



## Clinical trial results:

### A Multicenter, Open-label, Single-arm, Two-step Study to Evaluate the Safety and Single-dose Pharmacokinetics of Famciclovir and Multiple-dose Safety After Administration of Famciclovir Oral Pediatric Formulation to Children 1 to 12 Years of Age With Herpes Simplex Infection

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2015-004441-17   |
| Trial protocol           | Outside EU/EEA   |
| Global end of trial date | 07 December 2007 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 19 December 2016 |
| First version publication date | 19 December 2016 |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CFAM810B2303 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00098059 |
| 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? | No |

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 07 December 2007 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 07 December 2007 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the trial were:

Part A: To evaluate the safety and tolerability, and pharmacokinetics (PK) of a single dose of famciclovir oral pediatric formulation in children from 1 to 12 years of age with herpes simplex virus (HSV) infection, in order to define the dose in this age group which gives a similar exposure to a 500 milligrams (mg) dose in adults,

Part B: To evaluate the safety and tolerability of multiple doses of famciclovir pediatric formulation administered twice-daily for 7 days in subjects from 1 to 12 years of age who had HSV infection.

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                          | 05 February 2005 |
| 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: 63 |
| Country: Number of subjects enrolled | Panama: 11        |
| Worldwide total number of subjects   | 74                |
| 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)  | 17 |
| Children (2-11 years)                     | 53 |
| Adolescents (12-17 years)                 | 4  |

|                      |   |
|----------------------|---|
| 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 USA (6 centers):Part A; USA (8 centers), Panama (2 centers): Part B

### Pre-assignment

Screening details:

A total of 74 subjects (Part A: 27 subjects, Part B: 47 subjects) were enrolled in 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

|                              |                                   |
|------------------------------|-----------------------------------|
| Are arms mutually exclusive? | Yes                               |
| <b>Arm title</b>             | Famciclovir: Single dose (Part A) |

Arm description:

Subjects were orally administered with a single body weight stratified dose of famciclovir of 12.5 mg/kilogram (kg) body weight with a dose escalation up to a maximum dose of 500 mg. Subjects who had weight  $\geq 40$  kg received a famciclovir dose of 500 mg.

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

Dosage and administration details:

Subjects were orally administered with a single-dose closest to 12.5 mg/kg body weight with a maximum dose of 500 mg.

|                  |                                      |
|------------------|--------------------------------------|
| <b>Arm title</b> | Famciclovir: Multiple doses (Part B) |
|------------------|--------------------------------------|

Arm description:

Subjects were orally administered with famciclovir sprinkle capsules alone or with concomitant oral anti-herpes therapy twice daily (b.i.d.) with a dose separation of 12 hours for a period of 7 days. Subjects were administered with a body weight stratified daily dose in 8-step from 150 mg b.i.d. up to a maximum of 500 mg b.i.d. Subjects who had weight  $\geq 40$  kg received a famciclovir dose of 500 mg.

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

Dosage and administration details:

Subjects were orally administered with a body weight stratified dose ranged from 150 mg to 500 mg b.i.d. of famciclovir sprinkle capsules with a dose separation of 12 hours for a period of 7 days.

| <b>Number of subjects in period 1</b> | Famciclovir: Single dose (Part A) | Famciclovir: Multiple doses (Part B) |
|---------------------------------------|-----------------------------------|--------------------------------------|
| Started                               | 27                                | 47                                   |
| Completed                             | 27                                | 46                                   |
| Not completed                         | 0                                 | 1                                    |
| Protocol deviation                    | -                                 | 1                                    |

## Baseline characteristics

### Reporting groups

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | Famciclovir: Single dose (Part A) |
|-----------------------|-----------------------------------|

Reporting group description:

Subjects were orally administered with a single body weight stratified dose of famciclovir of 12.5 mg/kilogram (kg) body weight with a dose escalation up to a maximum dose of 500 mg. Subjects who had weight  $\geq 40$  kg received a famciclovir dose of 500 mg.

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Famciclovir: Multiple doses (Part B) |
|-----------------------|--------------------------------------|

Reporting group description:

Subjects were orally administered with famciclovir sprinkle capsules alone or with concomitant oral anti-herpes therapy twice daily (b.i.d.) with a dose separation of 12 hours for a period of 7 days. Subjects were administered with a body weight stratified daily dose in 8-step from 150 mg b.i.d. up to a maximum of 500 mg b.i.d. Subjects who had weight  $\geq 40$  kg received a famciclovir dose of 500 mg.

| Reporting group values                   | Famciclovir: Single dose (Part A) | Famciclovir: Multiple doses (Part B) | Total |
|--|-----------------------------------|--------------------------------------|-------|
| Number of subjects                       | 27                                | 47                                   | 74    |
| Age categorical<br>Units: Subjects       |                                   |                                      |       |
| Infants and toddlers (28 days-23 months) | 4                                 | 13                                   | 17    |
| Children (2-11 years)                    | 21                                | 32                                   | 53    |
| Adolescents (12-17 years)                | 2                                 | 2                                    | 4     |
| Age continuous<br>Units: years           |                                   |                                      |       |
| arithmetic mean                          | 6                                 | 5                                    |       |
| standard deviation                       | $\pm 4.61$                        | $\pm 3.74$                           | -     |
| Gender categorical<br>Units: Subjects    |                                   |                                      |       |
| Female                                   | 17                                | 24                                   | 41    |
| Male                                     | 10                                | 23                                   | 33    |

