

**Clinical trial results:****A Single-dose, Open-label, Randomized, Crossover Pivotal Bioequivalence Study in Healthy Participants to Assess the Bioequivalence of Darunavir 675 mg in the Presence of 150 mg Cobicistat When Administered as a Fixed Dose Combination (Darunavir/Cobicistat) Compared to the Co-administration of the Separate Agents (Darunavir and Cobicistat) Under Fed Conditions
Summary**

EudraCT number	2020-003397-43
Trial protocol	BE
Global end of trial date	01 March 2021

Results information

Result version number	v1 (current)
This version publication date	12 March 2022
First version publication date	12 March 2022

Trial information**Trial identification**

Sponsor protocol code	TMC114IFD1004
-----------------------	---------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04718805
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International NV
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium,
Public contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International NV, 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	01 March 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the single-dose pharmacokinetics (PK) and bioequivalence of darunavir (DRV) 675 milligrams (mg) in the presence of cobicistat (COBI) 150 mg when administered as a scored fixed dose combination (FDC) tablet (DRV/COBI) compared to the co-administration as the separate available tablet formulations (DRV 1*600 mg and 1*75 mg tablet and COBI 1*150 mg tablet), under fed conditions in healthy 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 (GCP) and applicable regulatory requirements. Safety assessments included adverse events, deaths, clinical laboratory tests, vital signs, and physical examination results.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 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	Belgium: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	22
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 22 subjects were enrolled in the study (in 2 treatment sequences: 11 subjects in each treatment sequence). All 22 enrolled 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	Sequence 1: A-B

Arm description:

Subjects received Treatment A (a single oral dose of Darunavir [DRV] 675 milligrams [mg] and Cobicistat [COBI] 150 mg as a scored fixed dose combination [FDC] tablet [DRV/COBI] under fed conditions) (test) on Day 1 of Treatment Period 1, followed by Treatment B (a single oral dose of DRV 675 mg tablet administered as 1*600 mg plus 1*75 mg and; COBI 1*150 mg tablet under fed conditions) (reference) on Day 1 of Treatment Period 2. For each individual subject, there was a washout period of at least 7 days between doses. Day 1 of a treatment period (day of study drug intake) was the first day of the washout period.

Arm type	Experimental
Investigational medicinal product name	DRV 675 mg/COBI 150 mg (DRV/COBI) FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral tablet of DRV/COBI 675/150 mg FDC on Day 1.

Investigational medicinal product name	DRV 675 mg and COBI 150 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received single oral tablets of DRV 600 mg, DRV 75 mg, and COBI 150 mg on Day 1.

Arm title	Sequence 2: B-A
------------------	-----------------

Arm description:

Subjects received Treatment B on Day 1 of Treatment Period 1, followed by Treatment A on Day 1 of Treatment Period 2. For each individual subject, there was a washout period of at least 7 days between doses. Day 1 of a treatment period (day of study drug intake) was the first day of the washout period.

Arm type	Experimental
Investigational medicinal product name	DRV 675 mg/COBI 150 mg (DRV/COBI) FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral tablet of DRV/COBI 675/150 mg FDC on Day 1.

Investigational medicinal product name	DRV 675 mg and COBI 150 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received single oral tablets of DRV 600 mg, DRV 75 mg, and COBI 150 mg on Day 1.

Number of subjects in period 1	Sequence 1: A-B	Sequence 2: B-A
Started	11	11
Completed	11	11

Baseline characteristics

Reporting groups

Reporting group title	Sequence 1: A-B
Reporting group description:	
Subjects received Treatment A (a single oral dose of Darunavir [DRV] 675 milligrams [mg] and Cobicistat [COBI] 150 mg as a scored fixed dose combination [FDC] tablet [DRV/COBI] under fed conditions) (test) on Day 1 of Treatment Period 1, followed by Treatment B (a single oral dose of DRV 675 mg tablet administered as 1*600 mg plus 1*75 mg and; COBI 1*150 mg tablet under fed conditions) (reference) on Day 1 of Treatment Period 2. For each individual subject, there was a washout period of at least 7 days between doses. Day 1 of a treatment period (day of study drug intake) was the first day of the washout period.	
Reporting group title	Sequence 2: B-A
Reporting group description:	
Subjects received Treatment B on Day 1 of Treatment Period 1, followed by Treatment A on Day 1 of Treatment Period 2. For each individual subject, there was a washout period of at least 7 days between doses. Day 1 of a treatment period (day of study drug intake) was the first day of the washout period.	

Reporting group values	Sequence 1: A-B	Sequence 2: B-A	Total
Number of subjects	11	11	22
Title for AgeCategorical Units: subjects			
Newborns (0-1 years)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	11	11	22
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
median	43	30	
full range (min-max)	20 to 51	18 to 45	-
Title for Gender Units: subjects			
Female	8	7	15
Male	3	4	7

End points

End points reporting groups

Reporting group title	Sequence 1: A-B
Reporting group description: Subjects received Treatment A (a single oral dose of Darunavir [DRV] 675 milligrams [mg] and Cobicistat [COBI] 150 mg as a scored fixed dose combination [FDC] tablet [DRV/COBI] under fed conditions) (test) on Day 1 of Treatment Period 1, followed by Treatment B (a single oral dose of DRV 675 mg tablet administered as 1*600 mg plus 1*75 mg and; COBI 1*150 mg tablet under fed conditions) (reference) on Day 1 of Treatment Period 2. For each individual subject, there was a washout period of at least 7 days between doses. Day 1 of a treatment period (day of study drug intake) was the first day of the washout period.	
Reporting group title	Sequence 2: B-A
Reporting group description: Subjects received Treatment B on Day 1 of Treatment Period 1, followed by Treatment A on Day 1 of Treatment Period 2. For each individual subject, there was a washout period of at least 7 days between doses. Day 1 of a treatment period (day of study drug intake) was the first day of the washout period.	
Subject analysis set title	Treatment A (test): DRV/COBI 675/150 milligrams (mg) FDC
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects received a single oral dose of DRV/COBI 675/150 mg as a scored FDC on Day 1 under fed condition.	
Subject analysis set title	Treatment B (reference): DRV/COBI 675/150 milligrams (mg)
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects received a single oral dose of DRV 675 mg as DRV 600 mg plus DRV 75 mg and COBI 150 mg on Day 1 under fed condition.	

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

End point title	Maximum Observed Plasma Analyte Concentration (C _{max}) of Darunavir (DRV)
End point description: C _{max} is the maximum observed plasma analyte concentration of DRV. Pharmacokinetics (PK) data analysis set included all subjects who had received at least 1 dose of study drug.	
End point type	Primary
End point timeframe: Predose, up to 72 hours postdose (Up to Day 4)	

End point values	Treatment A (test): DRV/COBI 675/150 milligrams (mg) FDC	Treatment B (reference): DRV/COBI 675/150 milligrams (mg)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: nanograms per millilitre (ng/mL)				
arithmetic mean (standard deviation)	7157 (± 1772)	7561 (± 1566)		

Statistical analyses

Statistical analysis title	Treatment A versus Treatment B
Statistical analysis description: Subjects analysed for both the treatments as per assigned treatment sequence in respective periods were 22.	
Comparison groups	Treatment A (test): DRV/COBI 675/150 milligrams (mg) FDC v Treatment B (reference): DRV/COBI 675/150 milligrams (mg)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Geometric Mean Ratio
Point estimate	94.07
Confidence interval	
level	90 %
sides	2-sided
lower limit	88.29
upper limit	100.22

Primary: Area Under the Analyte Concentration-Time Curve from Time 0 to Last Quantifiable Time (AUC [0-last]) of DRV

End point title	Area Under the Analyte Concentration-Time Curve from Time 0 to Last Quantifiable Time (AUC [0-last]) of DRV
End point description: AUC (0-last) is defined as area under the analyte concentration-time curve from time 0 to time of the last quantifiable concentration. AUC (0-last) was calculated by linear-linear trapezoidal summation of DRV. PK data analysis set included all subjects who had received at least 1 dose of study drug.	
End point type	Primary
End point timeframe: Predose, up to 72 hours postdose (Up to Day 4)	

End point values	Treatment A (test): DRV/COBI 675/150 milligrams (mg) FDC	Treatment B (reference): DRV/COBI 675/150 milligrams (mg)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: nanograms*hour per millilitre (ng*h/mL)				
arithmetic mean (standard deviation)	82049 (± 24678)	84952 (± 26230)		

Statistical analyses

Statistical analysis title	Treatment A versus Treatment B
Statistical analysis description: Subjects analysed for both the treatments as per assigned treatment sequence in respective periods were 22.	
Comparison groups	Treatment A (test): DRV/COBI 675/150 milligrams (mg) FDC v Treatment B (reference): DRV/COBI 675/150 milligrams (mg)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Geometric Mean ratio
Point estimate	96.24
Confidence interval	
level	90 %
sides	2-sided
lower limit	90.46
upper limit	102.39

Primary: Area Under the Analyte Concentration-Time Curve from Time 0 to Infinite Time (AUC [0-Infinity]) of DRV

End point title	Area Under the Analyte Concentration-Time Curve from Time 0 to Infinite Time (AUC [0-Infinity]) of DRV
End point description: AUC (0-infinity) is defined as area under the analyte concentration-time curve from time 0 to infinite time. PK data analysis set included all subjects who had received at least 1 dose of study drug.	
End point type	Primary
End point timeframe: Predose, up to 72 hours postdose (Up to Day 4)	

End point values	Treatment A (test): DRV/COBI 675/150 milligrams (mg) FDC	Treatment B (reference): DRV/COBI 675/150 milligrams (mg)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: ng*h/mL				
arithmetic mean (standard deviation)	82254 (± 24705)	85161 (± 26232)		

Statistical analyses

Statistical analysis title	Treatment A versus Treatment B
Statistical analysis description: Subjects analysed for both the treatments as per assigned treatment sequence in respective periods were 22.	
Comparison groups	Treatment A (test): DRV/COBI 675/150 milligrams (mg) FDC v Treatment B (reference): DRV/COBI 675/150 milligrams (mg)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Geometric Mean Ratio
Point estimate	96.23
Confidence interval	
level	90 %
sides	2-sided
lower limit	90.47
upper limit	102.36

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

End point title	Maximum Observed Plasma Analyte Concentration (Cmax) of Cobicistat (COBI)
End point description: Cmax is the maximum observed plasma analyte concentration of COBI. Pharmacokinetics (PK) data analysis set included all subjects who had received at least 1 dose of study drug.	
End point type	Secondary
End point timeframe: Predose, up to 72 hours postdose (Up to Day 4)	

End point values	Treatment A (test): DRV/COBI 675/150 milligrams (mg) FDC	Treatment B (reference): DRV/COBI 675/150 milligrams (mg)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: ng/mL				
arithmetic mean (standard deviation)	807 (± 236)	861 (± 199)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Area Under the Analyte Concentration-Time Curve from Time 0 to Last Quantifiable Time (AUC [0-last]) of COBI
-----------------	--

End point description:

AUC (0-last) is defined as area under the analyte concentration-time curve from time 0 to time of the last quantifiable concentration. AUC (0-last) was calculated by linear-linear trapezoidal summation of COBI. PK data analysis set included all subjects who had received at least 1 dose of study drug.

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

End point timeframe:

Predose, up to 72 hours postdose (Up to Day 4)

End point values	Treatment A (test): DRV/COBI 675/150 milligrams (mg) FDC	Treatment B (reference): DRV/COBI 675/150 milligrams (mg)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: ng*h/mL				
arithmetic mean (standard deviation)	6499 (± 2475)	6931 (± 2520)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Analyte Concentration-Time Curve from Time 0 to Infinite Time (AUC [0-Infinity]) of COBI

End point title	Area Under the Analyte Concentration-Time Curve from Time 0 to Infinite Time (AUC [0-Infinity]) of COBI
-----------------	---

End point description:

AUC (0-infinity) is defined as area under the analyte concentration-time curve from time 0 to infinite time. PK data analysis set included all subjects who had received at least 1 dose of study drug.

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

End point timeframe:

Predose, up to 72 hours postdose (Up to Day 4)

End point values	Treatment A (test): DRV/COBI 675/150 milligrams (mg) FDC	Treatment B (reference): DRV/COBI 675/150 milligrams (mg)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: ng*h/mL				
arithmetic mean (standard deviation)	6613 (± 2525)	7027 (± 2539)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Adverse Events (AEs) as a Measure of Safety and Tolerability

End point title	Number of Subjects with Adverse Events (AEs) as a Measure of Safety and Tolerability
-----------------	--

End point description:

An AE 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. Safety data analysis set included all subjects who had received at least 1 dose of study drug.

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

End point timeframe:

Up to 6 weeks

End point values	Treatment A (test): DRV/COBI 675/150 milligrams (mg) FDC	Treatment B (reference): DRV/COBI 675/150 milligrams (mg)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: subjects	4	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 6 weeks

Adverse event reporting additional description:

All subjects who were randomly assigned to treatment and received at least 1 dose of the study drug were included in the safety analysis.

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	23.1
--------------------	------

Reporting groups

Reporting group title	Treatment A (test)
-----------------------	--------------------

Reporting group description:

Subjects received a single oral dose of DRV/COBI 675/150 milligrams (mg) as a scored FDC on Day 1 under fed condition.

Reporting group title	Treatment B (reference)
-----------------------	-------------------------

Reporting group description:

Subjects received a single oral dose of DRV 675 mg as DRV 600 mg plus DRV 75 mg and COBI 150 mg on Day 1 under fed condition.

Serious adverse events	Treatment A (test)	Treatment B (reference)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (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 A (test)	Treatment B (reference)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 22 (18.18%)	6 / 22 (27.27%)	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 22 (9.09%)	2 / 22 (9.09%)	
occurrences (all)	5	2	
Muscle Contractions Involuntary			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	

General disorders and administration site conditions Catheter Site Oedema subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 22 (0.00%) 0	
Gastrointestinal disorders Abdominal Pain Upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1 1 / 22 (4.55%) 1 0 / 22 (0.00%) 0	1 / 22 (4.55%) 1 0 / 22 (0.00%) 0 1 / 22 (4.55%) 1	
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 22 (4.55%) 1	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 22 (0.00%) 0	
Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Neck Pain subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1 1 / 22 (4.55%) 1 0 / 22 (0.00%) 0	0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 1 / 22 (4.55%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported