Clinical trial results:
HIV Post-Exposure Prophylaxis with Darunavir/r (PEPDar)

Summary

EudraCT number	2011-001303-13
Trial protocol	DE
Global end of trial date	28 September 2013

Results information

Result version number	v1 (current)
This version publication date	09 June 2016
First version publication date	09 June 2016

Trial information

Trial identification

Sponsor protocol code	TMC114IFD3004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01516970
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag G.m.b.H
Sponsor organisation address	Jonson & Johnson Platz 1, Neuss, 41470, Germany,
Public contact	Clinical Registry Group, Janssen-Cilag G.m.b.H, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag G.m.b.H, ClinicalTrialsEU@its.jnj.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	28 September 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assesse the rate of early discontinuation from randomized Human Immunodeficiency Virus (HIV) Post exposure Prophylaxis (PEP) for any reason other than confirmation of the negative HIV infection status of the index person in Participants receiving HIV PEP for at least 28 days, and a maximum of 30 days.

Protection of trial subjects:

Safety assessments included the monitoring of adverse events, clinical laboratory tests (Haematology, serum chemistry, and urinalysis), vital sign measurements, electrocardiogram (ECG) recordings, and performing physical examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 November 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 312
Worldwide total number of subjects	312
EEA total number of subjects	312

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)	312
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 324 Participants were screened, 305 were assigned to the per-protocol (PP) population, 310 to the Modified Intention-to-Treat (mITT) population and 312 to the Safety population.

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	Darunavir/Ritonavir PEP (DRV/r PEP)

Arm description:

Darunavir (800 mg) in combination with low-dose ritonavir (100 mg) administered once a day for at least 28 days and a maximum of 30 days along with 2 nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs). The NRTIs (including tenofovir/emtricitabine [Truvada], lamivudine/zidovudine [Combivir]) was administered as per the individual Summary of Product Characteristics (SmPCs) at the discretion of either the treating physician or Investigator.

Arm type	Experimental
Investigational medicinal product name	Darunavir
Investigational medicinal product code	SUB23573
Other name	DARUNAVIR ETHANOLATE
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Darunavir 800 mg in combination with low-dose ritonavir (100 mg) administered orally once a day for at least 28 days and a maximum of 30 days.

Investigational medicinal product name	RITONAVIR
Investigational medicinal product code	SUB10342MIG
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Ritonavir 100 mg in combination with darunavir 800 mg administered orally once a day for at least 28 days and a maximum of 30 days along with 2 nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs).

Investigational medicinal product name	LAMIVUDINE
Investigational medicinal product code	SUB08392MIG
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The NRTIs (including lamivudine/zidovudine [Combivir]) administered as per the individual Summary of Product Characteristics (SmPCs) at the discretion of either the treating physician or Investigator.

Investigational medicinal product name	ZIDOVUDINE
Investigational medicinal product code	SUB00153MIG
Other name	

Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The NRTIs (including lamivudine/zidovudine [Combivir]) administered as per the individual Summary of Product Characteristics (SmPCs) at the discretion of either the treating physician or Investigator.

Arm title	Standard of care Postexposure Prophylaxis (SOCPEP)

Arm description:

Standard of care HIV PEP (as per German-Austrian Guidelines): Administration of the standard of care HIV PEP (postexposure prophylaxis) consisting of 2 NRTIs plus third partner. The NRTIs (tenofovir/emtricitabine [Truvada], lamivudine/zidovudine [Combivir]) and LPV/r (Kaletra) administered as per the individual Summary of Product Characteristics (SmPCs) at the discretion of either the treating physician or Investigator.

Arm type	Experimental
Investigational medicinal product name	LOPINAVIR
Investigational medicinal product code	SUB02970MIG
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Lopinavir administered as per the individual Summary of Product Characteristics (SmPCs) at the discretion of either the treating physician or Investigator.

Investigational medicinal product name	RITONAVIR
Investigational medicinal product code	SUB10342MIG
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Ritonavir administered as per the individual Summary of Product Characteristics (SmPCs) at the discretion of either the treating physician or Investigator.

Investigational medicinal product name	ZIDOVUDINE
Investigational medicinal product code	SUB00153MIG
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Zidovudine administered as per the individual Summary of Product Characteristics (SmPCs) at the discretion of either the treating physician or Investigator.

Investigational medicinal product name	LAMIVUDINE
Investigational medicinal product code	SUB08392MIG
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Lamivudine administered as per the individual Summary of Product Characteristics (SmPCs) at the discretion of either the treating physician or Investigator.

Investigational medicinal product name	EFAVIRENZ
Investigational medicinal product code	SUB06463MIG
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Efavirenz administered as per the individual Summary of Product Characteristics (SmPCs) at the discretion of either the treating physician or Investigator.

Investigational medicinal product name	EMTRICITABINE
Investigational medicinal product code	SUB01882MIG
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Emtricitabine administered as per the individual Summary of Product Characteristics (SmPCs) at the discretion of either the treating physician or Investigator.

Investigational medicinal product name	TENOFOVIR DISOPROXIL FUMARATE
Investigational medicinal product code	SUB12607MIG
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tenofovir disoproxil fumarate administered as per the individual Summary of Product Characteristics (SmPCs) at the discretion of either the treating physician or Investigator.

Number of subjects in period 1	Darunavir/Ritonavir PEP (DRV/r PEP)	Standard of care Postexposure Prophylaxis (SOCPEP)
Started	159	153
Completed	142	132
Not completed	17	21
Consent withdrawn by subject	1	1
Other	8	7
Adverse event, serious non-fatal	1	5
Lost to follow-up	7	8

Baseline characteristics

Reporting groups

Reporting group title	Darunavir/Ritonavir PEP (DRV/r PEP)

Reporting group description:

Darunavir (800 mg) in combination with low-dose ritonavir (100 mg) administered once a day for at least 28 days and a maximum of 30 days along with 2 nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs). The NRTIs (including tenofovir/emtricitabine [Truvada], lamivudine/zidovudine [Combivir]) was administered as per the individual Summary of Product Characteristics (SmPCs) at the discretion of either the treating physician or Investigator.

Reporting group title	Standard of care Postexposure Prophylaxis (SOCPEP)

Reporting group description:

Standard of care HIV PEP (as per German-Austrian Guidelines): Administration of the standard of care HIV PEP (postexposure prophylaxis) consisting of 2 NRTIs plus third partner. The NRTIs (tenofovir/emtricitabine [Truvada], lamivudine/zidovudine [Combivir]) and LPV/r (Kaletra) administered as per the individual Summary of Product Characteristics (SmPCs) at the discretion of either the treating physician or Investigator.

Reporting group values	Darunavir/Ritonavir PEP (DRV/r PEP)	Standard of care Postexposure Prophylaxis (SOCPEP)	Total
Number of subjects	159	153	312
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	159	153	312
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	34.2	32.3	
standard deviation	± 9.2	± 9.33	-
Title for Gender Units: subjects			
Female	28	28	56
Male	131	125	256

End points

End points reporting groups

Reporting group title	Darunavir/Ritonavir PEP (DRV/r PEP)

Reporting group description:

Darunavir (800 mg) in combination with low-dose ritonavir (100 mg) administered once a day for at least 28 days and a maximum of 30 days along with 2 nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs). The NRTIs (including tenofovir/emtricitabine [Truvada], lamivudine/zidovudine [Combivir]) was administered as per the individual Summary of Product Characteristics (SmPCs) at the discretion of either the treating physician or Investigator.

Reporting group title	Standard of care Postexposure Prophylaxis (SOCPEP)

Reporting group description:

Standard of care HIV PEP (as per German-Austrian Guidelines): Administration of the standard of care HIV PEP (postexposure prophylaxis) consisting of 2 NRTIs plus third partner. The NRTIs (tenofovir/emtricitabine [Truvada], lamivudine/zidovudine [Combivir]) and LPV/r (Kaletra) administered as per the individual Summary of Product Characteristics (SmPCs) at the discretion of either the treating physician or Investigator.

Subject analysis set title	Per-Protocol (PP) Population
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol population (PP) was defined as all subjects in the mITT (modified intention-to-treat) population and who had received at least 1 dose of study medication.

Subject analysis set title	Modified Intention-to-Treat (mITT) Population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mITT population was defined as all subjects who were assigned to receive randomized HIV PEP and were not discontinued due to confirmation of the negative HIV infection status of the index person.

Subject analysis set title	Safety Analysis Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Analysis Set included all participants who received at least one dose of randomized HIV PEP.

Primary: Number of participants with early discontinuation from randomized human immunodeficiency virus postexposure prophylaxis (HIV PEP)

End point title	Number of participants with early discontinuation from randomized human immunodeficiency virus postexposure prophylaxis (HIV PEP)[1]

End point description:

Number of participants with early discontinuation from randomized HIV PEP for any reason other than confirmation of the negative HIV infection status of the index person in participants receiving HIV PEP for at least 28 days and a maximum of 30 days.

End point type	Primary

End point timeframe:

Up to 30 days

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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Darunavir/Ritonavir PEP (DRV/r PEP)	Standard of care Postexposure Prophylaxis (SOCPEP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155[2]	150[3]		
Units: participants				
number (confidence interval 95%)	10 (3.5 to 11.5)	15 (6.2 to 15.8)		

Notes:

[2] - PP

[3] - PP

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Adverse Events

End point title	Number of Participants With Treatment-Emergent Adverse Events

End point description:

A treatment-emergent adverse event (TEAE) was defined as an event that occurred in the 14-days treatment period during which it emerged (i.e. started or worsened in severity, relation, or other attribute), and even if the event continued to be present.

End point type	Secondary

End point timeframe:

Up to Month 3

End point values	Darunavir/Ritonavir PEP (DRV/r PEP)	Standard of care Postexposure Prophylaxis (SOCPEP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159[4]	153[5]		
Units: participants				
number (not applicable)	131	125		

Notes:

[4] - SAS

[5] - SAS

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in Patient reported outcome questionaire

End point title	Changes from baseline in Patient reported outcome questionaire

End point description:

Patient reported outcome (PRO) assessment of functional impairment in conjunction with HIV PEP in 3 inter-related domains (work, social life, and family life), as calculated from subject responses to the Sheehan Disability Scale (SDS) questionnaire.

End point type	Secondary

End point timeframe:

Up to Month 3

End point values	Darunavir/Ritonavir PEP (DRV/r PEP)	Standard of care Postexposure Prophylaxis (SOCPEP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159[6]	153[7]		
Units: unit on a scale				
arithmetic mean (standard deviation)				
Impairment in work/school/studies	2.566 (± 2.775)	3.503 (± 2.891)		
Impairment in social life	2.465 (± 2.594)	3.464 (± 2.786)		
Impairment in family life	2.226 (± 2.624)	2.954 (± 2.713)		
Overall	6.987 (± 7.25)	9.451 (± 7.709)		

Notes:

[6] - SAS

[7] - SAS

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The statistical analysis between the two treatment groups was performed for the factors "Impairment in work/school/studies'' with Wilcoxon-Mann-Whitney test.

Comparison groups	Darunavir/Ritonavir PEP (DRV/r PEP) v Standard of care Postexposure Prophylaxis (SOCPEP)
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0022
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

The statistical analysis between the two treatment groups was performed for the factors "Impairment in social life'' with Wilcoxon-Mann-Whitney test.

Comparison groups	Darunavir/Ritonavir PEP (DRV/r PEP) v Standard of care Postexposure Prophylaxis (SOCPEP)

Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0008
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

The statistical analysis between the two treatment groups was performed for the factors "Impairment in family life'' with Wilcoxon-Mann-Whitney test.

Comparison groups	Darunavir/Ritonavir PEP (DRV/r PEP) v Standard of care Postexposure Prophylaxis (SOCPEP)
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0071
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

The statistical analysis between the two treatment groups was performed for the factors "Overall'' with Wilcoxon-Mann-Whitney test.

Comparison groups	Darunavir/Ritonavir PEP (DRV/r PEP) v Standard of care Postexposure Prophylaxis (SOCPEP)
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0017
Method	Wilcoxon (Mann-Whitney)

Secondary: Percentage of participants who developed detectable HIV antibodies

End point title	Percentage of participants who developed detectable HIV antibodies

End point description:

Seroconversion rate of HIV antibodies while receiving HIV PEP evaluated as the percentage of participants who developed detectable HIV antibodies.

End point type	Secondary

End point timeframe:

At Month 3

End point values	Darunavir/Ritonavir PEP (DRV/r PEP)	Standard of care Postexposure Prophylaxis (SOCPEP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155[8]	150[9]		
Units: percentage				
number (not applicable)				
Negative	99.3	100		
Positive	0.7	0		

Notes:

[8] - PP

[9] - PP

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Month 3

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Standard of care Postexposure Prophylaxis (SOCPEP)

Reporting group description:

Comparator standard of care HIV PEP (as per German-Austrian Guidelines): Administration of the standard of care HIV PEP (postexposure prophylaxis) consisting of 2 NRTIs plus third partner.

Reporting group title	Darunavir/Ritonavir PEP (DRV/r PEP)

Reporting group description:

DRV/r 800/100 mg q.d. with 2 NRTIs: darunavir (800 mg) in combination with low-dose ritonavir (100 mg) administered once a day for at least 28 days and a maximum of 30 days along with 2 nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs).

Serious adverse events	Standard of care Postexposure Prophylaxis (SOCPEP)	Darunavir/Ritonavir PEP (DRV/r PEP)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 153 (0.00%)	0 / 159 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Standard of care Postexposure Prophylaxis (SOCPEP)	Darunavir/Ritonavir PEP (DRV/r PEP)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	111 / 153 (72.55%)	96 / 159 (60.38%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 153 (1.31%)	6 / 159 (3.77%)	
occurrences (all)	2	6	
Dysgeusia			

subjects affected / exposed	5 / 153 (3.27%)	1 / 159 (0.63%)	
occurrences (all)	5	1	
Headache			
subjects affected / exposed	8 / 153 (5.23%)	19 / 159 (11.95%)	
occurrences (all)	8	21	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 153 (0.65%)	5 / 159 (3.14%)	
occurrences (all)	1	5	
Fatigue			
subjects affected / exposed	28 / 153 (18.30%)	21 / 159 (13.21%)	
occurrences (all)	28	21	
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	11 / 153 (7.19%)	14 / 159 (8.81%)	
occurrences (all)	13	14	
Diarrhoea			
subjects affected / exposed	76 / 153 (49.67%)	45 / 159 (28.30%)	
occurrences (all)	80	46	
Flatulence			
subjects affected / exposed	11 / 153 (7.19%)	5 / 159 (3.14%)	
occurrences (all)	11	5	
Nausea			
subjects affected / exposed	41 / 153 (26.80%)	24 / 159 (15.09%)	
occurrences (all)	42	26	
Vomiting			
subjects affected / exposed	9 / 153 (5.88%)	10 / 159 (6.29%)	
occurrences (all)	9	11	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 153 (2.61%)	7 / 159 (4.40%)	
occurrences (all)	5	7	
Psychiatric disorders			
Sleep Disorder			
subjects affected / exposed	6 / 153 (3.92%)	0 / 159 (0.00%)	
occurrences (all)	6	0	

Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	4 / 153 (2.61%) 4	5 / 159 (3.14%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 October 2011	The overall reason for the amendment was to include participants with nonoccupational event with documented or potential for HIV exposure. Clarification about duration of treatment and drug accountability was only recorded for DRV/r, inclusion of stratification by exposure type due to the inclusion of subjects with non-occupational exposure, and clarification of statistical analysis in case of premature study termination, deletion of safety evaluations not relevant to the study, and reference to SmPC for Prezista deleted.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported