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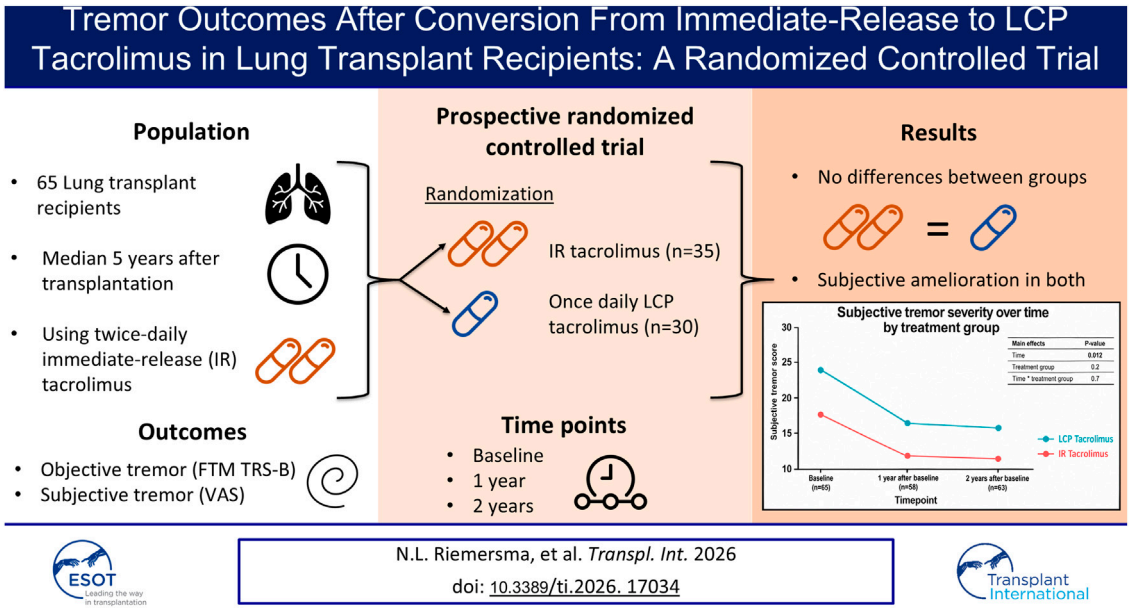
# Tremor outcomes after conversion from immediate-release to LCP tacrolimus in lung transplant recipients: a randomized controlled trial

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Tremor is an important, dose-dependent side effect of tacrolimus in lung transplant (LTx) recipients. We assessed whether once-daily extended-release Life Cycle Pharma (LCP) tacrolimus with lower peak concentrations results in less tremor compared with twice-daily immediate-release (IR) tacrolimus. The prospective, randomized, controlled REVOLUTION trial (NCT05001074) randomized LTx recipients to either continue IR-tacrolimus or to switch to LCP-tacrolimus. Tremor was assessed with linear mixed models, objectively with the Fahn-Tolosa-Marin Tremor Rating Scale part B and subjectively with a Visual Analog Scale, at baseline and after 1 and 2 years. We included 65 LTx recipients (56.9% men; median age: 61.8 [45.0–66.6] years), with a median of 4.9 [2.1–8.1] years having passed since their transplantation. Baseline tremor severity did not differ significantly between groups (objective tremor: IR: 5.5 [3.5–8.0] vs. LCP: 6.8 [5.5–8.3]; p = 0.3 and subjective tremor: IR: 10.0 [5.0–30.0] vs. LCP: 20.0 [10.0–30.0], p = 0.1). Tremor severity remained similar between groups over time after adjusting for age, time since transplantation, tacrolimus trough levels, and kidney function. Higher age and higher tacrolimus trough levels were associated with greater objective tremor severity (β = 0.22, p = 0.001 and β = 0.21, p = 0.036, respectively). This is, to our knowledge, the first randomized clinical trial in lung transplant recipients to evaluate the effect of conversion from IR to LCP tacrolimus on tremor severity showing no effect.
**Clinical Trial Registration:** ClinicalTrials.gov, identifier NCT05001074.

KEYWORDS
**life cycle pharma tacrolimus, lung transplantation (LTx), randomized controlled trial, tacrolimus, tremor**




GRAPHICAL ABSTRACT

## Introduction

Improving survival rates and expanding transplant programs have increased the number of lung transplant (LTx) recipients worldwide [1]. Health-related quality of life (HRQoL) may improve after lung transplantation, but generally remains lower compared to that of healthy individuals [2, 3]. One suggested cause is the need to adhere to a strict immunosuppressive treatment regimen, generally consisting of tacrolimus [4], with coinciding side effects [5].

Tremor is one of the most commonly reported side effects of tacrolimus and can significantly impair HRQoL by impairing daily activities such as eating, writing, or brushing one's teeth [6]. The exact mechanisms behind tacrolimus-induced tremor remain unclear, but the tremor characteristics are most consistent with the enhanced physiological tremor type [7, 8], which is typically a high-frequency, low-amplitude tremor of the upper limbs [9]. Previous studies have shown positive associations between tacrolimus trough levels and tremor severity [6, 8], which is particularly relevant in LTx recipients due to their relatively high target trough levels. Given this relationship, alternative tacrolimus formulations are being explored to reduce peak drug level-related neurotoxicity.

Once-daily Life Cycle Pharma (LCP) tacrolimus offers higher bioavailability, more stable exposure, and lower peak concentrations [10, 11], thereby potentially reducing neurotoxicity. Previous studies in stable kidney transplant recipients with tremor have shown reductions in tremor severity and improvements in HRQoL following conversion from twice-daily immediate-release (IR) to LCP tacrolimus [12, 13]. However, in LTx patients, this has not yet been investigated.

Therefore, this prospective, randomized, controlled trial aimed to assess whether conversion from IR to LCP tacrolimus reduces objective and subjective tremor severity in stable LTx recipients.

## Patients and methods

### Design and study population

This study was performed in accordance with the 2025 CONSORT (CONsolidated Standards Of Reporting Trials) statement [14]. The current study is ancillary to the REVOLUTION trial (ClinicalTrials.gov Identifier: NCT05001074; registered 1 July 2021) [15], and utilizes data from the conversion cohort. By dedicating a separate manuscript to the tremor results, we were able to conduct an in-depth longitudinal analysis of both objective and subjective tremor severity and its determinants. The REVOLUTION trial is an investigator-initiated, randomized, parallel-group, open-label, phase 3 clinical study, designed to compare the adverse effects of IR tacrolimus versus LCP tacrolimus in stable LTx recipients ≥1 year after transplantation. Additional inclusion criteria were an estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 $m^2$ and use of twice-daily immediate-release tacrolimus with stable target trough levels. All patients provided written informed consent between July 2020 and July 2021 at the University Medical Center Groningen (UMCG), the Netherlands. Exclusion criteria were the use of mammalian target of rapamycin (mTOR) inhibitors, quadruple immunosuppression, having received a kidney transplant, and having a disease/condition that could affect completion of the study. The study

**Abbreviations:** eGFR, estimated glomerular filtration rate; FTM TRS-B, Fahn-Tolosa-Marin Tremor Rating Scale part B; HRQoL, Health-related quality of life; IR, Immediate-release; ITT, intention-to-treat; LCP, Life Cycle Pharma; LTx, Lung transplantation.

was approved by the Institutional Review Board (METc 20.222; protocol number: 202000134), and adhered to the Declaration of Helsinki and the Declaration of Istanbul.

Eligible participants were randomly assigned (by HG or WNS) in a 1:1 ratio with ALEA clinical® online randomization software, after the baseline visit to either continue taking immediate-release tacrolimus or switch to LCP tacrolimus. Follow-up visits with tremor assessments took place 1 and 2 years after the baseline visit, resulting in a maximum of three longitudinal measurements per patient. Participants continued their standard post-LTx care, which involved routine outpatient visits every 3 months. The current study only included patients with tremor measurements at baseline and with at least one follow-up tremor measurement.

## Immunosuppressive regimen

LTx recipients who were converted to LCP tacrolimus started with a dose of 70% of the total daily dose of IR tacrolimus, taking the higher bioavailability of LCP tacrolimus into account [11]. Tacrolimus trough levels were monitored biweekly until stable target concentrations of 7–10 μg/L were reached. Immunosuppression was generally induced with basiliximab and additionally maintained with tacrolimus, mycophenolate mofetil, and prednisone. Azathioprine was used less often. There were no restrictions on the use of other treatments/medications, and monitoring of tacrolimus trough levels was conducted more frequently in cases of tacrolimus interactions with other drugs (e.g., azole antifungals).

## Tremor

Medical records were searched to assess the presence of a neurological disease (e.g., Parkinson's disease or essential tremor) before transplantation.

### Objective tremor

Tremor was objectively assessed with the Fahn-Tolosa-Marin Tremor Rating Scale part B (TRS-B) [16, 17]. This scale relates to action tremors of the upper extremities, such as handwriting and pouring liquids. The patients performed three types of tasks: (A) handwriting with the dominant hand, (B) drawing Archimede's spirals without crossing the lines (one large spiral and one small spiral; both with the dominant and non-dominant hands), and (C) drawing straight lines between three progressively narrower confines (with the dominant and non-dominant hands). The patients could not rest their arms or hands on the table during tasks B and C. An example of the assignment of a patient with severe tremor is shown in Supplementary Figure S1. Two movement disorder specialists with expertise in tremor disorders (CSJE and AMMS) rated each task (dominant/non-dominant hands separately) on an ordinal scale from 0 to 4, resulting in a maximum score of 7x4 = 28 points. A (non-validated) score of 7 or higher was considered clinically relevant tremor. Each tremor measurement was assigned a random number (by NLR), thereby blinding the raters to the patients and time point. The ratings were performed independently, and an average score was calculated. A previous study demonstrated good consistency between these raters [18]. Assessment of the inter-rater reliability was repeated for this study by calculating the intraclass correlation coefficient of the TRS-B sum scores using a two-way random effects model.

### Subjective tremor

Tremor was subjectively assessed with a Visual Analog Scale (VAS). Patients had to place a vertical mark on a horizontal line, anchored at the left end with 0 ("no tremor"), and at the right end with 100 ("worst imaginable tremor"). Participants were instructed to reflect on their tremor severity in general. The correlation between the subjective VAS and the objective TRS-B was previously shown to be weak [19].

## Additional data collection/covariates and confounders

The study visits took place in the morning and included blood tests, an evaluation of lung function, a medication review, an assessment of adverse effects, and standardized blood pressure measurements. Clinical and transplant-related parameters were obtained from the patient's medical records. Medication usage was subsequently verified and corrected with the patient. Body weight and height were measured with participants wearing indoor clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters (kg/m2). Blood pressure was measured 5 times after a resting period of at least 10 min. Newly diagnosed hypertension was defined as a mean systolic blood pressure >135 mmHg or a mean diastolic blood pressure >85 mmHg. Diabetes was defined based on the use of antidiabetic drugs, fasting glucose levels ≥7.0 mmol/L, and/or HbA1c levels ≥6.5% [20]. The 2021 CKD-EPI eGFR equation, which incorporates creatinine and cystatin C, showed the least deviation from measured GFR in LTx recipients, and was therefore used to assess kidney function [21, 22]. The 2021 CKD-EPI eGFR creatinine formula was used when cystatin C values were not available.

### Laboratory methods

Blood was drawn in the morning after an overnight fasting period of at least 8 h. Tacrolimus whole blood trough concentrations were determined by validated liquid chromatography mass-spectrometry (LC-MS) analyses at the UMCG [23]. Plasma creatinine levels were measured using a modified version of the Jaffé method (Roche Diagnostics, Basel, Switzerland). Other clinical chemistry assays, including the quantification of plasma cystatin C, serum albumin, serum C-reactive protein, serum glucose, and serum hemoglobin, were performed using routine laboratory methods (Roche Diagnostics, Basel, Switzerland).

## Statistical analyses

Patients were divided into two groups based on treatment randomization (IR/LCP tacrolimus). Baseline characteristics are shown as the mean ± standard deviation (SD) for normally distributed variables, the median [interquartile range (IQR)] for skewed variables, or the count (percentage) for categorical variables.

10.3389/ti.2026.17034

TABLE 1 Baseline characteristics of 65 lung transplantation recipients by medication group.

| Variables | Total (n = 65) | IR tacrolimus (n = 35) | LCP tacrolimus (n = 30) | P-value |
|---|---|---|---|---|
| **Recipients** | | | | |
| Male patients, n | 37 (56.9%) | 19 (54.3%) | 18 (60.0%) | 0.6 |
| Age, years | 61.8 [45.0–66.6] | 63.3 [42.1–65.8] | 60.8 [51.8–67.6] | 0.7 |
| Primary lung disease | | | | 0.8 |
| COPD | 26 (40.0%) | 14 (40.0%) | 12 (40.0%) | 0.8 |
| Fibrosis | 14 (21.5%) | 9 (25.7%) | 5 (16.7%) | |
| Pulmonary hypertension | 8 (12.3%) | 3 (8.6%) | 5 (16.7%) | |
| Cystic fibrosis | 8 (12.3%) | 4 (11.4%) | 4 (13.3%) | |
| Non-CF bronchiectasis | 1 (1.5%) | 1 (2.9%) | 4 (13.3%) | |
| Other | 8 (12.3%) | 4 (11.4%) | 4 (13.3%) | |
| Systolic blood pressure, mmHg | 132.6 ± 15.8 | 131.3 ± 16.4 | 134.2 ± 15.2 | 0.5 |
| Diabetes | 21 (32.3%) | 13 (37.1%) | 8 (26.7%) | 0.4 |
| BMI (kg/m$^2$) | 25.7 ± 4.3 | 25.7 ± 4.3 | 25.7 ± 4.4 | 1.0 |
| Time since transplantation, years | 4.9 [2.1–8.1] | 4.6 [2.0–7.7] | 5.0 [2.2–10.0] | 0.5 |
| **Lung function** | | | | |
| $FEV_1$ (L) | 2.7 ± 0.8 | 2.7 ± 0.8 | 2.6 ± 0.8 | 0.6 |
| FVC (L) | 3.7 ± 1.0 | 3.8 ± 1.0 | 3.7 ± 0.9 | 0.5 |
| $FEV_1$/FVC ratio (%) | 72.6 ± 13.0 | 72.7 ± 11.4 | 72.4 ± 14.9 | 0.9 |
| **Laboratory values** | | | | |
| eGFR (mL/min/1.73 m$^2$) | 56.0 ± 21.6 | 58.0 ± 19.5 | 53.6 ± 23.9 | 0.4 |
| Hemoglobin (mmol/L) | 7.7 ± 1.1 | 7.7 ± 1.1 | 7.7 ± 1.0 | 0.9 |
| Albumin (g/L) | 43.4 ± 2.8 | 43.2 ± 2.1 | 43.7 ± 3.4 | 0.5 |
| CRP (mg/L) | 1.1 [0.6–3.6] | 1.1 [0.5–4.0] | 1.2 [0.7–2.6] | 0.9 |
| Fasting glucose (mmol/L) | 5.9 [5.5–7.2] | 5.9 [5.4–7.6] | 6.0 [5.6–6.9] | 0.8 |
| Tacrolimus trough level (μg/L) | 8.0 ± 1.6 | 7.9 ± 1.7 | 8.2 ± 1.5 | 0.4 |
| **Other medication** | | | | |
| Mycophenolic acid | 49 (75.4%) | 26 (74.3%) | 23 (76.7%) | 0.8 |
| Azathioprine | 12 (18.5%) | 9 (25.7%) | 3 (10.0%) | 0.1 |
| Prednisone/prednisolone | 65 (100.0%) | 35 (100.0%) | 30 (100.0%) | - |
| Beta blocker | 16 (24.6%) | 9 (25.7%) | 7 (23.3%) | 0.8 |
| Bronchodilators | 4 (6.2%) | 3 (8.6%) | 1 (3.3%) | 0.4 |

Abbreviations: IR: immediate-release; LCP: life-cycle pharma; COPD: chronic obstructive pulmonary disease; CF: cystic fibrosis; BMI: body mass index; $FEV_1$: forced expiratory volume in 1 second; FVC: forced vital capacity; eGFR: estimated glomerular filtration as calculated with the 2021 CKD-EPI eGFR creatinine-cystatin C equation; CRP: C-reactive protein. Normally distributed variables are presented as mean ± standard deviation, skewed data as median [interquartile range], and categorical data as number (valid percentage). P-value displays statistical significance of the comparison of means between treatment groups, assessed with the T-test, Mann-Whitney U test, or chi-squared based on the data distribution.

The normality of the data was assessed using the Kolmogorov-Smirnov test, histograms, and quantile-quantile plots. The statistical significance of the differences between the groups at baseline was calculated with a Student's t-test, a Mann-Whitney U-test, or a Chi-Square test, based on the data distribution. Variables with >5% missing data are noted in the footnote of Table 1.

The primary analyses were performed on an intention-to-treat (ITT) basis, including all participants as originally assigned, regardless of protocol adherence or treatment received. The course of individual objective and subjective tremor scores was visualized with spaghetti plots. Potential reasons for outliers in the spaghetti plots were investigated using the patients' medical records.

Linear mixed models with a random intercept for patients were used to evaluate changes in tremor severity over time across medication groups. The main effects of the models were visit (baseline, 1 year after transplantation, and 2 years after

transplantation), treatment group (IR/LCP tacrolimus), and their interaction. Significance testing of the main effects was performed using ANOVA with Satterthwaite's method for degrees of freedom. In addition to reporting p-values, we calculated partial eta squared ($\eta^2$) as a measure of effect size, along with 95% confidence intervals, to quantify the magnitude and precision of the observed effects. The models were adjusted one by one for age at baseline, eGFR, time after transplantation at baseline, and tacrolimus trough level, to account for potential confounding factors. Exploratory models with square root transformation of all continuous variables were assessed for improved model fit that may have led to differences in outcomes. Exploratory *post hoc* pairwise comparisons were performed to identify potential differences between groups at each time point. P-values were interpreted descriptively, without adjustment for multiple comparisons, as these analyses were exploratory in nature and not intended for formal hypothesis testing.

Two sensitivity analyses using linear mixed models were performed for objective and subjective tremor: (1) an analysis using square-root-transformed tremor scores in a subpopulation of LTx recipients with an objective tremor score of ≥7 at baseline, and (2) a per-protocol analysis, which included only participants who fully adhered to the assigned intervention, to assess treatment efficacy under ideal conditions.

The model assumptions for the linear mixed models were assessed using the "DHARMa" package in R, which provides simulation-based residual diagnostics. Simulated scaled residuals were evaluated using quantile–quantile (Q–Q) plots. Additionally, residuals were plotted against continuous predictors to evaluate homoscedasticity using Levene's test and to evaluate within-group deviation from uniformity. All data were analyzed using R (Vienna, Austria, version: 2024.09.0). A p-value <0.05 was considered statistically significant in all analyses.

## Sample size estimation

Sample size estimation was performed for the primary outcome of the REVOLUTION trial, which was the difference in eGFR at 24 months. This calculation was based on previous studies of renal function decline because of immunosuppressants in solid organ transplant recipients [24–26]. A sample size of 63 patients was required to detect a 10 mL/min*1.73 $m^2$ difference in eGFR (power = 0.80, α = 0.05). Accounting for an expected 15% dropout rate [27], the aim was to include 75 participants.

# Results

## Baseline characteristics

In total, 75 participants were enrolled in the REVOLUTION trial. For the current study, 10 patients were excluded for missing the baseline visit (n = 6) or having no follow-up visit (n = 4), resulting in a population of 65 LTx recipients (Figure 1). Tremor measurements were available for 65 recipients at baseline, for 58 at 1 year, and for 63 at 2 years after transplantation. An assessment of the patients' medical records from these LTx recipients showed no neurological disease that could cause tremor. After switching to LCP tacrolimus, five patients had to switch back to IR tacrolimus because of difficulty achieving stable target trough levels (n = 2), acne (n = 1), tremor (n = 1), or a combination of tremor, headache, and hypertension (n = 1), resulting in 60 patients who completed the study per protocol.

The 65 LTx recipients (56.9% men; median [IQR] age of 61.8 [45.0–66.6] years) were included at a median of 4.9 [2.1–8.1] years after transplantation. Chronic obstructive pulmonary disease (COPD) was the most common primary lung disease, with a prevalence of 40.0%. At baseline, the mean ± SD $FEV_1$ was 2.7 ± 0.8L, and the mean tacrolimus trough level was 8.0 ± 1.6 μg/L. The use of concomitant medications that may influence tremor, such as beta-blockers or bronchodilators, was comparable between groups. Detailed baseline characteristics for the total population and by treatment group are shown in Table 1. There were no significant differences between the treatment groups at baseline.

## Objective tremor

### Inter-rater reliability

Before analyzing objective tremor severity, we assessed the inter-rater reliability of the TRS-B by calculating the intraclass correlation coefficient (two-way random effects model) between the two raters. The correlation coefficient was 0.895, indicating good agreement between the two raters.

### Objective tremor scores

Median objective tremor scores at baseline were not statistically significantly different between the groups (IR: 5.5 [3.5–8.0] vs. LCP: 6.8 [5.5–8.3], p = 0.3). Objective tremor scores appeared to increase in both groups, as shown in the spaghetti plot (Figure 2). The IR group showed a consistent trend toward higher objective tremor scores, while the LCP group's median score initially decreased at 1 year, followed by an increase that exceeded the baseline score. Three LCP group outliers were identified, of which one had an elevated tacrolimus trough level.

### Linear mixed models

In linear mixed models, estimated mean objective tremor scores did not change significantly over time (p = 0.2; $\eta^2$ = 0.02), and did not differ between treatment groups (p = 0.4; $\eta^2$ = 0.01; Figure 3). There was also no significant interaction between time and group (p = 0.2; $\eta^2$ = 0.03), indicating that the change in objective tremor severity over time was similar between the treatment groups. All effect sizes had wide 95% confidence intervals of 0.00–1.00, indicating that the true magnitude of the effect could not be estimated with precision. The model with square root-transformed objective tremor scores improved the model fit but yielded similar results. These results also remained after adjustment for age at baseline, eGFR, time after transplantation at baseline, or tacrolimus trough levels. Higher age at baseline and higher tacrolimus trough levels were associated with greater objective tremor severity (β = 0.22, p = 0.001 for age; β = 0.21, p = 0.036 for tacrolimus trough levels). Exploratory pairwise comparison analyses showed no significant differences between the groups at any time point (Table 2).

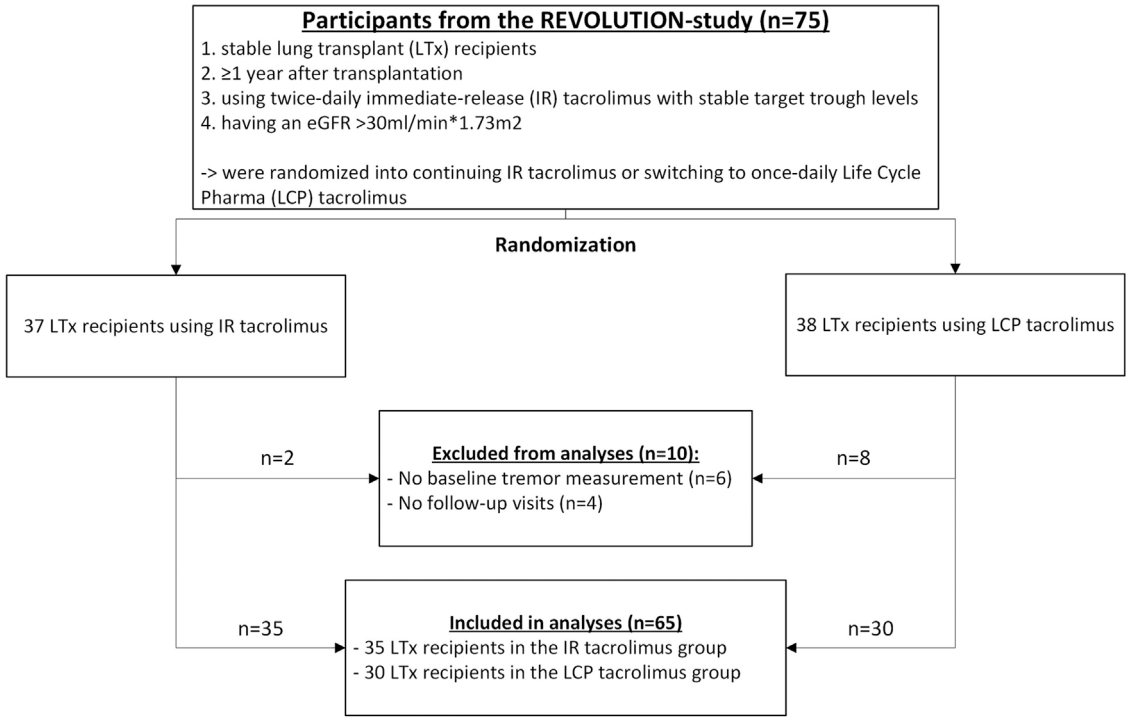



FIGURE 1
Flow diagram of patient inclusions. Abbreviations: LTx, lung transplantation; IR, immediate-release; LCP, Life Cycle Pharma.

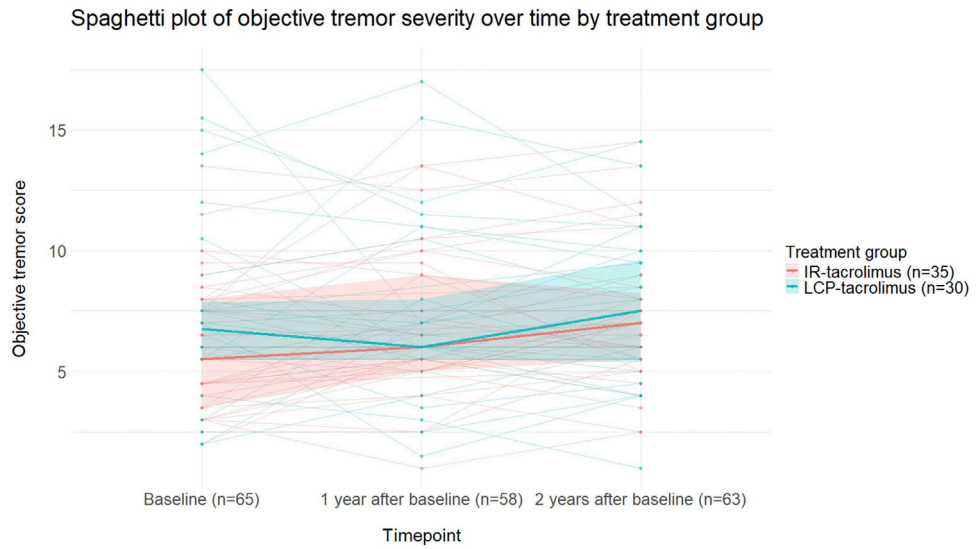



FIGURE 2
Spaghetti plot of objective tremor score over time by treatment group. The solid line represents the median score, while the shaded area indicates the interquartile range (IQR). Abbreviations: IR, immediate-release; LCP, Life Cycle Pharma.

## Sensitivity analysis in patients with tremor at baseline

A clinically relevant tremor was present in 29 (44.6%) LTx recipients, of whom 14 were in the IR group and 15 of whom were in the LCP group. The median [IQR] TRS-B scores in these subpopulations were 9.0 [7.5–11.0] for IR tacrolimus and 8.0 [7.0–11.5] for LCP tacrolimus (Mann-Whitney U test, p = 0.5). In linear mixed models, square root objective tremor scores did not change over time (p = 0.7), did not differ between groups

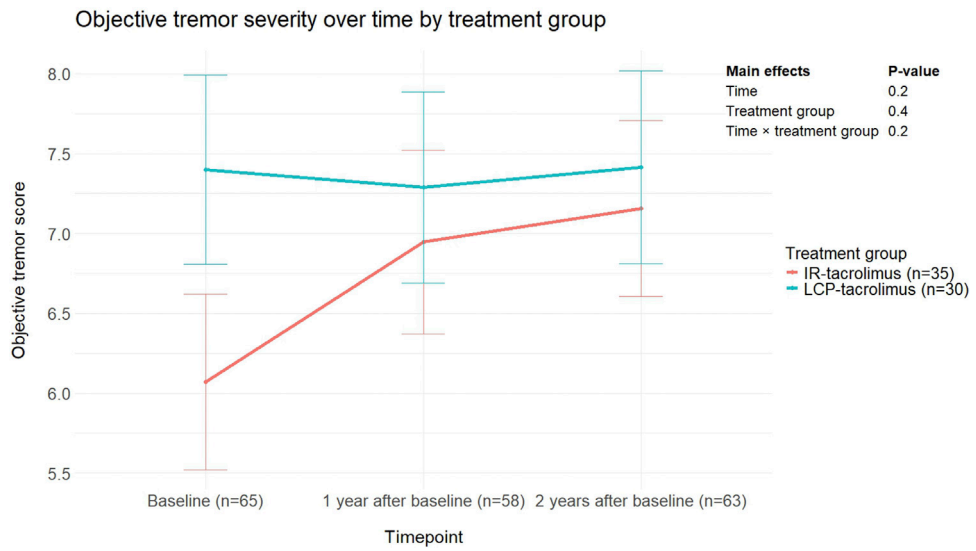



FIGURE 3
Estimated marginal mean objective tremor severity over time by treatment group. Values represent estimated marginal means from the linear mixed model; error bars indicate 95% confidence intervals. P-values for the main effects were obtained using ANOVA with Satterthwaite's method to estimate degrees of freedom. Abbreviations: IR, immediate-release; LCP, Life Cycle Pharma.

TABLE 2 **Exploratory pairwise comparisons of estimated marginal mean objective and subjective tremor scores in 65 lung transplantation recipients who were randomized to either IR tacrolimus or LCP tacrolimus.**

| Timepoint | IR tacrolimus (n = 35) | LCP tacrolimus (n = 30) | P-value |
|---|---|---|---|
| Objective tremor score [EMM (95% CI)] | | | |
| Baseline | 6.1 (5.0–7.2) | 7.4 (6.2–8.6) | 0.1 |
| 1 year after baseline | 7.0 (5.8–8.1) | 7.3 (6.1–8.5) | 0.7 |
| 2 years after baseline | 7.2 (6.1–8.3) | 7.4 (6.2–8.6) | 0.8 |
| Subjective tremor score [EMM (95% CI)] | | | |
| Baseline | 17.1 (11.3–23.0) | 23.8 (17.4–30.1) | 0.1 |
| 1 year after baseline | 13.2 (7.0–19.4) | 16.8 (10.4–23.2) | 0.4 |
| 2 years after baseline | 13.0 (7.0–18.9) | 15.9 (9.5–22.4) | 0.5 |

Abbreviations: IR: immediate-release; LCP: life-cycle pharma; EMM: Estimated Marginal Mean; CI: confidence interval. Objective tremor was measured with the Fahn-Tolosa-Marin Tremor Rating Scale part B; Subjective tremor was assessed with a visual analogue scale. P-value indicates statistical significance of the pairwise comparison between groups at each timepoint.

(p = 0.8), and showed no difference in change between groups over time (p = 0.2, Supplementary Figure S2).

## Per-protocol analysis

In the per-protocol analysis (n = 60), a significant increase in square-root objective tremor scores over time was observed (p = 0.029), in contrast to the intention-to-treat analysis (Supplementary Figure S3). However, this result lost significance after adjusting for eGFR. Adjustment for age at baseline, time since transplantation at baseline, or tacrolimus trough levels did not alter the results. In all analyses, there were no differences between groups (p = 0.3), and the changes over time were not different between the groups (p = 0.6).

# Subjective tremor

## Subjective tremor scores

Median subjective tremor scores at baseline were not significantly different between the groups (IR tacrolimus: 10.0 [5.0–30.0] vs. LCP tacrolimus: 20.0 [10.0–30.0], p = 0.1). The median subjective tremor scores of both groups remained relatively constant throughout the follow-up period, as shown in the spaghetti plot (Figure 4). Some outliers may be partially explained by information from the medical records, such as notes indicating that the patient had poor sleep, a cold, or elevated tacrolimus trough levels.

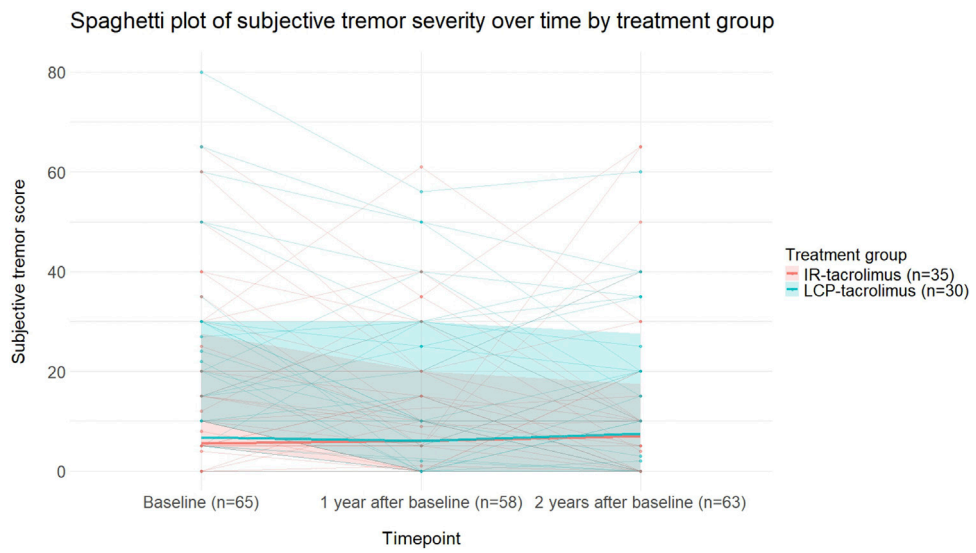



FIGURE 4
Spaghetti plot of subjective tremor score over time by treatment group. The solid line represents the median score, while the shaded area indicates the interquartile range (IQR). Abbreviations: IR, immediate-release; LCP, Life Cycle Pharma.

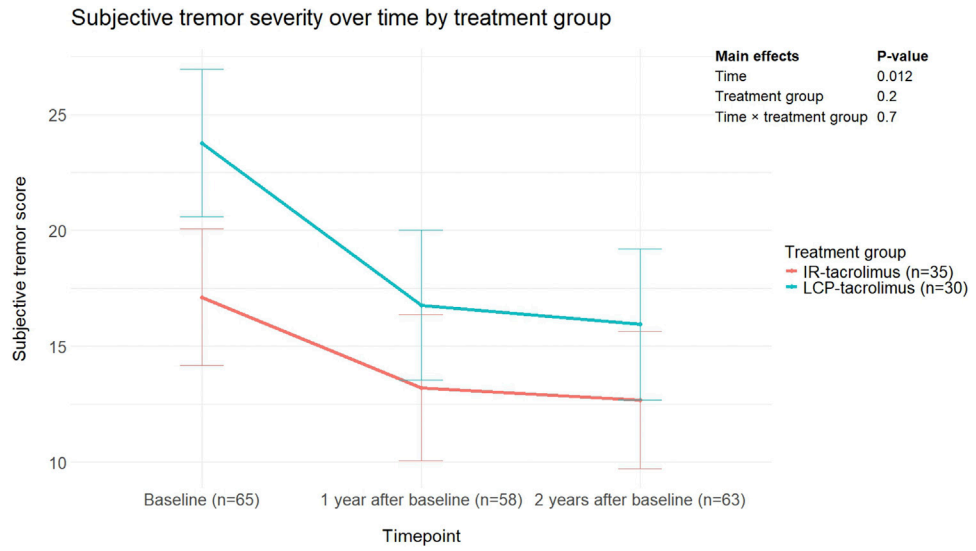



FIGURE 5
Subjective tremor severity over time by treatment group. Values represent estimated marginal means from the linear mixed model; error bars indicate 95% confidence intervals. P-values for the main effects were obtained using ANOVA with Satterthwaite's method to estimate degrees of freedom. Abbreviations: IR, immediate-release; LCP, Life Cycle Pharma.

## Linear mixed models

In linear mixed models, estimated mean subjective tremor scores decreased significantly over time ($p = 0.012$; $\eta^2 = 0.07$; Figure 5). However, there was no difference between the groups ($p = 0.2$; $\eta^2 = 0.02$), and the change over time was similar between the groups ($p = 0.7$; $\eta^2 = 0.02$). All effect sizes had wide 95% confidence intervals (0.01–1.00 for the effect of time; 0.00–1.00 for the effect of group and the interaction between time and group). The model with square root-transformed subjective tremor scores improved model fit but yielded similar results. These results also remained comparable after adjustment for age at baseline, eGFR, time after transplantation at baseline, and tacrolimus trough levels. Furthermore, exploratory pairwise comparison analyses showed no significant differences between the groups at any time point (Table 2).

### Sensitivity analysis in patients with tremor at baseline

In the linear mixed models, square root subjective tremor scores decreased over time in the 29 LTx recipients with objective tremor at baseline ($p = 0.036$), but did not differ between groups ($p = 0.9$), or did not differ in their change over time between groups ($p = 0.2$, Supplementary Figure S4).

### Per-protocol analysis

The results remained similar in the per-protocol analysis with 60 LTx recipients. Square- root-transformed subjective tremor scores decreased significantly over time ($p < 0.001$), but there was no difference between groups ($p = 0.1$), and the change over time did not differ between the groups ($p = 0.4$, Supplementary Figure S5). These results also remained consistent after adjustment for age at baseline, eGFR, time after transplantation at baseline, and tacrolimus trough levels.

## Discussion

To our knowledge, this is the first randomized clinical trial to evaluate the long-term effects of converting from twice-daily IR tacrolimus to once-daily LCP tacrolimus on objective and subjective tremor in LTx recipients. No difference in objective tremor outcomes between treatments was observed after conversion to once-daily LCP tacrolimus. Subjective tremor scores decreased similarly in both groups.

Tremor is a frequent side effect in LTx recipients that may impair daily activities and reduce HRQoL [6, 8]. It is therefore important to identify the immunosuppressive treatment with the least amount of tremor. Tacrolimus is the cornerstone of immunosuppressive therapy, and we hypothesized that lower peak concentrations of LCP tacrolimus would decrease tremor severity. We observed no effect of switching IR to LCP tacrolimus on tremor severity. Our results contrast with previous studies in kidney transplant recipients, which observed reduced tremor severity after switching from IR to LCP tacrolimus [12, 13]. However, these studies were uncontrolled and only included patients who had tremor. Our study population reflects the LTx population, in which not everyone experiences tremor. In sensitivity analyses among patients with objective tremor at baseline, the results remained similar. The median objective tremor scores in this subgroup of LTx recipients with tremor resembled those found in an essential tremor population [18], but were lower than those in a population of patients with Parkinson's Disease [28]. Another key difference from kidney transplant recipients is that LTx recipients require higher tacrolimus target trough concentrations. This results in a higher overall exposure, which may mask the potential benefit of lowering peak concentrations with LCP tacrolimus. Consequently, the potential tremor-reducing effect may be less pronounced in the LTx population. In addition, our population had already been exposed to IR tacrolimus for a median of 5 years, which may have caused damage. Randomizing patients immediately after transplantation to receive either IR or LCP tacrolimus would have allowed for a more valid comparison between treatment strategies. Future studies could also compare extended-release tacrolimus with LCP tacrolimus. Since tacrolimus concentrations are strongly linked to tremor severity, we can hypothesize that these two once-daily preparations may produce similar tremor outcomes to those observed when comparing twice-daily tacrolimus with LCP tacrolimus, as we did in this study.

Higher tacrolimus trough levels and older age at baseline were associated with more severe objective tremor, a finding consistent with those of a previous study in kidney transplant recipients [8]. Interestingly, tacrolimus trough levels were not linked to tremor severity scores in other studies [12, 29]. This is the first study to identify these potential determinants in lung transplant recipients.

We did observe a decrease in subjective tremor in both groups, possibly because of a study participation effect. A previous study in solid organ transplant recipients also found an association between time after transplantation and less patient-reported tremor-related impairment in daily life activities [6]. Objective tremor appeared to increase over time, but this association was no longer evident after adjusting for eGFR. Decreasing kidney function over time may partly mediate or confound the relationship between tremor severity and time. Additionally, a previous study of solid organ transplant recipients reported a negative correlation between objective tremor measured by accelerometry and time since transplantation [8].

Tremor assessments may only represent a snapshot in time. This is partly reflected by the outlying values and patterns observed in the spaghetti plots. Information from patient medical records suggested possible explanations for the majority of outliers, including elevated tacrolimus trough levels and situational factors, such as poor sleep or intercurrent illness. This is further supported by patient feedback, as patients reported that tremor severity can vary from day to day, and perhaps even from hour to hour, with fatigue being one of the most frequently identified causes of variation in tremor severity. We know that enhanced physiological tremor, the predominant tacrolimus-induced tremor type [8], can be influenced by many factors, such as hypoglycemia, vigorous exercise, caffeine, anxiety, or fatigue [30, 31]. It would be interesting for future studies to gain insight into intrapatient daytime tremor variability with accelerometers.

A potential benefit of switching to the once-daily LCP regimen can be an improvement in medication adherence because of regimen simplification [32]. Medication nonadherence is one of the most important and modifiable risk factors for tacrolimus intrapatient variability [33]. Previous studies have shown that high intra-patient tacrolimus variability is associated with shorter graft survival [33, 34]. Thus, simplifying tacrolimus to a once-daily regimen may improve adherence and prolong graft survival. In addition to intrapatient variability, tacrolimus also shows high interpatient variability [33]. This is demonstrated by the five patients in our study who had to switch back to IR tacrolimus because of side effects, while patients who already have tremors on the IR regimen may benefit from switching to the LCP regimen [12, 13]. This highlights the importance of personalized medicine and tailored immunosuppressive treatment regimens for solid organ transplant recipients.

One strength of our study is its randomized controlled design, which reduced (selection) bias and strengthened our ability to assess

the effect of switching from IR to LCP tacrolimus. However, it should be noted that tremor was a secondary outcome within the REVOLUTION trial; therefore, our results should be interpreted as exploratory. The study was powered to detect differences in eGFR rather than tremor outcomes, which may have limited our ability to detect differences in tremor. Future adequately powered noninferiority trials are needed to determine whether once-daily tacrolimus is not clinically worse than twice-daily tacrolimus with respect to tremor. In addition, low objective tremor scores in the total study population may have made it more difficult to detect differences between the treatment groups. On the other hand, the study population reflected the large population of stable LTx recipients. One weakness is the lack of tremor assessment before transplantation. We attempted to address this by reviewing patients' electronic health records for neurological diseases that could cause tremor.

In conclusion, this is the first randomized clinical trial in LTx recipients to assess the impact of conversion from IR to LCP tacrolimus. Our trial demonstrated no significant benefit with respect to objective or subjective tremor severity. Future studies could compare tacrolimus formulations immediately after transplantation, when higher doses of tacrolimus may worsen tremor.

## Data availability statement

The datasets presented in this article are not readily available because public participant data sharing was not included in the REVOLUTION-trial informed consent form. Requests to access the datasets should be directed to the corresponding author.

## Ethics statement

The studies involving humans were approved by the Institutional Review Board (METc 20.222; protocol number: 202000134). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

NR, DK, and JA wrote the draft manuscript. NR, DK, CE, AS, and SJB performed the data analysis. HG, WS, and TI performed the research and contributed to data collection. EV, HK, SPB, SJB, and CG were responsible for the supervision and research design. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

CG reports speaking activities, advisory committees, and consultancies for Chiesi Pharmaceuticals BV.

The remaining author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Generative AI statement

The author(s) declared that generative AI was used in the creation of this manuscript. During the preparation of this work, the author(s) used ChatGPT (OpenAI) to support the writing and editing of this manuscript by helping improve clarity, grammar and phrasing. Following use of this tool, the author(s) reviewed and edited the content as necessary and accept full responsibility for the final manuscript.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2026.17034/full#supplementary-material

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