



## Clinical trial results:

### EFFICACY AND SAFETY OF A SIMPLIFICATION STRATEGY BASED ON DOLUTEGRAVIR AND DARUNAVIR / COBICISTAT VS OPTIMIZED TREATMENT IN SUPPRESSED HIV-1-INFECTED PATIENTS CARRYING ARCHIVED MULTIDRUG RESISTANCE MUTATIONS

#### Summary

EudraCT number	2017-004750-42
Trial protocol	ES
Global end of trial date	10 August 2021

#### Results information

Result version number	v1 (current)
This version publication date	22 February 2024
First version publication date	22 February 2024

#### Trial information

##### Trial identification

Sponsor protocol code	2D-STUDY
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03683524
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Fundació de Lluita contra la SIDA, les Malalties Infeccioses i la Promoció de la Salut i La Ciència
Sponsor organisation address	S/N Carretera de Canyet, Badalona, Spain,
Public contact	Project Manager, Fundació Lluita contra les Infeccions, +34 93497 84 14, jtoro@fls-rs.com
Scientific contact	Project Manager, Fundació Lluita contra les Infeccions, +34 93497 84 14, jtoro@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	10 August 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 August 2021
Global end of trial reached?	Yes
Global end of trial date	10 August 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate and compare the efficacy of DTG plus DRV/cobi bithery as a once-daily simplification strategy versus maintenance of the current antiretroviral regimen in maintaining virological suppression (RNA HIV-1 < 50 copies/mL) at Week 48 (by Time to Loss of Virological Response, TLOVR) in well suppressed and highly experienced patients harboring archived DRM against at least two antiretroviral classes.

Protection of trial subjects:

When 75% of the planned sample has been enrolled and has reached its Week 12 visit, an interim efficacy review will be done by an independent Data Monitoring Committee (Internal DMC), to ensure the rate of virologic failure is not unacceptably high. An efficacy rate (by TLOVR) of < 80% will be considered unacceptable and cause the study to be prematurely stopped.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2018
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: 89
Worldwide total number of subjects	89
EEA total number of subjects	89

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)	89
From 65 to 84 years	0

85 years and over	0
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## Subject disposition

### Recruitment

Recruitment details:

The study was performed at Hospital Universitari Germans Trias I Pujol. The recruitment starts on December 2018 (being the First Patient First Visit) and ends in January 2021 (the Last Patient First Visit).

### Pre-assignment

Screening details:

The study population consists of HIV-1-infected and outpatient adults ( $\geq 18$  years) who have sustained virological suppression (RNA HIV-1  $< 50$  copies/mL) and harbour archived DRM against at least two antiretroviral classes, but with DRV/Cobi and Integrase Strand Transfer Inhibitor (INSTI) fully active.

### 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
<b>Arm title</b>	Experimental Arm

Arm description:

Bitherapy based on DTG (50 mg QD) plus DRV/cobi (800/150 mg QD)

Arm type	Experimental
Investigational medicinal product name	Dolutegravir
Investigational medicinal product code	
Other name	DTG QD
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosage: 50 mg daily.

Administration details: Orally administered during the 48 weeks of follow-up.

Investigational medicinal product name	Darunavir/cobicistat
Investigational medicinal product code	
Other name	DRV/Cobi QD
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

dosage: 800/150 mg od DRV/Cobi QD

Administration details: Orally administered during the 48 weeks of follow-up

<b>Arm title</b>	Control Group
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Arm description:

Continuation of their current stable ART.

The control treatment will be the participants' current stable TAR, including triple antiretroviral therapy based

on protease inhibitors, non-nucleoside and nucleoside reverse transcriptase inhibitors, integrase inhibitors and

CCR5 receptor antagonists on routine clinical practice

Arm type	Active comparator
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Investigational medicinal product name	Triple Antiretroviral Therapy
Investigational medicinal product code	
Other name	NRTI, NNRTI, NRTIs, PIs, INI, CCR5 Receptor antagonist
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The formulation of the study products will be the commercial one.

Both treatments will be orally administered during the 48 weeks of follow-up.

<b>Number of subjects in period 1</b>	Experimental Arm	Control Group
Started	45	44
Completed	39	42
Not completed	6	2
Adverse event, non-fatal	3	-
Lost to follow-up	3	-
Virological Failures	-	2

## Baseline characteristics

### Reporting groups

Reporting group title	Overall Trial
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Reporting group description:

Between December 2018 and January 2021, 96 subjects were randomized. One individual in each group withdrew his or her informed consent before baseline. In addition, three participants in the 2D group and two more in the SOC group were excluded before baseline due to protocol violation. Therefore, the ITT analysis set included 89 subjects: 45 in the 2D group and 44 in the SOC group

Reporting group values	Overall Trial	Total	
Number of subjects	89	89	
Age categorical			
The mean (SD) age of subjects was 55 (9.2) years, 68 (76.4%) were male and subjects had a median (IQR) time since HIV diagnosis of 25 (23.0 – 28.0) years.			
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)	89	89	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
median	55		
standard deviation	± 9.2	-	
Gender categorical			
68 (76.4%) of the study subjects were male			
Units: Subjects			
Female	21	21	
Male	68	68	

## End points

### End points reporting groups

Reporting group title	Experimental Arm
Reporting group description: Bithery based on DTG (50 mg QD) plus DRV/cobi (800/150 mg QD)	
Reporting group title	Control Group
Reporting group description: Continuation of their current stable ART. The control treatment will be the participants' current stable TAR, including triple antiretroviral therapy based on protease inhibitors, non-nucleoside and nucleoside reverse transcriptase inhibitors, integrase inhibitors and CCR5 receptor antagonists on routine clinical practice	
Subject analysis set title	ITT analysis set
Subject analysis set type	Intention-to-treat
Subject analysis set description: ITT analysis set included 89 subjects: 45 in the 2D group and 44 in the SOC group	

### Primary: Proportion of participants with HIV-1 RNA <50 copies/mL at week 48 with an analysis based on time to loss of virologic response (TLOVR)

End point title	Proportion of participants with HIV-1 RNA <50 copies/mL at week 48 with an analysis based on time to loss of virologic response (TLOVR)
End point description: Virologic failure was defined as detection of HIV-1 RNA $\geq 50$ copies/mL at 2 consecutive visits measured within 2 to 4 weeks or as a single determination of HIV-1 RNA $\geq 50$ copies/mL followed by premature treatment discontinuation. A genotyping test was performed at virologic failure confirmation. If adverse events resulted in treatment discontinuation or dropout, they were treated as virologic failure for efficacy assessment. The Kaplan-Meier estimation was used to describe TLOVR analysis for all participants and by treatment arm.	
End point type	Primary
End point timeframe: At week 48	

End point values	Experimental Arm	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	44		
Units: percent				
number (not applicable)	95.5	86.7		

### Statistical analyses

Statistical analysis title	The Kaplan-Meier estimator
Statistical analysis description: In the primary efficacy analysis, the Kaplan-Meier estimator will be used to describe the TLOVR, for all patients and by the treatment arms	

Comparison groups	Experimental Arm v Control Group
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[1]</sup>
P-value	= 0.392
Method	Logrank
Parameter estimate	noninferiority limit
Point estimate	12.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.05
upper limit	12.5
Variability estimate	Standard deviation
Dispersion value	0.05

Notes:

[1] - The sample size was estimated to provide 80% power with a two-sided alpha value of 0.05 to detect 90% efficacy (according to the TLVOR analysis) in the group of subjects treated with DTG plus DRV/c with a noninferiority limit of 12.5%

### Secondary: Number of participants developing ART-associated adverse events leading to treatment discontinuation

End point title	Number of participants developing ART-associated adverse events leading to treatment discontinuation
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End point description:

In the 2D group, 3 patients experienced adverse events leading to treatment discontinuation, and an additional 3 patients were lost to follow-up, as opposed to none in the SOC group.

End point type	Secondary
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End point timeframe:

At week 48

End point values	Experimental Arm	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	44		
Units: Number of participants	3	0		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of participants with HIV-1 RNA <50 copies/mL at week 48 per the Food and Drug Administration (FDA) snapshot algorithm

End point title	Proportion of participants with HIV-1 RNA <50 copies/mL at week 48 per the Food and Drug Administration (FDA) snapshot algorithm
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End point description:

The proportion with HIV-1 RNA <50 copies/mL at week 48 according to the FDA snapshot was evaluated. In the FDA snapshot analysis, participants were classified according to 3 outcomes:  
Responders: HIV-1 RNA <50 copies/mL at week 48



Nonresponders: HIV-1 RNA  $\geq 50$  copies/mL at week 48— participants with virologic failure or blips (in window) or participants who discontinued the study drug because of adverse events, death, or other reasons before week 48 with last available HIV-1 RNA  $\geq 50$  copies/mL

No virologic data: participants who discontinued the study drug before week 48 for reasons other than low efficacy, including adverse event and death with last available HIV-1 RNA  $< 50$  copies/mL, and participants who were still taking the study drug but for whom HIV-1 RNA data were missing at week 48

End point type	Secondary
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End point timeframe:

at week 48

End point values	Experimental Arm	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	44		
Units: Participants				
number (not applicable)	39	42		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Changes in CD4+ cell counts and biochemical parameters during the follow-up

End point title	Changes in CD4+ cell counts and biochemical parameters during the follow-up
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End point description:

The median (IQR) change from baseline in CD4+ cell count at week 48 was  $-1.0$  cells/mm<sup>3</sup> ( $-2.9$  to  $0.5$ ) in the 2D arm and  $0.4$  cells/mm<sup>3</sup> ( $-2.7$  to  $2.8$ ) in the SOC arm ( $P = .130$ )

End point type	Secondary
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End point timeframe:

At week 48

End point values	Experimental Arm	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	44		
Units: cells/mm <sup>3</sup>				
number (not applicable)	-1.0	0.4		

## Statistical analyses

No statistical analyses for this end point

## Secondary: The emergence of new DRMs in the protease and integrase genes of the

## HIV-1 in participants experiencing virologic failure

End point title	The emergence of new DRMs in the protease and integrase genes of the HIV-1 in participants experiencing virologic failure
End point description: Participants had a median 3 (2–8) and 5 (4–7) associated DRMs in the genes of protease and reverse transcriptase, respectively	
End point type	Secondary
End point timeframe: At 48 weeks	

End point values	Experimental Arm	Control Group	ITT analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	45	44	89	
Units: Mutations	0	0	0	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Changes in the lipid profile during the follow-up

End point title	Changes in the lipid profile during the follow-up
End point description: The median change in total cholesterol from baseline was –0.8 mg/dL (–19.3 to 26.0) in the 2D group and 3.00 mg/dL (–10.0 to 15.5) in the SOC group (P = .970).  Median changes in low- and high-density lipoprotein cholesterol were 0.0 mg/dL (–26.6 to 24.0) and –1.1 mg/dL (–6.4 to 4.4) in the 2D group and –2.3 mg/dL (–19.0 to 16.0) and –2.0 mg/dL (–5.4 to 2.8) in the SOC group (P = .590 and P = .740), respectively.  Triglyceride levels did not show significant changes, with a median change of –7.0 mg/dL (–35.3 to 60.0) in the 2D group and 10.0 mg/dL (–17.3 to 40.6) in the SOC group (P = .570).	
End point type	Secondary
End point timeframe: At week 48	

End point values	Experimental Arm	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	44		
Units: mg/dL				
number (not applicable)				
Cholesterol total	–0.8	3.0		
LDL	0.0	–2.3		
HDL	–1.1	–2.0		
Triglycerides	–7.0	10.0		

## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From 01-Jun-2018 to 10-Aug-2021

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	10
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### Reporting groups

Reporting group title	Experimental Group
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Reporting group description:

Bithérapie based on DTG (50 mg QD) plus DRV/cobi (800/150 mg QD)

Reporting group title	Control Group
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Reporting group description:

Continuation of their current stable ART

Serious adverse events	Experimental Group	Control Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 45 (6.67%)	3 / 44 (6.82%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Sleep disorder due to general medical condition, hypersomnia type			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	2 / 45 (4.44%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystectomy			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			

subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Hip prosthesis insertion			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Respiratory infection			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Experimental Group	Control Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 45 (51.11%)	24 / 44 (54.55%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Haematoma			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	2	
Injury			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	5	
General disorders and administration site conditions			
Dental discomfort			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	3	
Dental sepsis			

subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	1 / 44 (2.27%) 2	
Fever subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 44 (0.00%) 0	
Somnolence subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 2	0 / 44 (0.00%) 0	
Weight increased subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 44 (0.00%) 0	
Reproductive system and breast disorders Vaginal disorder subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 3	0 / 44 (0.00%) 0	
Prostatitis subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 44 (0.00%) 0	
Prostatism subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 44 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Pharyngitis subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 44 (0.00%) 0	
Cold subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 2	4 / 44 (9.09%) 9	
Tonsillitis subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 44 (2.27%) 1	
Respiratory infection subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 5	2 / 44 (4.55%) 5	
Influenza			

subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Catarrh			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	4	
Bronchitis			
subjects affected / exposed	1 / 45 (2.22%)	4 / 44 (9.09%)	
occurrences (all)	1	7	
Cough			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	3	
Tracheobronchitis bacterial			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	3	
Chest pain			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences (all)	5	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 45 (4.44%)	1 / 44 (2.27%)	
occurrences (all)	2	12	
Depression			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Stress			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Cardiac disorders			
Systolic dysfunction			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences (all)	4	0	
Nervous system disorders			

Anosmia subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 44 (2.27%) 1	
Eye disorders			
Stye subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 44 (0.00%) 0	
Blurry vision subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 44 (2.27%) 1	
Eyelid cyst subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 44 (2.27%) 1	
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 44 (2.27%) 2	
Visual acuity reduced subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 44 (2.27%) 1	
Gastrointestinal disorders			
Asthenia subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 44 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	4 / 44 (9.09%) 10	
Anal fissure subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 5	0 / 44 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 44 (0.00%) 0	
Gastritis bacterial subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 44 (0.00%) 0	
Gastritis viral			



subjects affected / exposed	1 / 45 (2.22%)	1 / 44 (2.27%)	
occurrences (all)	1	2	
Dyspepsia			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Reflux gastritis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	2	
Anal injury			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Dysplasia			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Steatohepatitis			
subjects affected / exposed	1 / 45 (2.22%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
Transaminases decreased			
subjects affected / exposed	0 / 45 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
Bowenoid papulosis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
Oedema mouth			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	3	
Herpes dermatitis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
Candida infection			
subjects affected / exposed	2 / 45 (4.44%)	0 / 44 (0.00%)	
occurrences (all)	4	0	
Onychomycosis			

subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Exeresis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	10	
Boil			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Infection urinary tract			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
Renal failure			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Gonalgia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	2 / 45 (4.44%)	1 / 44 (2.27%)	
occurrences (all)	2	2	
Carpal tunnel syndrome			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Pain back			
subjects affected / exposed	1 / 45 (2.22%)	1 / 44 (2.27%)	
occurrences (all)	1	3	
Arthromyalgia			

subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)
occurrences (all)	1	0
Trigger finger		
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	1
Whiplash injury		
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	2
Abdominal pain localized		
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)
occurrences (all)	2	0
Fracture		
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	12
Vertigo		
subjects affected / exposed	2 / 45 (4.44%)	0 / 44 (0.00%)
occurrences (all)	4	0
Osteoporosis		
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)
occurrences (all)	1	0
Lumbosacral pain		
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)
occurrences (all)	1	0
Muscular pain		
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)
occurrences (all)	2	0
Fasciitis plantar		
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	6
Trauma		
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	1
Post traumatic pain		
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	2
Omalgia		

subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 44 (2.27%) 3	
Infections and infestations Dent's disease subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 2	0 / 44 (0.00%) 0	

**More information**

**Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 July 2019	Expansion of centers including in the study the University Hospital and La Fe Polytechnic and Son Espases University Hospital and minor protocol changes (no relevants).

Notes:

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**Interruptions (globally)**

Were there any global interruptions to the trial? No

**Limitations and caveats**

None reported