Clinical trial results:
Phase II, open, one-site, pilot Clinical trial for assessing the pharmacokinetic characteristics, safety and tolerability after conversion of the immuno-suppressive regimen with Advagraf® to Envarsus® in patients with stable pulmonary transplant.

Summary

EudraCT number	2015-005519-34
Trial protocol	ES
Global end of trial date	09 May 2017

Results information

Result version number	v1 (current)
This version publication date	26 December 2021
First version publication date	26 December 2021

Trial information

Trial identification

Sponsor protocol code	ENVARUS

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	VHIR
Sponsor organisation address	Passeig Vall Hebron 119-129, Barcelona, Spain, 08035
Public contact	Joaquin Lopez Soriano, Fundació Hospital Universitari Vall d'Hebron - Institut de Recerca (VHIR), 0034 934894779, joaquin.lopez.soriano@vhir.org
Scientific contact	Antonio Román - Servicio de Neumología, Fundació Hospital Universitari Vall d'Hebron - Institut de Recerca (VHIR), 0034 934893000, aroman@vhebron.net

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	09 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determinate and compare the tacrolimus pharmacokinetic profile in stable pulmonary transplant patients after the conversion 1:0.7 from Advagraf® to Envarsus®

Protection of trial subjects:

Patients had been in postoperative follow-up for more than 6 months. On day 16 after enrollment, patients were admitted to the hospital for determination of their 24-hour pharmacokinetic profile. Patients with chronic allograft dysfunction and those with an episode of acute cellular rejection in the previous 3 months were excluded from the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2016
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: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	16
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

At recruitment, patients remained under ODT for 30 days per protocol. On day 16 after enrollment, patients were admitted to the hospital for determination of their 24-hour pharmacokinetic profile. On day 31, patients were switched from ODT to LCPTin a 1:0.7 (mg/mg) conversion ratio, according to manufacturer's recommendations.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	20
Number of subjects completed	20

Period 1

Period 1 title	ODT
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	ODT treatment

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

ODT: Oral Daily Treatment per 30 days
LCPT: Oral once-daily extended-release formulation, in ratio 0.7:1 (mg:mg) compared to ODT.
The dose of tacrolimus had to remain stable with an individualized target level of Cmin between 5 and 15 ng/mL in 2 determinations performed before enrollment,with a minimum interval of 6 days between them.

Number of subjects in period 1	ODT treatment
Started	20
Completed	20

Period 2

Period 2 title	LCPT
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	LCTP switch

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

ODT: Oral Daily Tretament per 30 days
LCPT: Oral once-daily extended-release formulation, in ratio 0.7:1 (mg:mg) compared to ODT.
The dose of tacrolimus had to remain stable with an individualized target level of Cmin between 5 and 15 ng/mL in 2 determinations performed before enrollment,with a minimum interval of 6 days between them.

Number of subjects in period 2	LCTP switch
Started	20
Completed	20

Baseline characteristics

Reporting groups

Reporting group title	ODT

Reporting group description: -

Reporting group values	ODT	Total	
Number of subjects	20	20	
Age categorical Units: Subjects			
Adults	20	20	
Gender categorical Units: Subjects			
Female	7	7	
Male	13	13	

Subject analysis sets

Subject analysis set title	ODT to LCTP conversion
Subject analysis set type	Full analysis

Subject analysis set description:

Afert recruitment, patients remained under ODT for 30 days per protocol. On day 16 after enrollment, patients were admitted to the hospital for determination of their 24-hour pharmacokinetic profile. On day 31, patients were switched from ODT to LCPTin a 1:0.7 (mg/mg) conversion ratio, according to manufacturer's recommendations in Europe as well as previous data in renal transplant

Reporting group values	ODT to LCTP conversion		
Number of subjects	20		
Age categorical Units: Subjects			
Adults	20		
Gender categorical Units: Subjects			
Female	7		
Male	13		

End points

End points reporting groups

Reporting group title	ODT treatment
Reporting group description: -	
Reporting group title	LCTP switch
Reporting group description: -	
Subject analysis set title	ODT to LCTP conversion
Subject analysis set type	Full analysis

Subject analysis set description:

Afert recruitment, patients remained under ODT for 30 days per protocol. On day 16 after enrollment, patients were admitted to the hospital for determination of their 24-hour pharmacokinetic profile. On day 31, patients were switched from ODT to LCPTin a 1:0.7 (mg/mg) conversion ratio, according to manufacturer's recommendations in Europe as well as previous data in renal transplant

Primary: AUC 0-24

End point title	AUC 0-24

End point description:

End point type	Primary

End point timeframe:

All study

End point values	ODT treatment	LCTP switch		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: units				
number (confidence interval 95%)	253.97 (225 to 282.94)	282.44 (169 to 452)		

Statistical analyses

Statistical analysis title	AUC 0-24
Comparison groups	ODT treatment v LCTP switch
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1762
Method	ANOVA

Primary: Cmin 0-24

End point title	Cmin 0-24

End point description:

End point type	Primary

End point timeframe:

All the study

End point values	ODT treatment	LCTP switch		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: ng/mL				
number (confidence interval 95%)	6.85 (5.99 to 7.7)	7.75 (6.83 to 8.66)		

Statistical analyses

Statistical analysis title	C min at 0-24
Comparison groups	ODT treatment v LCTP switch
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1552
Method	ANOVA

Primary: Cmax 0-24

End point title	Cmax 0-24

End point description:

End point type	Primary

End point timeframe:

All the study

End point values	ODT treatment	LCTP switch		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: ng/L				
arithmetic mean (confidence interval 95%)	18.70 (16.07 to 21.32)	17.57 (15.81 to 19.33)		

Statistical analyses

Statistical analysis title	Cmax 0-24 h
Comparison groups	LCTP switch v ODT treatment
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.849
Method	ANOVA

Primary: Tmax 0-24 h	
End point title	Tmax 0-24 h
End point description:	
End point type	Primary
End point timeframe:	
All the study	

End point values	ODT treatment	LCTP switch		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: hour				
arithmetic mean (confidence interval 95%)	2.07 (1 to 4.08)	5.28 (3 to 8.07)		

Statistical analyses

Statistical analysis title	Tmax 0-24 hour
Comparison groups	ODT treatment v LCTP switch
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All the study

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Total adverse events

Reporting group description: -

Serious adverse events	Total adverse events		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 20 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Atypical atrial flutte			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic lung allograft dysfunction			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Renal and urinary disorders Renal colic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 20 (5.00%) 0 / 1 0 / 0		
Infections and infestations Facial herpes subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 20 (5.00%) 0 / 1 0 / 0		

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

Non-serious adverse events	Total adverse events		
Total subjects affected by non-serious adverse events subjects affected / exposed	 16 / 20 (80.00%)		
Nervous system disorders Insomnia subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1		
Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all) Lupus anticoagulant hypoprothrombinaemia syndrome subjects affected / exposed occurrences (all) Hypertension subjects affected / exposed occurrences (all) Venous insufficiency subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 2 / 20 (10.00%) 2 1 / 20 (5.00%) 1		
Ear and labyrinth disorders Tinnitus			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Eye disorders			
Blurred vision			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Diarrhea			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Prostatic hyperplasia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Upper respiratory fungal infection			
subjects affected / exposed	10 / 20 (50.00%)		
occurrences (all)	10		
transitory worsening of respiratory function			

subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Skin and subcutaneous tissue disorders Papule subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1		
Renal and urinary disorders Worsening of renal function subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1		
Musculoskeletal and connective tissue disorders Ankle edema subjects affected / exposed occurrences (all) Intermitent claudication subjects affected / exposed occurrences (all) Achiles tendinopathy subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 3 / 20 (15.00%) 3 4 / 20 (20.00%) 4		
Infections and infestations Perianal streptococcal infection subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

A potential limitation of the study design is the short follow-up period, which prevents efficacy and safety from being assessed in the long term. The study population (mainly white) may not be representative of other ethnicities.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29965950