



## Clinical trial results:

### A Multicenter, Open-label, Single-arm Study to Evaluate the Safety and Pharmacokinetics of Famciclovir Single 1500 mg Dose in Adolescents With Recurrent Herpes Labialis

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

## Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-004443-40 |
| Trial protocol           | Outside EU/EEA |
| Global end of trial date | 02 June 2010   |

## Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 26 October 2018 |
| First version publication date | 26 October 2018 |

## Trial information

### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CFAM810B2305 |
|-----------------------|--------------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00878072 |
| 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)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-000019-PIP02-07 |
| 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                       | 02 June 2010 |
| Is this the analysis of the primary completion data? | No           |

|                                  |              |
|----------------------------------|--------------|
| Global end of trial reached?     | Yes          |
| Global end of trial date         | 02 June 2010 |
| Was the trial ended prematurely? | No           |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the trial was to assess the safety and tolerability of a single 1500 milligrams (mg) dose of famciclovir in adolescents with recurrent herpes labialis.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 25 March 2009 |
| 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 | United States: 53 |
| Worldwide total number of subjects   | 53                |
| EEA total number of subjects         | 0                 |

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)                 | 53 |

|                      |   |
|----------------------|---|
| 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 ten centers in the United States

### Pre-assignment

Screening details:

A total of 53 subjects were enrolled and 51 completed the study

### Period 1

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

Blinding implementation details:

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

### Arms

|           |             |
|-----------|-------------|
| Arm title | Famciclovir |
|-----------|-------------|

Arm description:

Subjects with recurrent herpes labialis, weighing at least 40 killogram (kg), were orally administered with a single dose of famciclovir 1500 mg (3\*500 mg tablets) for one day with a follow up of 7 days .

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Famciclovir  |
| Investigational medicinal product code | FAM810       |
| Other name                             | Famvir       |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Subjects were orally administered with famciclovir 1500 mg (3\*500 mg tablets) for one day.

| Number of subjects in period 1 | Famciclovir |
|--------------------------------|-------------|
| Started                        | 53          |
| Completed                      | 51          |
| Not completed                  | 2           |
| Consent withdrawn by subject   | 2           |

## Baseline characteristics

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Famciclovir |
|-----------------------|-------------|

Reporting group description:

Subjects with recurrent herpes labialis, weighing at least 40 killogram (kg), were orally administered with a single dose of famciclovir 1500 mg (3\*500 mg tablets) for one day with a follow up of 7 days .

| Reporting group values    | Famciclovir | Total |  |
|---------------------------|-------------|-------|--|
| Number of subjects        | 53          | 53    |  |
| Age categorical           |             |       |  |
| Units: Subjects           |             |       |  |
| Adolescents (12-17 years) | 53          | 53    |  |
| Age continuous            |             |       |  |
| Units: years              |             |       |  |
| arithmetic mean           | 14.4        |       |  |
| standard deviation        | ± 1.86      | -     |  |
| Gender categorical        |             |       |  |
| Units: Subjects           |             |       |  |
| Female                    | 33          | 33    |  |
| Male                      | 20          | 20    |  |

## End points

### End points reporting groups

|  |   |
|--|---|
| Reporting group title  | Famciclovir   |
| Reporting group description:<br>Subjects with recurrent herpes labialis, weighing at least 40 killogram (kg), were orally administered with a single dose of famciclovir 1500 mg (3*500 mg tablets) for one day with a follow up of 7 days .   |   |
| Subject analysis set title   | Subjects aged: 12 to <15 years: Famciclovir 1500 mg |
| Subject analysis set type  | Sub-group analysis                                  |
| Subject analysis set description:<br>All subjects aged between 12 to <15 years were orally administered with a single dose of famciclovir 1500 mg (3*500 mg tablets).  |   |
| Subject analysis set title   | Subjects aged: 15 to <18 years: Famciclovir 1500 mg |
| Subject analysis set type  | Sub-group analysis                                  |
| Subject analysis set description:<br>All subjects aged between 15 to <18 years were orally administered with a single dose of famciclovir 1500 mg (3*500 mg tablets)   |   |
| Subject analysis set title   | Subjects aged: 12 to <18 years: Penciclovir         |
| Subject analysis set type  | Sub-group analysis                                  |
| Subject analysis set description:<br>All subjects aged 12 to <18 years were orally administered with a single dose of famciclovir 1500 mg (3*500 mg tablets). Pharmacokinetic (PK) analysis included penciclovir and 6-deoxypenciclovir (first, intermediate metabolite from famciclovir which is converted further to the active metabolite penciclovir). |   |
| Subject analysis set title   | Subjects aged: 12 to <18 years: 6-deoxy penciclovir |
| Subject analysis set type  | Sub-group analysis                                  |
| Subject analysis set description:<br>All subjects aged 12 to <18 years were orally administered with a single dose of famciclovir 1500 mg (3*500 mg tablets).Pharmacokinetic (PK) analysis included penciclovir and 6-deoxypenciclovir (first, intermediate metabolite from famciclovir which is converted further to the active metabolite penciclovir).  |   |

### Primary: Number of subjects with Adverse Events (AEs), Serious Adverse Events (SAEs), AE leading to discontinuation and who died

|   |  |
|---|--|
| End point title   | Number of subjects with Adverse Events (AEs), Serious Adverse Events (SAEs), AE leading to discontinuation and who died <sup>[1]</sup> |
| End point description:<br>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 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 on safety set population defined as all patients who received study drug and had at least one post-baseline safety assessment. |  |
| End point type  | Primary  |
| End point timeframe:<br>From Day 1 to Day 30-36   |  |

#### 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 Summary data were produced. No statistical analysis were performed on counts.

| End point values                                | Subjects aged:<br>12 to <15<br>years:<br>Famciclovir<br>1500 mg | Subjects aged:<br>15 to <18<br>years:<br>Famciclovir<br>1500 mg |  |  |
|---|---|---|--|--|
| Subject group type                              | Subject analysis set  | Subject analysis set  |  |  |
| Number of subjects analysed                     | 28  | 25  |  |  |
| Units: Subjects                                 |   |   |  |  |
| AEs   | 2   | 2   |  |  |
| Deaths  | 0   | 0   |  |  |
| SAEs  | 0   | 0   |  |  |
| AEs leading to study drug<br>discontinuation    | 0   | 0   |  |  |
| AEs requiring significant additional<br>therapy | 2   | 2   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects with clinically significant laboratory abnormalities

|                 |  |
|-----------------|--|
| End point title | Number of subjects with clinically significant laboratory abnormalities <sup>[2]</sup> |
|-----------------|--|

End point description:

Subjects with laboratory values outside the defined normal range were graded as clinically significant laboratory abnormalities. Laboratory values were assessed according to the National Cancer Institute-Common terminology criteria for Adverse Events (NCI-CTCAE). Hematology and clinical chemistry were performed. The analysis was performed on the safety set.

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

End point timeframe:

At Day 1 (pre-dose) and Day 4

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 Summary data were produced. No statistical analysis were performed on counts.

| End point values            | Subjects aged:<br>12 to <15<br>years:<br>Famciclovir<br>1500 mg | Subjects aged:<br>15 to <18<br>years:<br>Famciclovir<br>1500 mg |  |  |
|-----------------------------|---|---|--|--|
| Subject group type          | Subject analysis set  | Subject analysis set  |  |  |
| Number of subjects analysed | 28  | 25  |  |  |
| Units: Subjects             |   |   |  |  |
| Hematology                  | 0   | 0   |  |  |
| Clinical chemistry          | 0   | 0   |  |  |
| Urinalysis                  | 0   | 0   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time of maximum observed plasma concentration (Tmax) of famciclovir

|                 |   |
|-----------------|---|
| End point title | Time of maximum observed plasma concentration (Tmax) of famciclovir |
|-----------------|---|

End point description:

Tmax was defined as the time to reach maximum plasma concentration. Penciclovir (active metabolite from famciclovir) and 6-deoxypenciclovir (first intermediate metabolite from famciclovir) were determined by using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method. The limit of quantification was 0.15 microgram (µg)/milliliter (mL) for both compounds. Calculations were done in WinNonlin 5.0.1, using non-compartmental methods. The analysis was performed in PK analysis set (PAS) population, defined as all patients who participated in the PK assessment part and who did not miss more than one PK blood sampling.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6 and 10 hours after famciclovir dosing

| End point values              | Subjects aged:<br>12 to <18<br>years:<br>Penciclovir | Subjects aged:<br>12 to <18<br>years: 6-deoxy<br>penciclovir |  |  |
|-------------------------------|--|--|--|--|
| Subject group type            | Subject analysis set                                 | Subject analysis set   |  |  |
| Number of subjects analysed   | 8  | 8  |  |  |
| Units: Hours                  |  |  |  |  |
| median (full range (min-max)) | 1 (0.83 to 3)  | 1 (0.5 to 2)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum plasma concentration (Cmax) of famciclovir

|                 |  |
|-----------------|--|
| End point title | Maximum plasma concentration (Cmax) of famciclovir |
|-----------------|--|

End point description:

Cmax was defined as the maximum observed plasma concentration. Penciclovir (active metabolite from famciclovir) and 6-deoxypenciclovir (first intermediate metabolite from famciclovir) were determined by using LC/MS/MS method. The limit of quantification was 0.15 µg/mL for both compounds. Calculations were done in WinNonlin 5.0.1, using non-compartmental methods. The analysis was performed in PAS population.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6 and 10 hours after famciclovir dosing



| End point values                                    | Subjects aged: 12 to <18 years: Penciclovir | Subjects aged: 12 to <18 years: 6-deoxy penciclovir |  |  |
|---|---|---|--|--|
| Subject group type                                  | Subject analysis set                        | Subject analysis set                                |  |  |
| Number of subjects analysed                         | 8   | 8   |  |  |
| Units: Microgram (µg)/milliliter(mL)                |   |   |  |  |
| geometric mean (geometric coefficient of variation) | 9.02 (± 28.6)                               | 2.67 (± 71.2)                                       |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area under the plasma concentration-time curve from time zero up to the last quantifiable concentration (Clast) calculated by the linear trapezoidal rule (AUC 0-tlast) of famciclovir

|                 |  |
|-----------------|--|
| End point title | Area under the plasma concentration-time curve from time zero up to the last quantifiable concentration (Clast) calculated by the linear trapezoidal rule (AUC 0-tlast) of famciclovir |
|-----------------|--|

End point description:

AUC 0-tlast was defined as the area under the plasma concentration-time curve from time zero up to the last quantifiable concentration (Clast) calculated by the linear trapezoidal rule. Penciclovir (active metabolite from famciclovir) and 6-deoxypenciclovir (first intermediate metabolite from famciclovir) were determined by using LC/MS/MS method. The limit of quantification was 0.15 µg/mL for both compounds. Calculations were done in WinNonlin 5.0.1, using non-compartmental methods. The analysis was performed in PAS population.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6 and 10 hours after famciclovir dosing

| End point values                                    | Subjects aged: 12 to <18 years: Penciclovir | Subjects aged: 12 to <18 years: 6-deoxy penciclovir |  |  |
|---|---|---|--|--|
| Subject group type                                  | Subject analysis set                        | Subject analysis set                                |  |  |
| Number of subjects analysed                         | 8   | 8   |  |  |
| Units: (microgram(µg)/milliliter(mL))*hour(h))      |   |   |  |  |
| geometric mean (geometric coefficient of variation) | 30.4 (± 17.9)                               | 4.6 (± 66.1)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area under the plasma concentration-time curve from time 0 to infinity (AUC 0-infinity) of famciclovir

|                 |   |
|-----------------|---|
| End point title | Area under the plasma concentration-time curve from time 0 to |
|-----------------|---|

## End point description:

AUC 0-infinity was defined as the area under the plasma concentration time curve from time zero to infinity = AUC 0-tlast + C last /  $\lambda_z$ , where  $\lambda_z$  is the apparent elimination rate constant estimated by linear regression analysis of the terminal portion of the log-linear plasma concentration-time curve. Penciclovir (active metabolite from famciclovir) and 6-deoxypenciclovir (first intermediate metabolite from famciclovir) were determined by using LC/MS/MS method. The limit of quantification was 0.15 µg/mL for both compounds. Calculations were done in WinNonlin 5.0.1, using non-compartmental methods. The analysis was performed in PAS population.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

At pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6 and 10 hours after famciclovir dosing

| End point values                                    | Subjects aged: 12 to <18 years: Penciclovir | Subjects aged: 12 to <18 years: 6-deoxy penciclovir |  |  |
|---|---|---|--|--|
| Subject group type                                  | Subject analysis set                        | Subject analysis set                                |  |  |
| Number of subjects analysed                         | 8   | 8   |  |  |
| Units: µg/mL*h                                      |   |   |  |  |
| geometric mean (geometric coefficient of variation) | 31.36 (± 17.4)                              | 5.75 (± 58.9)                                       |  |  |

## Statistical analyses

No statistical analyses for this end point

Secondary: Apparent terminal elimination half-life (T<sub>1/2</sub>) of famciclovir

|                 |  |
|-----------------|--|
| End point title | Apparent terminal elimination half-life (T <sub>1/2</sub> ) of famciclovir |
|-----------------|--|

## End point description:

T<sub>1/2</sub> was defined as the apparent terminal elimination half-life =  $\ln 2 / \lambda_z$ . Penciclovir (active metabolite from famciclovir) and 6-deoxypenciclovir (first intermediate metabolite from famciclovir) were determined by using LC/MS/MS method. The limit of quantification was 0.15 µg/mL For both compounds. Calculations were done in WinNonlin 5.0.1, using non-compartmental methods. The analysis was performed in PAS population.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

At pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6 and 10 hours after famciclovir dosing

| End point values              | Subjects aged: 12 to <18 years: Penciclovir | Subjects aged: 12 to <18 years: 6-deoxy penciclovir |  |  |
|-------------------------------|---|---|--|--|
| Subject group type            | Subject analysis set                        | Subject analysis set                                |  |  |
| Number of subjects analysed   | 8   | 8   |  |  |
| Units: Hours                  |   |   |  |  |
| median (full range (min-max)) | 1.75 (1.57 to 2.16)                         | 0.71 (0.62 to 1.19)                                 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Apparent oral clearance of penciclovir from plasma (CL/F) of famciclovir

|                 |  |
|-----------------|--|
| End point title | Apparent oral clearance of penciclovir from plasma (CL/F) of famciclovir |
|-----------------|--|

End point description:

CL/F was defined as the apparent oral clearance of penciclovir from plasma = dose of famciclovir\*0.7884/AUC 0-inf, where 0.7884 is the ratio of the molecular weight of penciclovir (253.3 g/mol) to famciclovir (321.3 g/mol). F is the bioavailability of penciclovir after oral administration of famciclovir. Penciclovir (active metabolite from famciclovir) and 6-deoxypenciclovir (first intermediate metabolite from famciclovir) were determined by using LC/MS/MS method. The limit of quantification was 0.15 µg/mL for both compounds. Calculations were done in WinNonlin 5.0.1, using non-compartmental methods. The analysis was performed in PAS population.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6 and 10 hours after famciclovir dosing

|   |  |  |  |  |
|---|--|--|--|--|
| <b>End point values</b>                             | Subjects aged:<br>12 to <18<br>years:<br>Penciclovir | Subjects aged:<br>12 to <18<br>years: 6-deoxy<br>penciclovir |  |  |
| Subject group type                                  | Subject analysis set                                 | Subject analysis set   |  |  |
| Number of subjects analysed                         | 8  | 8  |  |  |
| Units: Lites(L)/Hour(h)                             |  |  |  |  |
| geometric mean (geometric coefficient of variation) | 37.7 (± 16)  | 99999 (± 99999)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). All other adverse events are monitored from First Subject First Treatment until LSLV

Adverse event reporting additional description:

AE additional description

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 12.1 |
|--------------------|------|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Famciclovir |
|-----------------------|-------------|

Reporting group description:

Subjects with recurrent herpes labialis, weighing at least 40 kg, were orally administered with a single dose of famciclovir 1500 mg (3\*500 mg tablets) for one day with a follow up of 7 days .

| Serious adverse events                            | Famciclovir    |  |  |
|---|----------------|--|--|
| Total subjects affected by serious adverse events |                |  |  |
| subjects affected / exposed                       | 0 / 53 (0.00%) |  |  |
| number of deaths (all causes)                     | 0              |  |  |
| number of deaths resulting from adverse events    | 0              |  |  |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events                            | Famciclovir    |  |  |
|---|----------------|--|--|
| Total subjects affected by non-serious adverse events |                |  |  |
| subjects affected / exposed                           | 4 / 53 (7.55%) |  |  |
| Nervous system disorders                              |                |  |  |
| Dizziness   |                |  |  |
| subjects affected / exposed                           | 3 / 53 (5.66%) |  |  |
| occurrences (all)                                     | 3              |  |  |
| Headache  |                |  |  |
| subjects affected / exposed                           | 2 / 53 (3.77%) |  |  |
| occurrences (all)                                     | 3              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment  |
|----------------|--|
| 26 August 2009 | Incorporated FDA's comments on the protocol including addition of clinic visits, subject diary, urinalysis and stopping rules. A correction was also made to the Principle or Coordinating Investigator of the protocol. |

Notes:

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### 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.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Notes: