Clinical trial results:
A non-comparative phase II trial evaluating the capacity of the dual combination raltegravir/etravirine to maintain virological success in HIV-1 infected patients of at least 45 years of age with an HIV-RNA plasma viremia below 50 copies/mL under a current boosted protease inhibitor containing regimen.

Summary

EudraCT number	2014-000828-24
Trial protocol	ES
Global end of trial date	27 April 2018

Results information

Result version number	v1 (current)
This version publication date	18 April 2024
First version publication date	18 April 2024

Trial information

Trial identification

Sponsor protocol code	ANRS 163 ETRAL

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02212379
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Inserm-ANRS
Sponsor organisation address	101 rue de Tolbiac, Paris, France, 75013
Public contact	Pr. Christine Katlama, Service des Maladies Infectieuses et Tropicales, +33 1 42 16 01 42, christine.katlama@psl.aphp.fr
Scientific contact	Pr. Jacques Reynes, Département des Maladies Infectieuses et Tropicales, +33 4 67 33 72 20, j-reynes@chu-montpellier.fr

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	26 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate over 48 weeks of treatment the capacity to maintain virological success defined as the absence of 2 consecutive plasma viral loads > 50 copies/mL within 2 to 4 weeks of a dual raltegravir/etravirine regimen in HIV-1 infected patients, of at least 45 years of age, with suppressed plasma viremia switching from a boosted protease inhibitor-containing regimen.

Protection of trial subjects:

This study was conducted in accordance with the updated Declaration of Helsinki, in compliance with the approved protocol and its amendments, the International Council for Harmonisation guideline for Good Clinical Practice (ICH GCP), and French regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 January 2015
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	Spain: 21
Country: Number of subjects enrolled	France: 144
Worldwide total number of subjects	165
EEA total number of subjects	165

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)	146
From 65 to 84 years	19

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between January and November 2015, 219 patients from 20 centres were screened (signed inform consent) and 170 patients were enrolled in the study. 5 patients did not initiate the study treatment, leaving 165 patients for the analysis.

Pre-assignment

Screening details:

Main criteria:
Inclusion: at least 45 years old, documented HIV-1 infection, naïve to integrase inhibitor and etravirine.
Non-inclusion: previous exposure to raltegravir or etravirine, presence of any documented integrase integrase inhibitor mutation on DNA genotype at W-6/W-4 and/or on RNA in the medical history of the patient, HIV-2 infection

Period 1

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

Arms

Arm title	Single arm
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Raltegravir
Investigational medicinal product code	
Other name	RAL, Isentress®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Raltegravir will be administered as one 400 mg oral tablet twice daily after a meal (800 mg/day)

Investigational medicinal product name	Etravirine
Investigational medicinal product code	
Other name	ETR, Intelence®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Etravirine will be administered as one 200 mg oral tablet twice daily after a meal (400 mg/day).

Number of subjects in period 1	Single arm
Started	165
Primary endpoint analysis milestone	156
Completed	152
Not completed	13
Therapeutic failures	8
Virological failure	2

Treatment stop (not considered as failure)	3

Baseline characteristics

Reporting groups	
Reporting group title	Single arm

Reporting group description: -

Reporting group values	Single arm	Total	
Number of subjects	165	165	
Age categorical 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)	146	146	
From 65-84 years	19	19	
85 years and over	0	0	
Age continuous Units: years			
median	52		
inter-quartile range (Q1-Q3)	48 to 58	-	
Gender categorical Units: Subjects			
Female	48	48	
Male	117	117	

End points

End points reporting groups

Reporting group title	Single arm

Reporting group description: -

Primary: Virological success

End point title	Virological success[1]

End point description:

The proportion of patients remaining, at week 48, on virological success defined as the absence of 2 consecutive HIV-RNA plasma VL > 50 copies/mL 2 to 4 weeks apart.

End point type	Primary

End point timeframe:

At W48.

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: This endpoint concerns a single arm, adding statistical analyses create errors. See attachments for data.

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	165			
Units: Proportion of patients	99			

Attachments (see zip file)	ETRAL endpoint data/ETRAL_virological-success.png

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Participants reported adverse events during the entire trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Single arm

Reporting group description: -

Serious adverse events	Single arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 165 (17.58%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Papillary cystadenoma lymphomatosum			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Parathyroid tumour benign			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung cancer metastatic			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to bone			

subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Carotid arteriosclerosis			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Plastic surgery			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hysterectomy			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vocal cord operation			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Implantable defibrillator insertion			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	2 / 165 (1.21%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Asthenia				
subjects affected / exposed	1 / 165 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Prostatitis				
subjects affected / exposed	1 / 165 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Benign prostatic hyperplasia				
subjects affected / exposed	1 / 165 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Feminisation acquired				
subjects affected / exposed	1 / 165 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pneumothorax				
subjects affected / exposed	1 / 165 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 165 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Agitation				
subjects affected / exposed	1 / 165 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Persecutory delusion				

subjects affected / exposed	1 / 165 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	1 / 165 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Pulse absent				
subjects affected / exposed	1 / 165 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 165 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Stab wound				
subjects affected / exposed	1 / 165 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	2 / 165 (1.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Spinal column injury				
subjects affected / exposed	1 / 165 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	1 / 165 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post herpetic neuralgia			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar radiculopathy			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Macular hole			

subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Anal fistula			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tooth loss			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Glomerulonephritis minimal lesion			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	2 / 165 (1.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Tendonitis			

subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Prostatitis Escherichia coli			
subjects affected / exposed	2 / 165 (1.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Epididymitis			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anal abscess			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection bacterial			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4.85 %

Non-serious adverse events	Single arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	159 / 165 (96.36%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 165 (6.06%)		
occurrences (all)	16		
Blood creatine phosphokinase increased			
subjects affected / exposed	17 / 165 (10.30%)		
occurrences (all)	38		
Vascular disorders			
Hypertension			
subjects affected / exposed	14 / 165 (8.48%)		
occurrences (all)	15		
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 165 (12.73%)		
occurrences (all)	23		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	16 / 165 (9.70%)		
occurrences (all)	17		
Influenza like illness			
subjects affected / exposed	11 / 165 (6.67%)		
occurrences (all)	12		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	9 / 165 (5.45%)		
occurrences (all)	10		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	12 / 165 (7.27%)		
occurrences (all)	12		
Constipation			
subjects affected / exposed	17 / 165 (10.30%)		
occurrences (all)	19		
Diarrhoea			

subjects affected / exposed occurrences (all)	15 / 165 (9.09%) 16		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 15 / 165 (9.09%) 16		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 8 / 165 (4.85%) 8		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 13 / 165 (7.88%) 13		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 20 / 165 (12.12%) 24 18 / 165 (10.91%) 19 9 / 165 (5.45%) 10		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 17 / 165 (10.30%) 19 18 / 165 (10.91%) 21		
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all) Hypertriglyceridaemia	 8 / 165 (4.85%) 13		

subjects affected / exposed occurrences (all)	8 / 165 (4.85%) 14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2015	The substantial modifications included in the amendment 1 of the protocol are: - to change an inclusion criterion in the trial - to modify the time between pre-inclusion and inclusion - the modification of the project team of the clinical trial unit and of the composition of the scientific board - minor corrections/modifications to the protocol - minor corrections on the information note - to modify the summary of the trial in French for modifications of the inclusion criterion, contacts at the clinical trial unit.
21 February 2018	The substantial modifications included in the amendement 2 of the protocol are: - to add secondary objectives and criteria for a sub-study - to change the storage location for the biobank - to change the principal investigator to the Jean Verdier hospital in Bondy - some clarifications and corrections in the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31269208

http://www.ncbi.nlm.nih.gov/pubmed/30815916