Clinical trial results:
A Single-Dose, Open-Label, Randomized, Replicate Crossover Pivotal Bioequivalence Study in Healthy Subjects 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	2019-002245-37
Trial protocol	NL
Global end of trial date	10 April 2020

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	

Trial information

Trial identification

Sponsor protocol code	TMC114FD2HTX1005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04236453
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International N.V.
Sponsor organisation address	Archimedesweg 29, Leiden, Netherlands, 2333 CM
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)	EMEA-001825-PIP01-15
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 October 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 April 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is 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 as an fixed dose combination (FDC) (D/C/F/TAF) compared to the co-administration of the separate commercial formulations (DRV 1*600 mg and 1*75 mg tablets and F/TAF 1*200 mg/10 mg tablet and COBI 1*150 mg tablet), under fed conditions, in healthy subjects.

Protection of trial subjects:

Safety evaluations were based upon the type, incidence, and severity of treatment-emergent adverse events reported throughout the study, and on changes in vital sign measurements, electrocardiogram (ECG), clinical laboratory test results, physical examinations and allergic reactions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 January 2020
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: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

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)	16
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 16 subjects were randomized; 8 subjects each in Treatment Sequence ABBA and Treatment Sequence BAAB. Only 2 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 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 is separated by a washout period of 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	
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 tablets orally as Treatment A on Day 1 per assigned treatment sequences.

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

Dosage and administration details:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

Arm title	Treatment Sequence BAAB

Arm description:

Subjects received a single oral dose of DRV 600 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 a followed by Treatment A on Day 1 of Period 3 and, then Treatment B on Day 1 of Period 4. Each period is separated by a washout period of 7 days.

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

Dosage and administration details:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

Number of subjects in period 1	Treatment Sequence ABBA	Treatment Sequence BAAB
Started	8	8
Completed	2	0
Not completed	6	8
Study Terminated by Sponsor	6	7
Unspecified	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Sequence ABBA
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 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 is separated by a washout period of 7 days.	
Reporting group title	Treatment Sequence BAAB
Reporting group description:	
Subjects received a single oral dose of DRV 600 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 a followed by Treatment A on Day 1 of Period 3 and, then Treatment B on Day 1 of Period 4. Each period is separated by a washout period of 7 days.	

Reporting group values	Treatment Sequence ABBA	Treatment Sequence BAAB	Total
Number of subjects	8	8	16
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-55 years)	8	8	16
From 55to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	37.6	34.8	
standard deviation	± 12.99	± 12.48	-
Title for Gender Units: subjects			
Female	2	1	3
Male	6	7	13

End points

End points reporting groups

Reporting group title	Treatment Sequence ABBA

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 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 is separated by a washout period of 7 days.

Reporting group title	Treatment Sequence BAAB

Reporting group description:

Subjects received a single oral dose of DRV 600 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 a followed by Treatment A on Day 1 of Period 3 and, then Treatment B on Day 1 of Period 4. Each period is separated by a washout period of 7 days.

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

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 on Day 1.

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

Subject analysis set description:

Subjects received a single oral dose of Darunavir (DRV) 600 and 75 mg, Emtricitabine 200 mg/Tenofovir Alafenamide 10 mg (F/TAF) and Cobicistat (COBI) 150 mg tablet under fed conditions on Day 1.

Primary: Maximum Observed Analyte Concentration (Cmax) of Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (D/C/F/TAF)

End point title	Maximum Observed Analyte Concentration (Cmax) of Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (D/C/F/TAF)[1]

End point description:

Cmax is the maximum observed analyte concentration. Pharmacokinetic (PK) analysis set included all subjects who have received at least one dose of study drug and had PK sampling done.

End point type	Primary

End point timeframe:

Up to 72 hours post-dose

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 inferential statistical analyses was planned to report for the primary end point.

End point values	Treatment Sequence ABBA	Treatment Sequence BAAB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)	()	()		

Notes:

[2] - Due to batch expiry, the PK samples collected during the study were not analyzed and destroyed.

[3] - Due to batch expiry, the PK samples collected during the study were not analyzed and destroyed.

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Analyte Concentration-time Curve From Time Zero to Time of the Last Observed Quantifiable Concentration (AUC [0-last]) of Darunavir, Cobicistat, Emtricitabine and Tenofovir Alafenamide

End point title	Area Under the Analyte Concentration-time Curve From Time Zero to Time of the Last Observed Quantifiable Concentration (AUC [0-last]) of Darunavir, Cobicistat, Emtricitabine and Tenofovir Alafenamide[4]

End point description:

AUC(0-last) is area under the analyte concentration-time curve from time zero to the time of the last observed quantifiable concentration, calculated by linear-linear trapezoidal summation. PK analysis set included all subjects who have received at least one dose of study drug and had PK sampling done.

End point type	Primary

End point timeframe:

Up to 72 hours post-dose

Notes:

[4] - 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 inferential statistical analyses was planned to report for the primary end point.

End point values	Treatment Sequence ABBA	Treatment Sequence BAAB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: nanogram*hour per milliliter (ng*h/mL)				
arithmetic mean (standard deviation)	()	()		

Notes:

[5] - Due to batch expiry, the PK samples collected during the study were not analyzed and destroyed.

[6] - Due to batch expiry, the PK samples collected during the study were not analyzed and destroyed.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Analyte Concentration-Time Curve From Time Zero to Infinite Time (AUC[0-infinity]) of of Darunavir, Cobicistat, Emtricitabine and Tenofovir Alafenamide

End point title	Area Under the Analyte Concentration-Time Curve From Time Zero to Infinite Time (AUC[0-infinity]) of of Darunavir, Cobicistat, Emtricitabine and Tenofovir Alafenamide

End point description:

The AUC (0-infinity) is the area under the analyte 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 analyte 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 analysis set included all

subjects who have received at least one dose of study drug and had PK sampling done.

End point type	Secondary

End point timeframe:

Up to 72 hours post-dose

End point values	Treatment Sequence ABBA	Treatment Sequence BAAB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: ng*h/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[7] - Due to batch expiry, the PK samples collected during the study were not analyzed and destroyed.

[8] - Due to batch expiry, the PK samples collected during the study were not analyzed and destroyed.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Analyte Concentration (Cmax) of Cobicistat (COBI)

End point title	Maximum Observed Analyte Concentration (Cmax) of Cobicistat (COBI)

End point description:

Cmax is the maximum observed analyte concentration. PK analysis set included all subjects who have received at least one dose of study drug and had PK sampling done.

End point type	Secondary

End point timeframe:

Up to 72 hours post-dose

End point values	Treatment Sequence ABBA	Treatment Sequence BAAB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: ng/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[9] - Due to batch expiry, the PK samples collected during the study were not analyzed and destroyed.

[10] - Due to batch expiry, the PK samples collected during the study were not analyzed and destroyed.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Analyte Concentration-time Curve From Time Zero to Time of the Last Observed Quantifiable Concentration (AUC [0-last]) of COBI

End point title	Area Under the Analyte Concentration-time Curve From Time Zero to Time of the Last Observed Quantifiable Concentration

	(AUC [0-last]) of COBI

End point description:

AUC(0-last) is area under the analyte concentration-time curve from time zero to the time of the last observed quantifiable concentration. PK analysis set included all subjects who have received at least one dose of study drug and had PK sampling done.

End point type	Secondary

End point timeframe:

Up to 72 hours post-dose

End point values	Treatment Sequence ABBA	Treatment Sequence BAAB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[11]	0[12]		
Units: ng*h/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[11] - Due to batch expiry, the PK samples collected during the study were not analyzed and destroyed.

[12] - Due to batch expiry, the PK samples collected during the study were not analyzed and destroyed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Adverse Events

End point title	Number of Subjects with Adverse Events

End point description:

An adverse event is any untoward medical event that occurs in a participant administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. Safety analysis set included subjects who were administered at least one dose of the study drug.

End point type	Secondary

End point timeframe:

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

End point values	Treatment A	Treatment B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	12		
Units: Subjects	4	6		

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
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1
Reporting groups	
Reporting group title	Treatment B
Reporting group description:	
Subjects received a single oral dose of Darunavir (DRV) 600 and 75 mg, Emtricitabine 200 mg/Tenofovir Alafenamide 10 mg (F/TAF) and Cobicistat (COBI) 150 mg tablet under fed conditions on Day 1.	
Reporting group title	Treatment A
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 on Day 1.	

Serious adverse events	Treatment B	Treatment A	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Treatment B	Treatment A	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 12 (50.00%)	4 / 13 (30.77%)	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 12 (16.67%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Headache			

subjects affected / exposed	2 / 12 (16.67%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Catheter Site Haematoma			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Catheter Site Irritation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Influenza Like Illness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal Pain Lower			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Faeces Soft			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	2 / 12 (16.67%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Rash Macular			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Rash Pruritic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Infections and infestations			

Rhinitis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 13 (0.00%) 0	

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

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

The study was terminated by the Sponsor due to COVID-19, as the measures taken at the clinical site did not allow to complete the study before batch expiry of reference and test products, impacting the PK assessments of the enrolled subjects.

Notes: