Clinical trial results:
A multicenter, open-label, single-arm study to evaluate the single-dose pharmacokinetics, acceptability and safety of famciclovir oral pediatric formulation in infants 1 month to <1 year of age with herpes simplex virus infection

Summary

EudraCT number	2006-005010-12
Trial protocol	DE
Global end of trial date	17 November 2008

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	CFAM810B2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00448227
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office , Novartis Pharma AG, +41 613241111,
Scientific contact	Clinical Disclosure Office , Novartis Pharma AG, +41 613241111,

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 November 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 November 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the pharmacokinetics (PK) of a single dose of famciclovir in subjects aged 1 month to less than (<)1 year who were infected or at risk of infection by herpes simplex virus.

Protection of trial subjects:

No rescue medication was allowed in the study. Follow-up medical care was provided to all subjects who were prematurely withdrew from the study, or refereed for appropriate ongoing care by the investigator.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 October 2007
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	Guatemala: 3
Country: Number of subjects enrolled	United States: 11
Country: Number of subjects enrolled	Germany: 4
Worldwide total number of subjects	18
EEA total number of subjects	4

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)	18
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:

The study was conducted at 10 centres in 3 countries.

Pre-assignment

Screening details:

A total of 18 subjects were enrolled into the study.

Period 1

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

Blinding implementation details:

The study was open label, hence no blinding was performed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: 1 month to <3 months

Arm description:

Subjects aged 1 month to less than <3 months received a single, individualised dose of famciclovir between 25-50 mg based on body weight.

Arm type	Experimental
Investigational medicinal product name	Famciclovir
Investigational medicinal product code	FAM810
Other name	
Pharmaceutical forms	Chewable capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Weight stratified single dose of famciclovir (25-50 mg) was administered.

The content of sprinkle capsules was mixed with Ora-Sweet® just prior to dosing

Arm title	Group 2: 3 month to <6 months

Arm description:

Subjects aged 3 month to <6 months received a single, individualised dose of famciclovir between 50-100 mg based on body weight.

Arm type	Experimental
Investigational medicinal product name	Famciclovir
Investigational medicinal product code	FAM810
Other name	
Pharmaceutical forms	Chewable capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Weight stratified single dose of famciclovir (50-100 mg) was administered.

The content of sprinkle capsules was mixed with Ora-Sweet® just prior to dosing

Arm title	Group 3: 6 month to 12 months

Arm description:

Subjects aged 6 month to 12 months received a single, individualised dose of famciclovir between 75-175 mg based on body weight.

Arm type	Experimental
Investigational medicinal product name	Famciclovir
Investigational medicinal product code	FAM810
Other name	
Pharmaceutical forms	Chewable capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Weight stratified single dose of famciclovir (75-175 mg) was administered.

The content of sprinkle capsules was mixed with Ora-Sweet® just prior to dosing

Number of subjects in period 1	Group 1: 1 month to <3 months	Group 2: 3 month to <6 months	Group 3: 6 month to 12 months
Started	8	5	5
Completed	8	5	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall period

Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	18	18	
Age categorical Units: Subjects			
1 to <3 months	8	8	
3 to <6 months	5	5	
6 to 12 months	5	5	
Age continuous Units: months			
arithmetic mean	4		
standard deviation	± 3.6	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	11	11	

End points

End points reporting groups

Reporting group title	Group 1: 1 month to <3 months
Reporting group description:	
Subjects aged 1 month to less than <3 months received a single, individualised dose of famciclovir between 25-50 mg based on body weight.	
Reporting group title	Group 2: 3 month to <6 months
Reporting group description:	
Subjects aged 3 month to <6 months received a single, individualised dose of famciclovir between 50-100 mg based on body weight.	
Reporting group title	Group 3: 6 month to 12 months
Reporting group description:	
Subjects aged 6 month to 12 months received a single, individualised dose of famciclovir between 75-175 mg based on body weight.	

Primary: Time to maximum plasma concentration (Tmax) of penciclovir, the active metabolite of the prodrug famciclovir

End point title	Time to maximum plasma concentration (Tmax) of penciclovir, the active metabolite of the prodrug famciclovir[1]
End point description:	
Tmax was defined as the time taken to reach the maximum plasma concentration of penciclovir. The analysis was performed in the pharmacokinetic (PK) population defined as all subjects with evaluable penciclovir concentration data. Here, "Number of subjects analysed" signifies those subjects evaluable for time to maximum plasma concentration for each arm, respectively.	
End point type	Primary
End point timeframe:	
30 minutes, 1 hour, 4 hour and 6 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: Only descriptive summary statistics was planned for this outcome measure	

End point values	Group 1: 1 month to <3 months	Group 2: 3 month to <6 months	Group 3: 6 month to 12 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	2	3	
Units: Hour(s)				
median (full range (min-max))	1 (1 to 5.17)	4 (1 to 4.17)	1.02 (0.58 to 1.1)	

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Plasma Concentration (Cmax) of penciclovir

End point title	Maximum Plasma Concentration (Cmax) of penciclovir[2]

End point description:

Cmax was defined as the maximum plasma concentration of penciclovir, the active metabolite of the prodrug famciclovir. The analysis was performed in the pharmacokinetic (PK) population defined as all subjects with evaluable penciclovir concentration data. Here, "Number of subjects analysed" signifies those subjects evaluable for maximum plasma concentration for each arm, respectively.

End point type	Primary

End point timeframe:

30 minutes, 1 hour, 4 hour and 6 hours (Post-dose)

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: Only descriptive summary statistics was planned for this outcome measure

End point values	Group 1: 1 month to <3 months	Group 2: 3 month to <6 months	Group 3: 6 month to 12 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	5	5	
Units: Microgram(s)/millilitre				
arithmetic mean (standard deviation)	0.69 (± 0.41)	0.74 (± 0.17)	3.24 (± 1.01)	

Statistical analyses

No statistical analyses for this end point

Primary: Area under the concentration -time curve (AUC 0--tlast) of penciclovir

End point title	Area under the concentration -time curve (AUC 0--tlast) of penciclovir[3]

End point description:

The area under the concentration -time curve from time from zero to the last quantifiable concentration-time point (AUC 0--tlast) was used to measure the total drug exposure over time. The analysis was performed in the PK population. Here, "Number of subjects analysed" signifies those subjects evaluable for AUC (0-tlast) for each arm, respectively.

End point type	Primary

End point timeframe:

30 minutes, 1 hour, 4 hour and 6 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: Only descriptive summary statistics was planned for this outcome measure

End point values	Group 1: 1 month to <3 months	Group 2: 3 month to <6 months	Group 3: 6 month to 12 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	5	5	
Units: Hour*microgram/millilitre				
arithmetic mean (standard deviation)	2.09 (± 1.38)	3.16 (± 0.68)	8.68 (± 2.09)	

Statistical analyses

No statistical analyses for this end point

Primary: Area under the concentration -time curve from time zero to 6 hours (AUC 0-6h) of penciclovir

End point title	Area under the concentration -time curve from time zero to 6 hours (AUC 0-6h) of penciclovir[4]

End point description:

The area under the concentration- time curve from time zero to 6 hours (AUC 0-6h) was used to measure the total drug exposure over 6 hours after dose administration. The analysis was performed in the PK population. Here, "Number of subjects analysed" signifies those subjects evaluable for AUC (0-6h) for each arm, respectively.

End point type	Primary

End point timeframe:

30 minutes, 1 hour, 4 hour and 6 hours (Post-dose)

Notes:

[4] - 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: Only descriptive summary statistics was planned for this outcome measure

End point values	Group 1: 1 month to <3 months	Group 2: 3 month to <6 months	Group 3: 6 month to 12 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	5	5	
Units: Hour*milligram/millilitre				
arithmetic mean (standard deviation)	2.22 (± 1.23)	3.16 (± 0.68)	8.77 (± 2.14)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects experiencing tolerability reactions of famciclovir

End point title	Percentage of subjects experiencing tolerability reactions of famciclovir

End point description:

Subjects after dosing with famciclovir were assessed by study personnel using a 4-point scale for tolerability reactions of famciclovir as:
1. Subject with significant emesis
2. Subject spit out most of the dose ingesting less than half of what was administered
3. Subject spit out some of the dose, but ingested at least 50% of what was administered
4. Subject was able to ingest and retain the dose administered.
The analysis was performed in the safety (SAF) population defined as all subjects who received any dose (including partial dose) of study drug and had at least one post-baseline safety, tolerability or acceptability assessment.

End point type	Secondary

End point timeframe:

30 minutes (Post-dose)

End point values	Group 1: 1 month to <3 months	Group 2: 3 month to <6 months	Group 3: 6 month to 12 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	5	
Units: Percentage of subjects				
number (not applicable)				
Significant emesis occurred	12.5	0	0	
Spit out most of the dose, ingested less than half	0	0	0	
Spit out some of the dose, ingested at least 50 %	0	0	0	
Able to ingest and retain dose	87.5	100	100	

Statistical analyses

No statistical analyses for this end point

Secondary: Subjective assessment of acceptability of famciclovir by the caregivers

End point title	Subjective assessment of acceptability of famciclovir by the caregivers

End point description:

Subjects were assessed by caregiver using a 5-point scale for acceptability of famciclovir as:
1. Very badly accepted/unacceptable: subject showed great displeasure, compromising use of formulation,
2. Badly but accepted: subject showed displeasure with dosing but could be coaxed to take complete dose,
3. Neither good nor bad: subject showed no apparent displeasure and with little effort was coaxed to take complete dose,
4. Well accepted: subject appeared to enjoy the formulation and with little coaxing ingested most of dose, and
5. Very well accepted: subject appeared eager and ingested most of dose without special coaxing.
The analysis was performed in the SAF population.

End point type	Secondary

End point timeframe:

Immediately after dose administration

End point values	Group 1: 1 month to <3 months	Group 2: 3 month to <6 months	Group 3: 6 month to 12 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	5	
Units: Number of subjects				
Very badly / unacceptable	1	0	0	
Badly but accepted	0	0	1	
Neither good nor bad	0	2	1	
Well accepted	2	0	2	
Very well accepted	4	3	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Subjective assessment of acceptability of famciclovir by the study personnel

End point title	Subjective assessment of acceptability of famciclovir by the study personnel

End point description:

Subjects were assessed by study personnel using a 5-point scale for acceptability of famciclovir as:
1. Very badly accepted/unacceptable: subject showed great displeasure, compromising use of formulation,
2. Badly but accepted: subject showed displeasure with dosing but could be coaxed to take complete dose,
3. Neither good nor bad: subject showed no apparent displeasure and with little effort was coaxed to take complete dose,
4. Well accepted: subject appeared to enjoy the formulation and with little coaxing ingested most of dose, and
5. Very well accepted: subject appeared eager and ingested most of dose without special coaxing.
The analysis was performed in the SAF population.

End point type	Secondary

End point timeframe:

Immediately after dose administration

End point values	Group 1: 1 month to <3 months	Group 2: 3 month to <6 months	Group 3: 6 month to 12 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	5	
Units: Number of subjects				
Very badly / unacceptable	1	0	0	
Badly but accepted	0	0	1	
Neither good nor bad	0	2	2	
Well accepted	2	0	1	
Very well accepted	4	3	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with adverse events (AEs) and serious adverse events (SAEs)

End point title	Number of subjects with adverse events (AEs) and serious adverse events (SAEs)

End point description:

Adverse events (AEs) are defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during study, having been absent at baseline, or, if present at baseline, appears to worsen. Serious adverse events (SAEs) are any untoward medical occurrences that result in death, are life threatening, require (or prolong) hospitalization, cause persistent or significant disability/incapacity, result in congenital anomalies or birth defects, or are other conditions which in judgment of investigators represent significant hazards. The analysis was performed in the SAF population.

End point type	Secondary

End point timeframe:

Day 1 up to Day 38

End point values	Group 1: 1 month to <3 months	Group 2: 3 month to <6 months	Group 3: 6 month to 12 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	5	
Units: Number of subjects				
AEs	3	3	2	
SAEs	0	1	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	3 to <6 months
Reporting group description:	
3 to <6 months	
Reporting group title	1 to <3 months
Reporting group description:	
1 to <3 months	
Reporting group title	6 to 12 months
Reporting group description:	
6 to 12 months	

Serious adverse events	3 to <6 months	1 to <3 months	6 to 12 months
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	3 to <6 months	1 to <3 months	6 to 12 months
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)	3 / 8 (37.50%)	2 / 5 (40.00%)
Investigations			
Occult blood positive			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Encephalitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 5 (20.00%)	1 / 8 (12.50%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
Diarrhoea			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Infections and infestations Oral candidiasis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 8 (12.50%) 1	0 / 5 (0.00%) 0
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 8 (0.00%) 0	0 / 5 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 June 2007	Subjects with varicella zoster virus (VZV) infections were removed from the inclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/20160046