Evaluation of adherence and tolerability of prolonged-release tacrolimus (Advagraf™) in kidney transplant patients in Germany: A multicenter, noninterventional study

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Abstract
This study assessed adherence to prolonged-release tacrolimus (PR-T)-based immunosuppression during routine maintenance of renal transplant recipients in Germany. Patients had received PR-T for ≥1 month at inclusion. Data were collected during four visits (V): baseline (V1), 6 (V2), 12 (V3), and 18 (V4) months. Composite primary endpoint: nonadherence at V4, defined as self-reported nonadherence on the Basel Assessment of Adherence with Immunosuppressive Medication Scale (BAASIS©), investigator-rated nonadherence, and/or V4 tacrolimus trough level outside a predefined range. Secondary endpoints: individual BAASIS items, incidence of rejection, kidney function, and safety. Overall, 153 adult kidney recipients (mean [standard deviation] time post-transplant 5.8 [4.6] years) were included. Nonadherence was high at V4 (67.7% [95% confidence interval 58.9%, 75.6%]). Medication-taking adherence was 86.9% and 91.3% at V1 and V4, respectively; adherence to timing of medication intake was 58.2% and 58.3%, with little evidence of missed doses/drug holidays. Investigators rated adherence "good" in 85.6% of patients (V4). Two (1.3%) patients had acute rejection episodes. Kidney function remained stable (mean creatinine clearance, V1: 62.1 mL/min; V4: 65.3 mL/min). Investigators rated effectiveness of PR-T as "very good"/"good" in 91.5% of patients. Most patients (94.7%) found PR-T dosing more convenient than immediate-release tacrolimus. PR-T was well tolerated with high medication persistence.

KEYWORDS
immunosuppression, kidney transplantation, medication adherence, tacrolimus

1 | INTRODUCTION

Nonadherence to a patient's immunosuppressive regimen remains of concern during renal allograft maintenance.1,2 Dew et al concluded from a meta-analysis of 147 transplantation studies that nonadherence in renal allograft recipients was highest among solid organ transplant recipients, reaching 36 cases per 100 patients per year.2 Nonadherence has been associated with graft loss,4,5 and results from a recent meta-analysis indicated that the odds of allograft failure increased sevenfold in nonadherent renal transplant recipients.1 Furthermore, nonadherence has been recognized as an independent risk factor for the development of de novo donor-specific antibodies, a major cause of graft loss.6

Multiple causes of nonadherence have been identified, including socioeconomic factors, patient-related factors (eg, negative beliefs...
in medication), and treatment-related factors (eg, adverse events and duration of treatment). In particular, kidney transplant recipients face the challenge of lifelong immunosuppressive medication. However, persistence with immunosuppressive medications after renal transplantation has been shown to decline over time, with patients being more adherent in the early post-transplant period. Nonadherence to immunosuppressive treatment in renal transplant patients more than 1 year post-transplant is associated with an increased risk for late acute rejection during the following 5 years. Furthermore, the complexity of treatment regimens has been shown to negatively impact adherence to medication, with the probability of nonadherence increasing with dosing frequency. A randomized, controlled multicenter trial using electronic monitoring of medication intake revealed that adherence to the assigned regimen was significantly higher with once-daily, prolonged-release tacrolimus vs twice-daily, immediate-release tacrolimus (88.2% vs 78.8%, respectively; P = .0009). However, long-term adherence data from patients receiving prolonged-release tacrolimus in routine practice are lacking, with most studies focusing on nonadherent behavior in the first year post-transplant.

Moreover, the 2008 consensus conference on nonadherence to immunosuppressants defined nonadherence as "deviation from the prescribed medication regimen sufficient to influence adversely the regimen's intended effect" while recognizing that "a patient's drug taking behavior changes over time." This warrants a multilevel approach to evaluate patients' long-term adherence and persistence with their immunosuppression regimen in the complex setting of kidney transplantation. This prospective, noninterventional, 18-month, multicenter study assessed adherence to, and persistence with, their immunosuppression regimen in the complex setting of kidney transplantation. This prospective, noninterventional, 18-month, multicenter study assessed adherence to, and persistence with, their immunosuppression regimen in the complex setting of kidney transplantation. This prospective, noninterventional, 18-month, multicenter study assessed adherence to, and persistence with, a once-daily, prolonged-release tacrolimus-based regimen during routine maintenance of renal transplant recipients who had received prolonged-release tacrolimus for ≥1 month.

## 2 | PATIENTS AND METHODS

### 2.1 | Study design and patients

COMET was accepted as a noninterventional study by the ethics committee and was conducted in accordance with the Declaration of Helsinki. Ethics committee approval was obtained, and all patients provided written informed consent. The study was registered in the public database of the Association of Research-based Pharmaceutical Companies (Verband forschender Arzneimittelhersteller, VfA).

The study included adult (≥18 years of age) kidney transplant recipients who received prolonged-release tacrolimus (Advagraf™; Astellas Pharma Europe BV, Leiden, Netherlands) either as first-line or as replacement antirejection prophylaxis for ≥1 month. There was no limit on time since transplantation and number of renal allografts previously received by the patient.

During the 18-month observation period, data were recorded at baseline (Visit [V] 1), and at 6 (V2), 12 (V3), and 18 (V4) months (±2 weeks) postbaseline. At each visit, the following parameters were assessed: the laboratory parameters hemoglobin, serum creatinine, urine protein, and urine albumin; prolonged-release tacrolimus dose and trough levels; concomitant medication; rejection episodes and graft survival; dialysis dependence; vital signs (blood pressure and heart rate); and investigator/nurse assessment of adherence to prolonged-release tacrolimus over the previous 4 weeks (rated "good," "moderate," or "poor"). Patients could also use ProMate, an electronic device that records the time of blister insertion and, thereby, adherence.

The Basel Assessment of Adherence with Immunosuppressive Medication Scale (BAASIS) was completed at V1 and V4. BAASIS sum scores were also evaluated. If any one of the four BAASIS questions was answered with "yes," points (range 1-5) were allocated depending on the frequency of self-reported nonadherence. For the response "once a month," 1 point was assigned, 2 points for "every 2 weeks," 3 for "every week," 4 for "more than once a week," and 5 points for "every day." Thus, sum scores ranged between 0 (excellent adherence) and 20 (high nonadherence).

Investigator rating of overall effectiveness and tolerability of prolonged-release tacrolimus (based on a five-point rating scale, ranging from "very good" to "very poor"), assessment of patient satisfaction with therapy ("very satisfied," "satisfied," and "not satisfied"), and patient and graft survival were assessed at V4, or where applicable, at the time of premature study termination.

Adverse drug reactions (ADRs) were continuously monitored and were coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA®, Version 16.1, English).

Target tacrolimus trough levels were defined by treating physicians on an individual patient basis.

### 2.2 | Endpoints

The primary variable was a composite at V4 of three components: BAASIS outcomes; investigator rating of adherence; and tacrolimus blood target levels (Table 1). A single tacrolimus blood level value outside the predefined target range (set by investigators for each individual patient) was regarded as nonadherence. Patients were considered nonadherent for the composite primary variable if nonadherence was evident for at least one of the components.

Secondary variables included analyses of individual BAASIS components and sum scores, patient rating of adherence with the aid of the visual analog scale (VAS) (ranging from 0% = completely nonadherent, to 100% = fully adherent), patient and graft survival, rejection episodes, renal function and vital signs, investigator rating of the overall effectiveness and tolerability of prolonged-release tacrolimus at V4 (based on a five-point rating scale, ranging from "very good" to "very poor"), and assessment of patient satisfaction with therapy at V4 ("very satisfied," "satisfied," and "not satisfied").

### 2.3 | Statistical analysis

It was planned to enroll 150 patients. The full analysis set (FAS) included all patients treated with prolonged-release tacrolimus for whom data were recorded after V1. Quantitative variables (eg, age, sex, and tacrolimus levels) were presented using descriptive statistics (number of valid
observations, mean, and standard deviation (SD). If indicated, frequency distributions were supplied following grouping of data. Categorical variables were described by absolute and relative frequencies.

The primary variable was analyzed for patients in the FAS with valid data at V4, and three sensitivity analyses were conducted on the following: (i) all patients who attended V4; (ii) all patients with valid data; and (iii) all patients. In addition to frequency distributions, 95% confidence intervals (CI, Clopper-Pearson) were calculated. Subgroup analysis for the primary variable was performed for recipient sex and age (<40, 40–<50, 50–<60, and ≥60 years), organ source (deceased or living donor), and occurrence of rejection episodes, 95% confidence intervals (CI, Clopper-Pearson) were calculated. Subgroup analysis for the primary variable was performed for recipient sex and age (<40, 40–<50, 50–<60, and ≥60 years), organ source (deceased or living donor), and occurrence of rejection episode since last transplantation. All evaluations were performed using SAS® Version 9.2.

3 | RESULTS

3.1 | Patient disposition and baseline characteristics

The study was conducted between June 2009 and August 2013 in seven German transplant centers. The FAS comprised 153, predominantly male, kidney transplant recipients. Baseline characteristics are summarized in Table 2. Most patients (88.2%) had received their first transplant, were on average 5.8 years post-transplant, and had received dialysis prior to transplant (142 [92.8%] patients).

Data were available from 153 (100%) patients at V1, 142 (92.8%) at V2, 133 (86.9%) at V3, and 132 (86.3%) at V4. Reasons for premature study discontinuation of 21 patients were withdrawal of prolonged-release tacrolimus (n = 6, 3.9%), ADR (n = 2, 1.3%), lost to follow-up (n = 6, 3.9%), and "other" (n = 7, 4.6%). The mean (SD) observational period was 538 (102) days, considering only patients with data recordings after V1 (n = 144).

3.2 | Tacrolimus dose and trough levels

During the study, mean daily tacrolimus dose declined from 0.059 to 0.051 mg/kg at V1 and V4, respectively (Table 3). Mean (SD) number of dose adjustments per patient was seven (43). This included one patient with 533 dose adjustments whose regimen included two different doses on alternating days, and one patient with 58 dose adjustments; all other patients had 15 or fewer dose adjustments. Overall, a mean (SD) of 8.6 (5.8) tacrolimus trough levels were determined per patient. Mean tacrolimus levels remained similar throughout the observation period (5.3-5.6 ng/mL) (Table 3).

3.3 | Composite primary variable

Nonadherence, as assessed by the composite primary variable, was reported in 88 of 130 patients (67.7% [95% CI, 58.9%, 75.6%]). Nonadherence remained similar with each of the sensitivity analyses: (i) all patients who attended V4 (n = 132), 66.7% (95% CI, 57.9%, 74.6%); (ii) all patients with valid data (n = 141), 70.2% (61.9%, 77.6%); and (iii) all patients (n = 153), 64.7% (56.6%, 72.3%). In particular, nonadherence rates from the most conservative analysis (approach 2) were similar to those from the primary analysis, confirming the robustness of the results.

At V4, 57 of 127 (44.9%) patients were nonadherent for at least one aspect of the BAASIS questionnaire (Table 4), compared with 73 of 153 (47.7%) at V1.

For patients with valid data at V4, investigators rated adherence in two patients (1.5%) as "poor," and in 113 (85.6%) and 17 (12.9%) as "good" and "moderate," respectively; the remaining 21 patients could not be assessed at V4. At V1, ratings were "good" for 129 (84.3%) and "moderate" for 24 (15.7%) patients.

The bottom of the targeted tacrolimus trough range was 1-6 ng/mL across all patients, with the proportional distribution: <3 ng/mL, 3.6% of patients; 3 ng/mL, 20.8%; 4 ng/mL, 57.7%; 5 ng/mL, 16.1%; and 6 ng/mL, 1.2%. The top of the targeted tacrolimus trough range was 3-15 ng/mL across all patients: <5 ng/mL, 2.4%; 5 ng/mL, 10.1%; 6 ng/mL, 37.5%; 7 ng/mL, 20.2%; 8 ng/mL, 19.0%; and >8 ng/mL, 10.7%. Nonadherence was assumed if tacrolimus concentrations were either below the lower end of the targeted range or >15 ng/mL. Based on these criteria, 75 patients (49.0%) were nonadherent. Of these, 71 (46.4%) had at least one tacrolimus trough level below their predefined minimum concentration. Tacrolimus concentrations >15 ng/mL were observed in 11 (7.2%) transplant recipients.
The proportion of nonadherent patients was numerically higher in female vs male patients (75.5% vs 67.4%), patients aged <50 vs ≥50 years (80.3% vs 62.5%), recipients of living vs deceased donor organs (78.9% vs 67.3%), and patients with vs without prior rejection episodes (79.5% vs 66.3%) (Table 5). However, due to the small sample size in some subgroups, data should be interpreted with caution.

### 3.4 | Secondary adherence variables

Overall self-reported adherence using BAASIS was 52.3% and 55.1% at V1 and V4, respectively. For individual BAASIS items at V1 and V4, adherence was lowest for scheduled time (±2 hours) of medication intake (58.2% and 58.3%, respectively) vs ≥86% for all other items (Figure 1). There was no change in mean BAASIS sum score between V1 and V4. Additionally, using the BAASIS VAS, mean (SD) adherence was similar at V1 and V4 (96.1% [6.3] and 96.7% [7.0], respectively). Recordings from ProMate were not analyzed, as only three (2.0%) patients opted to use this device.

Adherence was rated as "good" for 84%-92% of patients across visits, and poor for 0%-3%, with only marginal differences between investigator and nurse assessments. At V4, all patients stated that they were either "very satisfied" or "satisfied" with the once-daily dosing regimen and most (94.7% of patients with valid data) considered the prolonged-release tacrolimus regimen to be more convenient and to facilitate greater adherence than twice-daily tacrolimus administration (Table 6).

### TABLE 2  Patient baseline characteristics

#### Demographic data

| Demographic data                                      |   |
|-------------------------------------------------------|---|
| Patients, n (%)                                       | 153 (100) |
| Sex, n (%)                                            |   |
| Male                                                  | 96 (62.7) |
| Female                                                | 57 (37.3) |
| Mean age, y (SD)                                      | 51.1 (12.3) |
| Range (y)                                             | 21-75  |
| Race, n (%)                                           |   |
| Caucasian                                             | 142 (92.8) |
| Asian                                                 | 3 (2.0) |
| Not specified                                         | 8 (5.2) |
| Primary reason for transplant, n (%)                  |   |
| Glomerulonephritis                                    | 37 (24.2) |
| Polycystic disease                                    | 18 (11.8) |
| Diabetic nephropathy                                  | 17 (11.1) |
| Chronic pyelonephritis                                | 16 (10.5) |
| Nephrosclerosis                                        | 9 (5.9) |
| Systemic vasculitis                                   | 6 (3.9) |
| Other                                                 | 38 (24.6) |
| Not specified                                         | 13 (8.5) |
| Dialysis prior to transplant, n (%)                   | 142 (92.8) |
| Mean time between dialysis start and last transplant, y (SD) | 4.4 (3.0) |
| Panel reactive antibodies, n (%)                      | 7 (4.6%) |

#### Number of transplants, n (%)

| Number of transplants, n (%)                          |   |
|-------------------------------------------------------|---|
| First graft                                           | 135 (88.2) |
| Second graft                                          | 15 (9.8) |
| Third graft                                           | 3 (2.0) |
| Mean time since last renal transplant, y (SD)         | 5.8 (4.6) |
| Range (y)                                             | 0.1-24.7 |

#### Rejection since last transplant, n (%)

| Rejection since last transplant, n (%)                |   |
|-------------------------------------------------------|---|
| None                                                  | 108 (71.1) |
| Acute rejection episode                               | 44 (28.8) |
| Chronic rejection                                     | 0 (0.0) |

#### Organ donation type, n (%)

| Organ donation type, n (%)                           |   |
|-------------------------------------------------------|---|
| Deceased donor                                        | 111 (72.5) |
| Living donor                                          | 40 (26.1) |
| Not specified                                         | 2 (1.3) |

#### Mean cold ischemia time, h (SD)

| Mean cold ischemia time, h (SD)                       |   |
|-------------------------------------------------------|---|
| Deceased donor                                        | 12.8 (5.9) |
| Living donor                                          | 2.1 (1.2) |

#### Mean creatinine clearance (Cockcroft-Gault estimate), mL/min (SD)

| Mean creatinine clearance (Cockcroft-Gault estimate), mL/min (SD) |   |
|-------------------------------------------------------------------|---|
| Recipients of deceased donor grafts                              | 60.0 (24) |
| Recipients of living donor grafts                                | 69.1 (17.7) |

#### Prolonged-release tacrolimus, n (%)

| Prolonged-release tacrolimus, n (%)                          |   |
|---------------------------------------------------------------|---|
| First-line prophylaxis                                        | 33 (21.6) |
| Converted from:                                               | 120 (78.4) |

(Continues)
3.5 | Clinical outcome measures

In two (1.3%) patients, one late acute rejection episode was reported, one of which was classed as calcineurin inhibitor-related nephropathy according to the biopsy result; both patients were considered nonadherent for the composite variable. Graft loss due to fibrosis 10 years post-transplant was recorded for one (0.7%) patient.

Renal function remained stable throughout the 18-month observation period. Mean creatinine clearance, estimated by Cockcroft-Gault, was 62.1 mL/min at V1 (n = 153) and 65.3 mL/min at V4 (n = 127). At V1, creatinine clearance was numerically higher in patients who had received a kidney from a living vs deceased donor and remained numerically higher throughout subsequent visits (V1: 69.1 mL/min vs 60.0 mL/min, respectively) (Figure 2). During the study, 10 (6.5%) patients required dialysis due to acute kidney injury; eight patients had one dialysis episode, one patient had two episodes, and one patient had three episodes. By end of the study, eight of the 10 patients had stopped dialysis.

Clinically-relevant abnormal urinary protein levels were reported for six (3.9%), eight (5.2%), three (2.0%), and three (2.0%) patients at V1-4, respectively. Clinically-relevant abnormal urinary albumin levels were reported for one (0.7%), four (2.6%), three (2.0%), and two (1.3%) patients, at V1-4, respectively.

Mean (SD) hemoglobin levels remained similar during the observation period (8.2 [1.0] mmol/L vs 8.3 [1.0] mmol/L at V1 and V4, respectively).

Investigators assessed the overall effectiveness of prolonged-release tacrolimus as "very good" or "good" in 91.5% of patients.

3.6 | Safety

No death was reported during the observation period. Overall, 15 ADRs were observed in 13 (8.5%) patients, primarily classified as "Infections and Infestations," which included clinical diagnoses of bronchitis (n = 1), endocarditis (n = 1), urinary tract infection (n = 3), and urosepsis (n = 2). Other ADRs (preferred terms) were basal cell carcinoma (n = 2), penile cancer (n = 1), hyperglycemia (n = 1), tremor (n = 2), alopecia (n = 1), and decrease in drug level (n = 1). The causal relationship was considered "probable" for six (40%) and "possible" for nine (60%) of these events. Overall, 11 of these ADRs were considered to be serious, requiring hospitalization. Nonserious ADRs comprised urinary tract infection (n = 1), tremor (n = 1), bronchitis (n = 1), and alopecia (n = 1). At V4, 10 ADRs were rated as recovered without sequelae, three as recovered with sequelae, one as recovering, and for one ADR, outcome was not specified.

Vital signs remained stable during the study. Mean (SD) systolic blood pressure was 130.3 (15.8) mm Hg (n = 150) at V1 and 130.2 (14.3) mm Hg (n = 130) at V4. Mean diastolic blood pressure was 79.6 (10.9) mm Hg (n = 149) and 79.5 (11.0) mm Hg (n = 130), and mean heart rate was 72.6 (11.6) beats/min (n = 148) and 72.7 (10.8) beats/min (n = 123), at V1 and V4, respectively.

Based on the FAS, physicians rated overall tolerability of prolonged-release tacrolimus as "very good" or "good" for 142 (92.8%) and "moderate" for two (1.3%) patients. For nine (5.9%) patients, no assessment was made.

### Table 3

Prolonged-release tacrolimus dose and trough levels

| Element | Visit | V1 | V2 | V3 | V4 |
|---------|-------|----|----|----|----|
| Total daily dose (mg/d) | | | | | |
| Mean (SD) | 4.4 (2.6) | 4.2 (2.3) | 4.0 (2.1) | 3.9 (2.0) |
| Range | 0.5-18.0 | 0.5-15.0 | 0.5-11.0 | 1.0-1.0 |
| Patients, n (%) | 153 (100) | 142 (92.8) | 133 (86.9) | 132 (86.3) |
| Dose adjusted to body weight (mg/kg/d) | | | | |
| Mean (SD) | 0.059 (0.034) | 0.056 (0.031) | 0.053 (0.029) | 0.051 (0.026) |
| Range | 0.005-0.220 | 0.005-0.160 | 0.005-0.170 | 0.010-0.130 |
| Patients, n (%) | 152 (99.3) | 141 (92.2) | 131 (85.6) | 127 (83.0) |
| Tacrolimus trough levels (ng/mL) | | | | |
| Mean (SD) | 5.6 (1.6) | 5.3 (1.8) | 5.3 (1.5) | 5.4 (1.7) |
| Range | 2.1-9.9 | 2.2-16.7 | 2.0-9.8 | 2.0-12.4 |
| Patients, n (%) | 153 (100) | 141 (92.2) | 127 (83.0) | 126 (82.4) |

SD, standard deviation; V, visit.

### Table 4

Assessment of primary composite variable

| Element | Number of patients (%) |
|---------|------------------------|
| Self-reported nonadherence to at least one item of the BAASIS questionnaire at V4 | 57/127a (44.9) |
| Investigator rating of adherence as "poor" at V4 | 2/132b (1.5) |
| Tacrolimus level outside predefined range at least once during study | 75/153 (49.0) |

BAASIS, Basel Assessment of Adherence with Immunosuppressive Medication Scale; V, visit.

aData missing for 21 patients, data not valid for 5 patients.

aData missing for 21 patients.
Nonadherence as assessed by a stringent composite endpoint in this long-term German observational study appeared high. Tacrolimus concentrations below the defined lower target levels and BAASIS self-reported nonadherence to timely medication intake (±2 hours from scheduled time) were the primary reasons for the observed outcome. There was little evidence for drug holidays. The overall rate of adherence to the “taking” domain of BAASIS at Visit 4 was high (91.3%) and was consistent with the finding for the prolonged-release tacrolimus dosing group (88.2%) from Kuyers et al.\textsuperscript{12} The latter study had enrolled 219 renal transplant recipients (2:1 randomization...
prolonged- vs immediate-release tacrolimus) and demonstrated significantly improved adherence ($P = .0009$) to the once-daily dosing regimen. There was also evidence that the evening dose was missed more often than the morning dose, with a mean percentage of missed doses of 14.2% and 11.7%, respectively ($P = .0035$). Most patients enrolled into our study preferred the convenience of a once-daily dosing regimen (morning dose).

The impact of conversion from a twice-daily to a once-daily tacrolimus regimen on nonadherence was demonstrated in a study including 125 stable liver transplant recipients. Nonadherence as assessed by BAASIS declined from 66.4% (immediate-release tacrolimus) at study entry to 30.9% (prolonged-release tacrolimus) at 1 year postconversion ($P < .0001$). The mean BAASIS sum score in this study was low and indicative of an acceptable overall adherence to the prescribed dosing regimen. However, most patients who had prior rejection episodes were assessed to be nonadherent (primary variable) during the observation period.

In this study, the nonadherence rate for the composite endpoint was primarily driven by timing (not taking) nonadherence using the BAASIS and tacrolimus trough levels outside a predefined range. The tacrolimus trough level data should be interpreted with caution. While intrapatient variability in tacrolimus trough levels has been associated with kidney transplant failure, whether a single tacrolimus trough level outside the predefined range can adversely affect clinical outcomes is unclear. Regarding the BAASIS, higher timing vs taking nonadherence has been reported previously. In line with Kuypers et al, taking nonadherence and nonadherence with administering the correct dosing were low in our study, low nonadherence in these BAASIS parameters may have driven the positive clinical outcomes observed.

| TABLE 6 | Assessment of patient satisfaction with prolonged-release tacrolimus |
|-------------------------------|----------------------|----------------------|----------------------|
| **Response**                                   | **Full analysis set, n (%)** | **Patients receiving first-line prolonged-release tacrolimus, n (%)** | **Patients converted to prolonged-release tacrolimus, n (%)** |
| How satisfied are you with the once-daily tacrolimus dosing? |  |  |
| Very satisfied                          | 86 (56.2)                | 21 (63.6)             | 65 (54.2) |
| Satisfied                               | 44 (28.8)                | 8 (24.2)              | 36 (30.0) |
| Not satisfied                           | 0 (0.0)                  | 0 (0.0)               | 0 (0.0)   |
| Not specified                           | 23 (15.0)                | 4 (12.1)              | 19 (15.8) |
| Do you think it is easier to remember when to take your tacrolimus capsule if you take it once daily? |  |  |
| Yes                                      | 120 (78.4)               | 25 (75.8)             | 95 (79.2) |
| No                                       | 11 (7.2)                 | 4 (12.1)              | 7 (5.8)   |
| Not specified                           | 22 (14.4)                | 4 (12.1)              | 18 (15.0) |
| Do you think that the once-daily administration of tacrolimus is more convenient than the twice-daily administration? |  |  |
| Yes                                      | 124 (81.0)               | 25 (75.8)             | 99 (82.5) |
| No                                       | 7 (4.6)                  | 4 (12.1)              | 3 (2.5)   |
| Not specified                           | 22 (14.4)                | 4 (12.1)              | 18 (15.0) |

**FIGURE 2** Mean creatinine clearance over time. SD, standard deviation; V, visit.
Patient and graft survival during the 18-month follow-up were 100% and 99.3%, respectively, and the incidence of acute rejection episodes was low (1.3%). This is in line with data reported by Guirado et al in the R-EVOLUTION study, which included a large cohort of renal transplant recipients (n = 1832) who were converted from an immediate- to a prolonged-release tacrolimus-based regimen a mean of 4.9 years post-transplant. Overall, 1496 patients completed the 3-year follow-up: 3-year patient and graft survival rates were high (95.1% and 93.9%, respectively), and rejection rates were low (0.6%, 1.1%, and 0.4% at years 1-3, respectively).17

Ten patients received dialysis during the 18-month study period; however, by the end of the study, eight of those 10 patients no longer required dialysis. Renal function as assessed by creatinine clearance (Cockcroft-Gault estimate) remained stable over the 18-month observation period (V1, mean: 62.1 mL/min; V4, mean: 65.3 mL/min). This is consistent with the stable mean (SD) estimated glomerular filtration rate reported following conversion from immediate- to prolonged-release tacrolimus in R-EVOLUTION (56.7 [19.8] vs 58.1 [24.6] mL/min/1.73 m² at baseline vs Month 36, respectively; P = .623).17

Clinical routine practice confirmed the safety and effectiveness of the prolonged-release tacrolimus regimen. This was also reflected in the investigator ratings of these parameters. Tacrolimus levels were generally maintained at the lower end of the therapeutic range and reflected those of recent controlled clinical trials.21,18

Limitations of the study include the lack of a control group and the small sample size in the subgroups. Some data were also missing, which is typical of noninterventional studies. Overall adherence was already high at baseline. Additionally, a single tacrolimus trough level measurement outside the target range may be considered a too stringent criterion for defining nonadherence, considering the likelihood of variations in assay sensitivity and timing of blood sampling. This strict criterion may have contributed to the high rate of patients (around 50%) with a tacrolimus level outside their predefined range and who were therefore considered nonadherent. The definition for the composite endpoint in our study may also have been too stringent. The use of a standardized adherence assessment tool with demonstrated validity, such as the Morisky Medication Adherence Scale, could have improved the strength of adherence measurements.

Although bias in self-reported adherence cannot be excluded in the studied population, the low incidence of rejection episodes and stable renal function over the 18-month follow-up period suggests adequate immunosuppression, supported by an overall high level of adherence. Nurse and investigator adherence estimates largely supported the overall BAASIS findings. Whether nonadherence to timely prolonged-release tacrolimus medication intake impacts the occurrence of rejection episodes and/or deterioration of graft function may require longer-term follow-up. As tacrolimus is a substance with a long half-life, it could be speculated that a single case of aberrance in timing should have a negligible effect. A multivariate analysis may provide further insight into this complex matter. It should also be noted that the patients in this study were low immunologic risk, and the impact of nonadherence might have been more pronounced in a higher-risk population. However, as this was a noninterventional study, the study drug was not provided by the sponsor, but was covered through health insurance, as is usual for post-transplant maintenance care in Germany. Therefore, we anticipate that the findings could be generalized to other kidney transplant populations in long-term routine care in many European countries, in which the cost of medication is covered by statutory comprehensive health insurance policies.

To further improve adherence, adequate self-management of renal transplant patients needs to be ensured. Our findings demonstrate that adherence with taking the prolonged-release tacrolimus formulation was satisfactory in our renal transplant recipients, and the once-daily formulation was associated with good clinical outcomes. However, in patients receiving long-term maintenance immunosuppression, adherence was low according to a strict interpretation of the BAASIS questionnaire (44.9%) and a rigid interpretation of drug levels, while adherence seemed high if measured by investigator assessment. The lack of a control group, however, is a major limitation of our study, and clinical outcome might have been as good or better with a twice-daily vs a once-daily formulation of tacrolimus. Although it has been shown in other studies that enhanced adherence can lead to improved clinical outcomes,21,22 we can only hypothesize from our findings that the use of a once-daily tacrolimus preparation may assist transplanted patients to achieve better adherence, which could eventually lead to better clinical outcomes. The results from our thorough observational study may provide a good basis for future interventional trials addressing this important topic.

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CONFLICT OF INTEREST

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AUTHORS’ CONTRIBUTIONS

LJ Lehner: Collected, analyzed, and interpreted data for the work, drafted the manuscript and critically revised it for important intellectual content, and provided final approval for the version to be published; P Reinke: Collected data for the work, critically revised the manuscript for important intellectual content, and provided final approval for the version to be published. LJ Lehner and P Reinke: Contributed equally to the study. J Hörstrup: Contributed to the conception and design of the study, collected data for the work, critically revised the manuscript for important intellectual content, and provided final approval for the version to be published. LJ Lehner and P Reinke: Contributed equally to the study. J Hörstrup: Contributed to the conception and design of the study, collected data for the work, critically revised the manuscript for important intellectual content, and provided final approval for the version to be published. T Rath: Collected data for the work, drafted and critically revised the manuscript for important intellectual content, and provided final approval for the version to be published. B Suwelack: Collected data for the work, analyzed and interpreted data for the work, critically revised the manuscript for important intellectual content, and provided final approval for the version to be published. BK Krämer: Contributed to the conception and design of the study, collected, analyzed, and interpreted data for the work, drafted the manuscript and critically revised it for important intellectual content, and provided final approval for the version to be published. K Budd: Collected, analyzed, and interpreted data for the work, drafted the manuscript and critically revised it for important intellectual content, and provided final approval for the version to be published. B Banas: Contributed to the conception and design of the study, collected, analyzed, and interpreted data for the work, drafted the manuscript and critically revised it for important intellectual content, and provided final approval for the version to be published as the Lead Scientific Physician for the study.

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