



## Clinical trial results:

### A Prospective Single Arm, Open-label, International, Multicenter Study to Evaluate the Safety of Atazanavir (ATV) Capsule Boosted with Ritonavir (RTV) with an Optimized NRTI Background Therapy, in HIV Infected, Antiretroviral Naive and Experienced Pediatric Subjects Greater Than or Equal to 6 Years to Less Than 18 Years

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2011-003300-21 |
| Trial protocol           | Outside EU/EEA |
| Global end of trial date |                |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1            |
| This version publication date  | 27 April 2016 |
| First version publication date | 27 April 2016 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | AI424-452 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01691794 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Bristol-Myers Squibb   |
| Sponsor organisation address | Chaussée de la Hulpe 185, Brussels, Belgium, 1170                                  |
| Public contact               | Bristol Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com |
| Scientific contact           | Bristol Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com |

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                                       | Interim          |
| Date of interim/final analysis                       | 05 December 2014 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 05 December 2014 |
| Global end of trial reached?                         | No               |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the study was to assess the safety and tolerability of atazanavir capsule boosted with ritonavir based regimens in pediatric subjects ages  $\geq 6$  years to  $<18$  years dosed for 24 weeks.

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 Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy:

2 Nucleoside reverse-transcriptase inhibitors (NRTI) were used as a background therapy in this study. NRTIs like zidovudine, stavudine, lamivudine, ritonavir, nelfinavir, nevirapine, lopinavir, indinavir, and efavirenz were prescribed based on viral resistance results, the local guidelines for antiretroviral treatment, and subject's treatment history.

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 29 November 2012 |
| 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 | Peru: 14              |
| Country: Number of subjects enrolled | Brazil: 14            |
| Country: Number of subjects enrolled | Russian Federation: 1 |
| Country: Number of subjects enrolled | United States: 5      |
| Country: Number of subjects enrolled | South Africa: 59      |
| Country: Number of subjects enrolled | Argentina: 6          |
| Country: Number of subjects enrolled | Mexico: 6             |
| Country: Number of subjects enrolled | Chile: 3              |
| Worldwide total number of subjects   | 108                   |
| EEA total number of subjects         | 0                     |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                    | 0 |
| Preterm newborn - gestational age $< 37$ wk | 0 |
| Newborns (0-27 days)                        | 0 |

|  |    |
|--|----|
| Infants and toddlers (28 days-23 months) | 0  |
| Children (2-11 years)                    | 50 |
| Adolescents (12-17 years)                | 58 |
| 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 22 study centers in 8 countries.

### Pre-assignment

Screening details:

Overall, 108 subjects were enrolled, and 59 received treatment. Reasons for not entering the treatment period: 1 subject withdrew consent, 1 lost to follow-up, 46 subjects no longer meets study criteria, 1 other reasons.

### Period 1

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

### Arms

|                              |   |
|------------------------------|---|
| Are arms mutually exclusive? | Yes   |
| <b>Arm title</b>             | Atazanavir, 150 mg + Ritonavir, 100 mg (Weight: 15 to <20 kg) |

Arm description:

Subjects with baseline weight of 15 to <20 kg received 150 mg of atazanavir plus 100 mg of ritonavir once daily with an optimized background therapy of 2 nucleoside reverse transcriptase inhibitors (NRTIs) for 24 weeks. In countries without locally approved pediatric indication for atazanavir, subjects may continue to receive study treatment, with regular 12-week visits, until the age of 18 years.

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Atazanavir    |
| Investigational medicinal product code | BMS-232632    |
| Other name                             | Reyataz™      |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

Atazanavir capsule 150-mg were administered orally once daily with food.

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

Dosage and administration details:

Ritonavir 100-mg capsule or tablet were administered orally once daily with food.

|                  |   |
|------------------|---|
| <b>Arm title</b> | Atazanavir, 200 mg + Ritonavir, 100 mg (Weight: 20 to <40 kg) |
|------------------|---|

Arm description:

Subjects with baseline weight of 20 to <40 kg received 200 mg of atazanavir plus 100 mg of ritonavir once daily with an optimized background therapy of 2 NRTIs for 24 weeks. In countries without locally approved pediatric indication for atazanavir, subjects may continue to receive study treatment, with regular 12-week visits, until the age of 18 years.

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Atazanavir    |
| Investigational medicinal product code | BMS-232632    |
| Other name                             | Reyataz™      |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

Atazanavir capsule 200-mg were administered orally once daily with food.

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

Dosage and administration details:

Ritonavir 100-mg capsule or tablet were administered orally once daily with food.

|                  |   |
|------------------|---|
| <b>Arm title</b> | Atazanavir, 300 mg + Ritonavir, 100 mg (Weight: $\geq 40$ kg) |
|------------------|---|

Arm description:

Subjects with baseline weight  $\geq 40$  kg received 300 mg of atazanavir plus 100 mg of ritonavir once daily with an optimized background therapy of 2 NRTIs for 24 weeks. In countries without locally approved pediatric indication for atazanavir, subjects may continue to receive study treatment, with regular 12-week visits, until the age of 18 years.

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Atazanavir    |
| Investigational medicinal product code | BMS-232632    |
| Other name                             | Reyataz™      |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

Atazanavir capsule 300-mg were administered orally once daily with food.

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

Dosage and administration details:

Ritonavir 100-mg capsule or tablet were administered orally once daily with food.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Atazanavir, 150 mg + Ritonavir, 100 mg (Weight: 15 to $< 20$ kg) | Atazanavir, 200 mg + Ritonavir, 100 mg (Weight: 20 to $< 40$ kg) | Atazanavir, 300 mg + Ritonavir, 100 mg (Weight: $\geq 40$ kg) |
|---|--|--|---|
| Started   | 3  | 33   | 23  |
| Completed   | 3  | 30   | 20  |
| Not completed                                       | 0  | 3  | 3   |
| Adverse event, non-fatal                            | -  | -  | 1   |
| Subject no longer meets study criteria              | -  | 2  | -   |
| Poor/non-compliance                                 | -  | -  | 1   |
| Lack of efficacy                                    | -  | 1  | 1   |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Out of 108 subjects who were enrolled, only 59 entered treatment period. Reason for not entering treatment period were: Subject no longer meets study criteria - 46, subject withdrew consent - 1, lost to follow-up - 1, other reason - 1.

## Baseline characteristics

### Reporting groups

|  |   |
|--|---|
| Reporting group title  | Atazanavir, 150 mg + Ritonavir, 100 mg (Weight: 15 to <20 kg) |
| Reporting group description:<br>Subjects with baseline weight of 15 to <20 kg received 150 mg of atazanavir plus 100 mg of ritonavir once daily with an optimized background therapy of 2 nucleoside reverse transcriptase inhibitors (NRTIs) for 24 weeks. In countries without locally approved pediatric indication for atazanavir, subjects may continue to receive study treatment, with regular 12-week visits, until the age of 18 years. |   |
| Reporting group title  | Atazanavir, 200 mg + Ritonavir, 100 mg (Weight: 20 to <40 kg) |
| Reporting group description:<br>Subjects with baseline weight of 20 to <40 kg received 200 mg of atazanavir plus 100 mg of ritonavir once daily with an optimized background therapy of 2 NRTIs for 24 weeks. In countries without locally approved pediatric indication for atazanavir, subjects may continue to receive study treatment, with regular 12-week visits, until the age of 18 years.   |   |
| Reporting group title  | Atazanavir, 300 mg + Ritonavir, 100 mg (Weight: ≥40 kg)       |
| Reporting group description:<br>Subjects with baseline weight ≥40 kg received 300 mg of atazanavir plus 100 mg of ritonavir once daily with an optimized background therapy of 2 NRTIs for 24 weeks. In countries without locally approved pediatric indication for atazanavir, subjects may continue to receive study treatment, with regular 12-week visits, until the age of 18 years.  |   |

| Reporting group values             | Atazanavir, 150 mg + Ritonavir, 100 mg (Weight: 15 to <20 kg) | Atazanavir, 200 mg + Ritonavir, 100 mg (Weight: 20 to <40 kg) | Atazanavir, 300 mg + Ritonavir, 100 mg (Weight: ≥40 kg) |
|------------------------------------|---|---|---|
| Number of subjects                 | 3   | 33  | 23  |
| Age categorical<br>Units: Subjects |   |   |   |

|   |     |        |        |
|---|-----|--------|--------|
| Age continuous<br>Units: years                |     |        |        |
| arithmetic mean                               | 6   | 10.7   | 14.7   |
| standard deviation                            | ± 0 | ± 2.67 | ± 1.72 |
| Gender categorical<br>Units: Subjects         |     |        |        |
| Female  | 2   | 17     | 11     |
| Male  | 1   | 16     | 12     |
| Ethnicity (NIH/OMB)<br>Units: Subjects        |     |        |        |
| Hispanic or Latino                            | 0   | 1      | 2      |
| Not Hispanic or Latino                        | 1   | 2      | 2      |
| Unknown or Not Reported                       | 2   | 30     | 19     |
| Race/Ethnicity, Customized<br>Units: Subjects |     |        |        |
| White   | 1   | 5      | 4      |
| Black/African American                        | 2   | 24     | 9      |
| Other   | 0   | 4      | 10     |
| Region of Enrollment<br>Units: Subjects       |     |        |        |
| Africa  | 2   | 24     | 8      |

|                            |   |    |    |
|----------------------------|---|----|----|
| Europe                     | 0 | 1  | 0  |
| North America              | 1 | 0  | 3  |
| South America              | 0 | 8  | 12 |
| Country<br>Units: Subjects |   |    |    |
| Argentina                  | 0 | 3  | 0  |
| Brazil                     | 0 | 3  | 4  |
| Chile                      | 0 | 1  | 2  |
| Mexico                     | 1 | 0  | 1  |
| Peru                       | 0 | 1  | 6  |
| Russia                     | 0 | 1  | 0  |
| South Africa               | 2 | 24 | 8  |
| United States              | 0 | 0  | 2  |

|                                    |       |  |  |
|------------------------------------|-------|--|--|
| <b>Reporting group values</b>      | Total |  |  |
| Number of subjects                 | 59    |  |  |
| Age categorical<br>Units: Subjects |       |  |  |

|   |    |  |  |
|---|----|--|--|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -  |  |  |
| Gender categorical<br>Units: Subjects                                   |    |  |  |
| Female  | 30 |  |  |
| Male  | 29 |  |  |
| Ethnicity (NIH/OMB)<br>Units: Subjects                                  |    |  |  |
| Hispanic or Latino  | 3  |  |  |
| Not Hispanic or Latino  | 5  |  |  |
| Unknown or Not Reported   | 51 |  |  |
| Race/Ethnicity, Customized<br>Units: Subjects                           |    |  |  |
| White   | 10 |  |  |
| Black/African American  | 35 |  |  |
| Other   | 14 |  |  |
| Region of Enrollment<br>Units: Subjects                                 |    |  |  |
| Africa  | 34 |  |  |
| Europe  | 1  |  |  |
| North America   | 4  |  |  |
| South America   | 20 |  |  |
| Country<br>Units: Subjects  |    |  |  |
| Argentina   | 3  |  |  |
| Brazil  | 7  |  |  |
| Chile   | 3  |  |  |
| Mexico  | 2  |  |  |
| Peru  | 7  |  |  |
| Russia  | 1  |  |  |

|               |    |  |  |
|---------------|----|--|--|
| South Africa  | 34 |  |  |
| United States | 2  |  |  |



## End points

### End points reporting groups

|  |   |
|--|---|
| Reporting group title  | Atazanavir, 150 mg + Ritonavir, 100 mg (Weight: 15 to <20 kg) |
| Reporting group description:<br>Subjects with baseline weight of 15 to <20 kg received 150 mg of atazanavir plus 100 mg of ritonavir once daily with an optimized background therapy of 2 nucleoside reverse transcriptase inhibitors (NRTIs) for 24 weeks. In countries without locally approved pediatric indication for atazanavir, subjects may continue to receive study treatment, with regular 12-week visits, until the age of 18 years. |   |
| Reporting group title  | Atazanavir, 200 mg + Ritonavir, 100 mg (Weight: 20 to <40 kg) |
| Reporting group description:<br>Subjects with baseline weight of 20 to <40 kg received 200 mg of atazanavir plus 100 mg of ritonavir once daily with an optimized background therapy of 2 NRTIs for 24 weeks. In countries without locally approved pediatric indication for atazanavir, subjects may continue to receive study treatment, with regular 12-week visits, until the age of 18 years.   |   |
| Reporting group title  | Atazanavir, 300 mg + Ritonavir, 100 mg (Weight: ≥40 kg)       |
| Reporting group description:<br>Subjects with baseline weight ≥40 kg received 300 mg of atazanavir plus 100 mg of ritonavir once daily with an optimized background therapy of 2 NRTIs for 24 weeks. In countries without locally approved pediatric indication for atazanavir, subjects may continue to receive study treatment, with regular 12-week visits, until the age of 18 years.  |   |

### Primary: Number of Subjects Who Died and With Serious Adverse Events (SAEs), Adverse Events (AEs) Leading to Discontinuation, Grade 2-4 Related AEs, Grade 3-4 AEs, Cardiac Abnormalities, and Centers for Disease Control (CDC) Class C AIDS Events

|  |  |
|--|--|
| End point title  | Number of Subjects Who Died and With Serious Adverse Events (SAEs), Adverse Events (AEs) Leading to Discontinuation, Grade 2-4 Related AEs, Grade 3-4 AEs, Cardiac Abnormalities, and Centers for Disease Control (CDC) Class C AIDS Events <sup>[1]</sup> |
| End point description:<br>AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Related=having certain, probable, possible, or unknown relationship to study drug. Grade 1=Mild, Grade 2=Moderate, Grade 3=Severe, Grade 4=Life-threatening or disabling, Grade 5=Death. The analysis was performed in all the subjects who received at least 1 dose of study drug. |  |
| End point type   | Primary  |
| End point timeframe:<br>Day 1 of treatment through Week 24   |  |

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive summary statistics were planned for this outcome measure.

| End point values            | Atazanavir, 150 mg + Ritonavir, 100 mg (Weight: 15 to <20 kg) | Atazanavir, 200 mg + Ritonavir, 100 mg (Weight: 20 to <40 kg) | Atazanavir, 300 mg + Ritonavir, 100 mg (Weight: ≥40 kg) |  |
|-----------------------------|---|---|---|--|
| Subject group type          | Reporting group   | Reporting group   | Reporting group   |  |
| Number of subjects analysed | 3   | 33  | 23  |  |
| Units: Subjects             |   |   |   |  |

|                                |   |    |   |  |
|--------------------------------|---|----|---|--|
| Death                          | 0 | 0  | 0 |  |
| SAEs                           | 0 | 1  | 3 |  |
| AEs leading to discontinuation | 0 | 1  | 1 |  |
| Grade 2-4 related AEs          | 0 | 22 | 7 |  |
| Grade 3-4 AEs                  | 0 | 3  | 5 |  |
| CDC Class C AIDS events        | 0 | 1  | 0 |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Laboratory Test Results Meeting the Criteria for Abnormal, Grades 1-4

|                 |  |
|-----------------|--|
| End point title | Number of Subjects With Laboratory Test Results Meeting the Criteria for Abnormal, Grades 1-4 <sup>[2]</sup> |
|-----------------|--|

End point description:

Hematocrit (%): Grade (Gr) 1=  $\geq 28.5$ -  $< 31.5$ ; Gr 2=  $\geq 24$ -  $< 28.5$ ; Gr 3=  $\geq 19.5$ -  $< 24$ ; Gr 4=  $< 19.5$ . Hemoglobin (g/dL): Grade (Gr) 1=8.5-10.0; Gr 2=7.5-8.4; Gr 3=6.50-7.4; Gr 4=  $< 6.5$ . Platelets (/mm<sup>3</sup>): Gr 1=100,000-124,999; Gr 2=50,000-99,999; Gr 3=25,000-49,999; Gr 4=  $< 25,000$ . White blood cells (/mm<sup>3</sup>): Gr 1=2000-2500; Gr 2=1500-1999; Gr 3=1000-1499; Gr 4=  $< 1000$ . Neutrophils (/mm<sup>3</sup>): Gr 1=1000-1500; Gr 2=  $\geq 750$ -1000; Gr 3=  $\geq 500$ -750; Gr 4=  $< 500$ . Alanine transaminase (ALT), alkaline phosphatase (ALP), aspartate transaminase (AST) (\*upper limit of normal [ULN]): Gr 1=1.5-2.5; Gr 2=2.6-5.0; Gr 3=5.1-10.0; Gr 4=  $> 10.0$ . Total bilirubin (adult and pediatric  $> 14$  days) (\*ULN): Gr 1=1.1-1.5; Gr 2=1.6-2.5; Gr 3=2.6-5.0; Gr 4=  $> 5.0$ . Albumin (g/dL): Gr 1= 3.1- $< LLN$ ; Gr 2=2.0-2.9; Gr 3=  $< 2.0$ ; Gr 4=NA. Amylase (\*ULN): Gr 1=1.10-1.39; Gr 2=1.40-2.09; Gr 3=2.10-5.0; Gr 4=  $> 5$ . Lipase (\*ULN): Gr 1=1.1-1.5; Gr 2=1.6-3.0; Gr 3=3.1-5.0; Gr 4=  $> 5.0$ . Analysis was performed in all subjects treated with study drug.

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

End point timeframe:

Day 1 of treatment to Week 24

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive summary statistics were planned for this outcome measure.

| End point values             | Atazanavir, 150 mg + Ritonavir, 100 mg (Weight: 15 to $< 20$ kg) | Atazanavir, 200 mg + Ritonavir, 100 mg (Weight: 20 to $< 40$ kg) | Atazanavir, 300 mg + Ritonavir, 100 mg (Weight: $\geq 40$ kg) |  |
|------------------------------|--|--|---|--|
| Subject group type           | Reporting group  | Reporting group  | Reporting group   |  |
| Number of subjects analysed  | 3  | 33   | 23  |  |
| Units: Subjects              |  |  |   |  |
| Hematocrit                   | 0  | 3  | 0   |  |
| Hemoglobin                   | 0  | 5  | 0   |  |
| Platelets                    | 0  | 0  | 1   |  |
| White blood cells            | 0  | 2  | 0   |  |
| Neutrophils+bands (absolute) | 0  | 11   | 3   |  |
| ALT                          | 1  | 3  | 7   |  |
| AST                          | 0  | 2  | 4   |  |
| ALP                          | 0  | 6  | 10  |  |
| Total bilirubin              | 2  | 20   | 15  |  |
| Albumin                      | 0  | 1  | 0   |  |
| Amylase                      | 2  | 27   | 14  |  |

|        |   |    |   |  |
|--------|---|----|---|--|
| Lipase | 0 | 11 | 7 |  |
|--------|---|----|---|--|

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Laboratory Test Results Meeting the Criteria for Abnormal, Grades 1-4 (Continued)

|                 |  |
|-----------------|--|
| End point title | Number of Subjects With Laboratory Test Results Meeting the Criteria for Abnormal, Grades 1-4 (Continued) <sup>[3]</sup> |
|-----------------|--|

End point description:

Blood urea nitrogen (\*upper limit of normal [ULN]): Grade (Gr) 1=1.25-2.5; Gr 2=2.6-5.0; Gr 3=5.1-10; Gr 4= >10. Uric acid (mg/dL): Gr 1=7.5-10.0; Gr 2=10.1-12; Gr 3=12.1-15.0; Gr 4= >15.0. Bicarbonate (mEq/L): Gr 1= 19.0-21.0; Gr 2=15.0-18.0; Gr 3=41-45; Gr 4= >45. Calcium, low (mg/dL): Gr 1=7.8-8.4; Gr 2=7.0-7.7; Gr 3=6.1-6.9; Gr 4= <6.1. Potassium (mEq/L), high: Gr 1=5.6-6.0; Gr 2=6.1-6.5; Gr 3=6.6-7.0; Gr 4= >7.0. Potassium (mEq/L), low: Gr 1=3.1-3.4; Gr 2=2.5-2.9; Gr 3=2.0-2.4; Gr 4= <2.0. Sodium (mEq/L), low: Gr 1=130-135; Gr 2=125-129; Gr 3=121-124; Gr 4= <1. Total cholesterol, fasting (mg/dL): Gr 1=200-239; Gr 2=240-300; Gr 3= >300; Gr 4=Not applicable (NA). Low-density lipoprotein (LDL) cholesterol, fasting (mg/dL): Gr 1=130-159; Gr 2=160-190; Gr 3= >190; Gr 4= NA. Glucose, low (mg/dL): Gr 1= 55-64; Gr 2=40-54; Gr 3=30-39; Gr 4= <30. Glucose, fasting (mg/dL): Gr 1=110-125; Gr 2=126-250; Gr 3=251-500; Gr 4 >500. The analysis was performed in all subjects treated with study drug.

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

End point timeframe:

Day 1 of treatment through Week 24

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive summary statistics were planned for this outcome measure.

| End point values                         | Atazanavir, 150 mg + Ritonavir, 100 mg (Weight: 15 to <20 kg) | Atazanavir, 200 mg + Ritonavir, 100 mg (Weight: 20 to <40 kg) | Atazanavir, 300 mg + Ritonavir, 100 mg (Weight: >=40 kg) |  |
|--|---|---|--|--|
| Subject group type                       | Reporting group   | Reporting group   | Reporting group  |  |
| Number of subjects analysed              | 3   | 33  | 23   |  |
| Units: Subjects                          |   |   |  |  |
| Blood urea nitrogen                      | 0   | 1   | 0  |  |
| Uric acid                                | 0   | 0   | 3  |  |
| Bicarbonate, low                         | 3   | 26  | 13   |  |
| Calcium, low                             | 0   | 2   | 0  |  |
| Potassium, high                          | 0   | 1   | 0  |  |
| Potassium, low                           | 0   | 1   | 0  |  |
| Total cholesterol, fasting (n=3, 31, 21) | 0   | 4   | 3  |  |
| Sodium, low                              | 1   | 11  | 0  |  |
| LDL cholesterol, fasting (n=3, 31, 21)   | 0   | 2   | 1  |  |
| Glucose, low (n=1, 11, 9)                | 0   | 3   | 0  |  |
| Glucose, fasting, high (3, 31, 22)       | 0   | 2   | 1  |  |

## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days after the last dose of the study drug

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Atazanavir, 150 mg + Ritonavir, 100 mg (Weight: 15 to <20 kg) |
|-----------------------|---|

Reporting group description:

Subjects with baseline weight of 15 to <20 kg received 150 mg of atazanavir plus 100 mg of ritonavir once daily with an optimized background therapy of 2 nucleoside reverse transcriptase inhibitors (NRTIs) for 24 weeks. In countries without locally approved pediatric indication for atazanavir, subjects may continue to receive study treatment, with regular 12-week visits, until the age of 18 years.

|                       |   |
|-----------------------|---|
| Reporting group title | Atazanavir, 200 mg + Ritonavir, 100 mg (Weight: 20 to <40 kg) |
|-----------------------|---|

Reporting group description:

Subjects with baseline weight of 20 to <40 kg received 200 mg of atazanavir plus 100 mg of ritonavir once daily with an optimized background therapy of 2 NRTIs for 24 weeks. In countries without locally approved pediatric indication for atazanavir, subjects may continue to receive study treatment, with regular 12-week visits, until the age of 18 years.

|                       |   |
|-----------------------|---|
| Reporting group title | Atazanavir, 300 mg + Ritonavir, 100 mg (Weight: ≥40 kg) |
|-----------------------|---|

Reporting group description:

Subjects with baseline weight ≥40 kg received 300 mg of atazanavir plus 100 mg of ritonavir once daily with an optimized background therapy of 2 NRTIs for 24 weeks. In countries without locally approved pediatric indication for atazanavir, subjects may continue to receive study treatment, with regular 12-week visits, until the age of 18 years.

| <b>Serious adverse events</b>                     | Atazanavir, 150 mg + Ritonavir, 100 mg (Weight: 15 to <20 kg) | Atazanavir, 200 mg + Ritonavir, 100 mg (Weight: 20 to <40 kg) | Atazanavir, 300 mg + Ritonavir, 100 mg (Weight: ≥40 kg) |
|---|---|---|---|
| Total subjects affected by serious adverse events |   |   |   |
| subjects affected / exposed                       | 0 / 3 (0.00%)   | 1 / 33 (3.03%)  | 3 / 23 (13.04%)   |
| number of deaths (all causes)                     | 0   | 0   | 0   |
| number of deaths resulting from adverse events    |   |   |   |
| Injury, poisoning and procedural complications    |   |   |   |
| Overdose  |   |   |   |
| subjects affected / exposed                       | 0 / 3 (0.00%)   | 1 / 33 (3.03%)  | 0 / 23 (0.00%)  |
| occurrences causally related to treatment / all   | 0 / 0   | 0 / 1   | 0 / 0   |
| deaths causally related to treatment / all        | 0 / 0   | 0 / 0   | 0 / 0   |
| Gastrointestinal disorders                        |   |   |   |
| Abdominal pain                                    |   |   |   |

|   |               |                |                |
|---|---------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 33 (0.00%) | 1 / 23 (4.35%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| <b>Hepatobiliary disorders</b>                  |               |                |                |
| Hyperbilirubinaemia                             |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 33 (3.03%) | 0 / 23 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 2 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| <b>Psychiatric disorders</b>                    |               |                |                |
| Abnormal behaviour                              |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 33 (0.00%) | 1 / 23 (4.35%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| <b>Infections and infestations</b>              |               |                |                |
| Appendicitis                                    |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 33 (0.00%) | 1 / 23 (4.35%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |

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

| <b>Non-serious adverse events</b>                     | Atazanavir, 150 mg + Ritonavir, 100 mg (Weight: 15 to <20 kg) | Atazanavir, 200 mg + Ritonavir, 100 mg (Weight: 20 to <40 kg) | Atazanavir, 300 mg + Ritonavir, 100 mg (Weight: ≥40 kg) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events |   |   |   |
| subjects affected / exposed                           | 3 / 3 (100.00%)   | 26 / 33 (78.79%)  | 19 / 23 (82.61%)  |
| <b>Injury, poisoning and procedural complications</b> |   |   |   |
| Head injury   |   |   |   |
| subjects affected / exposed                           | 1 / 3 (33.33%)  | 0 / 33 (0.00%)  | 0 / 23 (0.00%)  |
| occurrences (all)                                     | 1   | 0   | 0   |
| <b>Cardiac disorders</b>                              |   |   |   |
| Sinus arrhythmia                                      |   |   |   |
| subjects affected / exposed                           | 0 / 3 (0.00%)   | 2 / 33 (6.06%)  | 0 / 23 (0.00%)  |
| occurrences (all)                                     | 0   | 2   | 0   |
| Sinus bradycardia                                     |   |   |   |

|  |               |                 |                 |
|--|---------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 3 (0.00%) | 0 / 33 (0.00%)  | 2 / 23 (8.70%)  |
| occurrences (all)                                    | 0             | 0               | 2               |
| Atrioventricular block first degree                  |               |                 |                 |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 2 / 33 (6.06%)  | 0 / 23 (0.00%)  |
| occurrences (all)                                    | 0             | 3               | 0               |
| Nervous system disorders                             |               |                 |                 |
| Headache   |               |                 |                 |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 3 / 33 (9.09%)  | 2 / 23 (8.70%)  |
| occurrences (all)                                    | 0             | 3               | 3               |
| Blood and lymphatic system disorders                 |               |                 |                 |
| Neutropenia  |               |                 |                 |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 2 / 33 (6.06%)  | 1 / 23 (4.35%)  |
| occurrences (all)                                    | 0             | 2               | 1               |
| General disorders and administration site conditions |               |                 |                 |
| Pyrexia  |               |                 |                 |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 2 / 33 (6.06%)  | 0 / 23 (0.00%)  |
| occurrences (all)                                    | 0             | 2               | 0               |
| Ear and labyrinth disorders                          |               |                 |                 |
| Tympanic membrane perforation                        |               |                 |                 |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 2 / 33 (6.06%)  | 0 / 23 (0.00%)  |
| occurrences (all)                                    | 0             | 2               | 0               |
| Eye disorders  |               |                 |                 |
| Ocular icterus                                       |               |                 |                 |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 0 / 33 (0.00%)  | 2 / 23 (8.70%)  |
| occurrences (all)                                    | 0             | 0               | 2               |
| Gastrointestinal disorders                           |               |                 |                 |
| Vomiting   |               |                 |                 |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 7 / 33 (21.21%) | 3 / 23 (13.04%) |
| occurrences (all)                                    | 0             | 9               | 3               |
| Abdominal pain                                       |               |                 |                 |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 1 / 33 (3.03%)  | 5 / 23 (21.74%) |
| occurrences (all)                                    | 0             | 1               | 5               |
| Nausea   |               |                 |                 |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 2 / 33 (6.06%)  | 4 / 23 (17.39%) |
| occurrences (all)                                    | 0             | 2               | 5               |
| Diarrhoea  |               |                 |                 |

|  |                     |                       |                      |
|--|---------------------|-----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 2 / 33 (6.06%)<br>2   | 1 / 23 (4.35%)<br>1  |
| Toothache<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0  | 2 / 33 (6.06%)<br>2   | 0 / 23 (0.00%)<br>0  |
| Hepatobiliary disorders<br>Hyperbilirubinaemia<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 3 (0.00%)<br>0  | 2 / 33 (6.06%)<br>2   | 5 / 23 (21.74%)<br>6 |
| Jaundice<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 1 / 33 (3.03%)<br>1   | 6 / 23 (26.09%)<br>9 |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)         | 0 / 3 (0.00%)<br>0  | 8 / 33 (24.24%)<br>9  | 2 / 23 (8.70%)<br>2  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)   | 1 / 3 (33.33%)<br>1 | 0 / 33 (0.00%)<br>0   | 0 / 23 (0.00%)<br>0  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0  | 2 / 33 (6.06%)<br>2   | 0 / 23 (0.00%)<br>0  |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 3 (0.00%)<br>0  | 4 / 33 (12.12%)<br>4  | 2 / 23 (8.70%)<br>2  |
| Dermatitis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 2 / 33 (6.06%)<br>2   | 0 / 23 (0.00%)<br>0  |
| Infections and infestations<br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 2 / 3 (66.67%)<br>3 | 9 / 33 (27.27%)<br>13 | 2 / 23 (8.70%)<br>2  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 3 (33.33%)<br>1 | 3 / 33 (9.09%)<br>6   | 6 / 23 (26.09%)<br>7 |



|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Influenza                   |                |                |                |
| subjects affected / exposed | 1 / 3 (33.33%) | 3 / 33 (9.09%) | 2 / 23 (8.70%) |
| occurrences (all)           | 2              | 3              | 3              |
| Otitis media                |                |                |                |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 33 (6.06%) | 1 / 23 (4.35%) |
| occurrences (all)           | 1              | 2              | 1              |
| Tonsillitis                 |                |                |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 2 / 33 (6.06%) | 0 / 23 (0.00%) |
| occurrences (all)           | 0              | 2              | 0              |
| Bronchitis                  |                |                |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 2 / 33 (6.06%) | 0 / 23 (0.00%) |
| occurrences (all)           | 0              | 2              | 0              |
| Impetigo                    |                |                |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 33 (0.00%) | 2 / 23 (8.70%) |
| occurrences (all)           | 0              | 0              | 2              |
| Pharyngotonsillitis         |                |                |                |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 33 (0.00%) | 0 / 23 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Gastroenteritis             |                |                |                |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 33 (3.03%) | 0 / 23 (0.00%) |
| occurrences (all)           | 1              | 1              | 0              |
| Pharyngitis                 |                |                |                |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 33 (3.03%) | 0 / 23 (0.00%) |
| occurrences (all)           | 1              | 1              | 0              |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported