Clinical trial results:
PRotease-Inhibitors MOnotherapy Strategies as maintenance therapy in persons with fully suppressed HIV replication: results from an open-label randomized comparative trial (PRIMO Trial)

Summary

EudraCT number	2009-016697-32
Trial protocol	IT
Global end of trial date	10 October 2014

Results information

Result version number	v1 (current)
This version publication date	27 December 2019
First version publication date	27 December 2019

Trial information

Trial identification

Sponsor protocol code	INMI/001/09

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	National Institute for Infectious Diseases Lazzaro Spallanzani
Sponsor organisation address	Via Portuense 292, Rome, Italy, 00149
Public contact	Andrea Antinori, National Institute for Infectious Diseases Lazzaro Spallanzani, +39 0655170546, immunodeficienzevirali@inmi.it
Scientific contact	Andrea Antinori, National Institute for Infectious Diseases Lazzaro Spallanzani, +39 0655170546, immunodeficienzevirali@inmi.it

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	10 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 September 2013
Global end of trial reached?	Yes
Global end of trial date	10 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective of the trial was to compare the efficacy of different maintenance strategies based on PI/r monotherapy (LPV/r or DRV/RTV) in HIV-1 infected persons with fully suppressive PI/r based therapy.

Protection of trial subjects:

Exclusion of pregnant or breastfeeding woman

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 September 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 108
Worldwide total number of subjects	108
EEA total number of subjects	108

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)	102
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	122[1]
Number of subjects completed	108

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 4
Reason: Number of subjects	Physician decision: 10

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported to have started the pre-assignment period included 14 subjects who were screening failure and were not included inthe worldwide number enrolled in the trial.

Period 1

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

Blinding implementation details:

Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	ARM B

Arm description:

subjects switched to monotherapy based on LPV/r 800/200 mg QD

Arm type	Experimental
Investigational medicinal product name	monotherapy based on LPV/r 800/200 mg QD
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ARM B: Lopinavir/ritonavir 800/200 mg QD

Arm title	ARM C

Arm description:

subjects switched to monotherapy based on DRV/r 800/100 mg QD

Arm type	Experimental
Investigational medicinal product name	DRV/r 800/100 mg QD
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
subjects switched to monotherapy based on DRV/r 800/100 mg QD

Arm title	ARM A

Arm description:
ARM A: standard of care, participants continued triple therapy based on 2NRTI+1 boosted PI

Arm type	Active comparator
Investigational medicinal product name	2NRTI+1 boosted PI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
ARM A: standard of care, participants continued triple therapy based on 2NRTI+1 boosted PI

Number of subjects in period 1	ARM B	ARM C	ARM A
Started	35	38	35
Completed	17	29	24
Not completed	18	9	11
Consent withdrawn by subject	3	1	6
Physician decision	2	-	2
Adverse event, non-fatal	5	1	1
Pregnancy	1	1	-
Lost to follow-up	-	2	2
Lack of efficacy	7	4	-

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	108	108	
Age categorical			
Age at enrolement is calculated in years as the difference between the birth date and the screening date			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	102	102	
From 65-84 years	6	6	
85 years and over	0	0	
Age continuous			
Units: years			
median	45		
inter-quartile range (Q1-Q3)	36 to 50	-	
Gender categorical			
Units: Subjects			
Female	29	29	
Male	79	79	

End points

End points reporting groups

Reporting group title	ARM B
Reporting group description:	
subjects switched to monotherapy based on LPV/r 800/200 mg QD	
Reporting group title	ARM C
Reporting group description:	
subjects switched to monotherapy based on DRV/r 800/100 mg QD	
Reporting group title	ARM A
Reporting group description:	
ARM A: standard of care, participants continued triple therapy based on 2NRTI+1 boosted PI	
Subject analysis set title	Analisys B vs A
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention to treat population included all participants who were randomized and who have token at least one dose of study medication	
Subject analysis set title	Analisys C vs A
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention to treat population included all participants who were randomized and who have token at least one dose of study medication	

Primary: -Difference in percentage of subjects with a plasma HIV-RNA <50 cp/mL at week 48 of group B vs group A

End point title	-Difference in percentage of subjects with a plasma HIV-RNA <50 cp/mL at week 48 of group B vs group A[1]
End point description:	
The end point is the difference in percentage of subjects with a plasma HIV-RNA <50 cp/mL at week 48 of group B vs. group A	
End point type	Primary
End point timeframe:	
week 48	
Notes:	
[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: the groups of subjects applicable to this end point are only group B and group A	

End point values	ARM B	ARM A	Analisys B vs A	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	35	35	66	
Units: 40	17	23	40	

Statistical analyses

Statistical analysis title	non-inferiority design
Statistical analysis description:	
The end point is the difference in percentage of subjects with a plasma HIV-RNA <50 cp/mL at week 48 of group B vs. group A	
Comparison groups	ARM B v ARM A

Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	≤ 0.025 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Confidence interval	
sides	1-sided

Notes:

[2] - This analysis aims to test non-inferiority of arm B (LPV/r) versus arm A (triple regimen), with a non-inferiority margin of 12%, with one-sided significance level of p=0.025 and 80% power.
[3] - none comment

Primary: -Difference in percentage of subjects with a plasma HIV-RNA <50 cp/mL at week 48 of group C vs group A

End point title	-Difference in percentage of subjects with a plasma HIV-RNA <50 cp/mL at week 48 of group C vs group A[4]

End point description:

The end point is the difference in percentage of subjects with a plasma HIV-RNA <50 cp/mL at week 48 of group C vs. group A

End point type	Primary

End point timeframe:

week 48

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: the groups of subjects applicable to this end point are only group C and group A

End point values	ARM C	ARM A	Analisys C vs A	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	38	35	71	
Units: 27	27	23	50	

Statistical analyses

Statistical analysis title	non-inferiority design

Statistical analysis description:

The end point is the difference in percentage of subjects with a plasma HIV-RNA <50 cp/mL at week 48 of group C vs. group A

Comparison groups	ARM A v ARM C
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
P-value	≤ 0.025 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Confidence interval	
sides	1-sided

Notes:

[5] - This analysis aims to test non-inferiority of arm C (DRV/r) versus arm A (triple regimen), with a non-inferiority margin of 12%, with one-sided significance level of p=0.025 and 80% power

[6] - none comment

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to week 96

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	overall

Reporting group description: -

Serious adverse events	overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 103 (3.88%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Respiratory, thoracic and mediastinal disorders			
Pneumonia	Additional description: None additional description		
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Fracture	Additional description: None additional description		
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Necrosis	Additional description: femoral head necrosis		
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Febrile infection	Additional description: None additional description		

subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 103 (30.10%)		
Cardiac disorders			
pain	Additional description: praecordial pain and dyspnoea on exertion		
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Immune system disorders			
Rhinitis allergic	Additional description: allergic rhinoconjunctivitis		
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
reaction to ketoprofen	Additional description: cough, edema and eyelid erythema, itching of the trunk after taking Oki		
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	5 / 103 (4.85%)		
occurrences (all)	5		
Pain	Additional description: anal pain, pubic pain and fever		
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Gastroenteritis	Additional description: gastroenteritis		
alternative dictionary used: MedDRA 21			

subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Pregnancy			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Pharyngitis			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Bronchospasm			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
folliculitis			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Impetigo			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Wound	Additional description: lesion with secretion to left foot plant		
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Onychomycosis			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Anal fissure			

alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Fracture	Additional description: fibula and tibia fracture and patella right leg fracture		
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Umbilical hernia			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Back pain	Additional description: low back pain		
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Head injury			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Infections and infestations			
Anorectal infection	Additional description: anal condyloma wih high grade SIL		
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Herpes zoster	Additional description: one patient had mono dermatomeric herpes zooster and one patient had Thoracodorsal herpes zooster		
alternative dictionary used: MedDRA 21			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences (all)	2		
Varicella			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences (all)	2		
Viral skin infection	Additional description: plantar wart		

alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
diabetes			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Hyperamylasaemia			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Hyperlipidaemia			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 April 2011	PI substitution
10 March 2012	PI substitution
20 March 2012	PI substitution

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported