



## ORIGINAL ARTICLE

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# Comparative pharmacokinetics of tacrolimus in de novo pediatric transplant recipients randomized to receive immediate- or prolonged-release tacrolimus

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## Abstract

Phase 2, parallel-group, multicenter, open-label, 4-week study, comparing PK of PR-T vs IR-T in de novo pediatric patients undergoing primary kidney, liver, or heart transplantation. Patients randomized 1:1 to receive once daily, PR-T-, or twice-daily, IR-T-based regimens; dose adjustments permitted after Day 1. Twenty-four-hour PK profiles collected on Days 1, 7, and 28. Primary endpoint: tacrolimus AUC<sub>24</sub>. Secondary end points included tacrolimus C<sub>24</sub> and C<sub>max</sub>. Endpoints compared between PR-T and IR-T on Days 1, 7, and 28. Predefined similarity interval for CIs of LSM ratios: 80%-125%. PK analysis set comprised 33 patients (PR-T, n = 15; IR-T, n = 18). Overall, AUC<sub>24</sub> and C<sub>max</sub> were lower on Day 1 vs 7 and 28. Geometric LSM ratios of PR-T:IR-T on Days 1, 7, and 28 were 66.3%, 92.5%, 99.9%, respectively, for AUC<sub>24</sub>; 66.3%, 82.2%, 90.9% for C<sub>24</sub>; and 77.3%, 120.3%, 92.2% for C<sub>max</sub>. AUC<sub>24</sub> 90% CI within predefined similarity interval on Day 28; other 90% CIs fell outside. Linear relationship was similar between AUC<sub>24</sub> and C<sub>24</sub>, and between tacrolimus formulations, suggesting that the same therapeutic drug monitoring method can be used with both formulations in de novo pediatric allograft recipients.

**Abbreviations:** AUC<sub>24</sub>, area under the blood concentration–time curve over 24 hours; C<sub>24</sub>, concentration at 24 hours; CI, confidence interval; C<sub>max</sub>, maximum concentration; HPLC/MS/MS, high-performance liquid chromatography tandem mass spectrometry; IR-T, immediate-release tacrolimus; IV, intravenous; LSM, least squares mean; MMF, mycophenolate mofetil; N/A, not applicable; PKAS, pharmacokinetics analysis set; PK, pharmacokinetics; PR-T, prolonged-release tacrolimus; SD, standard deviation; T<sub>max</sub>, time to C<sub>max</sub>;  $\rho$ , Pearson correlation coefficient.

ClinicalTrials.gov identifier: NCT01614665.

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**KEYWORDS**

heart transplantation, kidney transplantation, liver transplantation, pediatrics, pharmacokinetics, tacrolimus

## 1 | INTRODUCTION

Tacrolimus is the mainstay of immunosuppression regimens after solid organ transplantation.<sup>1</sup> Due to its narrow therapeutic index, it is essential that tacrolimus exposure is maintained within a tightly-defined range, as over-exposure can cause drug-related toxicity and side effects,<sup>2</sup> and under-exposure is associated with poor clinical efficacy outcomes.<sup>3,4</sup> Oral bioavailability of tacrolimus shows large variability between patients<sup>5</sup>; therefore, the dose of tacrolimus is optimized on the basis of maintaining the patients' systemic exposure within a narrow therapeutic window. As AUC significantly impacts efficacy,<sup>2,6</sup> measurement of AUC would be the ideal method for determining a patient's tacrolimus exposure; however, this is not always easy or practical for the patient and/or treatment center. Trough tacrolimus plasma levels correlate with AUC<sup>7</sup> and, although this correlation may vary depending on clinical circumstances, they are widely used for monitoring tacrolimus exposure following solid organ transplantation in adult and pediatric patients.<sup>7</sup> Maintaining adequate exposure to tacrolimus is particularly important for transplant rejection prophylaxis in the early post-transplant period, when lower exposure (AUC over 12 hours) has been linked with a significantly higher risk of acute rejection.<sup>6</sup>

Oral tacrolimus immediate-release formulations for twice-daily administration are available as capsules, and granules for oral suspension; tacrolimus is also available as a once daily, prolonged-release formulation. The immediate-release formulations are approved for the prophylaxis of transplant rejection in adult and pediatric patients, while the prolonged-release formulation is approved for the prophylaxis of transplant rejection in adult kidney and liver recipients in several countries. Limited PK data for prolonged-release tacrolimus in pediatric patients are available from small studies that have been conducted in stable liver or kidney transplant patients converted from immediate- to prolonged-release tacrolimus.<sup>8,9</sup> The PK of the prolonged-release formulation have been characterized in the adult de novo transplant population,<sup>10-12</sup> and no differences in interactions with other immunosuppressive therapies compared with immediate-release tacrolimus were observed.<sup>12</sup> However, currently, no PK studies have assessed prolonged-release tacrolimus initiated immediately post-transplant in pediatric de novo solid organ transplant recipients. This study was undertaken to compare the PK of prolonged- vs immediate-release tacrolimus in pediatric de novo kidney, liver, and heart transplant patients.

## 2 | PATIENTS AND METHODS

### 2.1 | Study design

This was a 4-week, Phase 2, parallel-group, multicenter, open-label, randomized study (NCT01614665) comparing the PK of prolonged-release tacrolimus (Advagraf™, Astellas Pharma Europe BV, Netherlands) and immediate-release tacrolimus (Prograf™, Astellas Pharma Ltd, Chertsey, UK) in de novo pediatric allograft recipients. The study was conducted at eight sites in five countries (UK, France, Czech Republic, Italy, and Poland) between February 9, 2012 and June 23, 2016.

The study was conducted in accordance with Good Clinical Practice, International Council on Harmonisation guidelines, and the Declaration of Helsinki. The independent ethics committee and/or review board from each site granted approval for the study. Patients, or their parent/guardian, provided written informed consent to participate, and could withdraw from the study at any time.

### 2.2 | Patients

De novo pediatric patients aged <16 years, undergoing primary kidney, liver, or heart allograft transplantation, and able to swallow intact prolonged- or immediate-release tacrolimus capsules were included. Additionally, heart transplant patients, treated post-transplant with basiliximab or antithymocyte globulin/MMF/steroids, were required to have gastric motility and adequate renal function before the first PK assessment.

Exclusion criteria were: multiorgan transplant or previous receipt of an organ (including retransplantation), pulmonary vascular resistance ( $\geq 4$  Wood units despite medication), renal impairment (serum creatinine  $\geq 2.6$  mg/dL; except for kidney recipients), and liver disease (except for liver recipients). Other exclusion criteria were systemic immunosuppressive medication for indications other than transplantation, human immunodeficiency virus, hepatitis B or C virus, and need for medication or substances known to interfere with tacrolimus metabolism during, or within 28 days before, the study.

### 2.3 | Study treatment

Eligible patients were randomized (1:1, stratified by organ and center) on Day 1 post-transplantation to receive once daily, prolonged-release tacrolimus, or twice-daily, immediate-release tacrolimus-based

regimens. Prolonged-release tacrolimus was given as a single oral daily dose in the morning, while immediate-release tacrolimus was administered orally in two equal doses, in the morning and evening. If the patient was unable to swallow the capsule in the immediate post-transplantation period, administration of the capsule contents as a suspension, via nasogastric tube, or orally was permitted to initiate tacrolimus therapy.

The dose, and time post-transplantation, of first tacrolimus administration (designated Day 1) varied by organ transplanted. For heart transplant recipients, the initial daily dose of prolonged- or immediate-release tacrolimus (0.075 mg/kg) was administered within 4 days of skin closure; in liver transplant patients, the dose (0.3 mg/kg) was given within 2 days after skin closure; and for kidney transplant recipients, the dose (0.3 mg/kg) was introduced within 24 hours following reperfusion. Subsequent tacrolimus doses were adjusted based on clinical evidence of efficacy, adverse events, and in order to achieve recommended target whole blood trough levels (Days 1-21: 10-20 ng/mL; Days 22 onwards: 5-15 ng/mL).

Patients could receive concomitant basiliximab and MMF, administered as per standard clinical practice, and corticosteroids, as described in Table 1.

## 2.4 | Pharmacokinetic profiles assessment

Whole blood samples were collected before dosing (0 hours), and at 1, 2, 4, 6, 12, 13, 14, 16, 18, and 24 hours post-dose on Days 1 (day of first dose), 7, and 28, to provide PK profiles. The 12-hour sample was taken before the evening dose in the immediate-release tacrolimus arm. PK profiles on Days 7 and 28 were performed after a minimum of 3 days without a dose change.

Blood samples (2 mL aliquots) were collected into tubes containing ethylenediaminetetraacetic acid as an anticoagulant, mixed, and frozen at  $-20^{\circ}\text{C}$  within 2 hours of collection. Samples were then stored until shipment to the central laboratory for bioanalysis. Based on the method developed by Alak et al,<sup>13</sup> tacrolimus concentrations were measured using a validated HPLC/MS/MS assay (lower limit of quantification, 0.059 ng/mL). Whole blood calibrators, quality-control samples, and the study samples were thawed, and 1 mL aliquots were taken. Internal standard (tacrolimus analog FR900520; 20  $\mu\text{L}$ , 50 ng/mL) was added and mixed briefly. Aliquots were extracted by protein precipitation and solid-phase extraction using C18 200 mg/3 mL cartridges, and elutes were evaporated to dryness under a stream of nitrogen at  $40^{\circ}\text{C}$ . Residues were then redissolved in a 50:50 mix (vol/vol) of acetonitrile and water, mixed,

**TABLE 1** Corticosteroid dosing schedule

Type of transplantation Study day	Corticosteroid dose	
	Methylprednisolone or equivalent (once daily)	Prednisolone or equivalent (once daily)
<b>Kidney</b>		
Day -1	300-600 mg/m <sup>2</sup> IV bolus (pre-, intra- or post-operatively)	N/A
Day 1	60 mg/m <sup>2</sup>	N/A
Day 2	N/A	40 mg/m <sup>2</sup>
Day 3	N/A	30 mg/m <sup>2</sup>
Day 4	N/A	20 mg/m <sup>2</sup>
Day 5 onwards	N/A	0 mg/m <sup>2</sup>
<b>Liver</b>		
Day -2	300-600 mg/m <sup>2</sup> IV bolus (pre-, intra- or post-operatively)	N/A
Day -1	60 mg/m <sup>2</sup>	N/A
Day 1	N/A	40 mg/m <sup>2</sup>
Day 2	N/A	30 mg/m <sup>2</sup>
Day 3	N/A	20 mg/m <sup>2</sup>
Day 4 onwards	N/A	0 mg/m <sup>2</sup>
<b>Heart</b>		
Day -4	300-600 mg/m <sup>2</sup> IV bolus (pre-, intra- or post-operatively)	N/A
Day -3	60 mg/m <sup>2</sup>	N/A
Days -2 to 7	N/A	40 mg/m <sup>2</sup>
Days 8 to 14	N/A	30 mg/m <sup>2</sup>
Days 15 to 28	N/A	20 mg/m <sup>2</sup>

and centrifuged, before being submitted for HPLC/MS/MS.<sup>14</sup> All procedures were performed in compliance with the principles of Good Laboratory Practice.

Routine monitoring of whole blood trough levels of tacrolimus during the study was carried out locally using the center's usual assay method (such as HPLC/MS/MS) or immunoassay).

The primary endpoint was estimation of tacrolimus  $AUC_{24}$  on Days 1, 7, and 28 for prolonged- vs immediate-release tacrolimus. The secondary endpoints were estimation of maximum tacrolimus concentration ( $C_{max}$ ), time to  $C_{max}$  ( $T_{max}$ ), and concentration at 24 hours ( $C_{24}$ ) on Days 1, 7, and 28.

## 2.5 | Statistical analyses and sample size calculation

Based on previous experience, a sample size of 48 patients (24 [eight per transplanted organ type] per treatment arm), with three complete evaluable PK profiles, was proposed as adequate to provide additional evidence of the PK of prolonged-release relative to immediate-release tacrolimus in the patient populations included in this study. If there were insufficient patients in one organ group within a treatment arm, more patients could be included in the other organ groups to compensate. Eligible patients were assigned a number on Day 1, and randomized centrally, using an interactive voice response system. The randomization sequence for allocating patients to treatment arms was prepared under the responsibility of the Global Data Science Department of Astellas Pharma Global Development.

The PKAS included all randomized and transplanted patients who received at least one dose of study medication and provided three complete PK profiles. Analyses were performed on the PKAS overall and by treatment arm. Standard non-compartmental methods were used to estimate PK parameters.  $AUC_{24}$  was calculated using the linear-log trapezoidal rule. In the primary analysis,  $AUC_{24}$  was compared between prolonged- and immediate-release tacrolimus using an analysis of covariance model on the log-transformed PK parameter with treatment, organ transplanted, and site nested within organ transplanted, as fixed effects, and baseline age as a continuous covariate. Separate analyses were performed for dosing Days 1, 7, and 28, without adjustment for multiplicity. LSM differences between the treatments (and the corresponding 90% CI) were back transformed to the original scale, and expressed as a percentage, to obtain an estimate for the geometric LSM ratio of the treatments (prolonged-release:immediate-release tacrolimus) with 90% CI. The PK parameters  $C_{24}$  and  $C_{max}$  (morning  $C_{max}$  for patients receiving immediate-release tacrolimus) were analyzed using the same model as for the primary analysis. The predefined similarity interval for CIs of LSM ratios was 80%-125%.

Correlation of  $C_{24}$  to  $AUC_{24}$  for both treatments was assessed using a regression analysis and by calculating the  $\rho$ . All data processing, summarization, and analyses were performed using SAS Version 9.3 (SAS Institute Inc., Cary, NC, USA) or higher on Unix.

## 3 | RESULTS

### 3.1 | Study population

Of 47 patients assessed for eligibility, 44 were enrolled and received study treatment, of whom 33 provided three complete PK profiles and comprised the PKAS. Fifteen patients received prolonged-release tacrolimus (kidney,  $n = 10$ ; liver,  $n = 3$ ; heart,  $n = 2$ ), and 18 received the immediate-release formulation (kidney,  $n = 10$ ; liver,  $n = 5$ ; heart,  $n = 3$ ) (Figure 1).

The baseline demographics and characteristics were similar between treatment arms (Table 2). Most patients were male (81.8%) and white (96.4%), and the mean  $\pm$  SD age was  $10.1 \pm 3.2$  years (range 4-15 years). Overall, 63.6% of patients were children (aged  $\geq 2$  to  $\leq 11$  years) and 36.4% were adolescents (aged  $\geq 12$  to  $< 16$  years). The mean  $\pm$  SD weight and height were  $33.5 \pm 12.8$  kg and  $137.5 \pm 20.1$  cm, respectively, but there was wide variance. Donor characteristics were similar between arms, and most patients (78.8%) had received organs from deceased donors.

### 3.2 | Dosage and trough levels

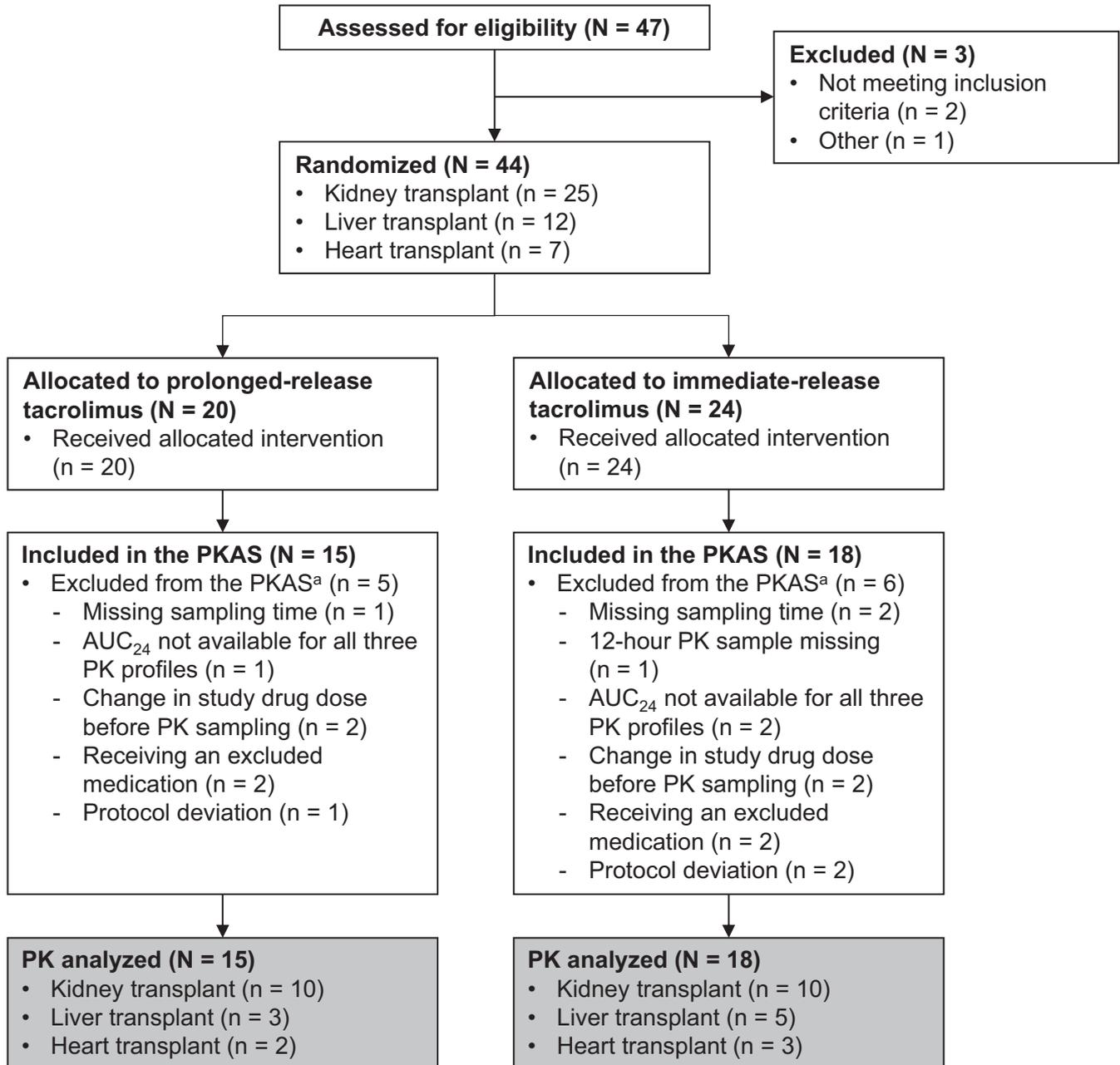
The mean  $\pm$  SD tacrolimus daily doses with immediate-release tacrolimus on Days 1, 7, and 28 were  $0.25 \pm 0.09$ ,  $0.22 \pm 0.10$ , and  $0.20 \pm 0.08$  mg/kg, respectively, and with prolonged-release tacrolimus were  $0.26 \pm 0.08$ ,  $0.27 \pm 0.11$ , and  $0.25 \pm 0.12$  mg/kg (Figure 2A). The mean  $\pm$  SD tacrolimus trough levels with immediate-release tacrolimus on Days 1, 7, and 28 were  $8.3 \pm 4.8$ ,  $9.5 \pm 2.9$ , and  $8.5 \pm 3.3$  ng/mL, respectively, and with prolonged-release tacrolimus were  $6.1 \pm 3.9$ ,  $8.8 \pm 4.1$ , and  $8.0 \pm 3.6$  ng/mL.

### 3.3 | Tacrolimus blood concentration-time profile

The mean whole blood tacrolimus concentration-time curve for the 24 hours after administration of prolonged-release tacrolimus was smooth, due to the once-daily dosing regimen. By contrast, immediate-release tacrolimus demonstrated a biphasic profile due to the twice-daily dosing regimen. The second concentration peak appeared around 14 hours, approximately 2 hours after the second dose.

### 3.4 | Pharmacokinetic parameters

In both treatment arms, mean  $AUC_{24}$  was lower on Day 1 than on Days 7 and 28 (Figure 2B). Systemic exposure to tacrolimus was lower on Day 1 with the prolonged- vs the immediate-release formulation, at an equivalent total daily dose (66.3%  $AUC_{24}$  geometric LSM ratio for prolonged-release:immediate-release tacrolimus) (Figure 2B). Following dose adjustment, the geometric LSM exposure ratios on Days 7 and 28 were 92.5% and 99.9%, respectively. The 90% CIs of the  $AUC_{24}$  LSM ratio were within the predefined similarity interval on Day 28 (80.6%, 123.8%), but not on Days 1 and 7 (Figure 2B).



**FIGURE 1** Patient flow through the study. <sup>a</sup>More than one reason for exclusion can apply to a patient

The geometric LSM of tacrolimus  $C_{24}$  was lower on Days 1, 7, and 28 with prolonged-release tacrolimus (4.3, 7.2, and 5.8 ng/mL, respectively) than with immediate-release tacrolimus (6.5, 8.8, and 6.4 ng/mL). The  $C_{24}$  geometric LSM ratio on Day 1 was 66.3% (Figure 2C), and increased to 82.2% and 90.9% on Days 7 and 28, respectively, following dose adjustment. However, the lower limit of the 90% CI fell outside the predefined similarity interval on all PK analysis days (Figure 2C).

For both prolonged- and immediate-release tacrolimus, linear relationships between tacrolimus AUC<sub>24</sub> and  $C_{24}$  were comparable, with a strong positive correlation (Figure 3). The Pearson correlation coefficient between AUC<sub>24</sub> and  $C_{24}$  was 0.83 and 0.84 for prolonged- and

immediate-release tacrolimus, respectively, and regression slopes were similar between formulations.

In both treatment arms, the observed LSM geometric  $C_{\max}$  was numerically lower on Day 1 than on Days 7 and 28. The  $C_{\max}$  geometric LSM ratios on Days 1, 7, and 28 were 77.3%, 120.3%, and 92.2%, respectively. On all days, either the lower or upper limit of the geometric LSM ratio 90% CI fell outside the predefined similarity interval (Figure 2D).

For both prolonged- and immediate-release tacrolimus, mean  $T_{\max}$  numerically decreased from Day 1 to Days 7 and 28.  $T_{\max}$  was longer with prolonged- vs immediate-release tacrolimus on all days, with the largest difference observed on Day 1 (mean  $\pm$  SD 6.0  $\pm$  6.1 vs 3.0  $\pm$  2.8 hours, respectively) (Table 3).

**TABLE 2** Patient baseline demographics and characteristics (PKAS)

Parameter	Prolonged-release tacrolimus (N = 15)	Immediate-release tacrolimus (N = 18)	Total (N = 33)	P value <sup>a</sup>
Recipient characteristics				
Age, years				
Mean ± SD	10.5 ± 3.1	9.8 ± 3.4	10.1 ± 3.2	0.551
Median	11.0	9.0	10.0	
Minimum, maximum	4.0, 15.0	4.0, 15.0	4.0, 15.0	
Age category, n (%) <sup>b</sup>				
≥2 to <11 y (children)	10 (66.7)	11 (61.1)	21 (63.6)	1.000
≥12 to <16 y (adolescents)	5 (33.3)	7 (38.9)	12 (36.4)	
Sex, n (%)				
Male	13 (86.7)	14 (77.8)	27 (81.8)	0.665
Female	2 (13.3)	4 (22.2)	6 (18.2)	
Race, n (%)				
White	13 (100.0)	14 (93.3)	27 (96.4)	1.000
Black/African American	0	0	0	
Asian	0	1 (6.7)	1 (3.6)	
Missing	2	3	5	
Baseline weight, kg				
Mean ± SD	35.8 ± 12.3	31.5 ± 13.3	33.5 ± 12.8	0.341
Median	33.5	26.7	30.0	
Minimum, maximum	15.5, 59.4	15.9, 63.0	15.5, 63.0	
Baseline height, cm				
Mean ± SD	141.7 ± 20.9	134.0 ± 19.3	137.5 ± 20.1	0.283
Median	137.0	130.5	133.0	
Minimum, maximum	101.0, 187.7	107.0, 171.0	101.0, 187.7	
Organ transplant, n (%)				
Kidney	10 (66.7)	10 (55.6)	20 (60.6)	0.887
Liver	3 (20.0)	5 (27.8)	8 (24.2)	
Heart	2 (13.3)	3 (16.7)	5 (15.2)	
Donor characteristics				
Age, years				
Mean ± SD	28.5 ± 15.4	26.7 ± 18.8	27.5 ± 17.1	0.760
Median	30.0	25.0	27.0	
Minimum, maximum	6.0, 49.0	6.0, 77.0	6.0, 77.0	
Type, n (%)				
Living related	4 (26.7)	3 (16.7)	7 (21.2)	-
Living non-related	0	0	0	
Deceased	11 (73.3)	15 (83.3)	26 (78.8)	

Due to rounding, percentages may not add up to 100%. <sup>a</sup>Statistical difference between treatment groups was evaluated using Fisher exact test in the case of categorical variables with some cells with expected frequency <5, chi-squared test in the case of categorical variables with cells with expected frequency of ≥5 and two-sample *T* test in the case of continuous variables. <sup>b</sup>For patients aged ≥0 to <27 d or ≥28 d to <23 mo, n = 0 for both treatment groups.

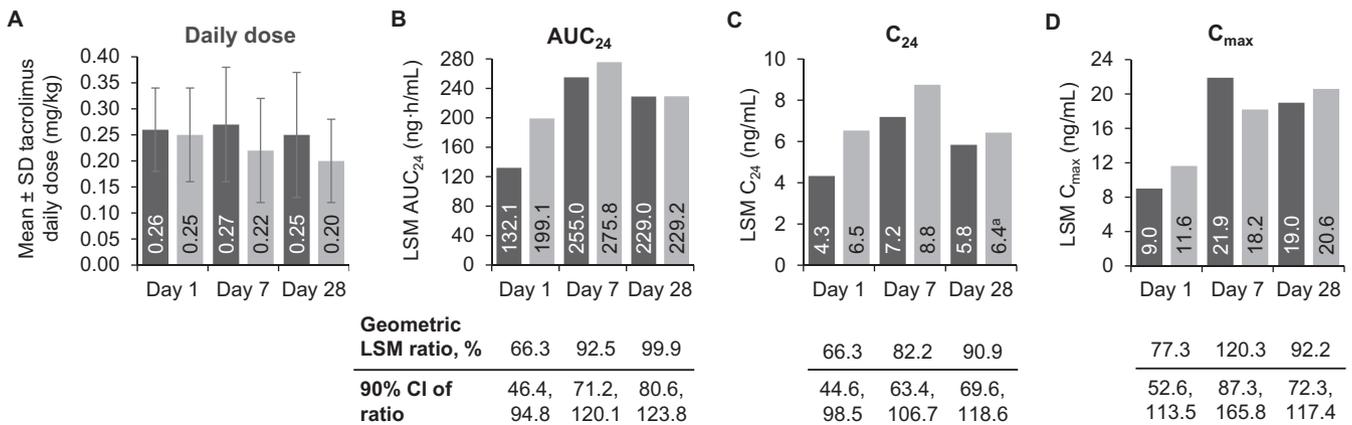
## 4 | DISCUSSION

This is the first PK study of prolonged-release tacrolimus in de novo pediatric kidney, liver, and heart allograft recipients, with a primary objective of comparing PK parameters with the immediate-release formulation.

After the first dose of tacrolimus, systemic exposure ( $AUC_{24}$ ) to tacrolimus was approximately 35% lower with the prolonged- vs the immediate-release formulation. However, at steady state, and

following dose adjustment,  $AUC_{24}$  was similar for both formulations by Day 28. These PK data are consistent with those reported for adult de novo transplant patients in two Phase 2 studies,<sup>10,11</sup> and two Phase 3 sub-studies.<sup>15,16</sup> In all studies, the mean  $AUC_{24}$  for tacrolimus after the first dose was lower with prolonged- vs immediate-release tacrolimus; however, exposure after repeated administrations was similar with both formulations,<sup>10,11,15,16</sup> as was efficacy and safety. Comparison studies in adult liver and kidney

- Prolonged-release tacrolimus (n = 15)
- Immediate-release tacrolimus (n = 18)



**FIGURE 2** Comparison of (A) daily dose, (B) AUC<sub>24</sub>, (C) C<sub>24</sub>, and (D) C<sub>max</sub> between prolonged- and immediate-release tacrolimus (PKAS). <sup>a</sup>n = 17

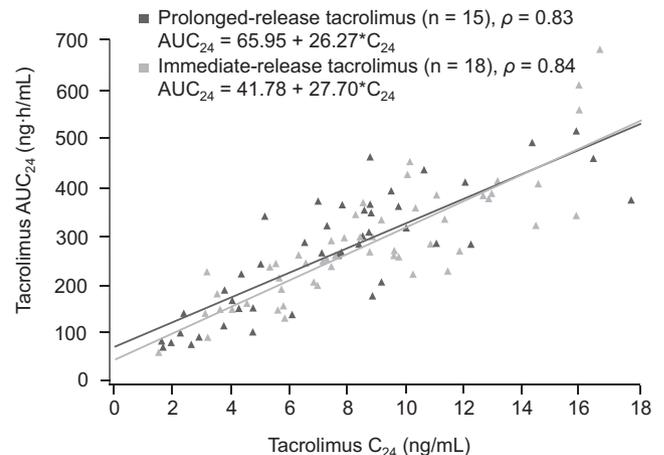
transplant recipients also showed that trough levels of the two formulations became similar over time and that prolonged- and immediate-release tacrolimus had similar efficacy and safety profiles.<sup>11,17,18</sup>

Importantly, in our study, the linear relationship between AUC<sub>24</sub> and C<sub>24</sub> was similar with prolonged- and immediate-release tacrolimus ( $\rho$  0.83 and 0.84, respectively), and the slope of the line of best fit was comparable. This indicates that the same target trough levels with prolonged- and immediate-release tacrolimus will result in similar systemic exposure to tacrolimus in pediatric de novo transplant patients, and that the same therapeutic drug monitoring method can be used. This PK profile is consistent with those seen in adult de novo kidney and liver transplant recipients, where there was strong correlation between AUC<sub>24</sub> and C<sub>24</sub> with both prolonged- ( $\rho$  0.83–0.96 across studies) and immediate-release tacrolimus ( $\rho$  0.76–0.94),<sup>10,11,15</sup> and the slope of the line of best fit was similar for both formulations.

In this study, mean C<sub>max</sub> and C<sub>24</sub> followed a similar pattern to the AUC for the three profiles. As expected, T<sub>max</sub> was longer with the prolonged- vs the immediate-release formulation (median 2.0–3.9 hours across study days vs 1.0–2.0 hours, respectively).

Consistent with studies in de novo adult kidney and liver transplant recipients,<sup>10,11</sup> mean daily tacrolimus dose (mg/kg) was numerically higher with prolonged- vs immediate-release tacrolimus. Following dose adjustment, the exposure was comparable between the two formulations by Day 7.

Due to the nature of the study, there are several limitations. Patient numbers were small and, therefore, it was not possible to stratify the analyses by organ type. The study sample included only one patient of Asian ethnicity and no black or African American patients. Owing to variations in numerous factors between ethnic groups, including the prevalence of genes involved in the rapid metabolism of tacrolimus,<sup>19–21</sup> ideally a more ethnically diverse



**FIGURE 3** Linear scatter plot of AUC<sub>24</sub> vs C<sub>24</sub> of tacrolimus after prolonged- or immediate-release tacrolimus administration (PKAS)

population would have been included in the study. Trough tacrolimus levels during the study were, however, optimized for each individual patient. Furthermore, the study did not include any children below 4 years of age; tacrolimus clearance is known to be higher in younger children.<sup>22</sup> Another barrier to the use of prolonged-release tacrolimus in younger children is that they commonly experience difficulty swallowing the capsules. Therefore, prolonged-release tacrolimus may be an unsuitable formulation for younger children.

In conclusion, this is the first PK study of prolonged-release tacrolimus in pediatric de novo kidney, liver, and heart allograft recipients. There was a similar linear relationship between tacrolimus AUC<sub>24</sub> and C<sub>24</sub>, with a strong positive correlation, and this relationship was comparable between prolonged- and immediate-release tacrolimus formulations. These results suggest that the same therapeutic drug monitoring method can be used with both tacrolimus

Day	$T_{\max}$ with prolonged-release tacrolimus, hours (N = 15)		$T_{\max}$ with immediate-release tacrolimus, hours (N = 18)	
	Mean $\pm$ SD	Median (minimum, maximum)	Mean $\pm$ SD	Median (minimum, maximum)
Day 1	5.98 $\pm$ 6.08	3.95 (0.98, 23.0)	3.03 $\pm$ 2.82	2.00 (0.00, 11.75)
Day 7	3.20 $\pm$ 3.92	2.00 (0.97, 13.0)	1.89 $\pm$ 1.41	1.00 (0.95, 6.05)
Day 28	1.92 $\pm$ 1.39	1.95 (0.92, 6.00)	1.49 $\pm$ 0.79	1.00 (0.93, 3.98)

**TABLE 3**  $T_{\max}$  with prolonged- and immediate-release tacrolimus (PKAS)

formulations in de novo pediatric allograft recipients, consistent with adult patients.

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## CONFLICT OF INTEREST

KV, AD, FP, NJAW, and AL report other and non-financial support from Astellas, during the conduct of the study. RG reports other and non-financial support from Astellas, during the conduct of the study, and other from Novartis, outside the submitted work. DD reports other and non-financial support from Astellas, during the conduct of the study, and other from Astellas, outside the submitted work. SDM reports other and non-financial support from Astellas, during the conduct of the study, and grants from Novartis, outside the submitted work. GK reports other and non-financial support from Astellas, during the conduct of the study, and GK is a consulting statistician working on behalf of Astellas. NU reports other and non-financial support from Astellas, during the conduct of the study, and NU is an employee of Astellas. This study was sponsored by Astellas Pharma Europe, Ltd. Medical writing support in the development of this manuscript was provided by Cello Health MedErgy, funded by Astellas Pharma, Inc.

## AUTHORS' CONTRIBUTIONS

Karel Vondrak contributed to patient recruitment and data collection, and critically revised the manuscript for important intellectual content. Anil Dhawan contributed to patient recruitment, and design and governance of the study, and critically revised the manuscript for important intellectual content. Francesco Parisi contributed to patient recruitment and data collection, and critically revised the manuscript for important intellectual content. Ryszard Grenda contributed to patient recruitment and data collection, and critically revised the manuscript for important intellectual

content. Dominique Debray contributed to patient recruitment and data collection, and critically revised the manuscript for important intellectual content. Stephen D. Marks contributed to patient recruitment and data collection, and critically revised the manuscript for important intellectual content. Nicholas J. A. Webb contributed to patient recruitment, and design and governance of the study, and critically revised the manuscript for important intellectual content. Alain Lachaux contributed to patient recruitment and data collection, and critically revised the manuscript for important intellectual content. Gbenga Kazeem performed the statistical analyses, analyzed and interpreted the data, and critically revised the manuscript for important intellectual content. Nasrullah Undre designed the study, collected, analyzed and interpreted the data, and critically revised the manuscript for important intellectual content.

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