting group title	Ganciclovir
Reporting group description: -	

Reporting group values	Valganciclovir	Ganciclovir	Total
Number of subjects	7	6	13
Age categorical Units: Subjects			
Adults (18-64 years)	6	6	12
From 65-84 years	1	0	1
Gender categorical Units: Subjects			
Female	1	5	6
Male	6	1	7

Subject analysis sets	
Subject analysis set title	Main analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

Due to the very small sample size of only 13 randomized patients and the premature study termination, statistical analyses were reduced to descriptive analyses for primary and secondary criteria based on the safety set. Summary statistics are provided but no confirmatory analyses were performed. Therefore, the hierarchical test procedure and calculation of confidence intervals for the primary efficacy and safety variable were not carried out. A log-rank test in the frame of the survival analysis for the primary efficacy variable was not performed. Confidence intervals for any type of proportions are not provided. No comparisons of treatment groups with the help of Wilcoxon rank-sum test or Fisher's exact test were done for secondary variables. Nevertheless, a complete safety analysis was carried out including a detailed analysis of AEs.

Reporting group values	Main analysis		
Number of subjects	13		
Age categorical Units: Subjects			
Adults (18-64 years)	12		
From 65-84 years	1		
Gender categorical Units: Subjects			
Female	6		
Male	7		

End points

End points reporting groups

Reporting group title	Valganciclovir
Reporting group description: -	
Reporting group title	Ganciclovir
Reporting group description: -	
Subject analysis set title	Main analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

Due to the very small sample size of only 13 randomized patients and the premature study termination, statistical analyses were reduced to descriptive analyses for primary and secondary criteria based on the safety set. Summary statistics are provided but no confirmatory analyses were performed. Therefore, the hierarchical test procedure and calculation of confidence intervals for the primary efficacy and safety variable were not carried out. A log-rank test in the frame of the survival analysis for the primary efficacy variable was not performed. Confidence intervals for any type of proportions are not provided. No comparisons of treatment groups with the help of Wilcoxon rank-sum test or Fisher's exact test were done for secondary variables. Nevertheless, a complete safety analysis was carried out including a detailed analysis of AEs.

Primary: The event-free survival (patients without CMV disease or death from any cause) within 180 days after SCT.

End point title	The event-free survival (patients without CMV disease or death from any cause) within 180 days after SCT.[1]

End point description:

Due to the very small sample size of only 13 randomized patients and the premature study termination, statistical analyses were reduced to descriptive analyses for primary and secondary criteria based on the safety set. Summary statistics are provided but no confirmatory analyses were performed. Therefore, the hierarchical test procedure and calculation of confidence intervals for the primary efficacy and safety variable were not carried out. A log-rank test in the frame of the survival analysis for the primary efficacy variable was not performed. Confidence intervals for any type of proportions are not provided. No comparisons of treatment groups with the help of Wilcoxon rank-sum test or Fisher's exact test were done for secondary variables. Nevertheless, a complete safety analysis was carried out including a detailed analysis of AEs.

End point type	Primary

End point timeframe:

within 180 days after SCT

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the very small sample size of only 13 randomized patients and the premature study termination, statistical analyses were reduced to descriptive analyses for primary and secondary criteria based on the safety set. Summary statistics are provided but no confirmatory analyses were performed.

End point values	Valganciclovir	Ganciclovir	Main analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	7	6	13	
Units: number	7	6	13	

Statistical analyses

No statistical analyses for this end point

Primary: The proportion of patients with severe neutropenia (absolute neutrophil count (ANC) <500 cells/µL) until 7 days after discontinuation of antiviral therapy with the Study Drug.

End point title	The proportion of patients with severe neutropenia (absolute neutrophil count (ANC) <500 cells/µL) until 7 days after discontinuation of antiviral therapy with the Study Drug.[2]

End point description:

Due to the very small sample size of only 13 randomized patients and the premature study termination, statistical analyses were reduced to descriptive analyses for primary and secondary criteria based on the safety set. Summary statistics are provided but no confirmatory analyses were performed. Therefore, the hierarchical test procedure and calculation of confidence intervals for the primary efficacy and safety variable were not carried out. A log-rank test in the frame of the survival analysis for the primary efficacy variable was not performed. Confidence intervals for any type of proportions are not provided. No comparisons of treatment groups with the help of Wilcoxon rank-sum test or Fisher's exact test were done for secondary variables. Nevertheless, a complete safety analysis was carried out including a detailed analysis of AEs.

End point type	Primary

End point timeframe:

until 7 days after discontinuation of antiviral therapy with the Study Drug

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the very small sample size of only 13 randomized patients and the premature study termination, statistical analyses were reduced to descriptive analyses for primary and secondary criteria based on the safety set. Summary statistics are provided but no confirmatory analyses were performed.

End point values	Valganciclovir	Ganciclovir	Main analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	7	6	13	
Units: number of subjects analysed	7	6	13	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs), serious and non-serious, encountered during treatment and up to day 180 post SCT, had to reported in the AE section of the eCRF.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Valganciclovir
Reporting group description: -	
Reporting group title	Ganciclovir

Reporting group description: -

Serious adverse events	Valganciclovir	Ganciclovir	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 7 (57.14%)	1 / 6 (16.67%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Arterial injury			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access complication			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multi-organ failure			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Adenovirus infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Valganciclovir	Ganciclovir	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	4 / 6 (66.67%)	
Vascular disorders			
Essential hypertension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Flushing			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Multi-organ failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Oedema			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral			
subjects affected / exposed	2 / 7 (28.57%)	2 / 6 (33.33%)	
occurrences (all)	2	2	
Pyrexia			

subjects affected / exposed	3 / 7 (42.86%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Arterial injury			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Vascular access complication			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Nonketotic hyperglycinaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Tachycardia			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Thrombocytopenia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Thrombocytosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Hearing impaired			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Eyelid oedema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Panophthalmitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Abdominal pain upper			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	

Diarrhoea			
subjects affected / exposed	2 / 7 (28.57%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Dyspepsia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Lichenification			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Petechiae			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	
Renal and urinary disorders			

Renal failure acute			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Rheumatoid arthritis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Infections and infestations			
Adenovirus infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Candidiasis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Cytomegalovirus infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Enterococcal infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Fungal infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Herpes simplex			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Lung infection			

subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pulmonary sepsis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Rhinovirus infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Calcium deficiency			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hyperuricaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

The sponsor terminated the study prematurely on 16-DEC-2011. The main factor for this decision was the slow patient recruitment with less than 2 patients per month resulting in a considerable timely delay of the study conduct.

Notes: