Clinical trial results:
A Phase II, open-label, multi-center study to assess the pharmacokinetics, long-term safety and tolerability of Tacrolimus in stable pediatric liver transplant participants converted from a Prograf^®-based Immunosuppression regimen to a Modified Release (MR) Tacrolimus-based immunosuppression regimen.

Summary

EudraCT number	2015-001076-22
Trial protocol	Outside EU/EEA
Global end of trial date	29 October 2008

Results information

Result version number	v2 (current)
This version publication date	04 June 2016
First version publication date	18 July 2015
Version creation reason	• Correction of full data set Updates required due to non-substantial reasons.

Trial information

Trial identification

Sponsor protocol code	03-0-160

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00282256
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc. (APGD)
Sponsor organisation address	Three Parkway North, Deerfield, United States, 60015
Public contact	Clinical Trial Disclosure , Astellas Pharma Global Development, Inc., Astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., Astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 October 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 October 2008
Global end of trial reached?	Yes
Global end of trial date	29 October 2008
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine and compare the pharmacokinetics of tacrolimus in stable pediatric liver transplant patients converted from a Prograf® based immunosuppression regimen to an extended-release tacrolimus (FK506E, MR)-based immunosuppressive regimen.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, ICH GCP Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.This protocol was reviewed and approved by the Institutional Review Board (IRB) of the participating institutions. The study was conducted in compliance with Good Clinical Practice (GCP) and in accordance with ethical principles that have their origin in the Declaration of Helsinki. The subject’s legal guardian read and signed an IRB-approved informed consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization prior to initiation of any study-related procedures. Subjects, 7 to 12 years of age, were fully informed and signed an IRB-approved assent form/authorization.

Background therapy:

This study included a 1-week exposure to Prograf, with participants already on a stable dose of Prograf-based immunosuppressive therapy for liver transplantation. All immunosuppressants and corticosteroids used in combination with Prograf at baseline/day 1 were maintained at constant doses throughout the pharmacokinetic (PK) treatment period. Once the day 14 PK visit was completed, corticosteroid and immunosuppressant dose adjustments were permitted. Use of sirolimus, intravenous methylprednisolone, or any investigational immunosuppressant was prohibited during the PK treatment period.

Evidence for comparator: -

Actual start date of recruitment	23 January 2004
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	54 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 19
Worldwide total number of subjects	19
EEA total number of subjects	0

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)	18
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Stable liver transplant recipients aged 12 years or younger receiving tacrolimus based immunosuppression regimen.

Pre-assignment

Screening details:

Pharmacokinetic (PK) treatment period was 14 days. Participants who completed the PK period were eligible to continue receiving tacrolimus MR in the extended treatment period, from Day 15 through Month 54.

Period 1

Period 1 title	Pharmacokinetic Treatment Period
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Tacrolimus (Prograf)

Arm description:

Participants continued to receive their stable twice daily dose of tacrolimus (Prograf) twice daily on Day 1 through Day 7 and on Day 8 were converted to Tacrolimus modified release (MR) once-daily in the morning for 7 days on a 1:1 (mg:mg) basis for their total daily dose. Participants who completed the 2-week pharmacokinetic treatment period were eligible to continue receiving tacrolimus MR as part of the extension treatment period of the study. The extended treatment period began on Day 15 and consisted of a single dose of tacrolimus MR once every morning through the end of the study.

Arm type	Experimental
Investigational medicinal product name	Tacrolimus Extended-Release Formulation
Investigational medicinal product code	FK506E
Other name	MR4,Advagraf,Astagraf XL
Pharmaceutical forms	Prolonged-release capsule
Routes of administration	Oral use

Dosage and administration details:

On day 8, participants were converted to tacrolimus extended release formulation on a 1:1 (mg:mg) basis for their total daily dose and received a daily oral dose of tacrolimus extended release formulation equivalent to their total twice-daily dose of Prograf. The dose was not to be altered if the trough level was within the therapeutic range of 5 to 20 ng/mL (levels below 5 ng/mL were acceptable as long as there were no clinical indications that the dose should be altered). Tacrolimus extended release formulation was administered orally once daily as 0.5, 1.0 or 5 mg capsules in the morning either 1 hour before or 2 hours after a meal, and participants were to have fasted for a minimum of 2 hours prior to being dispensed the morning dose on the day of a PK visit. The duration of the PK period was 2 weeks; 1 week of Prograf administration, followed by 1 week of tacrolimus extended release formulation administration.

Number of subjects in period 1	Tacrolimus (Prograf)
Started	19
Completed	18
Not completed	1
Withdrawal due to poor venous access	1

Period 2

Period 2 title	Extension Treatment Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Tacrolimus MR

Arm description:

Participants continued to receive their stable twice daily dose of tacrolimus twice daily on Day 1 through Day 7 and on Day 8 were converted to tacrolimus modified release (MR) once-daily in the morning for 7 days on a 1:1 (mg:mg) basis for their total daily dose. Participants who completed the 2-week pharmacokinetic treatment period were eligible to continue receiving tacrolimus MR as part of the extension treatment period of the study. The extended treatment period began on Day 15 and consisted of a single dose of tacrolimus MR once every morning through the end of the study.

Arm type	Experimental
Investigational medicinal product name	Tacrolimus Extended-Release Formulation
Investigational medicinal product code	FK506E
Other name	MR4,Advagraf,Astagraf XL
Pharmaceutical forms	Prolonged-release capsule
Routes of administration	Oral use

Dosage and administration details:

On day 8, participants were converted to tacrolimus extended release formulation on a 1:1 (mg:mg)basis for their total daily dose and received a daily oral dose of tacrolimus extended release formulation equivalent to their total twice-daily dose of Prograf. The dose was not to be altered if the trough level was within the therapeutic range of 5 to 20 ng/mL. (Levels below 5 ng/mL were acceptable as long as there were no clinical indications that the dose should be altered.) Tacrolimus extended release formulation was administered orally once daily as 0.5, 1.0 or 5 mg capsules in the morning either 1 hour before or 2 hours after a meal, and participants were to have fasted for a minimum of 2 hours prior to being dispensed the morning dose on the day of a PK visit. The duration of the PK period was 2 weeks; 1 week of Prograf administration, followed by 1 week of tacrolimus extended release formulation administration.

Number of subjects in period 2	Tacrolimus MR
Started	18
Completed	16
Not completed	2
Adverse event, non-fatal	2

Baseline characteristics

Reporting groups

Reporting group title	Pharmacokinetic Treatment Period

Reporting group description:

The pharmacokinetic evaluable set was defined as all pharmacokinetic participants who completed both pharmacokinetic profiles: one for tacrolimus, and one for tacrolimus MR.

Reporting group values	Pharmacokinetic Treatment Period	Total	
Number of subjects	19	19	
Age categorical			
Units: Subjects			

Age continuous			
Full analysis set was used to report baseline characteristics. It includes all patients who were enrolled in the study and received at least one dose of Prograf during the study.			
Units: years			
arithmetic mean	8.5		
standard deviation	± 2.29	-	
Gender categorical			
Full analysis set was used to report baseline characteristics. It includes all patients who were enrolled in the study and received at least one dose of Prograf during the study.			
Units: Subjects			
Male	6	6	
Female	13	13	
Race			
Full analysis set was used to report baseline characteristics. It includes all patients who were enrolled in the study and received at least one dose of Prograf during the study.			
Units: Subjects			
Caucasian/White	11	11	
Black	8	8	
Reason for End Stage Liver Disease			
Full analysis set was used to report baseline characteristics. It includes all patients who were enrolled in the study and received at least one dose of Prograf during the study.			
Units: Subjects			
Biliary Atresia	6	6	
Unknown	1	1	
Other	10	10	
Metabolic disease: tyrosinemia	2	2	
Type of Current Transplant			
Full analysis set was used to report baseline characteristics. It includes all patients who were enrolled in the study and received at least one dose of Prograf during the study.			
Units: Subjects			
Whole Cadaver	10	10	
Split Cadaver	5	5	
Living Donor	4	4	
Reason for Re-transplant			
Full analysis set was used to report baseline characteristics. It includes all patients who were enrolled in the study and received at least one dose of Prograf during the study.			
Units: Subjects			

No Retransplant	17	17	
Acute Rejection	1	1	
Other	1	1	
Re-Transplant			
Full analysis set was used to report baseline characteristics. It includes all patients who were enrolled in the study and received at least one dose of Prograf during the study.			
Units: Subjects			
Yes	2	2	
No	17	17	
Gender			
Modified Safety Analysis set was used for baseline characteristics reporting. It contains all patients who took at least 1 dose of both Prograf and tacrolimus extended release formulation during the pharmacokinetic period of the study. Number of patients in the Modified Safety Analysis and the pharmacokinetic period is 18			
Units: Subjects			
Male	5	5	
Female	13	13	
Not Recorded	1	1	
Height (cm)			
Full analysis set was used to report baseline characteristics. It includes all patients who were enrolled in the study and received at least one dose of Prograf during the study.			
Units: centimeters			
arithmetic mean	131		
standard deviation	± 15.65	-	
Weight (kg)			
Full analysis set was used to report baseline characteristics. It includes all patients who were enrolled in the study and received at least one dose of Prograf during the study.			
Units: kilogram(s)			
arithmetic mean	32.9		
standard deviation	± 14.7	-	
Total Daily Dose of Prograf at Baseline			
Full analysis set was used to report baseline characteristics. It includes all patients who were enrolled in the study and received at least one dose of Prograf during the study.			
Units: milligram(s)			
arithmetic mean	5.3		
standard deviation	± 3.19	-	

End points

End points reporting groups

Reporting group title	Tacrolimus (Prograf)

Reporting group description:

Participants continued to receive their stable twice daily dose of tacrolimus (Prograf) twice daily on Day 1 through Day 7 and on Day 8 were converted to Tacrolimus modified release (MR) once-daily in the morning for 7 days on a 1:1 (mg:mg) basis for their total daily dose. Participants who completed the 2-week pharmacokinetic treatment period were eligible to continue receiving tacrolimus MR as part of the extension treatment period of the study. The extended treatment period began on Day 15 and consisted of a single dose of tacrolimus MR once every morning through the end of the study.

Reporting group title	Tacrolimus MR

Reporting group description:

Participants continued to receive their stable twice daily dose of tacrolimus twice daily on Day 1 through Day 7 and on Day 8 were converted to tacrolimus modified release (MR) once-daily in the morning for 7 days on a 1:1 (mg:mg) basis for their total daily dose. Participants who completed the 2-week pharmacokinetic treatment period were eligible to continue receiving tacrolimus MR as part of the extension treatment period of the study. The extended treatment period began on Day 15 and consisted of a single dose of tacrolimus MR once every morning through the end of the study.

Subject analysis set title	Period 1 - Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set was defined as all participants who were enrolled in the study and received at least one dose of Prograf during the study. The full analysis set was the primary data set for all safety analyses.

Subject analysis set title	Period 1- Pharmacokinetic Evaluable Set
Subject analysis set type	Full analysis

Subject analysis set description:

The pharmacokinetic evaluable set was defined as all participants who completed both pharmacokinetic profiles: one for Prograf, and one for MR4. A complete pharmacokinetic profile was considered to be a profile that was adequate to determine AUC0-24, Cmax, and Cmin. The pharmacokinetic evaluable set was used to analyze other pharmacokinetic parameters derived from the concentration-time curve and was the primary data set for all pharmacokinetic analyses.

Subject analysis set title	Period 1- Trough Evaluable Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The trough evaluable set was defined as all participants with replicate whole blood trough measurements of both Prograf and MR4.

Subject analysis set title	Period 1- Per Protocol Set
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol set was defined as all participants who completed both pharmacokinetic profiles and did not have any major protocol deviations during the pharmacokinetic treatment period (including lack of 1:1 conversion and administration of prohibited medications).

Subject analysis set title	Period 2- Modified Full Analysis Set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified Full Analysis Set included all participants who took at least 1 dose of tacrolimus extended-release formulation during the extended treatment period. This population was the primary analysis set for efficacy data obtained during the extended treatment period.

Subject analysis set title	Period 2- Modified Safety Analysis Set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified Safety Analysis Set included all participants in the Full Analysis Set who took at least 1 dose of tacrolimus extended-release formulation during the pharmacokinetic period of the study. This population was the primary analysis set for safety data obtained during the extended treatment period, except for incidence of glucose intolerance/PTDM at each extended study visit, which was evaluated in the Modified Full Analysis Set

Primary: The primary measure of exposure for Tacrolimus (AUC0-24 - Area Under the Concentration-time Curve From Time 0 to 24 Hours)

End point title	The primary measure of exposure for Tacrolimus (AUC0-24 - Area Under the Concentration-time Curve From Time 0 to 24 Hours)

End point description:

The primary measure of exposure was area under the concentration-time curve from 0 to 24 hours (AUC0-24 (ng*hr/mL)). The area under the concentration-time curve was calculated from whole blood tacrolimus concentrations for both tacrolimus and tacrolimus MR at steady state using the linear trapezoidal rule. The AUC0-24 for tacrolimus was calculated as the sum of the AUC0-12 and AUC 12-24 for the morning and afternoon doses.

End point type	Primary

End point timeframe:

For tacrolimus, Day 7 at 0 (pre-dose), 0.5, 1, 2, 3, 6, 8, 12 (pre-dose), 13, 14, 15, 18, 20, and 24 hours. For tacrolimus MR, Day 14 at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 15, 18, 20, and 24 hours post-dose.

End point values	Tacrolimus (Prograf)	Tacrolimus MR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: Number				
arithmetic mean (standard deviation)	198.2 (± 99.2)	193 (± 78)		

Statistical analyses

Statistical analysis title	Statistical Analysis (AUC0-24) for Tacrolimus

Statistical analysis description:

The method of analysis of variance was used for the comparisons of AUC0-24. Exposure at steady state was used for tacrolimus (Prograf) (defined as Day 7) and for tacrolimus MR (defined as Day 14). The natural log (ln) was used to transform AUC0-24 prior to analysis and the results were transformed back to the original scale for the presentation of results. For this statistical analysis 18 participants were analysed.

Comparison groups	Tacrolimus MR v Tacrolimus (Prograf)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Ratio of means
Point estimate	100.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	90.8
upper limit	112.1

Notes:

[1] - Bioequivalence Test-If the 90% CI for AUC0-24 was found to lie entirely within the 80% to 125% range, then the exposure between the two formulations was considered to be bioequivalent.

Primary: Patient survival (Modified Full Analysis Set)

End point title	Patient survival (Modified Full Analysis Set)[2]

End point description:

Participant survival was defined as any participant known to be alive at the end of the study. Participants were enrolled on a stable twice-daily dose of Prograf on Day 1 and received Prograf twice daily on days 1 through 7. Participants received tacrolimus extended release formulation on a 1:1 (mg:mg) basis for their total daily dose once daily on days 8 through 14. The extended treatment period began on day 15 and consisted of a single dose of tacrolimus extended-release formulation once every morning through the end of the study (month 54). The initial total daily dose of tacrolimus extended-release formulation was to be equivalent to the participant's previous stable total daily dose of Prograf.

End point type	Primary

End point timeframe:

From enrollment until the end of study (up to 54 months).

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was specified for this endpoint.

End point values	Tacrolimus MR			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percent				
number (confidence interval 95%)	94.44 (83.86 to 100)			

Statistical analyses

No statistical analyses for this end point

Primary: Graft Survival (Modified Full Analysis Set)

End point title	Graft Survival (Modified Full Analysis Set)[3]

End point description:

Graft survival was defined for any participant who did not meet the definition of graft loss, where graft loss was defined as graft failure (re-transplant) or participant death. Participants were enrolled on a stable twice-daily dose of Prograf on Day 1 and received Prograf twice daily on days 1 through 7. Participants received tacrolimus extended release formulation on a 1:1 (mg:mg) basis for their total daily dose once daily on days 8 through 14. The extended treatment period began on day 15 and consisted of a single dose of tacrolimus extended release formulation once every morning through the end of the study (month 54). The initial total daily dose of tacrolimus extended-release formulation was to be equivalent to the participants previous stable total daily dose of Prograf.

End point type	Primary

End point timeframe:

From enrollment until the end of study (up to 54 months).

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was specified for this endpoint.

End point values	Tacrolimus MR			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percent				
number (confidence interval 95%)	94.44 (83.86 to 100)			

Statistical analyses

No statistical analyses for this end point

Primary: Minimum Observed Concentration of Tacrolimus (Cmin)(Pharmacokinetic Evaluable Set)

End point title	Minimum Observed Concentration of Tacrolimus (Cmin)(Pharmacokinetic Evaluable Set)

End point description:

The trough (minimum) concentration of Tacrolimus (Prograf) determined from the tacrolimus whole blood concentration value at the 12 hour post-dose concentration based on the evening dose (i.e., the 8 am concentration) for Tacrolimus and the 24-hour time point post-dose for Tacrolimus MR, prior to receiving the next dose.

End point type	Primary

End point timeframe:

Day 7 at 12 hours post-dose Tacrolimus (Prograf) and Day 14 at 24 hours post-dose (Tacrolimus MR).

End point values	Tacrolimus (Prograf)	Tacrolimus MR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: ng/mL				
arithmetic mean (standard deviation)	5.9 (± 2.9)	5.3 (± 2.6)		

Statistical analyses

Statistical analysis title	Minimum Observed Concentration of Tacrolimus -Cmin

Statistical analysis description:

The method of analysis of variance was used for the comparisons of Cmin. Exposure at steady state was used for tacrolimus (defined as Day 7) and for tacrolimus MR (defined as Day 14). The natural log (ln) was used to transform Cmin prior to analysis and the results were transformed back to the original scale for the presentation of results.

Comparison groups	Tacrolimus MR v Tacrolimus (Prograf)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of means
Point estimate	91.8

Confidence interval	
level	90 %
sides	2-sided
lower limit	82.6
upper limit	102.2

Secondary: Maximum Observed Concentration of Tacrolimus (Cmax) (Pharmacokinetic evaluable set)

End point title	Maximum Observed Concentration of Tacrolimus (Cmax) (Pharmacokinetic evaluable set)

End point description:

Time to reach the first observed maximum concentration of tacrolimus was calculated from whole blood tacrolimus concentrations for both tacrolimus and tacrolimus MR at steady state, without interpolation.

End point type	Secondary

End point timeframe:

For tacrolimus, Day 7 at 0 (pre-dose), 0.5, 1, 2, 3, 6, 8, 12 (pre-dose), 13, 14, 15, 18, 20, and 24 hours. For tacrolimus MR, Day 14 at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 15, 18, 20, and 24 hours post-dose.

End point values	Tacrolimus (Prograf)	Tacrolimus MR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: hours				
arithmetic mean (standard deviation)	20.7 (± 13.3)	15.2 (± 5.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Biopsy-confirmed Acute Rejection (Modified Full Analysis Set)

End point title	Percentage of Participants With Biopsy-confirmed Acute Rejection (Modified Full Analysis Set)

End point description:

Biopsy-confirmed acute rejection (BCAR) is defined as an episode of acute liver allograft rejection that was confirmed by biopsy results and was Banff grade ≥ I. Biopsies were graded by the pathologist at the clinical site according to the 1997 Banff criteria for grading of acute liver allograft rejection: Indeterminate: Portal inflammatory infiltrate that fails to meet the criteria for diagnosis of acute rejection; Grade I (Mild): Rejection infiltrate in a minority of the triads that is generally mild and confined within the portal spaces; Grade II (Moderate): Rejection infiltrate, expanding to most or all of the triads; Grade III (Severe): Rejection infiltrate, expanding to most or all of the triads, with spillover into periportal areas and moderate to severe perivenular inflammation that extends into the hepatic parenchyma and is associated with perivenular hepatocyte necrosis.

End point type	Secondary

End point timeframe:

From enrollment until the end of study (up to 54 months).

End point values	Tacrolimus (Prograf)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percent				
number (not applicable)				
Percentage with Biopsy-confirmed Acute Rejection	16.67			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Event for Patient Non-survival (Modified Full Analysis Set who died on study)

End point title	Time to Event for Patient Non-survival (Modified Full Analysis Set who died on study)

End point description:

For participants who died on study, the median number of days from first dose of study drug to death due to any cause.

End point type	Secondary

End point timeframe:

From enrollment until the end of study (up to 54 months)

End point values	Tacrolimus MR			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Days				
median (full range (min-max))	1204 (1204 to 1204)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Event for Graft Non-survival (Modified full analysis set with graft loss)

End point title	Time to Event for Graft Non-survival (Modified full analysis set with graft loss)

End point description:

For participants with graft loss, the median number of days from the first dose of study drug to graft loss. Graft loss was defined as graft failure (re-transplant) or participant death.

End point type	Secondary

End point timeframe:

From enrollment until the end of study (up to 54 months)

End point values	Tacrolimus MR			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Days				
median (full range (min-max))	1203 (1203 to 1203)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Biopsy-confirmed Acute Rejection (Participants in the modified full analysis set with a biopsy-confirmed acute rejection)

End point title	Time to First Biopsy-confirmed Acute Rejection (Participants in the modified full analysis set with a biopsy-confirmed acute rejection)

End point description:

For participants with a biopsy-confirmed acute rejection (BCAR), the median number of days from the first dose of study drug to the date of biopsy confirmation. BCAR is defined as an episode of acute liver allograft rejection that was confirmed by biopsy results and was Banff grade ≥ I. Biopsies were graded by the clinical site pathologist according to the 1997 Banff criteria for grading acute liver allograft rejection: Indeterminate: Portal inflammatory infiltrate that fails to meet the criteria for diagnosis of acute rejection; Grade I: Rejection infiltrate in a minority of the triads that is generally mild and confined within the portal spaces; Grade II: Rejection infiltrate, expanding to most or all of the triads; Grade III: Rejection infiltrate, expanding to most or all of the triads, with spillover into periportal areas and moderate to severe perivenular inflammation that extends into the hepatic parenchyma and is associated with perivenular hepatocyte necrosis.

End point type	Secondary

End point timeframe:

From enrollment until the end of study (up to 54 months).

End point values	Tacrolimus MR			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Days				
median (full range (min-max))				
Time to First Biopsy-confirmed Acute Rejection	748 (729 to 773)			

Statistical analyses

No statistical analyses for this end point

Secondary: Grade of Biopsy-confirmed Acute Rejection Episodes (Participants in the modified full analysis set with a biopsy-confirmed acute rejection)

End point title	Grade of Biopsy-confirmed Acute Rejection Episodes (Participants in the modified full analysis set with a biopsy-confirmed acute rejection)

End point description:

Biopsy-confirmed acute rejection (BCAR) is defined as an episode of acute liver allograft rejection that was confirmed by biopsy results and was Banff grade ≥ I. Biopsies were graded by the clinical site pathologist according to the 1997 Banff criteria for grading of acute liver allograft rejection: Indeterminate: Portal inflammatory infiltrate that fails to meet the criteria for diagnosis of acute rejection; Grade I (Mild): Rejection infiltrate in a minority of the triads that is generally mild and confined within the portal spaces; Grade II (Moderate): Rejection infiltrate, expanding to most or all of the triads; Grade III (Severe): Rejection infiltrate, expanding to most or all of the triads, with spillover into periportal areas and moderate to severe perivenular inflammation that extends into the hepatic parenchyma and is associated with perivenular hepatocyte necrosis. For participants with more than one biopsy-confirmed acute rejection episode, the worst case grade is reported.

End point type	Secondary

End point timeframe:

From enrollment until the end of study (up to 54 months)

End point values	Tacrolimus MR			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Participants				
number (not applicable)				
Grade I	2			
Grade II	1			
Grade III	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Receiving Anti-lymphocyte Antibody Therapy for Acute Rejection (Modified Full Analysis Set)

End point title	Number of Participants Receiving Anti-lymphocyte Antibody Therapy for Acute Rejection (Modified Full Analysis Set)

End point description:

Steroid-resistant rejection episodes were treated with anti-lymphocyte antibodies. If a participant had a histologically proven Banff Grade II or III rejection, they could be initiated on anti-lymphocyte antibody treatment per institutional practice.

End point type	Secondary

End point timeframe:

From enrollment until the end of study (up to 54 months).

End point values	Tacrolimus MR			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Multiple Rejection Episodes (Modified Full Analysis Set)

End point title	Number of Participants With Multiple Rejection Episodes (Modified Full Analysis Set)

End point description:

This analysis includes rejection episodes that were either confirmed by biopsy by the clinical site pathologist or were clinically treated.

End point type	Secondary

End point timeframe:

From enrollment until the end of study (up to 54 months).

End point values	Tacrolimus MR			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Participants				
number (not applicable)	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Treated Acute Rejection Episodes (Modified Full Analysis Set)

End point title	Number of Participants With Clinically Treated Acute Rejection Episodes (Modified Full Analysis Set)

End point description:

A clinically treated acute rejection episode was any biopsy-confirmed or suspected rejection episode that was treated with immunosuppressive therapy.

End point type	Secondary

End point timeframe:

From enrollment until the end of study (up to 54 months).

End point values	Tacrolimus MR			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Participants				
number (not applicable)	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Chronic Rejection

End point title	Number of Participants With Chronic Rejection

End point description:

Due to the low number of participants with biopsy-confirmed acute rejection episodes, chronic rejection was not analyzed

End point type	Secondary

End point timeframe:

From enrollment until the end of study (up to 54 months).

End point values	Tacrolimus (Prograf)			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: Participants				
number (not applicable)				

Notes:

[4] - Due to low number of participants chronic rejection was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment Failure

End point title	Number of Participants With Treatment Failure

End point description:

Treatment failure was defined as discontinuation of study drug for any reason. Due to discontinuation of the study by the sponsor, treatment failure was not analyzed

End point type	Secondary

End point timeframe:

From enrollment until the end of study (up to 54 months)

End point values	Tacrolimus (Prograf)			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: Participants				
number (not applicable)				

Notes:

[5] - Due to discontinuation of the study by the sponsor, treatment failure was not analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Primary Reason for Graft Loss

End point title	Primary Reason for Graft Loss

End point description:

The primary reason for graft loss was recorded by the Investigator. It was recorded as "Other" and was reported as unknown due to inability to access participant's records and death report from Mexico. Graft loss was defined as graft failure (re-transplant) or participant death. Modified full analysis set was used for this analysis.

End point type	Secondary

End point timeframe:

From enrollment until the end of study (up to 54 months)

End point values	Tacrolimus (Prograf)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Participants				
number (not applicable)				
Recurrent disease	0			
Unknown-Unable to check participants records	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety as Assessed by Clinical Signs and Symptoms, Laboratory Parameters and Diagnostic Tests

End point title	Safety as Assessed by Clinical Signs and Symptoms, Laboratory Parameters and Diagnostic Tests

End point description:

An adverse event (AE) is defined as any reaction, side effect or other untoward medical occurrence,

regardless of the relationship to study drug which occurred during the conduct of a clinical study. Clinically significant adverse changes in clinical status, routine laboratory studies or physical examinations were considered adverse events. A serious adverse event was any adverse event occurring at any dose that resulted in any of the following outcomes:Death, Life-threatening adverse event, Inpatient hospitalization or prolongation of existing hospitalization, Persistent or significant disability or incapacity, Congenital abnormality or birth defect,Important medical event.

End point type	Secondary

End point timeframe:

From the first dose of tacrolimus MR formulation through the last dose day plus 10 days (approximately 54 months).

End point values	Tacrolimus MR			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Participants				
number (not applicable)				
Adverse Events	12			
Serious Adverse Event	6			
Death	1			
Any AE leading to a change in study drug dose	3			
AE leading to study drug discontinuation	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Observed Concentration of Tacrolimus (Tmax)

End point title	Time to Maximum Observed Concentration of Tacrolimus (Tmax)

End point description:

Time to reach the first observed maximum concentration of tacrolimus was calculated from whole blood tacrolimus concentrations for both tacrolimus and tacrolimus MR at steady state, without interpolation.

End point type	Secondary

End point timeframe:

For tacrolimus, Day 7 at 0 (pre-dose), 0.5, 1, 2, 3, 6, 8, 12 (pre-dose), 13, 14, 15, 18, 20, and 24 hours. For tacrolimus MR, Day 14 at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 15, 18, 20, and 24 hours post-dose.

End point values	Tacrolimus (Prograf)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Number				
median (full range (min-max))				
Day 7: Tacrolimus	1 (0.5 to 19.7)			

Day 14: Tacrolimus MR	2 (0.9 to 6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of tacrolimus MR through the last dose day plus 10 days (approximately 54 months).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	6.1

Reporting groups

Reporting group title	Tacrolimus MR

Reporting group description: -

Serious adverse events	Tacrolimus MR		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 18 (33.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
Liver function test abnormal			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis eosinophilic			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neck pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia streptococcal			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Tacrolimus MR		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 18 (61.11%)		
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Blood triglycerides increased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Hepatic enzyme increased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Low density lipoprotein increased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Weight increased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
General disorders and administration site conditions			

Pyrexia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2		
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Respiratory, thoracic and mediastinal disorders Maxillary sinusitis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Skin and subcutaneous tissue disorders Urticaria subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Renal and urinary disorders Glomerulosclerosis subjects affected / exposed occurrences (all) Renal impairment subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1 1 / 18 (5.56%) 1		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Cat scratch disease subjects affected / exposed occurrences (all) Ear infection subjects affected / exposed occurrences (all) Epstein-Barr virus infection	1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1		

subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	2			
Escherichia urinary tract infection				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	2			
Gastroenteritis				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	2			
Herpes simplex				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	1			
Influenza				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	1			
Otitis media				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	4			
Pharyngitis streptococcal				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	1			
Pneumonia				
subjects affected / exposed	2 / 18 (11.11%)			
occurrences (all)	2			
Sinusitis				
subjects affected / exposed	2 / 18 (11.11%)			
occurrences (all)	3			
Tinea capitis				
subjects affected / exposed	2 / 18 (11.11%)			
occurrences (all)	2			
Upper respiratory tract infection				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	4			
Urinary tract infection				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	2			
Urinary tract infection staphylococcal				

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Glucose tolerance impaired			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported