Clinical trial results:
A Phase 3 Open-label Safety Study of Cobicistat-containing Highly Active Antiretroviral Regimens in HIV-1 Infected Patients with Mild to Moderate Renal Impairment

Summary

EudraCT number	2011-000488-29
Trial protocol	GB AT
Global end of trial date	16 February 2015

Results information

Result version number	v1 (current)
This version publication date	03 March 2016
First version publication date	03 March 2016

Trial information

Trial identification

Sponsor protocol code	GS-US-236-0118

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01363011
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	Clinical Trials Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trials Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.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	Final
Date of interim/final analysis	16 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study is to characterize the effect of cobicistat-based regimens on parameters of renal function in participants with HIV infection and who have mild to moderate renal impairment, and to assess the safety and tolerability of the regimens in order to generate appropriate dosing recommendations.

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 May 2011
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 Kingdom: 22
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	United States: 52
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Dominican Republic: 6
Country: Number of subjects enrolled	Australia: 6
Worldwide total number of subjects	106
EEA total number of subjects	27

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)	93
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at a total of 40 study sites in Australia, Europe, and North America. The first participant was screened on 13 May 2011. The last study visit occurred on 16 February 2015.

Pre-assignment

Screening details:

177 participants were screened.

Period 1

Period 1 title	Main Study
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	E/C/F/TDF (Cohort 1)

Arm description:

Main Study: Participants who had not received prior antiretroviral (ARV) treatment and who were virologically unsuppressed at baseline initiated treatment with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild®; E/C/F/TDF) single-tablet regimen (STR) once daily for up to 96 weeks.

Extension Phase: Participants continued their treatment until all participants discontinued from the study or commercial approval of E/C/F/TDF was received in the applicable country.

Arm type	Experimental
Investigational medicinal product name	E/C/F/TDF
Investigational medicinal product code	
Other name	Stribild®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (E/C/F/TDF) (150/150/200/300 mg) single-tablet regimen (STR) administered orally once daily

Arm title	COBI+PI+2 NRTIs (Cohort 2)

Arm description:

Main Study: Participants who had received prior ARV treatment and who were virologically suppressed at baseline switched their regimen's pharmacoenhancer component from ritonavir to cobicistat (Tybost®; COBI), while continuing the other components of their ARV regimen (atazanavir (ATV) or darunavir (DRV) plus 2 nucleoside reverse transcriptase inhibitors (NRTI)) for up to 96 weeks. These 2 NRTIs may have included abacavir (ABC), lamivudine (3TC)/zidovudine (ZDV), didanosine (DDI), emtricitabine (FTC), ABC/3TC, 3TC, tenofovir disoproxil fumarate (TDF), or emtricitabine/tenofovir disoproxil fumarate (Truvada®; FTC/TDF), administered according to prescribing information.

Extension Phase: Participants continued their treatment until all participants discontinued from the study or commercial approval of cobicistat was received in the applicable country.

Arm type	Experimental
Investigational medicinal product name	Cobicistat
Investigational medicinal product code	
Other name	Tybost®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details: Cobicistat (COBI) 150 mg tablet administered with food orally once daily	
Investigational medicinal product name	Atazanavir
Investigational medicinal product code	
Other name	Reyataz®
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Atazanavir (ATV) 300 mg tablet administered orally once daily	
Investigational medicinal product name	Darunavir
Investigational medicinal product code	
Other name	Prezista®
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Darunavir (DRV) 800 mg tablet administered orally once daily	
Investigational medicinal product name	Nucleoside reverse transcriptase inhibitor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Participants received 2 investigator-selected nucleoside reverse transcriptase inhibitors (NRTI), which may have included ABC, 3TC/ZDV, DDI, FTC, ABC/3TC, 3TC, TDF, or FTC/TDF, administered according to prescribing information.	

Number of subjects in period 1	E/C/F/TDF (Cohort 1)	COBI+PI+2 NRTIs (Cohort 2)
Started	33	73
Completed	29	64
Not completed	4	9
Withdrew Consent	1	4
Adverse event, non-fatal	2	3
Investigator's Discretion	1	1
Protocol Violation	-	1

Period 2

Period 2 title	Extension Phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	E/C/F/TDF (Cohort 1)

Arm description:

Main Study: Participants who had not received prior ARV treatment and who were virologically unsuppressed at baseline initiated treatment with E/C/F/TDF STR once daily for up to 96 weeks.

Extension Phase: Participants continued their treatment until all participants discontinued from the study or commercial approval of E/C/F/TDF was received in the applicable country.

Arm type	Experimental
Investigational medicinal product name	E/C/F/TDF
Investigational medicinal product code	
Other name	Stribild®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

E/C/F/TDF (150/150/200/300 mg) STR administered orally once daily

Arm title	COBI+PI+2 NRTIs (Cohort 2)

Arm description:

Main Study: Participants who had received prior ARV treatment and who were virologically suppressed at baseline switched their regimen's pharmacoenhancer component from ritonavir to COBI, while continuing the other components of their ARV regimen (ATV or DRV plus 2 NRTIs) for up to 96 weeks. These 2 NRTIs may have included ABC, 3TC/ZDV, DDI, FTC, ABC/3TC, 3TC, TDF, or FTC/TDF, administered according to prescribing information.

Extension Phase: Participants continued their treatment until all participants discontinued from the study or commercial approval of cobicistat was received in the applicable country.

Arm type	Experimental
Investigational medicinal product name	Cobicistat
Investigational medicinal product code	
Other name	Tybost®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

COBI 150 mg tablet administered with food orally once daily

Investigational medicinal product name	Atazanavir
Investigational medicinal product code	
Other name	Reyataz®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ATV 300 mg tablet administered orally once daily

Investigational medicinal product name	Darunavir
Investigational medicinal product code	
Other name	Prezista®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

DRV 800 mg tablet administered orally once daily

Investigational medicinal product name	Nucleoside reverse transcriptase inhibitor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received 2 investigator-selected NRTIs, which may have included ABC, 3TC/ZDV, DDI, FTC,

ABC/3TC, 3TC, TDF, or FTC/TDF, administered according to prescribing information.

Number of subjects in period 2[1]	E/C/F/TDF (Cohort 1)	COBI+PI+2 NRTIs (Cohort 2)
Started	18	49
Completed	13	41
Not completed	5	8
Withdrew Consent	-	1
Rolled Over to Another Gilead Study	2	1
Adverse event, non-fatal	1	1
Investigator's Discretion	2	2
Lost to follow-up	-	2
Lack of efficacy	-	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: For Cohort 1, 11 participants who completed the main study did not enroll into the extension phase. For Cohort 2, 15 participants who completed the main study did not enroll into the extension phase.

Baseline characteristics

Reporting groups	
Reporting group title	E/C/F/TDF (Cohort 1)

Reporting group description:

Main Study: Participants who had not received prior antiretroviral (ARV) treatment and who were virologically unsuppressed at baseline initiated treatment with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild®; E/C/F/TDF) single-tablet regimen (STR) once daily for up to 96 weeks.

Extension Phase: Participants continued their treatment until all participants discontinued from the study or commercial approval of E/C/F/TDF was received in the applicable country.

Reporting group title	COBI+PI+2 NRTIs (Cohort 2)

Reporting group description:

Main Study: Participants who had received prior ARV treatment and who were virologically suppressed at baseline switched their regimen's pharmacoenhancer component from ritonavir to cobicistat (Tybost®; COBI), while continuing the other components of their ARV regimen (atazanavir (ATV) or darunavir (DRV) plus 2 nucleoside reverse transcriptase inhibitors (NRTI)) for up to 96 weeks. These 2 NRTIs may have included abacavir (ABC), lamivudine (3TC)/zidovudine (ZDV), didanosine (DDI), emtricitabine (FTC), ABC/3TC, 3TC, tenofovir disoproxil fumarate (TDF), or emtricitabine/tenofovir disoproxil fumarate (Truvada®; FTC/TDF), administered according to prescribing information.

Extension Phase: Participants continued their treatment until all participants discontinued from the study or commercial approval of cobicistat was received in the applicable country.

Reporting group values	E/C/F/TDF (Cohort 1)	COBI+PI+2 NRTIs (Cohort 2)	Total
Number of subjects	33	73	106
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	50	54	
standard deviation	± 12.1	± 9.5	-
Gender categorical Units: Subjects			
Female	6	13	19
Male	27	60	87
Race Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	0	1	1
Black or African Heritage	13	14	27
White	14	56	70
Other	5	2	7
Ethnicity Units: Subjects			
Hispanic/Latino	9	19	28
Non-Hispanic/Latino	24	54	78
HIV Disease Status Units: Subjects			
Asymptomatic	28	37	65

Symptomatic HIV Infection	3	18	21
AIDS	2	18	20
Hepatitis B Virus (HBV) Surface Antigen Status Units: Subjects			
Positive	1	4	5
Negative	32	69	101
Hepatitis C Virus (HCV) Antibody Status Units: Subjects			
Positive	2	10	12
Negative	30	63	93
Indeterminate	1	0	1
HIV-1 RNA Category Units: Subjects			
< 50 copies/mL	0	73	73
≥ 50 to < 1,000 copies/mL	0	0	0
≥ 1,000 to ≤ 100,000 copies/ mL	24	0	24
> 100,000 copies/mL	9	0	9
CD4 Cell Count Units: Subjects			
≤ 50 cells/µL	1	0	1
51 to ≤ 200 cells/µL	3	3	6
201 to ≤ 350 cells/µL	13	5	18
351 to ≤ 500 cells/µL	10	16	26
> 500 cells/µL	6	49	55

End points

End points reporting groups

Reporting group title	E/C/F/TDF (Cohort 1)

Reporting group description:

Main Study: Participants who had not received prior antiretroviral (ARV) treatment and who were virologically unsuppressed at baseline initiated treatment with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild®; E/C/F/TDF) single-tablet regimen (STR) once daily for up to 96 weeks.

Extension Phase: Participants continued their treatment until all participants discontinued from the study or commercial approval of E/C/F/TDF was received in the applicable country.

Reporting group title	COBI+PI+2 NRTIs (Cohort 2)

Reporting group description:

Main Study: Participants who had received prior ARV treatment and who were virologically suppressed at baseline switched their regimen's pharmacoenhancer component from ritonavir to cobicistat (Tybost®; COBI), while continuing the other components of their ARV regimen (atazanavir (ATV) or darunavir (DRV) plus 2 nucleoside reverse transcriptase inhibitors (NRTI)) for up to 96 weeks. These 2 NRTIs may have included abacavir (ABC), lamivudine (3TC)/zidovudine (ZDV), didanosine (DDI), emtricitabine (FTC), ABC/3TC, 3TC, tenofovir disoproxil fumarate (TDF), or emtricitabine/tenofovir disoproxil fumarate (Truvada®; FTC/TDF), administered according to prescribing information.

Extension Phase: Participants continued their treatment until all participants discontinued from the study or commercial approval of cobicistat was received in the applicable country.

Reporting group title	E/C/F/TDF (Cohort 1)

Reporting group description:

Main Study: Participants who had not received prior ARV treatment and who were virologically unsuppressed at baseline initiated treatment with E/C/F/TDF STR once daily for up to 96 weeks.

Extension Phase: Participants continued their treatment until all participants discontinued from the study or commercial approval of E/C/F/TDF was received in the applicable country.

Reporting group title	COBI+PI+2 NRTIs (Cohort 2)

Reporting group description:

Main Study: Participants who had received prior ARV treatment and who were virologically suppressed at baseline switched their regimen's pharmacoenhancer component from ritonavir to COBI, while continuing the other components of their ARV regimen (ATV or DRV plus 2 NRTIs) for up to 96 weeks. These 2 NRTIs may have included ABC, 3TC/ZDV, DDI, FTC, ABC/3TC, 3TC, TDF, or FTC/TDF, administered according to prescribing information.

Extension Phase: Participants continued their treatment until all participants discontinued from the study or commercial approval of cobicistat was received in the applicable country.

Primary: Change From Baseline in Estimated Glomerular Filtration Rate (eGFR) Using the Cockcroft-Gault (CG) Equation at Week 24 (Cohort 1)

End point title	Change From Baseline in Estimated Glomerular Filtration Rate (eGFR) Using the Cockcroft-Gault (CG) Equation at Week 24 (Cohort 1)[1][2]

End point description:

Change from baseline in eGFR-CG equation at Week 24 was analyzed in Cohort 1 (treatment-naive).

End point type	Primary

End point timeframe:

Baseline; 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: No statistical analysis was planned or performed.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	E/C/F/TDF (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: mL/min				
median (inter-quartile range (Q1-Q3))				
Baseline (n = 33) Change at Week 24 (n = 30)	72.9 (64.7 to 81.1) -5.2 (-13.2 to 1)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in eGFR-CG at Week 24 (Cohort 2)

End point title	Change From Baseline in eGFR-CG at Week 24 (Cohort 2)[3][4]

End point description:

Change from baseline in eGFR-CG equation at Week 24 was analyzed in Cohort 2 (treatment-experienced).

End point type	Primary

End point timeframe:

Baseline; 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: No statistical analysis was planned or performed.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	COBI+PI+2 NRTIs (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: mL/min				
median (inter-quartile range (Q1-Q3))				
Baseline (n = 73) Change at Week 24 (n = 67)	71.4 (61.9 to 80.7) -3.7 (-7.4 to 2)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in eGFR Using the Modification of Diet in Renal (MDRD) Equation at Week 24 (Cohort 1)

End point title	Change From Baseline in eGFR Using the Modification of Diet in Renal (MDRD) Equation at Week 24 (Cohort 1)[5][6]

End point description:

Change from baseline in eGFR-MDRD equation at Week 24 was analyzed in Cohort 1 (treatment-naive). The calculation was normalized to 1.73 m^2 body surface area.

End point type	Primary

End point timeframe:

Baseline; Week 24

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned or performed.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	E/C/F/TDF (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: mL/min/1.73 m^2				
median (inter-quartile range (Q1-Q3))				
Baseline (n = 33)	77.1 (64.3 to 87.2)			
Change at Week 24 (n = 30)	-7.4 (-16.3 to -1.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in eGFR-MDRD at Week 24 (Cohort 2)

End point title	Change From Baseline in eGFR-MDRD at Week 24 (Cohort

End point description:

Change from baseline in eGFR-MDRD equation at Week 24 was analyzed in Cohort 2 (treatment-experienced). The calculation was normalized to 1.73 m^2 body surface area.

End point type	Primary

End point timeframe:

Baseline; Week 24

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned or performed.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	COBI+PI+2 NRTIs (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: mL/min/1.73 m^2				
median (inter-quartile range (Q1-Q3))				
Baseline (n = 73) Change at Week 24 (n = 67)	65.8 (56.2 to 75.2) -3.4 (-7.5 to 1.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in eGFR Using the Chronic Kidney Disease, Epidemiology Collaboration (CKD-EPI) Formula Based on Cystatin C Equation at Week 24 (Cohort 1)

End point title	Change From Baseline in eGFR Using the Chronic Kidney Disease, Epidemiology Collaboration (CKD-EPI) Formula Based on Cystatin C Equation at Week 24 (Cohort 1)[9][10]

End point description:

Change from baseline in eGFR-CKD-EPI based on cystatin C equation (not adjusted for age, sex, and race) at Week 24 was analyzed in Cohort 1 (treatment-naive). The calculation was normalized to 1.73 m^2 body surface area.

End point type	Primary

End point timeframe:

Baseline; Week 24

Notes:

[9] - 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 analysis was planned or performed.

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	E/C/F/TDF (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: mL/min/1.73 m^2				
median (inter-quartile range (Q1-Q3))				
Baseline (n = 33) Change at Week 24 (n = 30)	77.6 (61.7 to 90.5) 0.3 (-3.3 to 6.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in eGFR-CKD-EPI Formula Based on Cystatin C Equation at Week 24 (Cohort 2)

End point title	Change From Baseline in eGFR-CKD-EPI Formula Based on Cystatin C Equation at Week 24 (Cohort 2)[11][12]

End point description:

Change from baseline in eGFR-CKD-EPI based on cystatin C equation (not adjusted for age, sex, and race) at Week 24 was analyzed in Cohort 2 (treatment-experienced). The calculation was normalized to 1.73 m^2 body surface area.

End point type	Primary

End point timeframe:

Baseline; Week 24

Notes:

[11] - 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 analysis was planned or performed.

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	COBI+PI+2 NRTIs (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: mL/min/1.73 m^2				
median (inter-quartile range (Q1-Q3))				
Baseline (n = 73)	78.6 (67 to 94.4)			
Change at Week 24 (n = 67)	-2.7 (-6.8 to 1.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in eGFR-CKD-EPI Based on Cystatin C Equation, Adjusted at Week 24 (Cohort 1)

End point title	Change From Baseline in eGFR-CKD-EPI Based on Cystatin C Equation, Adjusted at Week 24 (Cohort 1)[13][14]

End point description:

Change from baseline in eGFR-CKD-EPI based on cystatin C equation (adjusted for age, sex, and race) at Week 24 was analyzed in Cohort 1 (treatment-naive). The calculation was normalized to 1.73 m^2 body surface area.

End point type	Primary

End point timeframe:

Baseline; Week 24

Notes:

[13] - 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 analysis was planned or performed.

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	E/C/F/TDF (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: mL/min/1.73 m^2				
median (inter-quartile range (Q1-Q3))				
Baseline (n = 33)	76.9 (61.7 to 90.1)			
Change at Week 24 (n = 30)	0.3 (-3.7 to 5.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in eGFR-CKD-EPI Based on Cystatin C Equation, Adjusted at Week 24 (Cohort 2)

End point title	Change From Baseline in eGFR-CKD-EPI Based on Cystatin C Equation, Adjusted at Week 24 (Cohort 2)[15][16]

End point description:

Change from baseline in eGFR-CKD-EPI based on cystatin C equation (adjusted for age, sex, and race) at Week 24 was analyzed in Cohort 2 (treatment-experienced). The calculation was normalized to 1.73 m^2 body surface area.

End point type	Primary

End point timeframe:

Baseline; Week 24

Notes:

[15] - 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 analysis was planned or performed.

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	COBI+PI+2 NRTIs (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: mL/min/1.73 m^2				
median (inter-quartile range (Q1-Q3))				
Baseline (n = 73)	78.2 (67.1 to 92.4)			
Change at Week 24 (n = 67)	-2.8 (-6.7 to 1.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Actual Glomerular Filtration Rate (aGFR) at Weeks 2, 4, and 24 (Cohort 1)

End point title	Change From Baseline in Actual Glomerular Filtration Rate (aGFR) at Weeks 2, 4, and 24 (Cohort 1)[17][18]

End point description:

Change from baseline in aGFR at Weeks 2, 4, and 24 was analyzed in Cohort 1 (treatment-naive). aGFR was calculated using iohexol plasma clearance.

Pharmacokinetic/Pharmacodynamic (PK/PD) Substudy Analysis Set (treatment-naive only): participants in the treatment-naive group who were enrolled and received at least one dose of study drug and who had data for steady-state PK parameters at the relevant time points were analyzed.

End point type	Primary

End point timeframe:

Baseline; Weeks 2, 4, and 24

Notes:

[17] - 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 analysis was planned or performed.

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	E/C/F/TDF (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: mL/min				
median (inter-quartile range (Q1-Q3))				
Baseline	81.6 (81.6 to 81.6)			
Change at Week 2	-12.1 (-12.1 to -12.1)			
Change at Week 4	-7.3 (-7.3 to -7.3)			
Change at Week 24	-3.3 (-3.3 to -3.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in aGFR at Weeks 2, 4, and 24 (Cohort 2)

End point title	Change From Baseline in aGFR at Weeks 2, 4, and 24 (Cohort 2)[19][20]

End point description:

Change from baseline in aGFR at Weeks 2, 4, and 24 was analyzed in Cohort 2 (treatment-experienced). aGFR was calculated using iohexol plasma clearance.

PK/PD Substudy Analysis Set (treatment-experienced only): participants in the treatment-experienced group who were enrolled and received at least one dose of study drug and who had data for steady-state PK parameters at the relevant time points were analyzed.

End point type	Primary

End point timeframe:

Baseline; Weeks 2, 4, and 24

Notes:

[19] - 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 analysis was planned or performed.

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	COBI+PI+2 NRTIs (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: mL/min				
median (inter-quartile range (Q1-Q3))				
Baseline	82.5 (55.3 to 112.9)			
Change at Week 2 (n=13)	1.6 (-12.3 to 9.2)			
Change at Week 4 (n=13)	7 (-14.6 to 14.6)			
Change at Week 24 (n=11)	-4.1 (-13.5 to 13.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 24 (Cohort 1)

End point title	Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 24 (Cohort 1)[21][22]

End point description:

The percentage of participants with HIV-1 RNA < 50 copies/mL at Week 24 was analyzed in Cohort 1 (treatment-naive) using the FDA snapshot analysis algorithm.

End point type	Primary

End point timeframe:

Week 24

Notes:

[21] - 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 analysis was planned or performed.

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	E/C/F/TDF (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percentage of participants				
number (not applicable)	84.8			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 24 (Cohort 2)

End point title	Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 24 (Cohort 2)[23][24]

End point description:

The percentage of participants with HIV-1 RNA < 50 copies/mL at Week 24 was analyzed in Cohort 2 (treatment-experienced) using the FDA snapshot analysis algorithm.

End point type	Primary

End point timeframe:

Week 24

Notes:

[23] - 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 analysis was planned or performed.

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	COBI+PI+2 NRTIs (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: percentage of participants				
number (not applicable)	90.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in eGFR-CG at Weeks 48 and 96 (Cohort 1)

End point title	Change From Baseline in eGFR-CG at Weeks 48 and 96 (Cohort 1)[25]

End point description:

Change from baseline in eGFR-CG at Weeks 48 and 96 were analyzed in Cohort 1 (treatment-naive). This outcome is to measure the long-term effect of COBI-containing regimens on renal parameters.

End point type	Secondary

End point timeframe:

Baseline; Weeks 48 and 96

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	E/C/F/TDF (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: mL/min				
median (inter-quartile range (Q1-Q3))				
Change at Week 48 (n = 28)	-7.6 (-12.2 to -2.2)			
Change at Week 96 (n = 25)	-7.9 (-14.2 to -4.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in eGFR-CG at Weeks 48 and 96 (Cohort 2)

End point title	Change From Baseline in eGFR-CG at Weeks 48 and 96 (Cohort 2)[26]

End point description:

Change from baseline in eGFR-CG at Weeks 48 and 96 were analyzed in Cohort 2 (treatment-experienced). This outcome is to measure the long-term effect of COBI-containing regimens on renal parameters.

End point type	Secondary

End point timeframe:

Baseline; Week 48

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	COBI+PI+2 NRTIs (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: mL/min				
median (inter-quartile range (Q1-Q3))				
Change at Week 48 (n = 63)	-3.8 (-9 to 0.8)			
Change at Week 96 (n = 50)	-5 (-13 to 0.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in eGFR-MDRD at Weeks 48 and 96 (Cohort 1)

End point title	Change From Baseline in eGFR-MDRD at Weeks 48 and 96 (Cohort 1)[27]

End point description:

Change from baseline in eGFR-MDRD at Weeks 48 and 96 were analyzed in Cohort 1 (treatment-naive). The calculation was normalized to 1.73 m^2 body surface area. This outcome is to measure the long-term effect of COBI-containing regimens on renal parameters.

End point type	Secondary

End point timeframe:

Baseline; Weeks 48 and 96

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	E/C/F/TDF (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: mL/min/1.73 m^2				
median (inter-quartile range (Q1-Q3))				
Change at Week 48 (n = 28)	-12.1 (-17.6 to -6.5)			
Change at Week 96 (n = 25)	-12.9 (-17.7 to -5.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in eGFR-MDRD at Weeks 48 and 96 (Cohort 2)

End point title	Change From Baseline in eGFR-MDRD at Weeks 48 and 96 (Cohort 2)[28]

End point description:

Change from baseline in eGFR-MDRD at Weeks 48 and 96 were analyzed in Cohort 2 (treatment-experienced). The calculation was normalized to 1.73 m^2 body surface area. This outcome is to measure the long-term effect of COBI-containing regimens on renal parameters.

End point type	Secondary

End point timeframe:

Baseline; Weeks 48 and 96

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	COBI+PI+2 NRTIs (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: mL/min/1.73 m^2				
median (inter-quartile range (Q1-Q3))				
Change at Week 48 (n = 63)	-3.9 (-8.1 to 1.4)			
Change at Week 96 (n = 50)	-2.8 (-13.7 to 2.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in eGFR-CKD-EPI Based on Cystatin C Equation at Weeks 48 and 96 (Cohort 1)

End point title	Change From Baseline in eGFR-CKD-EPI Based on Cystatin C Equation at Weeks 48 and 96 (Cohort 1)[29]

End point description:

Change from baseline in eGFR-CKD-EPI based on cystatin C equation (not adjusted for age, sex, and race) at Weeks 48 and 96 were analyzed in Cohort 1 (treatment-naive). The calculation was normalized to 1.73 m^2 body surface area. This outcome is to measure the long-term effect of COBI-containing regimens on renal parameters.

End point type	Secondary

End point timeframe:

Baseline; Weeks 48 and 96

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	E/C/F/TDF (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: mL/min/1.73 m^2				
median (inter-quartile range (Q1-Q3))				
Change at Week 48 (n = 28)	1.9 (-7.1 to 6.9)			
Change at Week 96 (n = 25)	12.4 (-0.6 to 20.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in eGFR-CKD-EPI Based on Cystatin C Equation at Weeks 48 and 96 (Cohort 2)

End point title	Change From Baseline in eGFR-CKD-EPI Based on Cystatin C Equation at Weeks 48 and 96 (Cohort 2)[30]

End point description:

Change from baseline in eGFR-CKD-EPI based on cystatin C equation (not adjusted for age, sex, and race) at Weeks 48 and 96 were analyzed in Cohort 2 (treatment-experienced). The calculation was normalized to 1.73 m^2 body surface area. This outcome is to measure the long-term effect of COBI-containing regimens on renal parameters.

End point type	Secondary

End point timeframe:

Baseline; Weeks 48 and 96

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	COBI+PI+2 NRTIs (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: mL/min/1.73 m^2				
median (inter-quartile range (Q1-Q3))				
Change at Week 48 (n = 63)	-4.7 (-12 to 4.3)			
Change at Week 96 (n = 50)	-2.4 (-7.3 to 9.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in eGFR-CKD-EPI Based on Cystatin C Equation

(Adjusted) at Weeks 48 and 96 (Cohort 1)

End point title	Change From Baseline in eGFR-CKD-EPI Based on Cystatin C Equation (Adjusted) at Weeks 48 and 96 (Cohort 1)[31]

End point description:

Change from baseline in eGFR-CKD-EPI based on cystatin C equation (adjusted for age, sex, and race) at Weeks 48 and 96 were analyzed in Cohort 1 (treatment-naive). The calculation was normalized to 1.73 m^2 body surface area. This outcome is to measure the long-term effect of COBI-containing regimens on renal parameters.

End point type	Secondary

End point timeframe:

Baseline; Weeks 48 and 96

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	E/C/F/TDF (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: mL/min/1.73 m^2				
median (inter-quartile range (Q1-Q3))				
Change at Week 48 (n = 28)	1.6 (-8 to 6.9)			
Change at Week 96 (n = 25)	12.6 (-0.9 to 19.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in eGFR-CKD-EPI Based on Cystatin C Equation (Adjusted) at Weeks 48 and 96 (Cohort 2)

End point title	Change From Baseline in eGFR-CKD-EPI Based on Cystatin C Equation (Adjusted) at Weeks 48 and 96 (Cohort 2)[32]

End point description:

Change from baseline in eGFR-CKD-EPI based on cystatin C equation (adjusted for age, sex, and race) at Weeks 48 and 96 were analyzed in Cohort 2 (treatment-experienced). The calculation was normalized to 1.73 m^2 body surface area. This outcome is to measure the long-term effect of COBI-containing regimens on renal parameters.

End point type	Secondary

End point timeframe:

Baseline; Weeks 48 and 96

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	COBI+PI+2 NRTIs (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: mL/min/1.73 m^2				
median (inter-quartile range (Q1-Q3))				
Change at Week 48 (n = 63)	-4.7 (-11.7 to 3.9)			
Change at Week 96 (n = 50)	-2.8 (-7.4 to 8.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Weeks 48 and 96 (Cohort 1)

End point title	Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Weeks 48 and 96 (Cohort 1)[33]

End point description:

The percentage of participants with HIV-1 RNA < 50 copies/mL at Weeks 48 and 96 were analyzed in Cohort 1 (treatment-naive) using the FDA snapshot analysis algorithm.

End point type	Secondary

End point timeframe:

Weeks 48 and 96

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	E/C/F/TDF (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percentage of participants				
number (not applicable)				
Week 48 (n = 33)	78.8			
Week 96 (n = 27)	88.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Weeks 48 and 96 (Cohort 2)

End point title	Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Weeks 48 and 96 (Cohort 2)[34]

End point description:

The percentage of participants with HIV-1 RNA < 50 copies/mL at Weeks 48 and 96 were analyzed in Cohort 2 (treatment-experienced) using the FDA snapshot analysis algorithm.

End point type	Secondary

End point timeframe:

Weeks 48 and 96

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	COBI+PI+2 NRTIs (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: percentage of participants				
number (not applicable)				
Week 48 (n = 73)	82.2			
Week 96 (n = 54)	90.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced Adverse Events (Cohort 1)

End point title	Percentage of Participants Who Experienced Adverse Events (Cohort 1)[35]

End point description:

Adverse events (AEs) occurring from baseline up to 30 days following the last dose of study drug were summarized for Cohort 1 (treatment-naive). A participant was counted once if they had a qualifying event.

End point type	Secondary

End point timeframe:

Up to 147 weeks plus 30 days

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	E/C/F/TDF (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percentage of participants				
number (not applicable)				
Any AE	100			
Drug-related AE	48.5			
Grade 3 or higher AE	21.2			

AE leading to drug discontinuation	12.1			
Serious AE	18.2			
AE of proximal renal tubulopathy	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced Adverse Events (Cohort 2)

End point title	Percentage of Participants Who Experienced Adverse Events (Cohort 2)[36]

End point description:

Adverse events (AEs) occurring from baseline up to 30 days following the last dose of study drug were summarized for Cohort 2 (treatment-experienced). A participant was counted once if they had a qualifying event.

End point type	Secondary

End point timeframe:

Up to 166 weeks plus 30 days

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	COBI+PI+2 NRTIs (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: percentage of participants				
number (not applicable)				
Any AE	93.2			
Drug-related AE	27.4			
Grade 3 or higher AE	28.8			
AE leading to drug discontinuation	11			
Serious AE	15.1			
AE of proximal renal tubulopathy	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced Graded Laboratory Abnormalities (Cohort 1)

End point title	Percentage of Participants Who Experienced Graded Laboratory Abnormalities (Cohort 1)[37]

End point description:

Laboratory abnormalities were summarized for Cohort 1 (treatment-naive) and were defined as values that increased at least one toxicity grade from baseline at any time postbaseline up to and including the

date of last dose of study drug plus 30 days. A participant was counted once if they had a qualifying event.

End point type	Secondary

End point timeframe:

Up to 147 weeks plus 30 days

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	E/C/F/TDF (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percentage of participants				
number (not applicable)				
Any laboratory abnormality	100			
Grade 3 or 4 laboratory abnormality	39.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced Graded Laboratory Abnormalities (Cohort 2)

End point title	Percentage of Participants Who Experienced Graded Laboratory Abnormalities (Cohort 2)[38]

End point description:

Laboratory abnormalities were summarized for Cohort 2 (treatment-experienced) and were defined as values that increased at least one toxicity grade from baseline at any time postbaseline up to and including the date of last dose of study drug plus 30 days. A participant was counted once if they had a qualifying event.

End point type	Secondary

End point timeframe:

Up to 166 weeks plus 30 days

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	COBI+PI+2 NRTIs (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	72[39]			
Units: percentage of participants				
number (not applicable)				
Any laboratory abnormality	100			
Grade 3 or 4 laboratory abnormality	50			

Notes:

[39] - Participants with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics of COBI: AUCtau (Cohort 1)

End point title	Plasma Pharmacokinetics of COBI: AUCtau (Cohort 1)[40]

End point description:

AUCtau was analyzed for Cohort 1 (treatment-naive) and was defined as the concentration of drug over time (area under the plasma concentration versus time curve over the dosing interval). Data presented are the mean values; standard deviation is not applicable because only 1 participant was analyzed.

End point type	Secondary

End point timeframe:

Blood samples were collected at 0 (predose), 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 8.0, 12.0, and 24.0 hours postdose at baseline and Weeks 2, 4, and 24.

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	E/C/F/TDF (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	1[41]			
Units: mean (h*ng/mL)				
number (not applicable)				
Week 2	16554.7			
Week 4	12704.1			
Week 24	9799.7			

Notes:

[41] - PK/PD Substudy Analysis Set (treatment-naive only)

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics of COBI: AUCtau (Cohort 2)

End point title	Plasma Pharmacokinetics of COBI: AUCtau (Cohort 2)[42]

End point description:

AUCtau was analyzed for Cohort 2 (treatment-experienced) and was defined as the concentration of drug over time (area under the plasma concentration versus time curve over the dosing interval).

End point type	Secondary

End point timeframe:

Blood samples were collected at 0 (predose), 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 8.0, 12.0, and 24.0 hours postdose at baseline and Weeks 2, 4, and 24.

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	COBI+PI+2 NRTIs (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	14[43]			
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Week 2 (n = 13)	12458 (± 6179.06)			
Week 4 (n = 13)	11165.3 (± 4185.86)			
Week 24 (n = 11)	13980.5 (± 8029.03)			

Notes:

[43] - Participants in the PK/PD Substudy Analysis Set with available postbaseline data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics of COBI: Cmax (Cohort 1)

End point title	Plasma Pharmacokinetics of COBI: Cmax (Cohort 1)[44]

End point description:

Cmax was analyzed for Cohort 1 (treatment-naive) and was defined as the maximum observed concentration of drug in plasma. Data presented are the mean values; standard deviation is not applicable because only 1 participant was analyzed.

End point type	Secondary

End point timeframe:

Blood samples were collected at 0 (predose), 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 8.0, 12.0, and 24.0 hours postdose at baseline and Weeks 2, 4, and 24.

Notes:

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	E/C/F/TDF (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	1[45]			
Units: mean (ng/mL)				
number (not applicable)				
Week 2	1734.6			
Week 4	1522.9			
Week 24	1266.4			

Notes:

[45] - PK/PD Substudy Analysis Set (treatment-naive only)

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics of COBI: Cmax (Cohort 2)

End point title	Plasma Pharmacokinetics of COBI: Cmax (Cohort 2)[46]

End point description:

Cmax was analyzed for Cohort 2 (treatment-experienced) and was defined as the maximum observed concentration of drug in plasma.

End point type	Secondary

End point timeframe:

Blood samples were collected at 0 (predose), 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 8.0, 12.0, and 24.0 hours postdose at baseline and Weeks 2, 4, and 24.

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	COBI+PI+2 NRTIs (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	14[47]			
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 2 (n = 13)	1366.7 (± 508.32)			
Week 4 (n = 13)	1297.7 (± 424.06)			
Week 24 (n = 11)	1586.6 (± 618.84)			

Notes:

[47] - Participants in the PK/PD Substudy Analysis Set with available postbaseline data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics of COBI: Ctau (Cohort 1)

End point title	Plasma Pharmacokinetics of COBI: Ctau (Cohort 1)[48]

End point description:

Ctau was analyzed for Cohort 1 (treatment-naive) and was defined as the observed drug concentration at the end of the dosing interval. Mean values are reported; standard deviation is not applicable because only 1 participant was analyzed.

End point type	Secondary

End point timeframe:

Blood samples were collected at 0 (predose), 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 8.0, 12.0, and 24.0 hours postdose at baseline and Weeks 2, 4, and 24.

Notes:

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	E/C/F/TDF (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	1[49]			
Units: ng/mL				
number (not applicable)				
Week 2	150.5			
Week 4	37.3			
Week 24	24.2			

Notes:

[49] - PK/PD Substudy Analysis Set (treatment-naive only)

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics of COBI: Ctau (Cohort 2)

End point title	Plasma Pharmacokinetics of COBI: Ctau (Cohort 2)[50]

End point description:

Ctau was analyzed for Cohort 2 (treatment-experienced) and was defined as the observed drug concentration at the end of the dosing interval.

End point type	Secondary

End point timeframe:

Blood samples were collected at 0 (predose), 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 8.0, 12.0, and 24.0 hours postdose at baseline and Weeks 2, 4, and 24.

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	COBI+PI+2 NRTIs (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	14[51]			
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 2 (n = 13)	79.9 (± 79.01)			
Week 4 (n = 13)	71.3 (± 61.27)			
Week 24 (n = 11)	139.8 (± 238.84)			

Notes:

[51] - Participants in the PK/PD Substudy Analysis Set with available postbaseline data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics of COBI: Tmax (Cohort 1)

End point title	Plasma Pharmacokinetics of COBI: Tmax (Cohort 1)[52]

End point description:

Blood samples were collected at 0 (predose), 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 8.0, 12.0, and 24.0 hours

postdose at baseline and Weeks 2, 4, and 24.

End point type	Secondary

End point timeframe:

Tmax was analyzed for Cohort 1 (treatment-naive) and was defined as the time of Cmax.

Notes:

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	E/C/F/TDF (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	1[53]			
Units: hours				
median (inter-quartile range (Q1-Q3))				
Week 2	4 (4 to 4)			
Week 4	2 (2 to 2)			
Week 24	4 (4 to 4)			

Notes:

[53] - PK/PD Substudy Analysis Set (treatment-naive only)

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics of COBI: Tmax (Cohort 2)

End point title	Plasma Pharmacokinetics of COBI: Tmax (Cohort 2)[54]

End point description:

Tmax was analyzed for Cohort 2 (treatment-experienced) and was defined as the time of Cmax.

End point type	Secondary

End point timeframe:

Blood samples were collected at 0 (predose), 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 8.0, 12.0, and 24.0 hours postdose at baseline and Weeks 2, 4, and 24.

Notes:

[54] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	COBI+PI+2 NRTIs (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	14[55]			
Units: hours				
median (inter-quartile range (Q1-Q3))				
Week 2 (n = 13)	3.92 (3 to 4.92)			
Week 4 (n = 13)	4.92 (3.02 to 5)			
Week 24 (n = 11)	3 (2 to 4.05)			

Notes:

[55] - Participants in the PK/PD Substudy Analysis Set with available postbaseline data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics of COBI: t1/2 (Cohort 1)

End point title	Plasma Pharmacokinetics of COBI: t1/2 (Cohort 1)[56]

End point description:

t1/2 was analyzed for Cohort 1 (treatment-naive) and was defined as the estimate of the terminal elimination half-life of the drug.

End point type	Secondary

End point timeframe:

Blood samples were collected at 0 (predose), 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 8.0, 12.0, and 24.0 hours postdose at baseline and Weeks 2, 4, and 24.

Notes:

[56] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	E/C/F/TDF (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	1[57]			
Units: hours				
median (inter-quartile range (Q1-Q3))				
Week 2	6.14 (6.14 to 6.14)			
Week 4	3.57 (3.57 to 3.57)			
Week 24	3.63 (3.63 to 3.63)			

Notes:

[57] - PK/PD Substudy Analysis Set (treatment-naive only)

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics of COBI: t1/2 (Cohort 2)

End point title	Plasma Pharmacokinetics of COBI: t1/2 (Cohort 2)[58]

End point description:

t1/2 was analyzed for Cohort 2 (treatment-experienced) and was defined as the estimate of the terminal elimination half-life of the drug.

End point type	Secondary

End point timeframe:

Blood samples were collected at 0 (predose), 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 8.0, 12.0, and 24.0 hours postdose at baseline and Weeks 2, 4, and 24.

Notes:

[58] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data are being presented as separate endpoints for each Cohort because the differing populations groups are not comparable.

End point values	COBI+PI+2 NRTIs (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	14[59]			
Units: hours				
median (inter-quartile range (Q1-Q3))				
Week 2 (n = 13)	4.37 (3.63 to 4.91)			
Week 4 (n = 12)	3.98 (3.53 to 4.34)			
Week 24 (n = 10)	3.77 (3.46 to 3.95)			

Notes:

[59] - Participants in the PK/PD Substudy Analysis Set with available postbaseline data were analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline through end of study drug treatment (average: Cohort 1 = 93.7 weeks; Cohort 2 = 101.2 weeks) plus 30 days

Adverse event reporting additional description:

Safety Analysis Set: participants were randomized and received at least one dose of study drug

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	E/C/F/TDF (Cohort 1)

Reporting group description:

Main Study: Participants who had not received prior ARV treatment and who were virologically unsuppressed at baseline initiated treatment with E/C/F/TDF STR once daily for up to 96 weeks.

Extension Phase: Participants continued their treatment until all participants discontinued from the study or commercial approval of E/C/F/TDF was received in the applicable country.

Reporting group title	COBI+PI+2 NRTIs (Cohort 2)

Reporting group description:

Main Study: Participants who had received prior ARV treatment and who were virologically suppressed at baseline switched their regimen's pharmacoenhancer component from ritonavir to COBI, while continuing the other components of their ARV regimen (ATV or DRV plus 2 NRTIs) for up to 96 weeks. These 2 NRTIs may have included ABC, 3TC/ZDV, DDI, FTC, ABC/3TC, 3TC, TDF, or FTC/TDF, administered according to prescribing information.

Extension Phase: Participants continued their treatment until all participants discontinued from the study or commercial approval of cobicistat was received in the applicable country.

Serious adverse events	E/C/F/TDF (Cohort 1)	COBI+PI+2 NRTIs (Cohort 2)	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 33 (18.18%)	11 / 73 (15.07%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hodgkin's disease			
subjects affected / exposed	1 / 33 (3.03%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoma			

subjects affected / exposed	1 / 33 (3.03%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 33 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 33 (3.03%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 33 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Skull fracture			
subjects affected / exposed	0 / 33 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 33 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			

subjects affected / exposed	0 / 33 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 33 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 33 (3.03%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 33 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Gastrointestinal fistula			
subjects affected / exposed	0 / 33 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 33 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	0 / 33 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	0 / 33 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 33 (3.03%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			

subjects affected / exposed	1 / 33 (3.03%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected cyst			
subjects affected / exposed	1 / 33 (3.03%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic inflammatory disease			
subjects affected / exposed	0 / 33 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 33 (3.03%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	E/C/F/TDF (Cohort 1)	COBI+PI+2 NRTIs (Cohort 2)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 33 (100.00%)	67 / 73 (91.78%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 33 (6.06%)	5 / 73 (6.85%)	
occurrences (all)	2	5	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 33 (9.09%)	5 / 73 (6.85%)	
occurrences (all)	3	5	

Oedema peripheral			
subjects affected / exposed	3 / 33 (9.09%)	5 / 73 (6.85%)	
occurrences (all)	4	5	
Pain			
subjects affected / exposed	2 / 33 (6.06%)	2 / 73 (2.74%)	
occurrences (all)	3	2	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 33 (0.00%)	4 / 73 (5.48%)	
occurrences (all)	0	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 33 (6.06%)	8 / 73 (10.96%)	
occurrences (all)	4	8	
Oropharyngeal pain			
subjects affected / exposed	2 / 33 (6.06%)	2 / 73 (2.74%)	
occurrences (all)	4	2	
Hiccups			
subjects affected / exposed	2 / 33 (6.06%)	0 / 73 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 33 (21.21%)	6 / 73 (8.22%)	
occurrences (all)	8	7	
Abnormal dreams			
subjects affected / exposed	1 / 33 (3.03%)	4 / 73 (5.48%)	
occurrences (all)	1	4	
Depression			
subjects affected / exposed	2 / 33 (6.06%)	3 / 73 (4.11%)	
occurrences (all)	2	3	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 33 (6.06%)	2 / 73 (2.74%)	
occurrences (all)	3	2	
Glomerular filtration rate decreased			

subjects affected / exposed	2 / 33 (6.06%)	2 / 73 (2.74%)	
occurrences (all)	3	2	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 33 (6.06%)	0 / 73 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 33 (18.18%)	10 / 73 (13.70%)	
occurrences (all)	7	11	
Dizziness			
subjects affected / exposed	3 / 33 (9.09%)	7 / 73 (9.59%)	
occurrences (all)	7	7	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 33 (9.09%)	1 / 73 (1.37%)	
occurrences (all)	4	1	
Lymphadenectomy			
subjects affected / exposed	2 / 33 (6.06%)	2 / 73 (2.74%)	
occurrences (all)	2	3	
Neutropenia			
subjects affected / exposed	2 / 33 (6.06%)	0 / 73 (0.00%)	
occurrences (all)	3	0	
Eye disorders			
Vision blurred			
subjects affected / exposed	3 / 33 (9.09%)	1 / 73 (1.37%)	
occurrences (all)	4	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	12 / 33 (36.36%)	10 / 73 (13.70%)	
occurrences (all)	16	14	
Nausea			
subjects affected / exposed	6 / 33 (18.18%)	9 / 73 (12.33%)	
occurrences (all)	7	10	
Vomiting			
subjects affected / exposed	5 / 33 (15.15%)	4 / 73 (5.48%)	
occurrences (all)	7	4	
Constipation			

subjects affected / exposed	3 / 33 (9.09%)	5 / 73 (6.85%)	
occurrences (all)	4	5	
Abdominal pain upper			
subjects affected / exposed	2 / 33 (6.06%)	4 / 73 (5.48%)	
occurrences (all)	2	4	
Dyspepsia			
subjects affected / exposed	3 / 33 (9.09%)	3 / 73 (4.11%)	
occurrences (all)	3	3	
Abdominal pain			
subjects affected / exposed	3 / 33 (9.09%)	1 / 73 (1.37%)	
occurrences (all)	3	1	
Proctalgia			
subjects affected / exposed	2 / 33 (6.06%)	0 / 73 (0.00%)	
occurrences (all)	2	0	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 33 (0.00%)	8 / 73 (10.96%)	
occurrences (all)	0	17	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 33 (6.06%)	8 / 73 (10.96%)	
occurrences (all)	3	9	
Skin lesion			
subjects affected / exposed	0 / 33 (0.00%)	5 / 73 (6.85%)	
occurrences (all)	0	6	
Actinic keratosis			
subjects affected / exposed	0 / 33 (0.00%)	4 / 73 (5.48%)	
occurrences (all)	0	6	
Pruritus			
subjects affected / exposed	2 / 33 (6.06%)	1 / 73 (1.37%)	
occurrences (all)	2	1	
Acne			
subjects affected / exposed	2 / 33 (6.06%)	0 / 73 (0.00%)	
occurrences (all)	2	0	
Dry skin			

subjects affected / exposed	2 / 33 (6.06%)	0 / 73 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 33 (3.03%)	6 / 73 (8.22%)	
occurrences (all)	1	9	
Nephrolithiasis			
subjects affected / exposed	2 / 33 (6.06%)	2 / 73 (2.74%)	
occurrences (all)	2	2	
Renal cyst			
subjects affected / exposed	2 / 33 (6.06%)	1 / 73 (1.37%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 33 (6.06%)	9 / 73 (12.33%)	
occurrences (all)	3	9	
Back pain			
subjects affected / exposed	5 / 33 (15.15%)	5 / 73 (6.85%)	
occurrences (all)	5	8	
Myalgia			
subjects affected / exposed	3 / 33 (9.09%)	6 / 73 (8.22%)	
occurrences (all)	3	6	
Pain in extremity			
subjects affected / exposed	4 / 33 (12.12%)	4 / 73 (5.48%)	
occurrences (all)	4	5	
Muscle spasms			
subjects affected / exposed	1 / 33 (3.03%)	5 / 73 (6.85%)	
occurrences (all)	2	5	
Musculoskeletal pain			
subjects affected / exposed	1 / 33 (3.03%)	5 / 73 (6.85%)	
occurrences (all)	1	6	
Osteoporosis			
subjects affected / exposed	2 / 33 (6.06%)	2 / 73 (2.74%)	
occurrences (all)	2	2	
Osteopenia			

subjects affected / exposed	2 / 33 (6.06%)	0 / 73 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 33 (18.18%)	14 / 73 (19.18%)	
occurrences (all)	15	22	
Upper respiratory tract infection			
subjects affected / exposed	1 / 33 (3.03%)	15 / 73 (20.55%)	
occurrences (all)	2	20	
Bronchitis			
subjects affected / exposed	3 / 33 (9.09%)	10 / 73 (13.70%)	
occurrences (all)	4	14	
Influenza			
subjects affected / exposed	4 / 33 (12.12%)	8 / 73 (10.96%)	
occurrences (all)	4	9	
Sinusitis			
subjects affected / exposed	4 / 33 (12.12%)	7 / 73 (9.59%)	
occurrences (all)	6	7	
Urinary tract infection			
subjects affected / exposed	5 / 33 (15.15%)	3 / 73 (4.11%)	
occurrences (all)	5	10	
Folliculitis			
subjects affected / exposed	2 / 33 (6.06%)	5 / 73 (6.85%)	
occurrences (all)	2	6	
Lower respiratory tract infection			
subjects affected / exposed	1 / 33 (3.03%)	5 / 73 (6.85%)	
occurrences (all)	1	10	
Rhinitis			
subjects affected / exposed	2 / 33 (6.06%)	4 / 73 (5.48%)	
occurrences (all)	2	7	
Acute sinusitis			
subjects affected / exposed	1 / 33 (3.03%)	4 / 73 (5.48%)	
occurrences (all)	1	6	
Syphilis			
subjects affected / exposed	4 / 33 (12.12%)	1 / 73 (1.37%)	
occurrences (all)	4	1	

Conjunctivitis			
subjects affected / exposed	0 / 33 (0.00%)	4 / 73 (5.48%)	
occurrences (all)	0	4	
Gastroenteritis			
subjects affected / exposed	2 / 33 (6.06%)	2 / 73 (2.74%)	
occurrences (all)	2	2	
Oral candidiasis			
subjects affected / exposed	3 / 33 (9.09%)	1 / 73 (1.37%)	
occurrences (all)	4	1	
Pyuria			
subjects affected / exposed	3 / 33 (9.09%)	1 / 73 (1.37%)	
occurrences (all)	3	2	
Chikungunya virus infection			
subjects affected / exposed	2 / 33 (6.06%)	1 / 73 (1.37%)	
occurrences (all)	2	1	
Herpes simplex			
subjects affected / exposed	2 / 33 (6.06%)	1 / 73 (1.37%)	
occurrences (all)	2	1	
Tinea pedis			
subjects affected / exposed	2 / 33 (6.06%)	1 / 73 (1.37%)	
occurrences (all)	2	1	
Urethritis			
subjects affected / exposed	2 / 33 (6.06%)	1 / 73 (1.37%)	
occurrences (all)	3	1	
Tinea cruris			
subjects affected / exposed	2 / 33 (6.06%)	0 / 73 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 33 (9.09%)	5 / 73 (6.85%)	
occurrences (all)	4	5	
Hypokalaemia			
subjects affected / exposed	1 / 33 (3.03%)	4 / 73 (5.48%)	
occurrences (all)	1	4	
Gout			

subjects affected / exposed	2 / 33 (6.06%)	2 / 73 (2.74%)	
occurrences (all)	2	4	
Hyperglycaemia			
subjects affected / exposed	2 / 33 (6.06%)	2 / 73 (2.74%)	
occurrences (all)	5	3	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 33 (0.00%)	4 / 73 (5.48%)	
occurrences (all)	0	5	
Hypercholesterolaemia			
subjects affected / exposed	2 / 33 (6.06%)	1 / 73 (1.37%)	
occurrences (all)	2	1	
Dehydration			
subjects affected / exposed	2 / 33 (6.06%)	0 / 73 (0.00%)	
occurrences (all)	2	0	
Hyperlipidaemia			
subjects affected / exposed	2 / 33 (6.06%)	0 / 73 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 October 2011	Changed inclusion and exclusion criteria based on FDA Guidance for Industry "Pharmacokinetics in Patients with Impaired Renal Function," and revised PK/PD substudy blood sampling procedures.
26 April 2013	Changed the study duration from 48 weeks to 96 weeks.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

There were no limitations affecting the analysis or results.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25397568

http://www.ncbi.nlm.nih.gov/pubmed/25469527