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Pharmacokinetics of enteric coated mycophenolate sodium in lupus nephritis (POEMSLUN)

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Author Contributions

DR, GTJ and JAR designed the study and wrote the protocol. HH, HL and RF advised and reviewed the study protocol. PK was involved with study recruitment. BCMcw, JAR and JU were involved in the analysis of samples. AL, MJR, MLP and RR were involved in the collection of blood samples. MHAA assisted in data analysis and preparation of the manuscript. All authors read and approved the final version of the manuscript.

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the Australian National Health and Medical Research Council Centre of Research Excellence (APP1099452).

Conflicts of Interests

Dwarakanathan Ranganathan and George T. John were principal investigators for ASCERTAIN study sponsored by Novartis Australia (Pty) Limited and Novartis India (Pty) Limited, respectively.

Compliance with Ethical Standard Statement

The study was conducted in accordance with Good Clinical Practice Guidelines, the principles that have their origins in the 'Declaration of Helsinki' adopted by the World Medical Association in October 1996, the National Health and Medical Research Council (NHMRCC) National Statement on Ethical Conduct in Human Research (2007) or replacement or other relevant NHMRC publication or guideline that relate to clinical trials [1]

Abstract

Introduction: Mycophenolate mofetil (MMF) or enteric coated mycophenolate sodium (EC-MPS) and steroids are used for induction and maintenance therapy in severe lupus nephritis (LN). Blood concentrations of mycophenolic acid (MPA), the active metabolite of these

drugs varies among LN patients. The objective of this study was to examine whether concentration controlled (CC) dosing (via therapeutic drug monitoring) of EC-MPS result in a higher proportion of participants achieving target exposure of MPA compared to fixed dosing (FD). An additional aim of the study was to evaluate the influence of CC dosing on clinical outcomes.

Methods: Nineteen participants were randomly assigned either to FD or CC group. All the participants were eligible to have free and total measurements of MPA over a period of 8-12 hours on three different occasions. Area under the concentration-time curve between 0 and 12 hours (AUC_{0-12}) was calculated using non-compartmental method. Dose of EC-MPS was titrated according to AUC_{0-12} in the CC group.

Results: Thirty-two AUC_{0-12} measurements were obtained from 9 FD and 9 CC participants. Large interpatient variability was observed in both groups but was more pronounced in FD group. There were no significant differences between FD and CC participants in any pharmacokinetic parameters across the study visits except for total C_0 (FD 2.0 ± 0.3 mg/L vs. CC 1.1 ± 0.3; p = 0.01) and dose-normalised C_0 (FD 2.9 ± 0.2 mg/L/g vs. CC 2.1 ± 0.7 mg/L/g; p = 0.04) at the second visit and total AUC_{0-12} (FD 66.6 ± 6.0 mg·h/L vs. CC 35.2 ± 11.4 mg·h/L; p = 0.03) at the third visit. At the first study visit, 33.3% of the FD and 11.1% of the CC participants achieved the target AUC (p = 0.58). From the second visit, none of the FD participants, compared to all the CC participants, achieved target AUC_{0-12} (p = 0.01). More CC participants achieved remission compared to FD participants (absolute difference of -22.2, 95% confidence interval −0.19-0.55; p = 0.62). The mean free MPA AUC_{0-12} was significantly lower in those who had complete remission.

Conclusions: CC participants reached target AUC_{0-12} quicker. Larger studies are required to test clinical efficacy.

Keywords: Pharmacokinetics, Therapeutic Drug Monitoring (TDM), Enteric Coated Mycophenolate Sodium (EC-MPS), Lupus Nephritis (LN)

Introduction

Regional and international guidelines are available for the management of lupus nephritis (LN) for both adult and paediatric populations.[1-5] These guidelines advocate steroids and mycophenolic acid (MPA) prodrugs, mycophenolate mofetil (MMF) or enteric coated mycophenolate sodium (EC-MPS) for induction and maintenance therapy in class III, IV and V LN.[3] Guidelines recommend gradual dose titration of MMF to 2000-3000 mg/day as induction therapy and 1000-2000 mg/day as maintenance treatment to achieve best possible toxicity/efficacy ratio.[3] An equivalent dose of EC-MPS at 1440-2160 mg is administered as induction therapy.[6] The dose of MMF varies in clinical studies and this partly accounts for variable efficacy. Further, adverse events lead to dose reduction and suboptimal outcome.[7] Therapeutic drug monitoring (TDM) is used to maximise the efficacy and minimise the side effects with therapy based on exposure rather than dose.[8] It is unclear if the TDM of MPA, the active entity and dose modulation of its prodrugs (MMF/EC-MPS) would improve outcome in LN patients. While some studies have shown that area under the concentration-time curve (AUC) of 35-45 mg·h/L of MPA is associated with remission and therapeutic efficacy, there are no randomised controlled trials.[9-13] Administration of 1000 mg of MMF and equivalent 720 mg of EC-MPS result in a similar 12-hour MPA AUC,[6] though the pharmacokinetic profiles of MMF and EC-MPS differ. There are limited data on concentration-controlled EC-MPS dosing (via TDM) in LN patients. Additionally, there are no data on free MPA pharmacokinetics and relationship to outcome in LN patients treated with EC-MPS. This is important in LN patients with hypoalbuminemia as MPA is highly protein bound and the unbound drug is responsible for pharmacological effect. We therefore

performed a randomised controlled trial to determine whether concentration-controlled (CC) dosing of EC-MPS via TDM results in a higher proportion of participants achieving target MPA exposure range in LN compared with fixed-dosing (FD). We also report on the efficacy of EC-MPS in both groups and free MPA exposure on their clinical outcome.

Materials and Method

The protocol of POEMSLUN has previously been published.[14]

ETHICAL CONSIDERATIONS

The Human Research Ethics Committee of the Royal Brisbane and Women's Hospital (RBWH) (HREC/10/QRBW/426) approved this study. The study was registered on the Australia New Zealand Clinical Trial Registry ACTRN12611000798965.

PARTICIPANTS

The participants who fulfil the inclusion and exclusion criteria were recruited from in-patients at RBWH Renal and Rheumatology Departments or patients attending the Renal Rheumatology Lupus Vasculitis Clinic. All participants who had biopsy proven Class III/IV/V LN and aged ≥18 years and received EC-MPS for more than two weeks either as induction or maintenance therapy were eligible for recruitment. All consenting participants were randomized to CC or FD group. The participants were stratified to induction and maintenance phase of treatment with EC-MPS.

RANDOMIZATION

Participants were block randomized into Group 1 or 2 in permuted block sizes of 2 and 4 with 33 and 66 percent respectively; stratified for induction and maintenance therapy. Due to the nature of intervention, research staff except the laboratory bio-analysts and participants, were

not masked to the treatment allocation. The participants were followed up for 12 months after the last participant was recruited.

STUDY INTERVENTION

Group 1: Fixed-dosing (FD)

Oral EC-MPS 30 mg/kg body weight was administered to induce remission. EC-MPS dosage was reduced by 180 mg twice daily on achieving complete remission or if there were side effects or if the total white cell count was <3500/mm^3.

Group 2: Concentration-controlled (CC)

The oral EC-MPS dose was titrated according to the AUC_{0-12}; tested at the first visit and adjusted to a target AUC_{0-12} of 40 to 60 mg·h/L at the second visit. The dosage was reduced if the AUC_{0-12} was above 60 mg·h/L. Once there was remission or if participants were randomized at maintenance phase of treatment, the AUC_{0-12} of 30 to 50 mg·h/L was maintained. Both groups received similar management other than EC-MPS dosing.

DATA COLLECTION

At the time of entry to study, clinical and demographic data were collected for each participant, including age, gender, weight, height, allergies, clinical information, other co-morbidities and concomitantly prescribed drugs. Laboratory investigations were performed every 12 weeks consisting of urine sediment examination, 24-hour urinary protein measurement and/ or urine protein to creatinine ratio (uPCR), renal function assessments-eGFR, liver function tests, complement components C3 and C4, antinuclear antibody (ANA), anti–double stranded DNA antibody and pharmacokinetic analysis of MPA.

PHARMACOKINETIC SAMPLING

Pharmacokinetic analysis of MPA was performed at different time points. Participants who entered the study at induction phase had their first analysis at 1-2 months, the second at 3-4 months and the third at 7-9 months. Protocol was amended and the participants in the maintenance phase had their assays at the time of entry and the second at three months later. Where participants were unable to attend for a 12-hour AUC determination, we extrapolated AUC_{0-12} from an 8-hour AUC determination as has been used elsewhere.[14] Blood samples were collected pre and post EC-MPS dose at 15-time points for the 8-hour group and, where participant consented, 17 samples for the 12-hour group. The pharmacokinetic values were calculated using non-compartmental methods. The AUC_{0-12} was calculated using the trapezoidal rule.

BIOANALYSIS

Total plasma MPA concentrations were determined using a validated ultra-high performance liquid chromatography- tandem mass spectrometry (UHPLC-MS/MS) method. MPA-d3 internal standard (Toronto Research Chemicals, Toronto, ON, Canada) in methanol was added to plasma, vortexed and centrifuged prior to analysis by UHPLC using an Acquity UPLC HSS T3 C18 analytical column (1.8 µm, 2.1 x 100 mm) and Acquity BEH C18 pre-column (1.7 µm, VanGuard 2.1 5 mm) (Water Corporation, Milford, MA, USA) maintained at 40 °C, with gradient elution using 2mM ammonium acetate and 0.1% formic acid in water (mobile phase A) and 2mM ammonium acetate and 0.1% formic acid in methanol (mobile phase B). Multiple reaction monitoring was carried out using positive electrospray ionization and detection of MPA (321.2>207.2) and MPA-d3 (324.3>310.2 transitions (Water Corporation, Milford, MA, USA).

Ultrafiltrates of plasma free mycophenolate were prepared by equilibrating 500µL of plasma at 37 ºC for 30 minutes in Centrifree regenerated cellulose 30,000 molecular weight cut-off centrifugal filter devices (Merck Millipore, Cork, Ireland) before centrifugation at 3040×g for 20 minutes at 37 ºC. The ultrafiltrate was then transferred to autosampler vials, mixed with MPA-d3 internal standard and injected directly into the UHPLC-MS/MS system described above. The assay was linear between 0.1-60 mg/L with intra-assay imprecision < 4% and inter-assay imprecision < 9%.

OUTCOME MEASURES

Primary

TDM of MPA was measured in CC and FD group to determine whether TDM-guided dosing of EC-MPS resulted in achieving established targets of MPA AUC_{0-12} of 40 to 60 mg·h/L in participants receiving induction therapy and target AUC_{0-12} of 30 to 50 mg·h/L in participants receiving maintenance therapy compared to the standard empirical dosing in participants with LN.

Secondary

Secondary outcome measures were complete and partial remission rates in the induction group and sustained remission/renal relapse in the maintenance group.

Complete remission was defined as a decrease in urinary protein measured over 24 hours to less than 500 mg/24 h, uPCR less than 0.5 mg/mg (50 mmol/mg), normal serum albumin and stabilisation (± 25%) or improvement in serum creatinine levels at week 24 from the initial sample.[5] Partial remission was defined as stabilisation (± 25%) or improved renal function (but still not to normal) with reduction of proteinuria by more than 50% ranging between 300 to 3000mg/24h and a serum albumin of more than 30 g/L.[5] Renal relapse was defined as

"recrudescence of renal disease after an initial response demonstrated by a recent increase in serum creatinine by >50% with active urinary sediment and or increase in proteinuria to 3500 mg/day or greater".[15] Proteinuria was measured using uPCR or by 24-hour urinary protein excretion.

Statistical methods

An interim analysis demonstrated slow recruitment and the trial was terminated as most patients in the CC group achieved target AUC before intervention. Continuous data were compared using the Student t-test or Mann-Whitney U test as appropriate and dichotomous variables were compared using the Pearson's chi-square or Fisher's exact test as appropriate. Correlations between individual MPA concentrations and AUC_{0-12} for total and free drug concentrations were evaluated by Pearson or Spearman correlation as appropriate. All data were analysed on an intention-to-treat basis, and a significance level of 0.05 was assumed. One of the coauthor, MHAA, who was masked to the study allocation and not involved in the clinical care of the participants adjudicated outcome measures.

Results

BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Twenty-seven patients were screened for eligibility, of whom 19 were randomly assigned to the FD (n = 9) or CC (n = 10) treatment groups. One participant was not compliant with treatment and was excluded from outcomes assessment. The final analysis only included 18 participants; nine participants in each treatment group (Figure 1).

The baseline characteristics of the 18 participants are presented in Table 1. There were no significant differences between FD and CC participants in any demographic and clinical characteristics at study entry. The mean (SD) follow-up time was 82.2 ± 33.3 weeks.

MYCOPHENOLIC ACID PHARMACOKINETICS

The total and free MPA pharmacokinetic parameters are summarised in Table 2. Thirty-two AUC_{0-12} measurements were obtained from 18 participants; 18 AUCs from the first visit, 9 from the second visit and 5 from the third visit. Large inter-patient variability (percentage coefficient of variation (%CV) of ≥40%) was observed in all pharmacokinetic parameters across both groups but these variations were more pronounced in the FD treatment group (%CV of ≥60%). Correlations between MPA concentrations at different sampling time-points, with AUC_{0-12} for total and free MPA are presented in Table 3. A moderate positive correlation was observed between MPA AUC_{0-12} and C_0, C_{max} and C_{12} for total and free MPA concentrations (Figure 2). Serum albumin inversely correlated with free C_{12} ($r = –0.42$; $p = 0.04$) and free MPA AUC_{0-12} ($r = –0.43$; $p = 0.03$). There were no significant differences between FD and CC participants in any pharmacokinetic parameters across the study visits except for total C_0 (FD 2.0 ± 0.3 mg/L vs. CC 1.1 ± 0.3; $p = 0.01$) and dose-normalised C_0 (FD 2.9 ± 0.2 mg/L/g vs. CC 2.1 ± 0.7 mg/L/g; $p = 0.04$) at the second visit and total AUC_{0-12} (FD 66.6 ± 6.0 mg·h/L vs. CC 35.2 ± 11.4 mg·h/L; $p = 0.03$) at the third visit (Table 2).

PRIMARY OUTCOME

The MPA exposure between FD and CC treatment groups across the three study visits is presented in Table 3 and Figure 3. Overall, 20.0% (n = 3/15) of FD participants and 52.9% (n = 9/17) of CC participants achieved the target MPA exposure range ($p = 0.06$). At the first study visit (week 4–6), only 33.3% (n = 3/9) of the FD participants and 11.1% (n = 1/9) of the CC participants achieved the target MPA exposure range ($p = 0.58$). However, from week 14, none of the FD participants achieved the target MPA exposure whilst all the CC participants did. Nevertheless, a statistically significant difference between the two treatment groups was only observed on the second study visit (week 14-16) (FD 0.0% [n = 0/4] vs. CC 100.0% [n = 5/5]; $p = 0.01$). Among those who failed to achieve the target exposure range

(Figure 4), 75% (n = 9/12) of the FD participants demonstrated supra-therapeutic MPA exposure (mean ± SD [range] MPA exposure 57.9 ± 36.5 [1-126.3] mg·h/L).

SECONDARY OUTCOMES

Table 4 presents the differences in participant characteristics between those who demonstrated complete remission/sustained remission and partial remission in this study. At 24 weeks, 7 of the 9 FD participants (77.8%) and 5 of the 9 CC participants (55.6%) demonstrated either complete remission in the induction group or sustained remission in the maintenance group (absolute difference of −22.2, 95% confidence interval −0.19-0.55; p = 0.62). In this study, no participants had renal relapse in the maintenance group. There was no significant difference in the mean total MPA AUC_{0-12} among participants who demonstrated complete and partial remission (37.8 ± 18.9 mg·h/L vs. 49.6 ± 41.7 mg·h/L; p = 0.32). However, the mean free MPA AUC_{0-12} was significantly lower in those who had complete remission than those with partial remission (311.6 ± 143.0 µg·h/L vs. 631.8 ± 332.8 µg·h/L; p = 0.01). In this study, clinical response was not significantly associated with the achievement of target MPA exposure (Table 4).

Serum creatinine, blood urea, estimated glomerular filtration rate, serum albumin, serum C3 and C4 were similar between FD and CC participants throughout the 48-week study period (Figure 5).

ADVERSE EVENTS

The total number of adverse events were similar between FD and CC treatment groups (Table 5). Nausea and vomiting as well as fever occurred in 2 patients for each group. The median (IQR) total MPA exposure of those participants with and without adverse events were 27.3 mg/L and 39.2 mg/L (p = 0.11), respectively. The median (IQR) free MPA exposure of participants with and without adverse events were 553.9 µg/L and 338.0 µg/L, respectively (p

= 0.404). Two participants in each treatment group had to discontinue EC-MPS due to treatment-related adverse events.

Discussion

Our study is the first randomised controlled trial in LN patients to determine if TDM adjusted dosing achieved established MPA exposure targets efficiently compared to FD of EC-MPS. All CC participants reached target MPA exposure earlier than the FD group. The difference was statistically significant at the second study visit as EC-MPS dose was adjusted based on MPA exposure during the first visit.

The objective of CC dosing is to improve the clinical outcome and reduce adverse events with adequate drug exposure. Mycophenolate Mofetil and EC-MPS are typically administered at a FD in patients with LN. There is wide interpatient variability of blood concentrations of MPA, the active metabolite of MMF and EC-MPS. There are several studies on MMF dosing based on TDM attempting to improve outcome in LN but there is little data on EC-MPS. Neuman et al. were the first to show that the MPA exposure from EC-MPS is comparable in 12 autoimmune patients (mean 27.3 ± 17.4 mg/L) and 11 renal transplant patients (mean 19.6 ± 15.7 mg/l).[16] Lertdurrongluk et al. studied the pharmacokinetics of MPA in 18 Thai patients with biopsy-proven LN, a month after initiating treatment with a FD of 1.0-1.5 g/D of MMF in 12 and 1080-1440 mg/D of EC-MPS in 6 patients respectively.[11] The responders had a significantly higher MPA AUC (>45mg·h/L). All these studies were either observational or retrospective and the pharmacokinetics of MPA was studied after administering FD of MPA prodrugs.

A large inter-patient variability was observed in all pharmacokinetic parameters across both the groups as in other studies; however, this was more pronounced in the FD group. We

observed a moderate correlation between MPA AUC_{0-12} with C_0 and C_{max} for total and free MPA and a stronger correlation between MPA AUC_{0-12} and C_{12} total and free MPA concentrations in contrast to the lack of correlation reported by Lertdumrongluk et al.[11] Djabarouti et al. studied TDM in 35 Systemic Lupus Erythematosus patients with no renal involvement, 21 receiving MMF and 14 taking EC-MPS.[17] They concluded, as we observed in our study with EC-MPS, that C12 after MMF ingestion could predict MPA AUC0-12. They however found the correlation to be weak in patients receiving EC-MPS.

We have shown earlier attainment of target AUC with lower doses using CC dosing in LN as compared with FD. This may be of importance with limiting side-effects in the longer term, especially in patients with history of past immunosuppression or immune impairment and in regions where LN is more resistant to therapy. More CC participants achieved remission with lower doses compared to FD participants although this difference did not reach statistical significance.

This is the first report to study the free MPA concentration on clinical outcome in LN patients treated with EC-MPS. Abd Rahman et al. studied the unbound fraction of MPA and its metabolite 7 -O-MPA-β-glucuronide (MPAG) in 25 LN patients receiving MMF.[18] They found similar MPA exposure between responders and non-responders. Our study also showed higher free MPA exposure in patients who had partial remission. Patients who had partial remission had lower albumin resulting in higher free MPA exposure. We found an inverse correlation of albumin to MPA exposure in LN patients receiving EC-MPS.

This study has limitations with small sample size and premature termination due to slow recruitment. Despite these limitations, we observed that therapeutic exposure of MPA could be achieved with CC dosing. A larger study would define if CC dosing of EC-MPS improves therapeutic outcome in LN patients.

Conclusions

Concentration-controlled dosing of EC-MPS resulted in a higher proportion of participants achieving target exposure of MPA quicker. Larger prospective studies on CC drug dosing and therapeutic outcome will likely demonstrate the clinical efficacy of this approach.

References

1. https://nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2007-updated-2018 accessed 19 February 20191. Groot N, de Graeff N, Marks SD, et al. European evidence-based recommendations for the diagnosis and treatment of childhood-onset lupus nephritis: the SHARE initiative. *Ann Rheum Dis.* 2017;76:1965-1973.

2. Mok CC, Yap DY, Navarra SV, et al. Overview of lupus nephritis management guidelines and perspective from Asia. *Int J Rheum Dis.* 2013;16:625-636.

3. Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. *Ann Rheum Dis.* 2012;71:1771-1782.

4. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res (Hoboken).* 2012;64:797-808.

5. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int.* 2012;2:1-138.

6. Pietruck F, Abbud-Filho M, Vathsala A, et al. Conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in stable maintenance renal transplant patients: pooled results from three international, multicenter studies. *Transplant Proc.* 2007;39:103-108.

7. Alexander S, Fleming DH, Mathew BS, et al. Pharmacokinetics of concentration-controlled mycophenolate mofetil in proliferative lupus nephritis: an observational cohort study. *Ther Drug Monit.* 2014;36:423-432.

8. van Gelder T, Berden JH, Berger SP. To TDM or not to TDM in lupus nephritis patients treated with MMF? *Nephrol Dial Transplant.* 2015;30:560-564.

9. Luszczynska P, Pawinski T. Therapeutic drug monitoring of mycophenolic acid in lupus nephritis: A review of current literature. *Ther Drug Monit.* 2015;37:711-717.

10. Djabarouti S, Breilh D, Duffau P, et al. Steady-state mycophenolate mofetil pharmacokinetic parameters enable prediction of systemic lupus erythematosus clinical flares: an observational cohort study. *Arthritis Res Ther.* 2010;12:R217.

11. Lertdumrongluk P, Somparn P, Kittanamongkolchai W, et al. Pharmacokinetics of mycophenolic acid in severe lupus nephritis. *Kidney Int.* 2010;78:389-395.

12. Zahr N, Arnaud L, Marquet P, et al. Mycophenolic acid area under the curve correlates with disease activity in lupus patients treated with mycophenolate mofetil. *Arthritis Rheum.* 2010;62:2047-2054.

13. Touw DJ, Neef C, Thomson AH, et al. Cost-effectiveness of therapeutic drug monitoring: a systematic review. *Ther Drug Monit.* 2005;27:10-17.

14. Ranganathan D, John GT, Healy H, et al. A Protocol for the Pharmacokinetics of Enteric Coated Mycophenolate Sodium in Lupus Nephritis (POEMSLUN): an open-label, randomised controlled trial. BMJ Open. 2013;3:pii:e003511.

15. Hill GS, Delahousse M, Nochy D, et al. Outcome of relapse in lupus nephritis: roles of reversal of renal fibrosis and response of inflammation to therapy. *Kidney Int.* 2002;61:2176-2186.

16. Neumann I, Fuhrmann H, Kanzler M, et al. Pharmacokinetics of enteric-coated mycophenolate sodium: comparative study in patients with autoimmune disease and renal allograft. *Expert Opin Pharmacother.* 2008;9:879-886.

17. Djabarouti S, Duffau P, Lazaro E, et al. Therapeutic drug monitoring of mycophenolate mofetil and enteric-coated mycophenolate sodium in patients with systemic lupus erythematosus. *Expert Opin Pharmacother.* 2010;11:689-699.

18. Abd Rahman AN, Tett SE, Abdul Gafor HA, et al. Exposure-effect relationship of mycophenolic acid and prednisolone in adult patients with lupus nephritis. *Br J Clin Pharmacol.* 2015;80:1064-1075.

Figure Legend

Figure 1: Study flow chart

Figure 2: Correlations between MPA C0 and MPA AUC0-12 for (A) total MPA and (B) free MPA concentrations, between MPA Cmax and AUC0-12 for (C) total MPA and (D) free MPA concentrations, and between MPA C12 and MPA AUC0-12 for (D) total MPA and (E) free MPA concentrations

Figure 3: Total and free MPA AUC0-12 between fixed-dosing and concentration-controlled participants across the study visits a,b

Figure 4: MPA exposure between fixed-dosing and concentration-controlled participants across the study visits a,b,c

Figure 5: Changes in treatment-related variables over the 48-week of study period

Table 1: Baseline demography and clinical characteristics of the study population [a]

	Fixed–dosing (n = 9)	Concentration–controlled (n = 9)	p–value[b]
Age (in years)	47.6 ± 16.0	50.9 ± 14.0	0.64
Gender, n (%)			
Male	2 (22.2)	2 (22.2)	1.00
Female	7 (77.8)	7 (77.8)	
Race, n (%)			
Caucasian	8 (88.9)	7 (77.8)	0.38
Asian	0 (0.0)	1 (11.1)	
Hispanic	0 (0.0)	1 (11.1)	
Other	1 (11.1)	0 (0.0)	
Weight (kg)	75.5 ± 14.2	81.0 ± 24.2	0.57
Renal pathology, n (%)			
ISN/RPS Class III	2 (22.2)	2 (22.2)	1.00
ISN/RPS Class IV	5 (55.6)	5 (55.6)	
ISN/RPS Class V	2 (22.2)	2 (22.2)	
Serum creatinine (µmol/L)	99.9 ± 40.7	83.9 ± 42.8	0.43
eGFR (mL/min/1.73 m^2)	67.3 ± 25.0	88.1 ± 39	0.20
eGFR classification, n (%)			
Urine protein (g/24 hours)	1.4 ± 1.5	2.9 ±3.8	0.39
Urine protein/creatinine ratio	38.0 (10.5 – 174.0)	18.0 (6.5 – 557.5)	0.80
Serum albumin (g/L)	36.4 ± 5.6	34.0 ± 8.9	0.50
Serum complement (g/L)			
C3	0.8 ± 0.3	1.0 ± 0.4	0.36
C4	0.2 ± 0.1	0.2 ± 0.1	0.94
Anti–dsDNA	33.0 ± 24.8	48.1 ± 38.6	0.46
EC–MPS dose (g/day)	1.44 (0.45 – 1.44)	1.44 (0.54 – 1.44)	0.78

EC–MPS dose (g/kg/day)	0.01 (0.01 – 0.02)	0.02 (0.01 – 0.03)	0.67
Prednisolone dose (mg/day)	10.0 (5.0 – 15.0)	8.0 (5.0 – 40.0)	0.86

ALP = alkaline phosphatase; ALT = alanine transaminase; Anti–dsDNA = anti–double strand DNA; ARB = angiotensin II receptor blocker; AST = aspartate transaminase; BMI = body mass index; EC–MPS = enteric–coated mycophenolate sodium; eGFR = estimated glomerular filtration rate; GGT = gamma–glutamyl transferase; ISN/RPS = International Society of Nephrology/Renal Pathology Society

[a]Data are presented as mean ± standard deviation or median (interquartile range) for continuous variables and number and percentage for categorical variables.

[b]Continuous variables were compared using the t–test or Mann–Whitney U–test as appropriate and dichotomous variables were compared using the Pearson's chi–square test or Fisher's exact test as appropriate.

Table 2: Summary of pharmacokinetic sampling and pharmacokinetic parameters of total and free mycophenolic acid in the study population[a]

Total number of MPA AUCs	32								
Number of MPA AUCs per study visit, n (%)									
First visit[b]	18 (56.3)								
Second visit[c]	9 (28.1)								
Third visit[d]	5 (15.6)								
	First visit			**Second visit**			**Third visit**		
Total MPA concentration	**FD** n = 9	**CC** n = 9	**p[e]**	**FD** n = 4	**CC** n = 5	**p[e]**	**FD** n = 2	**CC** n = 3	**p[e]**
AUC_{0-12} (mg·h/L)	49.0 ± 35.5	29.0 ± 16.6	0.15	62.4 ± 39.4	35.0 ± 3.9	0.26	66.6 ± 6.0	35.2 ± 11.4	**0.03**
Dose normalised AUC_{0-12} (mg·h/L/g)	117.9 ± 94.1	45.5 ± 27.1	0.05	92.9 ± 54.3	62.1 ± 6.3	0.34	92.5 ± 8.2	75.2 ± 17.4	0.37
C_0 (mg/L)	1.8 ± 1.3	1.2 ± 0.2	0.30	2.0 ± 0.3	1.1 ± 0.3	**0.01**	2.0 ± 0.0	2.7 ± 0.5	0.31
Dose normalised C_0 (mg/L/g)	4.6 ± 3.9	2.2 ± 1.5	0.14	2.9 ± 0.2	2.1 ± 0.7	**0.04**	2.8 ± 0.0	5.1 ± 1.2	0.23
C_{max} (mg/L)	15.5 ± 6.6	11.1 ± 7.1	0.20	23.4 ± 15.1	16.5 ± 6.3	0.44	17.0 ± 4.1	14.5 ± 15.1	0.86
Dose normalised C_{max} (mg/L/g)	43.5 ± 39.8	15.3 ± 8.4	0.08	35.4 ± 21.9	29.2 ± 11.5	0.64	23.6 ± 5.7	27.1± 27.6	0.88
C_{12} (mg/L)	2.7 ± 2.2	1.4 ± 0.6	0.13	2.6 ± 1.3	1.4 ± 0.5	0.14	2.9 ± 1.3	2.4 ± 0.8	0.70
Dose normalised C_{12} (mg/L/g)	6.9 ± 5.8	2.2 ± 1.0	0.06	3.8 ± 1.6	2.6 ± 1.0	0.25	4.0 ± 1.8	4.7 ± 1.9	0.76
T_{max} (h)	3.9 ± 2.3	3.7 ± 1.8	0.79	3.5 ± 1.4	4.0 ± 2.0	0.70	4.0 ± 4.2	3.3 ± 1.1	0.85
	First visit			**Second visit**			**Third visit**		
Free MPA concentration	**FD** n = 9	**CC** n = 9	**p[e]**	**FD** n = 4	**CC** n = 5	**p[e]**	**FD** n = 2	**CC** n = 3	**p[e]**
AUC_{0-12} (µg·h/L)	302.6	266.2	0.37	484.0	323.0	0.40	453.8	288.3	0.67

	(284.4 – 574.2)	(138.9 – 506.7)		(414.6 – 736.4)	(179.8 – 509.1)		(367.3 – 540.3)	(186.9 – 389.7)	
Dose normalised AUC_{0-12} (µg·h/L/g)	1431.1 (396.3 – 1595.0)	460.2 (324.1 – 1000)	0.14	672.3 (655.7 – 1022.7)	625.8 (333.0 – 956.6)	0.63	630.3 (510.2 – 750.4)	547.7 (373.8 – 721.7)	0.67
C_0 (µg/L)	10.1 (7.3 – 20.5)	11.9 (10.3 – 18.3)	0.63	12.5 (11.4 – 12.9)	6.2 (4.6 – 10.9)	0.11	16.9 (10.6 – 23.3)	18.5 (14.3 – 22.6)	1.00
Dose normalised C_0 (µg/L/g)	32.1 ± 19.7	26.6 ± 10.7	0.53	18.3 (17.8 – 18.8)	11.4 (8.6 – 21.5)	0.40	23.5 (14.7 – 32.4)	35.8 (26.5 – 45.2)	1.00
C_{max} (µg/L)	126.1 (88.1 – 160.3)	95.1 (22.9 – 199.0)	0.30	164.8 (162.3 – 274.6)	124.8 (51.1 – 468.7)	0.40	120.6 (88.2 – 153.1)	143.0 (39.5 – 246.4)	1.00
Dose normalised C_{max} (µg/L/g)	351.4 ± 238.6	218.7 ± 207.2	0.30	305.1 (263.6 – 419.6)	242.3 (94.6 – 873.66)	0.86	167.6 (122.5 – 212.6)	267.6 (79.0 – 456.3)	1.00
C_{12} (µg/L)	15.1 (8.5 – 20.5)	10.5 (9.2 – 25.8)	0.73	13.2 (11.8 – 21.9)	6.2 (4.6 – 17.6)	0.23	16.9 (10.6 – 23.3)	16.6 (10.5 – 22.6)	0.67
Dose normalised C_{12} (µg/L/g)	47.3 (14.0 – 94.4)	19.8 (18.0 – 41.5)	0.53	19.2 (18.8 – 30.8)	11.4 (8.6 – 34.9)	0.23	23.5 (14.7 – 32.3)	35.8 (26.5 – 45.2)	1.00
T_{max} (h)	3.3 ± 2.3	3.5 ± 1.8	0.84	2 (1.8 – 3)	5 (2 – 5.4)	0.40	4 (1 – 7)	3.5 (2.5 – 4.5)	1.00
Free MPA AUC_{0-12}/Total MPA AUC_{0-12} (%)	0.9 (0.5 – 1.0)	0.9 (0.6 – 1.2)	0.71	0.8 (0.7 – 0.8)	0.8 (0.8 – 1.5)	0.63	0.7 (0.6 – 0.8)	0.7 (0.7 – 0.8)	1.00

AUC = area under the concentration-time curve; AUC_{0-12} = area under the concentration-time curve between 0 and 12 hours; C_0 = pre-dose concentration before EC–MPS administration; C_{12} = trough concentration at 12 hours post-EC–MPS administration; C_{max} = maximal MPA concentration; MPA = mycophenolic acid; T_{max} = time when maximal MPA concentration is reached

[a]Data are presented as mean ± standard deviation or median (interquartile range) for continuous variables and number and percentage for categorical variables.

[b]4–6 weeks post–randomisation

[c]14–16 weeks post–randomisation

[d]28–32 weeks post–randomisation

[e]Variables were compared using the t–test or Mann–Whitney U–test as appropriate and dichotomous variables were compared using the Pearson's chi–square test or Fisher's exact test as appropriate. Bold values indicate statistical significance ($p<0.05$).

Table 3: Correlation between individual sampling time–point with total and free MPA $AUC_{0–12}$

Sampling time–point for total MPA concentration (h)	Total MPA $AUC_{0–12}$ (mg·h/L) (n = 32)		Sampling time–point for free MPA concentration (h)	Free MPA $AUC_{0–12}$ (µg·h/L) (n = 24)	
	r[a]	p–value		r[a]	p–value
C_0	0.63	**<0.001**	C_0	0.53	**0.008**
C_1	0.63	**0.004**	C_1	0.48	**0.02**
$C_{1.5}$	0.63	**<0.001**	$C_{1.5}$	0.58	**0.006**
C_2	0.72	**<0.001**	C_2	0.56	**0.005**
$C_{2.5}$	0.68	**<0.001**	$C_{2.5}$	0.60	**0.002**
C_3	0.69	**<0.001**	C_3	0.48	**0.02**
$C_{3.5}$	0.63	**<0.001**	$C_{3.5}$	0.58	**0.003**
C_4	0.54	**0.002**	C_4	0.47	**0.02**
$C_{4.5}$	0.47	**0.01**	$C_{4.5}$	0.49	**0.02**
C_5	0.32	0.08	C_5	0.36	0.08
$C_{5.5}$	0.45	**0.01**	$C_{5.5}$	0.47	**0.02**
C_6	0.47	**0.01**	C_6	0.56	**0.006**
$C_{6.5}$	0.70	**<0.001**	$C_{6.5}$	0.72	**<0.001**
C_7	0.77	**<0.001**	C_7	0.40	0.07
C_8	0.88	**<0.001**	C_8	0.72	**<0.001**
C_{10}	0.72	**0.009**	C_{10}	0.71	**0.02**
C_{12}	0.60	**<0.001**	C_{12}	0.63	**0.001**

AUC_{0-12} = area under the concentration-time curve between 0 and 12 hours; MPA = mycophenolic acid

[a]Correlations between MPA concentrations and $AUC_{0–12}$ were evaluated by Pearson or Spearman correlation as appropriate.

[b]Bold values indicate statistical significance ($p<0.05$)

Table 3: Achievement of target MPA exposure range between fixed–dosing and concentration–controlled participants stratified by study visit

	Overall (n = 32)	Study visit		
		1[a]	2[b]	3[c]
Participants with therapeutic MPA exposure, n (%)[d]				
Fixed–dosing	3 (20.0)	3 (33.3)	0 (0.0)	0 (0.0)
Concentration–controlled	9 (52.9)	1 (11.1)	5 (100.0)	3 (100.0)
p-value[e]	0.06	0.58	**0.01**	0.10
Absolute difference (95% confidence interval)	0.32 (-0.57 to 0.00)	-0.22 (-0.17 to 0.55)	1.00 (-1.00 to -0.34)	1.00 (-1.00 to -0.14)

$AUC_{0\text{-}12}$ = area under the concentration-time curve between 0 and 12 hours; MPA = mycophenolic acid

[a]Number of participants analysed (4–6 weeks post–randomisation): fixed–dosing = 9 and concentration–controlled = 9.

[b]Number of participants analysed (14–16 weeks post–randomisation): fixed–dosing = 4 and concentration–controlled = 5.

[c]Number of participants analysed (28–32 weeks post–randomisation): fixed–dosing = 2 and concentration-controlled = 3.

[d]Target MPA exposure for participants receiving EC–MPS as induction therapy was 40–60 mg·h/L and 30–50 mg·h/L for maintenance therapy.

[e]Comparisons were made using the Pearson's chi–square test or Fisher's exact test as appropriate. Bold values indicate statistical significance ($p<0.05$).

Table 4: Differences in clinical characteristics and MPA pharmacokinetic parameters between participants who demonstrated partial and complete remission at week 24 post-randomisation[a]

Variable	Partial remission (n = 6)	Complete remission (n = 12)	p-value[b]
Age (in years)	46.1 ± 16.2	50.8 ± 14.3	0.55
Gender, n (%)			
Male	2 (33.3)	2 (16.7)	0.57
Female	4 (66.7)	10 (83.3)	
Race, n (%)			
Caucasian	5 (83.3)	10 (83.3)	0.39
Asian	0 (0.0)	1 (8.3)	
Hispanic	0 (0.0)	1 (8.3)	
Other	1 (16.7)	0 (0.0)	
Weight (kg)	85.8 ± 21.3	74.5 ± 18.3	0.26
BMI (kg/m^2)	29.1 ± 6.0	26.4 ± 5.4	0.35
Renal pathology, n (%)			
ISN/RPS Class III	0 (0.0)	4 (33.3)	0.26
ISN/RPS Class IV	4 (66.7)	6 (50.0)	
ISN/RPS Class V	2 (33.3)	2 (16.7)	
eGFR ($mL/min/1.73\ m^2$)	70.4 ± 45.3	86.1 ± 25.0	0.37
Urine protein (g/24 hours)	2.6 ± 1.9	0.3 ± 0.37	**0.02**

Urine protein/creatinine ratio	155.5 (88.8 – 296.0)	8.0 (6.3 – 24.8)	**<0.001**
Serum albumin (g/L)	31.5 ± 10.2	39.5 ± 3.3	**0.03**
Serum complement (g/L)			
C3	1.1 ± 0.3	1.0 ± 0.3	0.75
C4	0.2 ± 0.2	0.2 ± 0.1	0.43
Anti–dsDNA	54.5 ± 31.6	33.0 ± 41.8	0.30
EC–MPS dose (mg/day)	1350.0 (810.0 – 1620.0)	1440.0 (1080.0 – 1440.0)	0.81
Prednisolone dose (mg/day)	8.8 (4.4 – 23.8)	5.0 (5.0 – 10.0)	0.30
MPA pharmacokinetic parameters			
Total MPA concentration			
$AUC_{0\text{-}12}$ (mg·h/L)	49.6 ± 41.7	37.8 ± 18.9	0.32
Dose normalised $AUC_{0\text{-}12}$ (mg·h/L/g)	77.8 ± 59.3	82.5 ± 70.7	0.88
C_0 (mg/L)	1.5 ± 1.1	1.5 ± 0.8	0.92
Dose normalised C_0 (mg/L/g)	2.5 ± 1.5	3.4 ± 3.0	0.42
C_{max} (mg/L)	18.2 ± 12.4	13.9 ± 6.4	0.25
Dose normalised C_{max} (mg/L/g)	28.2 ± 18.7	31.3 ± 30.0	0.80
C_{12} (mg/L)	2.4 ± 2.3	1.8 ± 0.8	0.36
Dose normalised C_{12} (mg/L/g)	3.8 ± 3.2	4.3 ± 4.3	0.81
Free MPA concentration			
$AUC_{0\text{-}12}$ (µg·h/L)	631.8 ± 332.8	311.6 ± 143.0	**0.01**
Dose normalised $AUC_{0\text{-}12}$ (µg·h/L/g)	1012.5 ± 383.1	731.9 ± 527.8	0.23

C_0 (µg/L)	12.1 (9.9 – 30.0)	10.4 (6.2 – 13.8)	0.44
Dose normalised C_0 (µg/L/g)	24.2 (14.0 – 41.7)	19.5 (11.9 – 38.6)	0.76
C_{max} (µg/L)	273.0 ± 189.6	103.4 ± 51.5	**0.01**
Dose normalised C_{max} (µg/L/g)	451.7 ± 317.1	252.7 ± 210.8	0.10
C_{12} (µg/L)	29.6 ± 25.0	10.9 ± 5.7	**0.02**
Dose normalised C_{12} (µg/L/g)	45.3 ± 32.1	28.2 ± 28.9	0.24
Participants with therapeutic MPA exposure range, n (%)[c]			
Overall	3 (33.3)	6 (33.3)	1.00
Therapeutic exposure on Visit 1	1 (16.7)	3 (25.0)	1.00
Therapeutic exposure on Visit 2	2 (66.7)	3 (50.0)	1.00
Treatment group, n (%)			
Fixed–dosing	2 (22.2)	7 (77.8)	0.62
Concentration–controlled	4 (44.4)	5 (55.6)	

ALP = alkaline phosphatase; ALT = alanine transaminase; Anti–dsDNA = anti-double strand DNA; ARB = angiotensin II receptor blocker; AST = aspartate transaminase; AUC = area under the concentration-time curve; AUC_{0-12} = area under the concentration-time curve between 0 and 12 hours; BMI = body mass index; C_0 = pre–dose concentration before EC–MPS administration; C_{12} = trough concentration at 12 hours post-EC–MPS administration; C_{max} = maximal MPA concentration; EC–MPS = enteric–coated mycophenolate sodium; eGFR = estimated glomerular filtration rate; GGT = gamma–glutamyl transferase; ISN/RPS = International Society of Nephrology/Renal Pathology Society; MPA = mycophenolic acid.

[a]Data are presented as mean ± standard deviation or median (interquartile range) for continuous variables and number and percentage for categorical variables.

[b]Continuous variables were compared using the t–test or Mann–Whitney U–test as appropriate and dichotomous variables were compared using the Pearson's chi–square test or Fisher's exact test as appropriate. Bold values indicate statistical significance ($p<0.05$).

[c]Target MPA exposure for participants receiving EC–MPS as induction therapy was 40–60 mg·h/L and 30–50 mg·h/L for maintenance therapy.

Table 5: Adverse events

Summary of adverse events, n (%)	Fixed–dosing (n = 9)	Concentration–controlled (n = 9)	p-value
Participants with ≥1 adverse event	1 (11.1)	1 (11.1)	1.00
Participants with adverse event leading to EC-MPS cessation	2 (22.2)	2 (22.2)	1.00
Total adverse events	5	7	0.32
Fever	1	1	
Infection	0	1	
Nausea & vomiting	1	1	
Other	3	4	

Figure 1: Study flow chart

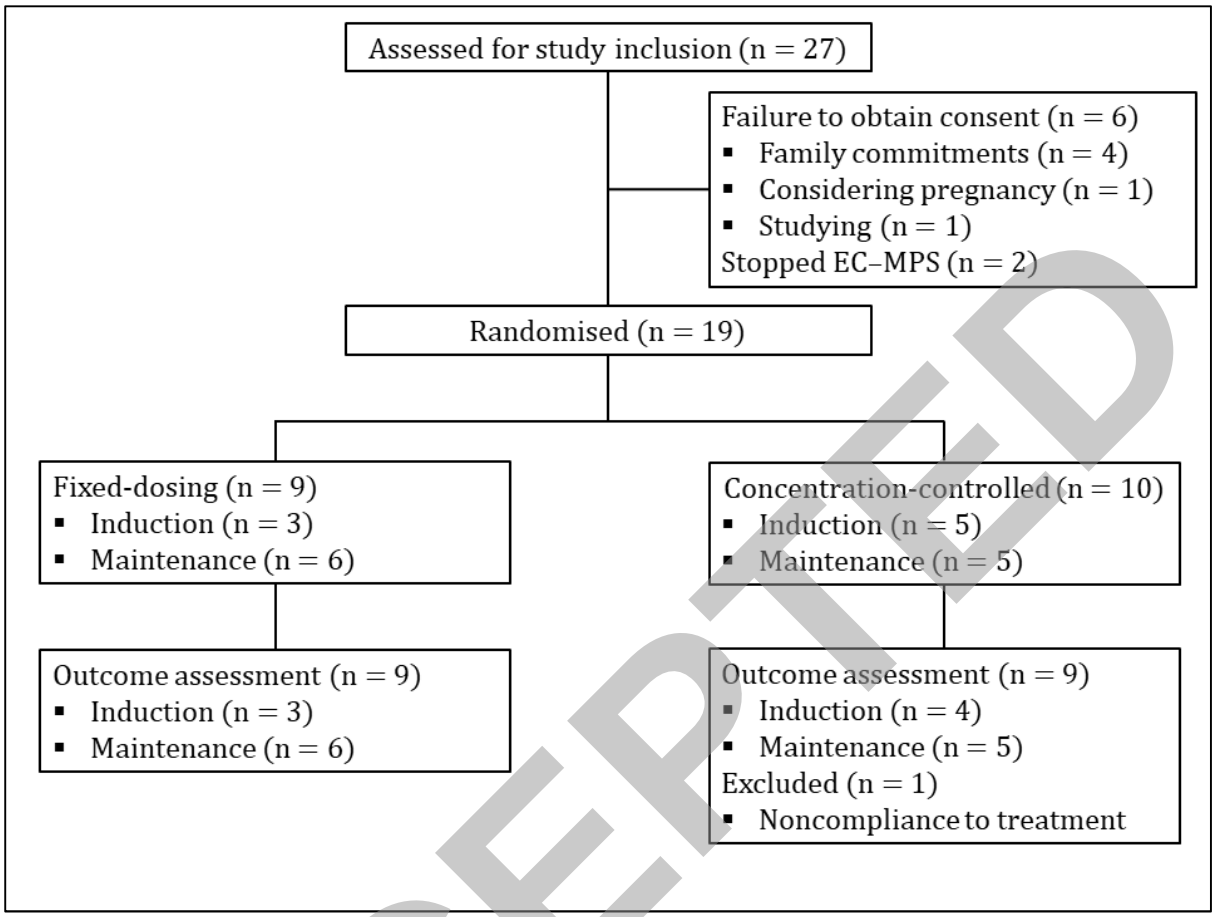
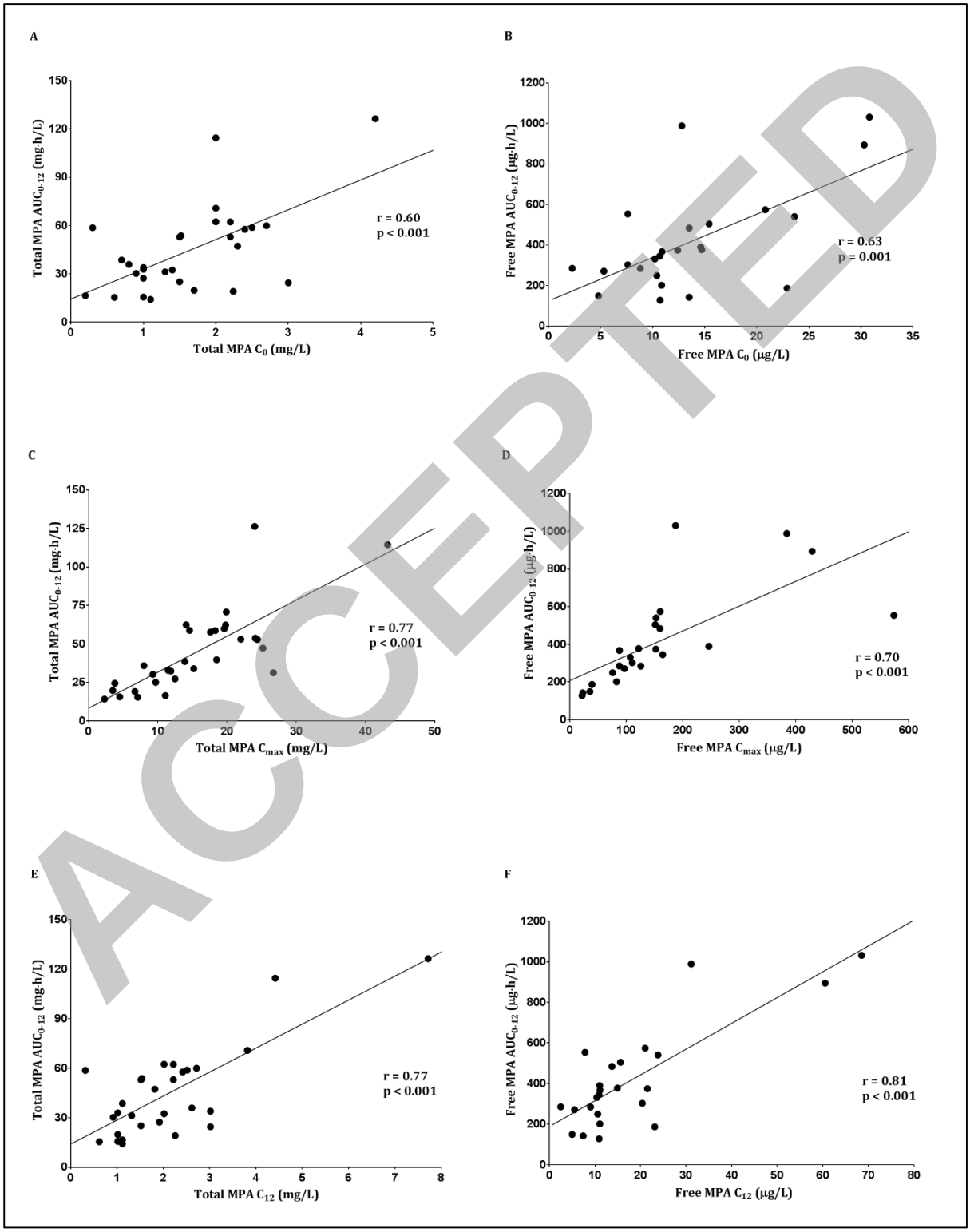
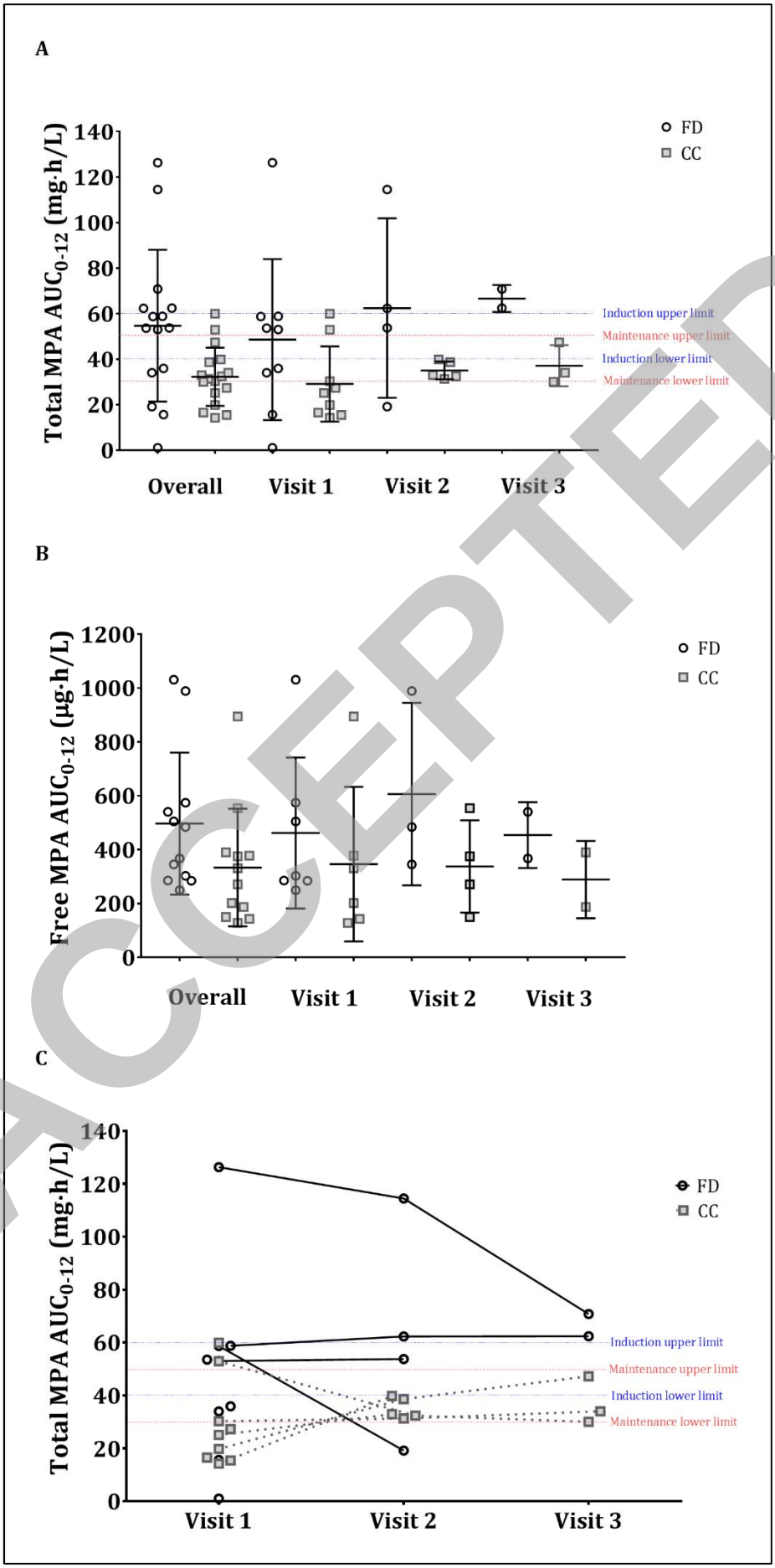


Figure 2: Correlations between MPA C_0 and MPA AUC_{0-12} for (A) total MPA and (B) free MPA concentrations, between MPA C_{max} and AUC_{0-12} for (C) total MPA and (D) free MPA concentrations, and between MPA C_{12} and MPA AUC_{0-12} for (D) total MPA and (E) free MPA concentrations



AUC_{0-12} = area under the concentration-time curve between 0 and 12 hours; C_0 = pre-dose concentration before EC-MPS administration; C_{max} = maximal MPA concentration C_{12} = trough concentration at 12 hours post-EC-MPS administration; MPA = mycophenolic acid.

Figure 3: Total and free MPA AUC_{0-12} between fixed-dosing and concentration-controlled participants across the study visits[a,b]

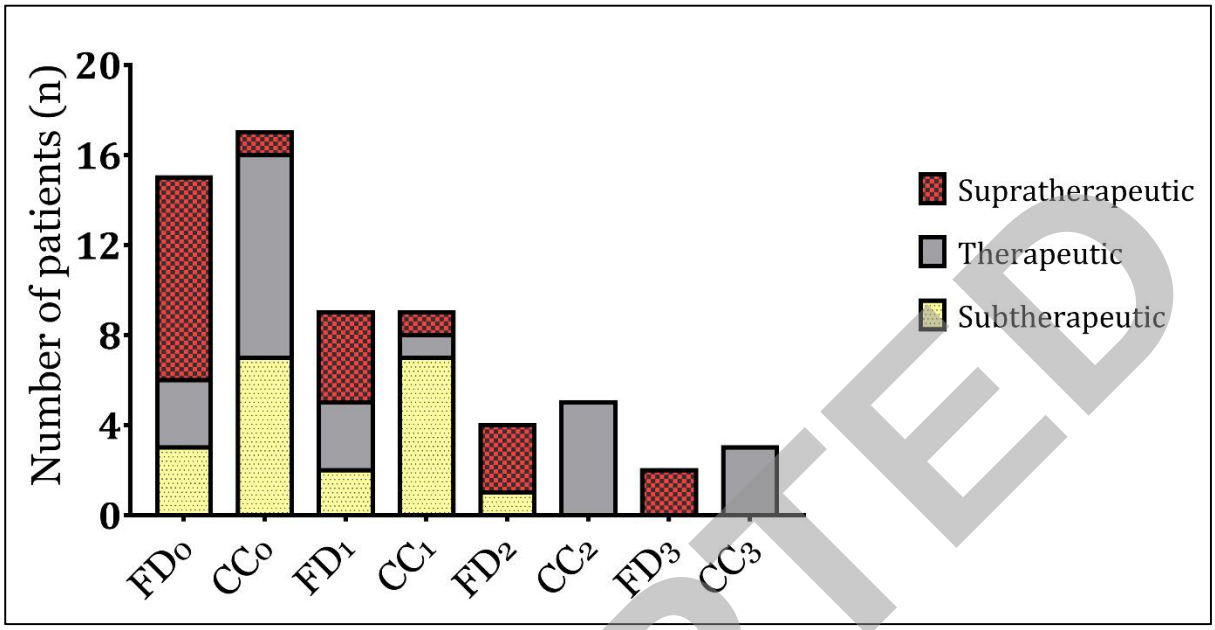


AUC_{0-12} = area under the concentration-time curve between 0 and 12 hours; CC = concentration–controlled; FD = fixed–dosing; MPA = mycophenolic acid.

[a]Means with standard deviations are presented.

[b]Dashed blue circles refer to the target MPA exposure range for patients receiving EC–MPS as induction therapy (40–60 mg·h/L) and dashed red lines refer to the target MPA exposure range for patients receiving EC–MPS as maintenance therapy (30–50 mg·h/L).

Figure 4: MPA exposure between fixed-dosing and concentration-controlled participants across the study visits[a,b,c]



[a]Target MPA exposure for participants receiving EC-MPS as induction therapy was 40-60 mg·h/L and 30-50 mg·h/L for maintenance therapy.

[b]Subtherapeutic MPA exposure for participants receiving EC-MPS as induction therapy was defined as <40 mg·h/L and <30 mg·h/L for maintenance therapy.

[c]Supratherapeutic MPA exposure for participants receiving EC-MPS as induction therapy was defined as >60 mg·h/L and >50 mg·h/L for maintenance therapy.

FD_0 = Overall MPA exposure of FD participants; CC_0 = Overall MPA exposure of CC participants; FD_1 = MPA exposure of FD participants on study visit 1; CC_1 = MPA exposure of FD participants on study visit 1; FD_2 = MPA exposure of FD participants on study visit 2; CC_2 = MPA exposure of CC participants on study visit 2; FD_3 = MPA exposure of FD participants on study visit 3; CC_3 = MPA exposure of CC participants on study visit 3.

Figure 5: Changes in treatment-related variables over the 48-week of study period[a]

CC = concentration controlled; FD = fixed-dosing; eGFR =estimated glomerular filtration rate

[a]No significant differences were observed in; (A) serum creatinine (p= 0.33), (B) blood urea (p = 0.17), (C) estimated glomerular filtration rate (p = 0.95), (D) serum albumin (p = 0.68), (E) serum C3 (p = 0.35), and (F) serum C4 (p = 0.63) between FD and CC participants throughout the study period.