### Subject analysis sets

|                            |                                       |
|----------------------------|---------------------------------------|
| Subject analysis set title | Subjects aged: 1 to <2 years (Part A) |
|----------------------------|---------------------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

All subjects aged between 1 to <2 years were orally administered with a single body weight stratified dose of famciclovir of 12.5 mg/kg weight with a maximum dose of 500 mg.

|                            |                                       |
|----------------------------|---------------------------------------|
| Subject analysis set title | Subjects aged: 2 to <6 years (Part A) |
|----------------------------|---------------------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

All subjects aged between 2 to <6 years were orally administered with a single body weight stratified dose of famciclovir of 12.5 mg/kg weight with a maximum dose of 500 mg.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Subjects aged: 6 to $\leq 12$ years (Part A) |
|----------------------------|--|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

All subjects aged between 6 to <12 years were orally administered with a single body weight stratified dose of famciclovir of 12.5 mg/kg weight with a maximum dose of 500 mg.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Subjects aged: 13 to $\leq 18$ years (Part A) |
|----------------------------|---|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

All subjects aged between 13 to <18 years were orally administered with a single body weight stratified dose of famciclovir of 12.5 mg/kg weight with a maximum dose of 500 mg.

|                            |                                       |
|----------------------------|---------------------------------------|
| Subject analysis set title | Subjects aged: 1 to <2 years (Part B) |
| Subject analysis set type  | Sub-group analysis                    |

Subject analysis set description:

All subjects aged between 1 to <2 years were orally administered with famciclovir sprinkle capsules alone or with concomitant oral anti-herpes therapy with a dose separation of 12 hours for a period of 7 days. Subjects were administered with a body weight stratified daily dose in 8-step from 150 mg b.i.d. up to a maximum of 500 mg b.i.d. Subjects who had weight  $\geq$  40 kg received a famciclovir dose of 500 mg.

|                            |                                       |
|----------------------------|---------------------------------------|
| Subject analysis set title | Subjects aged: 2 to <6 years (Part B) |
| Subject analysis set type  | Sub-group analysis                    |

Subject analysis set description:

All subjects aged between 2 to <6 years were orally administered with famciclovir sprinkle capsules alone or with concomitant oral anti-herpes therapy with a dose separation of 12 hours for a period of 7 days. Subjects were administered with a body weight stratified daily dose in 8-step from 150 mg b.i.d. up to a maximum of 500 mg b.i.d. Subjects who had weight  $\geq$  40 kg received a famciclovir dose of 500 mg.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Subjects aged: 6 to $\leq$ 12 years (Part B) |
| Subject analysis set type  | Sub-group analysis                           |

Subject analysis set description:

All subjects aged between 6 to <12 years were orally administered with famciclovir sprinkle capsules alone or with concomitant oral anti-herpes therapy with a dose separation of 12 hours for a period of 7 days. Subjects were administered with a body weight stratified daily dose in 8-step from 150 mg b.i.d. up to a maximum of 500 mg b.i.d. Subjects who had weight  $\geq$  40 kg received a famciclovir dose of 500 mg.

| Reporting group values                   | Subjects aged: 1 to <2 years (Part A) | Subjects aged: 2 to <6 years (Part A) | Subjects aged: 6 to $\leq$ 12 years (Part A) |
|--|---------------------------------------|---------------------------------------|--|
| Number of subjects                       | 4                                     | 13                                    | 8  |
| Age categorical<br>Units: Subjects       |                                       |                                       |  |
| Infants and toddlers (28 days-23 months) |                                       |                                       |  |
| Children (2-11 years)                    |                                       |                                       |  |
| Adolescents (12-17 years)                |                                       |                                       |  |
| Age continuous<br>Units: years           |                                       |                                       |  |
| arithmetic mean                          | 1                                     | 3.5                                   | 10.3   |
| standard deviation                       | $\pm$ 0                               | $\pm$ 1.2                             | $\pm$ 0.89                                   |
| Gender categorical<br>Units: Subjects    |                                       |                                       |  |
| Female                                   | 1                                     | 11                                    | 4  |
| Male                                     | 3                                     | 2                                     | 4  |

| Reporting group values                   | Subjects aged: 13 to $\leq$ 18 years (Part A) | Subjects aged: 1 to <2 years (Part B) | Subjects aged: 2 to <6 years (Part B) |
|--|---|---------------------------------------|---------------------------------------|
| Number of subjects                       | 2   | 13                                    | 16                                    |
| Age categorical<br>Units: Subjects       |   |                                       |                                       |
| Infants and toddlers (28 days-23 months) |   |                                       |                                       |
| Children (2-11 years)                    |   |                                       |                                       |
| Adolescents (12-17 years)                |   |                                       |                                       |

|   |              |          |               |
|---|--------------|----------|---------------|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 16<br>± 1.41 | 1<br>± 0 | 3.5<br>± 1.03 |
| Gender categorical<br>Units: Subjects                                   |              |          |               |
| Female  | 1            | 7        | 10            |
| Male  | 1            | 6        | 6             |

|  |  |  |  |
|--|--|--|--|
| <b>Reporting group values</b>  | Subjects aged: 6 to<br><=12 years (Part B) |  |  |
| Number of subjects   | 18   |  |  |
| Age categorical<br>Units: Subjects   |  |  |  |
| Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years) |  |  |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation                        | 9.1<br>± 2.14                              |  |  |
| Gender categorical<br>Units: Subjects  |  |  |  |
| Female   | 7  |  |  |
| Male   | 11   |  |  |



## End points

### End points reporting groups

|   |   |
|---|---|
| Reporting group title   | Famciclovir: Single dose (Part A)             |
| Reporting group description:<br>Subjects were orally administered with a single body weight stratified dose of famciclovir of 12.5 mg/kilogram (kg) body weight with a dose escalation up to a maximum dose of 500 mg. Subjects who had weight $\geq 40$ kg received a famciclovir dose of 500 mg.  |   |
| Reporting group title   | Famciclovir: Multiple doses (Part B)          |
| Reporting group description:<br>Subjects were orally administered with famciclovir sprinkle capsules alone or with concomitant oral anti-herpes therapy twice daily (b.i.d.) with a dose separation of 12 hours for a period of 7 days. Subjects were administered with a body weight stratified daily dose in 8-step from 150 mg b.i.d. up to a maximum of 500 mg b.i.d. Subjects who had weight $\geq 40$ kg received a famciclovir dose of 500 mg.                   |   |
| Subject analysis set title  | Subjects aged: 1 to $<2$ years (Part A)       |
| Subject analysis set type   | Sub-group analysis                            |
| Subject analysis set description:<br>All subjects aged between 1 to $<2$ years were orally administered with a single body weight stratified dose of famciclovir of 12.5 mg/kg weight with a maximum dose of 500 mg.  |   |
| Subject analysis set title  | Subjects aged: 2 to $<6$ years (Part A)       |
| Subject analysis set type   | Sub-group analysis                            |
| Subject analysis set description:<br>All subjects aged between 2 to $<6$ years were orally administered with a single body weight stratified dose of famciclovir of 12.5 mg/kg weight with a maximum dose of 500 mg.  |   |
| Subject analysis set title  | Subjects aged: 6 to $\leq 12$ years (Part A)  |
| Subject analysis set type   | Sub-group analysis                            |
| Subject analysis set description:<br>All subjects aged between 6 to $<12$ years were orally administered with a single body weight stratified dose of famciclovir of 12.5 mg/kg weight with a maximum dose of 500 mg.   |   |
| Subject analysis set title  | Subjects aged: 13 to $\leq 18$ years (Part A) |
| Subject analysis set type   | Sub-group analysis                            |
| Subject analysis set description:<br>All subjects aged between 13 to $<18$ years were orally administered with a single body weight stratified dose of famciclovir of 12.5 mg/kg weight with a maximum dose of 500 mg.  |   |
| Subject analysis set title  | Subjects aged: 1 to $<2$ years (Part B)       |
| Subject analysis set type   | Sub-group analysis                            |
| Subject analysis set description:<br>All subjects aged between 1 to $<2$ years were orally administered with famciclovir sprinkle capsules alone or with concomitant oral anti-herpes therapy with a dose separation of 12 hours for a period of 7 days. Subjects were administered with a body weight stratified daily dose in 8-step from 150 mg b.i.d. up to a maximum of 500 mg b.i.d. Subjects who had weight $\geq 40$ kg received a famciclovir dose of 500 mg.  |   |
| Subject analysis set title  | Subjects aged: 2 to $<6$ years (Part B)       |
| Subject analysis set type   | Sub-group analysis                            |
| Subject analysis set description:<br>All subjects aged between 2 to $<6$ years were orally administered with famciclovir sprinkle capsules alone or with concomitant oral anti-herpes therapy with a dose separation of 12 hours for a period of 7 days. Subjects were administered with a body weight stratified daily dose in 8-step from 150 mg b.i.d. up to a maximum of 500 mg b.i.d. Subjects who had weight $\geq 40$ kg received a famciclovir dose of 500 mg.  |   |
| Subject analysis set title  | Subjects aged: 6 to $\leq 12$ years (Part B)  |
| Subject analysis set type   | Sub-group analysis                            |
| Subject analysis set description:<br>All subjects aged between 6 to $<12$ years were orally administered with famciclovir sprinkle capsules alone or with concomitant oral anti-herpes therapy with a dose separation of 12 hours for a period of 7 days. Subjects were administered with a body weight stratified daily dose in 8-step from 150 mg b.i.d. up to a maximum of 500 mg b.i.d. Subjects who had weight $\geq 40$ kg received a famciclovir dose of 500 mg. |   |

up to a maximum of 500 mg b.i.d. Subjects who had weight  $\geq 40$  kg received a famciclovir dose of 500 mg.

### Primary: Time to reach maximum plasma concentration (Tmax) of famciclovir during Part A

|                 |   |
|-----------------|---|
| End point title | Time to reach maximum plasma concentration (Tmax) of famciclovir during Part A <sup>[1]</sup> |
|-----------------|---|

End point description:

Tmax was defined as the time to reach maximum plasma concentration. Penciclovir (metabolite of famciclovir) plasma concentrations were determined by using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method. The limit of quantification was 0.15 microgram ( $\mu\text{g}$ )/ millilitre (mL) for both compounds. The analysis was performed in pharmacokinetic analysis set (PAS) population, defined as all subjects who received at least one scheduled dose of famciclovir and provided all primary PK parameters in at least one treatment period.

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

End point timeframe:

At pre-dose, 1, 2, 3, 4, and 5 hours post treatment administration

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 stats available

| End point values              | Subjects aged: 1 to <2 years (Part A) | Subjects aged: 2 to <6 years (Part A) | Subjects aged: 6 to $\leq 12$ years (Part A) | Subjects aged: 13 to $\leq 18$ years (Part A) |
|-------------------------------|---------------------------------------|---------------------------------------|--|---|
| Subject group type            | Subject analysis set                  | Subject analysis set                  | Subject analysis set                         | Subject analysis set                          |
| Number of subjects analysed   | 4                                     | 13                                    | 8  | 2   |
| Units: hours                  |                                       |                                       |  |   |
| median (full range (min-max)) | 1.21 (1 to 1.5)                       | 1.07 (1 to 4.03)                      | 1 (1 to 2.07)                                | 1.47 (0.97 to 1.97)                           |

### Statistical analyses

No statistical analyses for this end point

### Primary: Maximum plasma concentration (Cmax) of famciclovir during Part A

|                 |   |
|-----------------|---|
| End point title | Maximum plasma concentration (Cmax) of famciclovir during Part A <sup>[2]</sup> |
|-----------------|---|

End point description:

Cmax was defined as the maximum plasma concentration. Penciclovir (metabolite of famciclovir) plasma concentrations were determined by using a validated LC/MS/MS method. The limit of quantification was 0.15  $\mu\text{g/mL}$  for both compounds. The analysis was performed in PAS population.

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

End point timeframe:

At pre-dose, 1, 2, 3, 4, and 5 hours post treatment administration

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 stats available

| End point values                          | Subjects aged: 1 to <2 years (Part A) | Subjects aged: 2 to <6 years (Part A) | Subjects aged: 6 to <=12 years (Part A) | Subjects aged: 13 to <=18 years (Part A) |
|---|---------------------------------------|---------------------------------------|---|--|
| Subject group type                        | Subject analysis set                  | Subject analysis set                  | Subject analysis set                    | Subject analysis set                     |
| Number of subjects analysed               | 4                                     | 13                                    | 8                                       | 2  |
| Units: microgram( $\mu$ g)/milliliter(mL) |                                       |                                       |   |  |
| arithmetic mean (full range (min-max))    | 2.84 (1.42 to 4.47)                   | 2.44 (0.42 to 3.81)                   | 2.82 (1.52 to 3.79)                     | 1.89 (1.06 to 2.72)                      |

## Statistical analyses

No statistical analyses for this end point

### Primary: Area under the plasma concentration time curve from time zero to the time point of the last measurable concentration (AUC 0-tlast) of famciclovir during Part A

|                 |  |
|-----------------|--|
| End point title | Area under the plasma concentration time curve from time zero to the time point of the last measurable concentration (AUC 0-tlast) of famciclovir during Part A <sup>[3]</sup> |
|-----------------|--|

End point description:

AUC 0-tlast was defined as the area under the plasma concentration time curve from time zero to the time point of the last measurable concentration. Penciclovir (metabolite of famciclovir) plasma concentrations were determined by using a validated LC/MS/MS method. The limit of quantification was 0.15  $\mu$ g/mL for both compounds. The analysis was performed in PAS population.

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

End point timeframe:

At pre-dose, 1, 2, 3, 4, and 5 hours post treatment administration

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 summary stats available

| End point values                                     | Subjects aged: 1 to <2 years (Part A) | Subjects aged: 2 to <6 years (Part A) | Subjects aged: 6 to <=12 years (Part A) | Subjects aged: 13 to <=18 years (Part A) |
|--|---------------------------------------|---------------------------------------|---|--|
| Subject group type                                   | Subject analysis set                  | Subject analysis set                  | Subject analysis set                    | Subject analysis set                     |
| Number of subjects analysed                          | 4                                     | 13                                    | 8                                       | 2  |
| Units: (microgram( $\mu$ g)/milliliter(mL))*hour(h)) |                                       |                                       |   |  |
| arithmetic mean (full range (min-max))               | 5.73 (3.02 to 8.45)                   | 5.71 (1.63 to 8.17)                   | 6.98 (4.72 to 8.66)                     | 4.81 (3.57 to 6.06)                      |

## Statistical analyses

No statistical analyses for this end point

### Primary: Area under the plasma concentration time curve from time zero to infinity (AUC 0-infinity) of famciclovir during Part A

|                 |  |
|-----------------|--|
| End point title | Area under the plasma concentration time curve from time zero to infinity (AUC 0-infinity) of famciclovir during Part A <sup>[4]</sup> |
|-----------------|--|

End point description:

AUC 0-infinity was defined as the area under the plasma concentration time curve from time zero to infinity. Penciclovir (metabolite of famciclovir) plasma concentrations were determined by using a

validated LC/MS/MS method. The limit of quantification was 0.15 µg/mL for both compounds. The analysis was performed in PAS population.

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

End point timeframe:

At pre-dose, 1, 2, 3, 4, and 5 hours post treatment administration

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 summary stats available

| End point values                       | Subjects aged: 1 to <2 years (Part A) | Subjects aged: 2 to <6 years (Part A) | Subjects aged: 6 to <=12 years (Part A) | Subjects aged: 13 to <=18 years (Part A) |
|--|---------------------------------------|---------------------------------------|---|--|
| Subject group type                     | Subject analysis set                  | Subject analysis set                  | Subject analysis set                    | Subject analysis set                     |
| Number of subjects analysed            | 4                                     | 13                                    | 8                                       | 2  |
| Units: µg/mL*h                         |                                       |                                       |   |  |
| arithmetic mean (full range (min-max)) | 6.17 (3.43 to 8.99)                   | 6.85 (3.19 to 9.12)                   | 8.15 (6.49 to 9.71)                     | 5.93 (4.84 to 7.01)                      |

## Statistical analyses

No statistical analyses for this end point

## Primary: Terminal elimination half-life (T<sub>1/2</sub>) of famciclovir during Part A

|                 |   |
|-----------------|---|
| End point title | Terminal elimination half-life (T <sub>1/2</sub> ) of famciclovir during Part |
|-----------------|---|

End point description:

T<sub>1/2</sub> was defined as the terminal elimination half-life. Penciclovir (metabolite of famciclovir) plasma concentrations were determined by using a validated LC/MS/MS method. The limit of quantification was 0.15 µg/mL for both compounds. The analysis was performed in PAS population.

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

End point timeframe:

At pre-dose, 1, 2, 3, 4, and 5 hours post treatment administration

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: only summary stats available

| End point values                       | Subjects aged: 1 to <2 years (Part A) | Subjects aged: 2 to <6 years (Part A) | Subjects aged: 6 to <=12 years (Part A) | Subjects aged: 13 to <=18 years (Part A) |
|--|---------------------------------------|---------------------------------------|---|--|
| Subject group type                     | Subject analysis set                  | Subject analysis set                  | Subject analysis set                    | Subject analysis set                     |
| Number of subjects analysed            | 4                                     | 13                                    | 8                                       | 2  |
| Units: Hours                           |                                       |                                       |   |  |
| arithmetic mean (full range (min-max)) | 1.09 (1.01 to 1.18)                   | 1.36 (1.1 to 1.7)                     | 1.6 (1.3 to 2.11)                       | 1.86 (1.6 to 2.12)                       |

## Statistical analyses

No statistical analyses for this end point

**Primary: Apparent oral clearance (if AUC 0-infinity is available) (CL/F) of famciclovir during Part A**

|                 |   |
|-----------------|---|
| End point title | Apparent oral clearance (if AUC 0-infinity is available) (CL/F) of famciclovir during Part A <sup>[6]</sup> |
|-----------------|---|

End point description:

CL/F was defined as the apparent oral clearance. Penciclovir (metabolite of famciclovir) plasma concentrations were determined by using a validated LC/MS/MS method. The limit of quantification was 0.15 µg/mL for both compounds. The analysis was performed in PAS population.

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

End point timeframe:

At pre-dose, 1, 2, 3, 4, and 5 hours post treatment administration

Notes:

[6] - 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 stats available

| End point values                       | Subjects aged: 1 to <2 years (Part A) | Subjects aged: 2 to <6 years (Part A) | Subjects aged: 6 to ≤12 years (Part A) | Subjects aged: 13 to ≤18 years (Part A) |
|--|---------------------------------------|---------------------------------------|--|---|
| Subject group type                     | Subject analysis set                  | Subject analysis set                  | Subject analysis set                   | Subject analysis set                    |
| Number of subjects analysed            | 4                                     | 13                                    | 8                                      | 2                                       |
| Units: Lites(L)/Hour(h)                |                                       |                                       |  |   |
| arithmetic mean (full range (min-max)) | 20.8 (11 to 28.8)                     | 25.1 (18.1 to 33.3)                   | 43.7 (32.4 to 60.8)                    | 68.8 (56.2 to 81.5)                     |

**Statistical analyses**

No statistical analyses for this end point

**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>[7]</sup> |
|-----------------|---|

End point description:

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 subjects who received any dose (including partial dose) of study medication and had at least one post-baseline safety or acceptability assessment.

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

End point timeframe:

From Day 1 up to Day 15

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: only summary stats available

| End point values                    | Subjects aged:<br>1 to <2 years<br>(Part A) | Subjects aged:<br>2 to <6 years<br>(Part A) | Subjects aged:<br>6 to <=12<br>years (Part A) | Subjects aged:<br>13 to <=18<br>years (Part A) |
|-------------------------------------|---|---|---|--|
| Subject group type                  | Subject analysis set                        | Subject analysis set                        | Subject analysis set                          | Subject analysis set                           |
| Number of subjects analysed         | 4   | 13  | 8   | 2  |
| Units: Subjects                     |   |   |   |  |
| AEs                                 | 0   | 2   | 1   | 2  |
| SAEs                                | 0   | 0   | 0   | 0  |
| Deaths                              | 0   | 0   | 0   | 0  |
| AEs leading to discontinuation      | 0   | 0   | 0   | 0  |
| AE requiring concomitant medication | 0   | 0   | 0   | 0  |

| End point values                    | Subjects aged:<br>1 to <2 years<br>(Part B) | Subjects aged:<br>2 to <6 years<br>(Part B) | Subjects aged:<br>6 to <=12<br>years (Part B) |  |
|-------------------------------------|---|---|---|--|
| Subject group type                  | Subject analysis set                        | Subject analysis set                        | Subject analysis set                          |  |
| Number of subjects analysed         | 13  | 16  | 18  |  |
| Units: Subjects                     |   |   |   |  |
| AEs                                 | 6   | 8   | 12  |  |
| SAEs                                | 0   | 0   | 0   |  |
| Deaths                              | 0   | 0   | 0   |  |
| AEs leading to discontinuation      | 0   | 0   | 0   |  |
| AE requiring concomitant medication | 4   | 1   | 3   |  |

## 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>[8]</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:

From Day 1 to Day 15

Notes:

[8] - 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 stats available

| End point values            | Subjects aged: 1 to <2 years (Part A) | Subjects aged: 2 to <6 years (Part A) | Subjects aged: 6 to <=12 years (Part A) | Subjects aged: 13 to <=18 years (Part A) |
|-----------------------------|---------------------------------------|---------------------------------------|---|--|
| Subject group type          | Subject analysis set                  | Subject analysis set                  | Subject analysis set                    | Subject analysis set                     |
| Number of subjects analysed | 4                                     | 13                                    | 8                                       | 2  |
| Units: Subjects             |                                       |                                       |   |  |
| Hematology                  | 0                                     | 0                                     | 0                                       | 0  |
| Clinical chemistry          | 0                                     | 0                                     | 0                                       | 0  |

| End point values            | Subjects aged: 1 to <2 years (Part B) | Subjects aged: 2 to <6 years (Part B) | Subjects aged: 6 to <=12 years (Part B) |  |
|-----------------------------|---------------------------------------|---------------------------------------|---|--|
| Subject group type          | Subject analysis set                  | Subject analysis set                  | Subject analysis set                    |  |
| Number of subjects analysed | 13                                    | 16                                    | 18                                      |  |
| Units: Subjects             |                                       |                                       |   |  |
| Hematology                  | 0                                     | 0                                     | 0                                       |  |
| Clinical chemistry          | 0                                     | 0                                     | 0                                       |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Assessment of acceptability of pediatric formulation during Part A

|                 |  |
|-----------------|--|
| End point title | Assessment of acceptability of pediatric formulation during Part A |
|-----------------|--|

End point description:

Assessment of acceptability was done using a modified, 5-point facial hedonic scale, subjects or caregivers were asked to complete an assessment of study medication. Subjects marked the scale with their response of choice. The scale represented a balance of choices from 'I did not like it' to 'I like it very much' with a mid-point of neither like nor dislike, with qualitative evaluation. The analysis was performed on the safety set.

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

End point timeframe:

At Day 1

| End point values            | Subjects aged: 1 to <2 years (Part A) | Subjects aged: 2 to <6 years (Part A) | Subjects aged: 6 to <=12 years (Part A) | Subjects aged: 13 to <=18 years (Part A) |
|-----------------------------|---------------------------------------|---------------------------------------|---|--|
| Subject group type          | Subject analysis set                  | Subject analysis set                  | Subject analysis set                    | Subject analysis set                     |
| Number of subjects analysed | 4                                     | 13                                    | 8                                       | 2  |
| Units: Subjects             |                                       |                                       |   |  |
| Bitter                      | 1                                     | 3                                     | 4                                       | 1  |
| Sweet                       | 2                                     | 5                                     | 4                                       | 0  |
| Other                       | 1                                     | 5                                     | 1                                       | 1  |
| Very badly / Unacceptable   | 1                                     | 0                                     | 0                                       | 0  |
| Badly but accepted          | 0                                     | 4                                     | 0                                       | 2  |
| Neither good nor bad        | 1                                     | 1                                     | 4                                       | 0  |

|                    |   |   |   |   |
|--------------------|---|---|---|---|
| Well accepted      | 0 | 5 | 2 | 0 |
| Very well accepted | 2 | 3 | 2 | 0 |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Assessment of acceptability of pediatric formulation during Part B

|                 |  |
|-----------------|--|
| End point title | Assessment of acceptability of pediatric formulation during Part B |
|-----------------|--|

End point description:

Assessment of acceptability was done using a modified, 5-point facial hedonic scale, subjects or caregivers were asked to complete an assessment of study medication. Subjects marked the scale with their response of choice. The scale represented a balance of choices from 'I did not like it' to 'I like it very much' with a mid-point of neither like nor dislike, with qualitative evaluation. The analysis was performed on the safety set. Here, 'clinic' and 'home' signifies post-first dose in clinic and home respectively and day 8 have been reported for post-last dose at home.

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

End point timeframe:

From Day 1 to Day 8

| End point values                                   | Subjects aged:<br>1 to <2 years<br>(Part B) | Subjects aged:<br>2 to <6 years<br>(Part B) | Subjects aged:<br>6 to <=12<br>years (Part B) |  |
|--|---|---|---|--|
| Subject group type                                 | Subject analysis set                        | Subject analysis set                        | Subject analysis set                          |  |
| Number of subjects analysed                        | 13  | 16  | 18  |  |
| Units: Subjects                                    |   |   |   |  |
| Bitter   | 3   | 6   | 9   |  |
| Sweet  | 3   | 5   | 2   |  |
| Other  | 7   | 5   | 7   |  |
| Very badly/unacceptable:Day 1(clinic)              | 0   | 2   | 0   |  |
| Badly but accepted: Day 1(clinic)                  | 9   | 4   | 7   |  |
| Neither good nor bad: Day 1(clinic)                | 2   | 1   | 2   |  |
| Well accepted: Day 1(clinic)                       | 1   | 4   | 5   |  |
| Very well accepted: Day 1(clinic)                  | 1   | 5   | 4   |  |
| Very badly/unacceptable:Day 1(home)                | 1   | 0   | 0   |  |
| Badly but accepted: Day 1(home)                    | 7   | 5   | 4   |  |
| Neither good nor bad: Day 1(home)                  | 2   | 2   | 4   |  |
| Well accepted: Day 1(home)                         | 2   | 5   | 5   |  |
| Very well accepted: Day 1(home)                    | 1   | 3   | 5   |  |
| Very badly/unacceptable: EoS/early discontinuation | 0   | 1   | 0   |  |
| Badly but accepted: EoS/early discontinuation      | 7   | 4   | 3   |  |
| Neither good nor bad: EoS/early discontinuation    | 3   | 3   | 3   |  |
| Well accepted: EoS/early discontinuation           | 1   | 3   | 5   |  |



|  |   |   |   |  |
|--|---|---|---|--|
| Very well accepted: EoS/early<br>discontinuation | 2 | 4 | 6 |  |
|--|---|---|---|--|

## Statistical analyses

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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

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 10.1 |
|--------------------|------|

### Reporting groups

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | Famciclovir: Single dose (Part A) |
|-----------------------|-----------------------------------|

Reporting group description:

Subjects were orally administered with a single body weight stratified dose of famciclovir of 12.5 mg/kg body weight with a dose escalation up to a maximum dose of 500 mg. Subjects who had weight  $\geq 40$  kg received a famciclovir dose of 500 mg.

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Famciclovir: Multiple doses (Part B) |
|-----------------------|--------------------------------------|

Reporting group description:

Subjects were orally administered with famciclovir sprinkle capsules alone or with concomitant oral anti-herpes therapy b.i.d. with a dose separation of 12 hours for a period of 7 days. Subjects were administered with a body weight stratified daily dose in 8-step from 150 mg b.i.d. up to a maximum of 500 mg b.i.d. Subjects who had weight  $\geq 40$  kg received a famciclovir dose of 500 mg.

| Serious adverse events                            | Famciclovir: Single dose (Part A) | Famciclovir: Multiple doses (Part B) |  |
|---|-----------------------------------|--------------------------------------|--|
| Total subjects affected by serious adverse events |                                   |                                      |  |
| subjects affected / exposed                       | 0 / 27 (0.00%)                    | 0 / 47 (0.00%)                       |  |
| number of deaths (all causes)                     | 0                                 | 0                                    |  |
| number of deaths resulting from adverse events    | 0                                 | 0                                    |  |

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

| Non-serious adverse events                            | Famciclovir: Single dose (Part A) | Famciclovir: Multiple doses (Part B) |  |
|---|-----------------------------------|--------------------------------------|--|
| Total subjects affected by non-serious adverse events |                                   |                                      |  |
| subjects affected / exposed                           | 5 / 27 (18.52%)                   | 26 / 47 (55.32%)                     |  |
| Investigations  |                                   |                                      |  |
| Blood uric acid increased                             |                                   |                                      |  |
| subjects affected / exposed                           | 0 / 27 (0.00%)                    | 1 / 47 (2.13%)                       |  |
| occurrences (all)                                     | 0                                 | 1                                    |  |
| Injury, poisoning and procedural complications        |                                   |                                      |  |

|   |                     |                     |  |
|---|---------------------|---------------------|--|
| Arthropod bite<br>subjects affected / exposed<br>occurrences (all)  | 0 / 27 (0.00%)<br>0 | 1 / 47 (2.13%)<br>1 |  |
| Contusion<br>subjects affected / exposed<br>occurrences (all)   | 0 / 27 (0.00%)<br>0 | 1 / 47 (2.13%)<br>1 |  |
| Skin laceration<br>subjects affected / exposed<br>occurrences (all)   | 0 / 27 (0.00%)<br>0 | 1 / 47 (2.13%)<br>1 |  |
| Vascular disorders<br>Haematoma<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 27 (0.00%)<br>0 | 1 / 47 (2.13%)<br>1 |  |
| Flushing<br>subjects affected / exposed<br>occurrences (all)  | 0 / 27 (0.00%)<br>0 | 1 / 47 (2.13%)<br>1 |  |
| Nervous system disorders<br>Clumsiness<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 27 (0.00%)<br>0 | 1 / 47 (2.13%)<br>1 |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)   | 1 / 27 (3.70%)<br>1 | 0 / 47 (0.00%)<br>0 |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)  | 2 / 27 (7.41%)<br>2 | 4 / 47 (8.51%)<br>4 |  |
| Psychomotor hyperactivity<br>subjects affected / exposed<br>occurrences (all)   | 0 / 27 (0.00%)<br>0 | 1 / 47 (2.13%)<br>1 |  |
| Somnolence<br>subjects affected / exposed<br>occurrences (all)  | 0 / 27 (0.00%)<br>0 | 1 / 47 (2.13%)<br>2 |  |
| General disorders and administration<br>site conditions<br>Chest pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 27 (0.00%)<br>0 | 1 / 47 (2.13%)<br>1 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| Irritability                                    |                |                 |  |
| subjects affected / exposed                     | 0 / 27 (0.00%) | 1 / 47 (2.13%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Pyrexia   |                |                 |  |
| subjects affected / exposed                     | 1 / 27 (3.70%) | 2 / 47 (4.26%)  |  |
| occurrences (all)                               | 1              | 2               |  |
| Vessel puncture site haematoma                  |                |                 |  |
| subjects affected / exposed                     | 0 / 27 (0.00%) | 1 / 47 (2.13%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Gastrointestinal disorders                      |                |                 |  |
| Abdominal pain upper                            |                |                 |  |
| subjects affected / exposed                     | 2 / 27 (7.41%) | 2 / 47 (4.26%)  |  |
| occurrences (all)                               | 2              | 3               |  |
| Diarrhoea                                       |                |                 |  |
| subjects affected / exposed                     | 0 / 27 (0.00%) | 4 / 47 (8.51%)  |  |
| occurrences (all)                               | 0              | 4               |  |
| Flatulence                                      |                |                 |  |
| subjects affected / exposed                     | 0 / 27 (0.00%) | 1 / 47 (2.13%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Gingival bleeding                               |                |                 |  |
| subjects affected / exposed                     | 0 / 27 (0.00%) | 1 / 47 (2.13%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Nausea  |                |                 |  |
| subjects affected / exposed                     | 0 / 27 (0.00%) | 3 / 47 (6.38%)  |  |
| occurrences (all)                               | 0              | 3               |  |
| Vomiting  |                |                 |  |
| subjects affected / exposed                     | 0 / 27 (0.00%) | 5 / 47 (10.64%) |  |
| occurrences (all)                               | 0              | 6               |  |
| Respiratory, thoracic and mediastinal disorders |                |                 |  |
| Cough   |                |                 |  |
| subjects affected / exposed                     | 0 / 27 (0.00%) | 3 / 47 (6.38%)  |  |
| occurrences (all)                               | 0              | 3               |  |
| Dysphonia                                       |                |                 |  |
| subjects affected / exposed                     | 0 / 27 (0.00%) | 1 / 47 (2.13%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Nasal congestion                                |                |                 |  |

|  |                |                |  |
|--|----------------|----------------|--|
| subjects affected / exposed            | 0 / 27 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Pharyngolaryngeal pain                 |                |                |  |
| subjects affected / exposed            | 0 / 27 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Rhinorrhoea                            |                |                |  |
| subjects affected / exposed            | 0 / 27 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Skin and subcutaneous tissue disorders |                |                |  |
| Blister                                |                |                |  |
| subjects affected / exposed            | 0 / 27 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Dry skin                               |                |                |  |
| subjects affected / exposed            | 0 / 27 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Pruritus                               |                |                |  |
| subjects affected / exposed            | 0 / 27 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Rash                                   |                |                |  |
| subjects affected / exposed            | 1 / 27 (3.70%) | 0 / 47 (0.00%) |  |
| occurrences (all)                      | 1              | 0              |  |
| Infections and infestations            |                |                |  |
| Furuncle                               |                |                |  |
| subjects affected / exposed            | 1 / 27 (3.70%) | 0 / 47 (0.00%) |  |
| occurrences (all)                      | 1              | 0              |  |
| Conjunctivitis viral                   |                |                |  |
| subjects affected / exposed            | 0 / 27 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Gastroenteritis                        |                |                |  |
| subjects affected / exposed            | 0 / 27 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Otitis media                           |                |                |  |
| subjects affected / exposed            | 0 / 27 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Metabolism and nutrition disorders     |                |                |  |

|                             |                |                |  |
|-----------------------------|----------------|----------------|--|
| Hypokalaemia                |                |                |  |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences (all)           | 0              | 1              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 07 July 2006     | Adjusted the dosing scheme in Part A and Part B according to the interim results from Part A of both studies (i.e. CFAM810B2303 and CFAM810B2304) and discussions with the FDA. It also added a criterion to exclude subjects who weighed <9 kg.   |
| 17 November 2006 | Requirement for PK and multiple-dose safety assessments in a cohort of subjects, 12 to 18 years of age and the upper age limit of the pediatric subjects to be studied from 12 to 18 years old was amended. The amendment created a new cohort for these adolescent subjects.  |
| 18 June 2007     | Cancelled the requirement for inclusion of adolescent subjects in the study by deleting the new cohort (which had been designated as cohort 4 to include subjects 12 to 18 years of age), amending the upper age limit of the pediatric subjects to be studied from 18 back to 12 years, and deleting the requirement for single-dose PK for 3 to 4 subjects in cohort 4. The amendment also readjusted the number of subjects per cohort in Part B to compensate for the removal of cohort 4. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported