Clinical trial results:
Efficacy of atazanavir/ritonavir monotherapy as maintenance in patients with viral suppression. Randomized, open label non inferiority trial. (MODAt STUDY)

Summary

EudraCT number	2010-020442-10
Trial protocol	IT
Global end of trial date	24 June 2015

Results information

Result version number	v1 (current)
This version publication date	04 March 2020
First version publication date	04 March 2020
Summary attachment (see zip file)	Modat1 (106.pdf) Modat2 (application-pdf.pdf) Modat3 (dkw031.pdf) Modat4 (immunoMODAt def.pdf)

Trial information

Trial identification

Sponsor protocol code	MODAt

Additional study identifiers

ISRCTN number	ISRCTN01511809
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ospedale San Raffaele
Sponsor organisation address	Via Stamira d'Ancona 20, Milan, Italy,
Public contact	Castagna Antonella, Ospedale San Raffaele, 0039 0226437934, castagna.antonella1@hsr.it
Scientific contact	Castagna Antonella, Ospedale San Raffaele, 0039 0226437934, castagna.antonella1@hsr.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	30 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2013
Global end of trial reached?	Yes
Global end of trial date	24 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To assess the non-inferiority of virological efficacy at week 48 of a monotherapy strategy with atazanavir/ritonavir vs atazanavir/ritonavir-based HAART, in patients treated with an ATV/r-based HAART since at least 48 weeks, fully suppressed since at least 24 weeks and with no previous virologic failures.

Protection of trial subjects:

Helsinky Declaration, CEE Regulations, GCP for trials on medical products in the European Coomunity, Italian ICH.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 October 2010
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	Italy: 103
Worldwide total number of subjects	103
EEA total number of subjects	103

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)	103
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Inclusion criteria:
- age > 18 years
- HIV infected patients
- First line ATV/r based HAART with ATV/r plus 2 NRTIs for at least 48 weeks
- Virological suppression (HIV-RNA<50 c/ml) by at least 24 weeks with ATV/r plus 2 NRTIs
- CD4 cells nadir >100 cells/µL
- PPI and H2-receptor antagonists as follows: the PPI were not allowed

Pre-assignment

Screening details:

Inclusion criteria:
- age > 18 years
- HIV infected patients
- First line ATV/r based HAART with ATV/r plus 2 NRTIs for at least 48 weeks
- Virological suppression (HIV-RNA<50 c/ml) by at least 24 weeks with ATV/r plus 2 NRTIs
- CD4 cells nadir >100 cells/µL
- PPI and H2-receptor antagonists as follows: the PPI were not allowed

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ATV/RTV monotherapy

Arm description:

Simplify therapy to ATV/RTV 300 mg/100 mg OD as a monotherapy

Arm type	Experimental
Investigational medicinal product name	ATV/RTV 300 mg/100 mg OD as a monotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ATV/RTV 300 mg/100 mg OD as a monotherapy

Arm title	Control Arm ATV/r 300/100 mg QD + 2 NRTI

Arm description:

Control Arm ATV/r 300/100 mg QD + 2 NRTI

Arm type	Active comparator
Investigational medicinal product name	Control Arm ATV/r 300/100 mg QD + 2 NRTI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Control Arm ATV/r 300/100 mg QD + 2 NRTI

Number of subjects in period 1[1]	ATV/RTV monotherapy	Control Arm ATV/r 300/100 mg QD + 2 NRTI
Started	50	51
Completed	41	32
Not completed	9	19
Consent withdrawn by subject	4	2
Physician decision	-	1
Drugs Interaction	-	1
Adverse event, non-fatal	3	13
Lost to follow-up	2	-
Lack of efficacy	-	2

Notes:

[1] - The number of subjects reported to be in the baseline 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 stop of the enrollment in the trial was the object of a specific amendment during the study (Amendment dated 22 Jul 2013).

Baseline characteristics

Reporting groups

Reporting group title	Atazanavir/ritonavir monotherapy

Reporting group description: -

Reporting group values	Atazanavir/ritonavir monotherapy	Total	
Number of subjects	101	101	
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)	101	101	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	14	14	
Male	87	87	

Subject analysis sets

Subject analysis set title	Primary efficacy analysis at week 48
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Assessment of noninferiority of ATV/r compared with ATV/r along with two NRTIs was done with a twosided 95% confidence interval (95% CI) of the difference in percentage of patients with treatment success (monotherapy – triple therapy): a lower limit of the 95% CI of the difference between the two proportions below the prespecified margin of noninferiority of 10% would establish inferiority.

Reporting group values	Primary efficacy analysis at week 48		
Number of subjects	103		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	103		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
Female	16		
Male	87		

End points

End points reporting groups

Reporting group title	ATV/RTV monotherapy
Reporting group description:	
Simplify therapy to ATV/RTV 300 mg/100 mg OD as a monotherapy	
Reporting group title	Control Arm ATV/r 300/100 mg QD + 2 NRTI
Reporting group description:	
Control Arm ATV/r 300/100 mg QD + 2 NRTI	
Subject analysis set title	Primary efficacy analysis at week 48
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Assessment of noninferiority of ATV/r compared with ATV/r along with two NRTIs was done with a twosided 95% confidence interval (95% CI) of the difference in percentage of patients with treatment success (monotherapy – triple therapy): a lower limit of the 95% CI of the difference between the two proportions below the prespecified margin of noninferiority of 10% would establish inferiority.	

Primary: Proportion of patient with treatment success at week 48

End point title	Proportion of patient with treatment success at week 48
End point description:	
End point type	Primary
End point timeframe:	
Intention to treat week 48	

End point values	ATV/RTV monotherapy	Control Arm ATV/r 300/100 mg QD + 2 NRTI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: Proportions	50	51		

Statistical analyses

Statistical analysis title	Assessment of non inferiority of monoth. ATV/RTV
Statistical analysis description:	
Assessment of noninferiority of ATV/r compared with ATV/r along with two NRTIs was done with a twosided 95% confidence interval (95% CI) of the difference in percentage of patients with treatment success (monotherapy – triple therapy): a lower limit of the 95% CI of the difference between the two proportions below the prespecified margin of noninferiority of 10% would establish inferiority.	
Comparison groups	Control Arm ATV/r 300/100 mg QD + 2 NRTI v ATV/RTV

	monotherapy
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	Mantel-Haenszel

Adverse events

Adverse events information	
Timeframe for reporting adverse events: from baseline to 96 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	AE of ATV/RTV monotherapy Arm
Reporting group description: -	
Reporting group title	AE in control arm triple therapy
Reporting group description: -	

Serious adverse events	AE of ATV/RTV monotherapy Arm	AE in control arm triple therapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 52 (7.69%)	2 / 51 (3.92%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Coronary artery occlusion			
subjects affected / exposed	4 / 52 (7.69%)	2 / 51 (3.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Rectal haemorrhage			
subjects affected / exposed	4 / 52 (7.69%)	2 / 51 (3.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			

subjects affected / exposed	0 / 52 (0.00%)	2 / 51 (3.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Right basal pneumonia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	AE of ATV/RTV monotherapy Arm	AE in control arm triple therapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 52 (11.54%)	20 / 51 (39.22%)	
Injury, poisoning and procedural complications			
Traumatic haematoma			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	0	
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	0	
Hepatobiliary disorders			
Hepatitis alcoholic			
subjects affected / exposed	4 / 52 (7.69%)	19 / 51 (37.25%)	
occurrences (all)	0	0	
Cholecystitis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	0	
Psychiatric disorders			

Panic attack			
subjects affected / exposed	1 / 52 (1.92%)	0 / 51 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 52 (0.00%)	3 / 51 (5.88%)	
occurrences (all)	0	0	
Proteinuria			
subjects affected / exposed	0 / 52 (0.00%)	2 / 51 (3.92%)	
occurrences (all)	0	0	
Haematuria			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	0	
Arthralgia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	0	
Infections and infestations			
Infection			
subjects affected / exposed	4 / 52 (7.69%)	0 / 51 (0.00%)	
occurrences (all)	0	0	
Infections			
subjects affected / exposed	0 / 52 (0.00%)	8 / 51 (15.69%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 October 2011	In order to facilitate the enrollment of patients in the national study as much as possible, the inclusion criteria are changed, making it possible to include patients under treatment with atazanavir / ritonavir 300/100 mg plus 2 NRTIs for at least 48 weeks with viral load suppressed (HIV-RNA <50 copies) for at least 24 weeks in the absence of previous virological failure after starting antiretroviral treatment. Patients with previous treatment schedules modified for toxicity or therapeutic simplification will be admitted provided that this has occurred during virological suppression and that there is such documentation available in the folder. The inclusion criterion in which the documentation of the genotype present at the beginning of the HAART certifying the absence of resistance to atazanavir was mandatory for entry into the study is eliminated.
29 October 2012	Following the slow enrollment of the satellite centers involved in the study and on the basis of the illustrated data, in order to protect the patients already enrolled, it is believed to amend the protocol in order to anticipate the interim evaluations confirming the effectiveness of the experimental treatment. Therefore, the sample size on which the interim analysis will be carried out is changed, reducing it from 171 to 100 patients.
03 December 2012	country specific amendment to include Spain in the enrollments (never enrollment were obtain)
22 July 2013	In consideration of the DSMB communication that assessed the interim analysis of the data carried out at week 48 of the first 103 patients enrolled, the protocol is amended in order to specify that no other patients will be screened and enrolled in the study. Based on DSMB recommendations, patients enrolled in the study to date (117) will be able to remain in the study and continue follow-up until the last patient has reached the 96th week of the study. Patients will therefore continue after week 96 to go to the center every 12 weeks for scheduled visits, agreeing to stay in the study by signing the new informed consent form for the patient version of 07/22/2013. The atazanavir drug for the arm of patients on monotherapy will continue to be supplied by BMS as per the existing contract.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported