



Clinical trial results:

EFFICACY OF THE NEW TACROLIMUS ONCE-DAILY DOSE LCTP (ENVARUSUS®) 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 |
| Public contact | Esteban Porrini, Hospital Universitario de Canarias. FIISC: Fundación Instituto Investigación de Canarias., 34 92267 8118, estebanlporrini@gmail.com |
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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 \geq 60 years or b) age $<$ 60 years and one of these two risk factors:
 - Glucose intolerance (glycemia after 120min of a standard OGTT \geq 140 and $<$ 200 mg/dl)
 - Metabolic syndrome (3 criteria): Impaired fasting glucose (100-125 mg/dl); Body Mass Index (BMI) \geq 28 kg/m²; BP ($>$ 140/90, or on antihypertensive medication); Triglycerides \geq 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 miltidose-technology formulation LCTP-Envarsus®) have recently been compared. The LCTP formulation delays (T_{max}) and reduces peak exposure (17% reduction in C_{max}) and increases bioavailability 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 (C_{max}) exposure as provided by the LCTP formulation. This may translate into a significant reduction in glycemia and glycototoxicity 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 (ENVARUSUS) |
|------------------|------------------|

Arm description:

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

| | |
|--|------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ENVARUSUS |
| 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 (ENVARUSUS) |
|--|------------------|------------------|
| Started | 30 | 32 |
| Completed | 27 | 25 |
| Not completed | 3 | 7 |
| Immunosuppression change | 1 | - |
| Randomized not transplanted | 1 | - |
| Adverse event + immunosuppression 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 (ENVARUSUS) |
| Reporting group description: | |
| Arm 2: Envarsus® as a single daily dose starting within 24 hours after transplantation. | |

| Reporting group values | IR-TAC (PROGRAF) | LCTP (ENVARUSUS) | 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 (ENVARUSUS) = 63.52 (46.53-69.66) | | | |
| Units: years | | | |
| median | 64.82 | 64.89 | |
| inter-quartile range (Q1-Q3) | 51.3 to 68.8 | 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 (ENVARUSUS)= 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 standard deviation | 82.9 ± 34.2 | 81.2 ± 36.5 | - |
| Triglycerides Units: mg/dl arithmetic mean standard deviation | 153.4 ± 94.4 | 149.2 ± 60.4 | - |
| Fasting Glucose (baseline) Units: mg/dl arithmetic mean standard deviation | 89.1 ± 13.3 | 91.8 ± 10.1 | - |
| HbA1c: Glycosylated haemoglobin Units: Percentage arithmetic mean standard deviation | 5.2 ± 0.41 | 5.2 ± 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 (ENVARUSUS) group |
| Subject analysis set type | Per protocol |

Subject analysis set description:

The initial per-protocol sample size was 32 patients for LCTP (ENVARUSUS). 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 (ENVARUSUS) group | |
|---|---|---|--|
| Number of subjects | 27 | 25 | |
| Age categorical Units: Subjects | | | |
| Adults (18 years and over) | 27 | 25 | |
| Age continuous | | | |
| <p>Attending the arm assigned, the median age was:</p> <p>IR-TAC (PROGRAF) = 64.82 (50.20-68.41) LCTP (ENVARUSUS) = 63.52 (46.53-69.66)</p> | | | |
| Units: years median inter-quartile range (Q1-Q3) | 64.82 50.20 to 68.41 | 63.52 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 (ENVARUSUS)= 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 (ENVARUSUS) |
| 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 (ENVARUSUS) group |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The initial per-protocol sample size was 32 patients for LCTP (ENVARUSUS). 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-transplantation | |

| End point values | Final sample included in IR-TAC (PROGRAF) group | Final sample included in LCTP (ENVARUSUS) group | | |
|-----------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 27 | 25 | | |
| Units: Subjects | | | | |
| Normal Glucose Tolerance | 11 | 14 | | |
| Impaired Fasting Glucose | 3 | 1 | | |
| Impaired 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 | Impaired Fasting Glucose - IR-TAC (PROGRAF) |
| Comparison groups | Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARUSUS) 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 | Impaired Fasting Glucose - LCTP (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 | Impaired Glucose Tolerance - IR-TAC (PROGRAF) |
| Comparison groups | Final sample included in IR-TAC (PROGRAF) group v Final sample included in LCTP (ENVARUSUS) 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 | Impaired Glucose Tolerance - LCTP (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUS) 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 (ENVARUS) |
| Comparison groups | Final sample included in LCTP (ENVARUS) 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 (ENVARUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUS) 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 (ENVARUS) 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 (ENVARUS) |
| Comparison groups | Final sample included in LCTP (ENVARUS) 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 (ENVARUS) 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 (ENVARUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) group | | |
|--------------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 27 | 25 | | |
| Units: ml/min/1,73m ² | | | | |
| 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUS) 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 (ENVARUS) 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 (ENVARUS) 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 (ENVARUS) |
| Comparison groups | Final sample included in LCTP (ENVARUS) 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 (ENVARUS) 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 (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) group | | |
|--------------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 27 | 25 | | |
| Units: Kg/m ² | | | | |
| 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (\pm 38.52) | 176.96 (\pm 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUS) 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 (ENVARUS) 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 (ENVARUS) |
| Comparison groups | Final sample included in LCTP (ENVARUS) 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 (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUS) 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 (ENVARUS) 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 (ENVARUS) 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 (ENVARUS) 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 (ENVARUS) 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 (ENVARUS) |
| Comparison groups | Final sample included in LCTP (ENVARUS) 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 (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS) 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 (ENVARUSUS) |
| Comparison groups | Final sample included in LCTP (ENVARUSUS) 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 (ENVARUSUS)- Female Sex |
|-----------------------|------------------------------|

Reporting group description:

This group is composed of female sex patients included in the study who have been treated with LCTP (ENVARUSUS) 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 (ENVARUSUS)- Male Sex |
|-----------------------|----------------------------|

Reporting group description:

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

| Serious adverse events | IR-TAC (PROGRAF)- Female Sex | LCTP (ENVARUSUS)- 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 (ENVARUSUS)- 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 (ENVARUSUS)- 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 (ENVARUSUS)- 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>