

**Clinical trial results:**

A Single-Dose, Open-Label, Randomized, Replicate Crossover Pivotal Bioequivalence Study in Healthy Adult Participants to Assess the Bioequivalence of Darunavir 675 mg, Emtricitabine 200 mg, and Tenofovir Alafenamide 10 mg in the Presence of Cobicistat 150 mg when Administered as a Fixed Dose Combination (Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide) Compared to the Co-administration of the Separate Agents (Darunavir, Cobicistat, and Emtricitabine/Tenofovir Alafenamide), Under Fed Conditions

Summary

EudraCT number	2020-003396-18
Trial protocol	NL
Global end of trial date	23 July 2021

Results information

Result version number	v1 (current)
This version publication date	03 July 2022
First version publication date	03 July 2022

Trial information**Trial identification**

Sponsor protocol code	TMC114FD2HTX1007
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04661397
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International N.V.
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, B-2340
Public contact	Clinical Registry Group, Janssen-Cilag International N.V., ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International N.V., ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001280-PIP01-12
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	23 July 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the single-dose pharmacokinetic (PK) and pivotal bioequivalence of 3 compounds (darunavir [DRV/D] 675 milligrams (mg), emtricitabine [FTC/F] 200 mg, and tenofovir alafenamide [TAF] 10 mg) in the presence of cobicistat (COBI/C) 150 mg when administered together as a fixed dose combination (FDC) tablet (D/C/F/TAF) compared to the co-administration as the separate commercial formulations (DRV 1*600 mg and 1*75 mg tablet and F/TAF 1*200 mg/10 mg tablet, and COBI 1*150 mg tablet), under fed conditions, in healthy adult subjects.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Safety evaluations were based upon the incidence of adverse events reported throughout the study, and on clinical laboratory tests, electrocardiogram (ECG), vital signs, and physical examination.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 January 2021
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	Netherlands: 37
Worldwide total number of subjects	37
EEA total number of subjects	37

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)	37
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 37 healthy subjects were randomized and treated (19 subjects in treatment sequence ABBA and 18 subjects in treatment sequence BAAB). Of these, 32 subjects completed the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Sequence ABBA

Arm description:

Subjects received a single oral dose of Darunavir (675 milligrams [mg])/Cobicistat (150 mg)/Emtricitabine (200 mg)/Tenofovir Alafenamide (10 mg) as one fixed dose combination (FDC) tablet (D/C/F/TAF) under fed conditions (Treatment A, test) on Day 1 of Period 1 followed by a single oral dose of Darunavir (DRV) 600 mg and 75 mg tablet, Emtricitabine 200 mg/Tenofovir Alafenamide 10 mg (F/TAF) and Cobicistat (COBI) 150 mg tablet under fed conditions (Treatment B, reference) on Day 1 of Period 2 followed by Treatment B again on Day 1 of Period 3 and, then Treatment A on Day 1 of Period 4. Each period was separated by a washout period of at least 7 days.

Arm type	Experimental
Investigational medicinal product name	Darunavir 675 mg/Cobicistat 150 mg/Emtricitabine 200 mg/Tenofovir Alafenamide (10 mg) (D/C/F/TAF) FDC
Investigational medicinal product code	
Other name	TMC114/JNJ-48763364/JNJ-35807551/JNJ-63625328
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of D/C/F/TAF 675/150/200/10 mg FDC tablet orally as Treatment A on Day 1 as per assigned treatment sequences.

Investigational medicinal product name	Emtricitabine 200 mg/Tenofovir Alafenamide 10 mg (F/TAF)
Investigational medicinal product code	
Other name	JNJ-35807551/JNJ-63625328
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of E/TAF 200/10mg tablet orally as a component of Treatment B on Day 1 as per assigned treatment sequences.

Investigational medicinal product name	Cobicistat (COBI) 150 mg
Investigational medicinal product code	
Other name	JNJ-48763364
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of COBI 150 mg tablet orally as a component of Treatment B on Day 1 as per assigned treatment sequences.

Investigational medicinal product name	Darunavir (DRV) 600 mg and 75 mg
Investigational medicinal product code	
Other name	TMC114
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of DRV 600 mg and 75 mg tablet orally as a component of Treatment B on Day 1 as per assigned treatment sequences.

Arm title	Treatment Sequence BAAB
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Arm description:

Subjects received a single oral dose of DRV 600 mg and 75 mg tablet, F/TAF 200/10 mg and COBI 150 mg tablet under fed conditions (Treatment B, reference) on Day 1 of Period 1 followed by a single oral dose D/C/F/TAF 675/150/200/10 mg as one fixed dose combination (FDC) tablet under fed conditions (Treatment A, test) on Day 1 of Period 2 followed by Treatment A on Day 1 of Period 3 and, then Treatment B on Day 1 of Period 4. Each period was separated by a washout period of at least 7 days.

Arm type	Experimental
Investigational medicinal product name	Darunavir (DRV) 600 mg and 75 mg
Investigational medicinal product code	
Other name	TMC114
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of DRV 600 mg and 75 mg tablet orally as a component of Treatment B on Day 1 as per assigned treatment sequences.

Investigational medicinal product name	Emtricitabine 200 mg/Tenofovir Alafenamide 10 mg (F/TAF)
Investigational medicinal product code	
Other name	JNJ-35807551/JNJ-63625328
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of E/TAF 200/10mg tablet orally as a component of Treatment B on Day 1 as per assigned treatment sequences.

Investigational medicinal product name	Cobicistat (COBI) 150 mg
Investigational medicinal product code	
Other name	JNJ-48763364
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of COBI 150 mg tablet orally as a component of Treatment B on Day 1 as per assigned treatment sequences.

Investigational medicinal product name	Darunavir 675 mg/Cobicistat 150 mg/Emtricitabine 200 mg/Tenofovir Alafenamide (10 mg) (D/C/F/TAF) FDC
Investigational medicinal product code	
Other name	TMC114/JNJ-48763364/JNJ-35807551/JNJ-63625328
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of D/C/F/TAF 675/150/200/10 mg FDC tablet orally as Treatment A on Day 1 as per assigned treatment sequences.

Number of subjects in period 1	Treatment Sequence ABBA	Treatment Sequence BAAB
Started	19	18
Completed	16	16
Not completed	3	2
Adverse event	1	-
Unspecified	1	1
Withdrawal by subject	1	1

Baseline characteristics

Reporting groups

Reporting group title	Treatment Sequence ABBA
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Reporting group description:

Subjects received a single oral dose of Darunavir (675 milligrams [mg])/Cobicistat (150 mg)/Emtricitabine (200 mg)/Tenofovir Alafenamide (10 mg) as one fixed dose combination (FDC) tablet (D/C/F/TAF) under fed conditions (Treatment A, test) on Day 1 of Period 1 followed by a single oral dose of Darunavir (DRV) 600 mg and 75 mg tablet, Emtricitabine 200 mg/Tenofovir Alafenamide 10 mg (F/TAF) and Cobicistat (COBI) 150 mg tablet under fed conditions (Treatment B, reference) on Day 1 of Period 2 followed by Treatment B again on Day 1 of Period 3 and, then Treatment A on Day 1 of Period 4. Each period was separated by a washout period of at least 7 days.

Reporting group title	Treatment Sequence BAAB
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Reporting group description:

Subjects received a single oral dose of DRV 600 mg and 75 mg tablet, F/TAF 200/10 mg and COBI 150 mg tablet under fed conditions (Treatment B, reference) on Day 1 of Period 1 followed by a single oral dose D/C/F/TAF 675/150/200/10 mg as one fixed dose combination (FDC) tablet under fed conditions (Treatment A, test) on Day 1 of Period 2 followed by Treatment A on Day 1 of Period 3 and, then Treatment B on Day 1 of Period 4. Each period was separated by a washout period of at least 7 days.

Reporting group values	Treatment Sequence ABBA	Treatment Sequence BAAB	Total
Number of subjects	19	18	37
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	19	18	37
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
median	26	27.5	
full range (min-max)	18 to 54	19 to 55	-
Title for Gender Units: subjects			
Female	8	5	13
Male	11	13	24

End points

End points reporting groups

Reporting group title	Treatment Sequence ABBA
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Reporting group description:

Subjects received a single oral dose of Darunavir (675 milligrams [mg])/Cobicistat (150 mg)/Emtricitabine (200 mg)/Tenofovir Alafenamide (10 mg) as one fixed dose combination (FDC) tablet (D/C/F/TAF) under fed conditions (Treatment A, test) on Day 1 of Period 1 followed by a single oral dose of Darunavir (DRV) 600 mg and 75 mg tablet, Emtricitabine 200 mg/Tenofovir Alafenamide 10 mg (F/TAF) and Cobicistat (COBI) 150 mg tablet under fed conditions (Treatment B, reference) on Day 1 of Period 2 followed by Treatment B again on Day 1 of Period 3 and, then Treatment A on Day 1 of Period 4. Each period was separated by a washout period of at least 7 days.

Reporting group title	Treatment Sequence BAAB
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Reporting group description:

Subjects received a single oral dose of DRV 600 mg and 75 mg tablet, F/TAF 200/10 mg and COBI 150 mg tablet under fed conditions (Treatment B, reference) on Day 1 of Period 1 followed by a single oral dose D/C/F/TAF 675/150/200/10 mg as one fixed dose combination (FDC) tablet under fed conditions (Treatment A, test) on Day 1 of Period 2 followed by Treatment A on Day 1 of Period 3 and, then Treatment B on Day 1 of Period 4. Each period was separated by a washout period of at least 7 days.

Subject analysis set title	Treatment A
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Subjects received a single oral dose of Darunavir (675 milligrams [mg])/Cobicistat (150 mg)/Emtricitabine (200 mg)/Tenofovir Alafenamide (10 mg) as one fixed dose combination (FDC) tablet (D/C/F/TAF) under fed conditions (Treatment A, test) on Day 1 of Period 1.

Subject analysis set title	Treatment B
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Subjects received a single oral dose of DRV 600 mg and 75 mg tablet, F/TAF 200/10 mg and COBI 150 mg tablet under fed conditions (Treatment B, reference) on Day 1 of Period 1.

Primary: Maximum Observed Plasma Concentration (C_{max}) of Darunavir (DRV)

End point title	Maximum Observed Plasma Concentration (C _{max}) of Darunavir (DRV)
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End point description:

C_{max} was defined as the maximum observed plasma concentration of Darunavir. Pharmacokinetic (PK) data analysis set included all subjects who completed all treatment periods and for which an evaluable PK parameter could be obtained in all treatment periods.

End point type	Primary
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End point timeframe:

Pre dose and 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48, 72 hours post dose

End point values	Treatment A	Treatment B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	32		
Units: nanograms per millilitre (ng/mL)				
arithmetic mean (standard deviation)	6363 (± 1449)	6426 (± 1277)		

Statistical analyses

Statistical analysis title	Treatment B Versus Treatment A
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Statistical analysis description:

Log transformed pharmacokinetic (PK) parameters were analyzed by mixed model analysis of variance with period, treatment, treatment sequence as fixed effects, and subject within-sequence as a random effect and the results were back-transformed using anti-logarithm.

Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	equivalence ^[1]
Parameter estimate	Geometric Mean Ratio
Point estimate	98.06
Confidence interval	
level	90 %
sides	2-sided
lower limit	94.1
upper limit	102.18

Notes:

[1] - Subjects analysed for statistical analysis in both the treatments (in each Treatment A and Treatment B) as per assigned treatment sequence were 32. Pre-defined bioequivalence limits were 80 to 125 percent (%).

Primary: Maximum Observed Plasma Concentration (Cmax) of Emtricitabine (FTC)

End point title	Maximum Observed Plasma Concentration (Cmax) of Emtricitabine (FTC)
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End point description:

Cmax was the maximum observed plasma concentration of FTC. PK data analysis set included all subjects who completed all treatment periods and for which an evaluable PK parameter could be obtained in all treatment periods.

End point type	Primary
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End point timeframe:

Pre dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72 hours post dose

End point values	Treatment A	Treatment B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	32		
Units: ng/mL				
arithmetic mean (standard deviation)	1806 (± 385)	1835 (± 366)		

Statistical analyses

Statistical analysis title	Treatment B Versus Treatment A
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Statistical analysis description:

Log transformed PK parameters were analyzed by mixed model analysis of variance with period, treatment, treatment sequence as fixed effects, and subject within-sequence as a random effect and the results were back-transformed using anti-logarithm.

Comparison groups	Treatment A v Treatment B
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Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	equivalence ^[2]
Parameter estimate	Geometric Mean Ratio
Point estimate	98.64
Confidence interval	
level	90 %
sides	2-sided
lower limit	93.66
upper limit	103.89

Notes:

[2] - Subjects analysed for statistical analysis in both the treatments (in each Treatment A and Treatment B) as per assigned treatment sequence were 32. Pre-defined bioequivalence limits were 80 to 125%.

Primary: Maximum Observed Plasma Concentration (C_{max}) of Tenofovir Alafenamide (TAF)

End point title	Maximum Observed Plasma Concentration (C _{max}) of Tenofovir Alafenamide (TAF)
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End point description:

C_{max} was the maximum observed plasma concentration of TAF. PK data analysis set included all subjects who completed all treatment periods and for which an evaluable PK parameter could be obtained in all treatment periods.

End point type	Primary
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End point timeframe:

Pre dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8 hours post dose

End point values	Treatment A	Treatment B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	32		
Units: ng/mL				
arithmetic mean (standard deviation)	144 (± 86.8)	134 (± 78.8)		

Statistical analyses

Statistical analysis title	Treatment B Versus Treatment A
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Statistical analysis description:

Log transformed PK parameters were analyzed by mixed model analysis of variance with period, treatment, treatment sequence as fixed effects, and subject within-sequence as a random effect and the results were back-transformed using anti-logarithm.

Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	equivalence ^[3]
Parameter estimate	Geometric Mean Ratio
Point estimate	105.23

Confidence interval	
level	90 %
sides	2-sided
lower limit	90.86
upper limit	121.87

Notes:

[3] - Subjects analysed for statistical analysis in both the treatments (in each Treatment A and Treatment B) as per assigned treatment sequence were 32. Pre-defined bioequivalence limits were 80 to 125%.

Primary: Area Under the Plasma Concentration-time Curve From Time Zero to Time of Last Measurable (Non-below Quantification Limit [non-BQL]) Concentration (AUC[0-last]) of Darunavir (DRV)

End point title	Area Under the Plasma Concentration-time Curve From Time Zero to Time of Last Measurable (Non-below Quantification Limit [non-BQL]) Concentration (AUC[0-last]) of Darunavir (DRV)
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End point description:

AUC(0-last) was area under the plasma concentration-time curve from time zero to the time of the last measurable (non-BQL) concentration, calculated by linear-linear trapezoidal summation. PK data analysis set included all subjects who completed all treatment periods and for which an evaluable PK parameter could be obtained in all treatment periods.

End point type	Primary
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End point timeframe:

Pre dose and 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48, 72 hours post dose

End point values	Treatment A	Treatment B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	32		
Units: hour*nanogram per millilitre (h*ng/mL)				
arithmetic mean (standard deviation)	74698 (± 23915)	72380 (± 22435)		

Statistical analyses

Statistical analysis title	Treatment B Versus Treatment A
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Statistical analysis description:

Log transformed PK parameters were analyzed by mixed model analysis of variance with period, treatment, treatment sequence as fixed effects, and subject within-sequence as a random effect and the results were back-transformed using anti-logarithm.

Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	equivalence ^[4]
Parameter estimate	Geometric Mean Ratio
Point estimate	102.74

Confidence interval	
level	90 %
sides	2-sided
lower limit	98.11
upper limit	107.6

Notes:

[4] - Subjects analysed for statistical analysis in both the treatments (in each Treatment A and Treatment B) as per assigned treatment sequence were 32. Pre-defined bioequivalence limits were 80 to 125%.

Primary: Area Under the Plasma Concentration-time Curve From Time Zero to Time of Last Measurable (non-BQL) Concentration (AUC[0-last]) of Emtricitabine (FTC)

End point title	Area Under the Plasma Concentration-time Curve From Time Zero to Time of Last Measurable (non-BQL) Concentration (AUC[0-last]) of Emtricitabine (FTC)
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End point description:

AUC(0-last) was area under the plasma concentration-time curve from time zero to the time of the last measurable non-BQL concentration, calculated by linear-linear trapezoidal summation. PK data analysis set included all subjects who completed all treatment periods and for which an evaluable PK parameter could be obtained in all treatment periods.

End point type	Primary
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End point timeframe:

Pre dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72 hours post dose

End point values	Treatment A	Treatment B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	32		
Units: h*ng/mL				
arithmetic mean (standard deviation)	9967 (± 1854)	9995 (± 1802)		

Statistical analyses

Statistical analysis title	Treatment B Versus Treatment A
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Statistical analysis description:

Log transformed PK parameters were analyzed by mixed model analysis of variance with period, treatment, treatment sequence as fixed effects, and subject within-sequence as a random effect and the results were back-transformed using anti-logarithm.

Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	equivalence ^[5]
Parameter estimate	Geometric Mean Ratio
Point estimate	100.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	98.83
upper limit	102.4

Notes:

[5] - Subjects analysed for statistical analysis in both the treatments (in each Treatment A and Treatment B) as per assigned treatment sequence were 32. Pre-defined bioequivalence limits were 80 to 125%.

Primary: Area Under the Plasma Concentration-time Curve From Time Zero to Time of Last Measurable (non-BQL) Concentration (AUC[0-last]) of Tenofovir Alafenamide (TAF)

End point title	Area Under the Plasma Concentration-time Curve From Time Zero to Time of Last Measurable (non-BQL) Concentration (AUC[0-last]) of Tenofovir Alafenamide (TAF)
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End point description:

AUC(0-last) was area under the plasma concentration-time curve from time zero to the time of the last measurable non-BQL concentration, calculated by linear-linear trapezoidal summation. PK data analysis set included all subjects who completed all treatment periods and for which an evaluable PK parameter could be obtained in all treatment periods.

End point type	Primary
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End point timeframe:

Pre dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8 hours post dose

End point values	Treatment A	Treatment B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	32		
Units: h*ng/mL				
arithmetic mean (standard deviation)	124 (± 36.7)	113 (± 44.1)		

Statistical analyses

Statistical analysis title	Treatment B Versus Treatment A
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Statistical analysis description:

Log transformed PK parameters were analyzed by mixed model analysis of variance with period, treatment, treatment sequence as fixed effects, and subject within-sequence as a random effect and the results were back-transformed using anti-logarithm.

Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	equivalence ^[6]
Parameter estimate	Geometric Mean Ratio
Point estimate	113.41
Confidence interval	
level	90 %
sides	2-sided
lower limit	106.82
upper limit	120.41

Notes:

[6] - Subjects analysed for statistical analysis in both the treatments (in each Treatment A and Treatment B) as per assigned treatment sequence were 32. Pre-defined bioequivalence limits were 80 to 125%.

Secondary: Area Under the Plasma was Concentration-time Curve From Time Zero to

Infinite Time (AUC[0-infinity]) of Darunavir

End point title	Area Under the Plasma was Concentration-time Curve From Time Zero to Infinite Time (AUC[0-infinity]) of Darunavir
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End point description:

The AUC (0-infinity) was the area under the plasma concentration-time curve from time zero to infinite time, calculated as the sum of AUC(last) and C(last)/lambda(z); wherein AUC(last) is area under the plasma concentration-time curve from time zero to last quantifiable time, C(last) is the last observed quantifiable concentration, and lambda(z) is elimination rate constant. PK data analysis set included all subjects who completed all treatment periods and for which an evaluable PK parameter could be obtained in all treatment periods.

End point type	Secondary
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End point timeframe:

Pre dose and 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48, 72 hours post dose

End point values	Treatment A	Treatment B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	32		
Units: h*ng/mL				
arithmetic mean (standard deviation)	74891 (± 23974)	72564 (± 22502)		

Statistical analyses

Statistical analysis title	Treatment B Versus Treatment A
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Statistical analysis description:

Log transformed PK parameters were analyzed by mixed model analysis of variance with period, treatment, treatment sequence as fixed effects, and subject within-sequence as a random effect and the results were back-transformed using anti-logarithm.

Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	equivalence ^[7]
Parameter estimate	Geometric Mean Ratio
Point estimate	102.73
Confidence interval	
level	90 %
sides	2-sided
lower limit	98.1
upper limit	107.58

Notes:

[7] - Subjects analysed for statistical analysis in both the treatments (in each Treatment A and Treatment B) as per assigned treatment sequence were 32. Pre-defined bioequivalence limits were 80 to 125%.

Secondary: Area Under the Plasma Concentration-time Curve From Time Zero to Infinite Time (AUC[0-infinity]) of Cobicistat

End point title	Area Under the Plasma Concentration-time Curve From Time Zero to Infinite Time (AUC[0-infinity]) of Cobicistat
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End point description:

The AUC (0-infinity) was the area under the plasma concentration-time curve from time zero to infinite

time, calculated as the sum of AUC(last) and C(last)/lambda(z); wherein AUC(last) is area under the plasma concentration-time curve from time zero to last quantifiable time, C(last) is the last observed quantifiable concentration, and lambda(z) is elimination rate constant. PK data analysis set included all subjects who completed all treatment periods and for which an evaluable PK parameter could be obtained in all treatment periods.

End point type	Secondary
End point timeframe:	
Pre dose and 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48, 72 hours post dose	

End point values	Treatment A	Treatment B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	32		
Units: h*ng/mL				
arithmetic mean (standard deviation)	6276 (± 2169)	6476 (± 2190)		

Statistical analyses

Statistical analysis title	Treatment B Versus Treatment A
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Statistical analysis description:

Log transformed PK parameters were analyzed by mixed model analysis of variance with period, treatment, treatment sequence as fixed effects, and subject within-sequence as a random effect and the results were back-transformed using anti-logarithm.

Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	equivalence ^[8]
Parameter estimate	Geometric Mean Ratio
Point estimate	97.68
Confidence interval	
level	90 %
sides	2-sided
lower limit	93.44
upper limit	102.1

Notes:

[8] - Subjects analysed for statistical analysis in both the treatments (in each Treatment A and Treatment B) as per assigned treatment sequence were 32. Pre-defined bioequivalence limits were 80 to 125%.

Secondary: Area Under the Plasma Concentration-time Curve From Time Zero to Infinite Time (AUC[0-infinity]) of Emtricitabine (FTC)

End point title	Area Under the Plasma Concentration-time Curve From Time Zero to Infinite Time (AUC[0-infinity]) of Emtricitabine (FTC)
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End point description:

The AUC (0-infinity) was the area under the plasma concentration-time curve from time zero to plasma time, calculated as the sum of AUC(last) and C(last)/lambda(z); wherein AUC(last) is area under the plasma concentration-time curve from time zero to last quantifiable time, C(last) is the last observed quantifiable concentration, and lambda(z) is elimination rate constant. PK data analysis set included all subjects who completed all treatment periods and for which an evaluable PK parameter could be obtained in all treatment periods. Here, N (Number of Subjects Analysed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Pre dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72 hours post dose

End point values	Treatment A	Treatment B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	28		
Units: h*ng/mL				
arithmetic mean (standard deviation)	10174 (\pm 1900)	10199 (\pm 1791)		

Statistical analyses

Statistical analysis title	Treatment B Versus Treatment A
Statistical analysis description: Log transformed PK parameters were analyzed by mixed model analysis of variance with period, treatment, treatment sequence as fixed effects, and subject within-sequence as a random effect and the results were back-transformed using anti-logarithm.	
Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	equivalence ^[9]
Parameter estimate	Geometric Mean Ratio
Point estimate	101.26
Confidence interval	
level	90 %
sides	2-sided
lower limit	99.31
upper limit	103.24

Notes:

[9] - Subjects analysed for statistical analysis in both the treatments (in each Treatment A and Treatment B) as per assigned treatment sequence were 25. Pre-defined bioequivalence limits were 80 to 125%.

Secondary: Area Under the Plasma Concentration-time Curve From Time Zero to Infinite Time (AUC[0-infinity]) of Tenofovir Alafenamide (TAF)

End point title	Area Under the Plasma Concentration-time Curve From Time Zero to Infinite Time (AUC[0-infinity]) of Tenofovir Alafenamide (TAF)
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End point description:

The AUC (0-infinity) was the area under the plasma concentration-time curve from time zero to infinite time, calculated as the sum of AUC(last) and C(last)/lambda(z); wherein AUC(last) is area under the plasma concentration-time curve from time zero to last quantifiable time, C(last) is the last observed quantifiable concentration, and lambda(z) is elimination rate constant. PK data analysis set included all subjects who completed all treatment periods and for which an evaluable PK parameter could be obtained in all treatment periods. Here, N (Number of Subjects Analysed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Pre dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8 hours post dose

End point values	Treatment A	Treatment B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	25		
Units: h*ng/mL				
arithmetic mean (standard deviation)	127 (± 38.4)	116 (± 43.8)		

Statistical analyses

Statistical analysis title	Treatment B Versus Treatment A
Statistical analysis description:	
Log transformed PK parameters were analyzed by mixed model analysis of variance with period, treatment, treatment sequence as fixed effects, and subject within-sequence as a random effect and the results were back-transformed using anti-logarithm.	
Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence ^[10]
Parameter estimate	Geometric Mean Ratio
Point estimate	115.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	107.31
upper limit	123.25

Notes:

[10] - Subjects analysed for statistical analysis in both the treatments (in each Treatment A and Treatment B) as per assigned treatment sequence were 19. Pre-defined bioequivalence limits were 80 to 125%.

Secondary: Maximum Observed Plasma Concentration (Cmax) of Cobicistat

End point title	Maximum Observed Plasma Concentration (Cmax) of Cobicistat
End point description:	
Cmax was the maximum observed plasma concentration of Cobicistat. PK data analysis set included all subjects who completed all treatment periods and for which an evaluable PK parameter could be obtained in all treatment periods.	
End point type	Secondary
End point timeframe:	
Pre dose and 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48, 72 hours post dose	

End point values	Treatment A	Treatment B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	32		
Units: ng/mL				
arithmetic mean (standard deviation)	842 (\pm 206)	898 (\pm 202)		

Statistical analyses

Statistical analysis title	Treatment B Versus Treatment A
Statistical analysis description:	
Log transformed PK parameters were analyzed by mixed model analysis of variance with period, treatment, treatment sequence as fixed effects, and subject within-sequence as a random effect and the results were back-transformed using anti-logarithm.	
Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	equivalence ^[11]
Parameter estimate	Geometric Mean Ratio
Point estimate	93.67
Confidence interval	
level	90 %
sides	2-sided
lower limit	89.63
upper limit	97.9

Notes:

[11] - Subjects analysed for statistical analysis in both the treatments (in each Treatment A and Treatment B) as per assigned treatment sequence were 32. Pre-defined bioequivalence limits were 80 to 125%.

Secondary: Area Under the Plasma Concentration-time Curve From Time Zero to Time of Last Measurable (non-BQL) Concentration (AUC[0-last]) of Cobicistat

End point title	Area Under the Plasma Concentration-time Curve From Time Zero to Time of Last Measurable (non-BQL) Concentration (AUC[0-last]) of Cobicistat
End point description:	
AUC(0-last) was area under the plasma concentration-time curve from time 0 to the time of the last measurable non-BQL concentration, calculated by linear-linear trapezoidal summation. PK data analysis set included all subjects who completed all treatment periods and for which an evaluable PK parameter could be obtained in all treatment periods.	
End point type	Secondary
End point timeframe:	
Pre dose and 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48, 72 hours post dose	

End point values	Treatment A	Treatment B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	32		
Units: h*ng/mL				
arithmetic mean (standard deviation)	6160 (± 2116)	6366 (± 2113)		

Statistical analyses

Statistical analysis title	Treatment B Versus Treatment A
Statistical analysis description:	
Log transformed PK parameters were analyzed by mixed model analysis of variance with period, treatment, treatment sequence as fixed effects, and subject within-sequence as a random effect and the results were back-transformed using anti-logarithm.	
Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	equivalence ^[12]
Parameter estimate	Geometric Mean Ratio
Point estimate	97.45
Confidence interval	
level	90 %
sides	2-sided
lower limit	93.18
upper limit	101.91

Notes:

[12] - Subjects analysed for statistical analysis in both the treatments (in each Treatment A and Treatment B) as per assigned treatment sequence were 32. Pre-defined bioequivalence limits were 80 to 125%.

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs)
End point description:	
An adverse event is any untoward medical event that occurs in a subject administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. TEAEs are defined as AEs with onset or worsening on or after date of first dose of study treatment. Safety analysis set included all subjects who received at least one dose of the study drug.	
End point type	Secondary
End point timeframe:	
Up to 5 weeks	

End point values	Treatment A	Treatment B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	36		
Units: Subjects	20	26		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing of the Informed consent form (ICF) till the last study-related activity (up to 9 weeks)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Treatment B
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Reporting group description:

Subjects received a single oral dose of DRV 600 mg and 75 mg tablet, F/TAF 200/10 mg and COBI 150 mg tablet under fed conditions (Treatment B, reference) on Day 1 of Period 1 followed by a single oral dose D/C/F/TAF 675/150/200/10 mg as one fixed dose combination (FDC) tablet under fed conditions (Treatment A, test) on Day 1 of Period 2 followed by Treatment A on Day 1 of Period 3 and, then Treatment B on Day 1 of Period 4. Each period was separated by a washout period of at least 7 days.

Reporting group title	Treatment A
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Reporting group description:

Subjects received a single oral dose of Darunavir (675 milligrams [mg])/Cobicistat (150 mg)/Emtricitabine (200 mg)/Tenofovir Alafenamide (10 mg) as one fixed dose combination (FDC) tablet (D/C/F/TAF) under fed conditions (Treatment A, test) on Day 1 of Period 1 followed by a single oral dose of Darunavir (DRV) 600 mg and 75 mg tablet, Emtricitabine 200 mg/Tenofovir Alafenamide 10 mg (F/TAF) and Cobicistat (COBI) 150 mg tablet under fed conditions (Treatment B, reference) on Day 1 of Period 2 followed by Treatment B again on Day 1 of Period 3 and, then Treatment A on Day 1 of Period 4. Each period was separated by a washout period of at least 7 days.

Serious adverse events	Treatment B	Treatment A	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 36 (0.00%)	0 / 36 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Treatment B	Treatment A	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 36 (58.33%)	20 / 36 (55.56%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 36 (5.56%)	2 / 36 (5.56%)	
occurrences (all)	2	3	
Headache			

subjects affected / exposed occurrences (all)	5 / 36 (13.89%) 6	6 / 36 (16.67%) 9	
General disorders and administration site conditions			
Catheter Site Bruise			
subjects affected / exposed	1 / 36 (2.78%)	2 / 36 (5.56%)	
occurrences (all)	1	3	
Fatigue			
subjects affected / exposed	3 / 36 (8.33%)	4 / 36 (11.11%)	
occurrences (all)	4	4	
Catheter Site Related Reaction			
subjects affected / exposed	7 / 36 (19.44%)	6 / 36 (16.67%)	
occurrences (all)	9	7	
Vessel Puncture Site Reaction			
subjects affected / exposed	0 / 36 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	2 / 36 (5.56%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Abdominal Discomfort			
subjects affected / exposed	2 / 36 (5.56%)	3 / 36 (8.33%)	
occurrences (all)	2	4	
Diarrhoea			
subjects affected / exposed	3 / 36 (8.33%)	2 / 36 (5.56%)	
occurrences (all)	3	2	
Nausea			
subjects affected / exposed	13 / 36 (36.11%)	8 / 36 (22.22%)	
occurrences (all)	19	11	
Vomiting			
subjects affected / exposed	3 / 36 (8.33%)	1 / 36 (2.78%)	
occurrences (all)	3	1	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 36 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Oropharyngeal Pain			

subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	2 / 36 (5.56%) 3	
Skin and subcutaneous tissue disorders Dry Skin subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	2 / 36 (5.56%) 2	
Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2 1 / 36 (2.78%) 1	0 / 36 (0.00%) 0 2 / 36 (5.56%) 3	
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	4 / 36 (11.11%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported