



## Clinical trial results:

### Pharmacokinetics and safety of valganciclovir in pediatric heart transplant recipients < 4 months of age.

#### Summary

EudraCT number	2010-021172-28
Trial protocol	ES
Global end of trial date	30 September 2013

#### Results information

Result version number	v1 (current)
This version publication date	11 July 2016
First version publication date	06 August 2015

#### Trial information

##### Trial identification

Sponsor protocol code	NP22523
-----------------------	---------

##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01165580
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, CH-4070, Basel, Basel, Switzerland,
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 061 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 061 6878333, global.trial_information@roche.com

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000072-PIP01-09
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?	Yes

Notes:

---

**Results analysis stage**

---

Analysis stage	Final
Date of interim/final analysis	30 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2013
Global end of trial reached?	Yes
Global end of trial date	30 September 2013
Was the trial ended prematurely?	No

Notes:

---

**General information about the trial**

---

Main objective of the trial:

The primary objective of the study was to characterize the pharmacokinetics of ganciclovir (GCV) following oral administration of valganciclovir (VGCV) in pediatric heart transplant recipients less than (<) 4 months of age.

Protection of trial subjects:

The investigator ensured that this study was conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 May 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: 2
Country: Number of subjects enrolled	United States: 15
Worldwide total number of subjects	17
EEA total number of subjects	2

Notes:

---

**Subjects enrolled per age group**

---

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	1
Infants and toddlers (28 days-23 months)	16
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: -

### Pre-assignment

Screening details:

Participants who were heart transplant recipients, aged < 4 months (<125 days), considered hemodynamically stable, at risk of cytomegalovirus (CMV) disease and are being treated with intravenous GCV or VGCV oral solution for the prevention of CMV disease.

### Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	VGCV: All treated participants
-----------	--------------------------------

Arm description:

Participants aged < 4 months received 2 doses (one dose per day on 2 consecutive days) of VGCV orally according to the following dosing algorithm: Dose of VGCV is equal to 7 times the multiplied value of the subject's body surface area (BSA) and creatinine clearance estimated by modified Schwartz formula (CrCLS) in milligrams (mg). If the calculated dose was greater than (>) 900 mg then dose given was 900 mg.

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

Dosage and administration details:

Participants received 2 doses of VGCV orally (one dose per day) according to the following dosing algorithm. Dose of VGCV is equal to 7 times the multiplied value of the subject's BSA and CrCLS. If the calculated dose was >900 mg then dose given was 900 mg.

<b>Number of subjects in period 1</b>	VGCV: All treated participants
Started	17
Completed	16
Not completed	1
Physician decision	1

## Baseline characteristics

### Reporting groups

Reporting group title	Overall study
-----------------------	---------------

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	17	17	
Age categorical Units: Subjects			
Age continuous Units: days arithmetic mean standard deviation	85.06 ± 33.39	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	10	10	

## End points

### End points reporting groups

Reporting group title	VGCV: All treated participants
Reporting group description: Participants aged < 4 months received 2 doses (one dose per day on 2 consecutive days) of VGCV orally according to the following dosing algorithm: Dose of VGCV is equal to 7 times the multiplied value of the subject's body surface area (BSA) and creatinine clearance estimated by modified Schwartz formula (CrCLS) in milligrams (mg). If the calculated dose was greater than (>) 900 mg then dose given was 900 mg.	

### Primary: Area Under the Concentration-Time Curve Over the Dosing Interval (AUC 0-24 hours) for GCV

End point title	Area Under the Concentration-Time Curve Over the Dosing Interval (AUC 0-24 hours) for GCV <sup>[1]</sup>
-----------------	--

End point description:

An integrated population pharmacokinetics (PopPK) model was used to characterize the pharmacokinetics (PK) of GCV which combined the results of this study in pediatric heart transplant participants along with other 3 studies (WP16296, WP16303 and WV16726). The PopPK model is a 2-compartment PK model with first order formation following administration of VGCV with a lag time.

End point type	Primary
----------------	---------

End point timeframe:

On study Days 2 and 3: pre-dose, 1-3 hours, 3-7 hours, 7-12 hours and 24 hours post-dose.

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: No statistical analysis was performed as this was not part of the planned primary endpoint analysis.

End point values	VGCV: All treated participants			
Subject group type	Reporting group			
Number of subjects analysed	14 <sup>[2]</sup>			
Units: microgram(s)*hour/millilitre				
arithmetic mean (standard deviation)	68.1 (± 19.8)			

Notes:

[2] - PopPK analysis was performed in the initial 14 participants, not all treated participants.

### Statistical analyses

No statistical analyses for this end point

### Primary: Apparent Volume of Distribution of GCV

End point title	Apparent Volume of Distribution of GCV <sup>[3]</sup>
-----------------	---

End point description:

PopPK model was used to characterize the PK of GCV which combined the results of this study in pediatric heart transplant participants along with other 3 studies (WP16296, WP16303 and WV16726). The PopPK model is a 2-compartment PK model with first order formation following administration of VGCV with a lag time.

End point type	Primary
----------------	---------

End point timeframe:

On study days 2 and 3: pre-dose, 1-3 hours, 3-7 hours, 7-12 hours and 24 hours post-dose.

Notes:

[3] - 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: No statistical analysis was performed as this was not part of the planned primary endpoint analysis.

<b>End point values</b>	VGCV: All treated participants			
Subject group type	Reporting group			
Number of subjects analysed	14 <sup>[4]</sup>			
Units: litre(s)				
arithmetic mean (standard deviation)				
Central volume	2.13 (± 0.396)			
Peripheral volume	2.09 (± 0.456)			

Notes:

[4] - PopPK analysis was performed in the initial 14 participants, not all treated participants.

## Statistical analyses

No statistical analyses for this end point

## Primary: Terminal Half-life of GCV

End point title	Terminal Half-life of GCV <sup>[5]</sup>
-----------------	--

End point description:

PopPK model was used to characterize the PK of GCV which combined the results of this study in pediatric heart transplant participants along with other 3 studies (WP16296, WP16303 and WV16726). The PopPK model is a 2-compartment PK model with first order formation following administration of VGCV with a lag time.

End point type	Primary
----------------	---------

End point timeframe:

On study days 2 and 3: pre-dose, 1-3 hours, 3-7 hours, 7-12 hours and 24 hours post-dose.

Notes:

[5] - 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: No statistical analysis was performed as this was not part of the planned primary endpoint analysis.

<b>End point values</b>	VGCV: All treated participants			
Subject group type	Reporting group			
Number of subjects analysed	14 <sup>[6]</sup>			
Units: hour(s)				
arithmetic mean (standard deviation)	1.97 (± 0.185)			

Notes:

[6] - PopPK analysis was performed in the initial 14 participants, not all treated participants.

## Statistical analyses

No statistical analyses for this end point

---

**Primary: Maximum Observed Concentration (Cmax) of GCV**

---

End point title	Maximum Observed Concentration (Cmax) of GCV <sup>[7]</sup>
-----------------	---

End point description:

PopPK model was used to characterize the PK of GCV which combined the results of this study in pediatric heart transplant participants along with other 3 studies (WP16296, WP16303 and WV16726). The PopPK model is a 2-compartment PK model with first order formation following administration of VGCV with a lag time.

End point type	Primary
----------------	---------

End point timeframe:

On study days 2 and 3: pre-dose, 1-3 hours, 3-7 hours, 7-12 hours and 24 hours post-dose.

---

Notes:

[7] - 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: No statistical analysis was performed as this was not part of the planned primary endpoint analysis.

<b>End point values</b>	VGCV: All treated participants			
Subject group type	Reporting group			
Number of subjects analysed	14 <sup>[8]</sup>			
Units: microgram(s)/millilitre				
arithmetic mean (standard deviation)	10.5 (± 3.35)			

Notes:

[8] - PopPK analysis was performed in the initial 14 participants, not all treated participants.

---

**Statistical analyses**

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs were assessed throughout the study period up to 7 (+/-2) days, post 2nd VGCV dose.

Assessment type	Non-systematic
-----------------	----------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	16.1
--------------------	------

### Reporting groups

Reporting group title	VGCV: All treated participants
-----------------------	--------------------------------

Reporting group description:

Participants aged < 4 months received 2 doses (one dose per day on 2 consecutive days) of VGCV POS according to dosing using the dosing algorithm: Dose of VGCV = 7 \* BSA \* CrCLS. If the calculated dose was >900 mg then dose given was 900 mg.

Serious adverse events	VGCV: All treated participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 17 (11.76%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Infections and infestations			
Postoperative wound infection			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 17 (5.88%)		
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	VGCV: All treated participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 17 (47.06%)		
Cardiac disorders			



Ventricular tachycardia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	4 / 17 (23.53%) 4		
Thrombocytosis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Diarrhoea subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Flatulence subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Haematochezia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Respiratory, thoracic and mediastinal disorders Tachypnoea subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Infections and infestations Respiratory tract infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Tracheitis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Urinary tract infection			

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Metabolic acidosis			
subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2010	This protocol amendment documented that two doses would be received, added a 24-hour PK sample collection, specified a 5-part differential cell count, added an upper limit to the CrCL, updated and specified route of administration, updated the adverse event intensity to a 3-point scale, updated serious adverse event reporting requirements, and added an interim analysis to be performed after four participants have been enrolled in the birth to < 6 weeks age group to assess the effectiveness of the dosing algorithm in this age group.
30 March 2012	This protocol amendment documented that dosing would not be automatically calculated on the electronic case report form (eCRF), added a window for the post-dosing assessment timeframe, specified when to start collecting previous/concurrent diseases and treatments in the screening assessments, clarified the supplies that would be provided for the administration of the Investigational Medicinal Product (IMP), and modified the inclusion criteria to state participants had to be < 125 days at the time of the last PK assessment and participants with any form of tube feeding can be included.
28 December 2012	This protocol amendment provided clarification regarding enrollment of 16 participants in the study but recruitment has not been met in the age group birth to < 6 weeks changed the participant numbers to permit a minimum of 16 and a maximum of 24 participants to be enrolled into the study. A maximum recruitment number (24 participants) was provided, allowing for a minimum of four, and maximum of eight participants in the birth to < 6 weeks of age group. The total number of participants to be enrolled in this younger group is dependent on results from ongoing PK data analysis, and whether the data are consistent (within agreed variability boundaries) with those observed in participants at least 4 months of age. The planned recruitment period has been extended to approximately 3 years to allow sufficient time to recruit the required number of participants within the birth to < 6 weeks of age group to facilitate dosing recommendations in this age group.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported