Clinical trial results:
A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Single Tablet Regimen (STR) in HIV-1 Infected Antiretroviral Treatment-Naive Adolescents

Summary

EudraCT number	2015-000313-40
Trial protocol	Outside EU/EEA
Global end of trial date	29 January 2018

Results information

Result version number	v1 (current)
This version publication date	05 August 2018
First version publication date	05 August 2018

Trial information

Trial identification

Sponsor protocol code	GS-US-236-0112

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01721109
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000970-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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 October 2015
Global end of trial reached?	Yes
Global end of trial date	29 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study were to evaluate the steady-state pharmacokinetics (PK) and confirm the dose of the elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) single-tablet regimen (STR) (Part A) and to evaluate the safety and tolerability of EVG/COBI/FTC/TDF STR through Week 48 (Part B) in HIV-1 infected, antiretroviral (ARV) treatment-naive adolescents.

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	06 December 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 14
Country: Number of subjects enrolled	South Africa: 22
Country: Number of subjects enrolled	Thailand: 14
Worldwide total number of subjects	50
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)	50
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States, South Africa, and Thailand. The first participant was screened on 06 December 2012. The last study visit occurred on 29 January 2018.

Pre-assignment

Screening details:

56 participants were screened.

Period 1

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

Arms

Arm title	EVG/COBI/FTC/TDF

Arm description:

EVG/COBI/FTC/TDF STR for 48 weeks, followed by EVG/COBI/FTC/TDF during the optional extension phase.

Arm type	Experimental
Investigational medicinal product name	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
Investigational medicinal product code	
Other name	EVG/COBI/FTC/TDF, Stribild®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150/150/200/300 mg STR administered once daily with food

Number of subjects in period 1	EVG/COBI/FTC/TDF
Started	50
Switched to commercial/IPU Stribild	34 [1]
Completed	43
Not completed	7
Non- Compliance with Study Drug	3
Withdrew Consent	1
Lost to follow-up	2
Lack of efficacy	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: These 34 participants were counted as "Completed" because they switched to commercial Stribild or to an individual patient use (IPU) program.

Baseline characteristics

Reporting groups	
Reporting group title	EVG/COBI/FTC/TDF
Reporting group description:	
EVG/COBI/FTC/TDF STR for 48 weeks, followed by EVG/COBI/FTC/TDF during the optional extension phase.	

Reporting group values	EVG/COBI/FTC/TDF	Total	
Number of subjects	50	50	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	15		
standard deviation	± 1.5	-	
Gender categorical Units: Subjects			
Female	15	15	
Male	35	35	
Race Units: Subjects			
Asian	14	14	
Black	34	34	
White	1	1	
Other	1	1	
Ethnicity Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	47	47	
Not Permitted	1	1	
HIV-1 RNA Category Units: Subjects			
≤ 100,000 copies/ mL	40	40	
> 100,000 copies/ mL	10	10	
CD4 Cell Count Category Units: Subjects			
≤ 199 cells/µL	2	2	
200 ≥ and ≤ 349 cells/µL	16	16	
350 ≥ and ≤ 499 cells/µL	22	22	
≥ 500 cells/µL	10	10	
HIV-1 RNA Units: log10 copies/mL			
arithmetic mean	4.60		
standard deviation	± 0.551	-	
CD4 Cell Count Units: cells/µL			
arithmetic mean	399		

standard deviation	± 127.6	-	

End points

End points reporting groups

Reporting group title	EVG/COBI/FTC/TDF
Reporting group description:	
EVG/COBI/FTC/TDF STR for 48 weeks, followed by EVG/COBI/FTC/TDF during the optional extension phase.	

Primary: For Part A, Pharmacokinetic (PK) Parameter: AUCtau of EVG

End point title	For Part A, Pharmacokinetic (PK) Parameter: AUCtau of EVG[1]
End point description:	
AUCtau is defined as concentration of drug over time (the area under the concentration verses time curve over the dosing interval). PK Substudy Analysis Set included all enrolled and treated participants from Part A who evaluable steady-state pharmacokinetic profiles of the respective analyte of interest at Day 10 intensive PK visit.	
End point type	Primary
End point timeframe:	
Predose, 2, 4, 4.5, 5, 8, and 12 hours postdose on Day 10	
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: The statistical analysis of this primary endpoint is provided in the attachment.	

End point values	EVG/COBI/FTC/TDF			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: ng•h/mL				
arithmetic mean (standard deviation)	31620.9 (± 13978.07)			

Attachments (see zip file)	Statistical Analysis/236-0112_Primary_Endpoint_StatsAnalysis.

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Treatment-Emergent Serious Adverse Events (SAEs) and All Treatment-Emergent Adverse Events (AEs)

End point title	Incidence of Treatment-Emergent Serious Adverse Events (SAEs) and All Treatment-Emergent Adverse Events (AEs)[2]
End point description:	
Safety Analysis Set included all participants who received at least 1 dose of study drug.	
End point type	Primary
End point timeframe:	
Up to Week 48 plus 30 days	

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: No statistical comparison was planned or performed.

End point values	EVG/COBI/FTC /TDF			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: participants				
number (not applicable)				
SAEs	4			
AEs	45			

Statistical analyses

No statistical analyses for this end point

Secondary: For Part A, PK Parameter: Ctau of EVG, FTC, Tenofovir (TFV), and COBI

End point title	For Part A, PK Parameter: Ctau of EVG, FTC, Tenofovir (TFV), and COBI

End point description:

Ctau is defined as the observed drug concentration at the end of the dosing interval. Participants in the PK Substudy Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Predose, 2, 4, 4.5, 5, 8, and 12 hours postdose on Day 10

End point values	EVG/COBI/FTC /TDF			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: ng/mL				
arithmetic mean (standard deviation)				
EVG	579.3 (± 455.20)			
FTC	102.6 (± 30.85)			
TFV	86.6 (± 23.58)			
COBI	39.7 (± 68.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: For Part A, PK Parameter: Cmax of EVG, FTC, TFV, and COBI

End point title	For Part A, PK Parameter: Cmax of EVG, FTC, TFV, and COBI

End point description:

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

End point type	Secondary

End point timeframe:

Predose, 2, 4, 4.5, 5, 8, and 12 hours postdose on Day 10

End point values	EVG/COBI/FTC/TDF			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: ng/mL				
arithmetic mean (standard deviation)				
EVG	2624.3 (± 1239.64)			
FTC	2217.4 (± 664.64)			
TFV	438.5 (± 170.69)			
COBI	1500.4 (± 975.29)			

Statistical analyses

No statistical analyses for this end point

Secondary: For Part A, PK Parameter: AUCtau of FTC, TFV, and COBI

End point title	For Part A, PK Parameter: AUCtau of FTC, TFV, and COBI

End point description:

AUCtau is defined as concentration of drug over time (the area under the concentration verses time curve over the dosing interval). Participants in the PK Substudy Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Predose, 2, 4, 4.5, 5, 8, and 12 hours postdose on Day 10

End point values	EVG/COBI/FTC/TDF			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: ng•h/mL				
arithmetic mean (standard deviation)				
FTC	15136.5 (± 4702.06)			
TFV	4450.7 (± 1312.27)			

COBI	11884.8 (± 11220.94)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Weeks 24 and 48 as Defined by the FDA Snapshot Analysis

End point title	Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Weeks 24 and 48 as Defined by the FDA Snapshot Analysis

End point description:

The percentage of participants achieving HIV-1 RNA < 50 copies/mL at Week 24 (or Week 48) was analyzed using the snapshot algorithm, which defines a participant's virologic response status using only the viral load at the predefined time point within an allowed window of time, along with study drug discontinuation status. Full Analysis Set included all participants who were enrolled in the study and received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Weeks 24 and 48

End point values	EVG/COBI/FTC/TDF			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: percentage of participants				
number (not applicable)				
Week 24	88.0			
Week 48	88.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HIV-1 RNA < 400 Copies/mL at Weeks 24 and 48 as Defined by the FDA Snapshot Analysis

End point title	Percentage of Participants With HIV-1 RNA < 400 Copies/mL at Weeks 24 and 48 as Defined by the FDA Snapshot Analysis

End point description:

The percentage of participants achieving HIV-1 RNA < 400 copies/mL at Week 24 (or Week 48) was analyzed using the snapshot algorithm, which defines a participant's virologic response status using only the viral load at the predefined time point within an allowed window of time, along with study drug discontinuation status. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Weeks 24 and 48

End point values	EVG/COBI/FTC /TDF			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: percentage of participants				
number (not applicable)				
Week 24	94.0			
Week 48	92.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma log10 HIV-1 RNA at Weeks 24 and 48

End point title	Change From Baseline in Plasma log10 HIV-1 RNA at Weeks 24 and 48
End point description:	
Participants in the Full Analysis Set were analyzed.	
End point type	Secondary
End point timeframe:	
Baseline; Weeks 24 and 48	

End point values	EVG/COBI/FTC /TDF			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: log10 copies/mL				
arithmetic mean (standard deviation)				
Change at Week 24	-3.08 (± 0.922)			
Change at Week 48	-3.16 (± 0.705)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CD4+ Cell Count at Weeks 24 and 48

End point title	Change From Baseline in CD4+ Cell Count at Weeks 24 and 48
End point description:	
Participants in the Full Analysis Set with available data were analyzed.	
End point type	Secondary

End point timeframe:
Change From Baseline in CD4+ Cell Count at Weeks 24 and 48

End point values	EVG/COBI/FTC/TDF			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: cells/µL				
arithmetic mean (standard deviation)				
Change at Week 24 (N = 49)	178 (± 165.4)			
Change at Week 48 (N = 48)	229 (± 245.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CD4 Percentage at Weeks 24 and 48

End point title	Change From Baseline in CD4 Percentage at Weeks 24 and 48

End point description:
Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:
Baseline; Weeks 24 and 48

End point values	EVG/COBI/FTC/TDF			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: percentage				
arithmetic mean (standard deviation)				
Change at Week 24 (N = 49)	7.4 (± 4.70)			
Change at Week 48 (N = 48)	8.1 (± 5.34)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to the last dose date plus 30 days (maximum exposure: 250.7 weeks)	
Adverse event reporting additional description:	
Safety Analysis Set included all participants who received at least 1 dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	EVG/COBI/FTC/TDF
Reporting group description:	
EVG/COBI/FTC/TDF STR for 48 weeks, followed by EVG/COBI/FTC/TDF during the optional extension phase.	

Serious adverse events	EVG/COBI/FTC/TDF		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 50 (10.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Immune reconstitution inflammatory syndrome			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Food poisoning			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal behaviour			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Disseminated tuberculosis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis shigella			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oral candidiasis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 50 (2.00%)		
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 %

Non-serious adverse events	EVG/COBI/FTC/TDF		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 50 (92.00%)		
Investigations			
Weight decreased			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 50 (24.00%)		
occurrences (all)	17		
Dizziness			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	5		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Gastrointestinal disorders			

Vomiting subjects affected / exposed occurrences (all)	10 / 50 (20.00%) 11		
Diarrhoea subjects affected / exposed occurrences (all)	8 / 50 (16.00%) 8		
Nausea subjects affected / exposed occurrences (all)	8 / 50 (16.00%) 8		
Haemorrhoids subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 4		
Toothache subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	8 / 50 (16.00%) 11		
Rash subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 4		
Dermatitis subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3		
Dermatitis contact subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 4		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	18 / 50 (36.00%) 35		

Pharyngitis subjects affected / exposed occurrences (all)	6 / 50 (12.00%) 8		
Bronchitis subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 6		
Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 5		
Influenza subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 4		
Oral herpes subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 4		
Oropharyngeal gonococcal infection subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 4		
Proctitis gonococcal subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3		
Respiratory tract infection viral subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 4		
Secondary syphilis subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3		
Tonsillitis subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3		
Urinary tract infection subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 4		
Metabolism and nutrition disorders Vitamin D deficiency			

subjects affected / exposed	9 / 50 (18.00%)		
occurrences (all)	9		
Decreased appetite			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 August 2012	• Added cystatin C at baseline and Weeks 2, 4, 24, and 48 as an exploratory measure to assess renal function • Added additional safety contact information by region • Updated toxicity grading scale to avoid overlap with central laboratory normal ranges; sodium, calcium, magnesium, phosphorus, uric acid, urine red blood cells • Updated Tanner stage to conform to standard clinical evaluations for determining Tanner stage classification • Added language to the effect that increases in the concentration of norgestimate when norgestimate/ethinyl estradiol-containing oral contraceptives are coadministered with Stribild are not known

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported