Melt-Dose:
Redefiniendo el tratamiento con tacrolimus:

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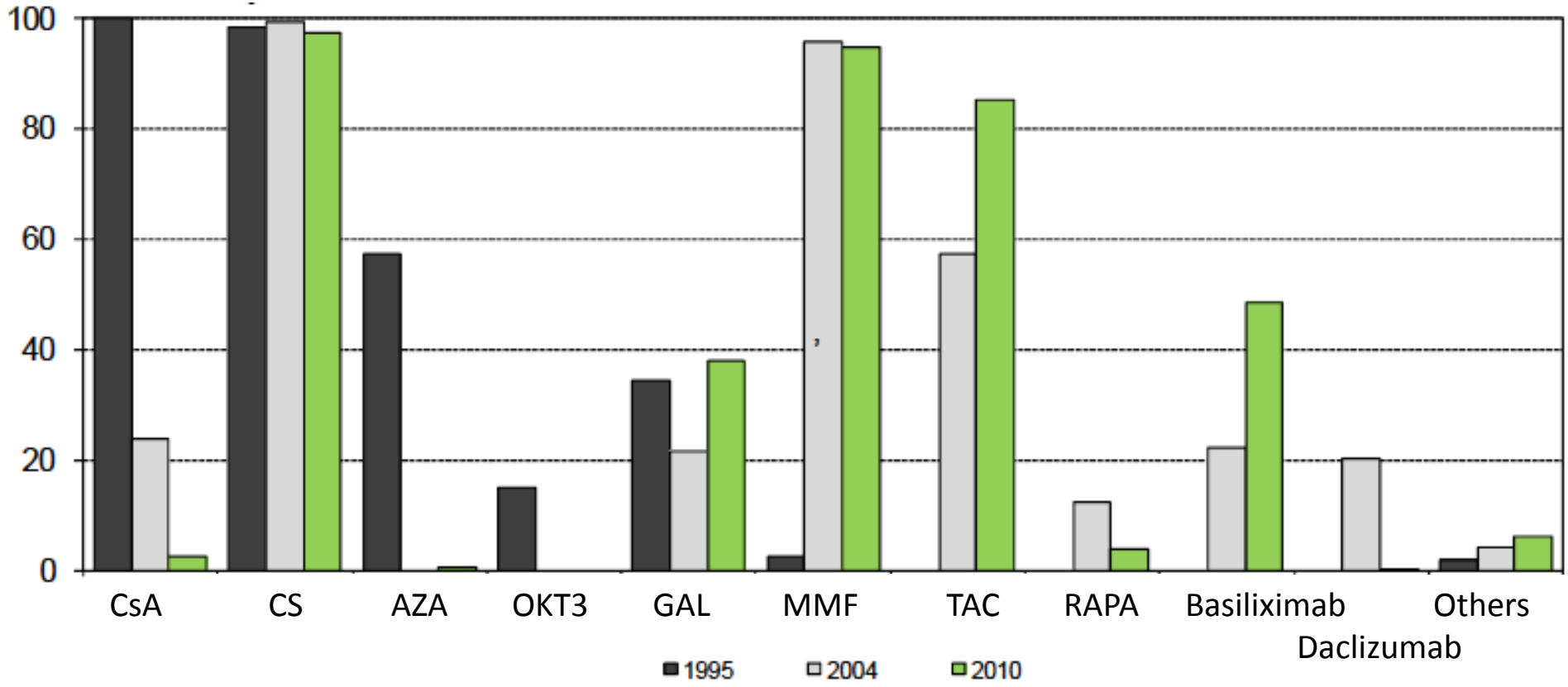
Immunosuppressive drugs used during the first six weeks after transplantation.
Transplants 1995, 2004, and 2010



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation

Henrik Ekberg, M.D., Ph.D., Helio Tedesco-Silva, M.D., Alper Demirbas, M.D., Štefan Vítko, M.D., Björn Nashan, M.D., Ph.D., Alp Gürkan, M.D., F.A.C.S., Raimund Margreiter, M.D., Christian Hugo, M.D., Josep M. Grinyó, M.D., Ulrich Frei, M.D., Yves Vanrenterghem, M.D., Ph.D., Pierre Daloze, M.D., and Philip F. Halloran, M.D., Ph.D., for the ELITE–Symphony Study*

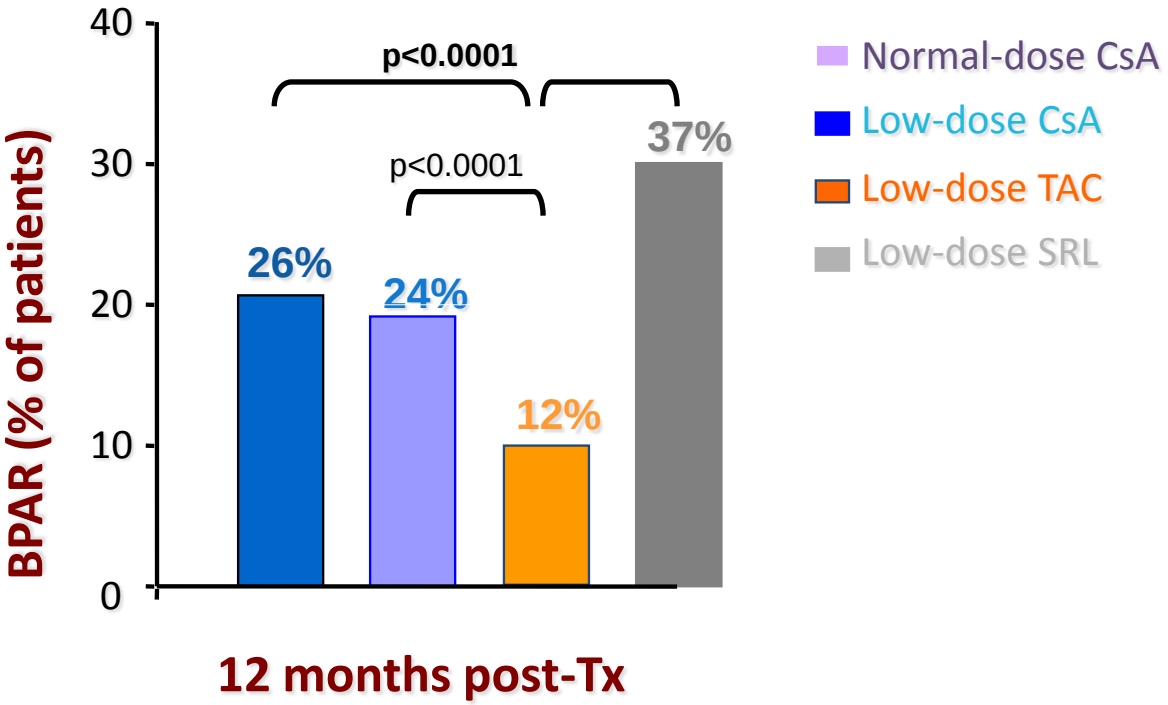
The *Symphony* trial

1. **Std cyclosporine+MMF+CS**
2. **Low dose tacrolimus (0.1 mg/kg/day)+MMF+CS**
3. **Low dose cyclosporine+MMF+CS**
4. **Low dose sirolimus+MMF+CS**

Daclizumab for 2 months after transplantation

Ekberg H et al., NEMJ 2007

Outcomes of the SYMPHONY trial



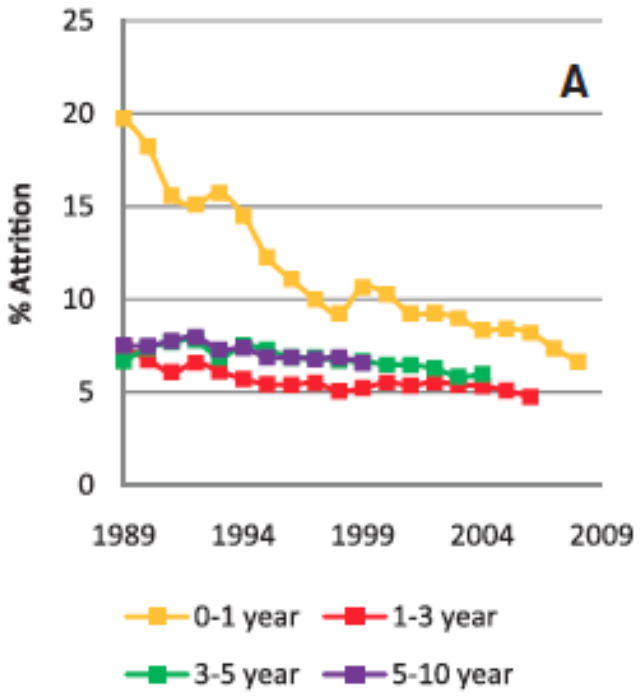
Low dose TAC (3-7 ng/mL) associated with

- Lower BPAR rates
- Higher eGFR function
- Higher graft and patients survival rates

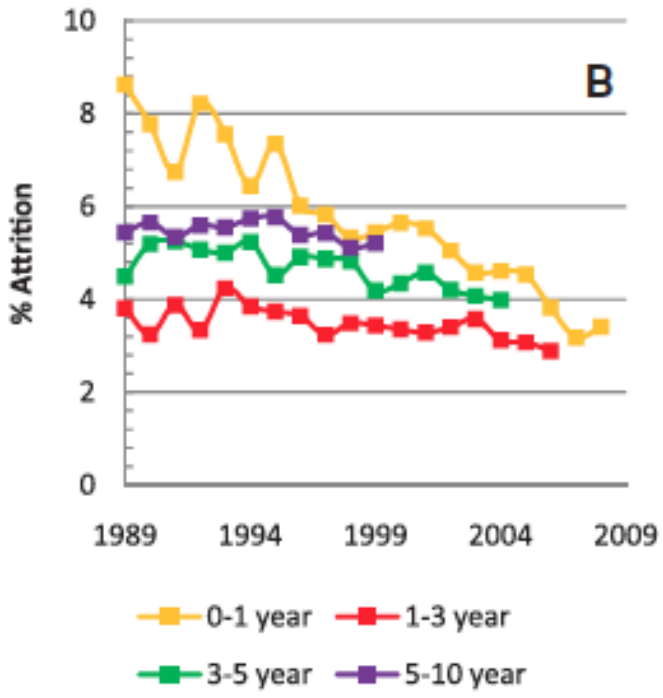
Ekberg H et al., NEMJ 2007

…Yearly long-term kidney graft attrition has not decreased as expected

Deceased SCD donor

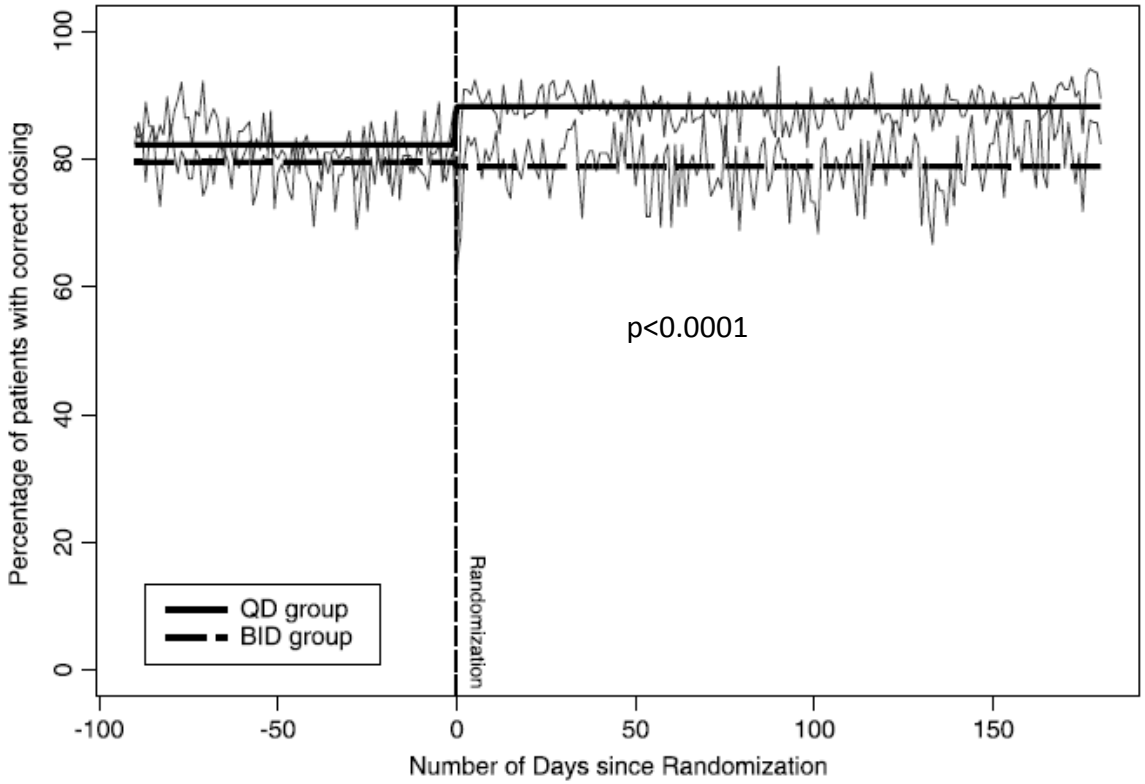


Living donor



Meier-Kriesche H-U et al. Am J Transplant 2011

Why a Prolonged-release formulation of Tacrolimus (TAC QD)?



- Compliance to treatment decreases over time
- Clinical trials show that reduced pill burden improve adherence to treatment

Kuypers D et al., Transplantation 2013

Caveats of currently available Tacrolimus

Narrow therapeutic index → individual dose titration

Efficacy vs dose-related toxicity

- large inter- and intra-individual variability
- low bioavailability
- wide peak-to-trough fluctuations (high peak Cmax after dosing)

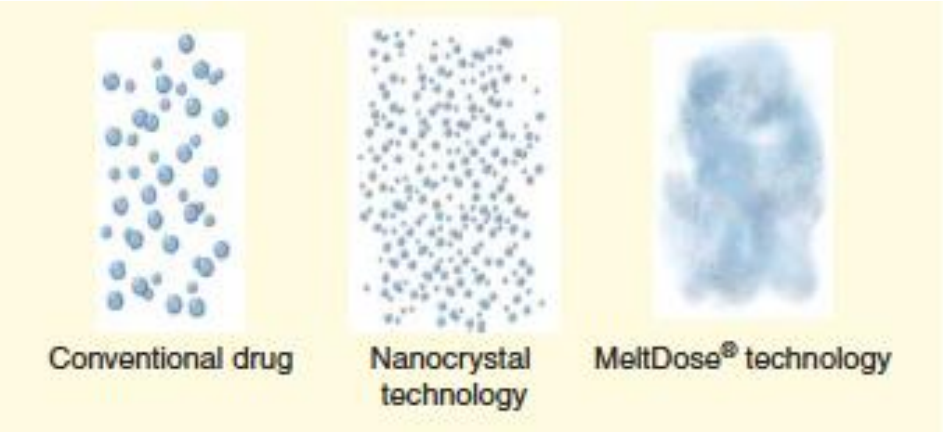
Staatz CE, Tett SE. Clin Pharmacokinet 2004
Provenzani A. World J Gastroenterol 2013
Niioka, et al.. Transplantation
Rath T. Expert Opin Pharmacother 2013

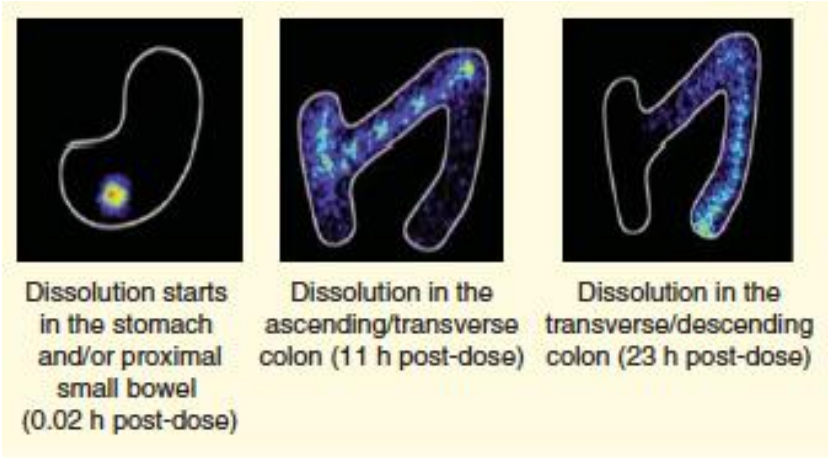
Once daily MeltDose® LCP-Tacro

→ **MeltDose** drug delivery technology designed to improve the bioavailability of drugs with low water solubility

→ Decreases a drug's particle size to a molecular level (Solid solution) → better dissolution and absortion

→ Broader absorption in the GI tract, sustaining consistent TAC concentrations





Nigro V et al ATC 2013

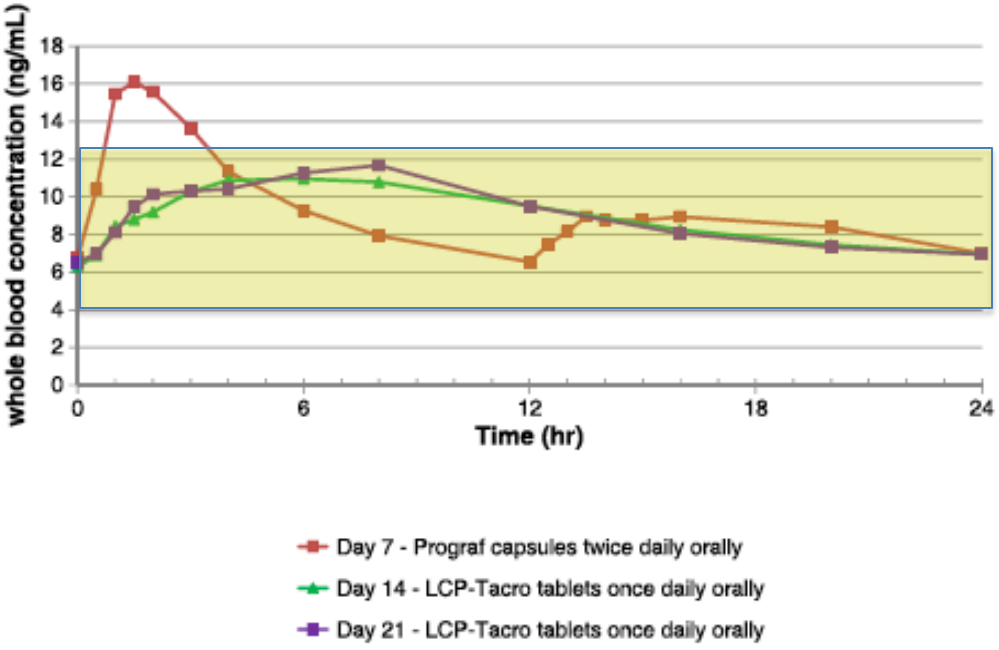
Melt-dose tacrolimus: Phase II trials

→ Evaluate the steady-state **Pharmacokinetics** in both **conversion** and **de novo** solid organ transplants

Study no.	Study 2011	Study 2012	Study 2012E*	Study 2017	Study 2018
Country	US	US	US	US	US
Patient population	Stable *kidney* transplant	Stable liver transplant	Stable liver (12-month extension of Study 2012)	*De novo* *kidney* transplant	*De novo* liver transplant
Comparator	Prograf®	Prograf®	None	Prograf®	Prograf®
Enrollment (patients)	51	57	43	63	58
Enrollment status	Closed	Closed	Closed	Closed	Closed

Pharmacokinetics in Phase II conversion trials from Prograf to LCP-TAC

- LCP-Tacro tablets show **lower peak (Cmax)**, **reduced peak-to-trough fluctuations**
- The PK profile is characterized by **flatter kinetics** (i.e., less fluctuation and swing)



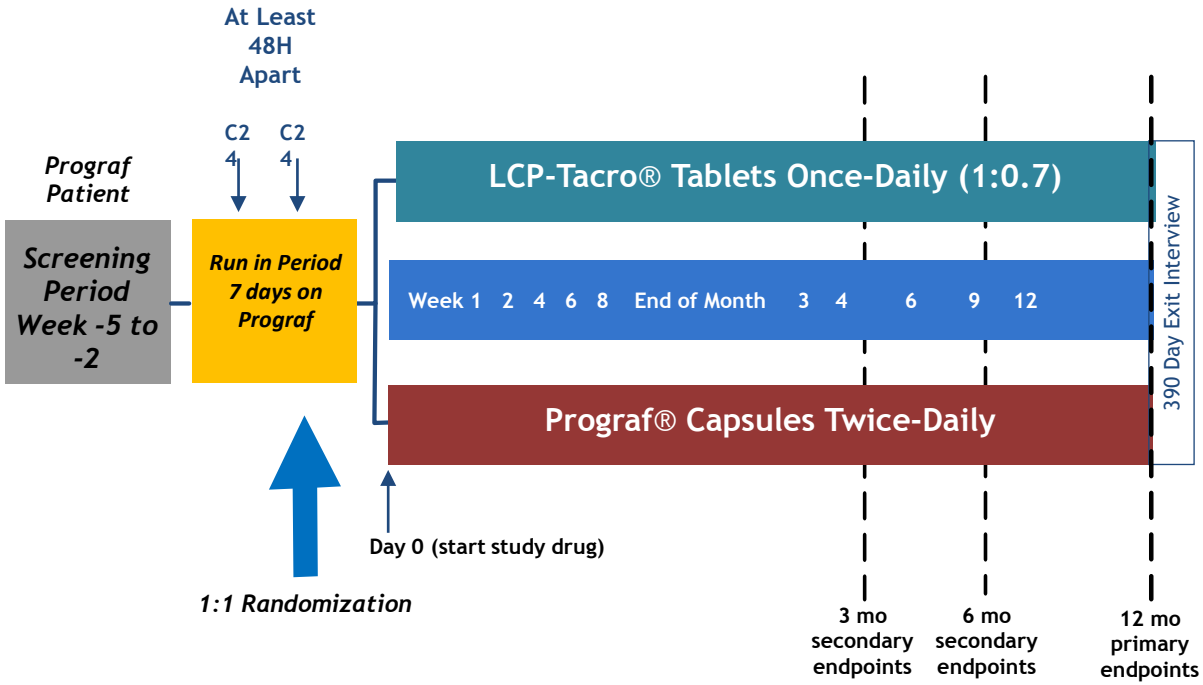
Optimal
Therapeutic range

Gaber AO Transplant 2013

Alloway RR et al, Liver Transpl. 2014

Kidney TX: Phase III LCP-Tacro **Conversion** trial

- Open-label "switch" study on patients stable on Prograf®
- 326 KT were randomized and switched to receive either LCP-Tacro with a 1:0.7 conversion rate, or to be continued on Prograf® at the same dose



Non inferiority study

Bunnapradist et al Am J Transplant. 2013

Primary efficacy

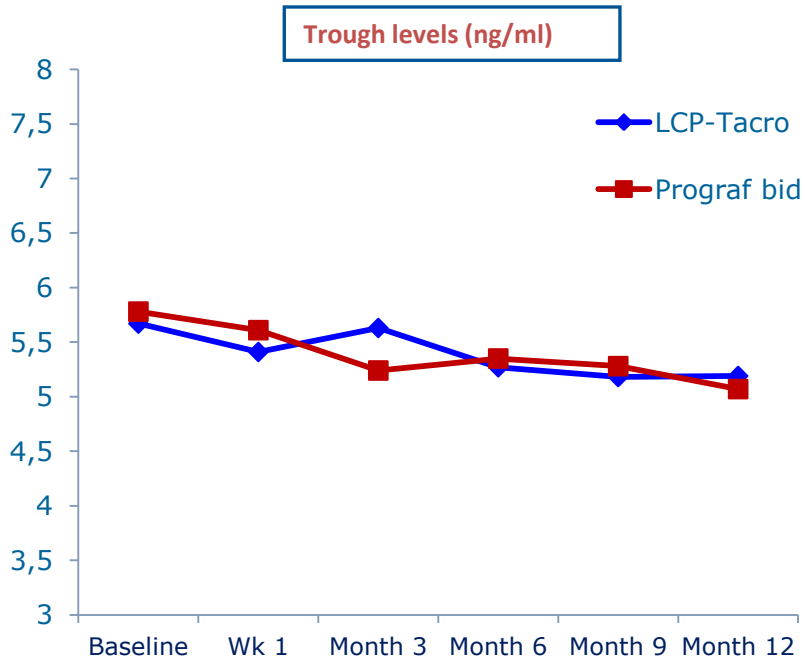
Proportion of patients with efficacy failures:
(death, graft failure, BPAR, or lost to follow-up) within 12 months

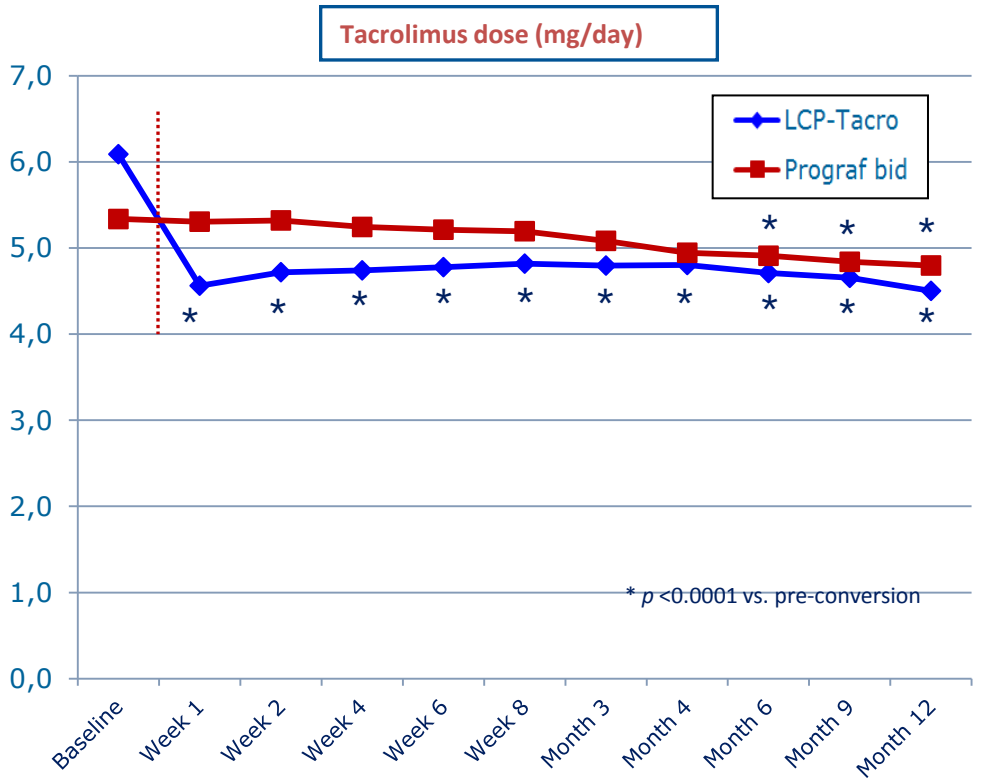
	Primary Efficacy (Local-biopsy reading)	
	LCP-Tacro (N=162)	**Prograf® (N=162)**
BPAR	2 (1.2%)	2 (1.2%)
Graft loss	0	0
Death	2 (1.2%)	1 (0.6%)
Lost to follow-up	0	1 (0.6%)
Composite endpoint	4 (2.5%)	4 (2.5%)
Treatment difference (95% CI)	**0% (-4.2,+4.2)**	

BPAR (Blinded central read.)	**1 (0.6%)**	**4 (2.5%)**
Composite endpoint	3 (1.9%)	6 (3.7%)
Treatment difference (95% CI)	-1.85% (-6.51,+2.30%)	

Bunnapradist et al Am J Transplant. 2013

Coverage after conversion





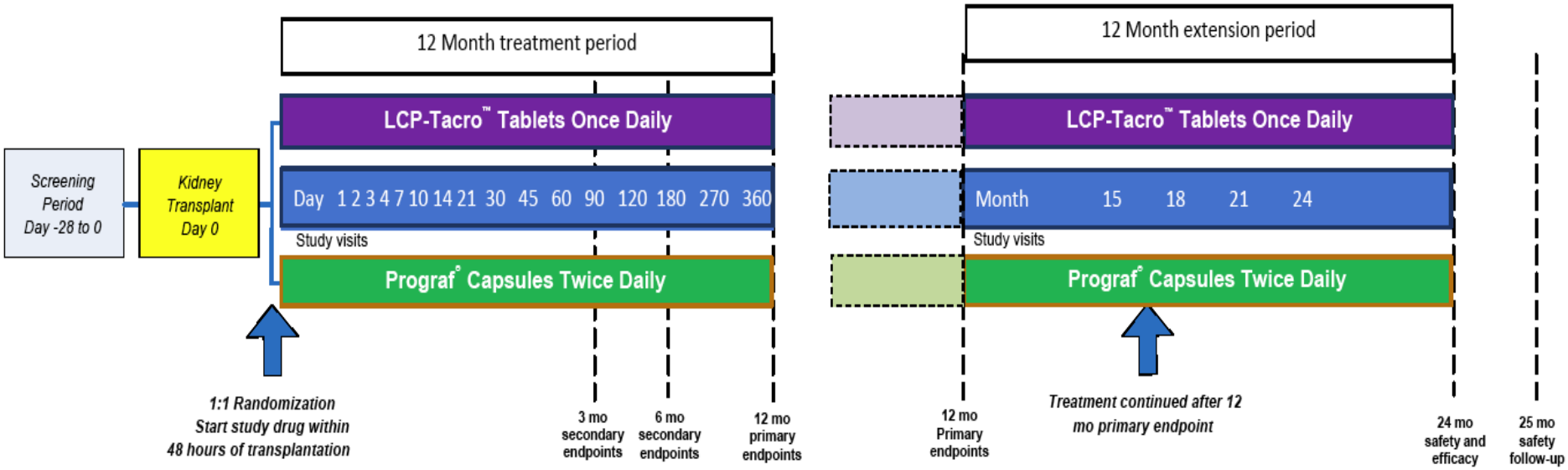
- Mean trough levels between groups were similar
- Mean daily dose of LCPT was significantly lower than preconversion tacrolimus dose (30% less)

Bunnapradist et al Am J Transplant. 2013

Kidney TX: Phase III LCP-Tacro ***de novo***

- Double-blind double-dummy efficacy and safety trial of LCP-Tacro vs. Prograf® in *de novo* kidney TX

- 543 KT randomized to receive standard triple therapy with either LCP-Tacro with a starting dose of 0.17 mg/kg/d, or Prograf® at 0.1 mg/kg/d

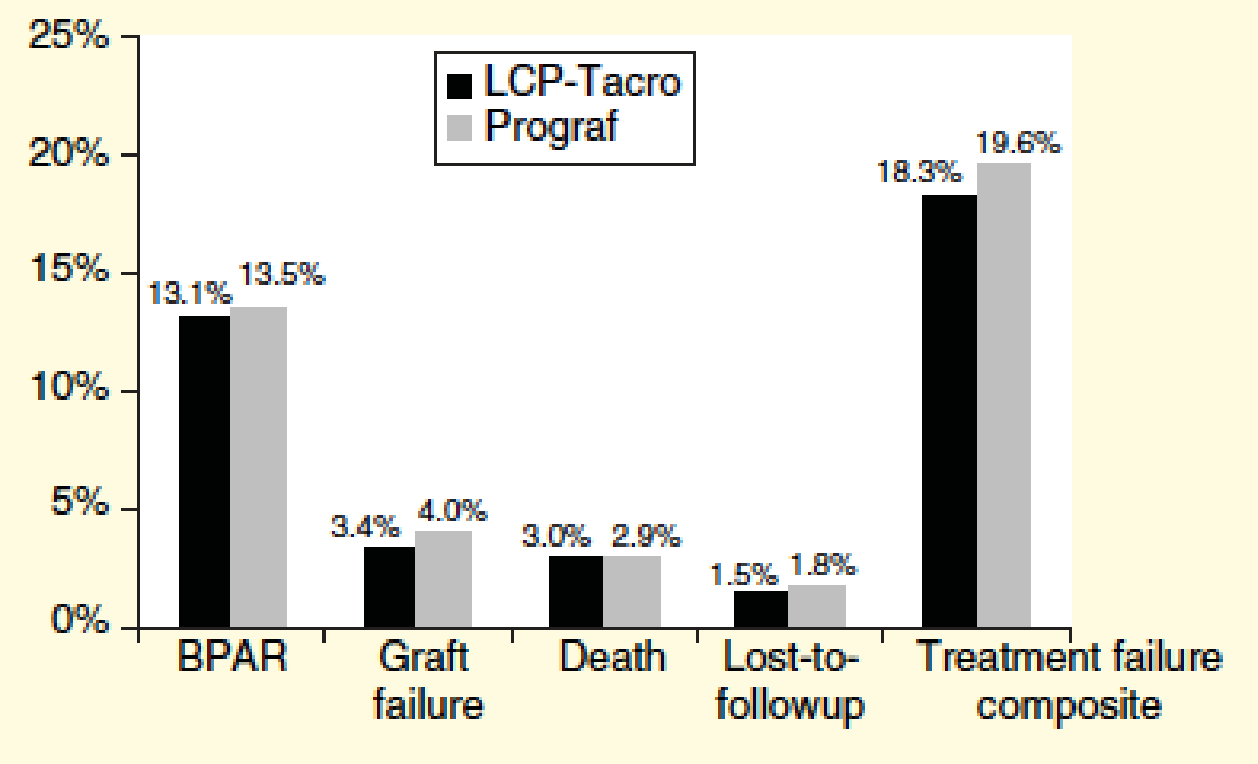


Non inferiority study

Budde K. et al. Am J Transplant 2014

Primary efficacy

Incidence of treatment failures:
death, graft failure, BPAR, or lost to follow-up within 12 months after randomization



Budde K. et al. Am J Transplant 2014

Renal function

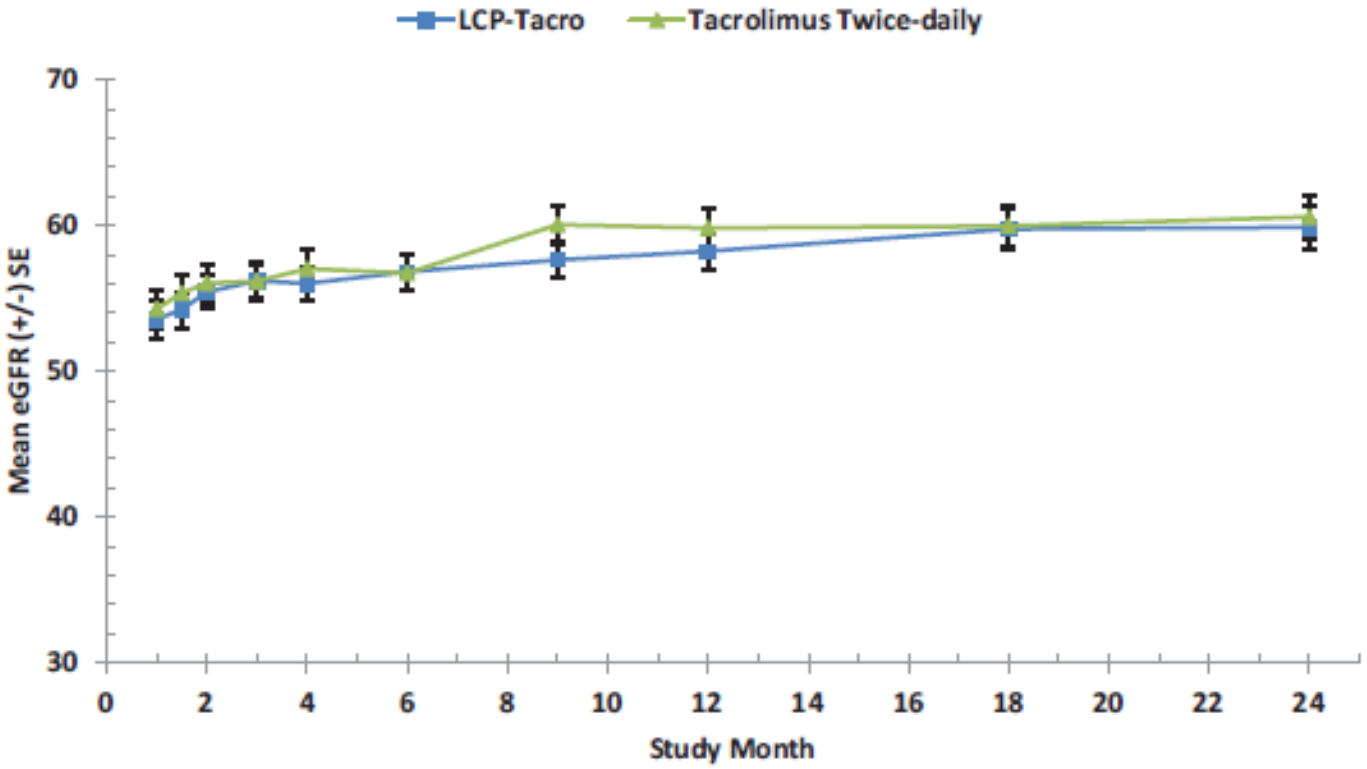
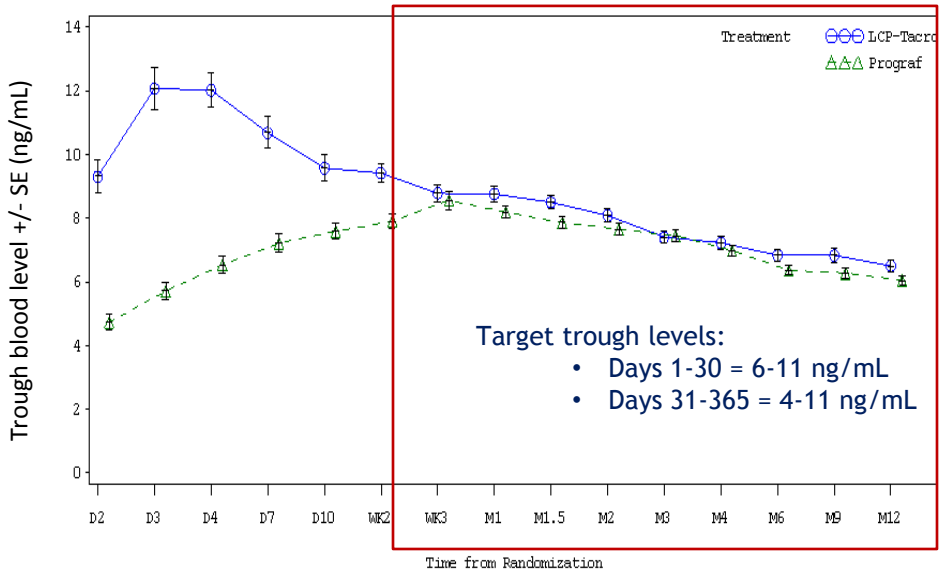


Figure 4: Renal function over the study period.

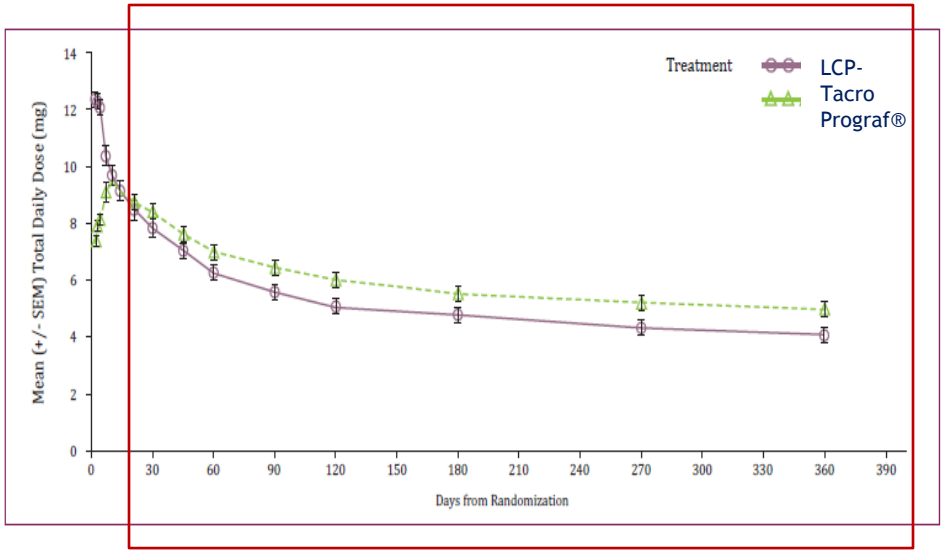
Budde K. et al. Am J Transplant 2014

Patients coverage in the first days post-Tx

Trough blood levels (ng/ml)



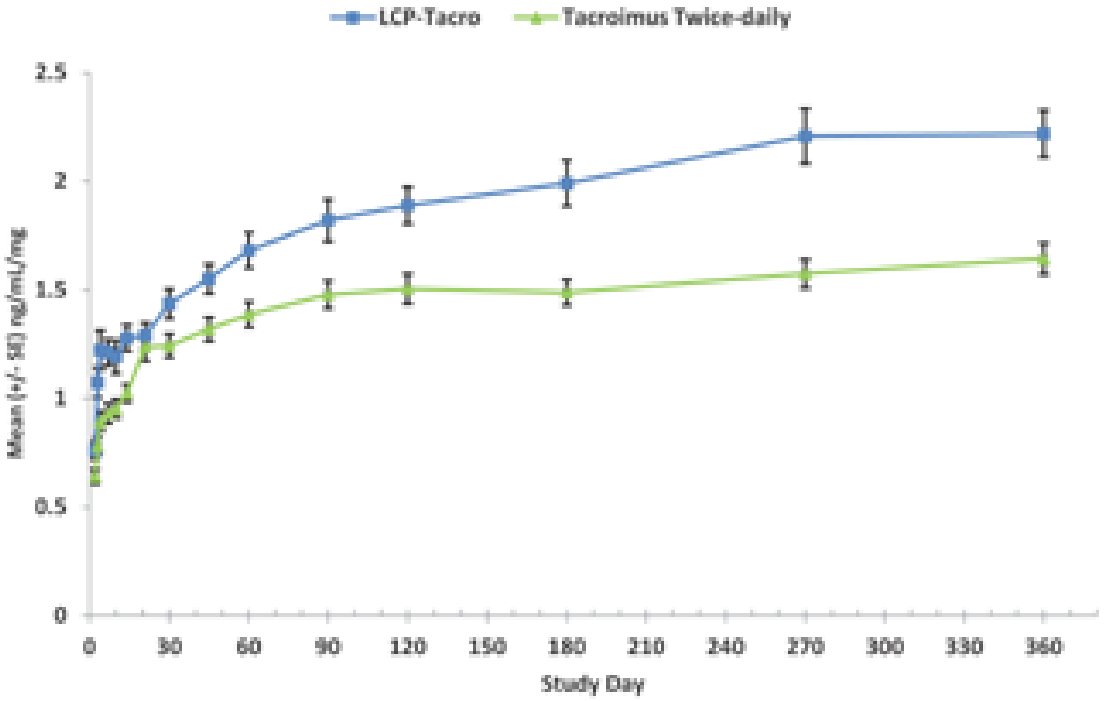
Total daily dose (mg/day)



- Mean trough levels between groups were similar
- Mean daily dose of LCPT significantly lower than Prograf® bid (30% less)

Budde K. et al. Am J Transplant 2014

Tacrolimus trough level (ng/mL) achieved per total daily dose (mg) (modified intent-to-treat set)



Budde K. et al. Am J Transplant 2014

Tolerability

Comparable safety profile

Discontinuation due to AEs: 8.6% LCP-Tacro vs. 9.8% Prograf®

	LCP-Tacro (N=268)	Prograf® (N=275)
Diarrhea	30.6%	33.5%
Anemia	26.1%	28.7%
Urinary tract infection	24.6%	24.4%
Hypertension	23.1%	22.5%
Constipation	18.3%	24.4%
Peripheral edema	15.7%	20.7%
Tremor	19.0%	16.7%
Diabetes	16.4%	13.5%
Low blood phosphate	13.4%	15.3%
Nausea	13.1%	14.9%

Budde K. et al. Am J Transplant 2014

Metabolic parameters

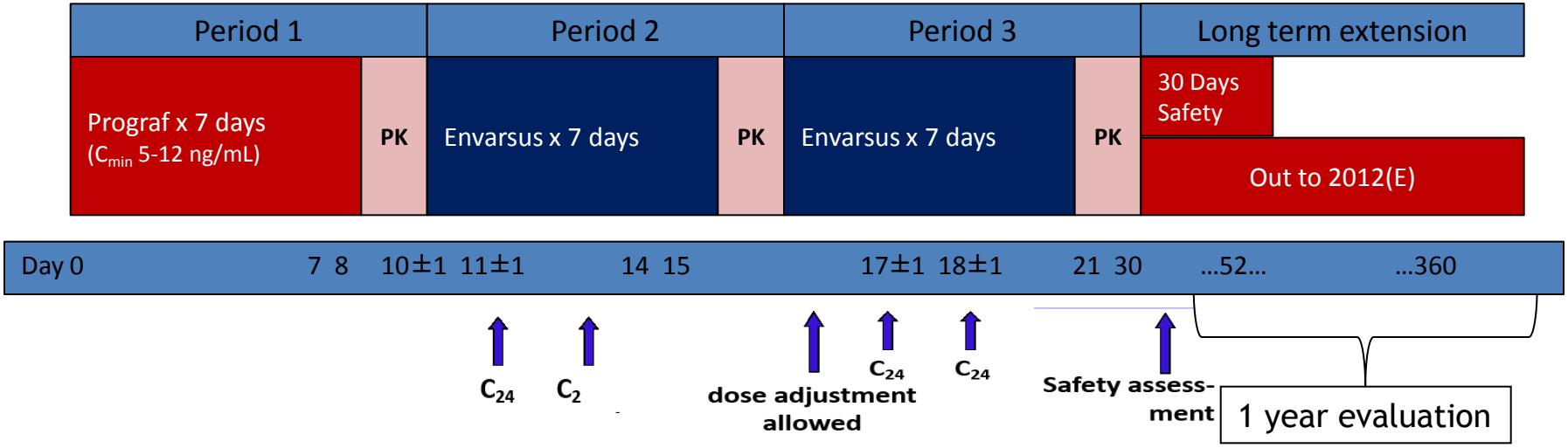
	Baseline		12 Months	
	LCP-Tacro	Tacrolimus twice-daily	LCP-Tacro	Tacrolimus twice-daily
HDL cholesterol (mg/dL)				
Median (range)	40.0 (14–97)	38.0 (14–103)	53.0 (21–119)	50.0 (15–136)
Change from baseline, mean (SE)			12.7 (1.14)	13.2 (0.87)
p-Value[1]				0.8473
LDL cholesterol (mg/dL)				
Median (range)	84.0 (20–314)	80.0 (20–214)	103.0 (23–230)	105.0 (3–257)
Change from baseline, mean (SE)			19.2 (2.71)	23.0 (2.77)
p-Value[1]				0.2528
Total cholesterol (mg/dL)				
Median (range)	149.0 (57–454)	140.0 (77–313)	184.0 (94–360)	185.0 (89–370)
Change from baseline, mean (SE)			36.0 (3.19)	41.9 (3.14)
p-Value[1]				0.1936
Triglyceride (mg/dL)				
Median (range)	84.0 (20–440)	86.0 (22–782)	132.0 (42–448)	148.0 (41–1856)
Change from baseline, mean (SE)			57.2 (5.09)	74.9 (9.19)
p-Value[1]				0.0578
HbA1c				
Median (range)	5.40 (4.0–11.4)	5.40 (4.3–10.4)	5.50 (4.4–12.6)	5.70 (4.6–14.6)
Change from baseline, mean (SE)			0.42 (0.08)	0.47 (0.06)
p-Value[1]				0.6124

HbA1c, hemoglobin A1c.
[1]p-Value from analysis of covariance controlling for baseline value.

Budde K. et al. Am J Transplant 2014

Liver TX: Phase II LCP-Tacro **Conversion** study

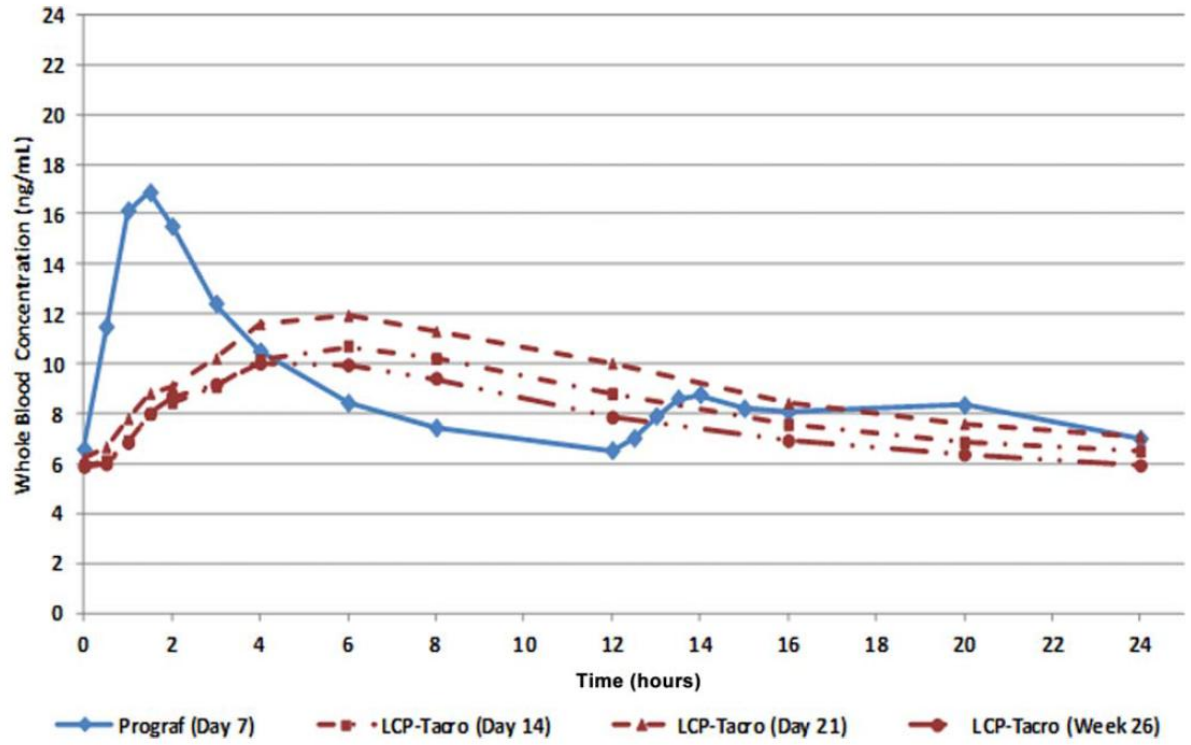
- Phase II, three-sequence, open label, multicenter, prospective study of liver transplant recipients **≥ 6 months** post-transplant on **stable** (7 days) oral Prograf® therapy with tacrolimus trough levels **5-12 ng/mL** for at least two weeks
- Patients were on Prograf twice-daily for seven days (days 1 to 7).
  On day 8 each patient was converted to LCP-Tacro (**dose conversion approx. 1: 0.70**)
  Full PK assessed 7 and 14 days post-conversion
  A follow-up safety visit was conducted on day 53.
  Dose adjustment (n=1) was allowed on Day 15



Alloway RR et al, Liver Transpl. 2014

AUCs

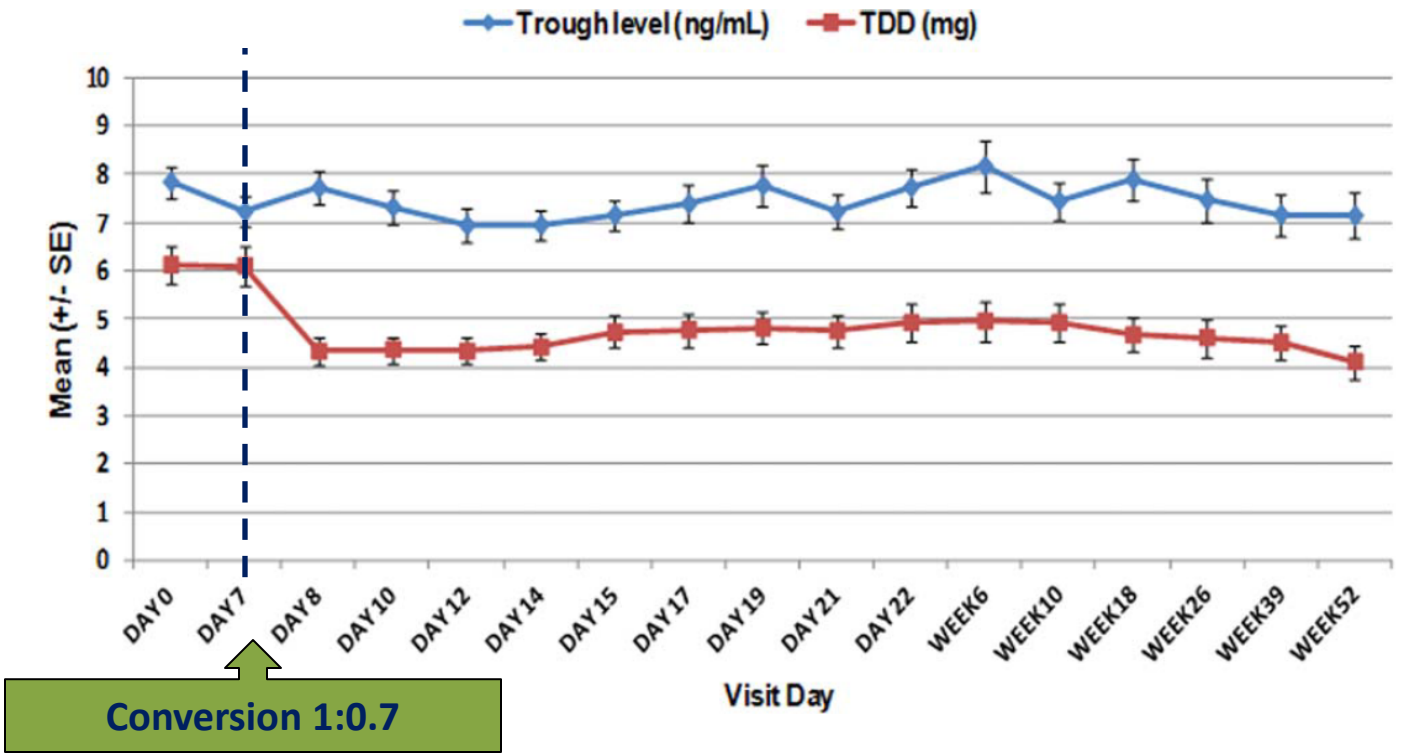
- Full PK profiles were taken pre-conversion (**Day 7**), 7 (**Day 14**), 14 (**Day 21**) and 21 days (Day 26) post-conversion



LCP-Tacro tablets are associated with a lower peak (Cmax) and reduced peak-to-trough fluctuations

Alloway RR et al, Liver Transpl. 2014

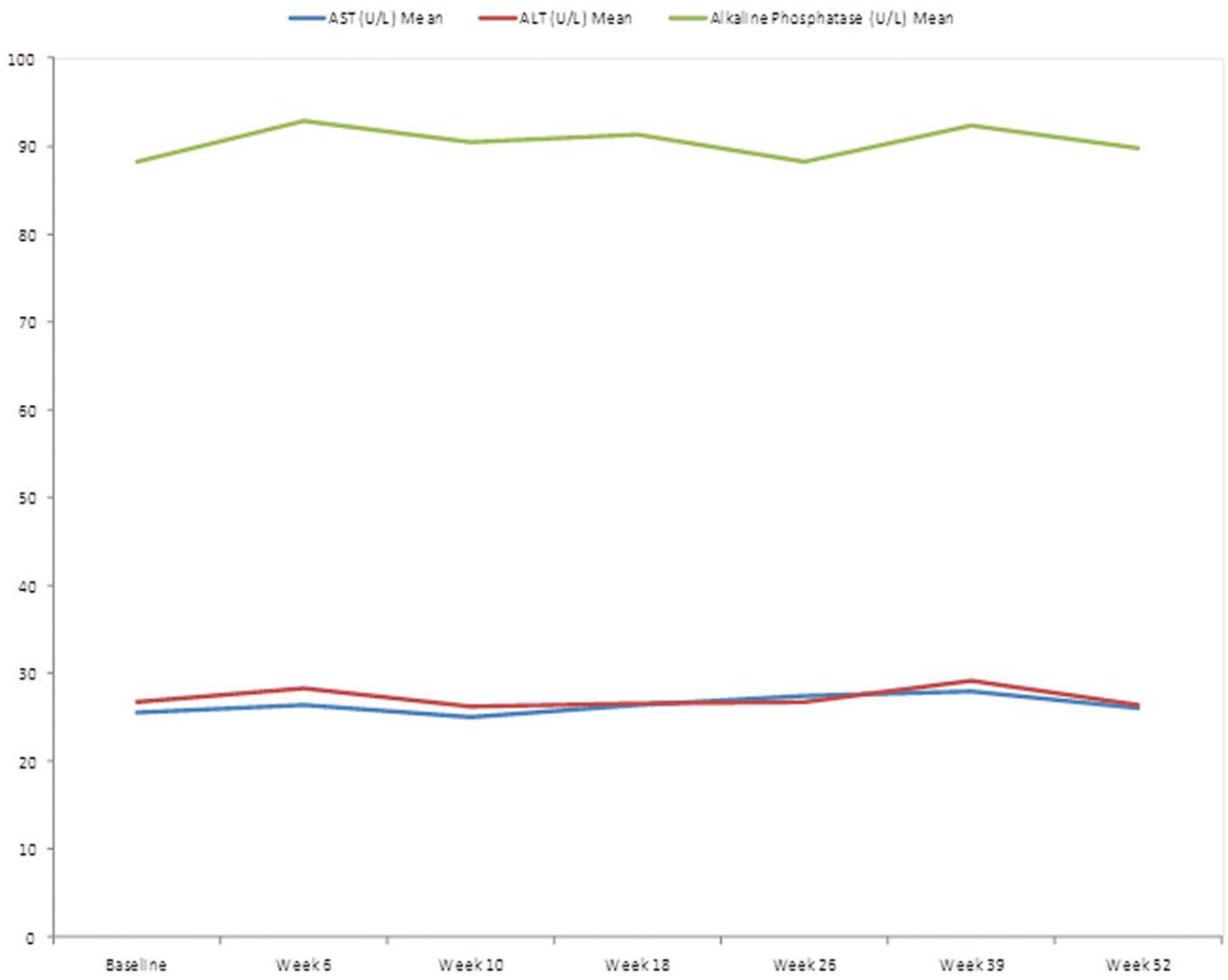
Dosing and Trough levels



The maintainance of a similar (AUC) exposure is achieved at a dose approximately 30% less than the total daily dose of Prograf bid

Alloway RR et al, Liver Transpl. 2014

Stable Long term liver function



Alloway RR et al, Liver Transpl. 2014

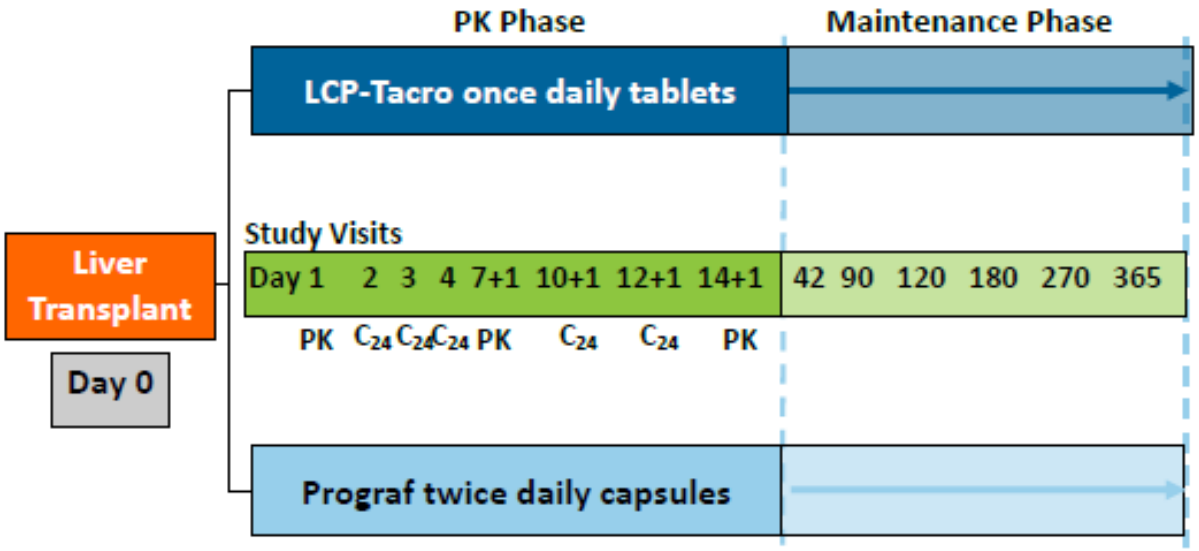
Safety profile

- Overall, the incidence, type, and severity of AEs were in the range expected in this patient population
- No unexpected AEs were reported
- There were no clinically significant changes in lab values, vital signs, or ECGs
- No unexpected issues in eGFR

Alloway RR et al, Liver Transpl. 2014

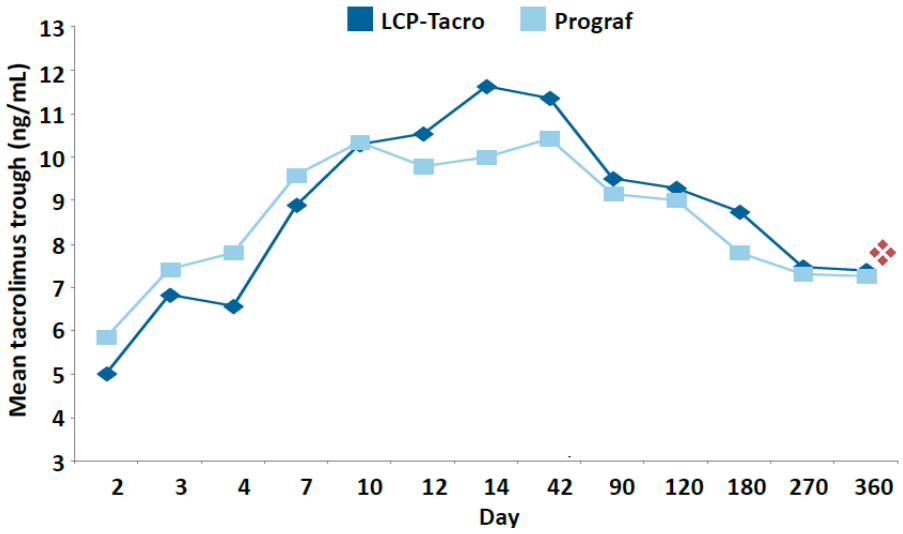
Liver TX: Phase II LCP-tacro ***de novo*** study

- Randomized, parallel-group, open-label, multicenter study in adult *de novo* liver transplant recipients
- **Patients were randomized to:**
  - **LCP-tacro 0.07-0.11 mg/kg qd (0-09-0.13 mg/kg for African Americans) or**
  - **Prograf® 0.10-0.15 mg/kg/day (divided twice daily)**
- Subsequent dosing was adjusted to maintain whole blood tacrolimus levels as 5-20 ng/mL

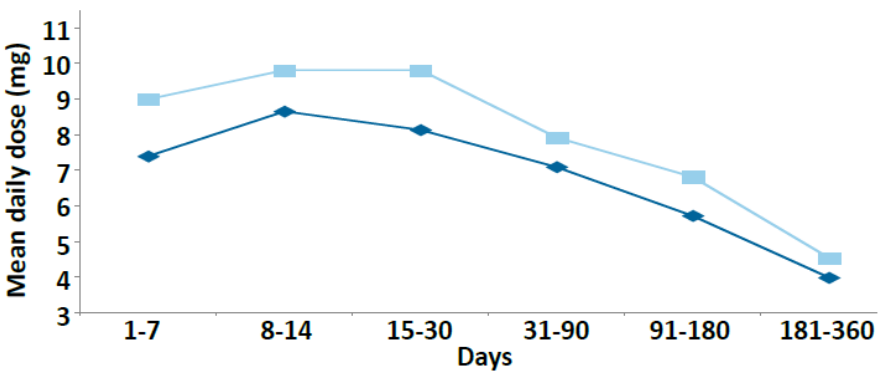


Dubay D et al ESOT 2015

Dosing and trough levels



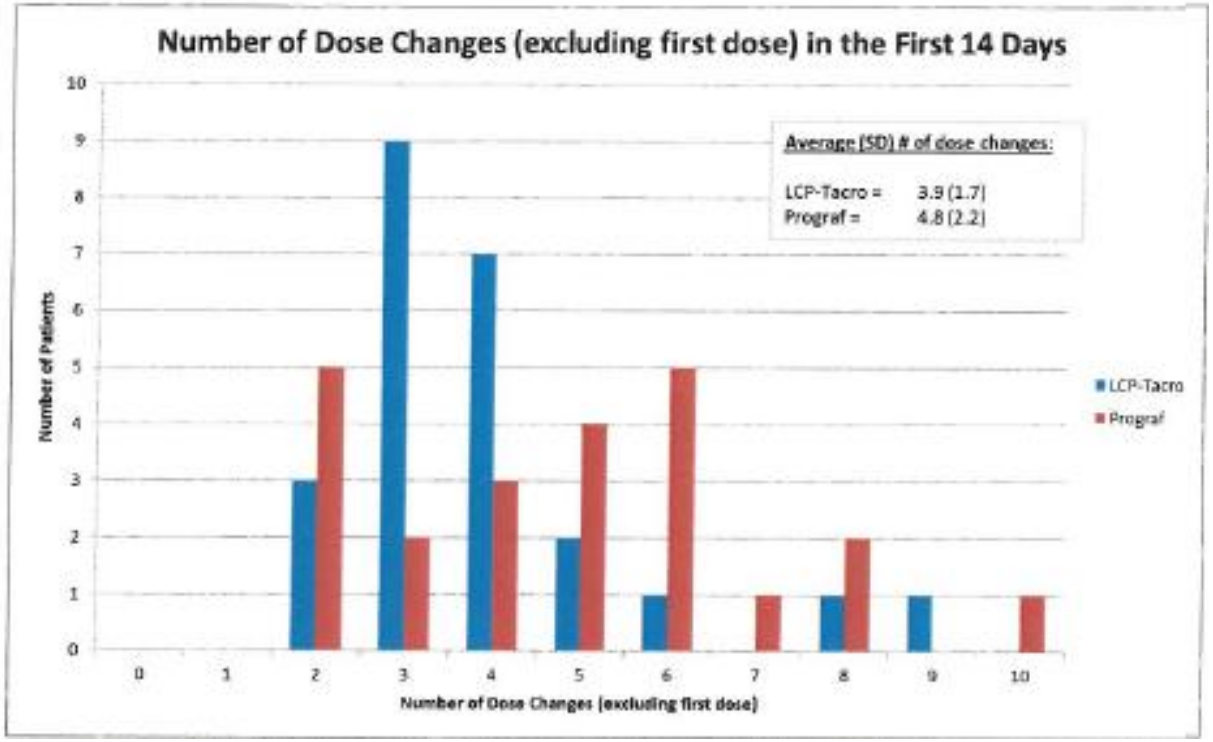
❖ Comparable trough levels



❖ Lower TDD

Dubay D et al ESOT 2015

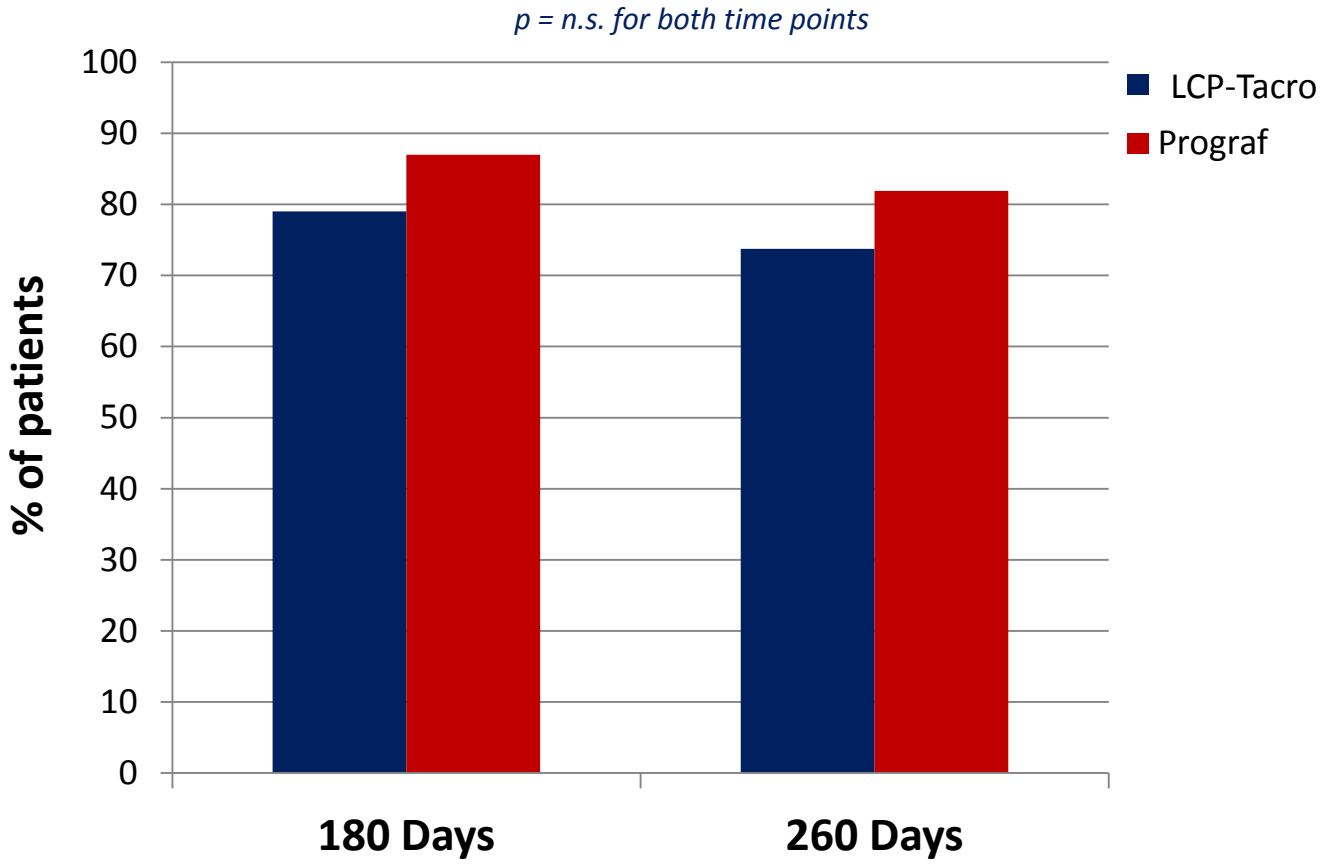
Dose Adjustments During the First 14 Days



Lower number of dose adjustments was done within the LCP-Tacro group

Dubay D et al ESOT 2015

Patients Free from BPAR



Dubay D et al ESOT 2015

Adverse Events

	LCP-Tacro (n=29)	Prograf® (n=29)
All AEs: n (%)	29 (100%)	29 (100%)
Mild	6 (20.7%)	8 (27.6%)
Moderate	14 (48.3%)	16 (55.2%)
Severe	9 (31.0%)	5 (17.2%)

	LCP-Tacro (n=29)	Prograf® (n=29)
All AEs: n (%)	29 (100%)	29 (100%)
Not suspected to be related	8 (27.6%)	16 (55.2%)
Suspected to be related	21 (72.4%)	13 (44.8%)

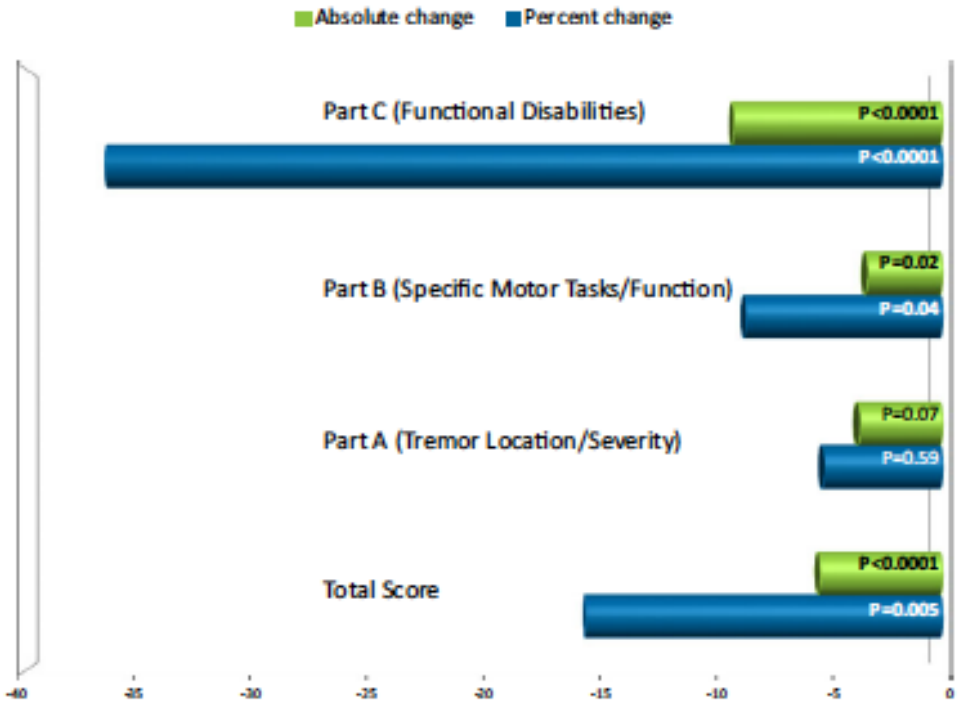
No differences regarding main AEs

Dubay D et al ESOT 2015

LCP-tacro reduces neurotoxic manifestations

- Phase IIIb conversion study in stable kidney Tx with severe hand tremors and TAC trough levels 3-7 ng/mL → Twice-daily Tacrolimus vs LCP-Tacro at day 7 after conversion
- FTM tremor score and QUEST questionnaire widely used to assess tremor in neurologic patients

Changes in FTM scores after 7 days of conversion

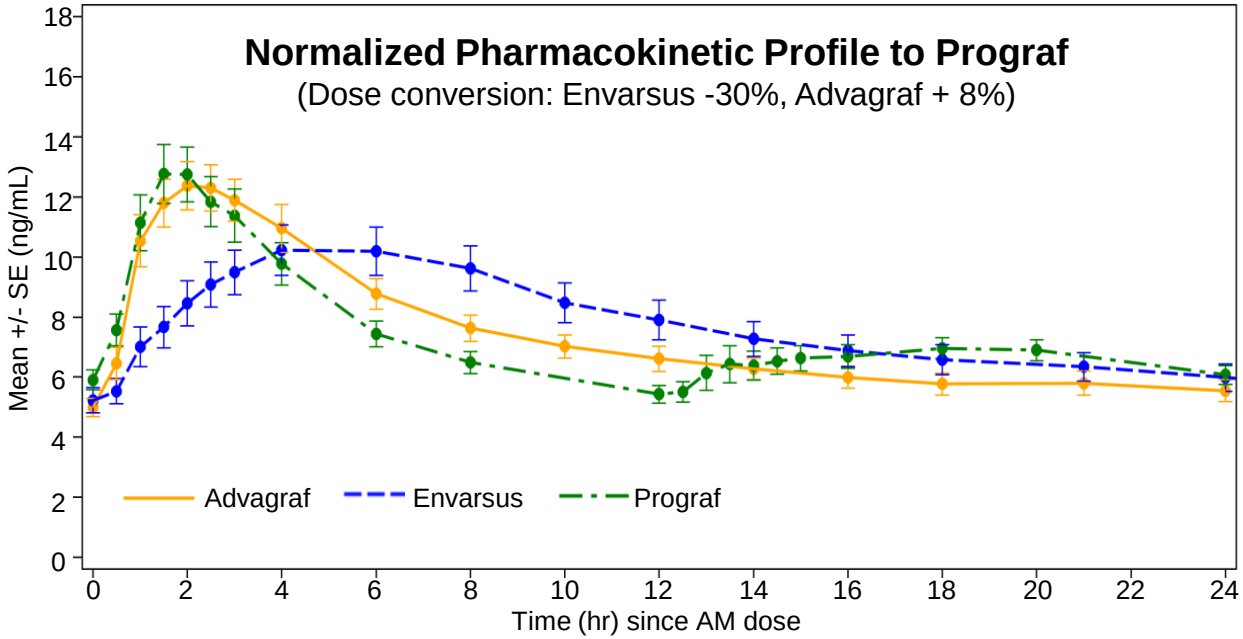


LCPT is associated with clinically meaningful improvement of hand tremor without dose reduction

Langone A, Clin Transplant 2015

ASTCOFF study. Comparison of LCP-tacro with Advagraf®

→Open label, randomized, crossover study to compare the steady-state PK of Envarsus® to Prograf® and Advagraf® in stable kidney transplant recipients



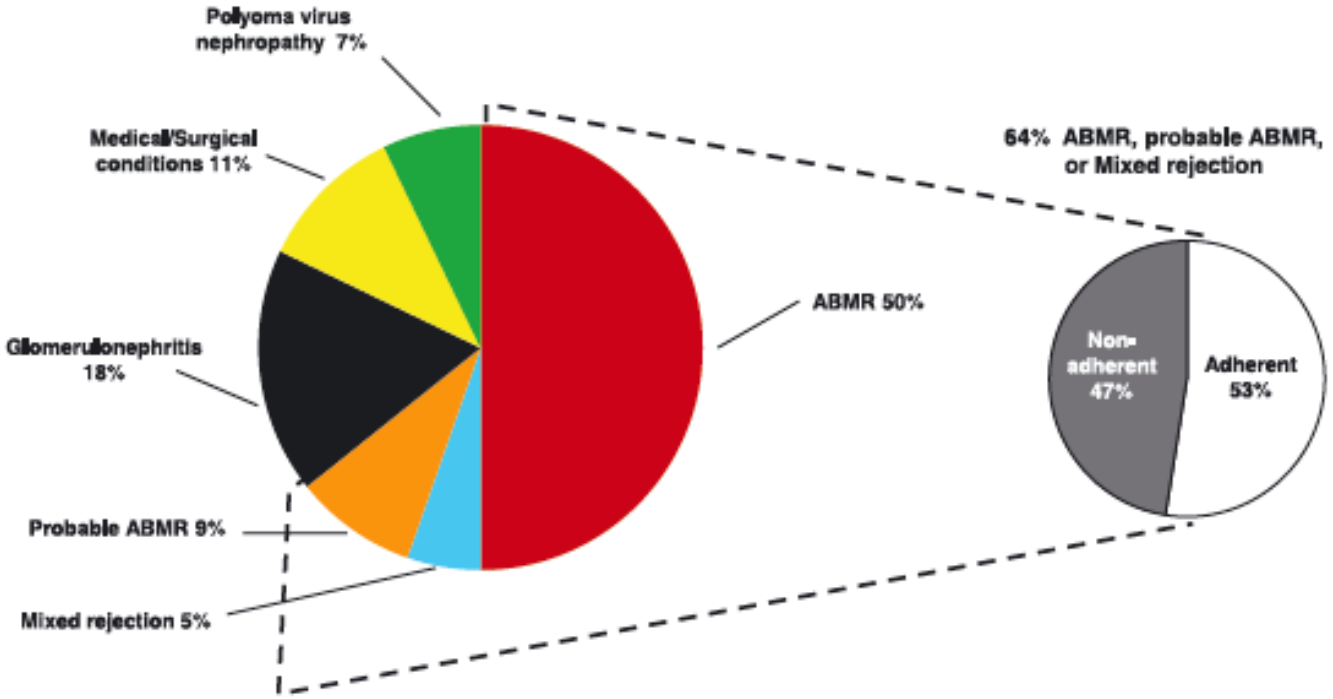
LCP-Tacro shows a flatter PK profile than Advagraf® and Prograf®
→ Less than 30%intra-day peak fluctuation
→ Higher median time to maximal concentration (Tmax)

Tremablay S et al ESOT 2015

Conclusions: MeltDose® tacrolimus

- Similar efficacy and safety than Prograf® in *de novo* and stable patients after *conversion*.
- Reduced doses to achieve similar target trough levels
- Patients show stable and consistent tacrolimus blood levels.
- May help to manage neurotoxic complications without need for levels reduction

Non-adherence as main cause of Chronic allograft rejection



Sellares J et al. Am J Transplant 2012
Bestard O & Sarwal M. Ped Nephrol 2015