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Kidney Transplant Recipients Switching to Prolonged-Release Tacrolimus: Five-Year Real-World Clinical Outcomes From the CHORUS Study

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Background: Tacrolimus trough-level concentration variability and patient non-adherence are risk factors for poorer graft and patient survival. This study investigated long-term outcomes in kidney transplant recipients who were converted from twice-daily immediate-release tacrolimus to once-daily prolonged-release tacrolimus.

Material/Methods: CHORUS (NCT02555787) is a 5-year, real-world, prospective, global, non-interventional study. Kidney transplant recipients (KTRs; ≥18 years, N=4389) were grouped by post-transplant conversion timing (early converters [ECs], ≤6 months; late converters [LCs], >6 months). The primary endpoint was the change from baseline in estimated glomerular filtration rate (eGFR) from conversion to 5 years. Secondary endpoints included tacrolimus dose and trough levels, clinical and biopsy-proven acute rejection (BPAR), graft and patient survival, emergence of donor-specific antibodies, and safety.

Results: The full analysis set included 4028 patients (1060 ECs and 2968 LCs). Overall, eGFR remained stable 5 years after conversion, with a mean change from baseline of -1.4 (ECs, 3.4; LCs, -3.0) mL/min/1.73 m^2. Mean daily

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tacrolimus dose and trough levels remained stable 5 years after conversion. Clinically diagnosed and BPAR-free survival 5-year estimates were 91.2% and 93.9%, respectively. Graft and patient 5-year survival estimates were 95.0% and 97.1%, respectively. Donor-specific antibody occurrence was observed in 4.9% of patients after conversion. Prolonged-release tacrolimus (PRT)–related adverse events were reported by 19.3% of patients and were the cause of discontinuation in 5.5% of patients.

Conclusions: In this large and diverse cohort of KTRs, conversion to PRT, independent of conversion timing, was effective and well tolerated in routine clinical practice, supporting its continued long-term use.

Keywords: **Delayed-Action Preparations • Prospective Studies • Tacrolimus • Transplantation**

Abbreviations: **AE** – adverse event; **BPAR** – biopsy-proven acute rejection; **CI** – confidence interval; **CKD-Epi** – Chronic Kidney Disease Epidemiology Collaboration; **CoV** – coefficient of variation; **COVID-19** – coronavirus disease 2019; **DSA** – donor-specific antibody; **EC** – early converter; **eGFR** – estimated glomerular filtration rate; **EOS** – end of study; **EOT** – end of treatment; **EPS** – enrolled patients set; **FAS** – full analysis set; **HLA** – human leukocyte antigen; **IRT** – immediate-release tacrolimus; **KTR** – kidney transplant recipient; **LC** – late converter; **MDRD-4** – Modification of Diet in Renal Disease 4-variable; **PRT** – prolonged-release tacrolimus; **SAE** – serious adverse event; **SD** – standard deviation

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Introduction

Kidney transplantation is the preferred treatment for most patients with end-stage renal disease, promising an improvement in survival and quality of life [1]. However, this lifesaving procedure necessitates lifelong immunosuppressive treatment in kidney transplant recipients (KTRs) [2] to prevent graft rejection along with the risk of associated graft loss [3,4]. Long-term graft and patient survival rates have not improved to the same extent as short-term outcomes in KTRs [5].

As time progresses following a kidney transplant, recipients often show poorer adherence, and in general have limited understanding of their immunosuppressive regimens [6]. This is crucial because variations in drug trough levels and non-adherence to immunosuppressive regimens have been identified as risk factors that contribute to acute rejection, donor-specific antibody (DSA) occurrence, and antibody-mediated rejection in KTRs [7-10]. Tacrolimus is recommended as the first-line calcineurin inhibitor by Kidney Disease Improving Global Outcomes guidelines [11] and, since its first approval in 1993 in Japan [12], tacrolimus has been available in more than 90 countries, with over 9 million patient-years of exposure globally. It is a key component of most modern immunosuppressive regimens, with over 90% of patients receiving tacrolimus as part of their maintenance immunosuppression [13].

Studies investigating the use of twice-daily immediate-release tacrolimus (IRT) have revealed variability in tacrolimus trough concentrations and non-adherence to IRT, both of which are potential factors associated with graft loss and rejection among KTRs [14-18]. In contrast to this, prolonged-release tacrolimus (PRT) use is associated with improved medication adherence [19,20], reduced tacrolimus exposure variability [21,22], stable renal function [23,24], and improved long-term outcomes [25]. Furthermore, PRT use has been associated with decreased healthcare costs due to improved adherence and graft survival [26]. However, there are limited data on the optimal time of PRT conversion [27] and long-term clinical outcomes in KTRs who converted from IRT to PRT.

Aiming to investigate long-term clinical outcomes after conversion from twice-daily IRT to once-daily PRT, the CHORUS study was a global, multicenter, prospective study of KTRs identified for conversion. The present study investigated long-term kidney function and other outcomes in KTRs converting from IRT to PRT, under clinical practice conditions, over a 5-year study period.

Material and Methods

Study Design and Patients

CHORUS (NCT02555787) [28] was a real-world, long-term (up to 5 years), multicenter, prospective, non-interventional study of KTRs who converted from IRT (Prograf®; Astellas Pharma Ltd., Surrey, UK) [29] to PRT (Advagraf®; Astellas Pharma Europe B.V., Leiden, Netherlands) [30]. Patients on IRT and identified for conversion to PRT were eligible for enrollment. Following study initiation, patients were entered prospectively from 127 centers

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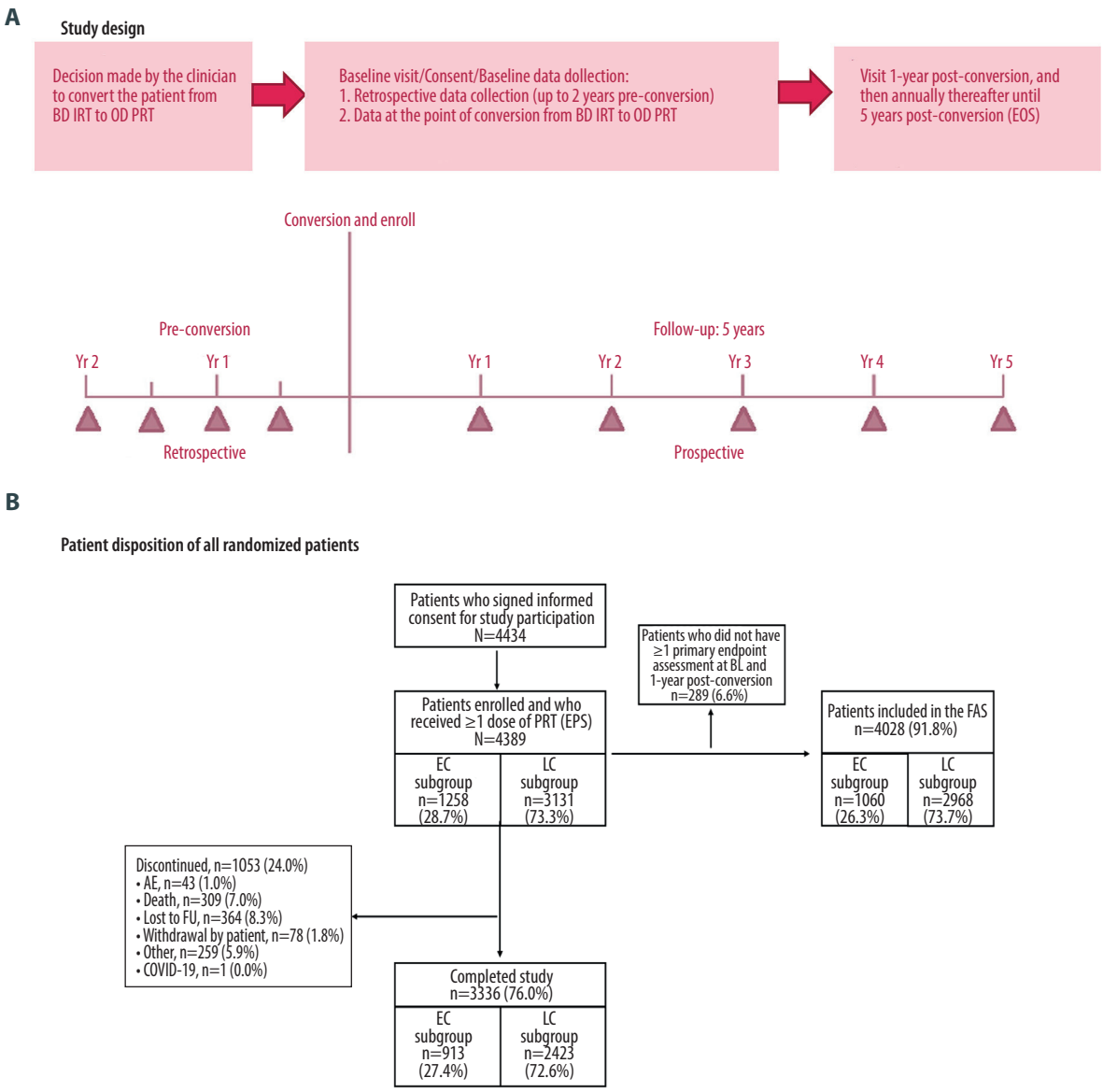

Figure 1. Study design (A) and patient disposition of all randomized patients (B). Data collected from March 2015 until September 2022. Overall cohort: all patients. Asian countries cohort: all patients from centers in Asia (South Korea, Japan, Vietnam, Thailand, Taiwan, Malaysia, Philippines, and Hong Kong). AE – adverse event; BD – twice-daily; BL – baseline; COVID-19 – coronavirus disease 2019; EC – early converter; EOS – end-of-study; EPS – enrolled patients set; FAS – full analysis set; FU – follow-up; IRT – immediate-release tacrolimus; LC – late converter; OD – once-daily; PRT – prolonged-release tacrolimus.

in 25 countries (**Figure 1A**). Patients already receiving PRT at enrollment were excluded. The end of treatment (EOT) occurred when PRT was stopped permanently and the end-of-study (EOS) visit occurred 5 years after conversion, or earlier in the case of death, withdrawal of consent, or loss to follow-up.

In this study, 20.7% of patients were from Asian countries. Given the discrepancies in organ transplantation access [31], kidney disease epidemiology [31], and differences in drug metabolism [32] between European/North American and Asian populations, a pre-specified analysis of a cohort of Asian patients was also conducted.

To explore outcomes at different time points for conversion, patients were divided into 2 subgroups based on the timing of IRT-to-PRT conversion: early converters (ECs; conversion ≤6 months after transplant) and late converters (LCs; conversion >6 months after transplant). The timing of conversion was flexible

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to reflect various clinical practices and has been used previously to describe PRT conversion [33]. Subgroups were further defined by categorized variables, notably tacrolimus trough levels with coefficient of variation (CoV) thresholds (<35% versus ≥35%).

Ethics

This study was conducted in accordance with protocol and ethical principles derived from international guidelines, including the Declaration of Helsinki, Good Clinical Practice, Good Pharmacovigilance Practice, International Council for Harmonisation guidelines, and applicable national laws and regulations. Independent Ethics Committee approval of the study protocol was obtained prior to study initiation. Informed consent was obtained from patients eligible for conversion to PRT or their legally authorized representatives (as per local regulations) prior to study participation.

In some patients, there were delays to the EOS visit due to the coronavirus disease 2019 (COVID-19) pandemic, meaning that data collection occurred beyond 5 years following a protocol amendment. While COVID-19 impacted the study timelines, as expected, there was no impact on the interpretation of study results or completion.

Outcomes

The primary endpoint was the change from baseline (time of IRT-to-PRT conversion) in renal function measured by estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease 4-variable (MDRD-4) formula [34]; MDRD-4 was chosen for the primary endpoint, as many of the study sites used assays derived from the Jaffe reaction or enzymatic assays for the quantification of creatinine. For patients who experienced graft loss, eGFR was set to zero on the day of graft loss and was not calculated for the remainder of the analysis period. Key secondary endpoints included: change from baseline in renal function measured by eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) formula [35], tacrolimus dose and trough levels, clinically diagnosed acute rejection, biopsy-proven acute rejection (BPAR), graft and patient survival, DSA occurrence, and safety. In the definition of BPAR, episodes were evaluated together with the classification of the rejection severity (Banff classification) [36], whether the rejection episode was treated or untreated, and whether it was steroid-sensitive or -resistant. Clinically diagnosed acute rejection episodes were defined as episodes where no biopsies were carried out but treatment for rejection was given.

Statistical Analysis

As this was a non-interventional study, no formal hypothesis testing was performed. For continuous variables, descriptive statistics (including the number of patients, mean, standard deviation [SD], median, minimum, and maximum) were used. Graft and patient survival rates were estimated using the Kaplan-Meier method. The enrolled patients set (EPS) comprised all patients who provided informed consent and received ≥1 dose of PRT and was used for the safety analysis. Efficacy was analyzed in the full analysis set (FAS), comprising all eligible patients in the EPS who converted to PRT, had ≥1 primary endpoint assessment at baseline, and ≥1 primary endpoint assessment 1 year after conversion or later. As this was a long-term study, 4 interim analyses were conducted annually.

Results

Study Participants

A total of 4389 KTRs were enrolled and received ≥1 dose of PRT. From the EPS, 3336 (76.0%) patients completed the study as planned (**Figure 1B**) and 1053 (24.0%) patients discontinued participation in the study, mostly due to loss to follow-up (364; 8.3%) and death (309; 7.0%) (**Table 1**). Overall, 4028 (91.8%) patients were included in the primary analysis population (FAS); with 1060 of those (26.3%) in the EC and 2968 (73.7%) in the LC subgroups (**Figure 1B**). In the Asian countries cohort, 910 patients (EC, 98 [10.8%]; LC, 812 [89.2%]) were included in the EPS. Of the 910 patients in the EPS, 887 (97.5%) patients were in the FAS (EC, 92 [10.4%]; LC, 795 [89.6%]).

Demographic and Clinical Characteristics

In the 4028 patients included in the FAS, the mean age of patients was 50.9 years and 2435 (60.5%) patients were male. This was a racially diverse patient population, with 1650 (63.3%) White and 922 (35.4%) Asian patients (**Table 2**). Overall, donor/recipient human leukocyte antigen (HLA) mismatch scores ≥3 were recorded in 2224/3364 (66.1%) patients with available HLA data (664 patients had missing data) (**Table 2**).

The mean (SD) duration between the last transplantation of patients and conversion was 48.3 (58.0) months. Before conversion, 84 (2.1%) patients received kidney biopsies and 76 (1.9%) patients received biopsies after conversion. Overall, clinical indications were the most common reason for conversion (**Table 2**). The baseline demographic and clinical characteristics of the Asian countries cohort were similar to the overall cohort (**Table 2**). In total, systemic corticosteroids were administered to 2879 (71.5%) patients and 3491 (86.7%), 331 (8.2%), and 91 (2.3%) patients received mycophenolate derivatives, everolimus, or sirolimus, respectively.

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Table 1. Study discontinuation and completion.

	Early converter (n=1258)	Late converter (n=3131)	Total (n=4389)
Completed study, n (%)	913 (72.6)	2423 (77.4)	3336 (76.0)
Discontinued, n (%)	345 (27.4)	708 (22.6)	1053 (24.0)
Primary reason for discontinuation*, n (%)			
AE	12 (1.0)	31 (1.0)	43 (1.0)
Death	92 (7.3)	217 (6.9)	309 (7.0)
Lost to follow-up	129 (10.3)	235 (7.5)	364 (8.3)
Withdrawal by patient	14 (1.1)	64 (2.0)	78 (1.8)
Other	98 (7.8)	161 (5.1)	259 (5.9)
COVID-19	0	1 (0.0)	1 (0.0)

* Only the primary reason for study discontinuation was collected. AE – adverse event; COVID-19 – coronavirus disease 2019.

Primary and Secondary Endpoints

Renal Function: eGFR Calculated Using MDRD-4 and CKD-Epi

The mean (SD) eGFR at the time of conversion was 56.1 (21.5) mL/min/1.73 m^2 (EC, 50.0 [21.9] mL/min/1.73 m^2; LC, 58.2 [20.9] mL/min/1.73 m^2). In the Asian countries cohort, the mean eGFR was 66.8 mL/min/1.73 m^2 at conversion.

Overall, the change from baseline in renal function remained relatively stable throughout the study, with the mean (SD) eGFR decreasing by 1.4 (17.2) mL/min/1.73 m^2 at 60 months after conversion (**Figure 2A**). Results were similar when eGFR was calculated using the CKD-Epi formula (mean change from baseline was -2.3 (17.3) mL/min/1.73m^2 at 60 months after conversion; **Figure 2B**).

In the EC subgroup, there was an initial clinically relevant improvement from baseline in renal function, with a peak mean (SD) eGFR change from baseline of 4.7 (17.7) mL/min/1.73 m^2 at 24 months after conversion. At 60 months after conversion, the mean (SD) change from baseline was 3.4 (20.3) mL/min/1.73 m^2. In the LC subgroup, there was a minor reduction in mean (SD) change from baseline in renal function throughout the study, with a value of -3.0 (15.6) mL/min/1.73 m^2 at 60 months after conversion (**Figure 2A**). In the Asian countries cohort, mean eGFR increasingly declined in value from baseline throughout the study. This trend was also observed in the EC and LC subgroups, with numerically greater increases observed in the EC subgroup. At 60 months after conversion, the mean (SD) change from baseline was -3.4 (16.2) mL/min/1.73 m^2 overall, -5.9 (19.2) mL/min/1.73 m^2 in the EC subgroup, and -3.1 (15.8) in the LC subgroup (**Figure 2C**).

Tacrolimus Dose and Exposure

Before conversion, the overall median daily dose of tacrolimus was 4.3 mg (EC, 7.0; LC, 3.6). From conversion to 12 months after conversion, the overall median daily dose of tacrolimus was 4.0 mg; thereafter, the dose decreased to 3.5 mg at 18 months after conversion and remained stable until EOT. The mean daily dose of tacrolimus remained consistent from conversion until EOT, varying from 4.7 to 3.9 mg (**Figure 3A**). From baseline to EOS, the median duration of PRT treatment was 1744 days. At EOS, 2850 (70.8%) patients remained on PRT, while 375 (9.3%) patients discontinued PRT but remained on other tacrolimus formulations. In the Asian countries cohort, overall, the median daily dose of PRT remained stable at 3.0 mg and the mean dose varied from 3.2 to 3.4 mg from conversion to EOT (**Figure 3B**). The median duration of PRT treatment in the Asian countries cohort (n=887) was 1771 days, and 694 (78.2%) patients remained on PRT at EOS.

At conversion, median tacrolimus trough levels in the FAS were 6.7 ng/mL. From 12 to 60 months after conversion, median trough values ranged from 5.6 to 5.9 ng/mL and mean trough values ranged from 5.8 to 6.1 ng/mL (**Figure 3C**). From baseline to EOS, tacrolimus trough levels CoV was ≥35% for 662 (17.5%) patients (**Table 3**). In the Asian countries cohort, the median tacrolimus trough concentration at conversion was 5.7 ng/mL. From 12 to 60 months after conversion, median trough tacrolimus concentrations ranged from 4.7 to 4.9 ng/mL and mean concentrations were 6.1 ng/mL at conversion and 5.1 ng/mL at EOS (**Figure 3D**).

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Table 2. Baseline demographic and clinical characteristics.

	Overall cohort			Asian countries cohort		
	Early converter (n=1060)	Late converter (n=2968)	Total (n=4028)	Early converter (n=92)	Late converter (n=795)	Total (n=887)
Sex, n (%)						
Male	669 (63.1)	1766 (59.5)	2435 (60.5)	65 (70.7)	458 (57.6)	523 (59.0)
Female	391 (36.9)	1202 (40.5)	1593 (39.5)	27 (29.3)	337 (42.4)	364 (41.0)
Race, n (%)						
White	377 (77.9)	1273 (60.0)	1650 (63.3)	0	1 (0.1)	1 (0.1)
Black	1 (0.2)	8 (0.4)	9 (0.3)	–	–	–
Asian	102 (21.1)	820 (38.6)	922 (35.4)	92 (100.0)	786 (99.9)	878 (99.9)
Other	4 (0.8)	21 (1.0)	25 (1.0)	–	–	–
Missing	576 (54.3)	846 (28.5)	1422 (35.3)	0	8 (1.0)	8 (0.9)
Age (years)						
Mean (SD)	51.7 (13.7)	50.6 (13.1)	50.9 (13.2)	50.6 (10.0)	49.4 (11.6)	49.5 (11.4)
Median	53.0	51.0	51.0	51.0	50.0	50.0
Min, Max	18, 83	18, 84	18, 84	26, 72	18, 76	18, 76
Age group (years), n (%)						
<50	452 (42.6%)	1353 (45.6%)	1805 (44.8%)	42 (45.7)	386 (48.6)	428 (48.3)
≥50	608 (57.4%)	1615 (54.4%)	2223 (55.2%)	50 (54.3)	409 (51.4)	459 (51.7)
Weight (kg)	**n=1011**	**n=2831**	**n=3842**	**n=87**	**n=726**	**n=813**
Mean (SD)	72.77 (15.55)	71.75 (16.06)	72.02 (15.93)	60.9 (11.0)	61.5 (12.0)	61.4 (11.9)
Median	72.5	70.0	71.0	60.6	60.0	60.0
Min, Max	37.2, 142.8	29.4, 142.0	29.4, 142.8	37.2, 101.4	29.4, 131.0	29.4, 131.0
Height (cm)	**n=977**	**n=2613**	**n=3590**	**n=78**	**n=680**	**n=758**
Mean (SD)	169.7 (9.9)	168.3 (10.0)	168.6 (10.0)	166.5 (11.2)	163.9 (8.8)	164.2 (9.1)
Median	170.0	169.0	169.0	168.0	164.1	165.0
Min, Max	108.0, 205.0	130.0, 208.0	108.0, 208.0	108.0, 187.0	130.5, 195.0	108.0, 195.0
BMI (kg/m^2)	**n=961**	**n=2596**	**n=3557**	**n=78**	**n=664**	**n=742**
Mean (SD)	25.1 (4.6)	25.2 (4.6)	25.2 (4.6)	22.4 (5.2)	22.9 (3.4)	22.8 (3.6)
Median	24.6	24.6	24.6	21.4	22.7	22.5
Min, Max	15.0, 57.4	12.6, 49.5	12.6, 57.4	15.0, 57.4	14.7, 36.3	14.7, 57.4
Time between last transplantation and conversion (months)						
Mean (SD)	2.3 (1.7)	64.7 (59.5)	48.3 (58.0)	3.3 (1.6)	61.8 (55.2)	55.7 (55.2)
Median	2.2	44.4	23.6	3.5	42.0	35.7
Min, Max	0.1, 6.0	6.1, 410.5	0.1, 410.5	0.2, 5.9	6.1, 369.0	0.2, 369.0

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Table 2 continued. Baseline demographic and clinical characteristics.

	Overall cohort			Asian countries cohort		
	Early converter (n=1060)	Late converter (n=2968)	Total (n=4028)	Early converter (n=92)	Late converter (n=795)	Total (n=887)
DSA occurrence prior to or at conversion, n (%)	**n=483**	**n=1052**	**n=1535**	**n=12**	**n=141**	**n=153**
Yes	72 (14.9)	209 (19.9)	281 (18.3)	3 (25.0)	31 (22.0)	34 (22.2)
No	411 (85.1)	843 (80.1)	1254 (81.7)	9 (75.0)	110 (78.0)	119 (77.8)
Undetermined	577	1916	2493	80	654	734
PRA grade	**n=774**	**n=1455**	**n=2229**			
Mean (SD)	8.0 (21.9)	5.6 (16.8)	6.4 (18.8)	–	–	–
PRA grade group, n (%)						
≤10%	665 (85.9)	1281 (88.0)	1946 (87.3)	–	–	–
>10%	109 (14.1)	174 (12.0)	283 (12.7)	–	–	–
Missing	286	1513	1799	–	–	–
HLA mismatches, n (%)	**n=1010**	**n=2354**	**n=3364**			
0	60 (5.9)	131 (5.6)	191 (5.7)	–	–	–
1	61 (6.0)	208 (8.8)	269 (8.0)	–	–	–
2	167 (16.5)	513 (21.8)	680 (20.2)	–	–	–
≥3	722 (71.5)	1502 (63.8)	2224 (66.1)	–	–	–
Missing	50	614	664	–	–	–
Reason for conversion, n (%)	**n=750**	**n=1656**	**n=2406**			
Compliance	64 (8.5)	393 (23.7)	457 (19.0)	–	–	–
To improve patient drug administration comfort	199 (26.5)	510 (30.8)	709 (29.5)	–	–	–
Clinical indications	438 (58.4)	566 (34.2)	1004 (41.7)	–	–	–
Trough level optimization	26 (3.5)	129 (7.8)	155 (6.4)	–	–	–
Other	23 (3.1)	58 (3.5)	81 (3.4)	–	–	–
Missing	508	1475	1983	–	–	–

BMI – body mass index; DSA – donor-specific antibody; FAS – full analysis set; HLA – human leukocyte antigen; PRA – panel-reactive antibody; SD – standard deviation.

Acute Rejection

Overall, after conversion to PRT, 133 (3.3%) patients had clinically diagnosed acute rejection episodes (5.8% [n=61] of all EC patients; 2.4% [n=71] of all LC patients), with 148 total episodes reported. Of these 148 episodes, 63 (42.6%) were corticosteroid-sensitive (a rejection episode treated with new or increased corticosteroids only and resolved irrespective of PRT or mycophenolate mofetil dose changes) and 53 (35.8%) were ongoing/unresolved. The Kaplan-Meier estimate (95% confidence interval [CI]) for clinically diagnosed acute rejection-free survival at 60 months after transplantation was 91.2% (89.9%; 92.4%) in the overall cohort (**Figure 4A**) and 93.2% (89.9%; 95.5%) in the Asian countries cohort (**Figure 4B**).

Overall, after conversion to PRT, 76 (1.9%) patients had BPAR (4.0% [n=42] of all EC patients; 1.1% [n=34] of all LC patients). The most BPARs were T-cell–mediated, occurring in 55

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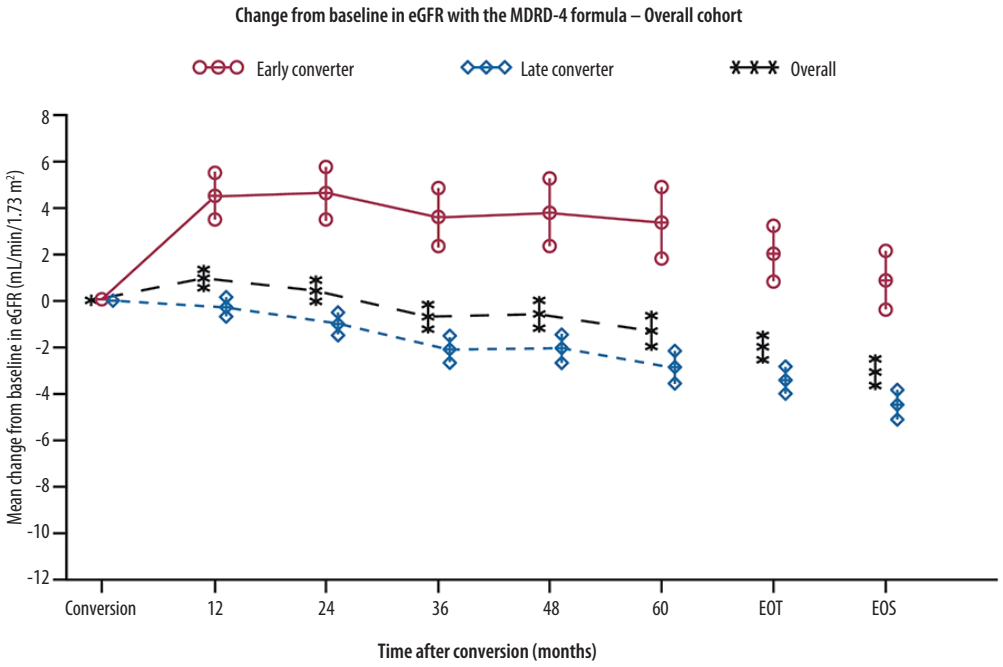
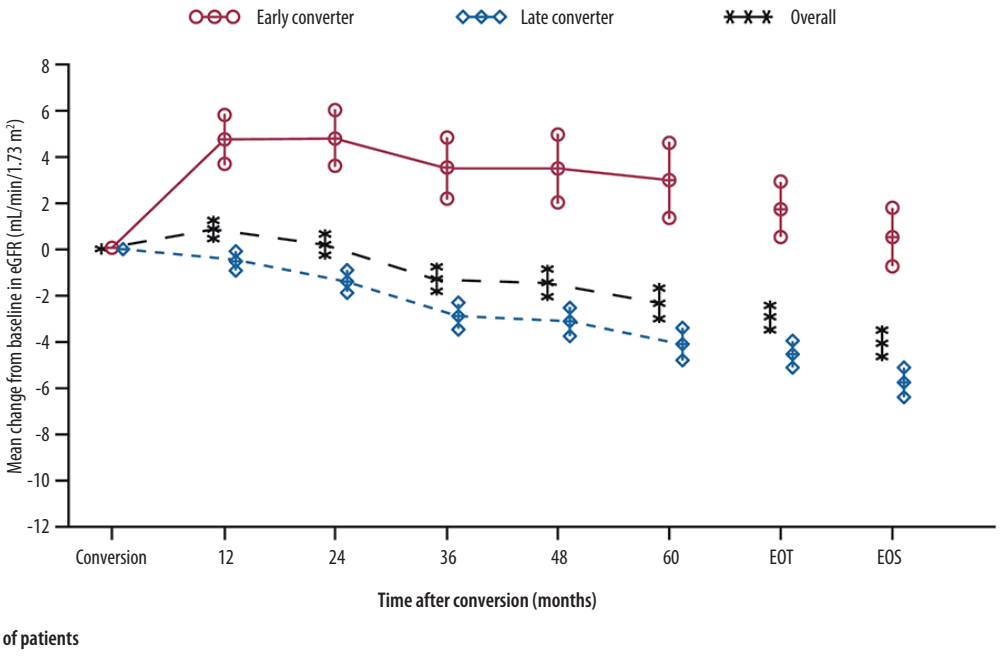
A



Number of patients

Overall	4028	3748	3421	3203	2976	2487	3941	4028
Early converter	1060	969	864	790	749	630	1032	1060
Late converter	2968	2779	2557	2413	2227	1857	2909	2968

B



Number of patients

Overall	4028	3748	3421	3203	2976	2487	3941	4028
Early converter	1060	969	864	790	749	630	1032	1060
Late converter	2968	2779	2557	2413	2227	1857	2909	2968

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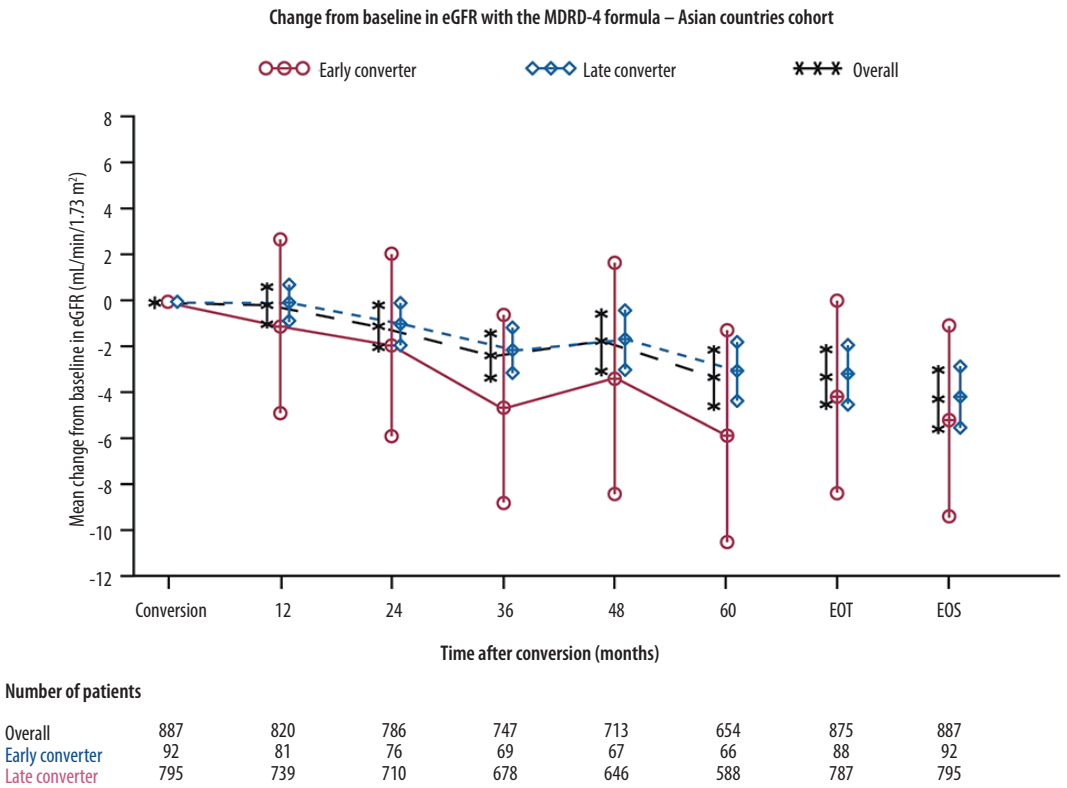

Figure 2. Mean change from baseline in eGFR with the MDRD-4 formula (A) and CKD-Epi formula (B) in the overall cohort and in the Asian countries cohort with the MDRD-4 formula (C). Mean eGFR change from baseline is displayed with 95% CI. For patients who experienced graft loss, eGFR was set to zero for the first value on or after the day of graft loss and was not calculated for the remainder of the analysis period. For patients who discontinued PRT therapy before the EOS, only data up until the date of the discontinuation of PRT were included in the analysis. EOT was the earliest among the last exposure dates, eCRF visit dates, and first exposure date plus 1916 days (the maximum window for collecting data). EOS was the earliest among the last eCRF visit date and first exposure date plus 2008 days (the maximum window for collecting data), except for exposure data. CI – confidence interval; eCRF – electronic case report form; eGFR – estimated glomerular filtration rate; EOS – end-of-study; EOT – end of treatment; MDRD-4 – Modulation Diet in Renal Disease 4-variable; PRT – prolonged-release tacrolimus.

(1.4%) patients. Among the 2029 patients who underwent transplantation within 24 months prior to conversion, 121 (6.0%) had ≥1 BPAR episode after transplantation. At 60 months after transplantation, the overall Kaplan-Meier estimated BPAR-free survival rate (95% CI) was 93.9% (92.8%; 94.9%) (**Figure 4C**). In the Asian countries cohort, 18/330 (5.5%) patients who underwent transplantation within 24 months before conversion had ≥1 BPAR after transplantation. The Kaplan-Meier estimate (95% CI) of BPAR-free survival was 94.5% (91.4%; 96.5%) (**Figure 4D**).

Graft Survival

In the FAS, 458 (11.4%) patients experienced graft loss after their latest transplantation (11.3% [n=120] of all EC patients; 11.4% [n=338] of all LC patients). The primary reason for graft loss was chronic allograft nephropathy. The Kaplan-Meier estimate (95% CI) of graft survival was 95.0% (94.3%; 95.7%) at 60 months after transplantation (**Figure 5A**). The graft survival rate remained high (92.1% [91.2%; 93.0%]) at 84 months after transplant. Overall, in an analysis examining patients in the <35% and ≥35% CoV subgroups, the 60-month graft survival estimate (95% CI) was numerically lower in the ≥35% subgroup. Survival estimates were similar between LCs in different CoV subgroups, but ECs in the ≥35% subgroup had a reduced survival estimate compared with ECs in the <35% subgroup (**Figure 5B**).

In the Asian countries cohort (n=887), 55 (6.2%) patients had graft loss after their latest transplantation (6.5% [n=6] of all EC patients; 6.2% [n=49] of all LC patients). The Kaplan-Meier estimate (95% CI) of graft survival was 97.8% (96.6%; 98.6%)

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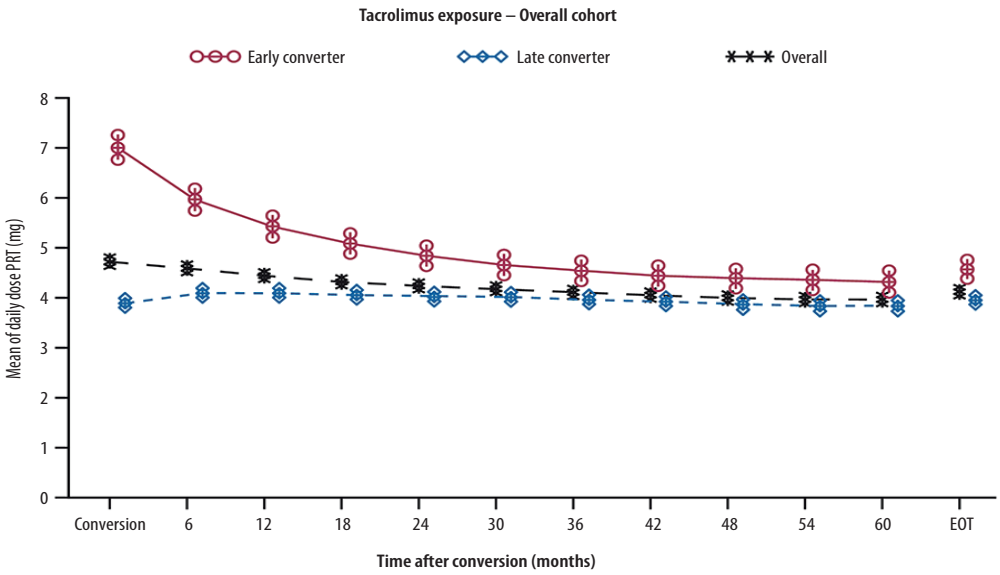
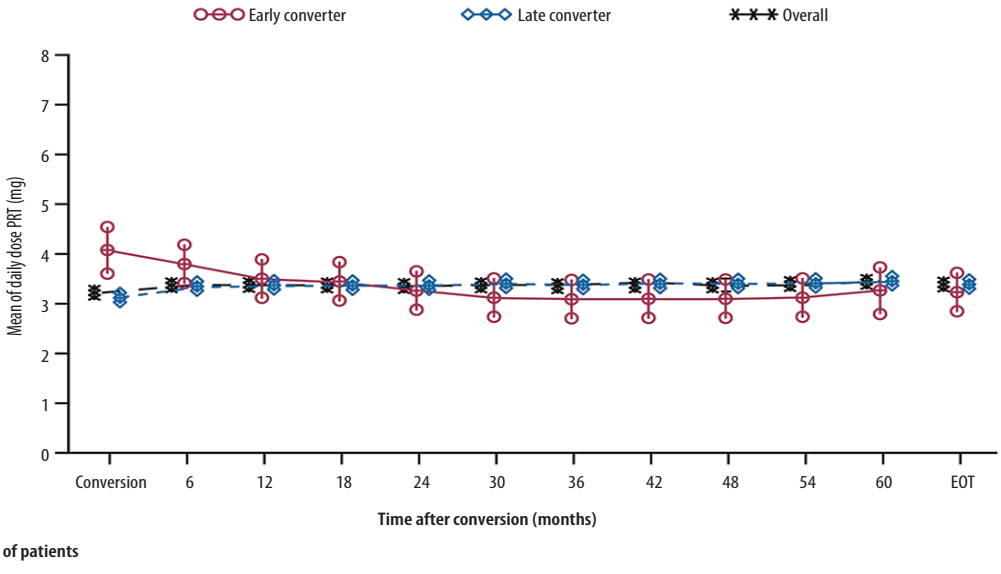
A



Number of patients

	Conversion	6	12	18	24	30	36	42	48	54	60	EOT
Overall	4028	3926	3760	3615	3526	3396	3306	3194	3090	2838	2112	4028
Early converter	1060	1023	967	921	899	857	831	803	776	717	521	1060
Late converter	2968	2903	2793	2694	2627	2539	2475	2391	2314	2121	1591	2968

B



Number of patients

	Conversion	6	12	18	24	30	36	42	48	54	60	EOT
Overall	887	867	819	809	794	771	754	740	727	698	587	887
Early converter	92	87	82	80	78	71	68	68	67	66	59	92
Late converter	795	780	737	729	716	700	686	672	660	632	528	795

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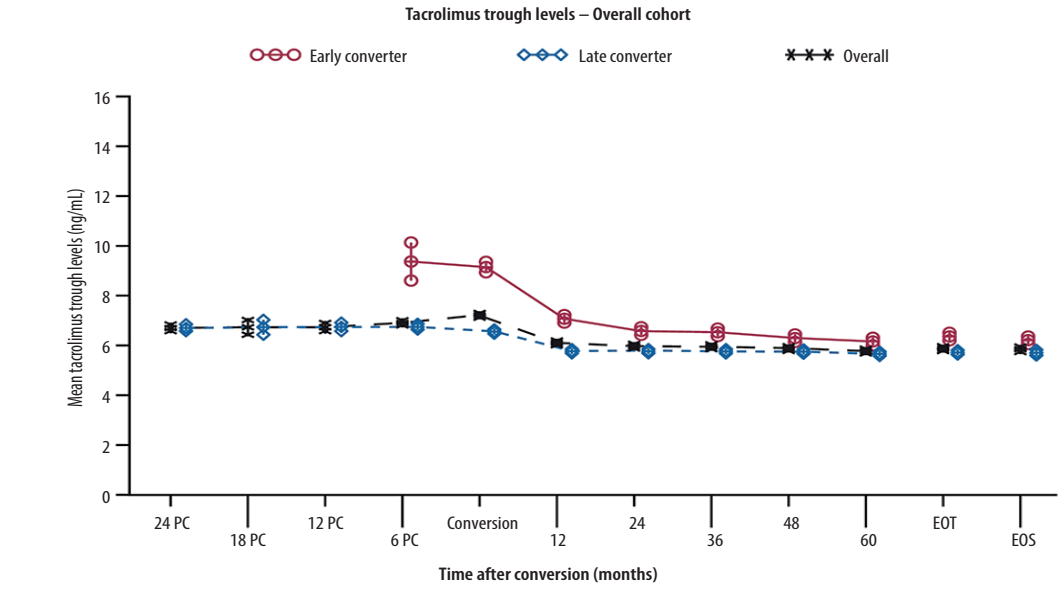
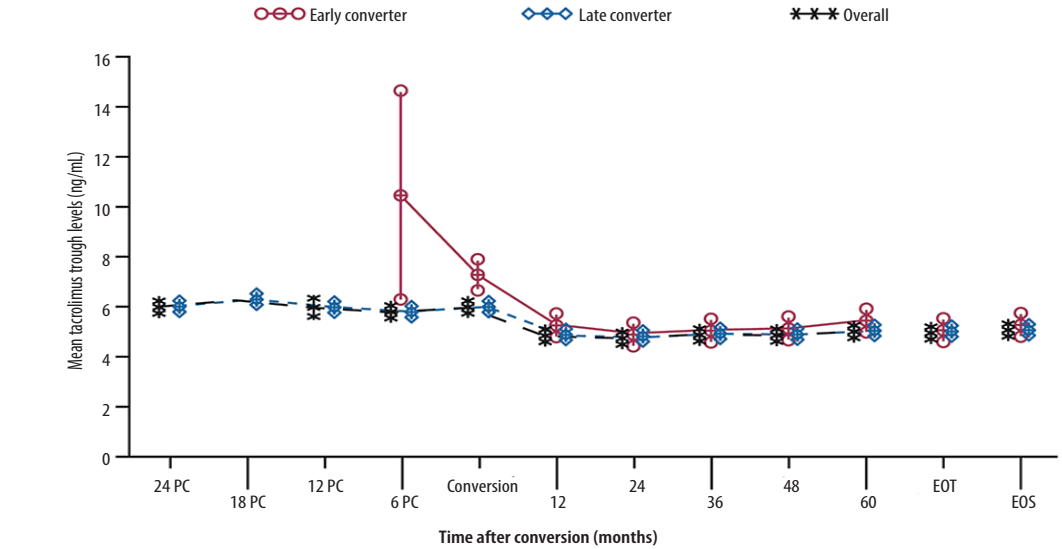


Number of patients

Overall	1678	1857	2285	2687	3964	3928	3585	3401	3204	2739	3942	4025
Early converter	0	0	0	150	1006	1022	913	838	798	677	1033	1060
Late converter	1678	1857	2285	2537	2958	2906	2672	2563	2406	2062	2909	2965

D



Number of patients

Overall	525	597	678	751	886	883	835	805	780	710	875	887
Early converter	0	0	0	18	91	91	82	75	73	72	88	92
Late converter	525	597	678	733	795	792	753	730	707	638	787	795

Figure 3. Summary of tacrolimus exposure after conversion in the overall (A) and Asian countries cohort (B), and mean tacrolimus trough levels in the overall (C) and Asian countries cohort (D). Mean daily dose of PRT and mean tacrolimus trough levels are displayed, and error bars represent 95% CI. EOT was the earliest among the last exposure dates, eCRF visit dates, and first exposure date plus 1916 days (the maximum window for collecting data). EOS was the earliest among the last eCRF visit date and first exposure date plus 2008 days (the maximum window for collecting data), except for exposure data. eCRF – electronic case report form; EOS – end-of-study; EOT – end of treatment; PC – months prior to conversion; PRT – prolonged-release tacrolimus.

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Table 3. Coefficient of variation for tacrolimus trough levels.

	Early converter (n=1060)	Late converter (n=2968)	Total (n=4028)
Baseline to 12 months after conversion (+6 months)			
Coefficient of variation for tacrolimus trough levels*, n (%)			
<35%	686 (84.2)	1580 (85.5)	2266 (85.1)
≥35%	129 (15.8)	267 (14.5)	396 (14.9)
Missing	245	1121	1366
Baseline to 24 months after conversion (+6 months)			
Coefficient of variation for tacrolimus trough levels*, n (%)			
<35%	707 (83.4)	1872 (84.3)	2579 (84.0)
≥35%	141 (16.6)	349 (15.7)	490 (16.0)
Missing	212	747	959
Baseline to 36 months after conversion (+6 months)			
Coefficient of variation for tacrolimus trough levels*, n (%)			
<35%	668 (83.5)	1983 (83.7)	2651 (83.6)
≥35%	132 (16.5)	387 (16.3)	519 (16.4)
Missing	260	598	858
Baseline to 48 months after conversion (+6 months)			
Coefficient of variation for tacrolimus trough levels*, n (%)			
<35%	645 (81.9)	2002 (84.4)	2647 (83.7)
≥35%	143 (18.1)	371 (15.6)	514 (16.3)
Missing	272	595	867
Baseline to 60 months after conversion (+6 months)			
Coefficient of variation for tacrolimus trough levels*, n (%)			
<35%	561 (83.4)	1743 (85.1)	2304 (84.7)
≥35%	112 (16.6)	304 (14.9)	416 (15.3)
Missing	387	921	1308
Baseline to end of treatment			
Coefficient of variation for tacrolimus trough levels*, n (%)			
<35%	768 (82.0)	2206 (84.4)	2974 (83.8)
≥35%	169 (18.0)	408 (15.6)	577 (16.2)
Missing	123	354	477
Baseline to end of study (whole period)			
Coefficient of variation for tacrolimus trough levels*, n (%)			
<35%	796 (80.2)	2325 (83.3)	3121 (82.5)
≥35%	196 (19.8)	466 (16.7)	662 (17.5)
Missing	68	177	245

* For each patient having at least 4 trough-level measurements, the coefficient of variation was calculated as the ratio of the standard deviation and mean (CoV [%]=(SD/mean)×100) of all trough-level measurements after conversion up to the time of analysis (last available visit). In case of multiple trough levels around a target time point, the value whose assessment day was the closest to the defined target day within these windows was used. CoV – coefficient of variation; SD – standard deviation.

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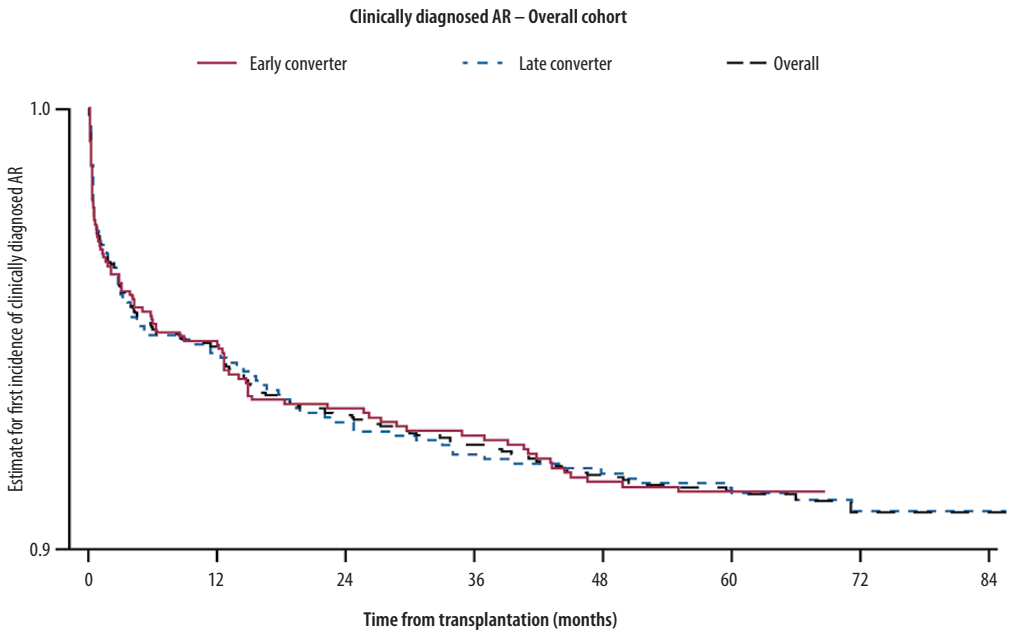
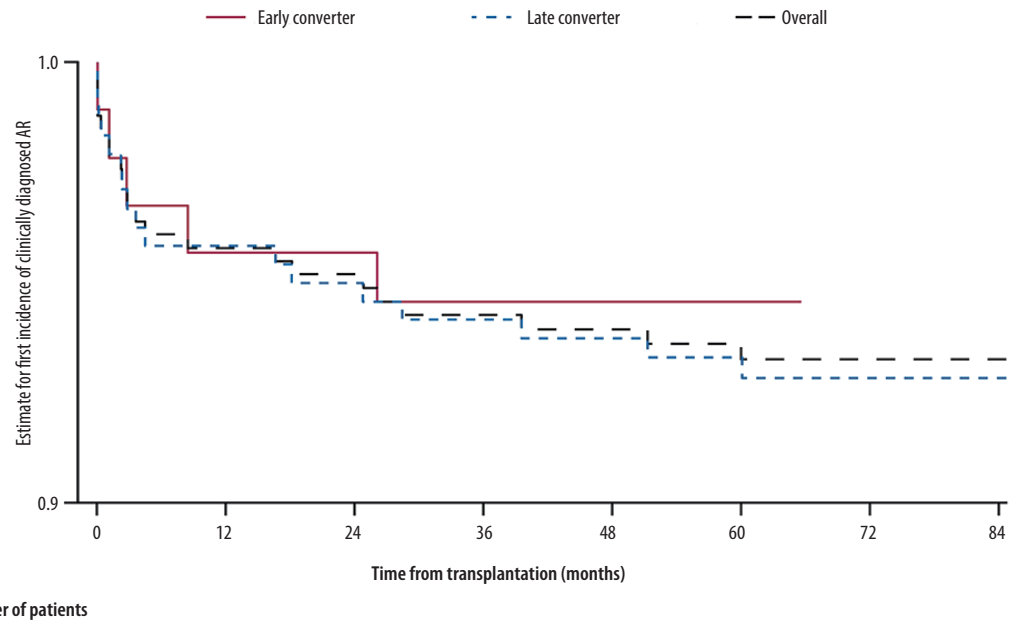


Number of patients

Overall	2029	1909	1828	1755	1669	1212	295	3
Early converter	1060	994	938	891	839	441	0	
Late converter	969	915	890	864	830	771	295	3

B



Number of patients

Overall	330	315	310	295	287	252	99	1
Early converter	92	87	84	74	74	51	0	
Late converter	238	228	226	221	213	201	99	1

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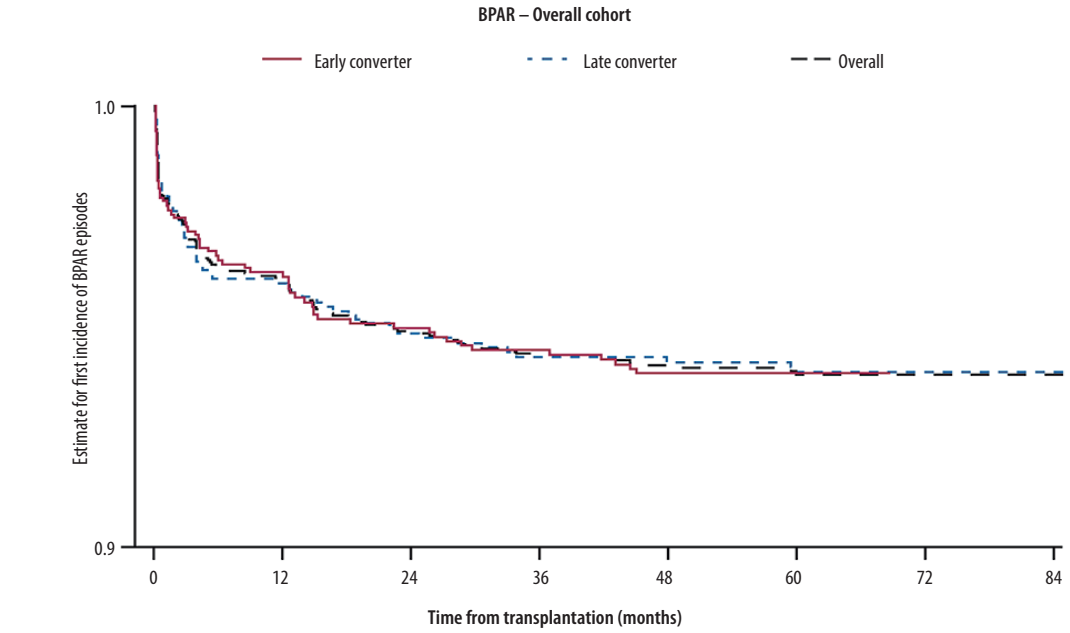
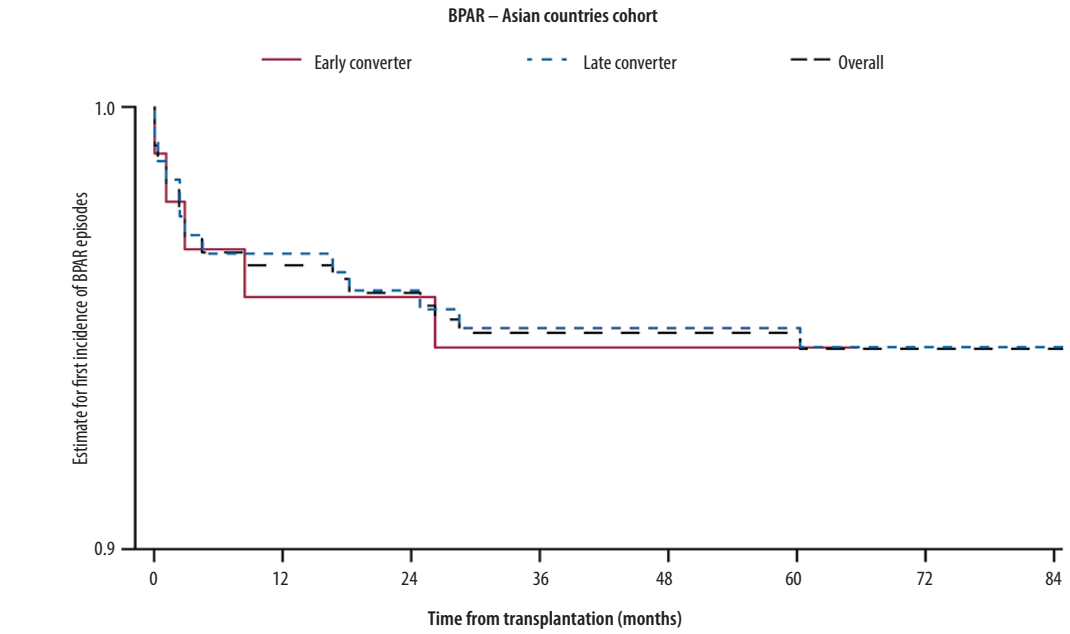


Number of patients

Overall	2029	1940	1862	1790	1710	1243	306	3
Early converter	1060	1010	954	906	858	449	0	
Late converter	969	930	908	884	852	794	306	3

D



Number of patients

Overall	330	317	312	297	290	256	102	1
Early converter	92	87	84	74	74	51	0	
Late converter	238	230	228	223	216	208	102	1

Figure 4. Kaplan-Meier estimates of time to first incidence of clinically diagnosed acute rejection in the overall (A) and Asian countries cohort (B), and time to first incidence of BPAR in the overall cohort (C) and Asian countries cohort (D).
AR – acute rejection; BPAR – biopsy-proven acute rejection.

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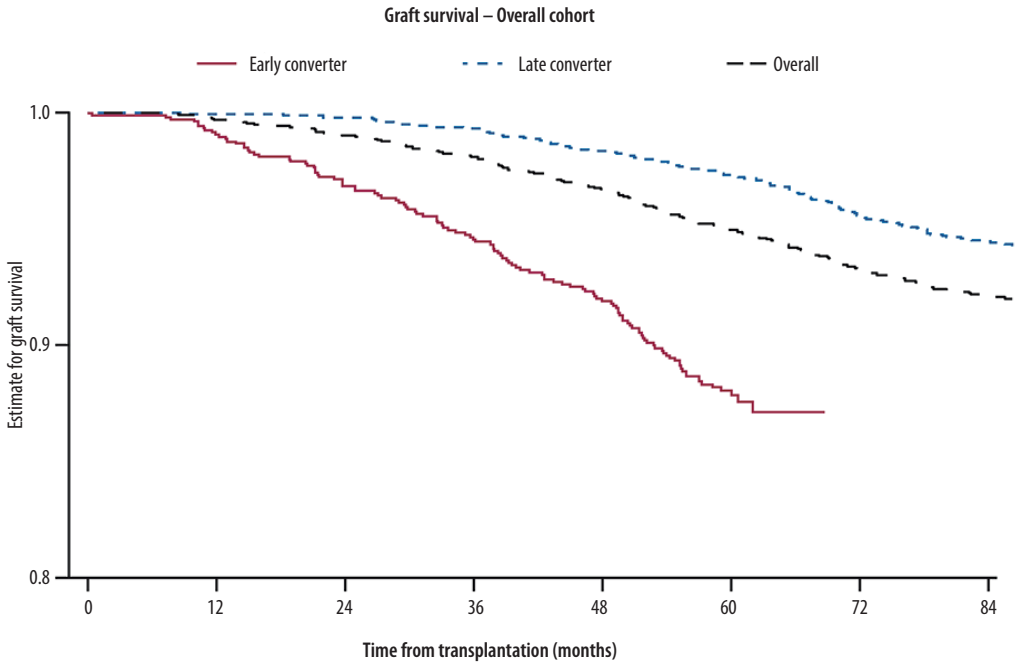
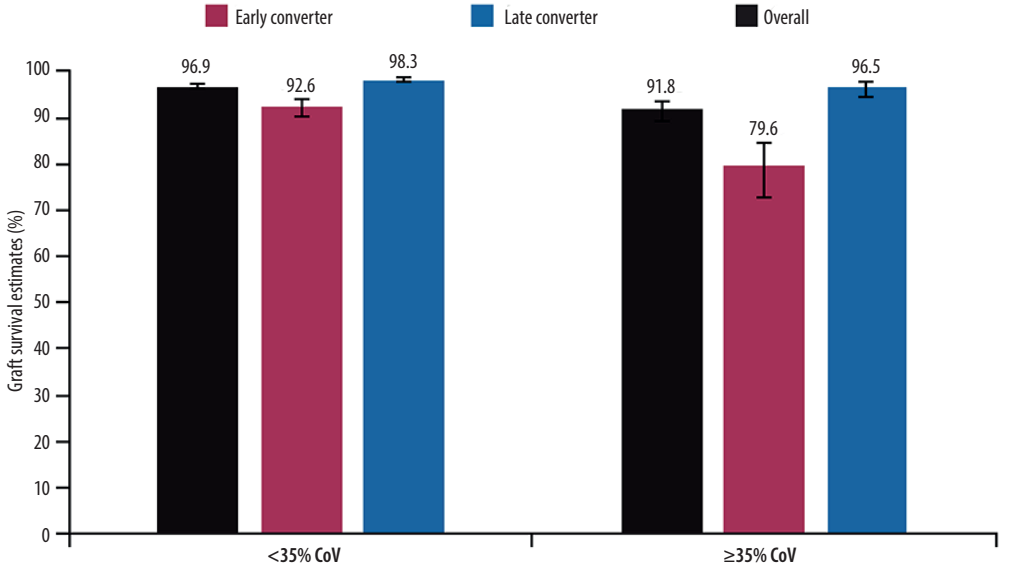
A



Number of patients

Overall	4028	4012	3949	3873	3773	3271	2251	1847
Early converter	1060	1045	995	942	892	472	0	
Late converter	2968	2967	2954	2931	2881	2799	2251	1847

B



Number of patients at risk	3121	796	2325	662	196	466

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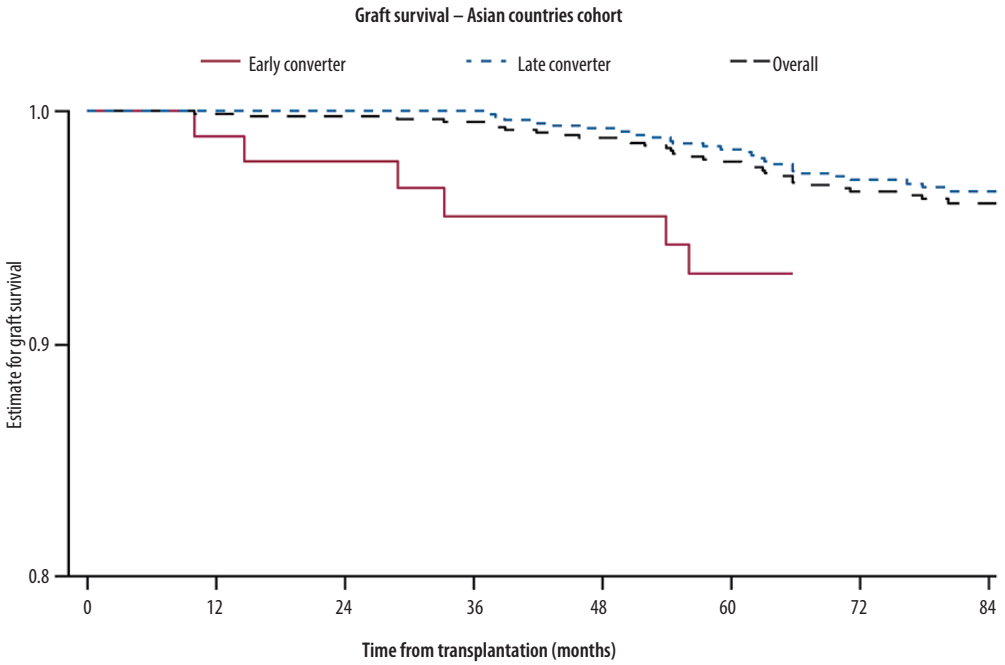
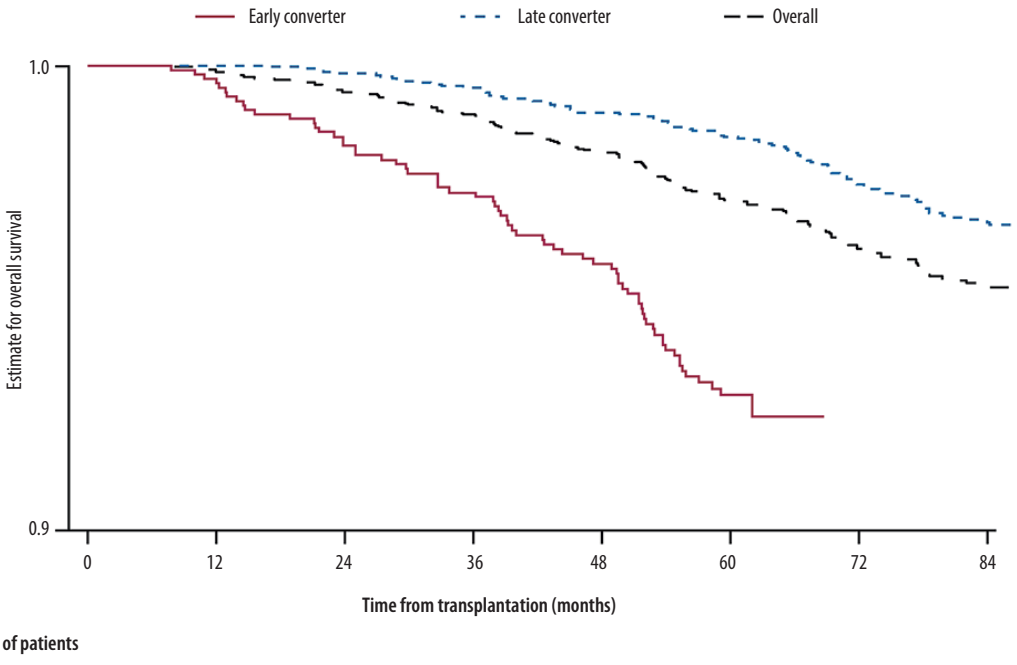


Number of patients

Overall	887	886	883	870	859	818	647	523
Early converter	92	91	88	78	78	55	0	
Late converter	795	795	795	792	781	763	647	523

D



Number of patients

Overall	4028	4016	3956	3893	3808	3296	2267	1853
Early converter	1060	1048	1001	958	914	479	0	
Late converter	2968	2968	2955	2935	2894	2817	2267	1853

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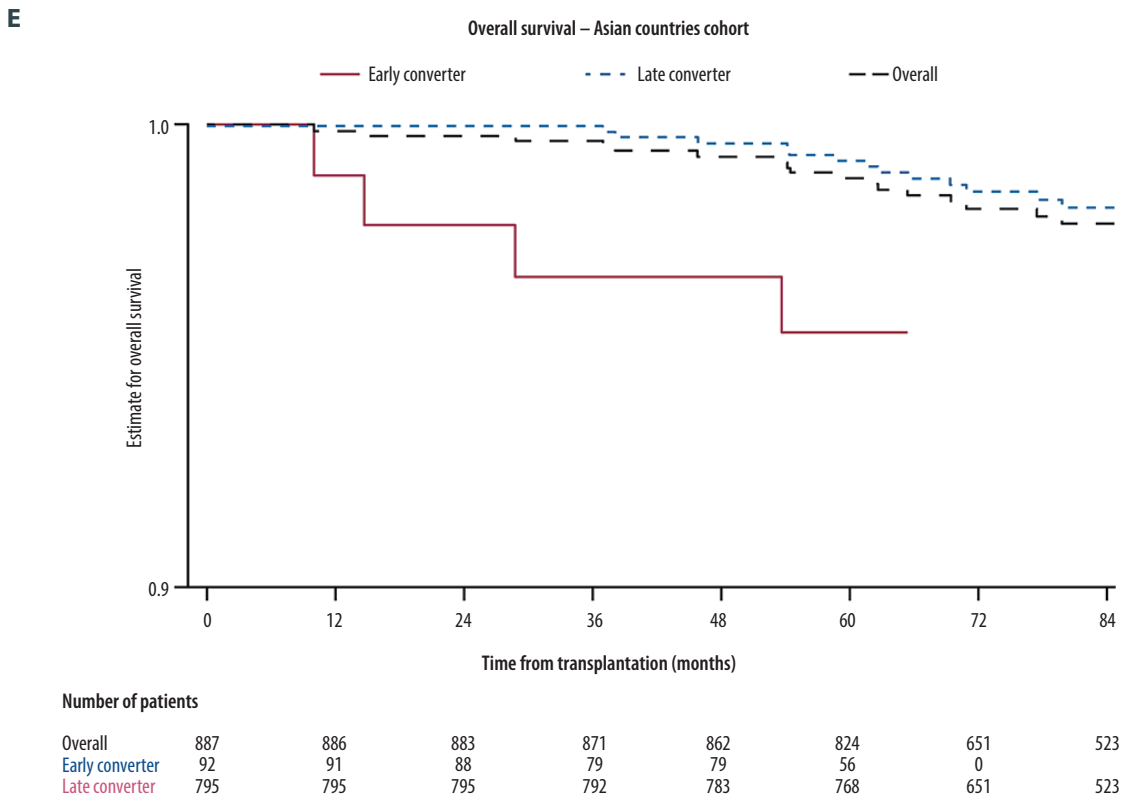

Figure 5. Kaplan-Meier estimates of graft survival in the overall cohort (A), 5-year post-transplant graft survival estimate by tacrolimus trough levels subgroups in the overall cohort (B), graft survival in the Asian countries cohort (C), and overall survival in the overall (D) and Asian countries cohort (E). For patient survival, only death counts as an event. Graft survival was defined as the incidence of re-transplantation, nephrectomy, death, or commencement of dialysis at the end of study or discontinuation. The survival estimates and 95% CIs are based on the Kaplan-Meier time-to-event estimates. The patient and graft survival times were calculated as the duration from the date of transplantation until an event occurred or the date of the last contact. The CoV data were missing for 245, 68, and 177 patients in the overall, early converter, and late converter cohorts, respectively. CI – confidence interval; CoV – coefficient of variation.

at 60 months after transplant, and it remained high (96.0% [94.4%; 97.2%]) at 84 months (**Figure 5C**).

Patient Survival

Overall, 258 (6.4%) patients died during the study period (6.5% [n=69] of all EC patients; 6.4% [n=189] of all LC patients). The Kaplan-Meier estimate (95% CI) of patient survival was 97.1% (96.5%; 97.6%) at 60 months after transplantation and remained high (95.3% [94.4%; 95.9%]) at 84 months (**Figure 5D**). In the Asian countries cohort (n=887), 29 (3.3%) patients died during the study period (4.3% [n=4] of all EC patients; 3.1% [n=25] of all LC patients). The survival estimate (95% CI) was 98.9% (97.9%; 99.4%) at 60 months after transplantation and remained high at 84 months after transplantation (97.8% [96.5%; 98.7%] (**Figure 5E**).

Donor-Specific Antibodies

A total of 1535 (38.1%) patients had a DSA test either prior to, or at conversion. Of these, 281 (18.3%) patients had DSA occurrence prior to or at conversion to PRT (**Table 2**). After PRT conversion, 536/1898 (28.2%) patients had DSA occurrence (**Table 4**). In the Asian countries cohort, 34/153 (22.2%) patients had DSA occurrence prior to or at conversion (**Table 4**), while 64/238 (26.9%) patients had DSA occurrence after conversion to PRT (**Table 4**).

Safety (EPS)

Adverse Events

Among the 4389 patients in the EPS, there were 18 615 adverse events (AEs) recorded in 3178 (72.4%) patients (**Table 5**). In 848 (19.3%) patients, AEs were considered to be related

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Table 4. Occurrences of donor-specific antibodies after conversion.

	Overall cohort			Asian countries cohort		
	Early converter (n=700)	Late converter (n=1198)	Total (n=1898)	Early converter (n=92)	Late converter (n=795)	Total (n=887)
At least 1 DSA occurrence after conversion, n (%)*						
Yes	212 (30.3)	324 (27.0)	536 (28.2)	9 (33.3)	55 (26.1)	64 (26.9)
No	488 (69.7)	874 (73.0)	1362 (71.8)	18 (66.7)	156 (73.9)	174 (73.1)
Missing	360	1770	2130	65	584	649
	Early converter (n=1060)	Late converter (n=2968)	Total (n=4028)	Early converter (n=92)	Late converter (n=795)	Total (n=887)
At least 1 DSA occurrence prior or before conversion and at least 1 DSA after conversion, n (%)**						
Yes	51 (4.8)	116 (3.9)	167 (4.1)	2 (2.2)	13 (1.6)	15 (1.7)
No	18 (1.7)	53 (1.8)	71 (1.8)	0	10 (1.3)	10 (1.1)
No DSA occurrence prior to or at conversion and at least 1 DSA occurrence after conversion, n (%)**						
Yes	82 (7.7)	115 (3.9)	197 (4.9)	4 (4.3)	8 (1.0)	12 (1.4)
No	303 (28.6)	566 (19.1)	869 (21.6)	3 (3.3)	55 (6.9)	58 (6.5)

* Percentages were calculated from the number of patients with available data. ** Percentages were calculated from all patients in the early converter, late converter, and overall subgroups. DSA – donor-specific antibody.

Table 5. Overview of adverse events in the overall cohort.

	Overall cohort			Asian countries cohort		
Events, n (%)	Early converter (n=1258)	Late converter (n=3131)	Total (n=4389)	Early converter (n=98)	Late converter (n=812)	Total (n=910)
AEs	1007 (80.0)	2171 (69.3)	3178 (72.4)	63 (64.3)	466 (57.4)	529 (58.1)
PRT-related* AEs	330 (26.2)	518 (16.5)	848 (19.3)	11 (11.2)	72 (8.9)	83 (9.1)
Deaths	92 (7.3)	217 (6.9)	309 (7.0)	5 (5.1)	27 (3.3)	32 (3.5)
SAEs**	741 (58.9)	1480 (47.3)	2221 (50.6)	40 (40.8)	297 (36.6)	337 (37.0)
PRT-related* SAEs**	174 (13.8)	281 (9.0)	455 (10.4)	9 (9.2)	49 (6.0)	58 (6.4)
AEs leading to permanent discontinuation of PRT	174 (13.8)	344 (11.0)	518 (11.8)	7 (7.1)	40 (4.9)	47 (5.2)
PRT-related* AEs leading to permanent discontinuation of PRT	88 (7.0)	154 (4.9)	242 (5.5)	2 (2.0)	20 (2.5)	22 (2.4)

* Possible, probable, or not assessable, as determined by the investigator, or records where the relationship is missing. ** Includes SAEs upgraded by the sponsor based on the review of the Sponsor's list of always serious terms or the important medical event process, if any upgrade. AE – adverse event; PRT – prolonged-release tacrolimus; SAE – serious adverse event.

to PRT. In both subgroups, the most common PRT-related AEs, recorded in ≥1% of transplant recipients, were tremor (2.3%), diarrhea (1.3%), and urinary tract infections (1.0%). The EC subgroup also reported BK virus infection (1.4%), basal cell carcinoma (1.1%), alopecia (1.1%), cytomegalovirus infection (1.0%), polyomavirus-associated nephropathy (1.0%), and acute kidney injury (1.0%). In the LC subgroup, apart from tremor, diarrhea, and urinary tract infections, no other PRT-related AEs were reported by ≥1% of transplant recipients.

A total of 7354 serious AEs (SAEs) were reported (EC, 2749; LC, 4605). Overall, 2221 (50.6%) patients reported SAEs. New-onset

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diabetes after transplantation was reported by 0.3% of patients (EC, 0.6%; LC, 0.2%).

There were 455 (10.4%) patients in whom SAEs were considered to be related to PRT. Permanent PRT discontinuation was reported to be caused by AEs in 518 (11.8%) patients. Treatment discontinuation was reported to be caused by PRT-related AEs in 242 (5.5%) patients. Overall, 309 (7.0%) patients had an AE leading to death; the deaths of 16 (0.4%) patients were considered PRT-related. In an additional 15 (0.3%) patients, the relationship of the AE leading to death and PRT was deemed non-assessable. COVID-19 or suspected COVID-19 infection was reported to be the cause of death in 21 (0.5%) patients. AEs and SAEs for the Asian countries cohort are provided in **Table 5**.

Discussion

The prospective CHORUS study was the first global, multicenter, real-world-evidence study with 5-year outcome data on PRT use after conversion from IRT at different time points, addressing the lack of long-term outcome data for KTRs following conversion. This study described results from a large cohort of diverse KTRs, including 910 (20.7%) patients from Asian countries. Our findings showed that independent of conversion timing, conversion from IRT to PRT was tolerable and effective in clinical practice, in support of previous short- and long-term findings [19,25].

Globally, the timing and reason for PRT conversion may differ among clinical practices, but conversion can improve treatment convenience and patient medication adherence [19,20]. Efforts to improve adherence through switching KTRs from IRT to PRT may be further hindered by concomitant treatment with twice-daily mycophenolate mofetil for patients on IRT. However, in this study, it was reassuring that over half of patients were treated concomitantly with mycophenolate mofetil, suggesting that conversion does occur in these patients.

The eGFR remained relatively stable in the overall cohort from the time of conversion to 5 years after conversion, with a mean change from baseline decrease of 1.4 mL/min/1.73 m^2 from a mean eGFR of 56.1 mL/min/1.73 m^2 at conversion. In the EC subgroup, there was an initial clinically relevant improvement from conversion to 12 months after conversion, which was maintained throughout the study. In the LC subgroup, there was a numerical but non-statistically significant reduction in eGFR. This decrease, measuring less than 2 mL/min/1.73 m^2, is unlikely to have clinical significance, as supported by the overlapping 95% CIs between the LC subgroup and the overall cohort. These results are similar to 2 long-term studies of PRT in de novo KTRs, where the 5-year mean eGFR was 51.1 [23] and 52.5 [24] mL/min/1.73 m^2, respectively. In the Asian countries cohort, renal function remained relatively stable throughout the 5-year study period, with an average decrease of 3.4 mL/min/1.73 m^2 from a mean eGFR of 66.8 mL/min/1.73 m^2 at conversion. This is consistent with results from 2 long-term Japanese studies assessing the long-term impact of PRT, which reported eGFR values of 48.7 mL/min/1.73 m^2 [37] and 46.7 mL/min/1.73 m^2 [38].

Low tacrolimus exposure has previously been associated with an increased risk of rejection [15]. In the present study, after an initial decrease in median tacrolimus daily dose and mean trough levels 12 months after conversion; tacrolimus dose and trough concentrations consistently remained within the therapeutic window under routine clinical practice conditions. Mean trough levels after conversion from IRT to PRT were numerically lower than when patients were treated with IRT before conversion. However, this decrease was approximately 1 ng/mL, and more than 60% of patients had tacrolimus trough levels between 5 and 10 ng/mL after conversion. Additionally, more than 80% of patients with available data had a CoV of <35%. Variable tacrolimus trough concentrations have been associated with an increased risk of rejection and graft loss [8,39]. This is demonstrated in the present study, as patients in the ≥35% CoV subgroup had a lower 60-month graft survival rate compared with patients in the <35% subgroup. This was particularly apparent in the EC subgroup, while there were no differences in the LC subgroup.

Overall, and in the Asia countries cohort, the estimates for clinically diagnosed acute rejection-free and BPAR-free survival were high (>90.0%) and in line with previously published long-term results in KTRs receiving PRT (74.2-86.0%) [23,24]. Graft and patient survival were high (≥95.0%) at 5 years after transplantation and remained high (≥90.0%) until 7 years after transplantation in both cohorts, and were generally comparable with other long-term studies investigating PRT use (patient survival, 90.8-98.1%; graft survival, 82.7-88.1%) [23-25,37,40].

Patients in the EC subgroup may have been more susceptible to early post-transplant events, such as rejection and graft loss, as their average time between transplantation and conversion was only 2 months, whereas patients in the LC subgroups were converted, on average, 65 months after transplantation. Since complications are likely to occur early in the post-transplant period [41], this may explain the differences between subgroups, especially when considering graft survival from the time of transplantation. Such issues have recently been discussed as “immortal time bias” [42].

There were no unexpected safety findings observed during the study period. After conversion to PRT, the AE rate was lower compared with previously reported AE rates for IRT treatment [43-45]. However, any direct comparisons between

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studies should be interpreted cautiously due to differences between study designs and populations. The incidence of the most commonly reported PRT-related AEs, such as tremors, diarrhea, and urinary tract infections, was in line with previous long-term studies of PRT [23,24,40].

The strengths of this study included its large, diverse patient population from 25 countries across Europe, Asia, and North America, with a substantial proportion from Asia, permitting analyses in a cohort of patients from Asia. This study's long-term, non-interventional design enabled data collection over 5 years, with over 75% of patients completing the study as planned. This approach helped address an evidence gap in the long-term effects of tacrolimus conversion. Additionally, as a real-world study, patients were treated according to local clinical practice, reflecting current treatment methods and enhancing the generalizability of these data. However, this study may have been limited by selection bias due to the non-randomized selection of sites or patients and immortal time bias [42]. The Kaplan-Meier methodology for estimating time to graft loss may have been biased by the competing risks of graft loss from other events. Additionally, it is possible that reporting of short-term outcomes may have differed between subgroups because the LC subgroup had a longer observation period compared with the EC subgroup. Furthermore, there are potential differences in target tacrolimus trough levels in clinical practice globally and in local therapeutic drug monitoring protocols, which may have impacted results. However, this real-world, non-interventional, prospective study, despite lacking a control group, offers valuable insights, and these findings should be interpreted with thoughtful consideration.

Conclusions

This 5-year, real-world study with a large and diverse cohort of patients indicates that both early and late conversion to PRT are associated with stable renal function, high graft and patient survival outcomes, and no new significant safety findings. Thus, converting KTRs from IRT to PRT independent of conversion timing was effective and well tolerated, and this study contributes to the evidence supporting the continued long-term use of PRT in clinical practice.

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Prior Publication

Data from this study were submitted as 2 abstracts to the 21st Biennial Congress of the European Society for Organ Transplantation (ESOT), which was held in Athens, Greece on 17-20 September 2023, and 1 abstract to the American Society of Nephrology Congress (Kidney Week 2023), which was held in Philadelphia, PA, USA on 2-5 November 2023.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Ghanta M, Jim B. Renal transplantation in advanced chronic kidney disease patients. Med Clin North Am. 2016;100(3):465-76
2. Neuberger JM, Bechstein WO, Kuypers DRJ, et al. Practical recommendations for long-term management of modifiable risks in kidney and liver transplant recipients. Transplantation. 2017;101(4S):S1-S56
3. James A, Mannon RB. The cost of transplant immunosuppressant therapy: Is this sustainable? Curr Transplant Rep. 2015;2(2):113-21
4. Neuwirt H, Rudnicki M, Schratzberger P, et al. Immunosuppression after renal transplantation. Memo. 2019;12(3):216-21
5. Hariharan S, Israni AK, Danovitch G. Long-term survival after kidney transplantation. N Engl J Med. 2021;385(8):729-43
6. Vankova B, Mala-Ladova K, Kubena AA, et al. Immunosuppressive therapy related adherence, beliefs and self-management in kidney transplant outpatients. Patient Prefer Adherence. 2018;12:2605-13
7. Sellares J, de Freitas DG, Mengel M, et al. Understanding the causes of kidney transplant failure: The dominant role of antibody-mediated rejection and nonadherence. Am J Transplant. 2012;12(2):388-99
8. Scheel J, Reber S, Stoessel L, et al. Patient-reported non-adherence and immunosuppressant trough levels are associated with rejection after renal transplantation. BMC Nephrol. 2017;18(1):107
9. Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. Am J Transplant. 2012;12(5):1157-67
10. Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Rates and determinants of progression to graft failure in kidney allograft recipients with de novo donor-specific antibody. Am J Transplant. 2015;15(11):2921-30
11. Kidney Disease: Improving Global Outcomes Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009;9(Suppl. 3):S1-S157
12. US Food and Drug Administration. PROGRAF® Prescribing Information. 2012 [cited 2025 Mar 19]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210115s000,050708s047,050709s040lbl.pdf
13. Lentine KL, Smith JM, Hart A, et al. OPTN/SRTR 2020 annual data report: Kidney. Am J Transplant. 2022; 22(Suppl. 2):21-136

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

14. Guerra G, Ciancio G, Gaynor JJ, et al. Randomized trial of immunosuppressive regimens in renal transplantation. J Am Soc Nephrol. 2011;22(9):1758-68
15. Gaynor JJ, Ciancio G, Guerra G, et al. Lower tacrolimus trough levels are associated with subsequently higher acute rejection risk during the first 12 months after kidney transplantation. Transpl Int. 2016;29(2):216-26
16. Gaynor JJ, Guerra G, Roth D, et al. Graft failure due to nonadherence among 150 prospectively-followed kidney transplant recipients at 18 years post-transplant: Our results and review of the literature. J Clin Med. 2022;11(5):1334
17. Rodrigo E, Segundo DS, Fernandez-Fresnedo G, et al. Within-patient variability in tacrolimus blood levels predicts kidney graft loss and donor-specific antibody development. Transplantation. 2016;100(11):2479-85
18. Paterson TSE, Demian M, Shapiro RJ, et al. Impact of once- versus twice-daily tacrolimus dosing on medication adherence in stable renal transplant recipients: A Canadian single-center randomized controlled trial. Can J Kidney Health Dis. 2019;6:205435811986799
19. Cassuto E, Pageaux GP, Cantarovich D, et al. Adherence to and acceptance of once-daily tacrolimus after kidney and liver transplant: Results from OSIRIS, a French observational study. Transplantation. 2016;100(10):2099-106
20. Lehner LJ, Reinke P, Horstrup JH, et al. Evaluation of adherence and tolerability of prolonged-release tacrolimus (Advagraf) in kidney transplant patients in Germany: A multicenter, noninterventional study. Clin Transplant. 2018; 32(1):ctr.13142
21. Stifft F, Stolk LM, Undre N, et al. Lower variability in 24-hour exposure during once-daily compared to twice-daily tacrolimus formulation in kidney transplantation. Transplantation. 2014;97(7):775-80
22. Wu MJ, Cheng CY, Chen CH, et al. Lower variability of tacrolimus trough concentration after conversion from Prograf to Advagraf in stable kidney transplant recipients. Transplantation. 2011;92(6):648-52
23. Pernin V, Glyda M, Viklicky O, et al. Long-term prolonged-release tacrolimus-based immunosuppression in de novo kidney transplant recipients: 5-Y prospective follow-up of patients in the ADVANCE study. Transplant Direct. 2023;9(3):e1432
24. Rummo O, Carmellini M, Kamar N, et al. Long-term, prolonged-release tacrolimus-based immunosuppression in de novo kidney transplant recipients: 5-year prospective follow-up of the ADHERE study patients. Transpl Int. 2020;33(2):161-73
25. Kuypers D, Weekers L, Blogg M, et al. Efficacy of prolonged-release tacrolimus after conversion from immediate-release tacrolimus in kidney transplantation: A retrospective analysis of long-term outcomes from the ADMIRAD study. Transplant Direct. 2023;9(4):e1465
26. Muduma G, Odeyemi I, Smith-Palmer J, Pollock RF. Budget impact of switching from an immediate-release to a prolonged-release formulation of tacrolimus in renal transplant recipients in the UK based on differences in adherence. Patient Prefer Adherence. 2014;8:391-99
27. Mendonca L, Diniz H, Silvano J, et al. Early versus late conversion from immediate to prolonged-release tacrolimus after renal transplantation: Clinical effects and treatment costs. Transplant Direct. 2019;5(1):e417
28. ClinicalTrials.gov. Global, Multicentre, Non Interventional Advagraf Conversion Registry in Kidney Transplant Patients (CHORUS) (NCT02555787). 2015 [cited 2024 10 May]; Available from: https://clinicaltrials.gov/study/NCT02555787
29. European Medicines Agency. Prograf. 2023 [cited 2023 19 December]; Available from: https://www.ema.europa.eu/en/medicines/human/referrals/prograf#ema-inpage-item-all-documents
30. European Medicines Agency. Advagraf. 2023 [cited 2023 19 December]; Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/advagraf
31. Mudiayi D, Shojai S, Okpechi I, et al. Global estimates of capacity for kidney transplantation in world countries and regions. Transplantation. 2022;106(6):1113-22
32. Tang JT, Andrews LM, van Gelder T, et al. Pharmacogenetic aspects of the use of tacrolimus in renal transplantation: Recent developments and ethnic considerations. Expert Opin Drug Metab Toxicol. 2016;12(5):555-65
33. Moal V, Grimbert P, Beauvais A, et al. A prospective, observational study of conversion from immediate- to prolonged-release tacrolimus in renal transplant recipients in France: The OPALE study. Ann Transplant. 2019;24:517-26
34. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the Modification of Diet in Renal Disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145(4):247-54
35. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: More accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. Am J Kidney Dis. 2010;55(4):622-27
36. Loupy A, Haas M, Roufosse C, et al. The Banff 2019 Kidney Meeting Report (I): Updates on and clarification of criteria for T cell- and antibody-mediated rejection. Am J Transplant. 2020;20(9):2318-31
37. Wakasugi N, Uchida H, Uno S. Safety and effectiveness of once-daily, prolonged-release tacrolimus in de novo kidney transplant recipients: 5-year, multicenter postmarketing surveillance in Japan. Transplant Proc. 2018;50(10):3296-305
38. Okumi M, Omoto K, Shimizu T, et al. Long-term prolonged-release tacrolimus outcomes in living donor kidney transplantation: The Japan Academic Consortium of Kidney Transplantation Study-II. Int J Urol. 2023;30(5):483-91
39. Goodall DL, Willicombe M, McLean AG, Taube D. High intrapatient variability of tacrolimus levels and outpatient clinic nonattendance are associated with inferior outcomes in renal transplant patients. Transplant Direct. 2017;3(8):e192
40. Silva HT Jr., Yang HC, Meier-Kriesche HU, et al. Long-term follow-up of a phase III clinical trial comparing tacrolimus extended-release/MMF, tacrolimus/MMF, and cyclosporine/MMF in de novo kidney transplant recipients. Transplantation. 2014;97(6):636-41
41. Levine MA, Schuler T, Gourishankar S. Complications in the 90-day postoperative period following kidney transplant and the relationship of the Charlson Comorbidity Index. Can Urol Assoc J. 2017;11(12):388-93
42. Gleiss A, Oberbauer R, Heinze G. An unjustified benefit: immortal time bias in the analysis of time-dependent events. Transpl Int. 2018;31(2):125-30
43. Albano L, Banas B, Klempnauer JL, et al. OSAKA trial: A randomized, controlled trial comparing tacrolimus QD and BD in kidney transplantation. Transplantation. 2013;96(10):897-903
44. Rostaing L, Bunnapradist S, Grinyó JM, et al. Novel once-daily extended-release tacrolimus versus twice-daily tacrolimus in de novo kidney transplant recipients: Two-year results of phase 3, double-blind, randomized trial. Am J Kidney Dis. 2016;67(4):648-59
45. Krämer BK, Charpentier B, Bäckman L, et al. Tacrolimus once daily (ADVAGRAF) versus twice daily (PROGRAF) in de novo renal transplantation: A randomized phase III study. Am J Transplant. 2010;10(12):2632-43

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