



## Clinical trial results:

**A Phase II, open-label trial, to investigate pharmacokinetics, safety, tolerability and antiviral activity of TMC114/rtv b.i.d. in treatment-experienced HIV-1 infected children and adolescents - Analysis with cut-off date of 10 April 2008, at which time all subjects had reached Week 48 or discontinued before**

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

## Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2005-006179-11          |
| Trial protocol           | GB ES IT Outside EU/EEA |
| Global end of trial date |                         |

## Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v2 (current)   |
| This version publication date  | 23 June 2016   |
| First version publication date | 03 August 2015 |
| Version creation reason        |                |

## Trial information

### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | TMC114-C212 |
|-----------------------|-------------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00355524 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Tibotec Pharmaceuticals   |
| Sponsor organisation address | Eastgate Village, Eastgate,, Little Island, Co Cork, Ireland,                     |
| Public contact               | Clinical Registry Group, Tibotec Pharmaceuticals,<br>ClinicalTrialsEU@its.jnj.com |
| Scientific contact           | Clinical Registry Group, Tibotec Pharmaceuticals,<br>ClinicalTrialsEU@its.jnj.com |

Notes:

## Paediatric regulatory details

|  |                     |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-000038-PIP01-07 |
| 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? | Yes                 |



Notes:

## Results analysis stage

|  |               |
|--|---------------|
| Analysis stage                                       | Interim       |
| Date of interim/final analysis                       | 10 April 2008 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | No            |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate long-term safety, tolerability and efficacy of darunavir (DRV) in combination with low-dose ritonavir administered twice daily (b.i.d) and other antiretroviral (ARV) agents over a 24-week treatment period at the selected pediatric (greater than or equal to [ $\geq$ ] 20 kilogram [kg] to less than [ $<$ ] 50 kg) and adult ( $\geq$  50 kg) doses.

Protection of trial subjects:

The safety assessments included clinical laboratory tests (hematology, coagulation, biochemistry, hepatitis serology/viremia and urinalysis), cardiovascular safety, vital signs, physical examination, electrocardiogram (ECG). Adverse events and vital signs were monitored throughout the study.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 13 July 2006 |
| Long term follow-up planned                               | Yes          |
| Long term follow-up rationale                             | Safety       |
| Long term follow-up duration                              | 12 Months    |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Brazil: 10        |
| Country: Number of subjects enrolled | Argentina: 17     |
| Country: Number of subjects enrolled | Canada: 3         |
| Country: Number of subjects enrolled | Spain: 5          |
| Country: Number of subjects enrolled | France: 4         |
| Country: Number of subjects enrolled | Italy: 3          |
| Country: Number of subjects enrolled | Romania: 15       |
| Country: Number of subjects enrolled | United States: 18 |
| Country: Number of subjects enrolled | South Africa: 5   |
| Worldwide total number of subjects   | 80                |
| EEA total number of subjects         | 27                |

Notes:



| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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)                     | 24 |
| Adolescents (12-17 years)                 | 56 |
| Adults (18-64 years)                      | 0  |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |



## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

In total, 96 participants were screened (52 in Part 1 and 44 in Part 2). Of these 96 participants, 80 participants were treated, and 16 were screening failures.

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | Part 2 (overall period)     |
| Is this the baseline period? | Yes                         |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

### Arms

|           |                          |
|-----------|--------------------------|
| Arm title | Darunavir plus Ritonavir |
|-----------|--------------------------|

Arm description:

Participants administered with Darunavir 600 milligram (mg) in combination with low dose ritonavir 100 mg twice daily along with other antiretroviral (ARV) agents.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | TMC114 ethanolate  |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Participants administered with Darunavir 300 mg twice daily along with other ARV agents.

|  |                    |
|--|--------------------|
| Investigational medicinal product name | TMC114 ethanolate  |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Participants administered with Darunavir 75 mg twice daily along with other ARV agents.

|  |               |
|--|---------------|
| Investigational medicinal product name | Norvir        |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, soft |
| Routes of administration               | Oral use      |

Dosage and administration details:

Participants administered with Ritonavir 100 mg twice daily along with other ARV agents.

|  |               |
|--|---------------|
| Investigational medicinal product name | Norvir        |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Oral solution |
| Routes of administration               | Oral use      |

Dosage and administration details:

Participants administered with Ritonavir 80 milligram(s)/millilitre (mg/ml) administered twice daily along with other ARV agents.



| <b>Number of subjects in period 1</b> | Darunavir plus Ritonavir |
|---------------------------------------|--------------------------|
| Started                               | 80                       |
| Completed                             | 70                       |
| Not completed                         | 10                       |
| Adverse event, serious fatal          | 1                        |
| Other                                 | 1                        |
| Unspecified                           | 5                        |
| Subject noncompliant                  | 3                        |



## Baseline characteristics

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Darunavir plus Ritonavir |
|-----------------------|--------------------------|

Reporting group description:

Participants administered with Darunavir 600 milligram (mg) in combination with low dose ritonavir 100 mg twice daily along with other antiretroviral (ARV) agents.

| Reporting group values                      | Darunavir plus Ritonavir | Total |  |
|---|--------------------------|-------|--|
| Number of subjects                          | 80                       | 80    |  |
| Title for AgeCategorical<br>Units: subjects |                          |       |  |
| Children (2-11 years)                       | 24                       | 24    |  |
| Adolescents (12-17 years)                   | 56                       | 56    |  |
| Title for AgeContinuous<br>Units: years     |                          |       |  |
| arithmetic mean                             | 13.1                     |       |  |
| standard deviation                          | ± 3.11                   | -     |  |
| Title for Gender<br>Units: subjects         |                          |       |  |
| Female                                      | 23                       | 23    |  |
| Male  | 57                       | 57    |  |



## End points

### End points reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Darunavir plus Ritonavir |
|-----------------------|--------------------------|

Reporting group description:

Participants administered with Darunavir 600 milligram (mg) in combination with low dose ritonavir 100 mg twice daily along with other antiretroviral (ARV) agents.

|                            |                 |
|----------------------------|-----------------|
| Subject analysis set title | PART-I: GROUP A |
|----------------------------|-----------------|

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

Subject analysis set description:

Participants administered with low doses of Darunavir in combination with Ritonavir (DRV) twice daily along with other antiretroviral (ARV) agents.

|                            |                 |
|----------------------------|-----------------|
| Subject analysis set title | PART-I: GROUP B |
|----------------------------|-----------------|

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

Subject analysis set description:

Participants administered with 20 to 33% higher dose of Darunavir in combination with Ritonavir (DRV) twice daily along with other antiretroviral (ARV) agents.

### Primary: Percentage of Participants With Confirmed Virologic Response

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With Confirmed Virologic Response <sup>[1]</sup> |
|-----------------|---|

End point description:

Virologic response defined as the percentage of participants with a confirmed decrease of at least 1 log<sub>10</sub> from baseline in plasma viral load at Week 24 calculated according to the Food and Drug Administration (FDA) time to loss of virologic response (TLOVR) algorithm.

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

End point timeframe:

Week 2, 4, 8, 12, 16, 20, 24, 32, 40 and 48

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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values                  | Darunavir plus Ritonavir |  |  |  |
|-----------------------------------|--------------------------|--|--|--|
| Subject group type                | Reporting group          |  |  |  |
| Number of subjects analysed       | 80                       |  |  |  |
| Units: Percentage of participants |                          |  |  |  |
| number (not applicable)           |                          |  |  |  |
| Week 2                            | 78.8                     |  |  |  |
| Week 4                            | 82.5                     |  |  |  |
| Week 8                            | 82.5                     |  |  |  |
| Week 12                           | 81.3                     |  |  |  |
| Week 16                           | 77.5                     |  |  |  |
| Week 20                           | 76.3                     |  |  |  |
| Week 24                           | 73.8                     |  |  |  |
| Week 32                           | 67.5                     |  |  |  |
| Week 40                           | 66.3                     |  |  |  |
| Week 48                           | 65                       |  |  |  |



## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Participants With Observed Virologic Response Rate (at Least 0.5 log<sub>10</sub> Decrease) at Week 2

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With Observed Virologic Response Rate (at Least 0.5 log <sub>10</sub> Decrease) at Week 2 <sup>[2]</sup> |
|-----------------|---|

End point description:

Participants observed with response at Week 2 defined as a drop in viral load (copies/mL) of at least 0.5 log<sub>10</sub> versus baseline.

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

End point timeframe:

At week 2

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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values                  | PART-I: GROUP A      | PART-I: GROUP B      |  |  |
|-----------------------------------|----------------------|----------------------|--|--|
| Subject group type                | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed       | 22                   | 20                   |  |  |
| Units: Percentage of participants |                      |                      |  |  |
| number (not applicable)           | 90.9                 | 100                  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Virologic Response

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants With Virologic Response |
|-----------------|--|

End point description:

Virologic response defined as the percentage of participants with confirmed virologic response (viral load less than [ $<$ ] 400 copies/milliliter [mL], TLOVR or viral load  $<$  50 copies/mL)

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

End point timeframe:

Week 2, 4,8, 12,16, 20, 24, 32, 40 and 48



|                                     |                          |  |  |  |
|-------------------------------------|--------------------------|--|--|--|
| <b>End point values</b>             | Darunavir plus Ritonavir |  |  |  |
| Subject group type                  | Reporting group          |  |  |  |
| Number of subjects analysed         | 80                       |  |  |  |
| Units: Percentage of participants   |                          |  |  |  |
| number (not applicable)             |                          |  |  |  |
| Week 2: Viral Load < 50 Copies/mL   | 5                        |  |  |  |
| Week 4: Viral Load < 50 Copies/mL   | 11.3                     |  |  |  |
| Week 8: Viral Load < 50 Copies/mL   | 26.3                     |  |  |  |
| Week 12: Viral Load < 50 Copies/mL  | 36.3                     |  |  |  |
| Week 16: Viral Load < 50 Copies/mL  | 46.3                     |  |  |  |
| Week 20: Viral Load < 50 Copies/mL  | 52.5                     |  |  |  |
| Week 24: Viral Load < 50 Copies/mL  | 50                       |  |  |  |
| Week 32: Viral Load < 50 Copies/mL  | 50                       |  |  |  |
| Week 40: Viral Load < 50 Copies/mL  | 48.8                     |  |  |  |
| Week 48: Viral Load < 50 Copies/mL  | 47.5                     |  |  |  |
| Week 2: Viral Load < 400 Copies/mL  | 33.8                     |  |  |  |
| Week 4: Viral Load < 400 Copies/mL  | 50                       |  |  |  |
| Week 8: Viral Load < 400 Copies/mL  | 56.3                     |  |  |  |
| Week 12: Viral Load < 400 Copies/mL | 65                       |  |  |  |
| Week 16: Viral Load < 400 Copies/mL | 66.3                     |  |  |  |
| Week 20: Viral Load < 400 Copies/mL | 66.3                     |  |  |  |
| Week 24: Viral Load < 400 Copies/mL | 65                       |  |  |  |
| Week 32: Viral Load < 400 Copies/mL | 62.5                     |  |  |  |
| Week 40: Viral Load < 400 Copies/mL | 60                       |  |  |  |
| Week 48: Viral Load < 400 Copies/mL | 58.8                     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Durability of Response

|                 |                        |
|-----------------|------------------------|
| End point title | Durability of Response |
|-----------------|------------------------|

End point description:

Durability of Response is defined as proportion of participants with at least 1 log<sub>10</sub> decrease in viral load or a viral load less than (<) 50 copies/milliliter (mL) at Week 48 versus Week 24. Here 'n' signifies the number of participants analysed at this time point.

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

End point timeframe:

Week 24 and week 48



|   |                          |  |  |  |
|---|--------------------------|--|--|--|
| <b>End point values</b>                         | Darunavir plus Ritonavir |  |  |  |
| Subject group type                              | Reporting group          |  |  |  |
| Number of subjects analysed                     | 80                       |  |  |  |
| Units: Percentage of participants               |                          |  |  |  |
| number (not applicable)                         |                          |  |  |  |
| At least 1 log10 decrease from Baseline (n= 59) | 88.1                     |  |  |  |
| VL < 50 copies/mL (n= 40)                       | 87.5                     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Log10 Viral Load

|  |  |
|--|--|
| End point title  | Change From Baseline in Log10 Viral Load |
| End point description:<br>The change in plasma log10 viral load from baseline was calculated using the (NC = F) algorithm where non-completers are considered as failures after treatment discontinuation. |  |
| End point type   | Secondary                                |
| End point timeframe:<br>Baseline, Week 2, 4,8, 12,16, 20, 24, 32, 40 and 48  |  |

|                                  |                          |  |  |  |
|----------------------------------|--------------------------|--|--|--|
| <b>End point values</b>          | Darunavir plus Ritonavir |  |  |  |
| Subject group type               | Reporting group          |  |  |  |
| Number of subjects analysed      | 80                       |  |  |  |
| Units: Copies/milliliter (mL)    |                          |  |  |  |
| arithmetic mean (standard error) |                          |  |  |  |
| Baseline                         | 4.64 (± 0.089)           |  |  |  |
| Change at Week 2                 | -1.63 (± 0.08)           |  |  |  |
| Change at Week 4                 | -1.83 (± 0.094)          |  |  |  |
| Change at Week 8                 | -1.88 (± 0.121)          |  |  |  |
| Change at Week 12                | -2.04 (± 0.122)          |  |  |  |
| Change at Week 16                | -1.99 (± 0.135)          |  |  |  |
| Change at Week 20                | -1.96 (± 0.138)          |  |  |  |
| Change at Week 24                | -1.98 (± 0.137)          |  |  |  |
| Change at Week 32                | -1.83 (± 0.147)          |  |  |  |
| Change at Week 40                | -1.8 (± 0.15)            |  |  |  |
| Change at Week 48                | -1.81 (± 0.151)          |  |  |  |



## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Cluster of Differentiation 4 (CD4+) Cell Count

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Cluster of Differentiation 4 (CD4+) Cell Count |
|-----------------|--|

End point description:

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

End point timeframe:

Baseline, Week 2, 4,8, 12,16, 20, 24, 32, 40 and 48

| End point values                  | Darunavir plus Ritonavir |  |  |  |
|-----------------------------------|--------------------------|--|--|--|
| Subject group type                | Reporting group          |  |  |  |
| Number of subjects analysed       | 80                       |  |  |  |
| Units: 10 <sup>6</sup> /liter (L) |                          |  |  |  |
| arithmetic mean (standard error)  |                          |  |  |  |
| Baseline                          | 390 (± 36.8)             |  |  |  |
| Week 2                            | 35 (± 13.7)              |  |  |  |
| Week 4                            | 70 (± 14.4)              |  |  |  |
| Week 8                            | 69 (± 13.1)              |  |  |  |
| Week 12                           | 116 (± 17.7)             |  |  |  |
| Week 16                           | 69 (± 22.1)              |  |  |  |
| Week 20                           | 97 (± 16.8)              |  |  |  |
| Week 24                           | 117 (± 16.8)             |  |  |  |
| Week 32                           | 108 (± 19.2)             |  |  |  |
| Week 40                           | 148 (± 27.3)             |  |  |  |
| Week 48                           | 147 (± 27.2)             |  |  |  |

## Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to Week 48

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

### Dictionary used

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

|                    |     |
|--------------------|-----|
| Dictionary version | 9.1 |
|--------------------|-----|

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Darunavir plus Ritonavir |
|-----------------------|--------------------------|

Reporting group description:

Darunavir 600 milligram (mg) in combination with low dose ritonavir 100 mg administered twice daily and other antiretroviral (ARV) agents.

| Serious adverse events                            | Darunavir plus Ritonavir |  |  |
|---|--------------------------|--|--|
| Total subjects affected by serious adverse events |                          |  |  |
| subjects affected / exposed                       | 20 / 80 (25.00%)         |  |  |
| number of deaths (all causes)                     | 1                        |  |  |
| number of deaths resulting from adverse events    |                          |  |  |
| Investigations                                    |                          |  |  |
| Alanine Aminotransferase Increased                |                          |  |  |
| subjects affected / exposed                       | 1 / 80 (1.25%)           |  |  |
| occurrences causally related to treatment / all   | 1 / 1                    |  |  |
| deaths causally related to treatment / all        | 0 / 0                    |  |  |
| Blood Alkaline Phosphatase Increased              |                          |  |  |
| subjects affected / exposed                       | 1 / 80 (1.25%)           |  |  |
| occurrences causally related to treatment / all   | 0 / 2                    |  |  |
| deaths causally related to treatment / all        | 0 / 0                    |  |  |
| Blood Amylase Increased                           |                          |  |  |
| subjects affected / exposed                       | 1 / 80 (1.25%)           |  |  |
| occurrences causally related to treatment / all   | 0 / 1                    |  |  |
| deaths causally related to treatment / all        | 0 / 0                    |  |  |
| Blood Albumin Decreased                           |                          |  |  |
| subjects affected / exposed                       | 1 / 80 (1.25%)           |  |  |
| occurrences causally related to treatment / all   | 0 / 0                    |  |  |
| deaths causally related to treatment / all        | 0 / 0                    |  |  |



|   |   |                |  |  |
|---|---|----------------|--|--|
| Nervous system disorders<br>Partial Seizures                    | subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
|   | occurrences causally related to treatment / all | 0 / 1          |  |  |
|   | deaths causally related to treatment / all      | 0 / 0          |  |  |
|   |   |                |  |  |
| General disorders and administration site conditions<br>Pyrexia | subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
|   | occurrences causally related to treatment / all | 0 / 1          |  |  |
|   | deaths causally related to treatment / all      | 0 / 0          |  |  |
|   |   |                |  |  |
| Blood and lymphatic system disorders<br>Febrile Neutropenia     | subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
|   | occurrences causally related to treatment / all | 0 / 1          |  |  |
|   | deaths causally related to treatment / all      | 0 / 0          |  |  |
|   |   |                |  |  |
| Gastrointestinal disorders                                      | Gastrointestinal Disorder                       |                |  |  |
|   | alternative assessment type: Systematic         |                |  |  |
|   | subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
|   | occurrences causally related to treatment / all | 0 / 1          |  |  |
|   | deaths causally related to treatment / all      | 0 / 0          |  |  |
|   |   |                |  |  |
|   | Gastrointestinal Fistula                        |                |  |  |
|   | subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
|   | occurrences causally related to treatment / all | 0 / 1          |  |  |
|   | deaths causally related to treatment / all      | 0 / 0          |  |  |
|   |   |                |  |  |
|   | Diarrhoea                                       |                |  |  |
|   | subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
|   | occurrences causally related to treatment / all | 0 / 1          |  |  |
|   | deaths causally related to treatment / all      | 0 / 0          |  |  |
|   |   |                |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Rales        | subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
|   | occurrences causally related to treatment / all | 0 / 1          |  |  |
|   | deaths causally related to treatment / all      | 0 / 0          |  |  |
|   |   |                |  |  |



|   |                |  |  |
|---|----------------|--|--|
| Skin and subcutaneous tissue disorders          |                |  |  |
| Ecchymosis                                      |                |  |  |
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Rash Maculo-Papular                             |                |  |  |
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Petechiae                                       |                |  |  |
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Arthritis                                       |                |  |  |
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Neck Pain                                       |                |  |  |
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Osteochondrosis                                 |                |  |  |
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Cellulitis                                      |                |  |  |
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hepatitis A                                     |                |  |  |



|   |                |  |  |  |
|---|----------------|--|--|--|
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Mastoiditis                                     |                |  |  |  |
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Osteomyelitis Chronic                           |                |  |  |  |
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Lobar Pneumonia                                 |                |  |  |  |
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pneumonia                                       |                |  |  |  |
| subjects affected / exposed                     | 5 / 80 (6.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 7          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pyothorax                                       |                |  |  |  |
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Endocarditis Bacterial                          |                |  |  |  |
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Isosporiasis                                    |                |  |  |  |
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Influenza                                       |                |  |  |  |



|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Herpes Zoster Disseminated                      |                |  |  |
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumonia Bacterial                             |                |  |  |
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Septic Shock                                    |                |  |  |
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Urinary Tract Infection                         |                |  |  |
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

|   |                          |  |  |
|---|--------------------------|--|--|
| <b>Non-serious adverse events</b>                     | Darunavir plus Ritonavir |  |  |
| Total subjects affected by non-serious adverse events |                          |  |  |
| subjects affected / exposed                           | 73 / 80 (91.25%)         |  |  |
| Investigations  |                          |  |  |
| International Normalised Ratio Increased              |                          |  |  |
| subjects affected / exposed                           | 4 / 80 (5.00%)           |  |  |
| occurrences (all)                                     | 4                        |  |  |
| Injury, poisoning and procedural complications        |                          |  |  |
| Excoriation   |                          |  |  |
| subjects affected / exposed                           | 4 / 80 (5.00%)           |  |  |
| occurrences (all)                                     | 4                        |  |  |
| Nervous system disorders                              |                          |  |  |



|   |                        |  |  |
|---|------------------------|--|--|
| Headache<br>subjects affected / exposed<br>occurrences (all)  | 10 / 80 (12.50%)<br>18 |  |  |
| Blood and lymphatic system disorders<br>Lymphadenopathy<br>subjects affected / exposed<br>occurrences (all)                       | 13 / 80 (16.25%)<br>28 |  |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)   | 8 / 80 (10.00%)<br>16  |  |  |
| General disorders and administration site conditions<br>Injection Site Nodule<br>subjects affected / exposed<br>occurrences (all) | 6 / 80 (7.50%)<br>8    |  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 22 / 80 (27.50%)<br>42 |  |  |
| Pain<br>subjects affected / exposed<br>occurrences (all)  | 5 / 80 (6.25%)<br>6    |  |  |
| Eye disorders<br>Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)   | 10 / 80 (12.50%)<br>11 |  |  |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)  | 6 / 80 (7.50%)<br>6    |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)   | 14 / 80 (17.50%)<br>20 |  |  |
| Abdominal Pain<br>subjects affected / exposed<br>occurrences (all)  | 10 / 80 (12.50%)<br>10 |  |  |
| Vomiting  |                        |  |  |



|  |                        |  |  |
|--|------------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 16 / 80 (20.00%)<br>18 |  |  |
| Respiratory, thoracic and mediastinal disorders  |                        |  |  |
| Cough  |                        |  |  |
| subjects affected / exposed                      | 18 / 80 (22.50%)       |  |  |
| occurrences (all)                                | 35                     |  |  |
| Asthma   |                        |  |  |
| subjects affected / exposed                      | 4 / 80 (5.00%)         |  |  |
| occurrences (all)                                | 7                      |  |  |
| Epistaxis  |                        |  |  |
| subjects affected / exposed                      | 7 / 80 (8.75%)         |  |  |
| occurrences (all)                                | 12                     |  |  |
| Bronchospasm                                     |                        |  |  |
| subjects affected / exposed                      | 7 / 80 (8.75%)         |  |  |
| occurrences (all)                                | 12                     |  |  |
| Pharyngolaryngeal Pain                           |                        |  |  |
| subjects affected / exposed                      | 5 / 80 (6.25%)         |  |  |
| occurrences (all)                                | 8                      |  |  |
| Rhinorrhoea                                      |                        |  |  |
| subjects affected / exposed                      | 4 / 80 (5.00%)         |  |  |
| occurrences (all)                                | 10                     |  |  |
| Wheezing   |                        |  |  |
| subjects affected / exposed                      | 4 / 80 (5.00%)         |  |  |
| occurrences (all)                                | 5                      |  |  |
| Nasal Congestion                                 |                        |  |  |
| subjects affected / exposed                      | 4 / 80 (5.00%)         |  |  |
| occurrences (all)                                | 6                      |  |  |
| Skin and subcutaneous tissue disorders           |                        |  |  |
| Rash   |                        |  |  |
| subjects affected / exposed                      | 6 / 80 (7.50%)         |  |  |
| occurrences (all)                                | 7                      |  |  |
| Acne   |                        |  |  |
| subjects affected / exposed                      | 8 / 80 (10.00%)        |  |  |
| occurrences (all)                                | 11                     |  |  |
| Musculoskeletal and connective tissue disorders  |                        |  |  |



|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| Arthralgia                  |                  |  |  |
| subjects affected / exposed | 4 / 80 (5.00%)   |  |  |
| occurrences (all)           | 6                |  |  |
| Infections and infestations |                  |  |  |
| Bronchitis                  |                  |  |  |
| subjects affected / exposed | 8 / 80 (10.00%)  |  |  |
| occurrences (all)           | 10               |  |  |
| Ear Infection               |                  |  |  |
| subjects affected / exposed | 7 / 80 (8.75%)   |  |  |
| occurrences (all)           | 12               |  |  |
| Herpes Zoster               |                  |  |  |
| subjects affected / exposed | 4 / 80 (5.00%)   |  |  |
| occurrences (all)           | 4                |  |  |
| Herpes Simplex              |                  |  |  |
| subjects affected / exposed | 14 / 80 (17.50%) |  |  |
| occurrences (all)           | 23               |  |  |
| Oral Candidiasis            |                  |  |  |
| subjects affected / exposed | 4 / 80 (5.00%)   |  |  |
| occurrences (all)           | 7                |  |  |
| Nasopharyngitis             |                  |  |  |
| subjects affected / exposed | 8 / 80 (10.00%)  |  |  |
| occurrences (all)           | 16               |  |  |
| Influenza                   |                  |  |  |
| subjects affected / exposed | 4 / 80 (5.00%)   |  |  |
| occurrences (all)           | 6                |  |  |
| Impetigo                    |                  |  |  |
| subjects affected / exposed | 7 / 80 (8.75%)   |  |  |
| occurrences (all)           | 8                |  |  |
| Rhinitis                    |                  |  |  |
| subjects affected / exposed | 7 / 80 (8.75%)   |  |  |
| occurrences (all)           | 10               |  |  |
| Pharyngitis                 |                  |  |  |
| subjects affected / exposed | 6 / 80 (7.50%)   |  |  |
| occurrences (all)           | 7                |  |  |
| Otitis Media                |                  |  |  |



|                                   |                  |  |  |
|-----------------------------------|------------------|--|--|
| subjects affected / exposed       | 8 / 80 (10.00%)  |  |  |
| occurrences (all)                 | 9                |  |  |
| Pneumonia                         |                  |  |  |
| subjects affected / exposed       | 13 / 80 (16.25%) |  |  |
| occurrences (all)                 | 15               |  |  |
| Tracheobronchitis                 |                  |  |  |
| subjects affected / exposed       | 5 / 80 (6.25%)   |  |  |
| occurrences (all)                 | 7                |  |  |
| Upper Respiratory Tract Infection |                  |  |  |
| subjects affected / exposed       | 21 / 80 (26.25%) |  |  |
| occurrences (all)                 | 42               |  |  |
| Sinusitis                         |                  |  |  |
| subjects affected / exposed       | 10 / 80 (12.50%) |  |  |
| occurrences (all)                 | 14               |  |  |
| Tonsillitis                       |                  |  |  |
| subjects affected / exposed       | 13 / 80 (16.25%) |  |  |
| occurrences (all)                 | 19               |  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment   |
|---------------|---|
| 18 April 2007 | The overall reason for the amendment was to adapt extension of the TMC114-C212 trial after Week 48 for participants less than or equal to ( $\leq$ ) 18 years at the moment of reaching the week 48 visit, who continue to benefit from treatment with darunavir (DRV)/ritonavir (rtv) and who are living in a region where DRV pediatric use is not yet part of the label. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported