The Opticept Trial

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Disclosures

Jesse Schold, PhD
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I have financial relationships within the last 5 years from:

Roche Pharmaceuticals

Wyeth Pharmaceuticals

This study was sponsored by Roche

Reference

Efficacy and Safety of Monitored Mycophenolate Mofetil in Combination with Low-Dose CNI in Renal Transplantation: The Opticept Trial

Gaston, R.S., Kaplan, B., Shah T., Cibrik D., Shaw L.W., Angelis M., Mulgaonkar S., Meier-Kriesche, H.-U., Patel D. and Bloom R.D.

American Journal of Transplantation 2009; 9: 1607-19.

Background

- Fixed-dose administration of MMF is the standard regimen used in kidney transplant recipients
- Mycophenolic acid (MPA) is the active metabolite of MMF
- There is known variation of exposure between patients with equivalent doses

Background

- Low area under the concentration curve (AUC) of MPA has been associated with acute rejection and high AUC is considered a risk for infection or malignancies
- Abbreviated MPA AUC sampling may be useful but requires intensive monitoring
- Trough monitoring is more common and appears to be a reasonable proxy for AUC but the utility has not been tested in a large trial particularly tested with concomitant tacrolimus

Background

- Among patients on cyclosporine and MMF, the APOMYRGE study demonstrated less treatment failure and acute rejection for patients on concentration-controlled dose based on MPA AUC.
  - Le Meur et al, AJT, 2007; 7: 2496-2503.
- A recent multi-center study found no difference in outcomes between fixed dose and concentration-controlled dosing of MMF.
  - van Gelder et al, Transplantation 2008; 86: 1043-51.

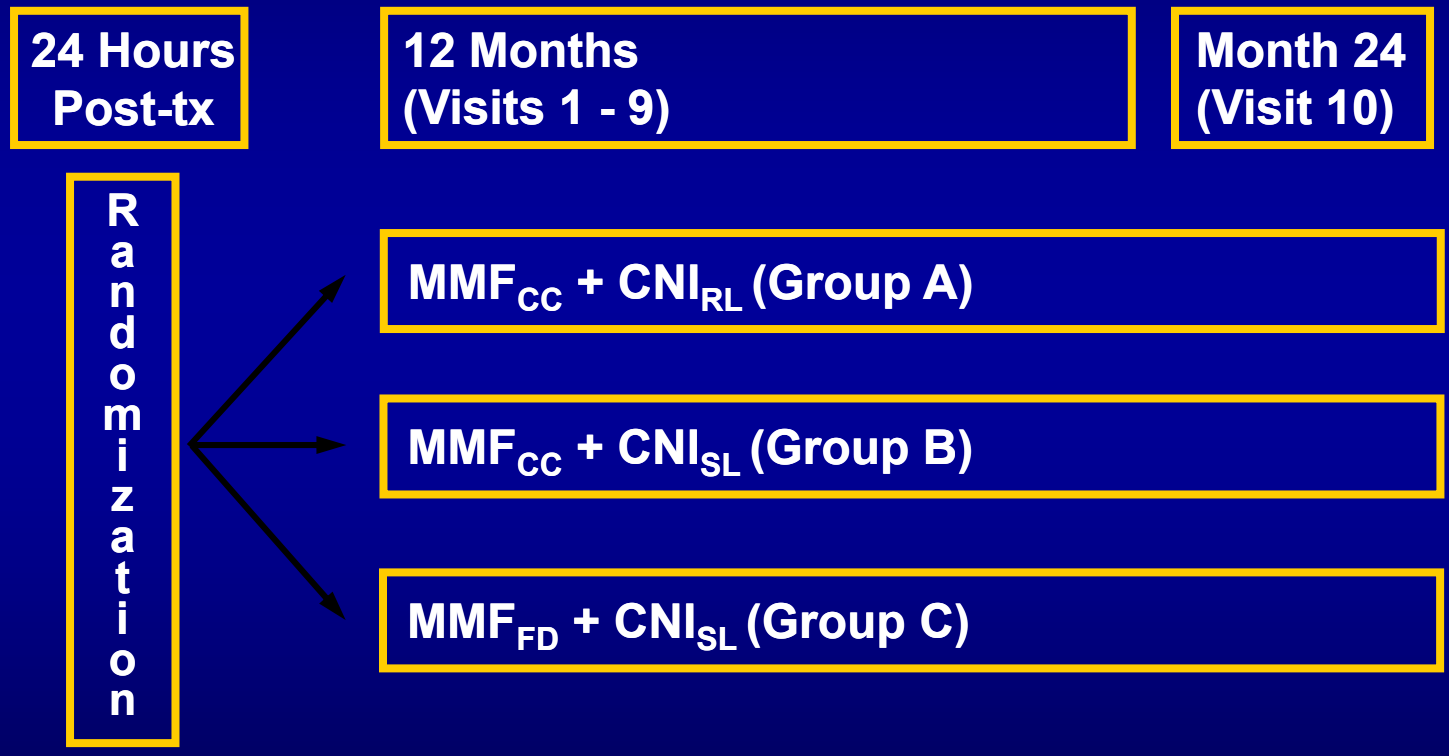
Study Objective

- To compare efficacy and safety of maintenance immunosuppression with either concentration-controlled or fixed-dose MMF in combination with a standard- or reduced-level CNI regimen

Trial Design

- Two-year open-label prospective randomized controlled trial
- 51 participating centers in the US
- Inclusion criteria:
  - Solitary kidney transplant
  - First or second transplant
  - Living or deceased donor recipients
  - Age 13-75
  - Ability to receive MMF within 24 hours
  - Negative pregnancy test
  - No known contraindications to study drugs
  - Ability to comply with treatment protocol

Trial Design



Target Population = 720 single-organ renal allograft recipients

Primary Endpoints

- Efficacy Endpoints
  - Treatment failure during the first 12 months
    - Biopsy-proven acute rejection
    - Graft loss
    - Death
    - Loss to follow-up
    - Withdrew consent
  - Change in eGFR (Nankivell) at 12 months

Safety Endpoints

- Safety Endpoints (6, 12 and 24 months)
  - All adverse events including:
    - Diarrhea
    - Leukopenia
    - Hypertension
    - Hyperlipidemia
    - Diabetes mellitus
  - Opportunistic infections
  - Malignancies
  - Renal function assessed by eGFR (Nankivell), SCr levels, and calculated CrCl (Cockroft-Gault)

Patient Demographics

	Group A MMF_{CC}/CNI_{RL} N=243	Group B MMF_{CC}/CNI_{SL} N=237	Group C MMF_{FD}/CNI_{SL} N=240
Sex*			
Male	163 (67%)	159 (67%)	163 (68%)
Female	80 (33%)	78 (33%)	77 (32%)
Race*			
Caucasian	160 (66%)	168 (71%)	167 (70%)
African American	65 (27%)	58 (25%)	62 (26%)
Other	18 (7%)	11 (5%)	11 (5%)
Age (years)*			
Mean ± SD	48.3 ± 12.8	48.8 ± 13.6	49.6 ± 13.2

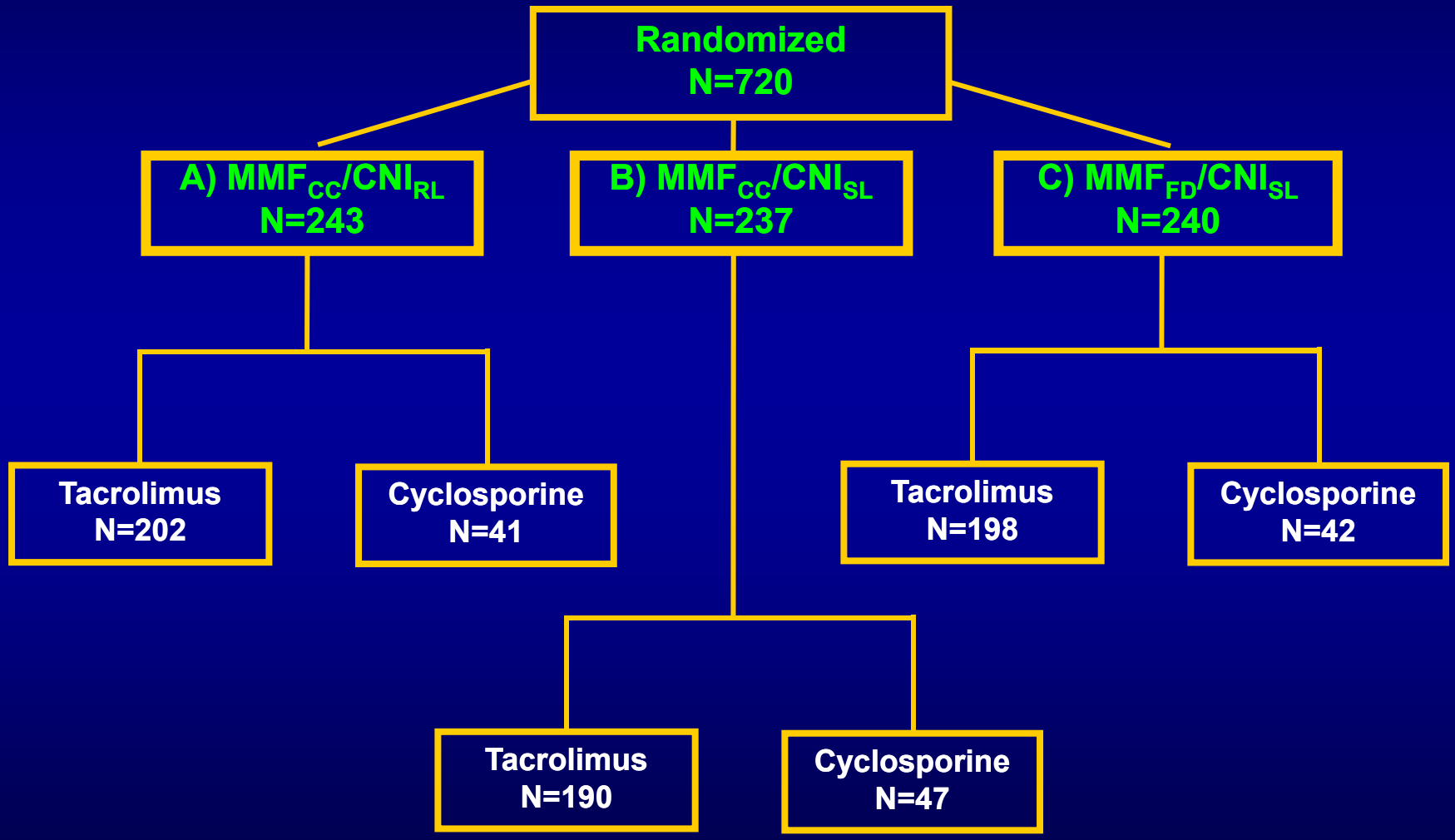
P=NS for between treatment group comparisons

Baseline Characteristics

	Group A MMF_{CC}/CNI_{RL} N=243	Group B MMF_{CC}/CNI_{S} ^{L} N=237	Group C MMF_{FD}/CNI_{SL} N=240
Type of Donor			
Deceased	119 (49%)	118 (50%)	124 (52%)
Living Related	73 (30%)	72 (30%)	61 (25%)
Living Unrelated	48 (20%)	46 (19%)	54 (23%)
PRA Level (highest assessment)			
0%	158 (65%)	152 (64%)	163 (68%)
1-19%	61 (25%)	60 (25%)	56 (23%)
≥20%	16 (7%)	20 (8%)	17 (7%)

P=NS for between treatment group comparisons

Patient Allocation to CNIs



* >80% received tacrolimus

Baseline Characteristics

- Baseline eGFR was similar between treatment arms
  - Group A: 67.5 mL/min
  - Group B: 67.1 mL/min
  - Group C: 65.6 mL/min
- 94-96% of patients treated with steroids at Week 1

Induction Therapy

	Group A MMF_{CC}/CNI_{RL} N=243	Group B MMF_{CC}/CNI_{SL} N=237	Group C MMF_{FD}/CNI_{SL} N=240
Antithymocyte Immunoglobulin	108 (44%)	100 (42%)	103 (43%)
Basiliximab	50 (21%)	55 (23%)	52 (22%)
Daclizumab	24 (10%)	25 (11%)	27 (11%)
Total No. Patients	182 (75%)	180 (76%)	182 (76%)

MMF Dose Adjustment

- Troughs chosen to achieve an MPA

  AUC ≥30 mg·h/L

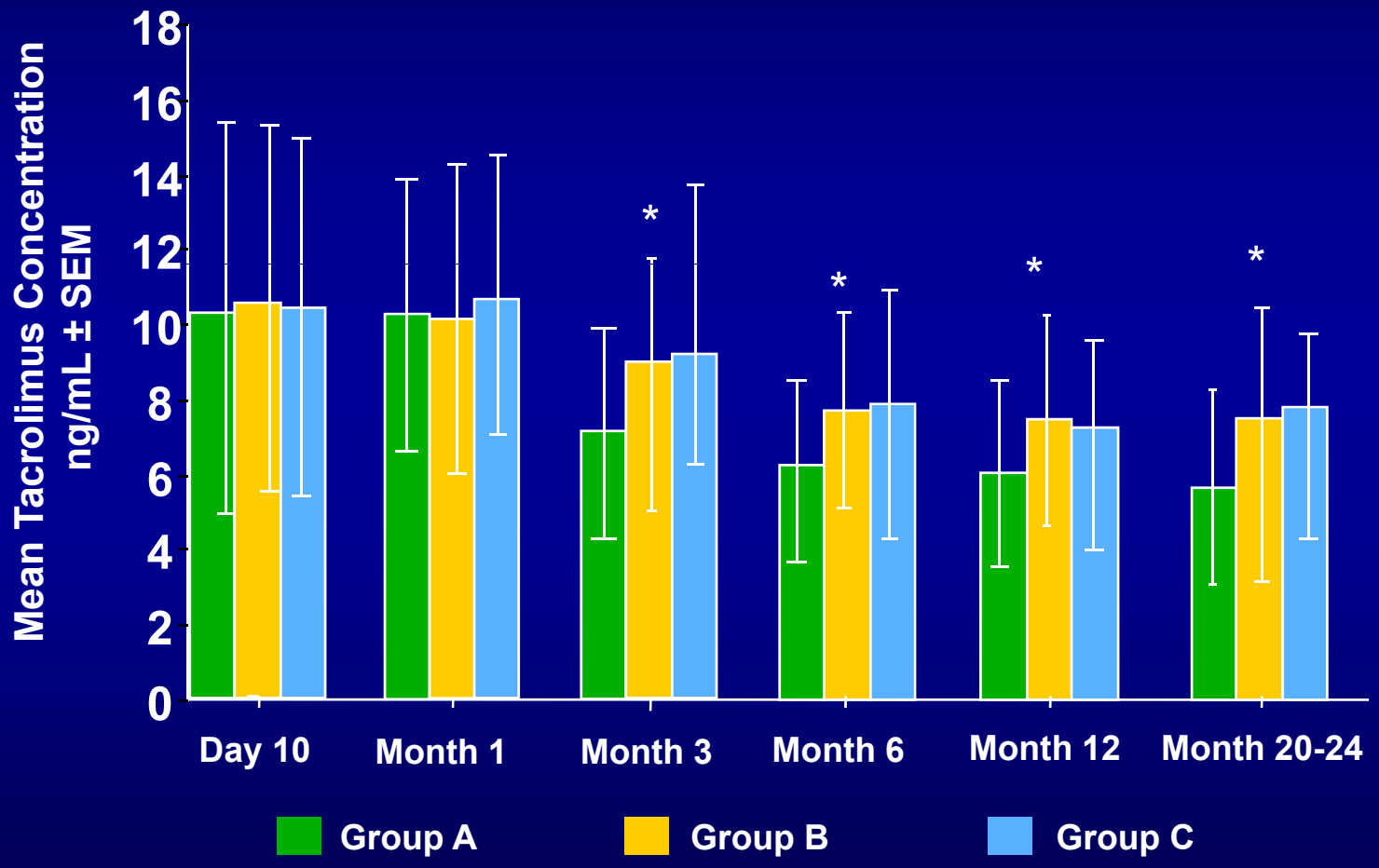
- MMF dose adjusted to achieve MPA trough levels of at least
  - 1.3 μg/mL for patients on CsA
  - 1.9 μg/mL for patients on TAC

CNI Dose Adjustment - Target Trough Level

	Group A		Groups B and C	
	CsA ng/mL	TAC ng/mL	CsA ng/mL	TAC ng/mL
Days 1 - 30	250-325	8-12	250-325	8-12
Days 30 - 90	125-165	4-6	250-270	8-10
Day 90 - 2 Years	95-145	3-5	190-220	6-8

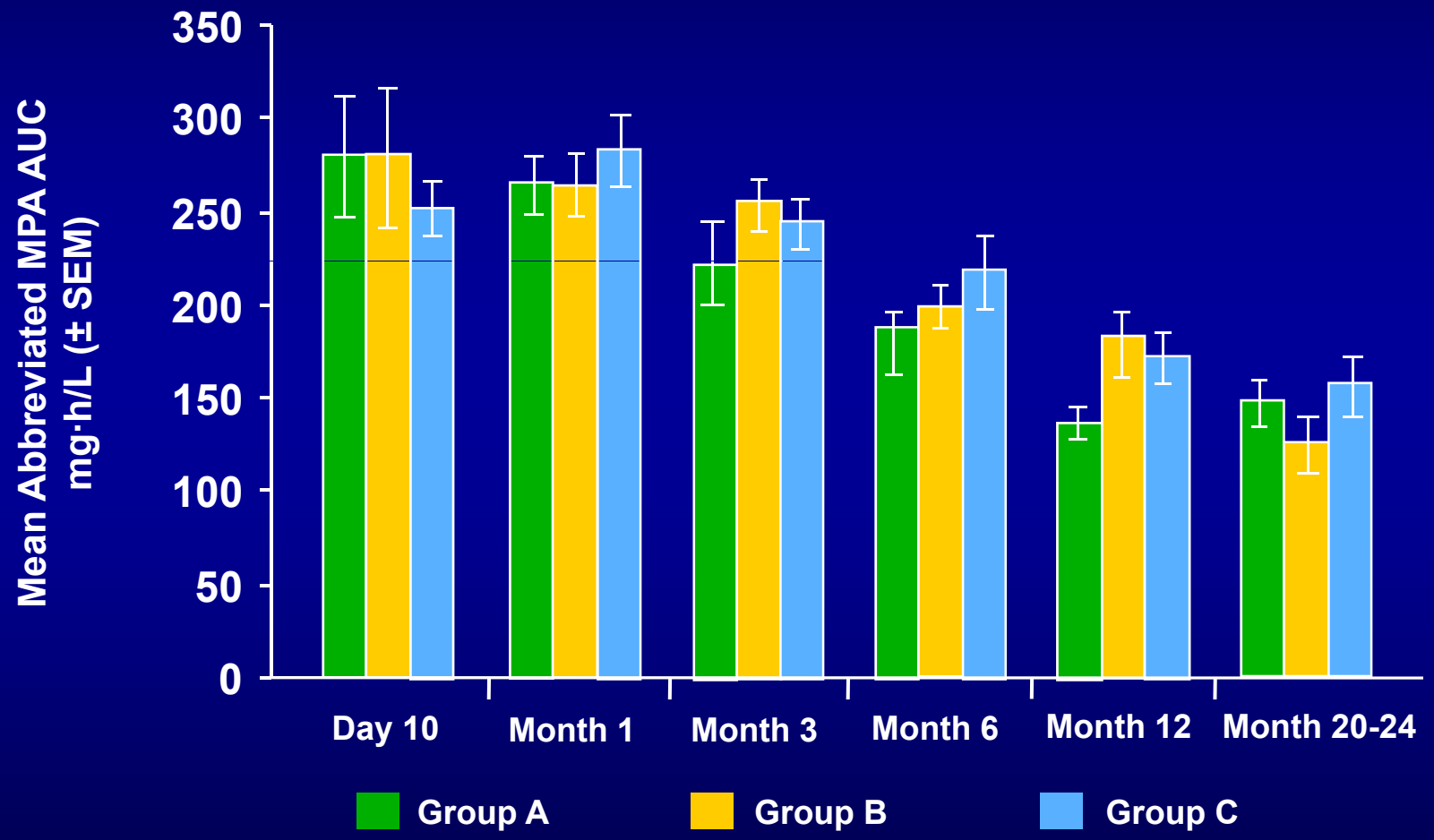
Results: Trough Levels and Dosing

Tacrolimus Trough Levels

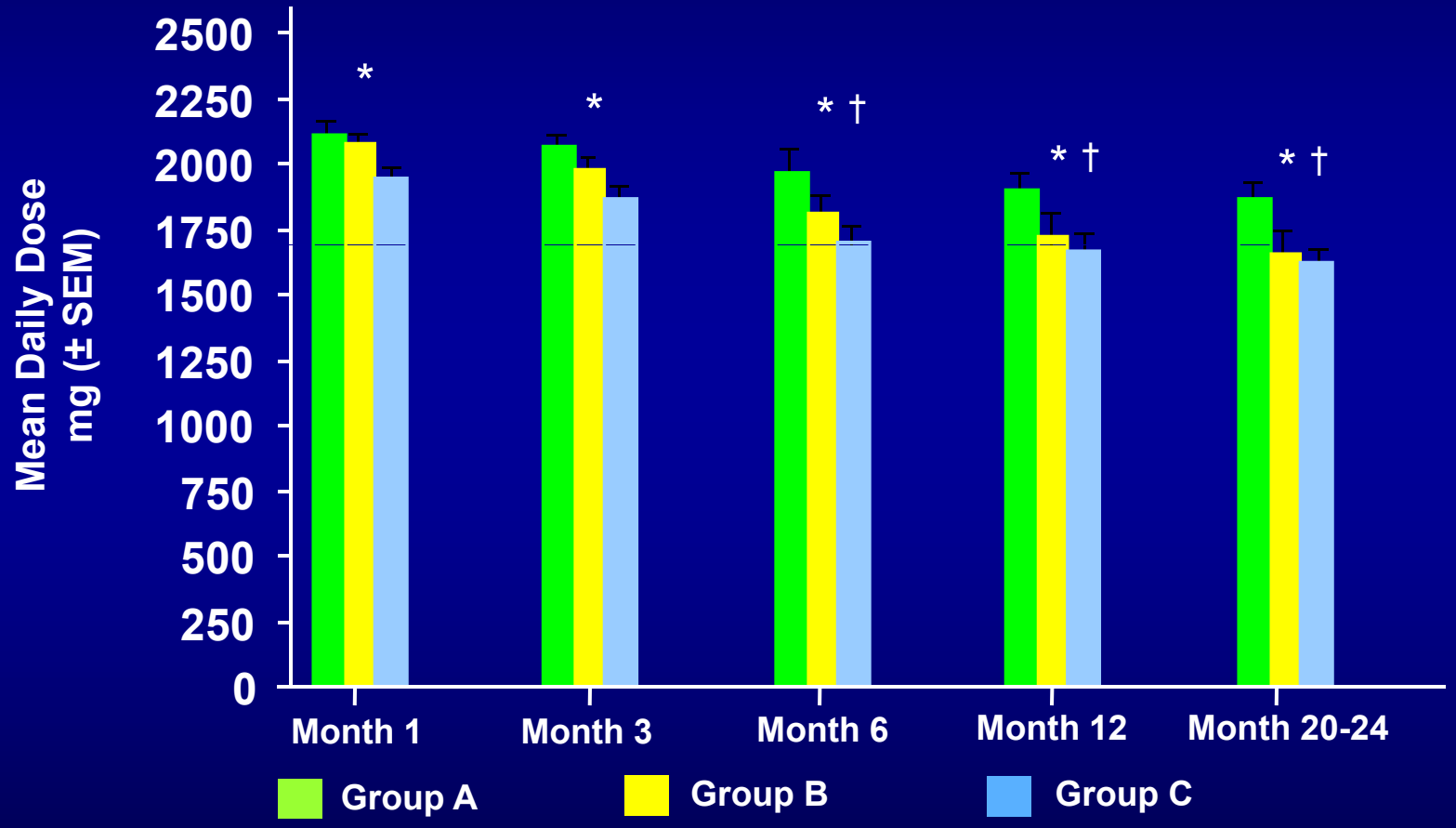


*P≤.0003 for Group A vs C; P≤.01 for Group A vs B.

Cyclosporine Trough Levels

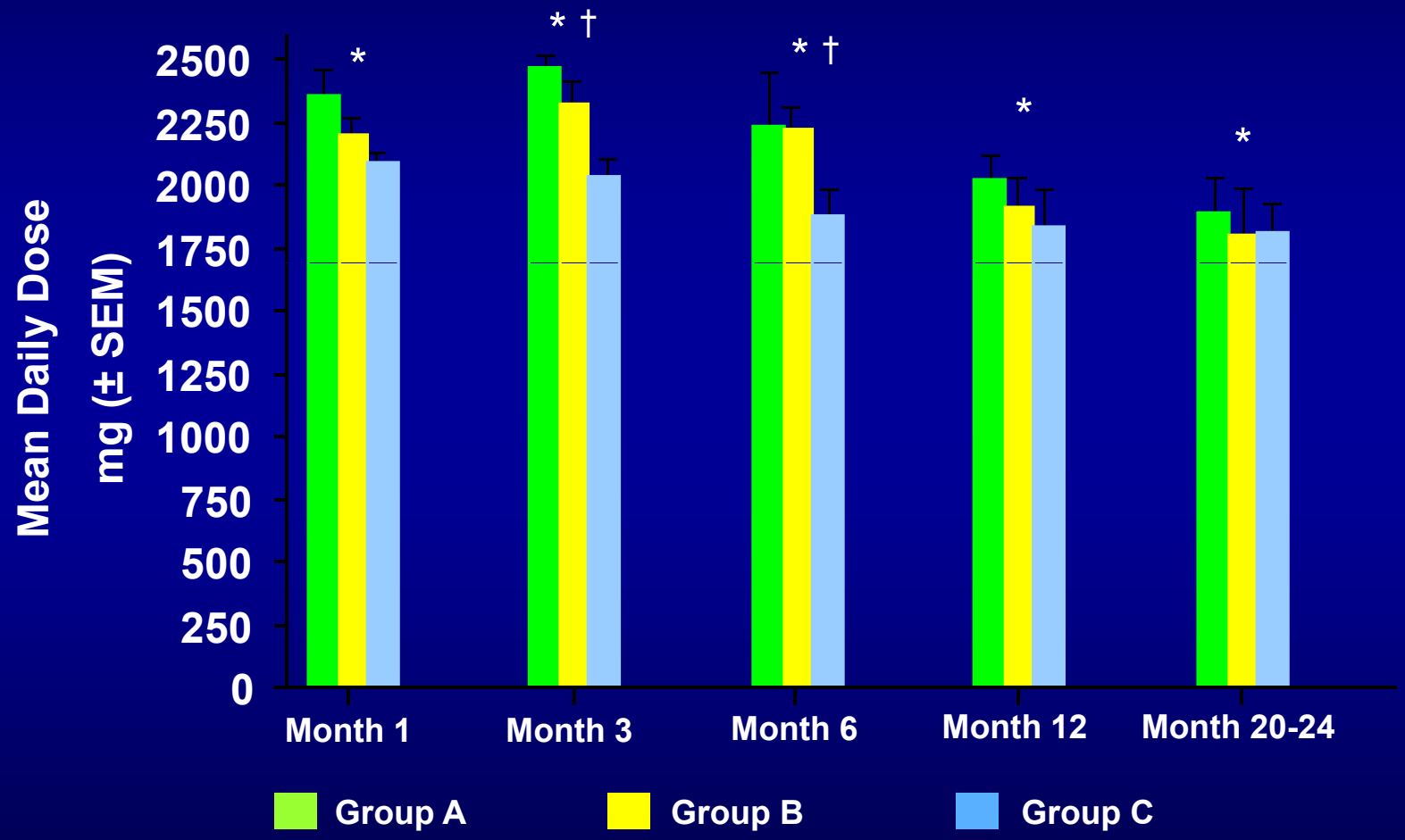


MMF Daily Dose: Tacrolimus Group



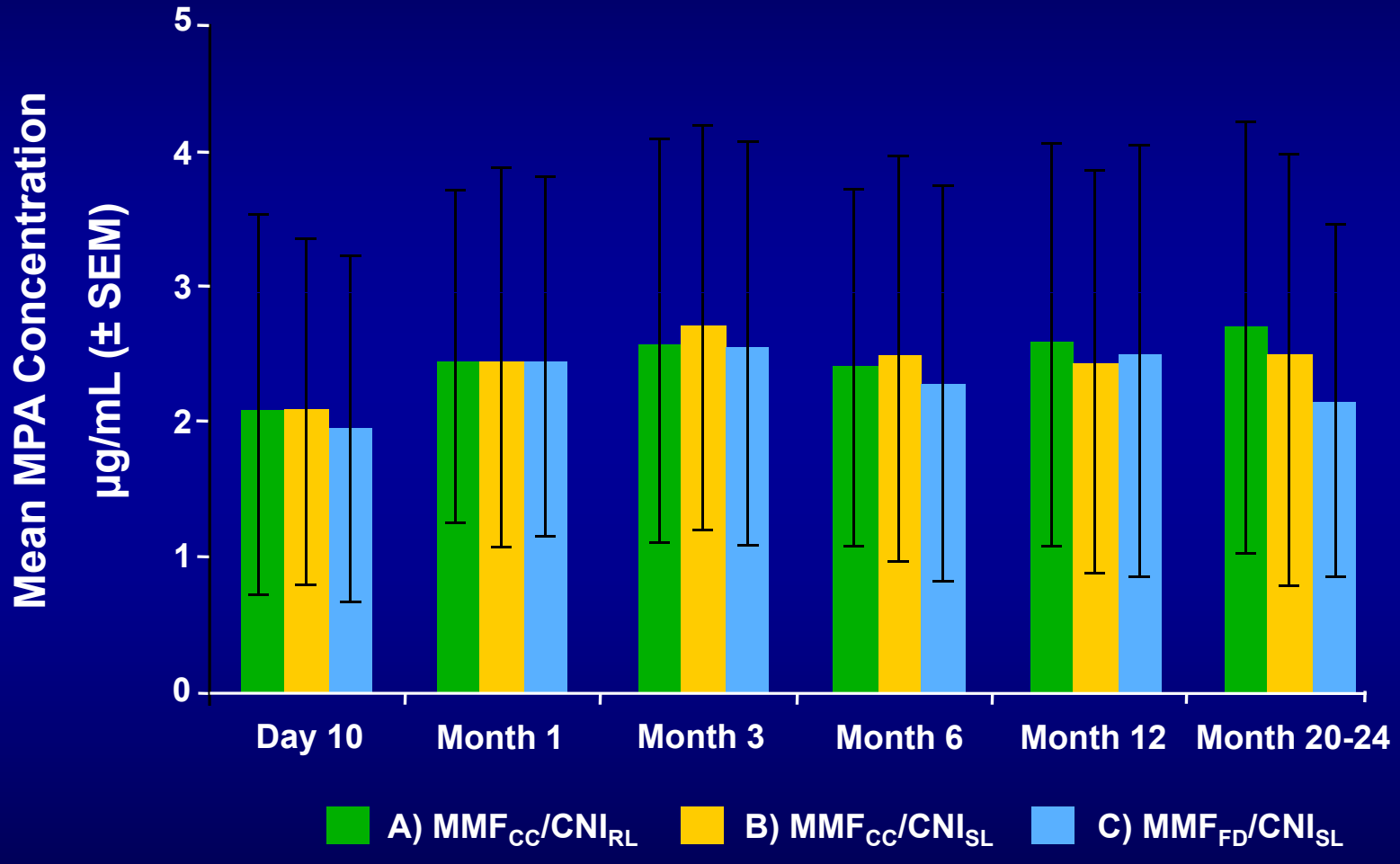
*P<.008 for Group A vs C at each time point.
†P<.02 for Group A vs B.

MMF Daily Dose: Cyclosporine Group



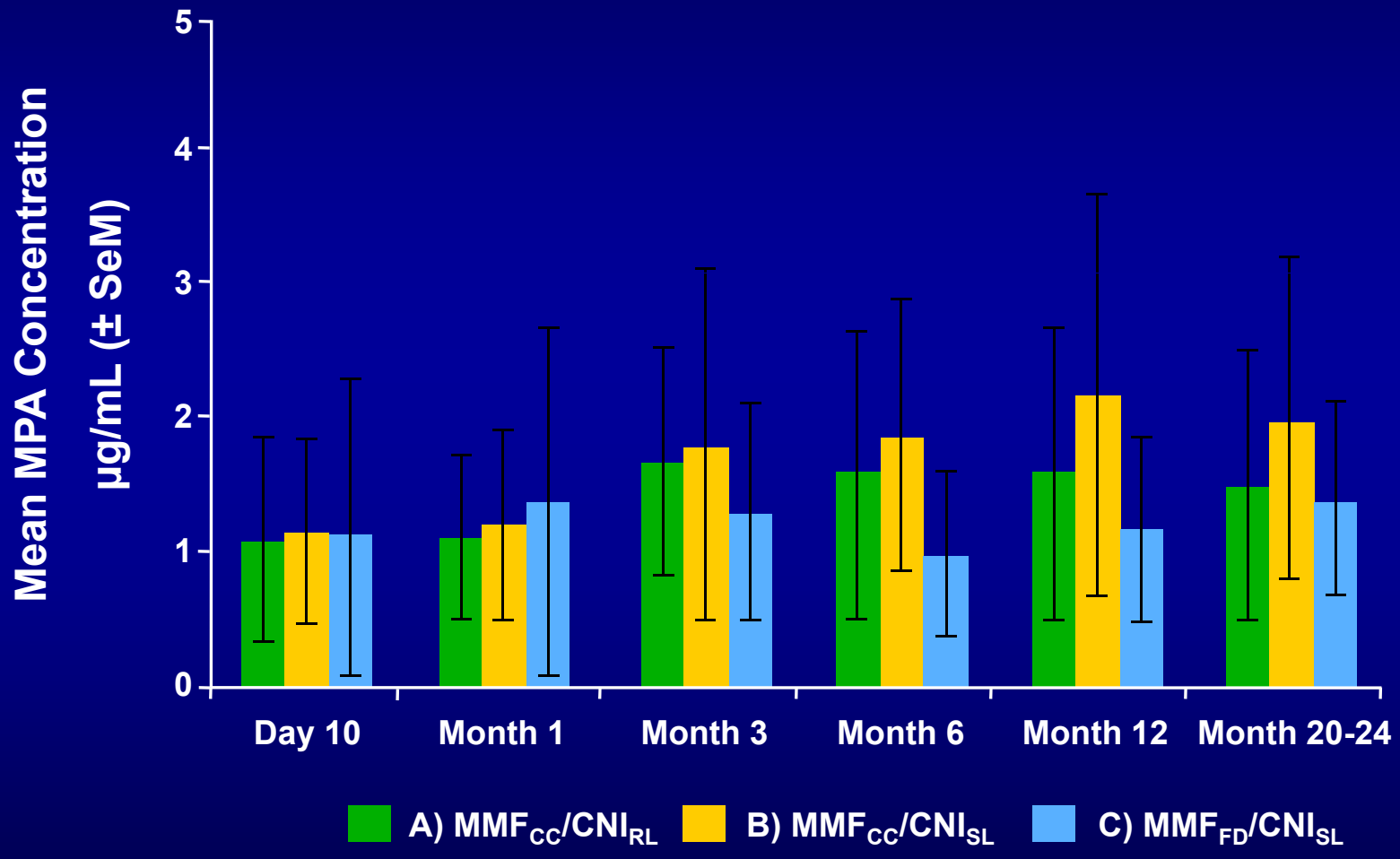
*P<.05 for Group A vs C; †P<.05 for Group B vs C.

MPA Trough Levels: Tacrolimus Group*



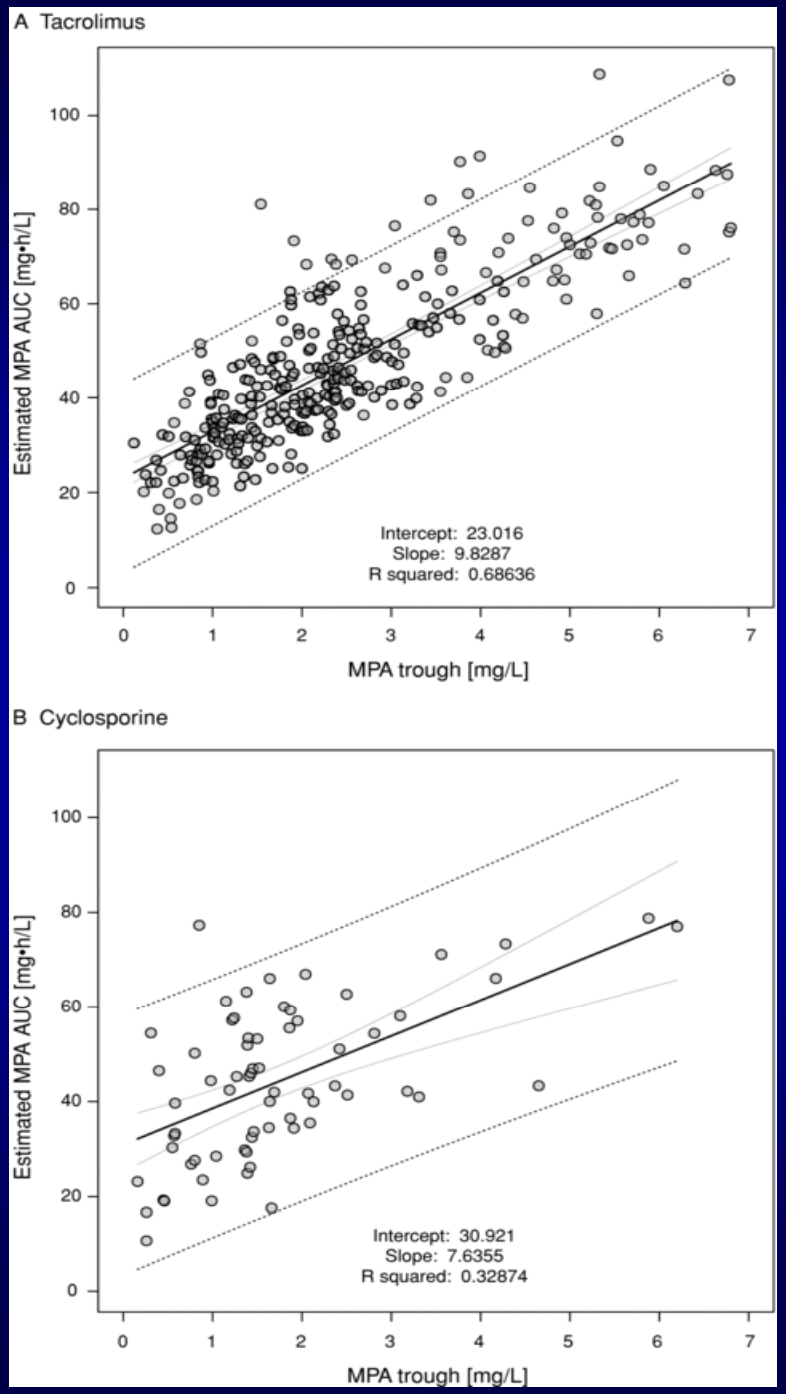
*P<.05 for TAC vs. CsA treatment groups at each time point except for Group B at Month 12.

MPA Trough Levels: Cyclosporine Group



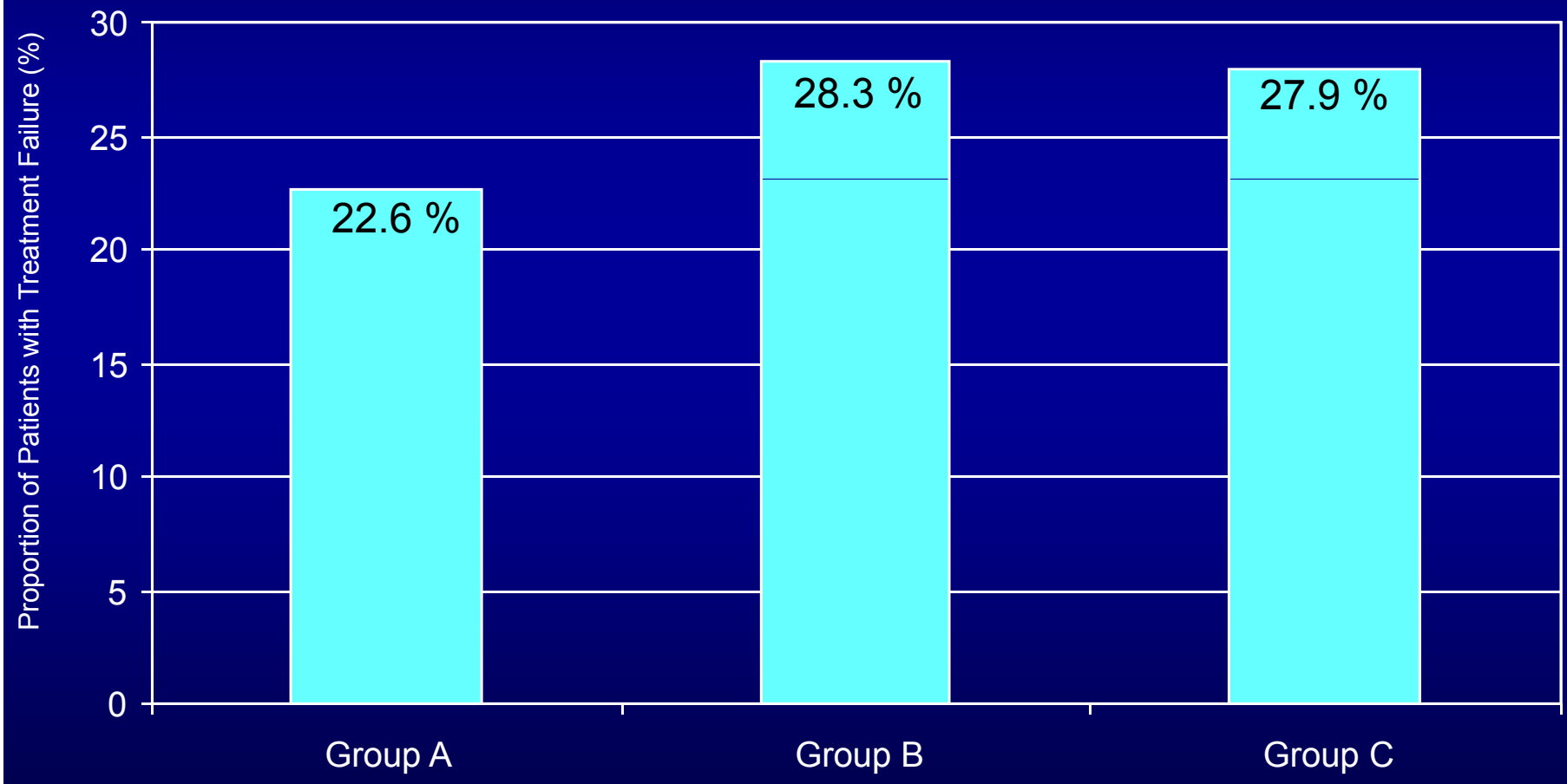
*P<.05 for TAC vs. CsA treatment groups at each time point except for Group B at Month 12.

Association of Trough Levels and MPA AUC by CNI



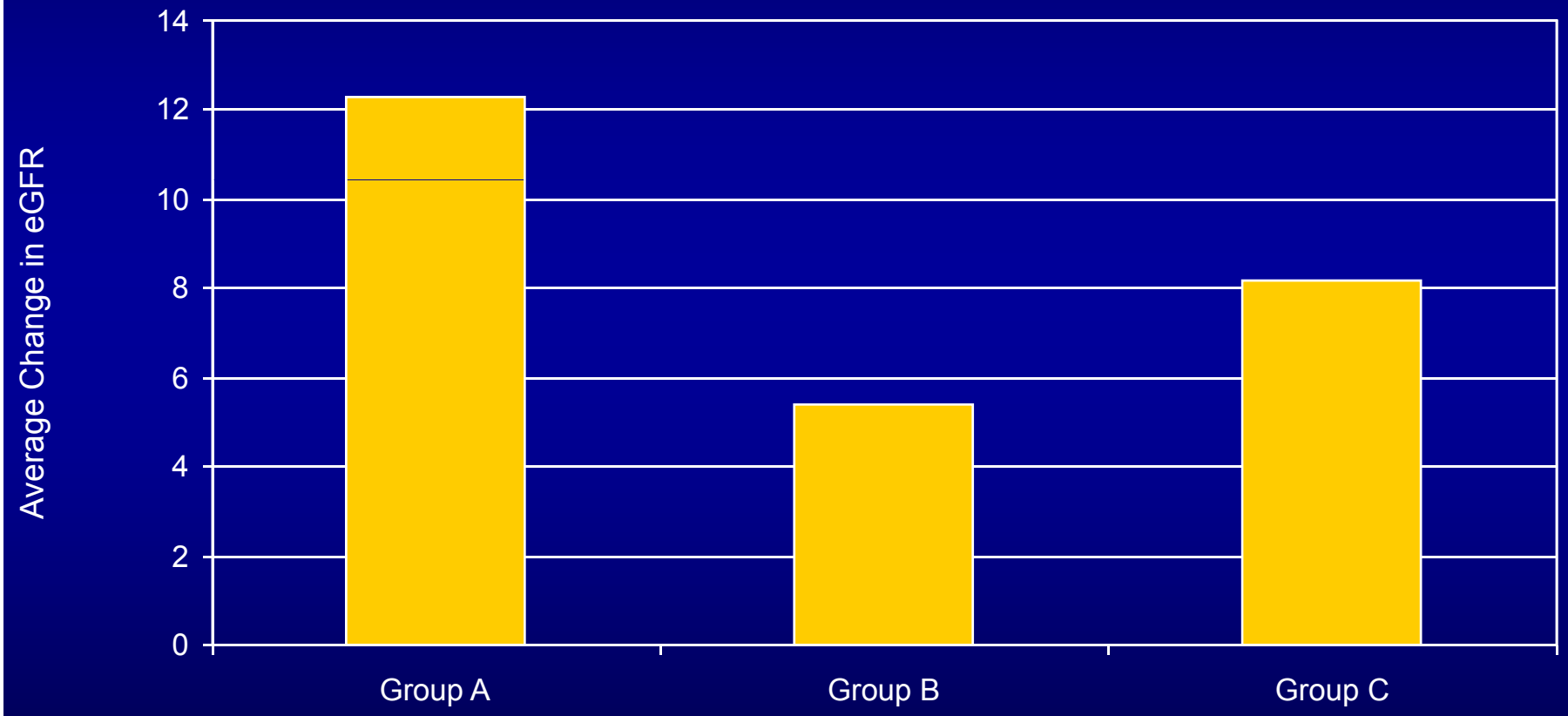
Results: Primary Endpoints

Primary Efficacy Endpoints: Treatment Failure



Group A vs. C p-value = 0.18, Group B vs. C p-value = 0.87, Group A vs. B p-value = 0.13

Primary Efficacy Endpoints: Change in eGFR



p-value = NS; pairwise comparisons not reported

Safety Endpoints

	Group A MMF_{CC}/CNI_{RL}		Group B MMF_{CC}/CNI_{SL}		Group C MMF_{FD}/CNI_{SL}	
	CsA N=40	TAC N=198	CsA N=45	TAC N-188	CsA N=42	TAC N=196
Diarrhea*	5 (13%)	93 (47%)	16 (36%)	86 (46%)	6 (14%)	90 (46%)
Leukopenia	19 (48%)	111 (56%)	28 (62%)	95 (51%)	18 (43%)	106 (54%)
Hypertension	7 (18%)	48 (23%)	8 (17%)	45 (22%)	11 (26%)	29 (19%)
Opportunistic Infections	5 (13%)	17 (9%)	6 (13%)	23 (12%)	3 (7%)	20 (10%)
Diabetes ** Mellitus	2 (5%)	32 (16%)	2 (4%)	23 (12%)	1 (2%)	18 (9%)
Malignancies	2 (5%)	3 (2%)	0 (0%)	6 (3%)	1 (2%)	6 (3%)
Hyperlipidemia	35 (85%)	158 (78%)	38 (81%)	139 (73%)	32 (76%)	148 (75%)

*** P<.0001: Impact of TAC on time to first episode within 90 days post-transplant**
****P<.05 TAC vs CsA treatment groups.**
P=NS for remaining between group comparisons.

Safety Endpoints

- No differences in CMV infection between treatment arms:
  - Group A (5.0%)
  - Group B (6.0%)
  - Group C (7.6%)

- No differences in BK-virus infection:
  - Group A (1.7%)
  - Group B (3.0%)
  - Group C (3.4%)

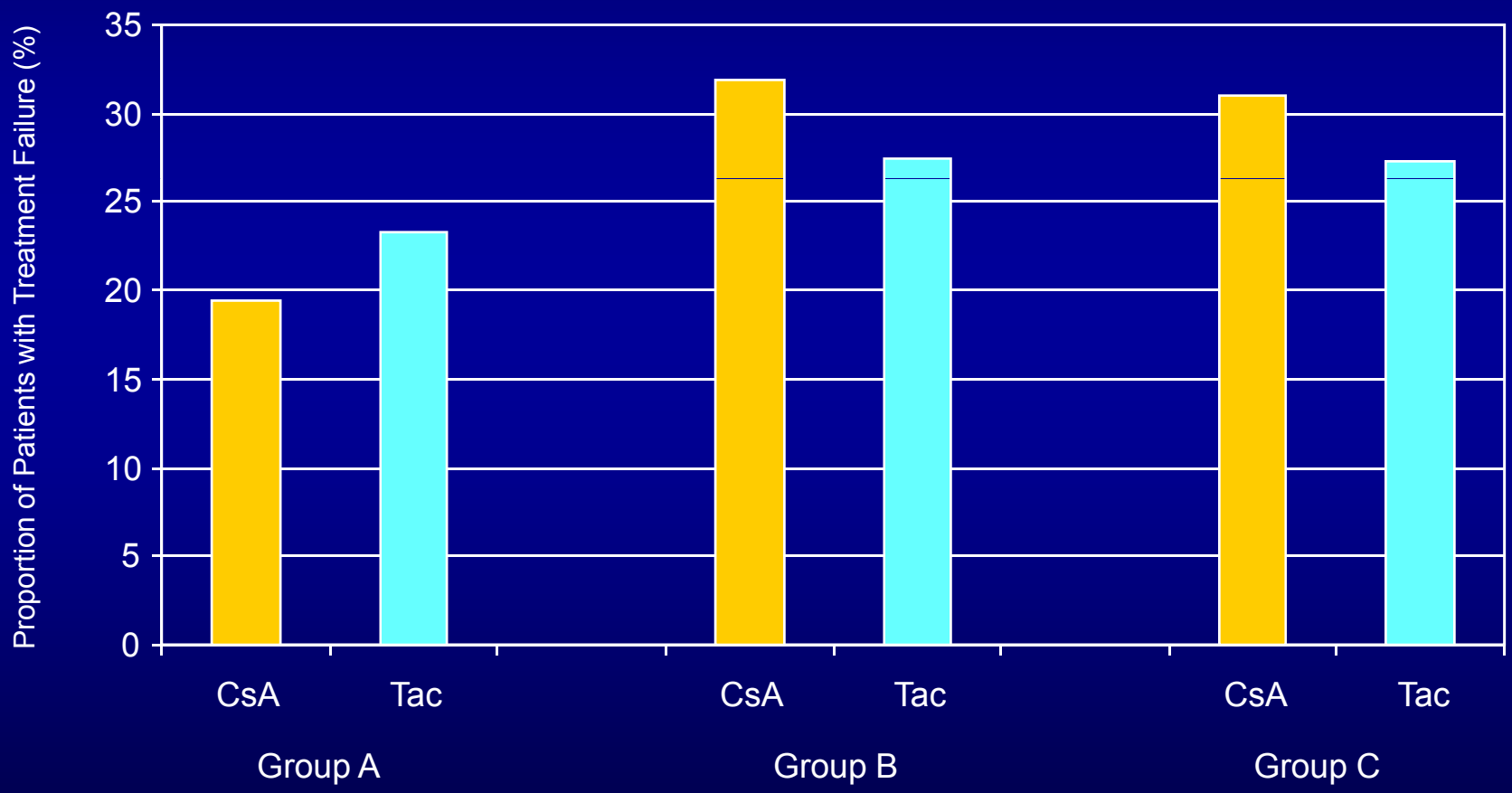
Treatment Failure at 12 Months

	Group A MMF_{CC}/CNI_{RL} N=243	Group B MMF_{CC}/CNI_{SL} N=237	Group C MMF_{FD}/CNI_{SL} N=240
Treatment Failure	55 (22.6%)*	67 (28.3%)	67 (27.9%)
Reason for Treatment Failure			
Biopsy-proven Acute Rejection	15 (6.2%)	23 (9.7%)	23 (9.6%)
Graft Loss	5 (2.1%)	4 (1.7%)	4 (1.7%)
Death	4 (1.6%)	2 (0.8%)	6 (2.5%)
Lost to Follow-up or Discontinued	15 (6.2%)	18 (7.6%)	22 (9.2%)
Withdrew Consent	16 (6.6%)	20 (8.4%)	12 (5.0%)

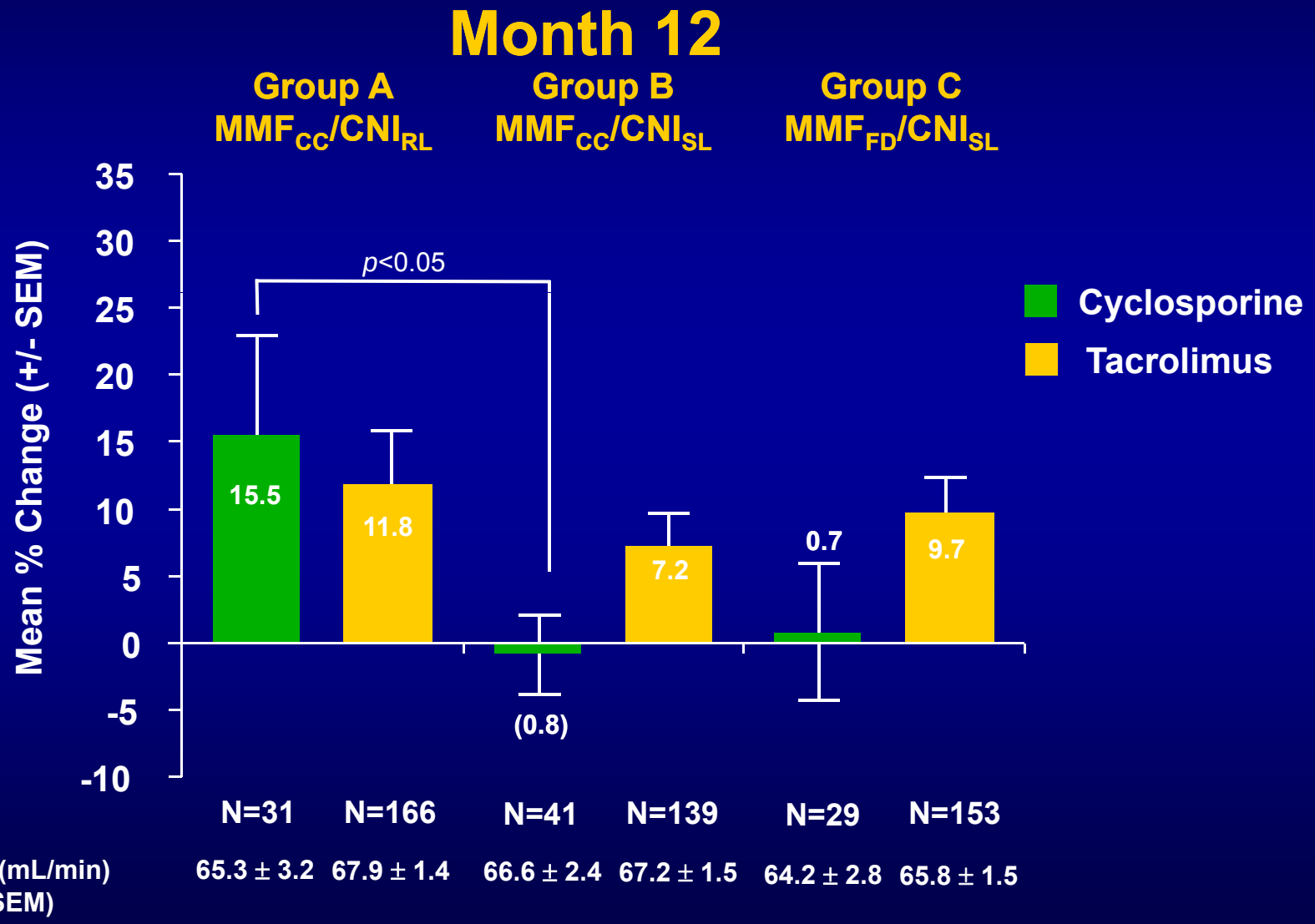
***P = NS for MMF_{CC}/CNI_{RL} vs MMF_{FD}/CNI_{SL}.**

Secondary Endpoints and Other Results

Treatment Failure by CNI



% Change from Baseline in GFR by CNI



P=NS for between group comparisons except as noted.

MPA Exposure and Time to First BPAR*

	Tacrolimus Subpopulation (N =590)			
	MPA Trough (Dose Corrected)		MPA AUC (Dose Corrected)	
	Risk Ratio	P-value	Risk Ratio	P-value
6 months posttransplant	0.490	0.0014	0.956	<0.0099
12 months posttransplant	0.593	0.0072	0.951	<0.0026
24 months posttransplant	0.583	0.0053	0.948	<0.0015

* Cox Proportional Hazards Model Estimate

Conclusions

- Concentration-controlled dosing of MMF was not inferior to a fixed-dose regimen of MMF for treatment failure
- No difference in the change in eGFR but a potential modifying effect by CNI
- Association of higher MPA trough levels with reduced time to AR

Limitations (my views)

- Reduced levels not fully achieved
- No comparative group of reduced fixed dose levels
- Overall acute rejection and graft loss rates low, potentially unable to demonstrate effects
- High contribution of patient withdrawals and discontinuations for composite endpoint
- Does this answer the question concerning the utility of trough monitoring with CNI-sparing?

Investigators and Study Centers

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Thank you

My Take Away Messages from this Trial

- No differences in treatment failure or renal function between fixed and concentration-controlled MMF regimens
- Secondary analyses suggest modifying effects based on CNI and an association of MPA trough levels with AR

Conclusions

- Greater MPA exposure is highly correlated with reduced risk of acute rejection.
- A regimen of concentration-controlled MMF/reduced-level CNI is not inferior to fixed-dose MMF/ standard-dose CNI as regards treatment failure or overall safety profile.
- Compared with standard-dose CNI, patients treated with a regimen of concentration-controlled MMF and reduced-level CNI
  - receive significantly higher doses of MMF regardless of CNI
  - have greater MPA exposure if taking cyclosporine
  - may tend to have reduced treatment failure rates, fewer rejections, and significantly lower withdrawal rates
  - demonstrate greater stability of eGFR

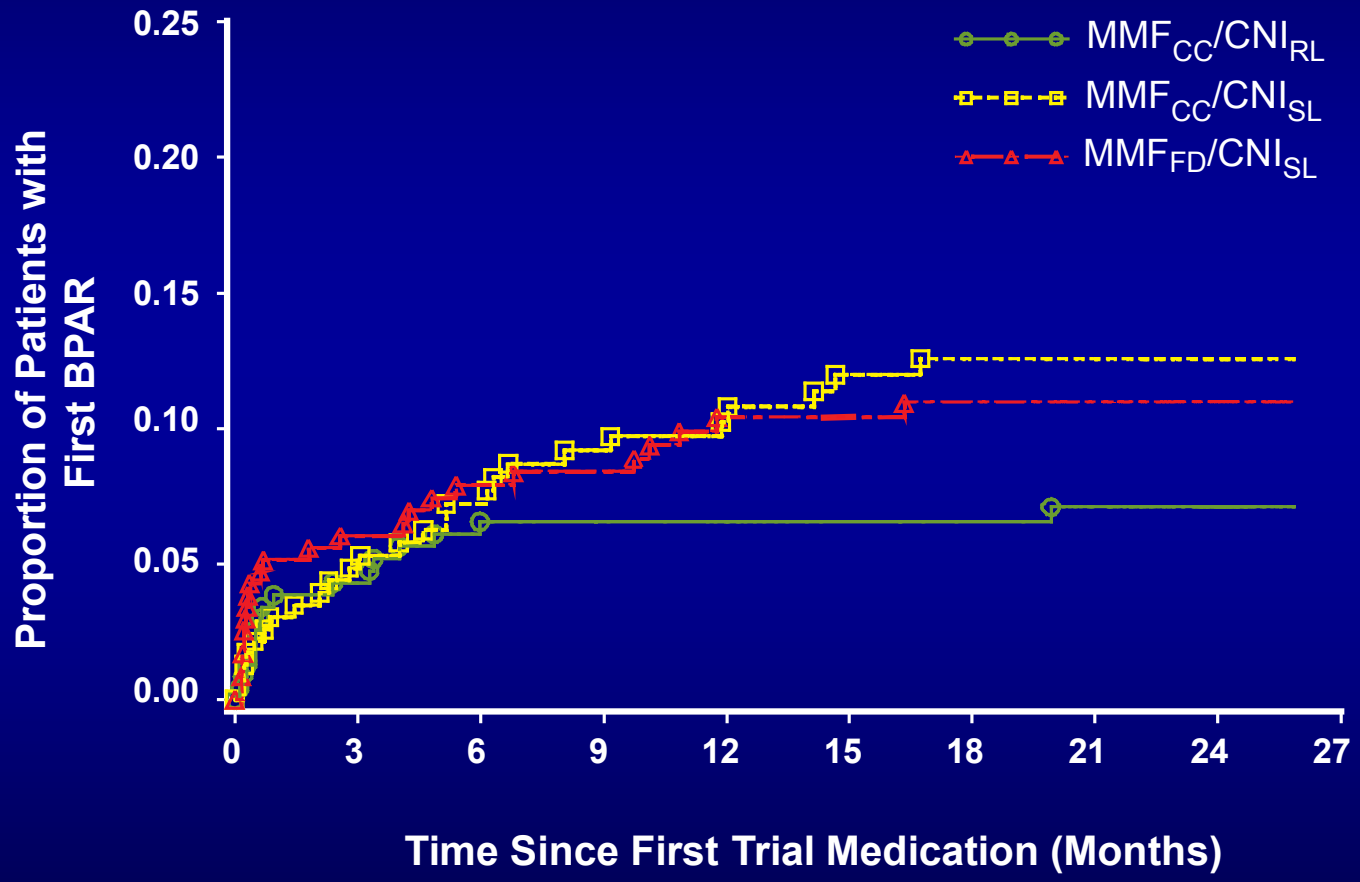
Secondary Endpoints

- Treatment failure within 24 months
- Proportion of patients with BPAR
- Proportion of patients with treatment for rejection between 12-24 months
- The number of BPAR per patients between 12-24 months
- The time to BPAR between 12-24 months
- The proportion of patients who died, experienced graft loss, or discontinued MMF between 12-24 months
- Time to treatment failure

Final Thoughts

- What is the value and interpretation of the post-hoc analyses?
- What is the meaning of non-inferiority in this context?
- What is the interpretation of the complex composite endpoint in this context?
- Does this answer the question concerning the utility of trough monitoring with CNI-sparing?

Kaplan-Meier Estimates of Time to First Biopsy-Proven Rejection Within 24 Months Posttransplant



Reasons for Patient Withdrawals

	Group A MMF_{CC}/CNI_{RL} N=243	Group B MMF_{CC}/CNI_{SL} N=237	Group C MMF_{FD}/CNI_{SL} N=240
Safety	23 (10%)	38 (16%)	36 (15%)
Adverse Event	18 (7%)	34 (14%)	34 (14%)
Death	5 (2%)	4 (2%)	2 (1%)
Nonsafety	40 (17%)	49 (21%)	51 (21%)
Total	63 (26%)*	87 (37%)	87 (36%)

Results

- No significant difference in secondary efficacy endpoints
- No significant difference in adverse events
  - CMV infections:
    - Group A: 5.0%
    - Group B: 6.0%
    - Group C: 7.6%
- Increased time to AR with lower trough levels

MPA Exposure and Time to First BPAR*

	Tacrolimus Subpopulation (N =590)			
	MPA Trough (Dose Corrected)		MPA AUC (Dose Corrected)	
	Risk Ratio	P-value	Risk Ratio	P-value
6 months posttransplant	0.490	0.0014	0.956	<0.0099
12 months posttransplant	0.556	0.0072	0.951	<0.0126
24 months posttransplant	0.583	0.0053	0.948	<0.0015

Higher MPA trough and AUC levels had a significant impact on time to first BPAR and a lower risk of rejection in patients on tacrolimus

* Cox Proportional Hazards Model Estimate

Safety Endpoints

- All Adverse events
- Opportunistic infections
- Malignancies
- Abnormal laboratory findings
- Renal function based on eGFR at 3, 6, and 24 months

Results

Mean Percent Change in eGFR by Treatment Regimen and CNI:

Group A (22.6%)
- CsA +15.5%
- Tac +11.8%

Group B (28.3%)
- CsA 0%
- Tac 7.2%

Group C (27.9%)
- CsA +0.7%
- Tac +9.7%%

- Group A with CsA vs Group B with CsA (p=0.0461)

Trial Design

- Initial dose of oral or intravenous MMF was 1 g twice daily for adults and 600 mg/m^2 twice daily for pediatric patients

- For patients in groups A and B, the dose was adjusted to achieve whole blood MPA trough levels of ≥ 1.3 µg/mL for cyclosporine-treated patients and ≥ 1.9 µg/mL for tacrolimus- treated patients

Primary Endpoints

- Efficacy at 12 months determined by the proportion of patients experiencing treatment failure (any of: BPAR, graft loss, death, lost to follow up or withdrawal of consent)
- Co-primary endpoint was change in renal function from baseline based on eGFR at 12 months by the Nankivell equation.