## 2 SYNOPSIS

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|---|---|---|
| **Name of Sponsor/Company:**<br>Universitätsklinikum Hamburg-Eppendorf<br>Martinistr. 52<br>20246 Hamburg<br>Germany | **Individual Study Table Referring to Part of the Dossier**<br><br>**Volume:**<br><br>**Page:** | **(For National Authority Use only)** |
| **Name of Finished Product:**<br>Envarsus® and Advagraf® | | |
| **Name of Active Ingredient:**<br>Tacrolimus | | |
| **Study Title** | Single center, 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. | |
| **Principal Investigator** | Prof. Dr. med. Uta Herden | |
| **Study center** | University Medical Center Hamburg-Eppendorf<br>Martinistr. 52<br>20246 Hamburg<br><br>CTC North GmbH & Co. KG<br>at University Medical Center Hamburg-Eppendorf<br>Martinistr. 64<br>20251 Hamburg | |
| **Publication (reference)** | na | |
| **Protocol No.** | PAKT (Sponsor), CTC151043 (CRO) | |
| **EudraCT-No.** | 2015-002935-16 | |
| **Study Period** | AUG 2016- APR2019 | |
| **Phase of development** | Phase III | |
| **Primary Objective** | 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®. | |
| **Secondary Objectives** | To compare the pharmacokinetic (PK) profile and bioavailability of two different once daily tacrolimus formulations (Envarsus® versus Advagraf®) in de novo liver transplant recipients. The extent and rate of tacrolimus exposure have been estimated in terms of trough level $C_0$, area under the curve AUC and the Highest concentration determined in the measuring interval ($C_{max}$) respectively. To compare the safety profile (Frequency and severity of Adverse Events (AEs)). | |

**Methodology**

This was a single center, open-label, randomized and controlled clinical cross over trial.
Patients were screened and randomized in treatment group 1 or 2 between liver transplantation (Ltx) and postoperative day (pod) 30 after Ltx.
After randomization the previous tacrolimus medication was stopped and Envarsus® or Advagraf® (depending on randomization) therapy were started the same morning.
Group 1: Envarsus® → Advagraf®
Group 2: Advagraf® → Envarsus®
All visits have been ambulatory or hospitalized except for PK visit 6 and 11 where the patients were hospitalized.

**Group 1**

| Tacrolimus formulations | Visit | Day | Comment |
|---|---|---|---|
| Tacrolimus based immunosuppressive therapy | 1 | -31 to -1 | Screening |
| Envarsus® dose conversion ratio of 0.7 compared to Tacrolimus based immunosuppressive premedication | 2 | 1 | Randomization |
| | 3 | 3 to 5 | Target level reached, otherwise dose adjustment. |
| | 4 | 6 to 8 | If target level reached, then continue with Visit 5. Otherwise, add optional visits. If >25 % dose adaption add at least one optional visit. If >50 % dose adaption add at least two optional visits. |
| | optional 1..i | V4 + 3 | Further optional visit will be added in three-day-intervals until no further dose adaption > 25% is performed. |
| | 5 | 9 to 11 (+n) n = 3 * i | Target level reached, no further adaption allowed. |
| | 6 | 14 (+n) | Steady state reached, PK sampling. |
| Advagraf® dose conversion ratio of 1.4 compared to Envarsus® | 7 | 15 (+n) | Cross-over |
| | 8 | 17 to 19 (+n) | Target level reached, otherwise dose adjustment |
| | 9 | 20 to 22 (+n) | If target level reached, then continue with Visit 10. Otherwise, add optional visits. If >25 % dose adaption add at least one optional visit. If >50 % dose adaption add at least two optional visits. |
| | optional 1..j | V9 + 3 | Further optional visit will be added in three-day-intervals until no further dose adaption > 25% is performed. |
| | 10 | 23 to 25 (+n) n = 3 * j | Target level reached, no further adaption allowed |
| | 11 | 28 (+n) | Steady state reached, PK sampling. |

<table>
<tr><td></td><td>
<table>
<tr><td colspan="4">Group 2</td></tr>
<tr><td>Tacrolimus formulations</td><td>Visit</td><td>Day</td><td>Comment</td></tr>
<tr><td>Tacrolimus based immuno-suppressive therapy</td><td>1</td><td>-31 to -1</td><td>Screening</td></tr>
<tr><td rowspan="5">Advagraf® dose conversion ratio of 1 compared to Tacrolimus based immunosuppressive pre-medication</td><td>2</td><td>1</td><td>Randomization</td></tr>
<tr><td>3</td><td>3 to 5</td><td>Target level reached, otherwise dose adjustment</td></tr>
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</table>
If patients' health status required medical intervention, additional tacrolimus $C_0$ level determinations plus dose adjustments between the visits were allowed, except for the time between visit 5 and 6, and 10 and 11, respectively. These interventions were not considered protocol deviations.
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<tr><td>Number of subjects</td><td>20 de novo liver transplant recipients were randomized in this cross-over trial. 9 patients fully completed the study.</td></tr>
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| **Indication** | Evaluation of the pharmacokinetic and bioavailability of Envarsus® in comparison to Advagraf® in de novo liver transplant recipients. |
| **Diagnosis and main criteria for inclusion:** | Tacrolimus is an immunosuppressive drug used mainly after allogeneic organ transplant to reduce the activity of the patient's immune system and to lower the risk of organ rejection.<br>1. Ability to understand the patient information and to personally sign and date the informed consent to participate in the clinical trial, before having completed any clinical trial related procedures.<br>2. Male or female recipients ≥ 18 years of a liver graft from a deceased or living donor<br>3. Females of child-bearing potential who agreed to comply with any applicable contraceptive requirements of the protocol or females who were permanently sterilized (at least 6 weeks post sterilization).<br>4. Non-pregnant, non-lactating female.<br>5. Recipients of a first or re-liver transplant in the last 30 days.<br>6. The patient had to receive a twice daily tacrolimus based immunosuppression treatment. |
| **Test product, dose and mode of administration, batch no.** | Two treatments have been investigated, separated without a wash-out period.<br>Both medicinal products are approved and have been used according to their marketing authorization.<br>Group 1: Envarsus® → Advagraf®<br>Group 2: Advagraf® → Envarsus®<br>Once daily (always at the same time) the appropriate dose according to the conversion rate has been administered p.o. in the morning in 24 hours interval for 14 days plus potentially a longer interval in case the target level has not been reached on Visit 4. On Visit 6 first PK sampling has been performed at the UKE or CTC North. On Visit 7 therapies have been switched for further 14 days plus potentially a longer interval in case of not reaching target level on Visit 9. On Visit 11 PK sampling has been performed at CTC North or at UKE. Administration happened after fasting with an adequate volume of water. |
| **Duration of treatment** | Clinical trial duration: 31 months<br>Duration per patient: 2 months; potentially longer depending on duration until the target level has been reached |
| **Reference product, dose and mode of administration, batch no.** | na |
| **Criteria for evaluation**<br>**Efficacy and Safety** | <u>Efficacy:</u><br>Equivalent dose:<br>$ED_{AV} = D_{AV(ENV)} / D_{AV(ADV)}$<br>Measures of conversion ratios:<br>$ED_{(Co)} = ( C_{0\,(ADV)}/dose_{ss(ADV)} )/( C_{0(ENV)}/dose_{ss(ENV)} )$<br>$ED_{(AUC)} = ( AUC_{(ADV)}/dose_{ss(ADV)} )/(AUC_{(ENV)}/dose_{ss(ENV)} )$<br>Bioavailability in terms of extent and rate of exposure:<br>$AUC_{0\text{-}24(ENV)}/AUC_{0\text{-}24(ADV)}$<br>$C_{max(ENV)}/C_{max(ADV)}$<br>$C_{0(ENV)}/C_{0(ADV)}$<br><u>Safety:</u><br>Frequency and severity of AEs |

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|---|---|
| **Statistical methods** | Analyses of variance (ANOVA) on log-transformed data has been performed for all primary PK variables, except for $D_{AV}$, where an ANOVA with non-transformed data was used, and $t_{max}$, which was analysed by medians and non-parametric CIs. ANOVA-CVs and adjusted 90%-CIs were calculated.<br><br>The individual patients' values for concentrations and PK parameters have been tabulated with descriptive statistics. |
| **PK Results** | For the concentration measures $C_0$, $AUC_{0-24}$ und $C_{max}$, which were predefined as measures of bioavailability, the adjusted geoM ratios lie within 100% and 115%, showing that the mean concentrations were similar for both treatments with slightly higher concentration values for Envarsus. There is no significant difference in these concentration measures, as each of their confidence intervals contains 100%. However, none of the 90%-CIs lies within the range of 80%-125%, that is usually used to determine bioequivalence [12], but this fact may be due to the small sample size of 9 subjects in the PK population (originally 20 were planed).<br><br>Concerning the administered doses, the ratio $C_0/dose_{ss}$ is significantly higher for Envarsus® (adj. geoM ratio: 176.2% (CI: 131.6% – 235.8%)), which means that the administered dose in relation to pre-dose concentration at steady state was lower for Envarsus®. Also, the average cumulative dose ($D_{AV}$) was lower for Envarsus® (adj. mean difference: 2.9 (CI: 5.9 – 0.1)).<br><br>With medians of 6.0 vs. 1.5 h, the timepoint when the maximum concentration is reached ($t_{max}$) is significantly earlier for Advagraf® (location shift: 4.0 (CI: 2.0 – 6.5)). The peak through fluctuation (PTF) was slightly higher for Advagraf® with adjusted geoMs of 1.1 and 1.4, respectively (ratio: 84.3% (CI: 46.6% – 152.5%)). |
| **Safety Results** | After treatment of Envarsus® 26 AEs occurred in 8 patients (53.3%), while for Advagraf® there were 36 AEs in 12 patients (92.3%). Most AEs were mild to moderate for both treatments. While for Envarsus® there were 8 mild AEs in 4 patients (26.7%) and 18 moderate AEs in 7 patients (46.7%), for Advagraf® there were 13 in 7 (53.8%), 22 in 7 (53.8%) and 1 in 1 (7.7%) for mild, moderate and severe respectively. Out of all AEs only one event after treatment of Advagraf® was classified as related to IMP. This was a nervous system disorder with the preferred term Tremor. |
| **Conclusion** | While the blood concentration measured by $C_0$, $AUC_{0-24}$ and $C_{max}$ was slightly higher for Envarsus, the dose at steady state in relation to the pre-dose concentration was significantly lower for Envarsus. The maximum concentration was reached significantly later for Envarsus.<br><br>The pure numbers of patients developing AEs, were 8/15 (53.3%) for Envarsus® and 12/13 (92.3%) for Advagraf®, indicating a higher safety for Envarsus®. The total numbers of AEs were 26 and 36, respectively. However, considering that there was only 1 event (mild in severity) classified as related to the IMP for Advagraf® and 0 for Envarsus®, both treatments were well tolerated. Overall, the clinical trial in 18 patients in the safety set was performed with only one related adverse event, but without any related serious adverse event, death or significant adverse event. No abnormal creatinine value was classified as clinically significant. No safety concerns or any safety signs raised at any time during the study conduct. |
| **Date of Report** | 07-APR-2020 |

**Table 1 Study schedule**

| Phase of study | Preop. | Screening | Treatment Period 1 Group1 / Group2 | | | | | | | Treatment Period 2 Group1 / Group2 | | | | | | End of study | Early termination |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | | **1** | **2 (randomization)** | **clinically relevant [a]** | **3** | **4** | **Optional [b]** | **5** | **6** | **7** | **8** | **9** | **Optional [b]** | **10** | **11** | **12** | **n.a.** |
| **Study day [a]** | **xx** | **-31 - -1** | **1** | | **3 to 5** | **6 to 8** | **V4 + 3** | **9 to 11 (+n)** | **14 (+n)** | **15 (+n)** | **17 to 19 (+n)** | **20 to 22 (+n)** | **V9 +3** | **23 to 25 (+n)** | **28 (+n)** | **29 (+n)** | **n.a.** |
| Informed Consent | x | x | | | | | | | | | | | | | | | |
| Inclusion /exclusion | | x | x | | | | | | | | | | | | | | |
| Randomization | | | x | | | | | | | | | | | | | | |
| Medical History & Demographics [d] | | x | | | | | | | | | | | | | | | |
| Physical Examination | | x | x | | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Vital Signs [e] | | x | x | | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Height and Weight [f] | | x | x | | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Clinical Chemistry, Coagulation, Hematology[g] | | x | | | | | | | x | | | | | | x | | x |
| Tacrolimus $C_0$ Level | | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Serum Pregnancy Test (beta hCG) | | x | | | | | | | | | | | | | | | |
| Ambulatory Visit [h] | | x | x | | x | x | x | x | | x | x | x | x | x | | x | x |
| Envarsus® / Advagraf® daily dose | | | x | x | x | x | x | x | x | x | x | x | x | x | x | | |

| Phase of study | Preop. | Screening | Treatment Period 1 Group1 / Group2 | | | | | | | Treatment Period 2 Group1 / Group2 | | | | | | End of study | Early termination |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | | **1** | **2 (randomization)** | **clinically relevant [a]** | **3** | **4** | **Optional [b]** | **5** | **6** | **7** | **8** | **9** | **Optional [b]** | **10** | **11** | **12** | **n.a.** |
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| Possible dose adjustment | | | | x | x | x | x | | | | x | x | x | | | | |
| Pharmacokinetic, Blood Sampling | | | | | | | | | x[j] | | | | | | x[j] | | |
| Adverse Events & Concomitant Medication | | x | x | | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Drug Accountability | | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | |

[a] If clinically important, additional Tacrolimus $C_0$ level determination and dose adaption between the regular visits were possible, except for the time between visit 5 and 6, and 10 and 11, respectively.

[b] Dose adaption based on the previous visit $C_0$, to be repeated for further adaption until the target level was reached.

[d] Age, gender, ethnic origin, underlying liver disease causal for Ltx, concomitant diseases and relevant prior diseases with date of diagnosis, relevant prior operations with date of surgery, Transplant data including donor age, type of organ (whole versus split organ), type of donor (living versus deceased donor organ), viral serology (Cytomegalovirus (CMV), Epstein–Barr virus (EBV), Hepatitis C Virus (HCV), Hepatitis B surface antigen (HBsAg)) from donor and recipient.

[e] Please refer to Table 2 for frequency of vital signs examinations.

[f] Height (only recorded at baseline)

[g] Hematology: hemoglobin, hematocrit, red blood cell count, leukocytes, platelet count, chemistry (sodium, potassium, glucose, albumin, creatinine, bilirubin, Alanine transaminase (ALT), Aspartate transaminase (AST), Gamma glutamyl transferase (GGT), C-reactive Protein (CRP)), coagulation (International Normalized Ratio (INR))

[h] Depending on patients condition ambulatory visits caned also be performed as stationary visits.

[i] Morning check-in and Morning check-out after 24 hours.

[j] Vital signs must be estimated before PK evaluations. Please refer to Table 2 for frequency of pharmacokinetic evaluations.

**Table 2 Detailed Time and Events**

| Study Day[a] | Time after Dose on Day 1 (hours) | Dosing | Plasma PK |
|---|---|---|---|
| 14/28 | 0 | x | x |
| 14/28 | 0.5 | | x |
| 14/28 | 1 | | x |
| 14/28 | 1.5 | | x |
| 14/28 | 2 | | x |
| 14/28 | 3 | | x |
| 14/28 | 4 | | x |
| 14/28 | 6 | | x |
| 14/28 | 8 | | x |
| 14/28 | 10 | | x |
| 14/28 | 12 | | x |
| 15/29 | 16 | | x |
| 15/29 | 20 | | x |
| 15/29 | 24 | | x |

[a] Depending on the starting time the study day has been adapted.