Clinical trial results:
Single centre, open-label, randomized, controlled, cross over study to evaluate the pharmacokinetic and bioavailability of Envarsus® in comparison to Advagraf® in de novo liver transplant recipients

Summary

EudraCT number	2015-002935-16
Trial protocol	DE
Global end of trial date	01 April 2019

Results information

Result version number	v1 (current)
This version publication date	13 November 2020
First version publication date	13 November 2020
Summary attachment (see zip file)	PAKT CSR Synopsis 2020_04_07 (CTC151043 CSR Synopse 2020_04_07 finale Version 1.0 2020_05_25.pdf)

Trial information

Trial identification

Sponsor protocol code	PAKT CTC 151043

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03241043
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Medical Center Hamburg-Eppendorf (UKE)
Sponsor organisation address	Martinistr. 52, Hamburg, Germany, 20246
Public contact	Study Coordinator, University Medical Center Hamburg-Eppendorf, Department of Visceral Transplant Surgery, 0049 40741056640, transplant-studien@uke.de
Scientific contact	Study Coordinator, University Medical Center Hamburg-Eppendorf, Department of Visceral Transplant Surgery, 0049 40741056640, transplant-studien@uke.de
Sponsor organisation name	University Medical Center Hamburg-Eppendorf
Sponsor organisation address	Martinistr. 52, Hamburg, Germany, 20246
Public contact	Prof. Dr. med. Uta Herden, University Medical Center Hamburg-Eppendorf, 040 741050822, uta.herden@uke.de
Scientific contact	Prof. Dr. med. Uta Herden, University Medical Center Hamburg-Eppendorf, 040 741050822, uta.herden@uke.de

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	17 March 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the equivalent dose of Envarsus® to achieve the same target trough level as achieved with Advagraf and to assess the conversion ratios Envarsus® Advagraf®.

Protection of trial subjects:

All patients included in the clinical trial underwent previous liver transplantation and required an immunosuppressive therapy normally based on a calcineurine inhibitor e.g. tacrolimus. Both IMPs (Envarsus® and Advagraf®) contained tacrolimus as active substance and were approved and have been used ac-cording to marketing authorization. Based on available information and the design of the clinical trial, the Sponsor and the PI considerd the trial to be ethically acceptable. The duration of confinement and the medical surveillance during the whole trial, especially at the points of treatment switch, were considered adequate to ensure safety of the patients.

Background therapy:

Induction therapy with Simulect® (Basiliximab); treatment with corticosteroids according to center practice; combined immunosuppressive therapy with an mTOR-inhibitor (everolimus/sirolimus) or combined immunosuppressive therapy with mycophenolate mofetil was allowed prior to randomisation, but had to be stopped during Envarsus®/Advagraf® treatment period.

Evidence for comparator:

A cross-over design is the most powerful design for a bioavailability and pharmacokinetic clinical trial because it removes the inter-subject variability from the comparison of the average bioavailability and pharmacokinetic profiles between the formulations and allows for the adjustment of period effects. In this design, each patient functioned as his own control when comparisons between different treatments/ medications were realized between the two subsequent treatment periods exclusively as opposed to comparisons in different patients.

Actual start date of recruitment	31 August 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	18
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient first visit (FPFV) was performed 31-Aug-2016. In total, 20 de novo liver transplant recipients have been enrolled. The patients have been recruited from the involved medical center, University Medical Center Hamburg-Eppendorf (UKE), Department for Hepatobiliary and Transplant Surgery, Germany.

Pre-assignment

Screening details:

Selection of study population: de novo liver transplant recipients. 20 patients were screened and randomized in treatment group 1 or 2 between liver transplantation (Ltx) and postoperative day (pod) 30 after Ltx.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: Envarsus® -> Advagraf®

Arm description:

Two treatments have been investigated, separated without a wash-out period. Group 1: Envarsus® -> Advagraf®. After randomization the previous tacrolimus medication was stopped and Envarsus® therapy was started the same morning. Therapy was given for 14 days plus eventually a longer interval in case the target level has not been reached in time. On Visit 7 (day 15 + n) therapy was switched to Advagraf® for further 14 days plus eventually a longer interval in case of not reaching the target level in a specified timeframe.

Arm type	cross over
Investigational medicinal product name	Envarsus®
Investigational medicinal product code	
Other name	Tacrolimus
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

The Tacrolimus target levels have been between 6 and 10 ng/mL. They have been defined individually for each patient based on clinical experience. The decision for the target level was based on the same principles and considerations as in all patients, whether they participated in this study or not. The starting dose after randomization was according to the conversion ratio 0.7 mg of Envarsus® per 1 mg Tacrolimus premedication. Once daily, the dose have been administered fasted in the morning in 24 hours interval. It should have been administered at the same time each day. Dose have been adjusted until the target level was reached.

Investigational medicinal product name	Advagraf®
Investigational medicinal product code	
Other name	Tacrolimus
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

The Tacrolimus target levels have been between 6 and 10 ng/mL. They have been defined individually for each patient based on clinical experience. The decision for the target level was based on the same principles and considerations as in all patients, whether they participated in this study or not. The starting dose after randomization was according to the conversion ratio 1.0 mg of Advagraf® per 1 mg Tacrolimus premedication. Once daily, the dose have been administered fasted in the morning in 24 hours interval. It should have been administered at the same time each day. Dose have been adjusted until the target level was reached.

Arm title	Group 2: Advagraf® -> Envarsus®

Arm description:

Two treatments have been investigated, separated without a wash-out period. Group 2: Advagraf® -> Envarsus®. After randomization the previous tacrolimus medication was stopped and Advagraf® therapy was started the same morning. Therapy was given for 14 days plus eventually a longer interval in case the target level has not been reached in time. On Visit 7 (day 15 + n) therapy was switched to Envarsus® for further 14 days plus eventually a longer interval in case of not reaching the target level in a specified timeframe.

Arm type	cross over
Investigational medicinal product name	Advagraf®
Investigational medicinal product code	
Other name	Tacrolimus
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

The Tacrolimus target levels have been between 6 and 10 ng/mL. They have been defined individually for each patient based on clinical experience. The decision for the target level was based on the same principles and considerations as in all patients, whether they participated in this study or not. The starting dose after randomization was according to the conversion ratio 1.0 mg of Advagraf® per 1 mg Tacrolimus premedication. Once daily, the dose have been administered fasted in the morning in 24 hours interval. It should have been administered at the same time each day. Dose have been adjusted until the target level was reached.

Investigational medicinal product name	Envarsus®
Investigational medicinal product code	
Other name	Tacrolimus
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

The Tacrolimus target levels have been between 6 and 10 ng/mL. They have been defined individually for each patient based on clinical experience. The decision for the target level was based on the same principles and considerations as in all patients, whether they participated in this study or not. The starting dose after randomization was according to the conversion ratio 0.7 mg of Envarsus® per 1 mg Tacrolimus premedication. Once daily, the dose have been administered fasted in the morning in 24 hours interval. It should have been administered at the same time each day. Dose have been adjusted until the target level was reached.

Number of subjects in period 1	Group 1: Envarsus® -> Advagraf®	Group 2: Advagraf® -> Envarsus®
Started	9	11
Completed	5	4
Not completed	4	7
Consent withdrawn by subject	3	3
other	1	4

Baseline characteristics

Reporting groups

Reporting group title	Group 1: Envarsus® -> Advagraf®

Reporting group description:

Two treatments have been investigated, separated without a wash-out period. Group 1: Envarsus® -> Advagraf®. After randomization the previous tacrolimus medication was stopped and Envarsus® therapy was started the same morning. Therapy was given for 14 days plus eventually a longer interval in case the target level has not been reached in time. On Visit 7 (day 15 + n) therapy was switched to Advagraf® for further 14 days plus eventually a longer interval in case of not reaching the target level in a specified timeframe.

Reporting group title	Group 2: Advagraf® -> Envarsus®

Reporting group description:

Two treatments have been investigated, separated without a wash-out period. Group 2: Advagraf® -> Envarsus®. After randomization the previous tacrolimus medication was stopped and Advagraf® therapy was started the same morning. Therapy was given for 14 days plus eventually a longer interval in case the target level has not been reached in time. On Visit 7 (day 15 + n) therapy was switched to Envarsus® for further 14 days plus eventually a longer interval in case of not reaching the target level in a specified timeframe.

Reporting group values	Group 1: Envarsus® -> Advagraf®	Group 2: Advagraf® -> Envarsus®	Total
Number of subjects	9	11	20
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
In total, mean age was 54.3 years with a standard deviation of 10.34 (ranging from 31 to 71 years).			
Units: years			
arithmetic mean	54	54	
full range (min-max)	31 to 71	31 to 71	-
Gender categorical			
In total, 4 subjects (22.2%) were female and 14 (77.8%) male.			
Units: Subjects			
Female	2	2	4
Male	7	9	16
ethnicity			
In total, 16 subjects (88.9%) were white, while 1 (5.6%) was indide and 1 (5.6%) oriental.			
Units: Subjects			
caucasian/white	8	10	18
indide		1	1
oriental	1		1

black			0
other			0

BMI			
The mean height [cm], weight [kg] and BMI at baseline were 174.8 ± 6.20, 81.4 ± 12.53 and 26.7 ± 4.22, respectively.			
Units: kg/m²			
arithmetic mean			
full range (min-max)			-
Age of donor			
Units: years			
arithmetic mean			
full range (min-max)			-

Subject analysis sets

Subject analysis set title	Group 1 safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
NA	
Subject analysis set title	Group 2 safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
NA	
Subject analysis set title	PK population
Subject analysis set type	Per protocol
Subject analysis set description:	
NA	

Reporting group values	Group 1 safety population	Group 2 safety population	PK population
Number of subjects	8	10	9
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
In total, mean age was 54.3 years with a standard deviation of 10.34 (ranging from 31 to 71 years).			
Units: years			
arithmetic mean	58.9	50.6	54
full range (min-max)	46.0 to 71.0	31.0 to 63.0	31 to 71
Gender categorical			
In total, 4 subjects (22.2%) were female and 14 (77.8%) male.			
Units: Subjects			

Female	2	2	2
Male	8	6	7

ethnicity			
In total, 16 subjects (88.9%) were white, while 1 (5.6%) was indide and 1 (5.6%) oriental.			
Units: Subjects			
caucasian/white	7	9	9
indide	0	1	
oriental	1	0	
black	0	0	
other	0	0	
BMI			
The mean height [cm], weight [kg] and BMI at baseline were 174.8 ± 6.20, 81.4 ± 12.53 and 26.7 ± 4.22, respectively.			
Units: kg/m²			
arithmetic mean	28.0	24.2	
full range (min-max)	21.8 to 34.1	20.1 to 34.6	
Age of donor			
Units: years			
arithmetic mean	62.5	52.0	
full range (min-max)	50.0 to 75.0	27.0 to 77.0	

End points

End points reporting groups

Reporting group title	Group 1: Envarsus® -> Advagraf®

Reporting group description:

Two treatments have been investigated, separated without a wash-out period. Group 1: Envarsus® -> Advagraf®. After randomization the previous tacrolimus medication was stopped and Envarsus® therapy was started the same morning. Therapy was given for 14 days plus eventually a longer interval in case the target level has not been reached in time. On Visit 7 (day 15 + n) therapy was switched to Advagraf® for further 14 days plus eventually a longer interval in case of not reaching the target level in a specified timeframe.

Reporting group title	Group 2: Advagraf® -> Envarsus®

Reporting group description:

Two treatments have been investigated, separated without a wash-out period. Group 2: Advagraf® -> Envarsus®. After randomization the previous tacrolimus medication was stopped and Advagraf® therapy was started the same morning. Therapy was given for 14 days plus eventually a longer interval in case the target level has not been reached in time. On Visit 7 (day 15 + n) therapy was switched to Envarsus® for further 14 days plus eventually a longer interval in case of not reaching the target level in a specified timeframe.

Subject analysis set title	Group 1 safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

NA

Subject analysis set title	Group 2 safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

NA

Subject analysis set title	PK population
Subject analysis set type	Per protocol

Subject analysis set description:

NA

Primary: Pharmacokinetic characteristics: C0/dose ss [µg / mg L] Envarsus®

End point title	Pharmacokinetic characteristics: C0/dose ss [µg / mg L] Envarsus®[1]

End point description:

The pharmacokinetic profiles of Envarsus® and Advagraf® were evaluated as a surrogate for the efficacy. In total, 19 plasma samples (9 subjects with 9 x 2 plasma samples each and one subjects who dropped out with one sample) are available. All 9 patients having both plasma profiles have been analyzed.

End point type	Primary

End point timeframe:

descriptive statistics of all considered pharmacokinetic characteristics

Notes:

[1] - 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: Original static evaluation not possible because target number of cases not reached.

End point values	PK population			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: µg / mg L				
arithmetic mean (full range (min-max))	1.2 (0.3 to 2.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic characteristics: AUC 0-24/dose ss [µg h/ mg L] Envarsus®

End point title	Pharmacokinetic characteristics: AUC 0-24/dose ss [µg h/ mg L] Envarsus®[2]

End point description:

The pharmacokinetic profiles of Envarsus® and Advagraf® were evaluated as a surrogate for the efficacy. In total, 19 plasma samples (9 subjects with 9 x 2 plasma samples each and one subjects who dropped out with one sample) are available. All 9 patients having both plasma profiles have been analyzed.

End point type	Primary

End point timeframe:

descriptive statistics of all considered pharmacokinetic characteristics

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: Original static evaluation not possible because target number of cases not reached.

End point values	PK population			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: µg h/ mg L				
arithmetic mean (full range (min-max))	40.9 (14.4 to 58.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic characteristics: AUC 0-24/dose ss [µg h / mg L] Advagraf®

End point title	Pharmacokinetic characteristics: AUC 0-24/dose ss [µg h / mg L] Advagraf®[3]

End point description:

The pharmacokinetic profiles of Envarsus® and Advagraf® were evaluated as a surrogate for the efficacy. In total, 19 plasma samples (9 subjects with 9 x 2 plasma samples each and one subjects who dropped out with one sample) are available. All 9 patients having both plasma profiles have been analyzed.

End point type	Primary

End point timeframe:

descriptive statistics of all considered pharmacokinetic characteristics

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: Original static evaluation not possible because target number of cases not reached.

End point values	PK population			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: µg h / mg L				
arithmetic mean (full range (min-max))	23.0 (12.3 to 38.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic characteristics: C0/dose ss [µg / mg L] Advagraf®

End point title	Pharmacokinetic characteristics: C0/dose ss [µg / mg L] Advagraf®[4]

End point description:

The pharmacokinetic profiles of Envarsus® and Advagraf® were evaluated as a surrogate for the efficacy. In total, 19 plasma samples (9 subjects with 9 x 2 plasma samples each and one subjects who dropped out with one sample) are available. All 9 patients having both plasma profiles have been analyzed.

End point type	Primary

End point timeframe:

descriptive statistics of all considered pharmacokinetic characteristics

Notes:

[4] - 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: Original static evaluation not possible because target number of cases not reached.

End point values	PK population			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: µg / mg L				
arithmetic mean (full range (min-max))	0.6 (0.3 to 1.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic characteristics: C max/dose ss [µg / mg L] Envarsus®

End point title	Pharmacokinetic characteristics: C max/dose ss [µg / mg L] Envarsus®

End point description:

The pharmacokinetic profiles of Envarsus® and Advagraf® were evaluated as a surrogate for the efficacy. In total, 19 plasma samples (9 subjects with 9 x 2 plasma samples each and one subjects who dropped out with one sample) are available. All 9 patients having both plasma profiles have been analyzed.

End point type	Secondary

End point timeframe:

descriptive statistics of all considered pharmacokinetic characteristics

End point values	PK population			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: µg / mg L				
arithmetic mean (full range (min-max))	3.0 (2.0 to 5.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic characteristics: C max/dose ss [µg / mg L] Advagraf®

End point title	Pharmacokinetic characteristics: C max/dose ss [µg / mg L] Advagraf®

End point description:

The pharmacokinetic profiles of Envarsus® and Advagraf® were evaluated as a surrogate for the efficacy. In total, 19 plasma samples (9 subjects with 9 x 2 plasma samples each and one subjects who dropped out with one sample) are available. All 9 patients having both plasma profiles have been analyzed.

End point type	Secondary

End point timeframe:

descriptive statistics of all considered pharmacokinetic characteristics

End point values	PK population			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: µg / mg L				
arithmetic mean (full range (min-max))	1.9 (1.1 to 2.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All AEs, including those associated with the protocol, were collected from the time that the patient was randomized, regardless of the relationship to the IMP. All AEs had to be recorded until the last trial day according to the clinical trial protocol.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	NA

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: All AEs, including those associated with the protocol, were collected from the time that the patient was randomized, regardless of the relationship to the IMP. All AEs had to be recorded until the last trial day according to the clinical trial protocol.

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