Clinical trial results:
EFFICACY OF THE NEW TACROLIMUS ONCE-DAILY DOSE LCTP (ENVARSUS®) FORMULATION TO PREVENT HYPERGLYCAEMIA AFTER KIDNEY TRANSPLANTATION IN AT-RISK PATIENTS: A RANDOMISED, CONTROLLED, OPEN-LABEL PILOT STUDY.

Summary

EudraCT number	2017-000718-52
Trial protocol	ES
Global end of trial date	26 September 2023

Results information

Result version number	v1 (current)
This version publication date	10 August 2024
First version publication date	10 August 2024

Trial information

Trial identification

Sponsor protocol code	DMPT-17

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Hospital Universitario de Canarias
Sponsor organisation address	Ofra s/n, La Laguna, Spain, 38320
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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	26 May 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 May 2022
Global end of trial reached?	Yes
Global end of trial date	26 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate whether de novo immunosuppression with the extended-release formulation of Tacrolimus®, Envarsus®, reduces the incidence of post-transplant diabetes mellitus (PTDM), defined by fasting blood glucose, after oral glucose tolerance test (OGTT) or by the use of antidiabetic drugs, compared to the standard formulation of Tacrolimus® (Prograf®), in patients at high risk of post-transplant diabetes.
INCLUSION CRITERIA
- 18 years or older were eligible to participate.
- One of the following "metabolic criteria" must be met inter alia:
a) Age ≥ 60 years or b) age < 60 years and one of these two risk factors:
- Glucose intolerance (glycemia after 120min of a standard OGTT ≥140 and <200 mg/dl)
- Metabolic syndrome (3 criteria): Impaired fasting glucose (100-125 mg/dl); Body Mass Index (BMI) ≥28 kg/m2; BP (>140/90, or on antihypertensive medication); Triglycerides ≥150 mg/dl; HDL cholesterol <40 mg/dl in men and <50 mg/dl in women.

Protection of trial subjects:

This is a Phase-IV clinical trial and all participants received standard of care to minimize pain and stress. In addition, all patients participating in this clinical trial have been covered by the contracted Insurance Policy.

Background therapy:

Mycophenolate mofetil (MMF) or Mycophenolic Acid
Corticosteroids (methylprednisolone; prednisone)
Induction therapy: Basiliximab (anti-CD25 antibody) or Thymoglobulin (depending on donor/recipient characteristics).
Treatment to prevent early glucotoxicity: I.V.Insulin.
Treatment of acute humoral rejection: plasmapheresis, immunoglobulins, and rituximab, alone or in combination.
Drugs to prevent the most common infections: Pneumocystis jirovecii (cotrimoxazol) and cytomegalovirus (gancyclovir and valgancyclovir).
Medications for dyslipidemia: statins or ezetimibe.

Evidence for comparator:

Tacrolimus use in patients with pre-transplant risk factors such as metabolic syndrome and insulin resistance increases the risk of PTDM.

The pharmacokinetics of different formulations of tacrolimus (immediate release: Prograf; sustained release: Advagraf; and the new once-daily meltdose-technology formulation LCTP-Envarsus®) have recently been compared. The LCTP formulation delays (Tmax) and reduces peak exposure (17% reduction in Cmax) and increases biodisponibility compared to Prograf and Advagraf without affecting overall exposure. This "flatter" pharmacokinetic profile of LCTP-Envarsus® compared to the other tacrolimus formulations may have clinical relevance if it is shown to result in less pancreatic beta-cell toxicity and thus a lower incidence of PTDM.

In other words, there is sufficient evidence to support the hypothesis that patients at high risk of PTDM may benefit from tacrolimus pharmacokinetics with lower peak (Cmax) exposure as provided by the LCTP formulation. This may translate into a significant reduction in glycemia and glycotoxicity and ultimately the incidence of PTDM in the first three months post-transplant compared to other tacrolimus formulations.

Actual start date of recruitment	30 August 2017
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: 62
Worldwide total number of subjects	62
EEA total number of subjects	62

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)	31
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

62 patients were randomized during the study period and 52 completed the study (27 in the Prograf arm and 25 in the Envarsus arm). According to the planned withdrawal criteria, 3 patients in the Prograf group and 7 in the Envarsus group were excluded (p=0.3).

Pre-assignment

Screening details:

There was no pre-assignment period

Period 1

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

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	IR-TAC (PROGRAF)

Arm description:

Arm 1: Prograf divided into two doses. On the day of transplantation, a single dose was administered before surgery. This is the standard clinical practice of the HUC Nephrology Department.

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

Dosage and administration details:

Arm 1: Prograf 0.1 mg/kg/day divided into two doses to maintain tacrolimus levels between 8-12 ng/ml for the first month and 6-10ng/ml until the third month. Before of transplantation, a single dose of 0.05 mg/kg or 0.10 mg/kg was administered before surgery, depending on whether the donor met the expanded criteria or not. This is the standard clinical practice of the HUC Nephrology Department.

Investigational medicinal product name	Mycophenolate mofetil (MMF)
Investigational medicinal product code	
Other name	Micofenolato mofetil (MMF)
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Mycophenolate mofetil (MMF) 2 g/day or mycophenolic acid (EC-MFA) 1.44 g/day for the first month post-transplant. From day 31 MMF or EC-MA will be reduced to 1 g/day or 720 mg/day, respectively.

Investigational medicinal product name	methylprednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Corticosteroids at reduced exposure: 0.25 g methylprednisolone intraoperatively and 60 mg on post-transplant day 1

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Corticosteroids at reduced exposure: Prednisone 0.3 mg/Kg/day (never >20 mg/day) until post-transplant day 14, 0. 2 mg/kg/day from day 15 to 28 (never >15 mg/day), 0.15 mg/kg/day from day 29 to 35 (never >10 mg/day), 0.1 mg/kg/day (never >7.5 mg/day) from day 36 to 42, and then 5 mg/day until 3 months.

Arm title	LCTP (ENVARSUS)

Arm description:

Arm 2: Envarsus® as a single daily dose starting within 24 hours after transplantation.

Arm type	Experimental
Investigational medicinal product name	ENVARSUS
Investigational medicinal product code	
Other name	Sustained-release tacrolimus
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Arm 2: Envarsus® 0.1 mg/kg/day as a single daily dose starting within 24 hours after transplantation to maintain tacrolimus levels of 8-12 ng/ml for the first month and 6-10 ng/ml until 3 months.

Investigational medicinal product name	Mycophenolate mofetil (MMF)
Investigational medicinal product code	
Other name	Micofenolato mofetil (MMF)
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Mycophenolate mofetil (MMF) 2 g/day or mycophenolic acid (EC-MA) 1.44 g/day for the first month post-transplant. From day 31 MMF or EC-MA will be reduced to 1 g/day or 720 mg/day, respectively.

Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Corticosteroids at reduced exposure: 0.25 g methylprednisolone intraoperatively, 60 mg on post-transplant day 1

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Corticosteroids at reduced exposure: From day 2 posttransplant prednisone 0.3 mg/Kg/day (never >20 mg/day) until post-transplant day 14, 0. 2 mg/kg/day from day 15 to 28 (never >15 mg/day), 0.15 mg/kg/day from day 29 to 35 (never >10 mg/day), 0.1 mg/kg/day (never >7.5 mg/day) from day 36 to 42, and then 5 mg/day until 3 months.

Number of subjects in period 1	IR-TAC (PROGRAF)	LCTP (ENVARSUS)
Started	30	32
Completed	27	25
Not completed	3	7
Immunosuppresion change	1	-
Randomized not transplanted	1	-
Adverse event + immunosupression change	-	5
Adverse event, non-fatal	-	2
Refusal of final OGTT	1	-

Baseline characteristics

Reporting groups	
Reporting group title	IR-TAC (PROGRAF)
Reporting group description:	
Arm 1: Prograf divided into two doses. On the day of transplantation, a single dose was administered before surgery. This is the standard clinical practice of the HUC Nephrology Department.	
Reporting group title	LCTP (ENVARSUS)
Reporting group description:	
Arm 2: Envarsus® as a single daily dose starting within 24 hours after transplantation.	

Reporting group values	IR-TAC (PROGRAF)	LCTP (ENVARSUS)	Total
Number of subjects	30	32	62
Age categorical Units: Subjects			
Adults (18 years and over)	30	32	62
Age continuous			
Attending the arm assigned, the median age was: IR-TAC (PROGRAF) = 64.82 (50.20-68.41) LCTP (ENVARSUS) = 63.52 (46.53-69.66)			
Units: years median inter-quartile range (Q1-Q3)	 64.82 51.3 to 68.8	 64.89 50.9 to 70.4	 -
Gender categorical Units: Subjects			
Female	11	9	20
Male	19	23	42
Recipient's Sex Units: Subjects			
Male	19	23	42
Female	11	9	20
Race			
Percentage of Caucasians: IR-TAC (PROGRAF)= 96.3% LCTP (ENVARSUS)= 92%			
Units: Subjects			
Caucasian	29	30	59
Other	1	2	3
Donor's Sex Units: Subjects			
Male	17	24	41
Female	13	8	21
Family history of diabetes			
Defined as first-degree relatives with Diabetes Mellitus			

Units: Subjects			
Yes	7	11	18
No	23	21	44
Polycystic kidney disease Units: Subjects			
Yes	5	8	13
No	25	24	49
Peritoneal dialysis Units: Subjects			
Yes	8	14	22
No	22	18	40
Tobacco Units: Subjects			
Yes	10	18	28
No	19	14	33
Not recorded	1	0	1
Pre-transplantation statins Units: Subjects			
Yes	21	20	41
No	9	12	21
Donor's Cardiac Death Units: Subjects			
Yes	9	7	16
No	21	25	46
Recipient's Age Units: Years			
median	60.9	60.4	
standard deviation	± 12.4	± 12.2	-
Donor's Age Units: Years			
arithmetic mean	57.9	58.2	
standard deviation	± 10.8	± 13.6	-
BMI			
Body Mass Index			
Units: kg/m2			
arithmetic mean	27.9	26.1	
standard deviation	± 4.9	± 4	-
Dialysis time			
Dialysis time measured in months			
Units: Months			
arithmetic mean	23.7	24.3	
standard deviation	± 13.8	± 21.6	-
Total cholesterol Units: mg/dl			
arithmetic mean	152.8	158	
standard deviation	± 38.1	± 39.1	-
HDL-cholesterol Units: mg/dl			
arithmetic mean	43.6	44.4	
standard deviation	± 13	± 10.7	-
LDL-cholesterol			

Units: mg/dl			
arithmetic mean	82.9	81.2	
standard deviation	± 34.2	± 36.5	-
Triglycerides			
Units: mg/dl			
arithmetic mean	153.4	149.2	
standard deviation	± 94.4	± 60.4	-
Fasting Glucose (baseline)			
Units: mg/dl			
arithmetic mean	89.1	91.8	
standard deviation	± 13.3	± 10.1	-
HbA1c: Glycosylated haemoglobin			
Units: Percentage			
arithmetic mean	5.2	5.2	
standard deviation	± 0.41	± 0.3	-
Cold ischemia time			
Units: Hours			
median			
inter-quartile range (Q1-Q3)			-

Subject analysis sets

Subject analysis set title	Final sample included in IR-TAC (PROGRAF) group
Subject analysis set type	Per protocol

Subject analysis set description:

The initial per-protocol sample size was 30 patients for IR-TAC (PROGRAF). However, 27 were included in the final analysis due to the exclusion of 3 patients from this group.

Subject analysis set title	Final sample included in LCTP (ENVARSUS) group
Subject analysis set type	Per protocol

Subject analysis set description:

The initial per-protocol sample size was 32 patients for LCTP (ENVARSUS). However, 25 patients were included in the final analysis due to the exclusion of 7 patients from this group.

Reporting group values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group	
Number of subjects	27	25	
Age categorical			
Units: Subjects			
Adults (18 years and over)	27	25	
Age continuous			
Attending the arm assigned, the median age was: IR-TAC (PROGRAF) = 64.82 (50.20-68.41) LCTP (ENVARSUS) = 63.52 (46.53-69.66)			
Units: years			
median	64.82	63.52	
inter-quartile range (Q1-Q3)	50.20 to 68.41	46.53 to 69.66	
Gender categorical			
Units: Subjects			
Female	10	6	

Male	17	19	

Recipient's Sex Units: Subjects			
Male	17	19	
Female	10	6	
Race			
Percentage of Caucasians: IR-TAC (PROGRAF)= 96.3% LCTP (ENVARSUS)= 92%			
Units: Subjects			
Caucasian	26	23	
Other	1	2	
Donor's Sex Units: Subjects			
Male	17	20	
Female	10	5	
Family history of diabetes			
Defined as first-degree relatives with Diabetes Mellitus			
Units: Subjects			
Yes	7	9	
No	17	14	
Polycystic kidney disease Units: Subjects			
Yes	5	6	
No	22	19	
Peritoneal dialysis Units: Subjects			
Yes	7	12	
No	19	13	
Tobacco Units: Subjects			
Yes	8	13	
No	18	12	
Not recorded	1	0	
Pre-transplantation statins Units: Subjects			
Yes	19	17	
No	7	8	
Donor's Cardiac Death Units: Subjects			
Yes	8	6	
No	19	19	
Recipient's Age Units: Years			
median	59.9	58.4	
standard deviation	± 11.96	± 12.9	
Donor's Age			

Units: Years			
arithmetic mean	56.70	55.24	
standard deviation	± 10.67	± 13.40	
BMI			
Body Mass Index			
Units: kg/m2			
arithmetic mean	28.61	25.53	
standard deviation	± 4.43	± 4.19	
Dialysis time			
Dialysis time measured in months			
Units: Months			
arithmetic mean	24.39	23.60	
standard deviation	± 13.82	± 22.86	
Total cholesterol			
Units: mg/dl			
arithmetic mean	152.92	158.59	
standard deviation	± 38.84	± 37.27	
HDL-cholesterol			
Units: mg/dl			
arithmetic mean	43.62	44.10	
standard deviation	± 13.32	± 11.42	
LDL-cholesterol			
Units: mg/dl			
arithmetic mean	82.58	79.71	
standard deviation	± 35.11	± 33.31	
Triglycerides			
Units: mg/dl			
arithmetic mean	156.31	154.91	
standard deviation	± 95.06	± 62.07	
Fasting Glucose (baseline)			
Units: mg/dl			
arithmetic mean	90.30	90.13	
standard deviation	± 12.97	± 8.58	
HbA1c: Glycosylated haemoglobin			
Units: Percentage			
arithmetic mean	5.19	5.22	
standard deviation	± 0.41	± 0.29	
Cold ischemia time			
Units: Hours			
median	11.42	10.12	
inter-quartile range (Q1-Q3)	6.54 to 18.67	7.66 to 16.58	

End points

End points reporting groups

Reporting group title	IR-TAC (PROGRAF)
Reporting group description:	
Arm 1: Prograf divided into two doses. On the day of transplantation, a single dose was administered before surgery. This is the standard clinical practice of the HUC Nephrology Department.	
Reporting group title	LCTP (ENVARSUS)
Reporting group description:	
Arm 2: Envarsus® as a single daily dose starting within 24 hours after transplantation.	
Subject analysis set title	Final sample included in IR-TAC (PROGRAF) group
Subject analysis set type	Per protocol
Subject analysis set description:	
The initial per-protocol sample size was 30 patients for IR-TAC (PROGRAF). However, 27 were included in the final analysis due to the exclusion of 3 patients from this group.	
Subject analysis set title	Final sample included in LCTP (ENVARSUS) group
Subject analysis set type	Per protocol
Subject analysis set description:	
The initial per-protocol sample size was 32 patients for LCTP (ENVARSUS). However, 25 patients were included in the final analysis due to the exclusion of 7 patients from this group.	

Primary: Glucose Metabolic Alteration

End point title	Glucose Metabolic Alteration
End point description:	
End point type	Primary
End point timeframe:	
3 months post-trasplantation	

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: Subjects				
Normal Glucose Tolerance	11	14		
Impared Fasting Glucose	3	1		
Impared Glucose Tolerance	8	4		
Post-Transplant Diabetes Mellitus	5	6		

Statistical analyses

Statistical analysis title	Normal Glucose Tolerance - IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.49
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	0.59

Statistical analysis title	Normal Glucose Tolerance - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.49
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.73

Statistical analysis title	Impared Fasting Glucose - IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.6
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.48

Statistical analysis title	Impared Fasting Glucose - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.6
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.34

Statistical analysis title	Impared Glucose Tolerance - IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.33
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.28

Statistical analysis title	Impared Glucose Tolerance - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.33
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.19

Statistical analysis title	PTDM- IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	0.37

Statistical analysis title	PTDM- LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	0.43

Primary: Post-transplant Oral Glucose Tolerance Test (OGTT)

End point title	Post-transplant Oral Glucose Tolerance Test (OGTT)

End point description:

Glucose Level (mg/dl) by oral glucose tolerance test at 3 months measured at 3 time points:
t0 (baseline)
t30 (30 minutes after OGTT)
t120 (120 minutes after OGTT)

End point type	Primary

End point timeframe:

3-month post-transplant

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: mg/dl				
median (inter-quartile range (Q1-Q3))				

Glycaemia t0	95.50 (87.75 to 104.25)	88 (78.50 to 96.25)		
Glycaemia t30	157 (138 to 178.50)	139 (123.50 to 155.75)		
Glycaemia t120	130.50 (108.25 to 170.25)	125.50 (100 to 196)		

Statistical analyses

Statistical analysis title	Glycaemia t0 - IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.24
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Glycaemia t0 - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.24
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Glycaemia t30 - IR-TAC (PROGRAF)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.02
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Glycaemia t30 - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.02
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Glycaemia t120 - IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.53
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Glycaemia t120 - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.53
Method	Wilcoxon (Mann-Whitney)

Primary: Insulinemia

End point title	Insulinemia

End point description:

Insulin levels (mcU/ml) at 3 months post-transplant OGTT measured at 3 time points:

t0 (baseline)
t30 (30 minutes after OGTT)
t120 (30 minutes after OGTT)

End point type	Primary

End point timeframe:

3 months post-transplant

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: mcU/ml				

median (inter-quartile range (Q1-Q3))				
Insulinemia t0	7.95 (5.25 to 10.43)	6.90 (5.05 to 10)		
Insulinemia t30	25.35 (13.95 to 41.23)	23.70 (8.45 to 47.23)		
Insulinemia t120	32.35 (11.03 to 45.58)	27.90 (3.80 to 44.73)		

Statistical analyses

Statistical analysis title	Insulinemia t0 - IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.84
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Insulinemia t0 - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.84
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Insulinemia t30 - IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.67
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Insulinemia t30 - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.67
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Insulinemia t120 - IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.32
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Insulinemia t120 - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.32
Method	Wilcoxon (Mann-Whitney)

Primary: ISI- Insulin Sensitivity Index

End point title	ISI- Insulin Sensitivity Index
End point description: 3-month post-transplant Insulin Sensitivity Index	
End point type	Primary
End point timeframe: 3 months post-transplant	

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: mcU/ml				
median (inter-quartile range (Q1-Q3))	7.57 (4.56 to 8.70)	9.22 (6.61 to 10.46)		

Statistical analyses

Statistical analysis title	ISI - IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	ISI - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2
Method	Wilcoxon (Mann-Whitney)

Primary: IGI- Insulinogenic Index	
End point title	IGI- Insulinogenic Index
End point description: 3-month post-transplant Insulinogenic Index	
End point type	Primary
End point timeframe: 3-month post-transplant	

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: mcU/ml				
median (inter-quartile range (Q1-Q3))	46.65 (19.10 to 68.90)	47.87 (24.46 to 172.78)		

Statistical analyses

Statistical analysis title	IGI - IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.96
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	IGI - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.96
Method	Wilcoxon (Mann-Whitney)

Primary: Fasting Glucose Levels (FGL)	
End point title	Fasting Glucose Levels (FGL)
End point description:	

End point type	Primary
End point timeframe:	

Fasting Glucose Levels at:
1 week
1 month
2 months
3 months

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: mg/dl				

median (inter-quartile range (Q1-Q3))				
1 week	106.50 (96.75 to 116)	100 (94.25 to 121.75)		
1 month	90 (84.50 to 98.25)	89.50 (86 to 99.75)		
2 months	100 (88.25 to 112.50)	89 (85.25 to 105)		
3 months	95.50 (87.75 to 104.25)	88 (78.50 to 96.25)		

Statistical analyses

Statistical analysis title	FGL - 1 week - IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.88
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	FGL - 1 week - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.88
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	FGL - 1 month - IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.69
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	FGL - 1 month - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.69
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	FGL - 2 months - IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.68
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	FGL - 2 months - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.68
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	FGL - 3 months - IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.24
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	FGL - 3 months - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.24
Method	Wilcoxon (Mann-Whitney)

Secondary: Delayed Graft Function

End point title	Delayed Graft Function
End point description:	
Delayed Graft Function is defined as needed for haemodialysis in the first-week post-transplantation	
End point type	Secondary
End point timeframe:	
Delayed Graft Function in the first-week post-transplantation	

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: subjects	10	2		

Statistical analyses

Statistical analysis title	Delayed Graft Function - R-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.02
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	0.56

Statistical analysis title	Delayed Graft Function - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.02
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.24

Secondary: Plasma Creatinine Levels

End point title	Plasma Creatinine Levels

End point description:

End point type	Secondary

End point timeframe:

Creatinine post-transplant levels at the following times:
1 month
2 months
3 months

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: mg/dl				
median (inter-quartile range (Q1-Q3))				
1 month	1.89 (1.66 to 2.64)	1.60 (1.24 to 1.77)		
2 months	1.85 (1.61 to 1.97)	1.41 (1.20 to 1.87)		
3 months	1.62 (1.42 to 1.93)	1.48 (1.14 to 1.79)		

Statistical analyses

Statistical analysis title	Plasma Creatinine Levels-1 month-IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.07
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Plasma Creatinine Levels-1 month-LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.07
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Plasma Creatinine Levels-2 months-IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.14
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Plasma Creatinine Levels-2 months-LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.14
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Plasma Creatinine Levels-3 months-IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.36
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Plasma Creatinine Levels-3 months-LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.36
Method	Wilcoxon (Mann-Whitney)

Secondary: Glomerular Filtration Rate (MDRD)

End point title	Glomerular Filtration Rate (MDRD)

End point description:

End point type	Secondary

End point timeframe:

Estimated glomerular filtration rate post-transplant at the following times:
1 month
2 months
3 months

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: ml/min/1,73m2				
arithmetic mean (standard deviation)				
1 month	39.23 (± 16.57)	49.16 (± 15.74)		
2 months	41.16 (± 14.36)	48.92 (± 13.95)		
3 months	44.68 (± 13.99)	51.28 (± 15.48)		

Statistical analyses

Statistical analysis title	GFR 1 month - IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.03
Method	t-student
Variability estimate	Standard deviation
Dispersion value	16.57

Statistical analysis title	GFR 1 month - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.03
Method	t-student
Variability estimate	Standard deviation
Dispersion value	15.74

Statistical analysis title	GFR 2 months - IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.05
Method	t-student
Variability estimate	Standard deviation
Dispersion value	14.36

Statistical analysis title	GFR 2 months - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.05
Method	t-student
Variability estimate	Standard deviation
Dispersion value	13.95

Statistical analysis title	GFR 3 months - IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.11
Method	t-student
Variability estimate	Standard deviation
Dispersion value	13.99

Statistical analysis title	GFR 3 months - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.11
Method	t-student
Variability estimate	Standard deviation
Dispersion value	15.48

Secondary: Proteinuria Levels	
End point title	Proteinuria Levels
End point description:	

End point type	Secondary
End point timeframe:	
Proteinuria level at 3 months post-transplant.	

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: mg/gr creatinine				
median (inter-quartile range (Q1-Q3))	153.62 (140.73 to 224.78)	146.73 (121.29 to 178.58)		

Statistical analyses

Statistical analysis title	Proteinuria - IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.9
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Proteinuria - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.9
Method	Wilcoxon (Mann-Whitney)

Secondary: Tacrolimus Levels

End point title	Tacrolimus Levels

End point description:

End point type	Secondary

End point timeframe:

Tacrolimus levels at the following times post-transplant:
1 week
1 month
2 months
3 months

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: ng/ml				

median (inter-quartile range (Q1-Q3))				
1 week	9.25 (6.65 to 12.75)	10.20 (9.40 to 11.30)		
1 month	9.40 (7.63 to 10.28)	9.20 (7.48 to 11.48)		
2 months	9.50 (6.80 to 11.25)	10.35 (7.93 to 12.03)		
3 months	7.70 (6.93 to 8.58)	10.35 (7.60 to 11.95)		

Statistical analyses

Statistical analysis title	1 week-Tacrolimus Level-IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.21
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	1 week-Tacrolimus Level-LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.21
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	1 month-Tacrolimus Level-IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.99
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	1 month-Tacrolimus Level-LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.99
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	2 months-Tacrolimus Level-IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.21
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	2 months-Tacrolimus Level-IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.21
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	3 months-Tacrolimus Level-IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	3 months-Tacrolimus Level-LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Pharmacokinetic Study (Median of 9 days post-transplantation)

End point title	Pharmacokinetic Study (Median of 9 days post-transplantation)

End point description:

End point type	Secondary

End point timeframe:

Average Tacrolimus doses and levels (mg/day) for each tacrolimus formulation at the following times:
C0-basal (ng/ml)
C1-2h (ng/ml)
C2-4h (ng/ml)
C3-6h (ng/ml)
C4-8h (ng/ml)
C5 12h (ng/ml)
C6 24h (ng/ml)

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: ng/ml				
arithmetic mean (standard deviation)				
C0-basal	9.7250 (± 3.81615)	10.4167 (± 3.36887)		
C1-2h	16.0250 (± 6.02197)	14.5550 (± 7.25846)		
C2-4h	13.110 (± 4.56577)	20.2000 (± 9.40097)		
C3-6h	11.0900 (± 3.11176)	19.8917 (± 8.11686)		
C4-8h	10.0500 (± 2.99710)	20.1813 (± 7.43310)		
C5 12h	8.5263 (± 2.73878)	16.3083 (± 5.90887)		
C6 24h	8.0550 (± 2.43342)	10.7958 (± 4.10551)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Magnesium Levels

End point title	Plasma Magnesium Levels

End point description:

End point type	Secondary

End point timeframe:

Plasma Magnesium Levels at the following times post-transplant.

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: mg/dl				
median (inter-quartile range (Q1-Q3))				
Mg - 1weeK	1.95 (1.70 to 2.18)	1.70 (1.63 to 2.08)		
Mg - 1month	1.50 (1.33 to 1.68)	1.60 (1.35 to 1.60)		
Mg - 2months	1.60 (1.50 to 1.70)	1.60 (1.43 to 1.70)		

Statistical analyses

Statistical analysis title	Mg - 1week-IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.42
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mg - 1week-LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.42
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mg - 1 month-IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.91
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mg - 1 month-Mg-LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.91
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mg - 2 month-IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.91
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mg - 2 month-Mg-LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.91
Method	Wilcoxon (Mann-Whitney)

Other pre-specified: Body Mass Index (BMI)

End point title	Body Mass Index (BMI)

End point description:

End point type	Other pre-specified

End point timeframe:

Body Mass Index (BMI) 3 months post-transplant.

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: Kg/m2				
arithmetic mean (standard deviation)	28.34 (± 4.64)	26.02 (± 3.71)		

Statistical analyses

Statistical analysis title	BMI - 3months - IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.06
Method	t-student

Statistical analysis title	BMI - 3months - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.06
Method	t-student

Other pre-specified: Cholesterol Levels

End point title	Cholesterol Levels

End point description:

End point type	Other pre-specified

End point timeframe:

Cholesterol Levels 3months post-transplant.

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	23		
Units: mg/dl				
arithmetic mean (standard deviation)	192.63 (± 38.52)	176.96 (± 40.17)		

Statistical analyses

Statistical analysis title	Cholesterol - 3months - IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.18
Method	t-student

Statistical analysis title	Cholesterol - 3months - LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.18
Method	t-student

Other pre-specified: HDL- Cholesterol

End point title	HDL- Cholesterol

End point description:

End point type	Other pre-specified

End point timeframe:

High-density cholesterol 3 months post-transplant

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	23		
Units: mg/dl				
arithmetic mean (standard deviation)	52.04 (± 15.24)	53.87 (± 16.92)		

Statistical analyses

Statistical analysis title	HDL- 3 months post-transplant-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7
Method	t-student
Variability estimate	Standard deviation
Dispersion value	15.24

Statistical analysis title	HDL- 3 months post-transplant-LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7
Method	t-student
Dispersion value	16.92

Other pre-specified: LDL- Cholesterol

End point title	LDL- Cholesterol

End point description:

End point type	Other pre-specified

End point timeframe:

Low-density cholesterol 3-months post-transplant

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	22		
Units: mg/dl				
arithmetic mean (standard deviation)	109.45 (± 32.16)	99.64 (± 33.63)		

Statistical analyses

Statistical analysis title	LDL - 3months-post-transplant-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.34
Method	t-student
Variability estimate	Standard deviation
Dispersion value	32.16

Statistical analysis title	LDL - 3months-post-transplant-LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group

Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.34
Method	t-student
Variability estimate	Standard deviation
Dispersion value	33.63

Other pre-specified: Triglycerides

End point title	Triglycerides
End point description:	
End point type	Other pre-specified
End point timeframe:	
Triglycerides 3 months post-transplant	

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: mg/dl				
median (inter-quartile range (Q1-Q3))	132 (101 to 170)	116 (100.50 to 143.50)		

Statistical analyses

Statistical analysis title	Triglycerides - 3 months-post-transplant-IR-TAC
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.36
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Triglycerides - 3 months-post-transplant-LCTP
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.36
Method	Wilcoxon (Mann-Whitney)

Other pre-specified: Cumulative Steroid Dosage

End point title	Cumulative Steroid Dosage

End point description:

End point type	Other pre-specified

End point timeframe:

Accumulated Steroid Dosage 3 months post-transplant

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: mg				
median (inter-quartile range (Q1-Q3))	1321.25 (1189.38 to 1561.25)	1195 (1173.75 to 1270)		

Statistical analyses

Statistical analysis title	CSD - 3 months-post-transplant-IR-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	CSD - 3 months-post-transplant-LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.05
Method	Wilcoxon (Mann-Whitney)

Other pre-specified: Acute Rejection

End point title	Acute Rejection

End point description:

End point type	Other pre-specified

End point timeframe:

Acute Rejection 3 months post-transplant

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: subjects	3	0		

Statistical analyses

Statistical analysis title	Acute Rejection - 3 months post-transplant-TAC
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Acute Rejection - 3 months post-transplant-LCTP
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2
Method	Wilcoxon (Mann-Whitney)

Other pre-specified: Ambulatory Blood Pressure Monitoring (ABPM)	
End point title	Ambulatory Blood Pressure Monitoring (ABPM)

End point description:

End point type	Other pre-specified

End point timeframe:

ABPM (Ambulatory Blood Pressure Monitoring) 3 months post-transplant

End point values	Final sample included in IR-TAC (PROGRAF) group	Final sample included in LCTP (ENVARSUS) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	25		
Units: mmHg				
arithmetic mean (standard deviation)				
ABPM systolic awake	129.60 (± 12.55)	129.84 (± 12.78)		
ABPM systolic asleep	124.68 (± 13.19)	129.48 (± 16.92)		
ABPM diastolic awake	79.92 (± 8.11)	80.48 (± 8.61)		
ABPM diastolic asleep	75.32 (± 8.46)	77.80 (± 8.75)		

Statistical analyses

Statistical analysis title	ABPM-systolic awake-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.95
Method	t-student

Statistical analysis title	ABPM-systolic awake-LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.95
Method	t-student

Statistical analysis title	ABPM-systolic asleep-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.27
Method	t-student

Statistical analysis title	ABPM-systolic asleep-LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.27
Method	t-student

Statistical analysis title	ABPM-diastolic awake-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.81
Method	t-student

Statistical analysis title	ABPM-diastolic awake-LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.81
Method	t-student

Statistical analysis title	ABPM-diastolic asleep-TAC (PROGRAF)
Comparison groups	Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARSUS) group
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.31
Method	t-student

Statistical analysis title	ABPM-diastolic asleep-LCTP (ENVARSUS)
Comparison groups	Final sample included in LCTP (ENVARSUS) group v Final sample included in IR-TAC (PROGRAF) group
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.31
Method	t-student

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events in the first three months post-transplantation

Adverse event reporting additional description:

The study collects the Severe and Non-Severe Adverse Effects of patients eventually included in both arms of the study.
An overall analysis is performed and stratified by sex.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	IR-TAC (PROGRAF)- Female Sex

Reporting group description:

This group is composed of female sex patients included in the study who have been treated with IR-CT (PROGRAF) from randomization to three-month follow-up.

Reporting group title	LCTP (ENVARSUS)- Female Sex

Reporting group description:

This group is composed of female sex patients included in the study who have been treated with LCTP (ENVARSUS) from randomization to three-month follow-up.

Reporting group title	IR-TAC (PROGRAF)- Male Sex

Reporting group description:

This group is composed of male sex patients included in the study who have been treated with IR-CT (PROGRAF) from randomization to three-month follow-up.

Reporting group title	LCTP (ENVARSUS)- Male Sex

Reporting group description:

This group is composed of randomized and transplanted male sex patients who have been treated with LCTP (ENVARSUS) from randomization to three-month follow-up.

Serious adverse events	IR-TAC (PROGRAF)- Female Sex	LCTP (ENVARSUS)- Female Sex	IR-TAC (PROGRAF)- Male Sex
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 10 (70.00%)	2 / 6 (33.33%)	9 / 17 (52.94%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	2 / 10 (20.00%)	0 / 6 (0.00%)	6 / 17 (35.29%)
occurrences causally related to treatment / all	0 / 2	0 / 0	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac disorders			

subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	2 / 17 (11.76%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	4 / 10 (40.00%)	2 / 6 (33.33%)	3 / 17 (17.65%)
occurrences causally related to treatment / all	1 / 5	0 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection			
subjects affected / exposed	5 / 10 (50.00%)	0 / 6 (0.00%)	4 / 17 (23.53%)
occurrences causally related to treatment / all	0 / 6	0 / 0	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Product Issues			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	LCTP (ENVARSUS)-Male Sex		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 19 (52.63%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Product issues			
Product Issues			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	IR-TAC (PROGRAF)-Female Sex	LCTP (ENVARSUS)-Female Sex	IR-TAC (PROGRAF)-Male Sex
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 10 (60.00%)	3 / 6 (50.00%)	7 / 17 (41.18%)
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Infections and infestations			
Infections and infestations			
subjects affected / exposed	6 / 10 (60.00%)	2 / 6 (33.33%)	6 / 17 (35.29%)
occurrences (all)	6	2	6

Non-serious adverse events	LCTP (ENVARSUS)-Male Sex		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 19 (26.32%)		
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Infections and infestations			
Infections and infestations			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2017	Protocol Version 2, 12JAN2018 Changes in the protocol generated in the initial authorization process by the AEMPS (Spanish Agency of Medicines and Health Products).
08 January 2018	Protocol version 3, 08JAN2018. Relevant Amendment nº1 Changes to the protocol and changes to the Patient Information and Consent Form.
19 February 2019	Protocol version 4, 17OCT2018. Relevant amendment Nº2 - The administration of Envarsus® in the trial was modified. It was remained under the responsibility of the project during the patient's stay in Hospital, and once the patient had been discharged, it was dispensed via Social Security outpatient prescription. - Extension of a Centre (Complejo Hospitalario de La Coruña)
17 February 2020	Protocol version 5, 17FEB2020. No relevant Amendment - Change of project manager and monitor. - Change of recruitment time and end of study. - Elimination of blood glucose during the last three days of the visits. - Oral Glucose Overload and Iohexol were administered only under clinical stability.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
14 March 2020	Transplant activity was reduced due to the COVID-19 pandemic.	-

Notes:

Limitations and caveats

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

No firm conclusions can be drawn from this study due to its exploratory nature.
Non-inclusion of a graft biopsy per protocol at the end of the study to provide a morphological substrate for the differences observed in the filtration between groups.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27340950

http://www.ncbi.nlm.nih.gov/pubmed/32463180

http://www.ncbi.nlm.nih.gov/pubmed/25278376

http://www.ncbi.nlm.nih.gov/pubmed/29162334

http://www.ncbi.nlm.nih.gov/pubmed/37116012

http://www.ncbi.nlm.nih.gov/pubmed/30552587

http://www.ncbi.nlm.nih.gov/pubmed/30450457

http://www.ncbi.nlm.nih.gov/pubmed/36083994

http://www.ncbi.nlm.nih.gov/pubmed/26538615

http://www.ncbi.nlm.nih.gov/pubmed/31611066

http://www.ncbi.nlm.nih.gov/pubmed/30622369