# Clinical trial results:
# A Phase 1, Single-dose Study to Evaluate the Relative Bioavailability of Cobicistat (COBI) Age-Appropriate Pediatric Tablet Formulations Compared with Adult COBI 150-mg Tablets in Healthy Adult Volunteers

## Summary

| | |
|---|---|
| EudraCT number | 2015-000466-57 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 05 January 2013 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 22 March 2016 |
| First version publication date | 22 July 2015 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | GS-US-216-0127 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | IND Number: 101283 |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Gilead Sciences |
| Sponsor organisation address | 333 Lakeside Drive, Foster City, CA, United States, 94404 |
| Public contact | Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com |
| Scientific contact | Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-000969-PIP01-10 |
| 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 | 05 January 2013 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 05 January 2013 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

This study was to evaluate the relative bioavailability of 2 age-appropriate pediatric formulations (immediate release tablet or dispersible tablet as suspension) of cobicistat (COBI) in healthy adult participants.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

| |
|---|
| Background therapy: - |
| Evidence for comparator: - |

| | |
|---|---|
| Actual start date of recruitment | 13 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 | United States: 62 |
| Worldwide total number of subjects | 62 |
| EEA total number of subjects | 0 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |

| | |
|---|---|
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 62 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled at a single study site in the United States. The first participant was screened on 13 November 2012. The last study visit occurred on 05 January 2013.

### Pre-assignment

Screening details:

120 participants were screened.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Cohort 1 |

Arm description:

COBI 1 x 150 mg adult immediate release tablet (Treatment A) or COBI 3 x 50 mg age-appropriate pediatric immediate release tablet (Treatment B)

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Cobicistat |
| Investigational medicinal product code | |
| Other name | Tybost®, GS-9350 |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

COBI 150 mg adult immediate release tablet, 50 mg age-appropriate pediatric immediate release tablet, or 20 mg age-appropriate pediatric dispersible tablet as suspension formulation administered orally in the morning immediately after a standard meal

| | |
|---|---|
| **Arm title** | Cohort 2 |

Arm description:

COBI 1 x 150 mg adult immediate release tablet (Treatment A) or COBI 7.5 x 20 mg age-appropriate pediatric dispersible tablet (Treatment C)

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Cobicistat |
| Investigational medicinal product code | |
| Other name | Tybost®, GS-9350 |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

COBI 150 mg adult immediate release tablet, 50 mg age-appropriate pediatric immediate release tablet, or 20 mg age-appropriate pediatric dispersible tablet as suspension formulation administered orally in the morning immediately after a standard meal

| **Number of subjects in period 1** | Cohort 1 | Cohort 2 |
|---|---|---|
| Started | 32 | 30 |
| Completed | 30 | 29 |
| Not completed | 2 | 1 |
| Subject withdrew consent | 1 | - |
| Protocol violation | 1 | - |
| Lost to follow-up | - | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Cohort 1 |
| Reporting group description: | |
| COBI 1 x 150 mg adult immediate release tablet (Treatment A) or COBI 3 x 50 mg age-appropriate pediatric immediate release tablet (Treatment B) | |
| Reporting group title | Cohort 2 |
| Reporting group description: | |
| COBI 1 x 150 mg adult immediate release tablet (Treatment A) or COBI 7.5 x 20 mg age-appropriate pediatric dispersible tablet (Treatment C) | |

| Reporting group values | Cohort 1 | Cohort 2 | Total |
|---|---|---|---|
| Number of subjects | 32 | 30 | 62 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 28 | 29 | |
| standard deviation | ± 6.9 | ± 7.3 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 13 | 8 | 21 |
| Male | 19 | 22 | 41 |
| Race<br>Units: Subjects | | | |
| Asian | 0 | 2 | 2 |
| Black or African American | 23 | 14 | 37 |
| White | 9 | 14 | 23 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 2 | 5 | 7 |
| Not Hispanic or Latino | 30 | 25 | 55 |

## End points

### End points reporting groups

| Reporting group title | Cohort 1 |
|---|---|

Reporting group description:

COBI 1 x 150 mg adult immediate release tablet (Treatment A) or COBI 3 x 50 mg age-appropriate pediatric immediate release tablet (Treatment B)

| Reporting group title | Cohort 2 |
|---|---|

Reporting group description:

COBI 1 x 150 mg adult immediate release tablet (Treatment A) or COBI 7.5 x 20 mg age-appropriate pediatric dispersible tablet (Treatment C)

| Subject analysis set title | Cohort 1, Treatment A |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants in Cohort 1 who received Treatment A (COBI 1 x 150 mg adult immediate release tablet) on Day 1 or 8

| Subject analysis set title | Cohort 1, Treatment B |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants in Cohort 1 who received Treatment B (COBI 3 x 50 mg age-appropriate pediatric immediate release tablet) on Day 1 or 8

| Subject analysis set title | Cohort 2, Treatment A |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants in Cohort 2 who received Treatment A (COBI 1 x 150 mg adult immediate release tablet) on Day 1 or 8

| Subject analysis set title | Cohort 2, Treatment C |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants in Cohort 2 who received Treatment C (COBI 7.5 x 20 mg age-appropriate pediatric dispersible tablet) on Day 1 or 8

| Subject analysis set title | Treatment A |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants in Cohorts 1 and 2 who received Treatment A (COBI 1 x 150 mg adult immediate release tablet) were analyzed.

| Subject analysis set title | Treatment B |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants in Cohort 1 who received Treatment B (COBI 3 x 50 mg age-appropriate pediatric immediate release tablet) were analyzed.

| Subject analysis set title | Treatment C |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants in Cohort 2 who received Treatment C (COBI 7.5 x 20 mg age-appropriate pediatric dispersible tablet) were analyzed.

## Primary: Plasma Pharmacokinetics of COBI as measured by AUClast and AUCinf

| End point title | Plasma Pharmacokinetics of COBI as measured by AUClast and AUCinf |
|---|---|

End point description:

AUClast is defined as the concentration of drug from time zero to the last quantifiable concentration.
AUCinf is defined as the concentration of drug extrapolated to infinite time.
Participants in the COBI PK Analysis Set were analyzed.

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

End point timeframe:

Predose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 20, 24, 28, 36, and 48 hours post-dose on Days 1 and 8

| End point values | Cohort 1, Treatment A | Cohort 1, Treatment B | Cohort 2, Treatment A | Cohort 2, Treatment C |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 30 | 30 | 30 | 30 |
| Units: ng*h/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| AUClast | 4705.1 (3906.5 to 5667) | 4468.6 (3776.3 to 5287.7) | 5664.3 (4720.7 to 6796.4) | 5471.5 (4490.7 to 6666.7) |
| AUCinf | 4748.7 (3942.6 to 5719.6) | 4509.4 (3813.2 to 5332.6) | 5707.4 (4761.3 to 6841.6) | 5513.6 (4529.6 to 6711.4) |

### Statistical analyses

| Statistical analysis title | Cohort 1: Treatment B/Treatment A for AUClast |
|---|---|

Statistical analysis description:

A parametric mixed effect analysis of variance (ANOVA) model was used to estimate the geometric mean ratio (Cohort 1: Treatment B/Treatment A) of the PK parameter and the corresponding 90% CI. "Subjects in this analysis" states 60; however, only 30 unique participants were analyzed, each reported for Treatment A and Treatment B.

| | |
|---|---|
| Comparison groups | Cohort 1, Treatment B v Cohort 1, Treatment A |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other[1] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 94.97 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 88.94 |
| upper limit | 101.42 |

Notes:

[1] - Intergroup comparison

| Statistical analysis title | Cohort 1: Treatment B/Treatment A for AUCinf |
|---|---|

Statistical analysis description:

A parametric mixed effect analysis of variance (ANOVA) model was used to estimate the geometric mean ratio (Cohort 1: Treatment B/Treatment A) of the PK parameter and the corresponding 90% CI. "Subjects in this analysis" states 60; however, only 30 unique participants were analyzed, each reported for Treatment A and Treatment B.

| | |
|---|---|
| Comparison groups | Cohort 1, Treatment B v Cohort 1, Treatment A |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other[2] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 94.96 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 88.93 |
| upper limit | 101.39 |

Notes:

[2] - Intergroup comparison

| **Statistical analysis title** | Cohort 2: Treatment C/Treatment A for AUClast |
|---|---|

Statistical analysis description:

A parametric mixed effect analysis of variance (ANOVA) model was used to estimate the geometric mean ratio (Cohort 2: Treatment C/Treatment A) of the PK parameter and the corresponding 90% CI. "Subjects in this analysis" states 60; however, only 30 unique participants were analyzed, each reported for Treatment A and Treatment C.

| | |
|---|---|
| Comparison groups | Cohort 2, Treatment A v Cohort 2, Treatment C |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other[3] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 96.6 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 90.01 |
| upper limit | 103.67 |

Notes:

[3] - Intergroup comparison

| **Statistical analysis title** | Cohort 2: Treatment C/Treatment A for AUCinf |
|---|---|

Statistical analysis description:

A parametric mixed effect analysis of variance (ANOVA) model was used to estimate the geometric mean ratio (Cohort 2: Treatment C/Treatment A) of the PK parameter and the corresponding 90% CI. "Subjects in this analysis" states 60; however, only 30 unique participants were analyzed, each reported for Treatment A and Treatment C.

| | |
|---|---|
| Comparison groups | Cohort 2, Treatment A v Cohort 2, Treatment C |

| | |
|---|---|
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other[4] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 96.6 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 90.07 |
| upper limit | 103.62 |

Notes:

[4] - Intergroup comparison

## Primary: Plasma Pharmacokinetics of COBI as measured by Cmax

| | |
|---|---|
| End point title | Plasma Pharmacokinetics of COBI as measured by Cmax |

End point description:

Cmax is defined as the maximum observed concentration of drug in plasma.
Participants in the COBI PK Analysis Set were analyzed.

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

End point timeframe:

Predose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 20, 24, 28, 36, and 48 hours post-dose on Days 1 and 8

| End point values | Cohort 1, Treatment A | Cohort 1, Treatment B | Cohort 2, Treatment A | Cohort 2, Treatment C |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 30 | 30 | 30 | 30 |
| Units: ng/mL | | | | |
| geometric mean (confidence interval 95%) | 803.7 (707.5 to 913) | 804.1 (699.9 to 923.8) | 924.2 (800.6 to 1066.8) | 849.5 (725.5 to 994.7) |

## Statistical analyses

| Statistical analysis title | Cohort 1: Treatment B/Treatment A for Cmax |
|---|---|

Statistical analysis description:

A parametric mixed effect analysis of variance (ANOVA) model was used to estimate the geometric mean ratio (Cohort 1: Treatment B/Treatment A) of the PK parameter and the corresponding 90% CI. "Subjects in this analysis" states 60; however, only 30 unique participants were analyzed, each reported for Treatment A and Treatment B.

| | |
|---|---|
| Comparison groups | Cohort 1, Treatment B v Cohort 1, Treatment A |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other[5] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 100.05 |

| | |
|---|---|
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 92.8 |
| upper limit | 107.86 |

Notes:

[5] - Intergroup comparison

| **Statistical analysis title** | Cohort 2: Treatment C/Treatment A for Cmax |
|---|---|

Statistical analysis description:

A parametric mixed effect analysis of variance (ANOVA) model was used to estimate the geometric mean ratio (Cohort 2: Treatment C/Treatment A) of the PK parameter and the corresponding 90% CI. "Subjects in this analysis" states 60; however, only 30 unique participants were analyzed, each reported for Treatment A and Treatment C.

| | |
|---|---|
| Comparison groups | Cohort 2, Treatment A v Cohort 2, Treatment C |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other[6] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 91.92 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 86.77 |
| upper limit | 97.37 |

Notes:

[6] - Intergroup comparison

## Secondary: Plasma Pharmacokinetics of COBI as measured by %AUCexp

| End point title | Plasma Pharmacokinetics of COBI as measured by %AUCexp |
|---|---|

End point description:

%AUCexp is defined as the percent area under the plasma concentration-time curve.
Participants in the COBI PK Analysis Set were analyzed.

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

End point timeframe:

Predose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 20, 24, 28, 36, and 48 hours post-dose on Days 1 and 8

| **End point values** | Cohort 1, Treatment A | Cohort 1, Treatment B | Cohort 2, Treatment A | Cohort 2, Treatment C |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 30 | 30 | 30 | 30 |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 0.9 (± 0.51) | 0.9 (± 0.38) | 0.8 (± 0.37) | 0.8 (± 0.39) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Pharmacokinetics of COBI as measured by Tmax and t1/2

| End point title | Plasma Pharmacokinetics of COBI as measured by Tmax and t1/2 |
|---|---|

End point description:

Tmax is defined as the time of Cmax. t1/2 is defined as the estimate of the terminal elimination half-life of the drug. Participants in the COBI PK Analysis Set were analyzed.

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

End point timeframe:

Predose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 20, 24, 28, 36, and 48 hours post-dose on Days 1 and 8

| End point values | Cohort 1, Treatment A | Cohort 1, Treatment B | Cohort 2, Treatment A | Cohort 2, Treatment C |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 30 | 30 | 30 | 30 |
| Units: hours | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Tmax | 2.5 (2 to 3.05) | 2.51 (2.5 to 3.02) | 2.5 (2.5 to 3.5) | 3.25 (2.5 to 4.5) |
| t1/2 | 3.27 (2.74 to 3.86) | 3.16 (2.73 to 3.8) | 3.36 (3 to 3.58) | 3.2 (2.76 to 3.72) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Acceptability for COBI formulations as measured by palatability rating

| End point title | Acceptability for COBI formulations as measured by palatability rating |
|---|---|

End point description:

Palatability ratings were assessed using a scale of 1 (dislike very much) to 7 (like very much). Participants in the Safety Analysis Set were analyzed by treatment received.

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

End point timeframe:

Days 1 and 8

| End point values | Treatment A | Treatment B | Treatment C | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 62 | 31 | 30 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 5 (± 1.5) | 6 (± 1.6) | 4 (± 1.5) | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Up to 15 days plus 30 days | |
| Adverse event reporting additional description: | |
| Safety Analysis Set | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 15.1 |

| Reporting groups | |
|---|---|
| Reporting group title | Treatment A |
| Reporting group description: | |
| Participants in Cohorts 1 and 2 who received Treatment A (COBI 1 x 150 mg adult immediate release tablet) were analyzed. | |
| Reporting group title | Treatment B |
| Reporting group description: | |
| Participants in Cohort 1 who received Treatment B (COBI 3 x 50 mg age-appropriate pediatric immediate release tablet) were analyzed. | |
| Reporting group title | Treatment C |
| Reporting group description: | |
| Participants in Cohort 2 who received Treatment C (COBI 7.5 x 20 mg age-appropriate pediatric dispersible tablet) were analyzed. | |

| Serious adverse events | Treatment A | Treatment B | Treatment C |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 31 (0.00%) | 0 / 30 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

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

| Non-serious adverse events | Treatment A | Treatment B | Treatment C |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 62 (3.23%) | 3 / 31 (9.68%) | 1 / 30 (3.33%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 62 (3.23%) | 3 / 31 (9.68%) | 1 / 30 (3.33%) |
| occurrences (all) | 2 | 3 | 1 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported