

# Early Everolimus-Facilitated Reduced Tacrolimus in Liver Transplantation: Results From the Randomized HEPHAISTOS Trial

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Everolimus-facilitated reduced-exposure tacrolimus (EVR + rTAC) at 30 days after liver transplantation (LT) has shown advantages in renal preservation. This study evaluated the effects of early initiation of EVR + rTAC in de novo LT recipients (LTRs). In HEPHAISTOS (NCT01551212, EudraCT 2011-003118-17), a 12-month, multicenter, controlled study, LTRs were randomly assigned at 7 to 21 days after LT to receive EVR + rTAC or standard-exposure tacrolimus (sTAC) with steroids. The primary objective was to demonstrate superior renal function (assessed by estimated glomerular filtration rate [eGFR]) with EVR + rTAC versus sTAC at month 12 in the full analysis set (FAS). Other assessments at month 12 included the evaluation of renal function in compliance set and on-treatment (OT) patients, efficacy (composite endpoint of graft loss, death, or treated biopsy-proven acute rejection [tBPAR] and individual components) in FAS, and safety. In total, 333 patients (EVR + rTAC, 169; sTAC, 164) were included in the FAS. A high proportion of patients was nonadherent in maintaining tacrolimus trough levels (EVR + rTAC, 36.1%; sTAC, 34.7%). At month 12, the adjusted least square mean eGFR was numerically higher with EVR + rTAC versus sTAC (76.2 versus 72.1 mL/minute/1.73 m<sup>2</sup>, difference: 4.1 mL/minute/1.73 m<sup>2</sup>;  $P = 0.097$ ). A significant difference of 8.3 mL/minute/1.73 m<sup>2</sup> ( $P = 0.03$ ) favoring EVR + rTAC was noted in the compliance set. Incidence of composite efficacy endpoint (7.7% versus 7.9%) and tBPAR (7.1% versus 5.5%) at month 12 as well as incidence of treatment-emergent adverse events (AEs) and serious AEs were comparable between groups. A lower proportion of patients discontinued EVR + rTAC than sTAC treatment (27.2% versus 34.1%). Early use of everolimus in combination with rTAC showed comparable efficacy, safety, and well-preserved renal function versus sTAC therapy at month 12. Of note, renal function was significantly enhanced in the compliance set.

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Alcohol-related cirrhosis, hepatocellular carcinoma (HCC), and viral hepatitis are the leading end-stage diseases for liver transplantation (LT) in Europe.<sup>(1,2)</sup> According to the Eurotransplant registry, Germany is

*Abbreviations: AE, adverse event; ANCOVA, analysis of covariance; AR, acute rejection; BMI, body mass index; BPAR, biopsy-proven acute rejection; CO, trough levels; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CMV,*

the country with the most LTs in this alliance, with more than 800 LTs per year. The 1-year and 5-year patient survival rates for deceased donor LT have been reported as 80% and 64%, respectively,<sup>(2-4)</sup> with the recurrence of the primary disease (mainly tumor) and cardiovascular, cerebrovascular, pulmonary, and renal complications as the most likely causes of post-LT mortality.<sup>(1)</sup>

Calcineurin inhibitors (CNIs) are the current standard of care in LT recipients (LTRs) in Germany.<sup>(5)</sup> However, long-term use of CNIs is associated with chronic renal toxicity, increased risk of infections, and de novo malignancies as well as the recurrence of

cytomegalovirus; CNi, calcineurin inhibitor; EVR, everolimus; EVR + rTAC, everolimus-facilitated reduced-exposure tacrolimus; eGFR, estimated glomerular filtration rate; FAS, full analysis set; GFR, glomerular filtration rate; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; KM, Kaplan-Meier; LOCF, last observation carried forward; LT, liver transplantation; LTR, liver transplant recipient; MDRD-4, Modification of Diet in Renal Disease 4-variable; MELD, Model for End-Stage Liver Disease; MMF, mycophenolate mofetil; MMRM, mixed model for repeated measures; mTORi, mammalian target of rapamycin inhibitor; OT, on-treatment; PP, per protocol; RAI, rejection activity index; rTAC, reduced-exposure tacrolimus; SAE, serious adverse event; sTAC, standard-exposure tacrolimus; TAC, tacrolimus; tBPAR, treated biopsy-proven acute rejection; ULN, upper limit of normal; UPCR, urinary protein to creatinine ratio.

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HCC.<sup>(6-8)</sup> One useful strategy to reduce CNi exposure and the resulting adverse events has been to introduce other immunosuppressive drugs, including mammalian target of rapamycin inhibitors (mTORis).<sup>(8)</sup>

Everolimus (EVR) is an mTORi, and its early introduction after LT has been shown to allow for CNi reduction and thus minimize related renal toxicity.<sup>(8)</sup> In addition, the antiproliferative property of EVR can prevent the onset of de novo cancer as well as the recurrence of HCC after LT.<sup>(9-12)</sup> In 2 pivotal trials, H2304 (in deceased donor LTRs) and H2307 (in living donor LTRs), EVR was introduced 30 ± 5 days after LT along with a reduced-exposure tacrolimus (rTAC) regimen. In both studies, the EVR-facilitated rTAC (EVR + rTAC) regimen versus a standard-exposure tacrolimus (sTAC) regimen showed comparable efficacy and safety with a better preservation of renal function over the long term.<sup>(13-17)</sup> The Preservation of Renal Function in Liver Transplant Recipients With Certican Therapy study conducted in Germany and the Netherlands revealed that EVR-facilitated CNi withdrawal versus a standard CNi regimen was associated with superior renal function plus comparable efficacy and safety during a long-term follow-up of 5 years.<sup>(18)</sup> Similarly, results from the multicenter SIMCER study in France confirmed the renal function superiority of EVR in combination with low-exposure tacrolimus (TAC) discontinued by month 4 plus a mycophenolate sodium regimen versus standard tacrolimus and a mycophenolate sodium regimen at 6 months.<sup>(19)</sup>

The HEPHAISTOS study was designed to evaluate the effects of the early initiation of EVR (latest day 21 after LT) in de novo LTRs. It was hypothesized that this early initiation of EVR in combination with reduced TAC would achieve similar efficacy as TAC alone with improved renal function.<sup>(20)</sup>

## Patients and Methods

### STUDY DESIGN AND POPULATION

HEPHAISTOS (NCT01551212, EudraCT no. 2011-003118-17) was a 12-month, multicenter, open-label, randomized, and controlled study conducted across 15 transplant centers in Germany. The study was initiated in May 2012 (first patient first visit) and completed in August 2017 (last patient last visit). The study design, inclusion, and exclusion criteria have been previously reported.<sup>(20)</sup> Adult (aged 18-65 years) male or female recipients of

full-size liver allografts entered into a run-in period (starting 3–5 days after LT) and received optional induction therapy, mycophenolate mofetil (MMF), and TAC—as per the investigator’s discretion—and mandatory corticosteroids (for at least 6 months after LT). The run-in period ended on the day of randomization. Patients with estimated glomerular filtration rates (eGFR; Modification of Diet in Renal Disease 4-variable [MDRD-4] formula)  $>30$  mL/minute/1.73 m<sup>2</sup> and acceptable graft functions (total bilirubin levels  $\leq 3$  times the upper limit of normal [ULN] and alkaline phosphatase, aspartate transaminase, alkaline transaminase levels  $\leq 5$  times ULN) without graft thrombosis were randomly assigned (1:1) at 7 to 21 days after LT to receive EVR + rTAC or sTAC along with steroids. The combination of TAC + MMF was not allowed because of regulatory constraints at the time of study initiation. Randomization was stratified by hepatitis C virus (HCV) status and laboratory Model for End-Stage Liver Disease (MELD) scores at LT. Patients with HCC only within the Milan criteria were included. Patients were excluded at time of randomization if they had uncontrolled hypercholesterolemia or hypertriglyceridemia, proteinuria  $>1$  g/day, and infections requiring intravenous antibiotic administration. The presence of wound-healing events was not an exclusion criterion. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. The study was approved by competent ethics committees and regulatory authorities of all participating centers. Informed consent was obtained by investigators from all patients enrolled into the study.

## IMMUNOSUPPRESSION

EVR was administered on the day of randomization at a dose of 1.0 mg twice daily. The target trough

levels (C<sub>0</sub>) of EVR (3–8 ng/mL) and TAC ( $<5$  ng/mL after EVR C<sub>0</sub> was achieved) in the EVR + rTAC group and in the sTAC group (6–10 ng/mL) were maintained from randomization to month 12. Corticosteroid use was mandatory in patients of both groups. It was initiated at or prior to LT as per the local practice and was continued for at least 6 months after LT. Patients received induction therapy as per center practice. Patients who received MMF as per the local practice were required to discontinue it before randomization. Rejection episodes were treated as per local practice or at the investigator’s discretion. Concomitant treatments according to local practice were permitted for prophylaxis of cytomegalovirus (CMV) infection, *Pneumocystis carinii* pneumonia, hepatitis B virus (HBV) infection, treatment of oral Candida, and HCV.

## OBJECTIVES AND ASSESSMENTS

The primary objective of the study was to demonstrate superior renal function with EVR + rTAC versus sTAC at month 12. The renal function was assessed in both groups by mean eGFR (MDRD-4) at month 12. Other secondary renal function-related endpoints included evolution of mean eGFR (MDRD-4) over time; assessment of eGFR using the Nankivell, Cockcroft-Gault, Chronic Kidney Disease Epidemiology collaboration (CKD-EPI), and Hoek formulas; eGFR in different subgroups based on age ( $<60$  and  $\geq 60$  years); sex; renal function strata ( $<60$  and  $\geq 60$  mL/minute/1.73 m<sup>2</sup>); HCV status; laboratory MELD score categories ( $\leq 14$ , 15–19, 20–24, 25–29,  $\geq 30$ ); and urinary protein to creatinine ratio (UPCR) over 12 months.

The key secondary objective was to evaluate the efficacy at month 12. Key efficacy outcome was incidence of composite endpoint of graft loss, death, or treated biopsy-proven acute rejection (tBPAR). Graft loss, death, acute rejection (AR), treated AR, and biopsy-proven AR (BPAR) were assessed as composite or individual components at month 12. The episodes of BPAR and tBPAR were classified based on rejection activity index (RAI) scores into mild, moderate, and severe categories. In a post hoc analysis, renal and efficacy outcomes were evaluated in patients receiving induction versus those not receiving induction. Safety outcomes included incidence of adverse events (AEs), serious adverse events (SAEs), AEs leading to study drug discontinuation, and infection in both groups at month 12.

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## STATISTICAL ANALYSIS

The analyses were performed on (1) the full analysis set (FAS) comprising all randomly assigned patients who received at least 1 dose of the study drug; (2) the per-protocol (PP) population comprising all patients of the FAS without any major deviations from the protocol that may impact the study outcome; (3) the on-treatment (OT) analysis including all FAS patients in which only the values until treatment discontinuation were taken into account; and (4) the compliance set, which is a subset from FAS only including patients whose measured TAC C0 levels were within the target range for at least 3 visits between month 3 and month 12. Renal function was assessed in all populations, whereas efficacy was only evaluated in the FAS and PP populations. Safety analyses were done on the safety population, which included all patients who had received at least 1 dose of the study drug with at least 1 safety assessment after baseline.

The study tested the hypothesis that there is no difference in renal function between EVR + rTAC and sTAC regimens versus the alternative hypothesis that the difference is 7.0 mL/minute/1.73 m<sup>2</sup> in favor of EVR + rTAC. The analysis of covariance (ANCOVA) model was used to assess the superiority of renal function in the EVR + rTAC group over the sTAC group. In the ANCOVA model, treatment, center, HCV class (positive/negative), and laboratory MELD score ( $\leq 30$  versus  $> 30$ ) were included as factors, and eGFR at visit 2 (baseline) was a covariate (with a 5% 2-sided significance level). A sample size of 105 in each group had 80% power to detect a difference in means by  $\geq 7.0$  (18.0) mL/minute/1.73 m<sup>2</sup> in favor of EVR + rTAC group. After considering a dropout rate of 20%, the sample size was adjusted to 165 randomly assigned patients in each group. Raw as well as adjusted least square means of eGFR were presented for the treatment contrast together with a *P* value (5% 2-sided significance level) and the appropriate confidence interval (CI). Missing values in eGFR were imputed with the last observation carried forward (LOCF) for that patient. The primary analysis was repeated with PP set using the same ANCOVA model. As a further supportive analysis, a mixed model for repeated measures (MMRM) and multiple imputation were done. The eGFR calculated by CKD-EPI, Cockcroft-Gault, Nankivell, and Hoek formulas were analyzed using the ANCOVA model. Descriptive statistics was used for describing eGFR in all subgroups. The incidence of efficacy endpoints was

estimated using the Kaplan-Meier (KM) method in the FAS population. Time-to-event efficacy endpoint was presented by KM curve, and both groups were compared using the log-rank test. The severity to efficacy events were also compared between both groups in both the FAS and PP populations.

## Results

### PATIENT POPULATION

A total of 642 patients were screened, 333 of whom were randomly assigned and treated with EVR + rTAC (*n* = 169) or sTAC (*n* = 164). Screen failures prior to randomization were excluded from the study because of abnormal laboratory values, retransplantation, death, graft failure/renal insufficiency, or incurrent medical event. A high proportion of patients in both groups completed the 12-month study (EVR + rTAC, 98.2%; sTAC, 90.2%). A lower proportion of patients discontinued the study and study drug in the EVR + rTAC group (1.8% and 27.2%, respectively) compared with the sTAC group (9.8% and 34.1%, respectively). AEs were the major reasons for study drug discontinuation in both groups (Fig. 1).

Demographic and baseline characteristics were comparable between the EVR + rTAC and sTAC groups and are displayed in Table 1. Most participants were male and Caucasian with a mean age in both groups of approximately 54 years. A majority of patients were aged 65 years or younger. The mean donor age was higher in the EVR + rTAC group compared with the sTAC group. HCC and alcohol-related cirrhosis, followed by sclerosing cholangitis, were the leading causes for LT. The mean cold ischemia time was approximately 9 hours, and nearly 90% of patients in both groups had mean laboratory MELD scores  $< 30$ . The mean eGFRs (MDRD-4) at baseline were 85.1 and 89.9 mL/minute/1.73 m<sup>2</sup> in the EVR + rTAC and sTAC groups, respectively, and the mean duration from transplantation to randomization was approximately 15 days in both groups, with nearly one-half of the population being randomized between 7-14 days in both treatment group (Supporting Table 1).

### IMMUNOSUPPRESSION

Nearly half of the patient population, 75/169 patients in the EVR + rTAC group and 69/164 in the sTAC group, received induction therapy. Of these, the majority

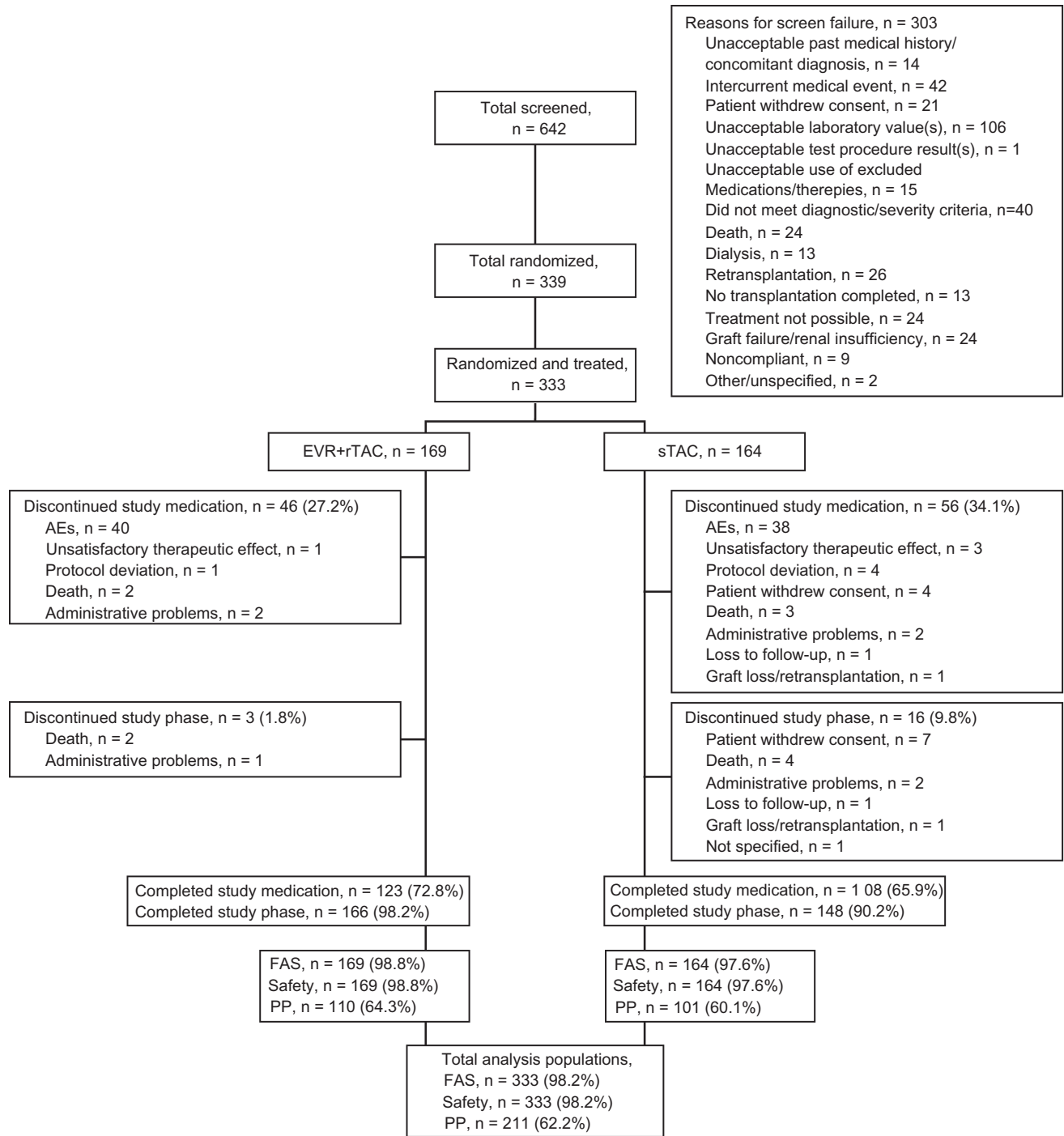


FIG. 1. Patient disposition.

received basiliximab (69 and 65, respectively), whereas the remaining patients received antithymocyte globulin (6 and 4, respectively). In the EVR + rTAC group, the mean EVR C0 were within the target range, 3.5 ng/mL at day 8, increasing to 5.3 ng/mL by month 3, and

remaining steady thereafter up to month 12 (Supporting Fig. 1A). The mean TAC C0 in the EVR + rTAC group were above the target range from day 1 (7.6 ng/mL) to month 3 (5.2 ng/mL) and within the range thereafter, although toward the higher threshold (between 4.6 and

**TABLE 1. Demographics and Baseline Characteristics (Full analysis set over month 12)**

Characteristics	EVR + rTAC (n = 169)	sTAC (n = 164)
<b>Recipient</b>		
Age, years	53.7 ± 9.4	53.5 ± 9.6
≤65	157 (95.7)	166 (98.2)
>65	7 (4.3)	3 (1.8)
Male	133 (78.7)	121 (73.8)
<b>Race</b>		
Caucasian	168 (99.4)	157 (95.7)
Black	1 (0.6)	1 (0.6)
Asian	0 (0.0)	3 (1.8)
Other*	0 (0.0)	3 (1.8)
BMI, kg/m <sup>2</sup>	26.3 ± 4.7	26.9 ± 5.1
<b>End-stage disease leading to LT</b>		
HCC	43 (25.4)	44 (26.8)
Alcohol-related cirrhosis	47 (27.8)	39 (23.8)
Sclerosing cholangitis	19 (11.2)	20 (12.2)
HCV	14 (8.3)	12 (7.3)
Cryptogenic cirrhosis	9 (5.3)	12 (7.3)
Primary biliary cirrhosis	4 (2.4)	4 (2.4)
HBV	4 (2.4)	4 (2.4)
Metabolic disease	2 (1.2)	1 (0.6)
Others	27 (16.0)	28 (17.1)
Presence of HCC at LT	51 (30.2)	58 (35.4)
Laboratory MELD score	17.1 ± 8.2	15.6 ± 8.3
<30	153 (90.5)	152 (92.7)
≥30	16 (9.5)	12 (7.3)
Cold ischemia time, hours	9.2 ± 2.5	9.3 ± 2.2
eGFR (MDRD-4) at baseline, mL/minute/1.73 m <sup>2</sup>	85.1 ± 31.1	89.9 ± 33.9
Duration of LT to baseline visit, days	15.2 ± 4.0	15.3 ± 4.0
<b>Donor</b>		
Age, years	57.3 ± 16.2	53.1 ± 18.5
≤65	110 (65.1)	117 (71.3)
>65	59 (34.9)	47 (28.7)
Male	97 (57.4)	86 (52.4)

NOTE: Data are provided as mean ± standard deviation or n (%).  
\*indicates race other than Caucasian, Black and Asian.

4.8 ng/mL from month 6 to month 12; Supporting Fig. 1B). The mean TAC C0 levels in the sTAC group were within the target range, increasing from 7.8 to 9.0 ng/mL from day 1 to month 1 and thereafter steadily declining to 7.1 ng/mL at month 12 (Supporting Fig. 1B). At month 12, 56.2% of patients were within the EVR target C0, whereas 11.2% and 5.9% were below and above the threshold, respectively. The TAC non-adherence rate at month 12 was 36.1% (above the C0

target) in the EVR + rTAC group and 34.7% in the sTAC group (27.4% below and 7.3% above the C0 target) (Supporting Fig. 2A,B). No specific trend was seen with regard to induction therapy. In the EVR + rTAC group, adherence to TAC C0 levels was slightly higher from day 1 to month 6 and lower at month 9 and month 12 among patients receiving induction compared with those without induction (Supporting Fig. 3).

## RENAL FUNCTION

Renal function assessed by eGFR (MDRD-4) achieved a significant between-group difference of approximately 8 mL/minute/1.73 m<sup>2</sup> ( $P < 0.01$ ) in favor of the EVR + rTAC group in the PP and OT populations. The adjusted least squares mean eGFR in the EVR + rTAC and sTAC groups was noted to be highest in the compliance set (82.0 versus 73.7 mL/minute/1.73 m<sup>2</sup>), with a significant between-group difference of 8.3 mL/minute/1.73 m<sup>2</sup> ( $P = 0.03$ ) in favor of the EVR + rTAC group. In the primary analysis set (FAS), renal function was numerically higher with the EVR + rTAC compared with the sTAC regimen (adjusted least squares mean at month 12: 76.2 versus 72.1 mL/minute/1.73 m<sup>2</sup> [LOCF method]), with a between-group difference of approximately 4 mL/minute/1.73 m<sup>2</sup> in favor of EVR + rTAC irrespective of the imputation method. However, no statistical significance could be reached in the FAS (Table 2).

The evolution of renal function during the 12-month study duration showed that the mean eGFR (MDRD-4) was comparable between the EVR + rTAC and sTAC groups at all time points in the FAS (Fig. 2A). The mean eGFR at month 12 was 73.5 mL/minute/1.73 m<sup>2</sup> in the EVR + rTAC group versus 71.9 mL/minute/1.73 m<sup>2</sup> in the sTAC group.

The observed mean change in eGFR in the FAS population from baseline to month 12 was -11.7 and -18.0 mL/minute/1.73 m<sup>2</sup> ( $P < 0.05$ ) in the EVR + rTAC and sTAC groups, respectively. Similarly, in all other populations (PP, OT, and compliance set), EVR + rTAC versus sTAC showed a significantly better sustained renal function (PP, OT, and compliance set), with the decline in eGFR being significantly less at month 12 (PP, -9.4 versus -18.9 mL/minute/1.73 m<sup>2</sup> [ $P = 0.01$ ]; OT, -10.2 and -19.7 mL/minute/1.73 m<sup>2</sup> [ $P < 0.01$ ]; compliance set, -7.2 versus -19.3 mL/minute/1.73 m<sup>2</sup> [ $P = 0.02$ ]).

The difference in renal function by approximately 4 mL/minute/1.73 m<sup>2</sup> in favor of EVR + rTAC in the

TABLE 2. eGFR (MDRD-4) by ANCOVA at Month 12

Adjusted Least Squares Mean (mL/minute/1.73 m <sup>2</sup> )	EVR + rTAC	sTAC	EVR + rTAC Versus sTAC	95% CI; P Value
PP	77.9	69.9	8.0	2.1 to 14.0; 0.01*
OT				
LOCF	79.6	71.8	7.9	3.0 to 12.8; <0.01*
Compliance set				
LOCF	82.0	73.7	8.3	0.7 to 15.9; 0.03*
FAS				
LOCF	76.2	72.1	4.1	-0.7 to 8.9; 0.10
Multiple imputation	77.2	72.6	4.6	-0.2 to 9.4; 0.06
MMRM	75.2	71.1	4.2	-0.7 to 9.0; 0.09

NOTE: \*indicates P values are significant.

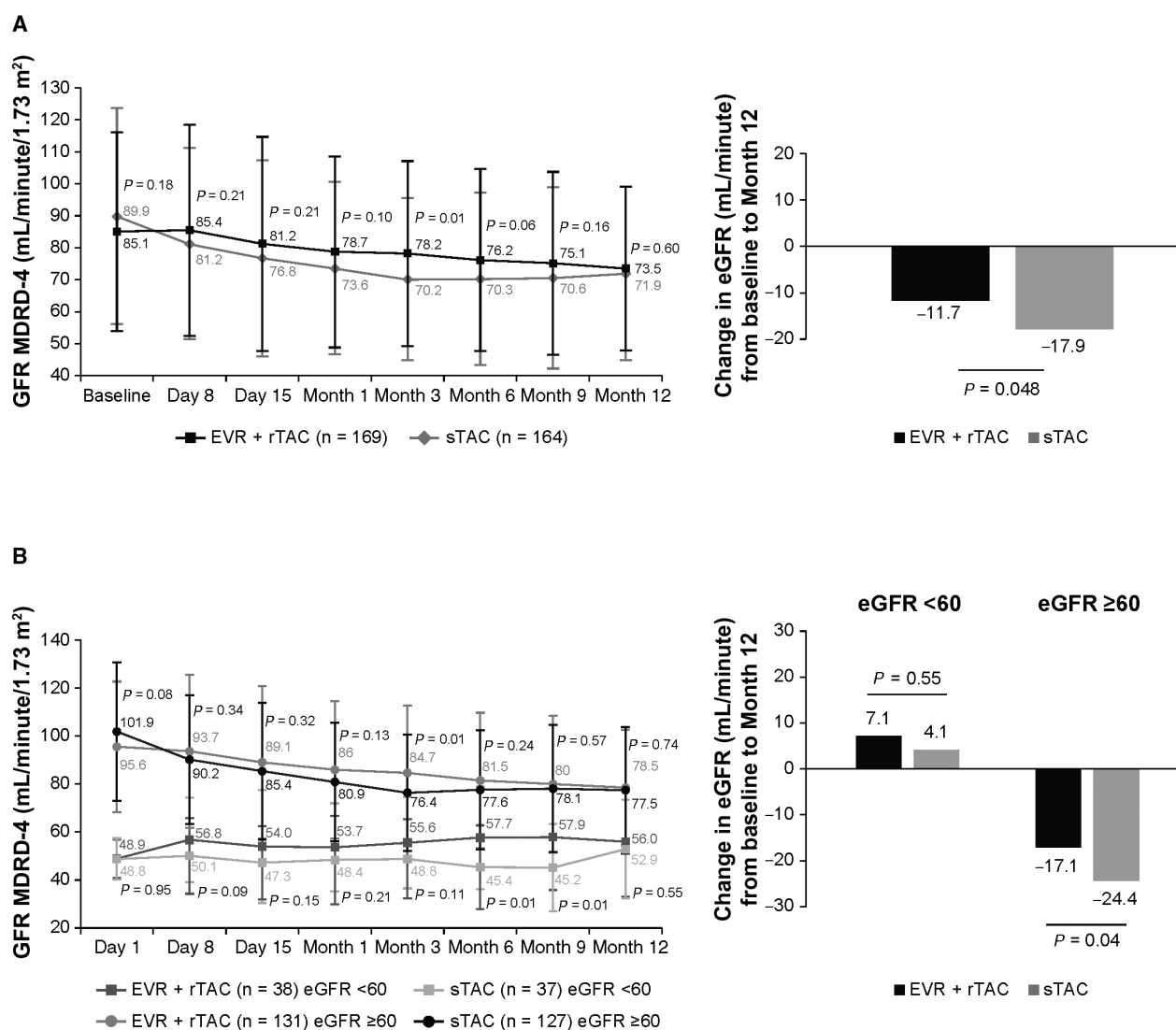


FIG. 2. Evolution of renal function (eGFR; MDRD-4) over month 12: (A) overall population and (B) subgroups with baseline eGFR <60 and ≥60 mL/minute/1.73 m<sup>2</sup>.

FAS population was maintained as estimated by the Cockcroft-Gault and CKD-EPI formulas. Similarly, in the PP and OT populations, renal function was significantly better with EVR + rTAC versus sTAC, with a between-group difference ranging from approximately 5 to 8 mL/minute/1.73 m<sup>2</sup>, as estimated by the Cockcroft-Gault, Nankivell, CKD-EPI, and Hoek formulas (Supporting Table 2).

Among the subgroups, renal function was better in patients aged younger than 60 years than in those aged 60 years and older as well as in men versus women. Renal function at month 12 was higher in patients already starting with eGFR  $\geq$ 60 mL/1.73m<sup>2</sup>, but the difference was narrowed (Fig. 2B). With induction, eGFR decline was greater after 12 months compared with baseline (Supporting Table 3) versus no induction.

With regard to treatment, renal function (eGFR; MDRD-4 [mL/minute/1.73 m<sup>2</sup>]) at month 12 was comparable between EVR + rTAC and sTAC in the subgroups analyzed by age, sex, induction therapy, and baseline renal function. At month 12, the mean eGFR was better among patients who were HCV positive in the EVR + rTAC group, whereas it was comparable between both groups in patients who were HCV negative. The EVR + rTAC group showed better eGFR than the sTAC group, except for MELD score categories 15 to 19 and 20 to 24, where it was comparable.

The median UPCr was already higher in the EVR + rTAC group than in the sTAC group prior to randomization and continued to maintain an almost

consistent difference ranging from 20 to 30 mg/g between the EVR + rTAC group versus the sTAC group up to month 12. UPCr was below nephrotic range (<200 mg/g)<sup>(21)</sup> in both groups during the 12 months (Fig. 3).

## EFFICACY

Composite endpoint of graft loss, death, or tBPAR was comparable between the EVR + rTAC and sTAC groups over time (Fig. 4), with an incidence of 7.7% in the EVR + rTAC group and 7.9% in the sTAC group at month 12 (Table 3). The incidence of composite endpoint of graft loss, death, tBPAR, or loss to follow-up was lower in patients treated with EVR + rTAC than in patients treated with sTAC (8.3% versus 14.0%). The incidences of death, graft loss, BPAR, and tBPAR were comparable between both groups (Table 3). A total of 22 patients (11 patients randomly assigned in each treatment group) had a BPAR or AR (without biopsy) before randomization. One patient randomly assigned to EVR + rTAC had severe BPAR before randomization. All remaining rejection episodes were mild or moderate.

In the EVR + rTAC or sTAC group, the incidence rate of events was similar for BPAR (FAS, 17/14; PP, 10/8) and tBPAR (FAS, 15/11; PP, 8/5). In the PP population, no severe BPAR occurred in either group (Supporting Table 4). Patients who received induction therapy had lower incidence rates regardless of the study treatment regimen (Supporting Table 5).

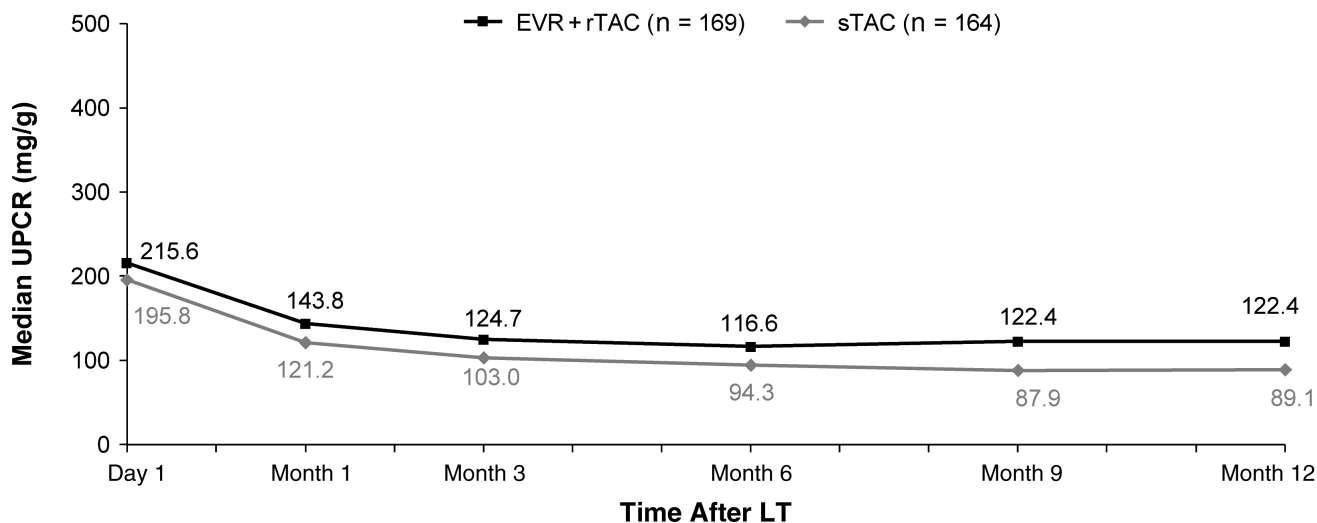


FIG. 3. Median UPCr over month 12 (safety set).



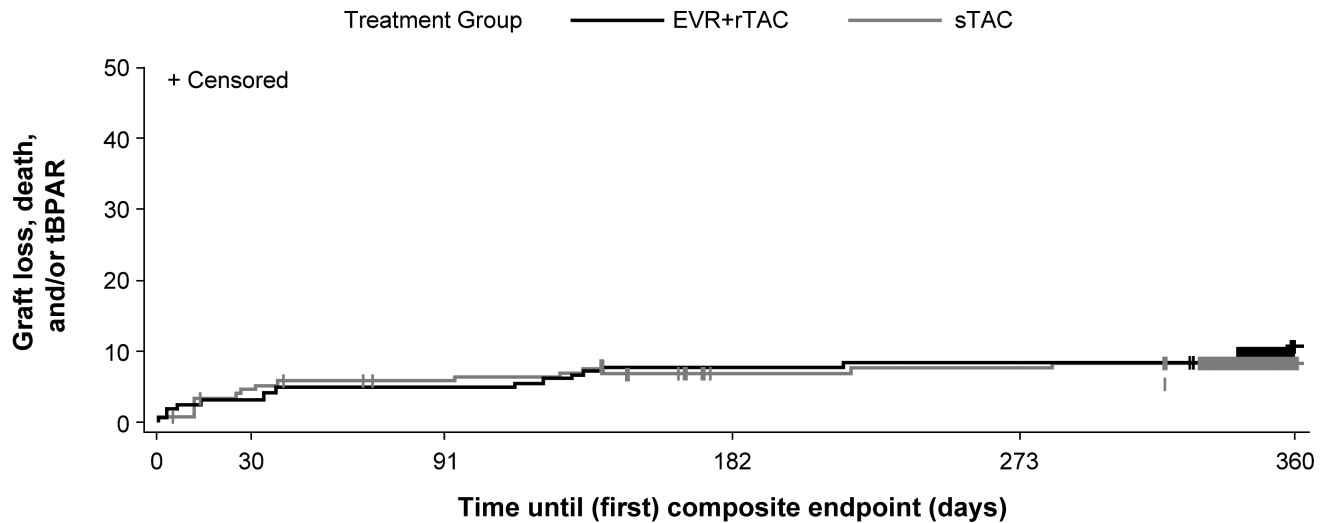


FIG. 4. Kaplan-Meier curve plot for composite endpoint (Full analysis set over month 12).

TABLE 3. Efficacy Endpoints at Month 12 (FAS\*)

Efficacy Parameter	EVR + rTAC (n = 169)	sTAC (n = 164)	P Value <sup>†</sup>
Graft loss, death, or tBPAR	13 (7.7)	13 (7.9)	>0.99
Graft loss, death, or BPAR	15 (8.9)	15 (9.1)	>0.99
Graft loss, death, tBPAR, or loss to follow-up	14 (8.3)	23 (14.0)	0.12
BPAR	14 (8.3)	11 (6.7)	0.68
tBPAR	12 (7.1)	9 (5.5)	0.65
AR	16 (9.5)	11 (6.7)	0.42
Treated AR	13 (7.7)	9 (5.5)	0.51
Graft loss	0 (0.0)	3 (1.8)	0.12
Death	2 (1.2)	3 (1.8)	0.68
Death or graft loss	2 (1.2)	4 (2.4)	0.44

NOTE: Data are provided as n (%).

\*Efficacy-related endpoints until 30 days after end of treatment.

<sup>†</sup>Fisher’s exact test.

### SAFETY

The incidences of treatment-emergent AEs (100% versus 99.4%) and SAEs (65.7% versus 61.6%) were comparable between the EVR + rTAC and sTAC groups, respectively, at month 12 (Table 4). Moreover, the incidences of treatment-emergent AEs leading to study drug discontinuation were low and comparable between both groups (24.8% versus 25.6%; Supporting Table 6), whereas AEs leading to study drug interruption/adjustment were higher in the EVR + rTAC group compared with the sTAC group (37.3% versus

19.5%). Patients treated with sTAC had higher discontinuation rates for neurological (4.9% versus 0%) or renal disorders (8.5% versus 2.4%).

The AEs more frequently observed with the EVR + rTAC regimen as opposed to the sTAC regimen included leukopenia, incisional hernia, headache, peripheral edema, proteinuria, and hypercholesterolemia. Diarrhea and hypertension were common in both groups. The infection rate was 77.5% in the EVR + rTAC group and 73.2% in the sTAC group. CMV, urinary tract, and upper respiratory tract infections were the most common infections observed in both groups (Table 4).

TABLE 4. Safety (Safety Population over Month 12)

Safety Event	EVR + rTAC (n = 169)	sTAC (n = 164)	P Value*
Any treatment-emergent AEs	169 (100.0)	163 (99.4)	0.49
Any AE leading to study drug interruption/adjustment	63 (37.3)	32 (19.5)	<0.001
Any treatment-emergent SAE	111 (65.7)	101 (61.6)	0.49
Any fatal SAE	3 (1.8)	4 (2.4)	0.72
Any nonfatal SAE	110 (65.1)	101 (61.6)	0.57
Any nonfatal SAE leading to study drug discontinuation	18 (10.7)	16 (9.8)	0.86
Any nonfatal SAE leading to study drug interruption/adjustment	28 (16.6)	9 (5.5)	<0.01
Any treatment-emergent AEs, $\geq 15\%$ in any group			
Diarrhea	46 (27.2)	42 (25.6)	0.80
Leukopenia	45 (26.6)	12 (7.3)	<0.0001
Incisional hernia	44 (26.0)	14 (8.5)	<0.001
Headache	42 (28.4)	22 (13.4)	0.01
Peripheral edema	39 (23.1)	17 (10.4)	<0.01
Hypertension	28 (16.6)	24 (14.6)	0.65
Proteinuria	28 (16.6)	12 (7.3)	0.01
Hypercholesterolemia	30 (17.8)	9 (5.5)	<0.001
Infections, $>5\%$ in any group <sup>†</sup>	131 (77.5)	120 (73.2)	0.38
CMV infection	29 (17.2)	30 (18.3)	0.89
HCV	6 (3.6)	11 (6.7)	0.22
Pneumonia	15 (8.9)	9 (5.5)	0.29
Urinary tract infection	32 (18.9)	28 (17.1)	0.67
Viral upper respiratory tract infection	43 (25.4)	29 (17.7)	0.08

NOTE: Data are provided as n (%). Treatment-emergent AEs were defined as AEs starting at or later to randomization. AEs occurring at  $\geq 30$  days after study drug discontinuation were not considered treatment emergent. A patient with multiple occurrences of an AE was counted only once in the corresponding category.

\*Fisher's exact test done for comparing the EVR + rTAC group versus the sTAC group.

<sup>†</sup>Infection reported as treatment-emergent AEs.

## Discussion

Initiation of EVR-based reduction of TAC 1 month after LT has been shown to be an advantageous strategy for achieving good renal function outcomes without impacting the efficacy and safety in deceased donor recipients (H2304 study) and living donor recipients (H2307 study).<sup>(13,16)</sup> HEPHAISTOS is a prospective randomized controlled study evaluating the effect of early initiation of EVR (between 7 and 21 days after LT) in combination with rTAC in LT recipients. The goal of this study was to evaluate superiority of renal function with investigational treatment EVR + rTAC versus standard TAC therapy as the primary objective. In contrast, the H2304 and H2307 studies tested for noninferiority of EVR-based regimens versus sTAC.<sup>(13,16)</sup>

A prospective study in Spain showed that early EVR introduction and simultaneous TAC reduction preserved renal function when compared with TAC

monotherapy (here assessed by serum creatinine), which is most likely attributed to reduced TAC exposure in the EVR group ( $<4$  ng/mL).<sup>(22)</sup> Generally, preservation of renal function over time is an important factor to consider given that the high risk of end-stage renal disease and mortality are associated with a renal function decline of  $\sim 30\%$  in patients with baseline eGFRs  $\geq 60$  mL/minute/1.73 m<sup>2</sup> during a 2-year period.<sup>(23)</sup> Similar results were shown in the EPOCAL study. Here, the EVR + rTAC group showed a significantly better preserved renal function over 24 months (median difference in eGFR [MDRD-4] between EVR + rTAC versus sTAC: 20, 24, 32, and 36 mL/minute/1.73 m<sup>2</sup> at 1, 6, 12, and 24 months, respectively).<sup>(24)</sup> Renal function in our study was estimated instead of being measured directly, but this reflects the current state in all studies, including renal transplant studies. We observed that the investigational therapy in our study resulted in numerically better renal function as measured by eGFR at month 12 in FAS but

could not show superiority (Table 2). Renal function was assessed using different formulas to ensure consistency of results (Supporting Table 2). This study outcome was comparable with the results of the H2304 and H2307 studies.<sup>(13,16)</sup> In our study, a high proportion of patients in the EVR + rTAC arm had TAC C0 above the protocol-defined target range throughout the study (31.4%–76.9% versus 7.3%–23.8%). Interestingly, this is consistent with similar findings in the H2304 and H2307 studies.<sup>(13,16)</sup> This is most probably attributed to the oral mode of absorption, which makes it more complicated, particularly in the initial phase, to achieve a stable C0. Furthermore, one can assume that the investigators were hesitant to reduce TAC levels because of efficacy concerns. As a result, the between-group difference in TAC exposure was not met as planned. Most important, renal function in the compliance set patients was indeed significantly better in favor of the EVR group, clearly indicating that TAC exposure matters. Furthermore, when renal function was assessed by the Cockcroft-Gault, Nankivell, or CKD-EPI formulas, a significant enhancement was observed in the EVR + rTAC group versus the sTAC group in both the PP and OT populations.

The decline in renal function was significantly lower from baseline to month 12 in favor of EVR + rTAC versus sTAC. A greater difference in the decline of renal function was seen in the compliance set. A similar renal-preserving effect of EVR has been consistently reported in the literature, with a difference ranging from 4 to 9 mL/minute/1.73 m<sup>2</sup>.<sup>(13,16)</sup>

In our study, the efficacy with regard to incidence of the composite endpoint (graft loss, death, or tBPAR), BPAR, and tBPAR was comparable between groups at 12 months. Although no graft loss was reported in EVR + rTAC, it was seen in 1.8% of patients in the sTAC group at month 12. Incidence of death was comparable in both arms. A similar incidence of rejection episodes were noted in the Spanish study, with histologically proven acute cellular rejection reported in 7.8% of patients in EVR + rTAC compared with 9.6% in the sTAC group ( $P = 0.62$ ).<sup>(22)</sup> However, the Italian study showed divergent results, with a higher incidence of composite failure because of TAC minimization under suboptimal EVR C0.<sup>(24)</sup> Patients who received induction therapy (basiliximab in the majority of patients) had lower incidence rates regardless of the study treatment regimen. This finding is in line with previous reports showing that induction with the interleukin 2 receptor antagonist

is associated with a lower risk of AR compared with a noninduction group (RR, 0.83; 95% CI, 0.73–0.96).<sup>(25)</sup> Similarly, in a randomized controlled trial, induction with basiliximab was associated with a lower incidence of biopsy-confirmed AR 6 months after transplantation compared with placebo (35.1% versus 43.5%).<sup>(26)</sup>

Overall, the safety was comparable between both groups. None of the patients in our study treated with EVR + rTAC experienced a hepatic artery thrombosis, whereas 1 event was noted in a patient treated with sTAC. Renal failure and neurological disorders were the major reasons for study drug discontinuation in the sTAC group, whereas in the EVR + rTAC group, leukopenia and peripheral edema were the most frequent causes of drug discontinuation. The median UPCr (mg/g) was below nephrotic range<sup>(21)</sup> in both groups throughout the study, consistent with the H2304 study results.<sup>(13)</sup> No new safety signal was detected; however, higher CMV infection rates were observed in both arms when compared with other LT studies.<sup>(13,16,27)</sup>

CMV prophylaxis was administered as per local practice and was recommended only for patients who were high risk (CMV Donor+/Recipient-) and following any antibody treatment of an AR episode. In fact, only a few of our patients received prophylaxis (EVR + rTAC, 14.8%; sTAC, 10.4%). The incidence rates observed here are even comparable with those seen in populations of patients with no prophylactic treatment at all.<sup>(28)</sup> Many renal transplantation studies have shown that EVR treatment has a significantly CMV protective effect when administered de novo rather than in conversion regimens.<sup>(29,30)</sup> As EVR treatment in this study could be started from day 7 at the earliest, no difference between the 2 treatment arms was expected. This supports that blocking mammalian target of rapamycin complex 1 activity at very early time points after viral infection results in the most profound effects on viral translation and overall infection efficiency compared with later time points.<sup>(30)</sup>

In solid organ transplantation, 2 aspects are associated with the use of proliferation inhibitors such as mTORis or MMF/mycophenolic acid, wound healing in the early postoperative phase, and incisional hernias usually appearing half a year after transplantation.<sup>(31,32)</sup> Experiences in renal transplant studies have shown that using de novo EVR at a target range of 3 to 8 ng/mL in combination with reduced-exposure cyclosporine exhibits similar incidences of wound-healing complications compared with standard mycophenolic acid-based therapy.<sup>(31)</sup> Recent data from the H2304 and H2307 studies

with the introduction of EVR 1 month after transplantation also demonstrated a comparable rate of wound-healing complications in both treatment groups.<sup>(13,16)</sup> In our study, the incidence of wound complications—infected seroma, wound infection, abdominal wound dehiscence, and wound dehiscence—was comparable in the EVR + rTAC group versus the sTAC group, except for incisional hernia, which was noted to be significantly higher in the EVR + rTAC group. This finding might be caused by the antiproliferative effect of EVR. It should be noted that the time of randomization had no influence on the events, and nearly one-half of the patients with an event were randomly assigned from day 15 after transplantation (Supporting Table 7). The EPOCAL study with early EVR introduction demonstrated a higher incidence of wound complications (18.3% versus 0%) and incisional hernia (25.8% versus 6.4%) as well.<sup>(24)</sup> In addition, this study has shown that there is a wide variability between different centers, suggesting that surgical technique has a certain impact on the incisional hernia incidence, a finding that we can confirm from our study as well (center range, 0%-53%). In conclusion, surgical technique, patient population, and proliferation inhibitors (eg, mTORi, Inosine-5'-monophosphate dehydrogenase inhibitors) are well known as potential factors of incisional hernias.

Interestingly, the EVR discontinuation rate attributed to AEs was with 23.7% in our LT study compared with the renal transplant studies ATHENA<sup>(33)</sup> and TRANSplant efficacy and safety Outcomes with an everolimus-based regiMen<sup>(34)</sup> with discontinuation rates of 31.0% and 27.2%, respectively, which might indicate that physicians performing LTs seem to be comfortable using EVR and managing resulting AEs. Sommerer et al.<sup>(33,35)</sup> reported a discrepancy in study drug discontinuation rates across centers in the ATHENA study, and Chadban et al.<sup>(35)</sup> speculated that it could largely be attributed to the clinician's level of experience with EVR. In this study, AEs leading to study drug interruption or adjustment were noted to be higher with EVR than in the standard group, whereas the overall discontinuation rate of study drug was higher in the sTAC group.

In conclusion, the HEPHAISTOS study demonstrates that the early initiation of EVR with an overall TAC reduction of more than 35% was feasible and showed excellent survival and efficacy with comparable and low rejection rates, no unexpected safety events, and overall better study and treatment completion rates in the EVR + rTAC group. Renal function was well preserved with EVR + rTAC therapy versus sTAC therapy at month 12, and a significant benefit was

noted in the PP, OT, and compliance set. The most satisfactory results were achieved when compliance to the predefined TAC C0 levels was strictly followed, clearly showing that TAC exposure matters.

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