Clinical trial results:
An open-label, randomized, controlled clinical trial to assess the safety, tolerability and efficacy of two dolutegravir-based simplification strategies in HIV-infected patients with prolonged virological suppression

Summary

EudraCT number	2015-000274-35
Trial protocol	ES
Global end of trial date	21 November 2019

Results information

Result version number	v1 (current)
This version publication date	02 February 2022
First version publication date	02 February 2022

Trial information

Trial identification

Sponsor protocol code	DOLAM

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	FUNDACIÓ CLÍNIC PER A LA RECERCA BIOMÈDICA
Sponsor organisation address	C/ Rosselló, 149-153, Barcelona, Spain,
Public contact	Sponsor, FUNDACIÓ CLÍNIC PER A LA RECERCA BIOMÈDICA (ESPAÑA), ++34 93 227 55 74, ESTEBANM@clinic.cat
Scientific contact	Clinical Research Associates, Fundació Lluita contra la SIDA, ++34 934978414, cherrero@fls-rs.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	31 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the virological efficacy at week 48 of the bitherapy dolutegravir plus lamivudine and the monotherapy dolutegravir in comparison with a triple antiretroviral regimen.

Protection of trial subjects:

not specific

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 June 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 265
Worldwide total number of subjects	265
EEA total number of subjects	265

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)	265
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was done at six major HIV clinics in Catalonia, Spain (July 2015 - October 2018):

- H. Germans Trias i Pujol, Badalona
- H. Clínic de Barcelona
- H. U. de Bellvitge, Hospitalet de Llobregat
- H. U. Vall d'Hebron, Barcelona
- H. de la Santa Creu i Sant Pau, Barcelona
- H. Arnau de Vilanova, Lleida

Pre-assignment

Screening details:

DOLAM is a phase 4, randomised, open-label, non-inferiority trial. Adults with HIV-1 receiving a triple ART regimen, aged 18 years or older, with virological suppression, a CD4 nadir of at least 200 cells per µL, who were HBsAg-negative, and without previous viral failure or resistance mutations to study drugs were eligible.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Control Arm

Arm description:

To continue current triple ART

Arm type	Control
Investigational medicinal product name	Triple ART
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Orally once daily

Arm title	Experimental Arm

Arm description:

switched to dolutegravir 50 mg plus lamivudine 300 mg orally once daily

Arm type	Experimental
Investigational medicinal product name	Dolutegravir 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Orally once daily (every 24 hours)

Investigational medicinal product name	Lamivudine 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet

Routes of administration	Oral use

Dosage and administration details:

Lamivudine 300mg orally once daily (every 24 hours)

Number of subjects in period 1	Control Arm	Experimental Arm
Started	134	131
Completed	124	122
Not completed	10	9
Consent withdrawn by subject	2	1
Treatment discontinuation	4	3
Virological failure	2	3
Lost to follow-up	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Control Arm
Reporting group description:	
To continue current triple ART	
Reporting group title	Experimental Arm
Reporting group description:	
switched to dolutegravir 50 mg plus lamivudine 300 mg orally once daily	

Reporting group values	Control Arm	Experimental Arm	Total
Number of subjects	134	131	265
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	134	131	265
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
median	46	45	
full range (min-max)	39 to 51	37 to 53	-
Gender categorical			
Units: Subjects			
Female	18	20	38
Male	116	111	227

End points

End points reporting groups

Reporting group title	Control Arm
Reporting group description: To continue current triple ART	
Reporting group title	Experimental Arm
Reporting group description: switched to dolutegravir 50 mg plus lamivudine 300 mg orally once daily	

Primary: Proportion of people with HIV RNA values of at least 50 copies per mL at week 48

End point title	Proportion of people with HIV RNA values of at least 50 copies per mL at week 48
End point description: The primary endpoint was the proportion of people with HIV RNA values of at least 50 copies per mL at week 48 (US Food and Drug Administration [FDA] snapshot algorithm, 8% non-inferiority margin) evaluated in the intention-to-treat exposed population	
End point type	Primary
End point timeframe: at week 48	

End point values	Control Arm	Experimental Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	131		
Units: Proportion of people				
number (confidence interval 95%)	2 (-3.3 to 5.2)	3 (-3.3 to 5.2)		

Statistical analyses

Statistical analysis title	Newcombe Method
Statistical analysis description: The proportions of people with confirmed HIV of at least 50 copies per mL were assessed in each group and the 95% CI of the difference was based on the Newcombe method. Non-inferiority would be proven if the upper bound of the CI of the difference in proportions did not cross over the prespecified margin of 8%. If the lower bound was above 0, then superiority would be assessed using the Fisher's exact test.	
Comparison groups	Control Arm v Experimental Arm
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.05
Method	Diff. in proportion (Newcombe method 10)

Secondary: Changes in CD4 cells

End point title	Changes in CD4 cells

End point description:

End point type	Secondary

End point timeframe:
at week 48

End point values	Control Arm	Experimental Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	131		
Units: cells per µl				
number (confidence interval 95%)	32 (-11 to 75)	30 (-15 to 74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in CD8 cells

End point title	Changes in CD8 cells

End point description:

End point type	Secondary

End point timeframe:
at week 48

End point values	Control Arm	Experimental Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	131		
Units: Cells per µL				
number (confidence interval 95%)	-7 (-56 to 41)	24 (-26 to 74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in fasting plasma lipids: Total Cholesterol	
End point title	Changes in fasting plasma lipids: Total Cholesterol
End point description:	

End point type	Secondary
End point timeframe:	
baseline Vs Week 48	

End point values	Control Arm	Experimental Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	131		
Units: mg/dL				
number (confidence interval 95%)				
Baseline	186 (179 to 192)	188 (180 to 193)		
At week 48	187 (181 to 194)	185 (178 to 192)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in fasting plasma lipids: LDL Cholesterol	
End point title	Changes in fasting plasma lipids: LDL Cholesterol
End point description:	

End point type	Secondary
End point timeframe:	
Baseline Vs Week 48	

End point values	Control Arm	Experimental Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	131		
Units: mg/dL				
number (confidence interval 95%)				
Baseline	112 (106 to 119)	112 (107 to 118)		
Week 48	114 (108 to 121)	112 (106 to 118)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in fasting plasma lipids: Total-to-HDL cholesterol ratio

End point title	Changes in fasting plasma lipids: Total-to-HDL cholesterol ratio

End point description:

End point type	Secondary

End point timeframe:

Baseline Vs Week 48

End point values	Control Arm	Experimental Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	131		
Units: mg/dL				
number (confidence interval 95%)				
Baseline	4.07 (3.87 to 4.27)	4.36 (4.16 to 4.56)		
Week 48	3.88 (3.68 to 4.08)	4.05 (3.85 to 4.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in fasting plasma lipids: HDL Cholesterol

End point title	Changes in fasting plasma lipids: HDL Cholesterol

End point description:

End point type	Secondary

End point timeframe:

Baseline Vs Week 48

End point values	Control Arm	Experimental Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	131		
Units: mg/dL				
number (confidence interval 95%)				
Baseline	47 (44 to 49)	47 (45 to 49)		
48 Weeks	50 (47 to 52)	48 (46 to 51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated glomerular filtration rate

End point title	Estimated glomerular filtration rate

End point description:

End point type	Secondary

End point timeframe:

at week 48

End point values	Control Arm	Experimental Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	131		
Units: mL/min per 1.73 m2				
median (inter-quartile range (Q1-Q3))	98 (82 to 107)	96 (84 to 106)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proteinuria

End point title	Proteinuria

End point description:

End point type	Secondary

End point timeframe:

At week 48

End point values	Control Arm	Experimental Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	131		
Units: mg/g creatinine				
median (inter-quartile range (Q1-Q3))	63 (41 to 85)	70 (41 to 98)		

Statistical analyses

No statistical analyses for this end point

Secondary: Weight

End point title	Weight

End point description:

End point type	Secondary

End point timeframe:

At week 48

End point values	Control Arm	Experimental Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	131		
Units: Kg				
median (inter-quartile range (Q1-Q3))	72 (67 to 79)	75 (67 to 83)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of blips

End point title	Incidence of blips

End point description:

End point type	Secondary

End point timeframe:

At week 48

End point values	Control Arm	Experimental Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	131		
Units: Episodes per 100 patient-years				
number (not applicable)	9.3	14.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with one or more blips

End point title	Number of participants with one or more blips

End point description:

End point type	Secondary

End point timeframe:

At week 48

End point values	Control Arm	Experimental Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	131		
Units: Participants				
number (not applicable)	10	15		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From Baseline to week 48 follow up	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	DAIDS AE GRADING
Dictionary version	2.0
Reporting groups	
Reporting group title	Control Arm
Reporting group description: To continue current triple ART	
Reporting group title	Experimental Arm
Reporting group description: switched to dolutegravir 50 mg plus lamivudine 300 mg orally once daily	

Serious adverse events	Control Arm	Experimental Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 134 (3.73%)	3 / 131 (2.29%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Severe Aortic Stenosis			
subjects affected / exposed	1 / 134 (0.75%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Appendicitis			
subjects affected / exposed	1 / 134 (0.75%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Hip Fracture			
subjects affected / exposed	0 / 134 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Listeria monodytogenes bacteremia			
subjects affected / exposed	1 / 134 (0.75%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial endocarditis			
subjects affected / exposed	1 / 134 (0.75%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Liver abscess			
subjects affected / exposed	0 / 134 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Control Arm	Experimental Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	78 / 134 (58.21%)	73 / 131 (55.73%)	
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	3 / 134 (2.24%)	0 / 131 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Neurological			
subjects affected / exposed	8 / 134 (5.97%)	14 / 131 (10.69%)	
occurrences (all)	8	14	
Blood and lymphatic system disorders			
Systemic			
subjects affected / exposed	16 / 134 (11.94%)	19 / 131 (14.50%)	
occurrences (all)	16	19	
Laboratory test abnormal			
subjects affected / exposed	5 / 134 (3.73%)	1 / 131 (0.76%)	
occurrences (all)	5	1	
Eye disorders			

Ocular o visual			
subjects affected / exposed	0 / 134 (0.00%)	2 / 131 (1.53%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	23 / 134 (17.16%)	26 / 131 (19.85%)	
occurrences (all)	23	26	
Respiratory, thoracic and mediastinal disorders			
Respiratory			
subjects affected / exposed	17 / 134 (12.69%)	18 / 131 (13.74%)	
occurrences (all)	17	18	
Skin and subcutaneous tissue disorders			
Dermatological			
subjects affected / exposed	8 / 134 (5.97%)	14 / 131 (10.69%)	
occurrences (all)	8	14	
Renal and urinary disorders			
Genitourinary			
subjects affected / exposed	16 / 134 (11.94%)	12 / 131 (9.16%)	
occurrences (all)	16	12	
Musculoskeletal and connective tissue disorders			
Musculoskeletal			
subjects affected / exposed	19 / 134 (14.18%)	16 / 131 (12.21%)	
occurrences (all)	19	16	
Infections and infestations			
Infections			
subjects affected / exposed	35 / 134 (26.12%)	28 / 131 (21.37%)	
occurrences (all)	35	28	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2016	(1) Interim Analysis report at 6 months from the last patient included in the phase A. (2) No-follow up after virological failure
27 May 2017	(1) Study design modification: Deletion of the monotherapy arm in phase B (following DSMB recommendation) (2) Sites extension (3) Update of concomitant medication for the control arm (4) New sample number, modification of the study inclusion. (3) Update of the statistical analysis according to the new legislation (RD 1090/2015).
26 February 2018	(1) Sponsor Change (From Fundació Lluita Contra la Sida to Fundació Clínic per la recerca biomèdica) (2) Change of the PI from Hospital Arnau de Vilanova (3) Update of the study calendar (4) Update of the selection criteria (5) Update of the study Schedule (6) Update secundary variables and endpoints. (7) Safety and adverse events section update (8) Section update of Insurance policy and budget (9) Creation of a new substudy protocol about lumbar punction.

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/34358497