Clinical trial results:
Evaluation of the pharmacokinetic properties and the tolerance of raltegravir during the third trimester of pregnancy

Summary

EudraCT number	2013-004571-12
Trial protocol	FR
Global end of trial date	31 January 2017

Results information

Result version number	v1 (current)
This version publication date	08 March 2024
First version publication date	08 March 2024
Summary attachment (see zip file)	Summary of final report ANRS RalFE (RRF-ANRS 160 RalFE.pdf)

Trial information

Trial identification

Sponsor protocol code	ANRS 160 Ralfe

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02099474
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Inserm-ANRS
Sponsor organisation address	101 rue de Tolbiac, Paris, France, 75013
Public contact	Jade Ghosn, CHU Hôtel Dieu, +33 1 42 34 88 52, jade.ghosn@htd.aphp.fr
Scientific contact	Jade Ghosn, CHU Hôtel Dieu, +33 1 42 34 88 52, jade.ghosn@htd.aphp.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	30 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2017
Global end of trial reached?	Yes
Global end of trial date	31 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To study pharmacokinetic properties of raltegravir in pregnant women infected by HIV-1, during the third trimester of pregnancy (between 30 and 37 weeks of amenorrhoea) and 1 month after childbirth (between W4 and W6 post-partum), as well as in their neonate.

Protection of trial subjects:

This study is 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	30 June 2014
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	France: 43
Worldwide total number of subjects	43
EEA total number of subjects	43

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)	43
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From June 2014 to May 2016, 45 participants were screened from 12 sites (2 maternity and 10 departments of infectious disease or internal medicine).

Pre-assignment

Screening details:

Main criteria for the expecting mothers:
Inclusion: pregnant women at least 18 years old, between W30 and W37 of amenorrhoea, infected by HIV-1.
Non-inclusion: under 18 years old, infected by HIV-2.

Main criteria for the pharmacologic study in neonates:
Inclusion: mother included in the study, weight >=1000kg.
Non-inclusion: weight <1000k.

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	RalFE arm
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Raltégravir
Investigational medicinal product code	
Other name	Isentress®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dosage of 400mg twice a day.

Number of subjects in period 1	RalFE arm
Started	43
Completed	42
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	RalFE arm

Reporting group description: -

Reporting group values	RalFE arm	Total	
Number of subjects	43	43	
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)	43	43	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	33		
inter-quartile range (Q1-Q3)	29 to 38	-	
Gender categorical Units: Subjects			
Female	43	43	
Male	0	0	

End points

End points reporting groups

Reporting group title	RalFE arm

Reporting group description: -

Primary: Pharmacokinetic properties of raltegravir in pregnant women

End point title	Pharmacokinetic properties of raltegravir in pregnant women[1]

End point description:

The principal objective of this trial is to study pharmacokinetic properties of raltegravir in pregnant women infected by HIV-1, during the third trimester of pregnancy (between 30 and 37 weeks of amenorrhoea) and 1 month after childbirth (between 4 and 6 weeks post-partum), as well as in their neonates.

End point type	Primary

End point timeframe:

Pharmacokinetic study conducted twice, once between W30 and W37 of amenorrhoea and once between W4 and W6 post-partum.

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 attachment for additional informations.

End point values	RalFE arm			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: concentration				
number (not applicable)	43			

Attachments (see zip file)	RalFE

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From 30-Jun-2014 to 30-Apr-2017

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Raltegravir

Reporting group description:

All women have been prescribed raltegravir before study participation.
17 subjects were affected by serious adverse events: 8 mothers and 9 children.

Serious adverse events	Raltegravir		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 43 (39.53%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
overdose	Additional description: Neonate Serious Adverse Event		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
skull fracture	Additional description: Neonate Serious Adverse Event		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
subdural haematoma	Additional description: Neonate Serious Adverse Event		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
brachydactyly	Additional description: Neonate Serious Adverse Event		

subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
enteric duplication	Additional description: Neonate Serious Adverse Event		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
congenital genitourinary abnormality	Additional description: Neonate Serious Adverse Event		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
polydactyly	Additional description: Neonate Serious Adverse Event		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
renal aplasia	Additional description: renal agenesis with pericardial effusion diagnosed during pregnancy		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
pericardial effusion	Additional description: renal agenesis with pericardial effusion diagnosed during pregnancy		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
subarachnoid haemorrhage	Additional description: Neonate Serious Adverse Event		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
foetal growth restriction			

subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
foetal heart rate disorder			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
poor weight gain neonatal	Additional description: Neonate Serious Adverse Event		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
gestational diabetes			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
foetal malnutrition	Additional description: Neonate Serious Adverse Event		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
pre-eclampsia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
premature baby	Additional description: Neonate Serious Adverse Event		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
vomiting in pregnancy			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
microcytic anaemia			

subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
general physical health deterioration			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
gastrooesophageal reflux disease	Additional description: Neonate Serious Adverse Event		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
cholestasis of pregnancy			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
hepatocellular injury			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
hyperbilirubinaemia neonatal	Additional description: Neonate Serious Adverse Event		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
abdominal wall abscess			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
oral fungal infection	Additional description: Neonate Serious Adverse Event		

subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
pyelonephritis acute	Additional description: Neonate Serious Adverse Event		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Raltegravir		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 43 (90.70%)		
Vascular disorders			
hypertension arterial			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	0		
Pregnancy, puerperium and perinatal conditions			
false labour			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	0		
fœtal growth restriction			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	0		
pre-eclampsia			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	0		
gestational diabetes			
subjects affected / exposed	6 / 43 (13.95%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
anaemia			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	0		
Gastrointestinal disorders			

vomiting			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	0		
Infections and infestations			
gastroenteritis	Additional description: Neonate Serious Adverse Event		
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	0		
nasopharyngitis	Additional description: Neonate Serious Adverse Event		
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	0		
oral candidiasis	Additional description: Neonate Serious Adverse Event		
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	0		
vaginal infection			
subjects affected / exposed	8 / 43 (18.60%)		
occurrences (all)	0		
vulvovaginal mycotic infection			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2015	The substantial modifications included in the Amendment 1 of the protocol are: - Update of the centres' list and main investigators. - Modification of authorized range to carry out the pre-inclusion visit: between W28 and W37 of amenorrhoea.
18 December 2015	The substantial modifications included in Amendment 2 of the protocol are: - Extension of the enrolment period and modification of the number of participants to include.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported