Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Mycophenolate sodium

Proprietary Product Name: Myfortic

Sponsor: Novartis Pharmaceuticals Australia Pty Limited

Date of First Round CER: 7 January 2011

Date of Supplementary CER: 3 April 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
Aave	Average enzyme activity
AEC	Area under the enzyme activity-time curve
Amax	Maximum enzyme activity
Amin	Minimum enzyme activity
Ao	Enzyme activity immediately before dosing
CR	Complete remission
CV	Coefficient of variation
EC-MPS	Enteric-coated mycophenolate sodium
Emax	Maximum inhibitory effect
GI	Gastrointestinal
GN	Glomerulonephritis
Imax	Maximum enzyme inhibition
IVC	Intravenous cyclophosphamide
LN	Lupus nephritis
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid
MPAG	Mycophenolic acid glucuronide
PR	Partial remission
SLE	Systemic lupus erythematosus
UPCR	Protein and creatinine excretion ratio
WHO	World Health Organisation

1. Clinical rationale

Myfortic is an anti-proliferative immunosuppressant belonging to the anti-metabolite class of immunosuppressants. Mycophenolic acid (MPA), the active ingredient in Myfortic enteric coated tablets (EC-MPS), is a non-nucleoside, non-competitive, reversible inhibitor of inosine monophosphate dehydrogenase, which is the rate limiting enzyme in the de novo synthesis pathway of guanosine triphosphate. Both T and B lymphocytes are highly dependent on this pathway for the generation of guanosine nucleotides, whereas non-lymphoid cells can utilise a salvage pathway for generation of guanosine triphosphate. Mycophenolic acid selectively decreases the lymphocyte nucleotide pool and is considered to have potential to decrease recruitment of lymphocytes and monocytes into sites of chronic inflammation.

Approximately 60% of patients with systemic lupus erythematosus (SLE) have been documented to develop clinically relevant lupus nephritis characterised by deposition of immune complexes in the glomeruli and subsequent tissue injury. Using estimates of prevalence of lupus nephritis, the estimated maximum number of Australians with lupus nephritis is 1,362 for non-indigenous persons and 286 for indigenous individuals.[1]

This application is specific to Australia, and has been submitted in response to a request from the Chair of the Expert Advisory Panel on Aboriginal and Torres Strait Islander Medicines, to address the current lack specific lupus nephritis treatments on the Pharmaceutical Benefits Scheme.

The World Health Organization (WHO) definitions of Class III, IV and V lupus nephritis is shown below in Table 1.

Table 1. World Health Organization morphologic classification of lupus nephritis (modified in 1982)

Class	Characteristics
Class I	Normal glomeruli a. Nil (by all techniques) b. Normal by light microscopy, but deposits by electron or immunofluorescence microscopy
Class II	Pure mesangial alterations (mesangiopathy) a. Mesangial widening and/or mild hypercellularity (+) b. Moderate hypercellularity (++)
Class III	Focal segmental glomerulonephritis (associated with mild or moderate mesangial alterations) a. With “active” necrotizing lesions b. With “active” and sclerosing lesions c. With sclerosing lesions

[1] Novartis’ Application for Orphan Drug Designation, submitted 1 December 2009

Class	Characteristics
Class IV	Diffuse glomerulonephritis (severe mesangial, endocapillary or mesangiocapillary proliferation and/or extensive subendothelial deposits) a. Without segmental lesions b. With "active" necrotizing lesions c. With "active" and sclerosing lesions d. With sclerosing lesions
Class V	Diffuse membranous glomerulonephritis a. Pure membranous glomerulonephritis b. Associated with lesions of class II c. Associated with lesions of class III d. Associated with lesions of class IV
Class VI	Advanced sclerosing glomerulonephritis

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

This was a literature-based submission. A pre-submission meeting with the Therapeutic Goods Administration was held on 2 February 2010 at which time the literature search strategy was provided by the sponsor. The TGA assessment concluded that the search strategies provided a good coverage of the clinical trials and studies for Myfortic. Updated searches from September 2009 to May 2010 were recommended.

The clinical efficacy of Myfortic in the treatment of patients with lupus nephritis was assessed by obtaining evidence on the following:

- Efficacy and safety of Myfortic in treatment of patients with lupus nephritis
- Pharmacokinetic and therapeutic equivalence of Myfortic and mycophenolate mofetil
- Efficacy of mycophenolate mofetil in patients with lupus nephritis.

The dossier included Module 1 in the Australian prescribed format and the remaining documentation in European Union Common Technical Document format.

One CD-ROM was supplied containing copies of supporting documentation. The evaluation was based on the electronic copy of the submission dossier. The following documents were provided:

- Clinical overview and summary prepared by an external Australian expert
- The latest Periodic Safety Update Report (PSUR) covering the period 1 November 2006 to 31 October 2009
- A recent Adverse Drug Reactions Advisory Committee report
- Literature references including two review publications released after the search date.

No risk management plan was included. Exemption from this requirement was granted by the Monitoring and Compliance Group [of TGA]. As part of the company's local post-marketing surveillance activities, Novartis Pharmaceuticals Australia plans to establish a patient registry to monitor the safety of Myfortic when used in patients with lupus nephritis. At the time of submission, the specifics of the registry design were still under development but were to include the capture of key demographic and outcome information.

2.2. Orphan medicinal products

The submission has received Orphan designation.

2.3. Good clinical practice

Evidence of good clinical practice was supplied for all studies evaluated below except for that of Tedesca-Silva *et al.,* 2005.

3. Clinical efficacy and safety of Myfortic in lupus nephritis

The documentation submitted in direct support of the use of EC-MPS in treatment of lupus nephritis comprised two retrospective reports of case series (Kityakara *et al*., 2008[2], Mak *et al*., 2008[3]) one report of a prospective study with historical controls (Traitanon *et al*., 2008[4]), and one report of a case series of efficacy of EC-MPS in treatment of subacute cutaneous systemic lupus erythematosus (Kreuter *et al*., 2007[5]).

The retrospective studies included a total of 29 Asian patients with lupus nephritis WHO class III, IV and V[6] with age range from 14 to 50 years and predominantly female study population. Induction, maintenance and relapsed patients were included. The dose of EC-MPS was 1,440 mg daily for 12 of the patients, and between 1,080 – 1,440 mg daily for 17 patients.

Of the 29 patients included in the retrospective studies, one was successfully maintained in remission after conversion from MMF. Of the remaining 28 patients:

- Eight achieved complete remission defined as reduction in urinary protein and creatinine excretion ratio (UPCR) < 1 with serum creatinine increasing < 0.5 mg/dL
- Four achieved partial remission defined as ≥ 50% reduction in UPCR
- Six achieved complete remission defined as proteinuria < 0.3 g/day, with normal urinary sediments, normal serum albumin and creatinine levels
- Six achieved partial remission defined as proteinuria in the range of 0.3–3.0 g/day, with serum albumin above 30 g/L and stabilization or improvement in renal function.

The historically controlled study included patients who had failed induction therapy with intravenous cyclophosphamide (IVC), and compared 6 months results for 16 patients treated prospectively with EC-MPS 720 mg twice daily with 17 historic controls with matched with

[2] Kitiyakara C *et al*. Treatment of lupus nephritis and primary glomerulonephritis with enteric-coated mycophenolate sodium. *Clinical nephrology* 2008;69:90-101
[3] Mak S-K *et al*. Efficacy of enteric-coated mycophenolate sodium in patients with active lupus nephritis. *Nephrology* 2008; 13: 331 – 336
[4] Traitanon O *et al*. Efficacy of enteric-coated mycophenolate sodium in patients with resistant-type lupus nephritis: a prospective study. *Lupus* 2008; 17: 774 – 751
[5] Kreuter A *et al*. Mycophenolate sodium for subacute cutaneous lupus erythematosus resistant to standard therapy. *British Journal of Dermatology* 2007; 156: 1321 – 1327
[6] WHO classification of LN is summarised in Table 1

baseline characteristics who were treated with extended course IVC 0.5 – 1.0 g/m^2 monthly for 6 months. All patients were treated with prednisolone 0.5 – 1 mg/kg/day.

For the 16 patients treated with EC-MPS

- Two achieved complete response defined as stabilisation or improvement in renal function, proteinuria < 0.5 g/day and absence of haematuria and cellular casts.
- Seven achieved partial response was defined as proteinuria between 0.5 – 1.5 g/day with stable renal function and absence of haematuria.

The result for combined response was 33.3% in the IVCY group and 56.3% in the EC-MPS group.

With regard to overall safety, two EC-MPS patients were reported to suffer nausea/vomiting, two suffered diarrhoea and 2 suffered abdominal pain.

4. Equivalency of Myfortic and mycophenolate mofetil

Twelve study reports were submitted to support pharmacokinetic, pharmacodynamic, efficacy and safety equivalence of EC-MPS and MMF.

4.1. Arns - Pivotal – single dose pharmacokinetics

Arms et al. Enteric-coated mycophenolate sodium delivers bioequivalent MPA exposure compared with mycophenolate mofetil. Clin Transplant. 2005:19: 199 – 206. Supported by Novartis

4.1.1. Design

A Phase I, single centre, randomised, open-label, the three-way crossover single dose study comparing the relative bioavailability of two EC-MPS doses 640 and 720 mg, with MMF 1000 mg.

4.1.2. Inclusion criteria

- Male and female stable renal transplant patients
- At least 3 months after first or second renal transplant
- Stable serum creatinine levels ≤ 177 µmol/L at randomisation
- Cyclosporine based regimen since transplantation with trough level 100-250 ng/mL
- MMF therapy withheld for 36–48 h prior to study dosing.

4.1.3. Study regimen

During each treatment period, patients received a single dose of one of the following study treatments. There was a washout period of 7 – 12 days between treatment periods.

- 640 mg EC-MPS
- 720 mg EC-MPS
- 1000 mg MMF.

4.1.4. Sampling and analysis

Pharmacokinetic sampling was performed for measurement of mycophenolic acid (MPA) and its main metabolite mycophenolic acid glucuronide (MPAG). The time points were 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 8, 12, 16, 24, 36, and 48 h post-dose. MPA and MPAG concentrations in plasma were determined by high performance liquid chromatography (sensitivity limit, 0.1 µg/mL).

4.1.5. Disposition and demographics

Seventeen male and seven female Caucasian patients aged 31 – 65 years were enrolled and completed the study. Height ranged between 151 and 190 cm and weight was between 43.5 and 92.0 kg. Two patients, one male and one female, has a body mass index below 20.

4.1.6. Pharmacokinetic results

- Mean AUC for MMF 1000 mg was 63.7 µg.h/mL
- Mean AUC for EC-MPS 640 mg was 60.7 µg.h/mL; 90% CI (87–104)
- Mean AUC for EC-MPS 720 mg was 66.5 µg.h/mL; 90% CI (91–109)
- For both EC-MPS doses, the 90% CI was within the 80–125% limit
- Median tmax for EC-MPS was 2.0 hours vs. 0.75 hours for MMF
- Median Cmax for MMF 1000 was 30.2 µg/mL
- Median Cmax for EC-MPS 640 mg was 30.1 µg/mL:90% CI was (71–140%)
- Median Cmax for EC-MPS 720 mg was 26.1 µg/mL: 90% CI (57–112%)
- High inter patient coefficient of variation was reported (CV > 40%) of the Cmax parameter for all three treatments and lower Cmax observed with 720 mg EC-MPS
- The 90% CIs for MPAG (the main, inactive metabolite) Cmax and $AUC_{0-\infty}$ fell in the range 80 – 125%.

4.1.7. Discussion

4.1.7.1. Author

This study has shown that single doses of EC-MPS, both 640 and 720 mg, are bioequivalent to 1000 mg MMF for MPA $AUC_{0-\infty}$ and for MPAG $AUC_{0-\infty}$ and Cmax. The 720 mg dose was considered to most closely approximate the MPA content of 1000 mg MMF. Previous studies have shown that the highest efficacy in renal transplants has been achieved at MPA AUC of approximately 60.0 µg h/mL. Both doses of EC-MPS in this study resulted in this level of MPA absorption.

The high inter-patient variability did not allow the bioequivalence criteria for Cmax to be met. However, in the present study, the CV was similar between the test formulations: 41% for 640 mg EC-MPS; 47% for 720 mg EC-MPS; 47% for 1000 mg MMF, and so should not adversely affect direct comparisons between the formulations.

The current study assessed the bioequivalence of single doses. Both EC-MPS and MMF are intended for twice daily dosing. The current study was conducted in patients receiving cyclosporine-based therapy and bioequivalence of MPA exposure between EC-MPS and MMF cannot be assumed for patients receiving concomitant therapy with other immunosuppressive agents. Further studies in patients receiving twice-daily dosing of EC-MPS and MMF under conditions of different concomitant therapies are thus required to confirm these findings.

4.1.7.2. Evaluator

The paper presents two studies; the first designed to determine the primary site of MPA delivery in the GI tract after EC-MPS treatment by in vitro analysis of the pH required for dissolution of the enteric coat of EC-MPS tablets. Dissolution testing was undertaken. The results are not within the scope of the clinical evaluator to critique.

While single doses of EC-MPS 640 and 720 mg were demonstrated to be bioequivalent to 1000 mg MMF for MPA $AUC_{0-\infty}$ in patients with stable renal function following renal transplantation. Tmax was delayed for EC-MPS compared to MMF, and Cmax was lower for EC-

MPS that for MMF, and was lower for the 720 mg dose than for the 640mg dose, with 90% confidence intervals outside the accepted bioequivalence levels; well outside those limits for the 720 dose. Based on the result of this study the two formulations cannot be considered truly bioequivalent, although it is accepted that variability is a consideration.

Cyclosporine inhibits the MRP2 transporter that excretes mycophenolic acid glucuronide (MPAG) into the bile. The impaired excretion leads to reduced enterohepatic recycling of mycophenolic acid. Considering the patient population and concomitant medication in this study, validity in lupus nephritis population cannot be assumed.

4.2. Budde - Pivotal – multiple dose pharmacokinetics

Budde K et al. Pharmacokinetic and pharmacodynamic comparison of enteric-coated mycophenolate sodium and mycophenolate mofetil in maintenance renal transplant patients. American Journal of Transplantation 2007: 7:888 – 898. Supported by Novartis

4.2.1. Design

This was a single centre sub-study of ERLB302 reported more fully under *Budde: Pivotal – safety and efficacy,* below.

4.2.2. Objective

The aim was to assess pharmacokinetics of enteric-coated mycophenolate sodium and mycophenolate mofetil at steady state in maintenance renal transplant patients on cyclosporine based immune suppression. Pharmacodynamic parameters were also assessed with reference to effect of EC-MPS and MMF on the time course of IMPDH enzyme activity in mononuclear cells.

4.2.3. Inclusion/exclusion

Adult male and female, stable renal transplant recipients were enrolled. Inclusion and exclusion criteria are discussed below under *Budde: Pivotal – safety and efficacy*. At first and last pharmacokinetic assessments, patients had received MMF and EC-MPS for at least 3 months.

4.2.4. Sampling and analysis

PK assessments were performed 14 days prior to randomisation when all patients were taking MMF, at Day 1 of study treatment, and at 3 and 12 months after randomisation. Additional PK profiling was done during the post study extension phase when all patients had taken EC-MPS for 3 months.

4.2.5. Disposition

Twenty-four patients were entered, 18 of whom completed all five assessments; 9 were randomised to receive EC-MPS and 9 to receive MMF. All patients were Caucasian.

4.2.6. Demographic characteristics

Summarised demographic characteristics are provided for the 18 patients who contributed data to the analysis. There were 15 males and 3 females included with age range 20 – 62 years.

4.2.7. Pharmacokinetic results

The ratio of geometric mean AUCs EC-MPS/MMF was 0.98, 90% CI (0.87, 1.11).

The EC-MPS/MMF Cmax ratio was 0.89; 90% CI (0.70–1.13). The lower limit fell below bioequivalence range.

EC-MPS, Cmax occurred later and was more variable than for MMF: EC-MPS tmax median 1.5 h, range 0 – 6h: MMF tmax median 0.8 h, range 0.5 – 2 h.

Mean pre-dose MPA plasma concentrations (C_0) were higher in EC-MPS treated patients than with MMF and this difference remained significant even when outliers with C_0 concentrations

> 10 µg/mL (n=2) were excluded. The geometric mean of C_0 EC-MPS/MMF ratio was 1.51–2.90. Based on individual ratios, pre dose MPA concentrations were on average about twofold higher with EC-MPS than with MMF and exhibited a higher variability. The geometric mean ratio of Cmin amounted to 1.34 indicating that Cmin was just one third higher with EC-MPS compared to MMF.

Steady-state MPA pharmacokinetic parameters are shown in Table 2. Substantial inter-individual and intra-individual variation of approximately 25 – 30% was reported. Inter-individual variability of Cmax and AUC were similar between both formulations.

Table 2. Budde *et al* 2007: Steady-state pharmacokinetic parameters

	MMF[1]	EC-MPS[2]	Geometric mean of EC-MPS/MMF ratios (90% CI)[3]
AUC (µg h/mL)	58.39 ± 14.08 (24)	57.43 ± 15.03 (26)	0.98 (0.87–1.11)
C_{max} (µg/mL)	21.30 ± 9.13 (43)	18.93 ± 7.86 (42)	0.89 (0.70–1.13)
T_{max} (h)	0.8 (0.5–2.0)	1.5 (0–6.0)	0.5 (–1.5 to 5.5)[4]
C_0 (µg/mL)	1.80 ± 0.75 (42)	4.35 ± 3.59 (82)	2.10 (1.51–2.91)
C_{min} (µg/mL)	1.51 ± 0.66 (34)	1.96 ± 0.67 (34)	1.34 (1.13–1.59)
C_{avg} (µg/mL)	4.87 ± 1.18 (26)	4.79 ± 1.25 (26)	0.98 (0.87–1.11)
PTF (%)	406 ± 160 (38)	331 ± 127 (38)	0.82 (0.64–1.04)

Mean ± SD (CV%), except t_{max} which is presented as median (range).
[1]Assessed prior to randomization to study treatments (run-in period).
[2]Assessed at month 15 (extension phase).
[3]Calculated from log-transformed data.
[4]$p < 0.05$, Wilcoxon signed rank test on the untransformed data.

4.2.8. Pharmacodynamic results

Due to missing IMPDH values, the area–effect curve was calculated only for 16 patients. The finding was 14% lower area under the enzyme activity curve (AEC) for EC-MPS compared to MMF.

4.2.9. Discussion

4.2.9.1. Author

The authors state that it is generally agreed that MPA AUC is the most reliable parameter of efficacy, particularly early after transplantation (references 15–19).[7] Currently, an AUC of 30-60 µg.h/mL or pre-dose MPA concentrations of 1–3.5 µg/mL have been proposed for the early post-transplantation period when MMF is prescribed with cyclosporine (see references 15–19). This range has been mainly adopted from a prospective trial (reference 16), where patients were randomly allocated to three different exposure groups, and patients randomised to an exposure of 32 µg h/mL had the best outcome with respect to efficacy and toxicity. For maintenance patients no such window has yet been defined. Accepting this therapeutic window, the average MPA exposure results for both treatments were in the upper part of the proposed range.

4.2.9.2. Evaluator

The finding of bioequivalence with regard to AUC are in general agreement with the findings of the single dose study reported by Arns *et al*. The MPA Cmax result for 720 mg EC-MPS was less than that of MMF; the EC-MPS MPA tmax was delayed as it was in the single dose study and in keeping with the enteric coating of the EC-MPS formulation. With repeated doses, the EC-MPS, MPA Cmin averaged approximately twice that of MMF.

It is likely that these pharmacokinetic and pharmacodynamic differences would not be clinically significant in the renal transplant population. However, this assumption would benefit from specific study in the event that EC-MPS were substituted for MMF in the treatment of lupus nephritis.

[7] These references were not included in the submission dossier

4.3. Budde - Supportive – pre-dose pharmacokinetics

Budde et al. Enteric-Coated Mycophenolate Sodium Provides Higher Mycophenolic Acid Predose Levels Compared With Mycophenolate Mofetil: Implications for Therapeutic Drug Monitoring. Short communication. Ther Drug Monit 2007; 29 (3): 381 – 384. Supported by Novartis

This was a systematic retrospective review of EC-MPS studies undertaken to assess pre-dose C_0 MPA levels during EC-MPS treatment compared to those during MMF treatment. Three clinical trials (B302, 2302, and 2408) were identified and their MPA pre-dose data examined post-hoc. In all three studies, an intra individual comparison between EC-MPS and MMF was performed.

The overall magnitude of change in MPA C_0 levels was expressed as the percentage increase or decrease from population medians in patient groups who had received both EC-MPS and MMF. In addition, the number of participants with a very prolonged MPA release was determined defined as a MPA C_0 level 15 mg/mL or greater. In study 2408, intra- individual coefficients of variation were determined for MPA C_0 levels. In terms of study design, trial 2480 had the highest sensitivity to detect variability. The relationship between MPA pre-dose levels and $AUC_{0-12\,h}$ for each formulation was assessed by linear regression analysis and the significance judged by the r2 values.

In total, 537 MPA pre-dose levels were available for 88 patients. Sixty-five percent of the C_0 samples were collected in Study 2408 followed by Study B302 (20%) and Study 2302 (15%). Only patients from studies B302 and 2302 provided $AUC_{0-12\,h}$ data (n = 64).

The majority of patients were male (~ 70%) and Whites (~ 60%); mean age ranged from 43 to 49 years. Mean CsA trough values were comparable between the trials.

In all three studies median MPA C_0 values were consistently higher with EC-MPS (2.33-2.71 mg/mL) compared with MMF (1.78–2.14 mg/mL). Overall, eight of 265 samples (3.0%) collected in patients on EC-MPS showed MPA pre-dose levels 15 mg/mL or greater, suggesting a very prolonged release of MPA from the previous evening dose of EC-MPS. No such high value was observed in patients on MMF.

Based on pooled analysis, the overall median MPA C_0 concentration was 31.1% higher in patients treated with EC-MPS (median, 2.40 mg/mL; mean, 3.57 mg/mL; range, 0.49-39.30 mg/mL) than in patients receiving MMF (median, 1.83 mg/mL; mean, 2.30 mg/mL; range, 0.1–12.80 mg/mL). Specifically, percentage increases in median MPA C_0 levels on conversion from MMF to EC-MPS or vice versa were 35.4%, 26.6%, and 29.4%in studies B302, 2302, and 2408, respectively.

Apart from the eight outliers, there was a substantial overlap in the distribution of MPA C_0 values. Inter individual coefficients of variation were 123% (EC-MPS) and 76% (MMF). Intra individual coefficients of variation were 64% (EC-MPS) and 42% (MMF) based on study 2408. MPA pre-dose levels correlated poorly with MPA AUC for both treatments (r2, 0.5; for both P=0.001).

4.3.1. Discussion

4.3.1.1. Author

The principal findings can be summarised as follows:

1. on average, MPA predose levels are approximately 30% higher in patients on EC-MPS compared with MMF, evidently as a result of its enteric coating;
2. rare cases of a very prolonged release of MPA from EC-MPS are observed resulting in MPA C0 levels 15 mg/mL or greater;
3. there is a poor correlation between MPA predose levels and MPA AUC, for both EC-MPS and MMF;

4. inter-patient variability of MPA C0 appears to be greater with EC-MPS than with MMF.

The rise in MPA plasma concentrations associated with the enterohepatic recirculation described for MPA occurs later with EC-MPS and may impact on the next MPA C_0 determination.

The use of different bioanalytic MPA assays in the three studies pooled may have had an impact on the absolute median/mean values of MPA concentrations, whereas it is unlikely that the percentage change in MPA C_0 levels was relevantly influenced because patients received both EC-MPS and MMF (ie, both groups were similarly affected). Moreover, because Study 2408 contributed most of the data, it may have dominated the analysis, although percentage increases in median MPA C_0 levels were comparable between studies.

The findings have relevance to use of pre-dose plasma concentrations for therapeutic drug monitoring.

4.3.1.2. Evaluator

Overall, 3.0% of EC-MPS samples showed MPA predose levels 15 mg/mL or greater, suggesting a very prolonged release of MPA from the previous evening dose of EC-MPS. No such high value was observed in patients on MMF. It appears that EC-MPS and MMF pre-dose levels are not bioequivalent. The patients with very high pre-dose levels would benefit from further study particularly with regard to safety. It is possible that a proportion of patients metabolise MPA more slowly.

4.4. Tedesco-Silva – multiple dose pharmacokinetics: active metabolite

Tedesco-Silva H et al. Mycophenolic acid metabolite profile in renal transplant patients receiving enteric-coated mycophenolate sodium or mycophenolate mofetil. Transplantation Proceedings. 2005; 37: 852 – 855

There was no conflict of interest statement; however, several of the authors have been involved in other studies funded by Novartis. There was no statement regarding ethics/good clinical practice.

4.4.1. Design

Open-label, two-period, crossover study to characterise the time course of mycophenolic acid (MPA) and its metabolites, mycophenolic acid glucuronide (MPAG) and acyl mycophenolic acid glucuronide (AcMPAG) in renal transplant patients exposed to 28 days of MMF and EC-MPS. Each treatment preceded by 48 h washout. Each treatment was for 28 days followed by 12 h PK study.

4.4.2. Inclusion/exclusion

- Renal transplant patients, stable for at least 3 months post transplant (1st or 2nd)
- Age 18 – 65 years
- Serum creatinine < 2.5 mg/dL (~ 225 μmol/L)

4.4.3. Study therapy

- EC-MPS 720 mg twice daily
- MMF 1000 mg twice daily
- Cyclosporine-based immunosuppressive regime to maintain cyclosporine level 90-250 ng/mL

4.4.4. Baseline characteristics

40 patients, mean age 43.28 years, 62.5% were male, 57.5% were Caucasian and 32.5% were mixed race. Weight range 46.9 – 97.1 kg.

4.4.5. Participant disposition

All patients completed the study.

4.4.6. Results

In the ITT analysis:

- The ratio of MPA AUCs: 1.18; 90% CI (1.08 to 1.29)
- The estimated ratio of means of Cmax (EC-MPS: MMF) was 1.16 (90% CI 0.94 to 1.42). It was unclear in the text whether this result included results of all 40 patients
- Mean Cmin results were similar between groups
- Mean %CV results indicated considerable variability
- The mean baseline MPA level (C_0) and [CV] for EC-MPS: 4.6 g/mL [121] versus 2.4 [55] g/mL for MMF
- For both EC-MPS and MMF, the ratio of MPAG to MPA was 23:1. MPAG AUC ratio was 1.22 with 90% CI (1.13 - 1.30). Cmax ratio was 1.22 with 90% CI (1.10 - 1.34)
- For AcMPAG, the mean Cmax, Cmin, and AUC were similar for both formulations. EC-MPS and MMF were bioequivalent with respect to AcMPAG.. The AcMPAG AUC ratio was 1.04 with 90% CI (0.96 to 1.12). The Cmax ratio was 1.02 with 90% CI (0.91 to 1.14).

No patient was reported to have drug related adverse event.

4.4.7. Discussion

4.4.7.1. Author

The onset of MPA exposure was delayed for EC-MPS compared with MM leading to possible carryover of a portion of the MPA evening dose into the following day, an effect probably responsible for the higher MPA C_0 values seen in four patients in the EC-MPS treatment phase. Such carry over effects may also contribute, at least in part, to the higher mean Cmax values that were associated with EC-MPS during the study. These minor differences in pharmacokinetics did not affect MPA Cmin, which did not differ between formulations, indicating no accumulation of MPA during EC-MPS treatment.

For both MMF and EC-MPS, MPAG and AcMPAG reached their maximal concentrations soon after MPA, confirming the rapid conjugation of MPA. MPAG was confirmed as the major metabolite.

The pharmacokinetic profile of AcMPAG was similar to that of the parent MPA, except for an apparently slower rate of elimination. Comparison of the mean AUC values of AcMPAG and MPA (adjusting for the 1.55-fold difference in molecular weight) yielded a molar ratio of metabolite to parent of 17% and 20% for EC-MPS and MMF, respectively. These values are higher than the 10% previously reported for MMF in paediatric patients, possibly due to the different patient populations studied.[8]

AcMPAG is of interest because it has been shown to have some IMPDH-II inhibitory activity, although not as potent as MPA, and because it may undergo hydrolysis, molecular rearrangement and covalent binding to proteins and nucleic acids (reference 8). The formation of such stable adducts has been suggested to play a role in the manifestation of drug toxicities, either through direct disruption of the function of critical proteins or through antigen formation with subsequent hyper- sensitivity and other immune reactions.(reference 11).

[8] Shipkova M, Armstrong VW, Weber L, *et al*: Pharmacokinetics and protein adduct formation of the pharmacologically active acyl glucuronide metabolite of mycophenolic acid in pediatric renal transplant recipients. *Ther Drug Monit* 24:390, 2002. Reference not included in the submission.

The present study demonstrates that AcMPAG exposure is of sufficient magnitude to potentially contribute to MPA based immunosuppression and toxicity. With EC-MPS, AcMPAG may contribute on a molar basis about 14% of the exposure to active drug after administration of MPA. This potential for toxic effect would likely be greatest late in the dosing interval when the molar ratio of AcMPAG to MPA is highest.

4.4.7.2. Evaluator

In general, it would not be considered appropriate to include a study without a statement of GCP, however the guideline on clinical trials in small populations, CHMP/EWP/83561/2005 states that it is important that every patient participating in a study contributes as much information as possible to make a benefit–risk assessment possible.

This study is included because it was the only one to address the active metabolite AcMPAG and the comments of the authors are considered relevant and important. In addition, the possibility of different results occurring in different populations is mentioned with reference to a previously studied paediatric population. The population for which the INDICATION is being sought differs from the population studied here. The proposed INDICATION does not specify adults.

4.5. Salvadori - Pivotal – efficacy and safety

Salvadori M et al. Enteric-coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in de novo renal transplant patients. American Journal of Transplantation 2003; 4: 231–236. Sponsored by Novartis

4.5.1. Design

Phase III, international, randomised, double-blind, parallel group 12 month equivalence study of EC-MPS vs. MMF in patients undergoing de novo renal transplantation.

4.5.2. Endpoints and definitions

Primary outcome: efficacy failure, defined as biopsy-proven acute rejection (BPAR), graft loss, death or loss to follow-up at 6 months.

Secondary efficacy endpoints were the incidence of BPAR, graft loss, death, clinically diagnosed rejection, treated rejection, rejection requiring antibody therapy and biopsy-proven chronic rejection evaluated at 6 and 12 months. Acute rejection episodes were verified by core biopsies before or within 24 hours following the start of anti-rejection therapy and rated according to the Banff 97 classification.

4.5.3. Inclusion/exclusion

Patients were of either sex aged 18 – 75 years, following first cadaveric, living-unrelated or HLA-mismatched living related donor kidney transplant.

4.5.4. Study therapy

- EC-MPS 720 mg twice daily
- MMF 1000 mg twice daily
- In the event of moderate to severe adverse events, the study medication dose could be reduced by 50% or eliminated completely until these events resolved
- Concomitant cyclosporine microemulsion and corticosteroids.

4.5.5. Statistics

Equivalence of the primary efficacy endpoint was assessed by the two-sided 95% CI of the difference in event rates being entirely within the pre-determined interval of (- 12, + 12).

Safety was evaluated for all randomised patients who received at least one dose of study medication. No adjustment was made for multiplicity when assessing other efficacy and safety parameters.

The sample size was based on a calculation considered likely to have power of 0.85. Patients were randomised according to a computer generated schedule. Study medication was packaged so as to maintain the double-blind. Patients received study drug and matching placebo. Patients, investigators, study centre personnel and any Novartis personnel in direct contact with the study centres were blinded until the 12 month analysis was complete.

Key efficacy analyses were performed on the intent-to-treat population which comprised patients who were randomised and had at least one assessment after the start of the trial medication.

4.5.6. Participant disposition

A total of 423 patients were recruited and randomised to either EC-MPS (213) or MMF (210). Twelve months of study treatment was completed by 151 patients in the EC-MPS group (70.9%) and 158 in the MMF group (75.2%). Most of the discontinuations occurred in the first 6 months. The main reasons for discontinuation are provided in the publication.

4.5.7. Baseline characteristics

Demographics of the two groups were similar though more patients in the EC-MPS group had reported cold ischemia time ≥ 24 hours. The majority of patients were male and Caucasian.

4.5.8. Efficacy results

The incidence of efficacy failure was 25.8% in the EC-MPS group and 26.2% in the MMF group. The 95% CI for the difference was (-8.7, 8) in keeping with equivalence. Efficacy outcomes are summarised in Table 3.

Table 3. Efficacy outcomes

Outcome	EC-MPS	MMF	CI for the difference
Primary Objective			
Efficacy failure at 6 months	25.8%	26.2%	(-8.7, 8)
Secondary objectives			
Efficacy failure at 12 months	28.6%	28.1%	(-8.0, 9.1)
BPAR	22.5%	24.3%	(-9.8, 6.3)
Efficacy failure: biopsy proven acute rejection (BPAR), graft loss, death or loss to followup.			

4.5.9. Safety results

Adverse events were similar between treatment groups. Serious infections were reported for 22.1% of the EC-MPS group and 27.1% of the MMF group. Gastrointestinal adverse events were reported for 80.8% and 80.0% respectively. Upper gastrointestinal events were reported by 53.5% and 54.3%. Non-upper gastrointestinal events were reported by 68.5% and 68.1%. The incidence of suspected drug-related adverse events was 53.1% and 60.5%, a non-significant difference. Five patients in each group reported malignancies. CMV infection was similar in each

group 21.6% and 20.5% of the EC-MPS and MMF groups respectively. The incidence of dose changes, defined as the composite of discontinuation, dose reduction of dose interruption for gastrointestinal adverse events was 13.1% in the EC-MPS group and 19.5% of the MMF group, a non-significant difference.

4.5.10. Discussion

4.5.10.1. Author

Enteric-coated-MPS and MMF demonstrated therapeutic equivalence in de novo renal transplant patients, with a comparable safety profile. Enteric-coated-MPS offers transplant physicians and their patients an alternative MPA therapy that is as effective and safe as MMF. Additional studies are needed before any definite conclusions can be drawn regarding the benefit of the enteric-coated formulation on GI tolerability.

4.5.10.2. Evaluator

Jadad score 5 NHMRC II. This appeared to be a well constructed and well reported trial.

With regard to equivalence testing, it appears that the ITT population was used in the analysis, while the per-protocol analysis is generally preferred when testing equivalence, with secondary ITT analysis . Use of the ITT population in analysis of equivalence can bias towards equivalence. The ICH Guideline E9 states that 'Subjects who withdraw or dropout of the treatment group or the comparator group will tend to have a lack of response, and hence the results of using the full analysis set may be biased toward demonstrating equivalence'. In an equivalence or non-inferiority trial use of the full analysis set is generally not conservative and its role should be considered very carefully.

External validity is problematic as the population and concomitant medication differs from that of lupus nephritis patients.

4.6. Budde: Pivotal – safety and efficacy

Budde K et al. Enteric-coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: results of a 1-year study. American Journal of Transplantation 2003; 4: 237 – 243. Supported by Novartis

4.6.1. Design

A 12 month, Phase III, randomised, double-blinded, double-dummy, international, multicentre, parallel group study to investigate whether renal transplant patients could be safely converted from mycophenolate mofetil to EC-MPS. (Study ERLB302). Inclusion and exclusion criteria are summarised in the publication.

4.6.2. Objectives

The primary safety objective was to evaluate the incidence and severity of gastrointestinal adverse events at 3 months and neutropenia (< 1500 cells/mm^3) within the first 3 months of study drug administrations.

Secondary safety endpoints evaluated for the entire duration of the study included of the incidence and severity of gastrointestinal adverse events and neutropenia, the incidence and severity of adverse events and infections, and discontinuations due to adverse events.

Efficacy was assessed as a secondary objective. The incidence of efficacy failure, a composite variable of biopsy-proven acute rejection (BPAR), graft loss or death was evaluated at 6 months and 12 months. Incidence of biopsy-proven chronic rejection was also evaluated.

4.6.3. Study therapy

After a run-in period of two weeks during which all patients received open-label MMF capsules 2000 mg/d, patients were randomised according to a computer generated schedule, to either EC-MPS 720 mg twice daily (n = 159) or MMF 1000 mg twice daily (n = 163).

The basic immunosuppressive regime was cyclosporine with target trough levels between 200 – 200 ng/mL, and corticosteroids according to local practice, but with dose to remain unchanged for the first 3 months. When gastrointestinal prophylactic treatment was administered, it was to be consistently given to all patients at a given centre and was to be unchanged for the first 3 months of each patient's participation.

4.6.4. Statistics

Patients were randomised according to a computer-generated schedule. Study medication was packaged to maintain the double-blinded trial design. The patients, investigators, study centre personnel and any Novartis personnel in direct contact with the study centres were blinded until completion of the 12 month analysis.

The safety population included all patients who had received at least one dose of study drug and at least one tolerability/safety assessment. The efficacy population (intent-to-treat) was defined as all patients who had received at least one dose of study drug and had at least one post-baseline assessment. It was estimated that for sample size of 150 patients per treatment arm, there would be power of between 50% and 82% to detect difference for the individual adverse events.

Safety variables were evaluated by frequency distribution and descriptive statistics. Continuous variables were tested for baseline comparability using the Wilcoxon rank-sum test. Categorical variables were tested using the Chi-square or Fishers' exact test. Confidence intervals for the differences in incidence rates were obtained using exact or asymptotic normal approximation methods. All significance tests were two sided. The incidence rates of efficacy events and also the 95% confidence intervals for the difference in rates.

4.6.5. Patient disposition

The ITT and safety populations were identical: 159 patients in the EC-MPS group and 163 patients in the MMF group. Study discontinuations are summarised in the publication.

4.6.6. Baseline characteristics

Baseline characteristics were similar between groups.

4.6.7. Safety results

There was no statistically significant difference between EC-MPS and MMF with respect to nausea, dyspepsia, upper abdominal pain, gastro oesophageal reflux disease, gastritis and anorexia, diarrhoea.

Neutropenia was reported for 0.6% of EC-MPS patients and 3.1% of MMF patients and remained unchanged throughout the study. The 95% CI for the difference was (- 6.74, 0.80).

The overall incidence of infections was similar in both groups (58.5% and 58.9% for EC-MPS and MMF, respectively), however, there were approximately 50% fewer serious infections associated with EC-MPS (8.8% vs. 16.0%).

The incidence of serious adverse events was not statistically significantly different: 23.3% in the EC-MPS group vs. 30.1% of the MMF group.

4.6.8. Efficacy result

Efficacy failure was 2.5% in the EC-MPS group and 6.1% in the MMF group 95% CI (-8.0, 0.8). Biopsy proven chronic rejection was reported in 1.3% of patients in the EC-MPS group and 3.1% of the MMF group.

4.6.9. Discussion

4.6.9.1. Author

With the exception of the incidence of serious infections, no statistically significant differences between EC-MPS and MMF were identified in the safety and efficacy parameters measured. No consistent numerical or statistically significant trend in favour of either treatment group was observed for GI AEs.

The similarity of the overall observed rates of GI AEs in the treatment groups in this study might be explained by several factors:

i. different factors can contribute to the occurrence of GI events;

ii. the daily fluctuations as well as the subjectivity of the symptoms make documentation and interpretation of GI AEs difficult when collected in the context of standard case report forms; and

iii. patients that entered this study were already receiving and therefore tolerating MMF at a dose level of 2000 mg, which may introduce a bias as this population may not be representative of the overall transplant population. Studies more specifically designed to address GI tolerability are needed in order to better identify the impact of this new formulation.

4.6.9.2. Evaluator

This study has been assigned a Jadad score of 5 and level II of the NHMRC evidence hierarchy.

There was no pre-specified difference in primary endpoint upon which study numbers could be calculated to provide a sufficiently powered analysis There was no accounting for multiplicity and thus the validity of p = 0.5 for difference in severe infection rate is questionable.

The safety of EC-MPS and MMF in combination with cyclosporine, in treatment of stable renal transplant patients did not differ in any major way. In particular the reported gastrointestinal adverse events were similar in frequency. The rationale for development of EC-MPS is stated to be to reduce gastrointestinal side effects and the point is argued above. However, it is possible that MPA has a systemic effect on the gastrointestinal tract or that the local effect was delayed until the product reached the small intestine.

As with other studies in renal transplant patients, external validity is a consideration.

4.7. Mycophenolate mofetil in treatment of lupus nephritis

4.7.1. Zhu *et al.* – Meta-analysis

Zhu B et al. Mycophenolate mofetil in induction and maintenance therapy of severe lupus nephritis: a meta-analysis of randomized controlled trials. Nephrol Dial Transplant 2007 22: 1933–1942.
There were no competing interests and financial supports

4.7.1.1. Design

Meta-analysis of trials of MMF in treatment of severe lupus nephritis.

Search strategy: EMBASE and Medline/Pubmed January 1990 to June 2006 Cochrane Central Register of Controlled Trials without restriction of language.

Study validity assessment: Unmasked evaluation of study validity was done independently and in duplicate. The quality of the studies was assessed from the point of view of allocation concealment, blinding, intention to treat analysis and completeness of follow-up. When necessary data were missing or incomplete, the investigators of selected trials were contacted for clarification. An assessment score according to the criteria of Jadad was assigned.

Data extraction: Two independent reviewers analysed each included trial. Data were extracted for the following:

Induction therapy

- Number of complete remission patients
- Number of partial remission
- Overall number of remissions
- Number of patients who had side effects including amenorrhoea, gastrointestinal symptoms, herpes zoster, infection leucopoenia
- Number of patients with end-stage renal disease during follow-up
- Number of deaths

Maintenance therapy

- Number of patients with end-stage renal disease
- Number of patients whose serum creatinine doubled
- Number of patients who died
- Number of patients who relapsed
- Number with side effects including amenorrhoea or herpes zoster.

The definitions of remission were considered insufficiently different to preclude combining data.

4.7.1.2. Statistics

- The distribution in an individual trial, of patients with various types of lupus nephritis in the MMF group versus the control was analysed by the chi-square test.
- The pooled relative risk and 95% confidence intervals were computed with random effects models (DerSimonian and Laird for dichotomous outcomes).
- Heterogeneity of treatment effects was tested using I2 statistics.
- Publication bias was assessed using Funnel plots, Egger's regression asymmetry test and Begg's test.
- Forest plots were used for graphic representation of data.
- A p-value of < 0.05 was considered statistically significant.
- Data were analysed with STATA 8.0.

4.7.1.3. Results

Five reports were chosen including a total of 307 patients. Four of the reports provided the data for comparison of MMF with cyclophosphamide (CYC) for induction therapy: Chan 2000 (reference 44), Chan 2005 (reference 45), Ginzler (reference 42), Ong (reference 43). For the meta-analysis of induction therapy results, the Chan 2005 article was the main source of data rather than the Chan 2000 report. Two reports provided data for comparing MMF with

azathioprine (AZA) for maintenance therapy of severe lupus nephritis: Chan 2005 and Contreras (reference 46).

All studies analysed in the meta-analysis were included in the submission and are further discussed under the relevant heading below (Ginzler, Ong, Chan 2000, Chan 2005 and Contreras).

Allocation concealment was stated by the authors to be adequate in three trials.(questionable) No trial was double-blinded. All reported an intention to treat analysis. The relevant tests did not disclose publication bias.

4.7.1.4. Efficacy result – induction

- MMF vs. CYC: Three trials were included in the analysis: Ginzler, Ong and Chan (2005) MMF did not increase the following rates compared with CYC:
  - Complete remission: RR 1.81, 95% CI (0.70 - 4.68), p = 0.22, heterogeneity p = 0.03, chi-square = 7.27, I^2 = 72.5%;
  - Partial remission: RR 1.06, 95% CI (0.71–1.59), p = 0.78, heterogeneity p = 0.71, chi-square = 0.70, I^2 = 0%);
  - Overall remission: RR 1.20, 95% CI (0.85–1.69), p = 0.31, heterogeneity p = 0.05, chi-square = 6.06, I^2 = 67.0%.

Significant heterogeneity existed in complete remission and overall remission results across the trials, and was due to the effect of the Ginzler trial as determined by a Galbraith Plot for heterogeneity (data was not shown). However, after excluding the Ginzler trial, the differences between MMF and CYC remained insignificant in both the complete remission: RR1.13, 95% CI (0.62–2.07), p = 0.69, heterogeneity p = 0.24, chi-square = 1.40, I^2 = 28.5%) and the overall remission: RR 1.01, 95%CI (0.92–1.10), p = 0.91, heterogeneity p = 0.71, chi-square = 0.14, I^2 = 0.0%.

4.7.1.5. Sensitivity analysis

Only patients in the Chan trial received daily oral CYC; those in the other two trials received pulsed IVC. When the Chan trial results were removed, complete remission rate was significantly higher in patients receiving MMF compared with those receiving IVC: RR 3.10, 95% CI (1.38, 7.01) p = 0.006, heterogeneity p = 0.50, chi-square = 0.45, I^2 = 0%.

The other results were said not to have been altered significantly by removing the results of Chan. The relevant supplementary figure was not included in the submission.

4.7.1.6. Efficacy result – maintenance

The Chan 2005 and Contreras studies comparing MMF vs. AZA did not report significant differences in any of the following:

- Incidence of death: RR 0.7, 95% CI (0.05, 10.1) p = 0.80, heterogeneity p = 0.22, chi-square = 1.51, I^2 = 33.7%
- ESRD: RR 0.70, 95% CI (0.05, 10.1), p = 0.80, heterogeneity p = 0.22, chi-square = 1.51, I^2 = 33.7%
- Relapse: RR 0.89, 95% CI (0.41, 1.94), p = 0.77, heterogeneity p = 0.23, chi-square = 1.47 I^2 = 32.1%
- Doubling of serum creatinine: RR 0.71, 95% CI (0.17, 3.02) p = 0.64, heterogeneity p = 0.80, chi-square = 0.07, I^2 = 0%.

4.7.1.7. Safety result – induction

- MMF vs. CYC: Three trials were included in the analysis: Ginzler, Ong, and Chan (2005)

- Infection: RR 0.65, 95% CI (0.51, 0.82) p = < 0.001, heterogeneity p = 0.40, chi-square = 1.81, I^2 =0% (significant decrease)
- Amenorrhoea: RR 0.22, 95% CI (0.04, 1.22), p = 0.08, heterogeneity p = 0.80, chi-square = 0.45, I^2 = 0%
- Leucopoenia: RR 0.61, 95% CI (0.37, 1.03), p = 0.07, heterogeneity p = 0.26, chi-square = =2.68, I^2 = 25.3%
- Gastrointestinal symptoms: RR 1.33, 95% CI (0.97, 1.84), p = 0.08, heterogeneity p = =0.84, chi-square = 0.35, I^2 = 0%.

4.7.1.8. Sensitivity analysis

Based on the two studies comparing MMF with IVC, the risk of leucopoenia was significantly lower in patients receiving MMF: RR 0.66, 95% CI (0.44, 0.97), p = 0.04, heterogeneity p = 0.80, chi-square = 0.06 I^2 = 0%. The other results were said not to have altered significantly after the removal or the results of Chan. The relevant supplementary figure was not included in the submission.

4.7.1.9. Safety result – maintenance

MMF vs. AZA: Two trials included: Contreras, Chan 2005

No significant difference was noted for the following:

- Amenorrhoea: RR 0.49, 95% CI (0.16, 1.52) p = 0.21, heterogeneity p = 0.32, chi-square = 1.01, I^2 = 0.5%
- Herpes zoster: RR 0.66, 95% CI (0.11, 3.78) p = 0.64, heterogeneity p = 0.19, chi-square = 1.69, I^2 = 41%.

The data on other side effects, infection, leucopoenia and gastrointestinal symptoms were shown in a supplementary table which was not included in the submission, and were stated to have shown that gastrointestinal symptoms occurred more frequently in the MMF group than the AZA group but that MMF tended to decrease the risk of leucopoenia.

4.7.1.10. Discussion

4.7.1.10.1. Authors

The authors conclude that MMF is superior in inducing complete remission in severe lupus nephritis compared to pulsed CYC with fewer side effects, particularly reduced risks of infection and leucopoenia, though with greater risk of gastrointestinal symptoms. They also conclude that MMF is an alternative to AZA for maintenance therapy of severe LN, without significant difference in prognosis, or risks of amenorrhoea or herpes zoster.

The limitations outlined by the authors include:

- None of the studies were double-blind.
- Only three of the trials describe allocation concealment.
- The Contreras trial had small numbers of participants, particularly at the end of the 3 year follow-up.
- Although it was considered that induction treatment should be given only to class IV or Vb LN there were a few patients with type III or V LN who have better prognoses included with potential to result in bias.
- The authors consider that maintenance therapy should be given only to patients in remission; some patients not in remission were included in the maintenance arm of the two trials included in the maintenance analysis of this report.

- The distribution of race varies between trials.

The authors conclude that further studies are required and they need to report use of ITT population and allocation concealment.

4.7.1.10.2. Evaluator

- Method of assigning weight to the various studies was not specified.
- Conclusion of superiority of MMF compared to IVC is considered to require a well designed study with primary efficacy objective to specifically test superiority.
- The two studies on which the claim of superiority was base have considerable flaws in design which, in addition to the non-blinded nature of the studies, were considered to result in considerable potential for bias. In particular these concerns were as follows:
    1. Ginzler *et al*, in a 24 weeks study, allowed assessment of results at 12 weeks and cross-over of treatment at that time if early response had not occurred. Cross-over was uneven and the reason was not given as to why some patients apparently meeting the criteria, were not crossed over. In addition, 12 weeks is very early to be deciding on failure of induction. In essence the result of the study was considered to have been decided at 12 weeks rather than at 24. In addition, the result for the IVC group at 24 weeks was remarkably low.
    2. Ong: there were large numbers of patients excluded after randomisation, particularly in the MMF group, and the exclusions were based on revision of the results of renal biopsies required by the pre-defined inclusion criteria.

Zhu *et al* stated that allocation concealment was adequate in three of the studies. The evaluator was unable to find information relating to allocation concealment in any study report other than that of Ginzler *et al*. The authors acknowledged Professor TM Chan for providing additional data relating to his trial. The inference taken by the evaluator is that additional data were not sourced from other investigators. It is possible that allocation concealment was confirmed by Professor Chan in personal communication, though it is puzzling that allocation concealment was said to be adequate in the Chan 2005 study but not the Chan 2000 study.

The disposition of patients was in general, so poorly described that it was found virtually impossible to determine loss to follow-up in all studies, but in particular the Contreras study in which the authors of the meta-analysis conclude that there was no loss to follow-up, while the Kaplan-Meier figures in the Contreras report suggest the possibility of a very different picture.

The assigned Jadad scores are all greater than 3, which is the maximum that could be assigned to a non-blinded study according to the paper referenced in the meta-analysis, which is also the paper upon which the evaluator bases Jadad scores[9]. Three of the studies were assigned a Jadad score of 6, which is one more than it is possible to assign to a randomised and double-blinded study.

Results of this meta-analysis were not re-analysed, however, the failing reported above, do not aid confidence. Despite these comments, this meta-analysis appeared to have better structure than the other meta-analysis submitted, for which brief discussions are included below.

4.7.2. Walsh *et al* – Meta-analysis

Walsh M, James M, Jayne D et al. Mycophenolate mofetil for induction therapy of lupus nephritis: a systematic review and meta-analysis. Clin J Am Soc Nephrol 2007; 2: 968-975

[9] Jadad AR, *et al*. assessing the quality of reports of randomised clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1 - 12

4.7.2.1. Design

A meta-analysis to determine the relative risk for failure to induce remission of lupus nephritis in patients treated with mycophenolate mofetil compared to cyclophosphamide for induction therapy.

The following study reports were examined for the meta-analysis.

- Flores-Suarez LF, Villa AR: Abstract (reference 52): Open randomised trial comparing mycophenolate mofetil versus intravenous cyclophosphamide as induction therapy for severe lupus nephritis. *J Am Soc Nephrol* 15: PO257, 2004
- Chan *et al* (45) Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. *J Am Soc Nephrol* 16: 1076–1084, 2005
- Ginzler EM *et al* (42). Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 353: 2219–2228, 2005
- Ong LM *et al* (43). Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. *Nephrol* 10: 504–510, 2005

Non randomised

- Hu W *et al* (50). Mycophenolate mofetil vs cyclophosphamide therapy for patients with diffuse proliferative lupus nephritis. *Chin Med J (Engl)* 115: 705–709, 2002
- Lin YK *et al* (51). A comparison of response between mycophenolate mofetil and cyclophosphamide therapy for lupus nephritis. *J Clin Derm* 31: 636–638, 2002

The reports of Flores-Suarez, Hu and Lin were not included in the submission.

The following problems were considered to have reduced reliability of the analysis:

- Non-randomised studies were included
- Foreign language reports were include
- One of the authors had a financial relationship with Roche and Aspreva.

4.7.3. Moore and Derry – Meta-analysis

Moore A, Derry S. Systematic review and meta-analysis of randomised trials and cohort studies of mycophenolate mofetil in lupus nephritis. Arthritis Research & Therapy 2006, 8: 175 – 185.
Funded by Aspreva

The problems encountered with this report are as follows:

- Heterogeneity testing was not used. The EMEA guideline: *Points to consider on application with 1. Meta-analysis; 2. One pivotal study* CPMP/EWP/2330/99 states that such testing important.
- Insufficient information was supplied on the randomised controlled trials included. This information may have been present in “Additional file 2”; however, this file was not supplied for evaluation.
- Inclusion of a number of cohort studies was considered to increase the possibility of bias in the results.
- The work was funded by Aspreva, who in 2003 entered into a collaboration agreement with Roche for the exclusive worldwide rights to develop and commercialise their leading transplantation drug worldwide, CellCept (MMF).

4.7.4. Appel *et al.* 2009– MMF induction treatment of lupus nephritis

Gerald B. Appel et al. Mycophenolate Mofetil versus Cyclophosphamide for Induction Treatment of Lupus Nephritis J Am Soc Nephrol 2009; 20: 1103–1112. Funded by Roche

4.7.4.1. Design

Prospective, randomised, open-label, parallel-group, multicentre study to test whether MMF is superior to intravenous cyclophosphamide (IVC) in the treatment of lupus nephritis.

Duration of the induction phase was 24 weeks. After screening, randomisation and initiation of treatment, patients were assessed at weeks 2 and 4 and then every 4th week. Patients were withdrawn at week 12 if their serum creatinine as ≥30% above baseline on two successive measurements separated by at least 4 weeks or if they required other immunosuppressive treatment. Patients could be withdrawn if the MMF dosage fell below 2g/d for >14 days or was stopped for >7 days.

Statistics are summarised in the publication. There was no discussion of method of assessing superiority.

4.7.4.2. Endpoints and definitions

The primary end point was the proportion of patients responding to treatment defined as:

- Stabilisation (±25%) or improvement in serum creatinine at 24 weeks and
- Decrease in urine protein/creatinine ratio (P/Cr) calculated form a 24 hour urine collection.

For patients with baseline nephrotic range P/Cr ≥3, response was defined as P/Cr of < 3 (not a very rigorous endpoint).

For patients with sub-nephrotic baseline P/Cr < 3, the response was defined as a decrease ≥50%.

4.7.4.3. Secondary end points included

- The proportion of patients who achieved complete remission, defined as return to normal serum creatinine, urine protein ≤0.5 g/d, and inactive urinary sediment (≤5 white blood cells per high-power field and ≤5 red blood cells per high-power field, and a reading of lower than 2+ on dipstick and absence of red cell casts)
- The proportion of patients who achieved any one of these renal outcomes
- Safety assessments.

4.7.4.4. Inclusion criteria

Patients aged 12 to 75 years with active of active/chronic disease confirmed by kidney biopsy within 6 months before randomisation. Patients with International Society of Nephrology/Renal Pathology Society 2003 class III, IV-s or IV-G, V, III + V, or IV + V were eligible. Patients with Class III or V must have had proteinuria of at least 2 g/day. Exclusion criteria are summarised in the publication.

4.7.4.5. Study therapy

MMF: target dosage 3 g/d.

IVC: 0.5 to 1.0 g/m^2 in monthly pulses.

Both groups received prednisone, tapered from a maximum starting dosage of 60 mg/d.

4.7.4.6. Participant disposition

A total of 370 patients were enrolled between July 2005 and October 2006, in 88 centres in 20 countries in North America, Latin America, Asia, Australia and Europe.

Patient disposition is summarised in the publication. Six randomly assigned patients (one in the MMF group and five in the IVC group) were excluded from the safety analysis because they received no study drug.

At week 24, 306 (82.7%) patients remained in the study. In the MMF group, 35 (18.9%) patients withdrew from the study, compared with 29 (15.7%) in the IVC group. There was a higher rate of withdrawal from the MMF group for adverse event than from the IVC group. There were no crossovers between treatments during the study.

4.7.4.7. Baseline characteristics

Patient demographic and baseline disease characteristics were similar. Approximately 40% of each group was White and approximately one third Asian.

4.7.4.8. Exposure

The mean duration of treatment was 156.2 d for the MMF group and 162.5 d for the IVC group. The median dosage was calculated for 179 patients in the MMF group as 2.6 g/d; median average dosage was similar for each of the racial group. The corresponding mean ±SD average dosage was 2.47 ±0.58 g/d. A maximum MMF dosage of 2.5 to 3.0 g/d was achieved in 168 (91.3%) of 184 patients. For 180 patients in the IVC group and for patients in each of the self reported racial groups, the median number of doses was 6.0. Overall, the median total dosage per infusion of IVC was 0.75 g/m^2.

Overall, the mean dosage of prednisone did not differ between groups (25.8 and 26.0 mg/d for the MMF and IVC groups, respectively), with steady decrease in prednisone dosage in each group.

4.7.4.9. Efficacy result

The primary efficacy end point was achieved in 104 (56.2%) patients receiving MMF, compared with 98 (53.0%) patients receiving IVC (odds ratio 1.2; 95% CI 0.8 to 1.8. There were statistically significant interactions between treatment group and race (p = 0.047) and between treatment group and region (p = 0.069).

4.7.4.10. Safety results

Of the 184 patients treated with MMF and 180 with IVC, the proportions reporting adverse events were similar (96.2% for MMF vs. 95.0% for IVC; treatment difference 1.20%; 95% CI (3.02 to 5.42%). Numerically there were more AEs in the IVC group (2,088) than in the MMF group (1,485) during the 24-wk treatment period. In both treatment groups, the most common types of AE were infections: 68.5% with MMF and 61.7% with IVC; treatment difference 6.81%; 95% CI (-96 to 16.58%) and gastrointestinal disorders (61.4% with MMF; 66.7% with IVC). There were 24 withdrawals (13.0%) as a result of AEs in the MMF group compared with 13 (7.2%) in the IVC group. Treatment difference was 5.82%; 95% CI (-0.34, 11.99). The most commonly reported adverse events are shown in Table 4 below. AEs considered to be at least possibly related to study treatment were not reported.

Table 4. Appel *et al* 2009. Incidences of adverse events reported by >10% of patients

Parameter	Patients Who Experienced at Least One AE	
	MMF (*n* = 184)	IVC (*n* = 180)
Deaths	9 (4.9)	5 (2.8)
Withdrawals as a result of AEs	24 (13.0)	13 (7.2)
All AEs	177 (96.2)	171 (95.0)
diarrhea	52 (28.3)	23 (12.8)
headache	38 (20.7)	47 (26.1)
peripheral edema	35 (19.0)	30 (16.7)
arthralgia	29 (15.8)	43 (23.9)
nausea	27 (14.7)	82 (45.6)
hypertension	26 (14.1)	25 (13.9)
nasopharyngitis	25 (13.6)	29 (16.1)
vomiting	25 (13.6)	68 (37.8)
cough	24 (13.0)	16 (8.9)
anemia	23 (12.5)	12 (6.7)
alopecia	20 (10.9)	64 (35.6)
abdominal pain	19 (10.3)	13 (7.2)
back pain	19 (10.3)	16 (8.9)
muscle spasms	19 (10.3)	17 (9.4)
rash	19 (10.3)	21 (11.7)
urinary tract infection	19 (10.3)	17 (9.4)

In the safety population, 51 (27.7%) patients in the MMF group and 41 (22.8%) in the IVC group had at least one serious adverse event. Treatment difference was 4.90%; 95% CI (-4.01, 13.81%). The most commonly reported types of SAEs in both groups were infections, occurring in 22 (12.0%) patients with MMF and 18 (10.0%) patients with IVC; gastrointestinal disorders, occurring in eight (4.3%) patients treated with MMF and three (1.7%) patients with IVC; and renal and urinary disorders, occurring in eight (4.3%) patients with MMF and three (1.7%) patients with IVC.

There were nine deaths in the MMF group and five in the IVC group. In the MMF group, seven deaths were due to infection and none were due to SLE, vs. two due to infections and two due to SLE in the IVC group.

4.7.4.11. Discussion

4.7.4.11.1. Author

In this study, MMF did not show superiority over IVC for the induction therapy of LN, as measured by renal response rate after 24 wk of treatment. There was a statistically significant interaction between treatment group and race and between treatment group and region. Interactions between treatment and race and between treatment and region were not explained by differences in disease characteristics at baseline between the subgroups. Sub-analyses revealed that statistically significantly fewer patients responded to IVC than to MMF in the "other" group, most of whom were black or Latin American mixed race. Similarly, fewer Hispanic patients responded to IVC than to MMF. The wide variation in response by race/ethnicity for IVC may have been confounded by regional variations, possibly as a result of differences in clinical practice.

Although meta-analyses of smaller studies have suggested that more patients respond to MMF than to IVC, results from the large and racially diverse population of this study indicate that

these drugs in combination with prednisone have similar efficacy in short-term induction therapy.

4.7.4.11.2. Evaluator

NHMRC II, Jadad score 3. In both efficacy and safety result sections, supplementary tables were mentioned but were not included in the submission.

The statistical method for assessing superiority was not stated. Use of the odds ratio would appear to be an unusual method of approach. The possibility that it was employed post-hoc could not be excluded. The odds ratio which includes 1 does not necessarily mean that the two treatments are equivalent. The FDA's most recent guidance for industry includes the recommendation that superiority studies are performed. This seems an unusual approach in a trial with active rather than a placebo control – non-inferiority with option to progress to superiority would seem more logical. There is not yet an EMEA guideline available.

The finding of significant interactions based on race and region is considered important and has the potential to limit external validity.

4.8. Ginzler – MMF induction therapy

Ginzler et al Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Eng J Med. 2005 353(21); 2219 – 2228. Supported by FDA Orphan Products Development program and supplemented by funding from Roche

4.8.1. Design

Twenty-four week, multicentre, randomised, open-label, noninferiority trial of MMF compared to IVC in treatment of lupus nephritis.

4.8.2. Endpoints and definitions

Primary endpoint complete remission defined as return to within 10% of normal values of serum creatinine, proteinuria and urine sediment

Secondary endpoint

- partial remission defined as improvement of 50% in all abnormal renal measurements without worsening within 10% of any measurement
- change in renal function, complement components, anti double-stranded DNA titres and serum albumin levels

Early response at 12 weeks was defined as:

- improvement of 30% in at least 2 measures of renal function if all three measures were abnormal at baseline or
- improvement of 30% in one measure if one or two measures were abnormal at baseline

Treatment failure was defined:

- A condition requiring higher doses of corticosteroid for disease control
- Failure to meet the criteria for an early response
- Failure to reach complete or partial remission at 24 weeks
- Toxic effects requiring discontinuation of study drug
- Withdrawal from the study for any other reason

4.8.3. Inclusion/exclusion

Inclusion

- Renal biopsy showing WHO class III (focal) IV (diffuse) or V (membranous) and one or more of the following:
  - Serum creatinine > 88.4 µmol/L
  - Proteinuria > 500 mg/24 hour
  - RBC > 5/HPF
  - Presence of cellular casts
  - Increasing proteinuria with rising levels of serum creatinine,
  - Active urine sediment
  - Those with class III or V were required to meet creatinine level above or to have > 2 g/24 hours

Exclusion

- Creatinine clearance < 30 mL/min
- Creatinine > 265.2 µmol/L
- Severe coexisting conditions
- Treatment with MMF or IVC within the preceding 12 months
- Monoclonal therapy within the preceding 30 days
- Pregnancy/lactation

4.8.4. Study therapy

MMF 1000 mg per day increasing to 3000 mg per day

IVC 0.5 g/m^2 monthly increasing to 1.0 g/m^2

Dosage of both modified on basis of WBC count

A change to alternative regimen was allowed at 12 weeks in patients who did not have early response

Oral prednisone tapered over time, plus option of three day pulses of IV prednisolone for flares.

No protocol specified maintenance therapy.

4.8.5. Statistics

Non-inferiority defined as lower bound of the two-sided 95% confidence interval for the difference in rates of complete remission must exceed -10%.

4.8.6. Participant disposition

Enrolled140 patients: MMF 71 patients; IVC 69 patients

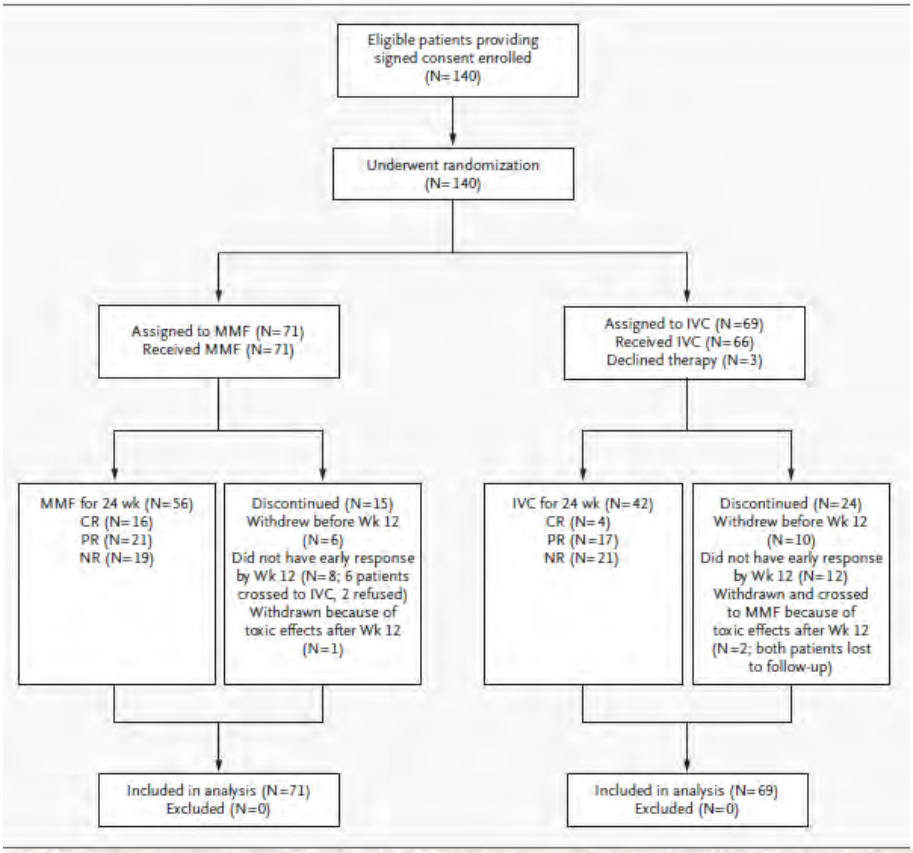
- Discontinuations (Figure 1 below): MMF 15; IVC 24
- Withdrew before week 12: MMF 6; IVC 10
- Did not have early response: MMF 8; IVC 12
- Due to toxic effects after week 12: MMF 1; IVC 2 (both IVC patients lost to follow-up)
- Crossed treatment at week 12: MMF 6; IVC 12

Disposition according to the text:

- Response at week 12: MMF 56; IVC 42

- By inference: numbers not achieving early response MMF 15 and IVC 27 (difficult to tally with Figure 1 and begs the question, why weren't more patients offered cross-over treatment)
- Lost to follow-up: MMF 7; IVC 15

Figure 1. Enrolment of Patients, Treatment Assignments, and Outcomes, According to the Intention-to-Treat Analysis.



MMF denotes mycophenolate mofetil, IVC intravenous cyclophosphamide, CR complete response, PR partial response, and NR no response.

4.8.7. Baseline characteristics

There were proportionally more Black patients in the MMF group 43/71 vs. 36/69 in the IVC group, and more Hispanic patients in the IVC group 18/69 compared to 10/71 in the MMF group.

Renal biopsy class was similar between groups. MMF and IVC respectively: class III 15% and 16%; class IV 55% and 56%; class V 20% and 19%.

Mean duration of SLE 43.7 months in the MMF group compared to 58.7 months in the IVC but both had very large associated standard deviations. Other characteristics were similar between groups.

4.8.8. Efficacy results

Complete response ITT analysis:

- MMF 16/71 (22.5%); IVC 4/69 (5.8%)
- Difference (95% CI) 16.7% (5.6%, 27.9%) p = 0.005
- As the lower boundary of the 95% CI exceeded -10%, non-inferiority was concluded. As the lower boundary of the 95% CI exceeded 0%, superiority was concluded.

Complete response: Sensitivity analysis excluding patients with missing data:

- MMF 16/64 (25.0%) ICV 4/54 (7.4%)
- Difference (95% CI) 17.6% (4.9%, 30.3%) p = 0.01

Partial response:

- MMF 21/71 (29.6%); IVC 17/69 (24.6%)

Treatment failure:

- MMF 34/71 (47.9%) IVC 48/69 (69.6%)

4.8.9. Safety results

Deaths: MMF 0; IVC 2 (cerebral haemorrhage after first dose; sepsis and active lupus after second dose. Relatedness was not reported.

The duration of therapy in patient-weeks was: MMF 1,738 and IVC 1,350.The reported figures in each of the two groups include those initially assigned to the regime and those who crossed over to the regime. The incidence of upper gastrointestinal adverse events was similar between groups; diarrhoea was more common in the MMF group while menstrual irregularities, alopecia and lymphopaenia were more common in the IVC group.

4.8.10. Discussion

4.8.10.1. Author

The authors concluded that the toxicity and tolerability profile of MMF compared favourably with that of cyclophosphamide.

The limitation cited by the authors was lack of blinding. The authors stated that potential bias was minimised by selecting a primary end point with the use of objective laboratory measures. The authors concede that crossover design may have led to a premature designation of treatment failure, and state that reports in the literature have the average time to remission with cyclophosphamide at 10 months. They also concede the limitation of short study time overall and lack of maintenance study.

The low response rate with cyclophosphamide may reflect an inability to achieve the recommended NIH protocol dosing; doses were regulated on the basis of toxic effects, primarily gastrointestinal symptoms. The trend toward better response with higher doses of cyclophosphamide highlights the association between efficacy and tolerability.

4.8.10.2. Evaluator

Although the early crossover design was chosen for safety it almost certainly led to a premature designation of treatment failure. Added to this concern is the confusion between information contained in the text and in Figure 1, above, over the numbers reported to have not achieved partial remission. In addition the report lacked any explanation as to why some patients who appeared to have qualified for cross-over treatment did not cross over.

Assessment of results at 12 weeks combined with lack of blinding and alibility to crossover treatments was considered to result in potential for considerable bias and confounding. Although the authors specifically deny an interim analysis, an informal analysis appears likely and thus multiplicity may also need to be considered.

The very low IVC response rate is considered problematic in the light of results of other studies.

4.9. Ong – MMF induction therapy - lupus nephritis

Ong *LM et al. Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. Nephrology 2005; 10: 504 – 510.* Roche supplied MMF

4.9.1. Design

Six month, multicentre, randomised open-label trial to evaluate efficacy and safety of mycophenolate mofetil in induction therapy of proliferative lupus nephritis.

4.9.2. Endpoints and definitions

Primary outcome: combined remission of nephritis including complete and partial remission.

Partial remission was defined as stabilisation or improvement in renal function, urinary RBCs <10/HPF and reduction of proteinuria < 3 g/day and at least 50% reduction in proteinuria or <1 g/day if the baseline proteinuria was in the subnephrotic range. Stabilisation of renal function was defined as a change in serum creatinine concentration of less than 20% of baseline. Improvement in renal function was defined as reduction in serum creatinine of at least 20% compared with baseline. Complete remission was similarly defined except for reduction of proteinuria to < 0.3 g/d.

4.9.3. Inclusion/exclusion

Inclusion

- Newly diagnosed WHO class III or IV lupus nephritis
- Age sixteen years or older

Exclusion

- Serum creatinine > 200 μmol/L
- White blood cell count < 3.5 x 109/L
- Evidence of major infection
- History of cancer
- Pregnancy/lactation
- Alcohol or substance abuse
- Active peptic ulcer disease
- Use of study drug in preceding 6 months
- Known allergy to study drug/s

4.9.4. Study therapy

First stage:

The first nine patients were randomly selected for treatment with MMF.

Second stage:

- If ≥1 patient responded, the study continued with patients randomly assigned to either MMF or IVC
- MMF 1.0 g orally twice daily
- IVC 0.75 – 1 g/m^2 monthly

Dose of each was modified on the basis of WBC count, and in addition dose of MMF was modified on the basis of gastrointestinal symptoms.

Prednisolone commenced at 60 mg/day reducing to 5 – 10 mg/day

4.9.5. Statistics

Simon's optimal two-stage design was used. Randomisation done centrally, 1:1, with code generated separately for each centre using random permuted block method with varying block size.

Results of analysis of primary objective were reported as proportions with 95% confidence intervals. Analysis was based on Intent-to-treat population defined as those who received at least one dose of study medication. Repeated measure ANOVA was used for serial measurement.

4.9.6. Participant disposition

54 patients were screened and randomised: 28 to the IVC group, 26 to the MMF Group. Patient disposition is summarised in the publication. Based on this figure,10.7% of the IVC group and 26.9% of the MMF group were excluded after randomisation, the main reason being the reclassification of the renal biopsies. A total of 44 patients received study drug: MMF group 19; IVC group 25 (ITT population by study definition).

4.9.7. Baseline characteristics

- In the IVC group 14 (56%) were Malay and 10 (40%) were Chinese. In the MMF group 8 (42.1%) were Malay and 10 (52.6%) Chinese
- Mean age was 30.5 for the IVC group and 31.3 years for the MMF group
- WHO class IV: IVC 17 (68%); MMF 10 (52.6%)
- WHO class IV with membranous changes: IVC 6 (24%); MMF 7 (36.8%)

The mean duration of SLE differed between groups however large standard deviations indicated wide spread of data. Patients in the IVC group had a higher mean level of proteinuria than those in the MMF group. Five patients in the MMF group and 12 in the IVC group had nephrotic syndrome at presentation. The IVC group also higher mean activity index score than the MMF group.

4.9.8. Efficacy results

Combined remission : IVC 13 (52%) 95% CI [32%, 72%]); MMF 11 (58%) 95% CI [36%, 80%]) p = 0.70.

Complete remission: IVC 3 (12%, 95% CI [0%, 25%]); MMF 5 (26%, 95% CI [7%, 46%]) p = 0.22.

The mean time to remission was 11.7 ±7.3 weeks and 12.4 ±5.0 weeks for the IVC and MMF groups, respectively. The mean time to complete remission was 11.4 ± 9.4 weeks for the IVC group and 13.0 ±5.7 weeks for the MMF group.

4.9.9. Safety

- Adverse event rate was 0.48 episodes per patient-month for IVC vs. 0.60 for MMF.
- One patient in the IVC group reported oligomenorrhoea vs. none in the MMF group.
- Leucopoenia was reported for 52% of the IVC group and 36.8% of the MMF group.
- There was no difference in incidence of infection between groups. Incidence of gastrointestinal adverse events per patient month was 0.08 for IVC and 0.07 for MMF.

4.9.10. Discussion

4.9.10.1. Author

The study excluded patients with severe disease. They conclude that MMF 2 g/day in conjunction with steroids is an effective induction therapy for patients with moderately severe proliferative lupus nephritis. They suggest that severe lupus nephritis may behave differently in various ethnic groups and results might not be generalised across borders. The authors made no statistical claims in their discussion.

4.9.10.2. Evaluator

The study was rated a Jadad score of 3. The use of Simon's optimal two-stage design was considered unusual. The exclusion of patients after randomisation and after reassessment of the renal biopsies, the larger proportion, over ¼ of those randomised, being in the MMF group, raises concern about the lack of bias in this unblinded study and possibly contributed to the reported inequalities in baseline characteristics.

4.10. Chan 2000 – MMF induction therapy - lupus nephritis

Chan TM et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. NEJM 2000; 343 (16) 139 – 145. Roche supplied MMF

4.10.1. Design

Twelve month randomised, controlled, open-label, study of efficacy and safety of MMF compared to oral cyclophosphamide (CTX) in the treatment of diffuse proliferative nephritis class IV.

4.10.2. Endpoints and definitions

Primary Endpoint:

- Complete remission defined as:
  - Urinary protein < 0.3 g/24 hours
  - Normal urine sediment
  - Serum creatinine ≤ 15% above baseline
  - Creatinine clearance ≤ 15% above baseline

Secondary endpoints

- Partial remission defined as:
  - Urinary protein between 0.3 and 2.9 g/24 hours and
  - Serum albumin ≥ 3.0 g/dL

Other secondary endpoints: adverse events; doubling of serum creatinine; relapse of lupus and death.

Treatment failure defined as follows. Renal relapse was confirmed by biopsy.

- Urinary protein ≥ 3 g/24 hours or
- Urinary protein 0.3 to 2.9 g/24 hours with serum albumin concentration < 3.0 g/dL
- Increase in serum creatinine ≥ 50 µmol/L
- Serum creatinine > 15% above baseline
- Discontinuation due to adverse events

4.10.3. Inclusion/exclusion

Included were patients with history of compliance, with renal biopsy showing WHO Class IV diffuse proliferative LN ±membranous features, urinary protein excretion ≥1 g/24 hours, serum albumin ≤3.5 g/dL and serum creatinine < 300 μmol/L. Exclusion criteria are listed in the publication.

4.10.4. Study therapy

Induction therapy 6 months

- Group 1 MMF 1.0 g twice daily orally
- Group 2 Cyclophosphamide 2.5 mg/kg/day orally
- Doses of MMF and cyclophosphamide were not changed during the first 6 months except on the basis of adverse events
- Prednisone 0.8 mg/kg/day reducing to 10 mg/day

Maintenance after 6 months

- Group 1: MMF 0.5 g twice daily
- Group 2: oral azathioprine 1.5 mg/kg/day; cyclophosphamide ceased.

After 12 months

- Group 1 azathioprine 1 mg/kg/day
- Group 2 azathioprine 1 mg/kg/day

Hypertension was treated with calcium-channel blocker and beta blocker added if necessary. Isoniazid prophylaxis was given for patients with history of clinical or radiological evidence of tuberculosis.

4.10.5. Participant disposition

Patient disposition was not discussed.

42 patients enrolled: 21 patients randomly assigned to each group

4.10.6. Baseline characteristics

All participants were Chinese

New diagnosis of SLE: 16/21 in Group 1 vs. 13/21 in Group 2

Baseline

- Mean serum C3 was higher in group 1 than group 2: 62 mg/dL vs. 46 mg/dL
- Mean urinary protein was higher in group 1 than group 2: 5.8 g/24 hours vs. 3.7 g/24 hours
- Mean creatinine clearance was higher in group 1 than group 2: 86 vs 77 mL/min/1.73 m^2
- Mean serum albumin and creatinine were similar between groups

4.10.7. Efficacy results

Statistical approach is summarised in the publication. By inference, based on reported proportions, analysis population was ITT.

Primary outcome: *Complete remission*

Group 1 17/21 (81% 95% CI [58, 95]); Group 2 16/21 (76% 95% CI [53, 92)

Difference 5% 95% CI (-20, 30); p= 1.00

Secondary outcome:

Partial remission

Group 1 3/21 (14%); Group 2 3/21 (14%); Difference 0% 95% CI (-21, 21)

Treatment failure

Group 1 1/21 (5%); Group 2 2/21 (10%); Difference -5% 95% CI (-21, 11)

Relapse

Group 1 3/20 (15%); Group 2 2/19 (11%); Difference 4% 95% CI (-16, 25)

Mean values for serum C3 and for serum albumin rose from baseline with significant increase reported for each group. Mean serum creatinine and mean urinary protein excretion fell from baseline with significant decrease reported for each group.

4.10.8. Safety results

There were 2 deaths in group 2, one at 11 weeks due to miliary tuberculosis and adult respiratory distress syndrome, without having response to treatment; one death at week 28 due to cerebral haemorrhage unrelated to thrombocytopenia or hypertension. There were no other deaths.

Discontinuations: Group 1 one patient with diarrhoea; Group 2 one patient with leucopoenia.

Infection was reported for 11 patients in each group.

The incidence of hair loss or amenorrhoea was not significantly different between groups.

4.10.9. Discussion

4.10.9.1. Author

The authors consider that the results or treatment with MMF compare favourably with those of conventional therapy, with efficacy and toxicity results similar to those of treatment with cyclophosphamide followed by azathioprin. The authors commented that the more favourable response in this study compared to results reported in other studies may have been due to earlier diagnosis and treatment as evidenced by lower indices of chronicity.

4.10.9.2. Evaluator

Jadad score 1 was assigned. Disposition was not formally discussed. Patients were said to be randomly assigned to treatment; the method of doing so was not discussed. Allocation concealment was not possible to asses and in the absence of blinding, bias could not be ruled out.

No hypothesis was stated and no means of testing a hypothesis mentioned. The wide confidence intervals for the primary analysis and for secondary analyses reflect the small study numbers and make the result difficult to interpret. Where confidence intervals included zero it cannot be concluded that because there is no statistical difference detected, that a statistically significant difference may not exist.

Inclusion of only medication compliant, Chinese patients compromise external validity.

4.11. Chan 2005

Chan T-M et al Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. J Am Soc Nephrol 2005 16: 1076-1084

4.11.1. Design

Randomised, controlled, open-label, long-term extension of the study reported above, with added patients and with median follow-up of 63 months. The aim was to assess the role of MMF as continuous induction-maintenance treatment for diffuse proliferative lupus nephritis. Inclusion and exclusion criteria are summarised in the publication. Random assignment was by drawing envelopes; no other detail supplied.

4.11.2. Endpoints and definitions: study extension

The primary outcome for between group comparisons was the serial measurements of serum creatinine. Secondary outcomes were relapse, infection, creatinine clearance, doubling of baseline creatinine and the composite of end-stage renal failure or death.

End stage renal failure was defined by need to start dialysis or undergo renal transplantation. Renal relapse was histologically confirmed. For patients in complete or partial remission the definition included clinical manifestations indicating activity ±serologic reactivation and increase in prednisolone dose ≥15 mg/day.

4.11.3. Study therapy

Treatment to 6 months

- MMF commenced at 1.0 g twice daily orally
- CTX commenced at 2.5 mg/kg/day orally as described in the Chan 2000 report

Treatment from 6 – 12 months underwent some change over time:

- Group 1MMF 0.5 g twice daily according to original protocol, was changed to 0.75 g twice daily
- Group 2: oral azathioprine 1.5 mg/kg/day; cyclophosphamide ceased.

After 12 months

- Group 1 MMF 0.5 g bd for at least 12 months before tapering (original protocol specified cross to azathioprine)
- Group 2 azathioprine 1 mg/kg/day given for at least 12 months before tapering considered
- Prednisone continued tapering to 5 – 7.5 mg/kg/day

Severe or diffuse proliferative changes were treated with repeat cycle of induction immunosuppression. Corticosteroids were given with doses and routes dependent on severity of disease.

4.11.4. Participant disposition

33 patients were enrolled in the MMF group; 31were enrolled in the CTX group. One patient from each group withdrew within 4 weeks. A total of 3.585 patient months of longitudinal data from the remaining 62 patients were analysed.

The duration of MMF treatment was 12 months for 20 patients, and mean (SD) 28.3 (7.2) months for 12 patients. Similar information for the CTX group was not included.

4.11.5. Baseline characteristic

The study population was Chinese with mean age (SD) in the MMF group 38.1 (10.2) years; in the CTX group 41.8 (8.9) years. Baseline proteinuria was greater in the MMF group than the CTX group: MMF group 6.21 g/24 hours; CTX group 4.44 g/24 hours. Membranous changes were noted in seven patients in the MMF group and five in the CTX group. Mean serum creatinine,

creatinine clearance, serum protein, activity score and chronicity score were similar between groups.

4.11.6. Efficacy results

The statistical approach is summarised in the publication.

Both groups showed no significant change in serum creatinine over time and there was no significant between group difference in serial serum creatinine levels; -0.015 95% CI (-2.83, 0.253).There was no significant difference in creatinine clearance between groups; 11.0 95% CI (-3.4, 22.5).

Proteinuria decreased over time in both groups. The difference between groups was not found to be significant. The level of baseline proteinuria influenced the result.

Four patients in the MMF group and three in the CTX group underwent progressive renal impairment. Relapse after achieving remission was reported for 11 patients in the MMF group and 9 in the CTX group.

4.11.7. Safety results

- The incidence of infection was reported to be 1/234 patient months in the MMF group and 1/102.5 patient months in the CTX group: rate ratio 2.284 95% CI (0.960, 5.432)
- The incidence of hospitalised infections was 1/ 327.6 patient months in the MMF group and 1/177.0 patient months in the CTX group: rate ratio 1.851 95% CI (0.643, 5.327)
- One patient in the MMF group and two in the CTX group had multiple infections
- Four patients in the CTX group reached the composite end point of end-stage renal failure
- Other reported adverse events were in keeping with known safety profiles
- There were two deaths in the CTX group; both were noted in the 12 month study
- Two patients in the CTX group developed end-stage renal failure

4.11.8. Discussion

4.11.8.1. Author

The authors concluded that the efficacy of MMF was equivalent to that of CTX-AZA and that results demonstrated an improved safety profile and tolerability of MMF compared to oral CTX followed by AZA. The possible external validity of the study with respect to race was discussed.

4.11.8.2. Evaluator

It was not possible to determine whether the initial protocol included an extension phase. It is not apparent to what extent statistical analyses were prospectively planned or post-hoc.

Randomisation was barely described, allocation concealment was not mentioned and the results of the previous study may have been known at the time of enrolling additional participants in this non-blinded trial. Thus, this study is considered an observational with hypothesis generating findings. Due to the difficulty of enrolling large numbers of patients with lupus nephritis, the study is considered to have generated useful information. However, an observational study is in general not considered of sufficient quality to be included in a meta-analysis.

4.12. Contreras – MMF treatment of lupus nephritis - long term

Contreras G, Roth D et al. Sequential therapies for proliferative lupus nephritis. N Engl J Med 2004;350:971-80. Supported by Roche

4.12.1. Design

A single-centre, randomised, open-label, controlled trial between August 1996 and May 2003 to assess the long-term efficacy and safety of two sequential regimens – intravenous cyclophosphamide followed by either oral mycophenolate mofetil or azathioprine, compared with the efficacy and safety of long-term therapy with intravenous cyclophosphamide in treatment of proliferative lupus nephritis. Statistical approach is summarised in the publication.

4.12.2. Endpoints and definitions

Primary endpoint: renal survival (not defined), and patient survival. Chronic renal failure was defined as an increase for more than four months in serum creatinine to at least twice the lowest value reached during the induction phase of the study, or the need for long-term maintenance dialysis or transplantation.

Secondary endpoints included hospitalisation, infection, other adverse events and renal relapse defined as a doubling of the urinary protein: creatinine ratio, or by an increase in serum creatinine of ≥50% for more than one month; amenorrhoea for ≥12 months

Remission was defined as:

- A decrease in urinary protein: creatinine ratio to less than 3 in patients with baseline urinary protein: creatinine ratio > 3
- Decrease by 50% in patients with baseline urinary protein: creatinine ratio <3, accompanied by either improvement in baseline serum creatinine level ≥25% or stable serum creatinine level within 25% of baseline level.

4.12.3. Inclusion/exclusion

Patients aged at least 18 years with renal biopsy confirmed proliferative lupus nephritis WHO class III, IV or IVb and creatinine clearance >20 mL/min were included

4.12.4. Study therapy

4.12.4.1. Induction therapy

Corticosteroids dose and route of administration not specified, plus a maximum of seven monthly boluses of IVC 0.5 – 1.0 g/m^2 to induce nadir leukocyte count no less than 2,000 cells/mm^3.

After induction, patients were randomly assigned to treatment regimen, in order of enrolment by means of sealed envelopes, and were stratified into two groups: blacks and others. Specific method of randomisation was not discussed.

4.12.4.2. Maintenance

Prednisone up to 0.5 mg/kg/day or equivalent corticosteroid, plus one of the following, with dose titrated to minimise gastrointestinal side effects and to maintain a leukocyte count of no less than 2000 cells/mm^3.

IVC 0.5 – 1.0 g/m^2 every three months; Mesna to prevent haemorrhagic cystitis and granisetron hydrochloride to prevent nausea and vomiting.

AZA 1 – 3 mg/kg/day

MMF 500 – 3000 mg per day

4.12.5. Patient disposition

Sixty patients were randomised. One patient randomised to azathioprine was subsequently excluded. There were nineteen patients in the AZA group and twenty in each of the MMF and IVC groups.

4.12.6. Baseline characteristic

Roughly half the patients in each group were black and half Hispanic. There were more class III patients included in the AZA group 6/19 than in the IVC group 2/20 and the MMF group 4/20. The only IVb patient included was randomised to the IVC group. Before commencing maintenance therapy, the mean protein: creatinine ratios were: AZA 1.3; IVC 2.3, MMF 1.5. In other respects the difference in groups was not considered clinically significant.

4.12.7. Efficacy results

The median duration of treatment was 25 months in the cyclophosphamide group, 29 months in the mycophenolate mofetil group, and 30 months in the azathioprine group.

Primary endpoint: The event-free survival rate for the composite end point of death or chronic renal failure was higher in the azathioprine and mycophenolate mofetil groups than in the cyclophosphamide group ($p = 0.009$ and $p = 0.05$ respectively).

Deaths: MMF 1 (pneumocystis pneumonia and acute respiratory distress syndrome) IVC 4 (sepsis).

Chronic renal failure: MMF 1; AZA 1; IVC 3.

Secondary endpoint: Relapse during maintenance: MMF 3; AZA 6, IVC 8 patients.

4.12.8. Safety results

The cumulative probability that hospitalisation during maintenance treatment would not be required was lower in the IVC group than in the AZA or MMF groups. Hospital days/ patient-year: MMF 1; AZA 1; IVC 10.

Infection and serious infection rate was higher in the IVC group than the other 2 groups.

- Infection total: MMF 32%; AZA 29%; IVC 77%
- Major infection MMF 2%; AZA 2%; IVC 15%

4.12.9. Discussion

4.12.9.1. Author

The study included predominantly high risk Black and Hispanic patients. The study demonstrated a lower rate of death or chronic renal failure for patients treated with AZA or MMF than for those treated with IVC. The study demonstrated that the MMF and AZA study groups had better safety profiles than the long-term IVC group. The results cannot be generalised to children or to patients with mild forms of lupus nephritis.

4.12.9.2. Evaluator

The results appear to favour azathioprine however the small number of patients included in each arm and the very small number remaining at the end are considered problematic Censoring is not indicated in the diagrams; the falloff in numbers is not generally due of and an event and to a large extent, it was not possible to determine why the numbers at risk declined. There were also some potentially important differences in baseline characteristics.

4.13. Bolin- Gastrointestinal events

Bolin P et al. Improvement in 3-Month Patient-Reported Gastrointestinal Symptoms after Conversion from Mycophenolate Mofetil to Enteric-Coated Mycophenolate Sodium in Renal Transplant Patients. Transplantation 2007;84: 1443–1451. Funded by Novartis

This observational study reported on the result of a questionnaire (GSRS) designed to assess the severity of symptoms associated with common gastrointestinal disorders and previously validated in renal transplant recipients.

The GSRS is a 15-item instrument designed to assess the severity of symptoms associated with common GI disorders, previously been validated in renal transplant recipients. It consists of five subscales (abdominal pain, reflux, diarrhoea, indigestion, and constipation). Subscale scores range from 1 – 7 with higher scores representing higher symptom burden.

The study was a 3-month, longitudinal, multicentre, open-label, prospective trial in adult renal transplant patients receiving MMF in combination with either cyclosporine or tacrolimus, and who were experiencing mild or moderate GI symptoms that were considered by their physician to be related to MMF therapy. The study evaluated results of 728 participants.

A significant improvement in GSRS score was observed from baseline of 2.61, 95% CI (2.54 – 2.68) to month 1 (1.87, 95% CI 1.81–1.93) after conversion to EC-MPS and was sustained to month 3 (1.81, 95% CI 1.74 –1.88; both $p < 0.0001$ versus baseline). The mean change in overall GSRS score from baseline to month 1 was - 0.74 overall (cyclosporine - 0.73 and tacrolimus - 0.74; each $p < 0.0001$ versus baseline), with a slight further improvement (- 0.79) at month 3 (cyclosporine: -0.82 and tacrolimus: - 0.78; all $P = 0.0001$ versus baseline).

Non-GI complications were reported by 326 patients (45%: 90 cyclosporine [40%], 236 tacrolimus [47%]), of which the majority were mild or moderate. In total, 140 patients (19.2%) experienced GI and non-GI adverse events with a suspected relation to EC-MPS (55 patients with non-GI events [7.6%] and 106 patients with GI events [14.6%]). Diarrhoea was the most frequent GI event to be reported with a suspected relation to EC-MPS (59 patients, 8.1%). Leucopoenia, neutropenia, anaemia, and thrombocytopenia with a suspected relation to EC-MPS occurred in 22, 8, 1, and 1 patient, respectively. Infections were reported in 151 patients (21%: 32 cyclosporine [14%], 119 tacrolimus [24%]), including cytomegalovirus infection in two patients receiving cyclosporine and five patients receiving tacrolimus.

4.14. Chan – gastrointestinal events

Chan L et al. Patient-Reported Gastrointestinal Symptom Burden and Health-Related Quality of Life following Conversion from Mycophenolate Mofetil to Enteric-Coated Mycophenolate Sodium Transplantation 2006;81: 1290–1297. Funded by Novartis

This observational study was authored by one of the investigators listed on the study report of Bolin *et al* (above). The study centres differed from those of Bolin *et al* and included nine centres in Australia.

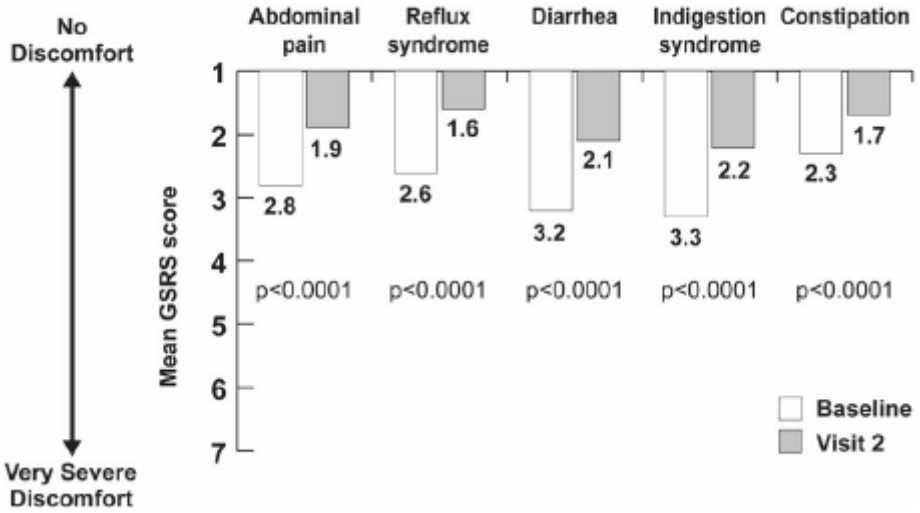
The study, longitudinal, multicentre, open-label, prospective trial in adult renal transplant patients receiving MMF in combination with either cyclosporine or tacrolimus, and who were experiencing mild or moderate GI symptoms that were considered by their physician to be related to MMF therapy. The aim was to determine the effect of transferring treatment from MMF to EC-MPS. As with the study above, he Gastrointestinal Symptom Rating Scale (GSRS) was employed.

Patients in Cohort A were converted to equimolar dose of EC-MPS. Over the course of the study, the mean daily dose of EC-MPS in Cohort A was 1024.8 ± 351.6 mg (71.2% of nominal dose).

Thirty-eight patients (17.7%) in Cohort A experienced GI adverse events, rated mild in 17 patients (7.9%), moderate in 15 patients (7.0%) and severe in six patients (2.8%). Three patients experienced serious GI adverse events (two of diarrhoea and one GI haemorrhage) that were considered to be related to EC-MPS.

The GSRS result is illustrated in Figure 2 below.

Figure 2 Patient-reported outcomes scores on GSRS (n= 176)



Visit 2 occurred at 4 - 6 weeks post baseline

4.14.1. Discussion

4.14.1.1. Evaluator

These two observational studies, open-label and funded by an interested party are not considered high quality evidence. (Jadad score 0). Such a study is potentially subject to bias and confounding. It is noted that 14.6% of patients treated with EC-MPS in the Bolin study reported gastrointestinal events with suspected relationship to EC-MPS, most commonly diarrhoea. In the study by Chan *et al*. summarised above, 17.7 percent of patients treated with EC-MPS reported gastrointestinal events, again with diarrhoea the most common event. While the reported reduction in the GSRS score was rated highly significant in both studies, the mean baseline score was relatively low and the difference was not great. Clinical significance is considered borderline.

5. Post marketing experience

5.1. Post marketing safety update report

The PSUR for the period 01 November 2006 to 31 October 2009 was included in the submission.

During the reporting period, there was no marketing authorisation withdrawal or suspension, or failure to obtain a marketing authorisation renewal for safety reasons.

Changes made to the Company Reference Safety Information have been incorporated into the Australian Product Information.

The PSUR documented an increase in rate of reporting of neoplasm, infection and of fatalities. The majority of fatalities reported were “infections only”.

The following published report summary included in the PSUR, is relevant to the proposed change to the INDICATION The article was not included in the submission dossier.

Lupus nephritis, Joy *et al* (2009) studied 18 patients with biopsy-confirmed lupus nephritis who were receiving maintenance therapy with mycophenolic acid for at least 2 weeks to evaluate the pharmacokinetics of MPA and its metabolite mycophenolic acid glucuronide (MPAG), in this population and to determine the effects of clinical parameters (urinary protein excretion as measured by the urinary protein: creatinine ratio, serum albumin level, and creatinine

clearance) and demographic variables (age, race, sex) on the pharmacokinetics of total and unbound mycophenolic acid and MPAG. Creatinine clearance and serum albumin level were identified as primary contributors to MPA exposure and should be considered when evaluating dosages. The authors highlight the importance of close monitoring clinical changes in order to maintain efficacy and reduce toxicity if MPA is used in patients with lupus nephritis.

5.2. Adverse Drug Reactions Advisory Committee report

Nineteen cases with a variety of reactions were reported. All except one case included at least one other suspect drug. The one case with Myfortic listed as the only suspect drug included adverse reactions: neutropenia, infection and pyrexia in a transplant recipient. No safety signal was detected.

6. Summary and discussion

The evidence submitted in support of registration of Myfortic (enteric coated mycophenolate sodium EC- MPS) was presented a total of 45 publications in four main groups:

- Efficacy and safety of Myfortic in treatment of patients with lupus nephritis
- Equivalency of Myfortic and mycophenolate mofetil
- Efficacy of mycophenolate mofetil in patients with lupus nephritis
- Other references

The sponsor did not indicate which of the study reports were considered pivotal or supportive. This failure considerably slowed and complicated the process of evaluation.

6.1. Myfortic in treatment of patients with lupus nephritis

In direct support of the proposed INDICATION, three articles were submitted, each reporting results of EC-MPS treatment of selected Asian patients, predominantly female, aged 14 to 50 years with WHO Class III, IV and V lupus nephritis. Included were two cohort studies, and one prospective study with historical controls treated with monthly intravenous cyclophosphamide.

A total of 45 patients were treated in these non-randomised, non blinded trials. One patient was maintained in remission following change in treatment from MMF to EC-MPS. Of the remainder, 16/44 achieved complete remission and 17/44 achieved partial remission.

It is conceded that in the process of evaluation of an orphan drug, concessions may have to be made in standards of evidence presented.

6.2. Pharmacokinetic equivalence of Myfortic and MMF

Eight pharmacokinetic studies comparing MMF with EC-MPS were evaluated and five were chosen as illustrative of different points. One single dose study, two multiple dose studies and one pre-dose study were undertaken in stable adult renal transplant patients also treated with cyclosporine. There were no studies including patients with lupus nephritis. One study included patients with nephritis (IgA) also treated with low dose prednisolone.

All studies reported longer time to tmax for the enteric coated formulation as would be expected. All studies reported considerable inter-individual and intra-individual variation. The single dose study of Arns *et al* and the multiple dose study of Budde *et al* reported bioequivalent MPA exposure for MMF 1000 mg and and EC-MPS 720 mg and lower MPA Cmax for both EC-MPS; for the single and the multiple dose studies respectively: 90% CI (57 - 140) and (70 – 113).

The single dose study also reported bioequivalent MPAG Cmax and AUC while the multiple dose study of Budde *et al* reported IMPDH AUC 14% lower for EC-MPS than for MMF.

Budde *et al*. systematic review of results of three multiple dose studies found that MPA C_0 values were consistently higher for EC-MPS than for MMF. This report also documented a number of outliers with relatively high values.

The multiple dose study of Tedesco-Silva reported results for AcMPAG, thought to be an active metabolite. The MPA AUC and Cmax results in this study differed from those of Budde *et al* and are summarised thus:

- The ratio of MPA AUCs and Cmax was outside the bioequivalence range: 125% 90% CI (108 – 129), and 116% 90% CI (94 – 142) respectively.
- The MPA Cmin results were similar between groups.
- Inactive metabolite MPAG AUC and Cmax were estimated to be 22% higher for EC-MPS than for MMF with 90% CI outside the bioequivalence range.
- For potentially active metabolite AcMPAG, both AUC and Cmax were within bioequivalence range.

The results of the study were stated to be influenced by values for 4 of the 40 patients with relatively high C_0 levels.

In addition, the study of Tedesco-Silva *et al* reported that the metabolite AcMPAG had slower clearance than MPA. This is of interest because it has been shown to have some IMPDH-II inhibitory activity, although not as potent as MPA, and because it may undergo hydrolysis, molecular rearrangement and covalent binding to proteins and nucleic acids (8). The formation of such stable adducts has been suggested to play a role in the manifestation of drug toxicities, either through direct disruption of the function of critical proteins or through antigen formation with subsequent hyper- sensitivity and other immune reactions.[10]

A further consideration was identified in the PSUR in which summary of a study of pharmacokinetics of mycophenolic acid were examined in lupus nephritis.[11] Both creatinine clearance and serum albumin level were identified as primary contributors to mycophenolic acid exposure and should be considered when evaluating dosages. The author concluded: Clinicians need to be mindful of clinical changes that occur throughout the course of lupus nephritis in order to maintain efficacy and reduce toxicity from mycophenolic acid therapy.

Finally it is noted that at present the DOSAGE AND ADMINISTRATION section of the Product Information states: "A dose of 1440mg/day of mycophenolate sodium has been shown to be equivalent to 2 g/day of mycophenolate mofetil. Myfortic and CellCept (mycophenolate mofetil) should not be indiscriminately interchanged or substituted because of their different pharmacokinetic profiles." This statement is clearly at odds with the Sponsor's current attempt to show equivalence of pharmacokinetic profiles.

6.3. Equivalence of efficacy and safety of Myfotic and MMF

Five reports were included: two were considered pivotal, one for efficacy and one for safety. Each of these included renal transplant patients co-administered cyclosporine with or without corticosteroid.

[10] Pumford NR, Halmes NC, Hinson JA: Covalent binding of xenobiotics to specific proteins in the liver. *Drug Metab Rev* 29:39, 1997. Reference not included in the submission documents.
[11] Joy MS *et al*. Pharmacokinetics of mycophenolic acid in patients with lupus nephritis. *Pharmacotherapy* 2009; 29 (1): 7 – 16 (not submitted for evaluation; copy obtained by the evaluator)

The study of Salvadori *et al* was rated NHMRC level II and Jadad score 5. The study was designed to evaluate statistical equivalence of treatment with EC-MPS compared to MMF. The primary outcome was efficacy failure based on the incidence of biopsy-proven acute rejection, graft loss, death or loss to follow-up at 6 months. There were 213 patients in the EC-MPS group and 210 in the MMF group. The patient population was predominantly Caucasian.

Within the first 6 months post-transplant, on the basis of ITT analysis, the incidence of efficacy failure, defined as the incidence of BPAR, graft loss, death or loss to follow up, was similar for EC-MPS and MMF (25.8% and 26.2%, respectively). The 95% CI for efficacy failure was [−8.7, +8.0], indicating clinical equivalence between the two study treatments.

The study of Budde *et al* also rated NHMRC level II, Jadad score 5. The aim was to investigate whether renal transplant patients could be safely converted from treatment with MMF to EC-MPS. The primary objective was to assess safety with respect to gastrointestinal adverse events and neutropenia at 3 months. Efficacy was a secondary objective and was assessed as for the study or Salvadori *et al* above. There were 159 patients in the EC-MPS group and 163 patients in the MMF group. The patient population was predominantly Caucasian.

There was no statistically significant difference detected between the two groups with respect to nausea, dyspepsia, upper abdominal pain, gastro oesophageal reflux, gastritis, anorexia or diarrhoea, nor for neutropenia or for efficacy failure. There was no sample size calculation and the study numbers may have been too small to detect statistically significant differences.

6.4. Mycophenolate mofetil in patients with lupus nephritis

Three articles reporting meta-analyses were included, one of which was considered pivotal. Reasons for not regarding the other two as pivotal are specified in the discussions above on the *Walsh et al – Meta-analysis* and *Moore and Derry – Meta-analysis.*

The meta-analysis of Zhu *et al* was considered to have a satisfactory search strategy; the authors stated the absence of competing interests and financial supports. The issue of heterogeneity was addressed.

In this analysis, three induction trials compared MMF with cyclophosphamide: Ginzler and Ong used IVC; Chan *et al* used oral CYC. Two trials, Contreras and Chan, documented results of maintenance therapies including MMF, cyclophosphamide and azathioprine.

For analysis purposes the authors accepted the individual investigators definition of complete remission. For induction therapy the calculated risk ratio for complete remission was 1.81 in favour of MMF, with 95% CI (0.70, 4.68). For partial remission the RR was 1.06 with 95% CI (0.71, 1.59). In both instances the RR included 1. For safety findings, the RR for infection was 0.65 95% CI (0.51, 0.82). For amenorrhoea, leucopoenia and gastrointestinal symptoms the 95% CI included 1.

The authors undertook a sensitivity analysis including only the two studies with IVC treatment arms. The risk ratio for complete remission then becomes significant in favour of MMF: 3.10 95% CI (1.38, 7.01). Other results were said not to have been altered by the removal of results for the study of Chan *et al*. On the basis of this analysis, the authors claimed efficacy superiority for MMF compared to IVC.

For maintenance therapy, the risk ratio of results for MMF compared with azathioprine included 1 for the following: incidence of death, ESRD, relapse and doubling of serum creatinine. For safety results, there was no statistical difference shown for amenorrhoea and herpes zoster. Results for other adverse events were not included in the submission.

Although this was considered the best of the three submitted meta-analyses, there were concerns. The following problems identified by the authors:

- None of the studies were double blind

- There were small numbers of participants in all studies
- Inclusion of patients with WHO class III and V LN with better prognosis
- Maintenance treatment given to patients not in remission
- The distribution of races.

The following additional problems were identified by the evaluator.

- The method of assigning weight to the various studies was not specified
- The conclusion of "superiority" is considered to require a well designed study with superiority as the pre-defined objective
- There were significant problems detected in the individual studies included in this analysis as described under the above sections discussing Ginzler 2005, Ong 2004, Chan 2000, Chan 2005, and Contreras 2005.
- The considerable heterogeneity detected by Zhu relates to primary objectives, statistical approaches and length of time of treatment before analysis.

Eight articles reporting individual studies were evaluated; five were considered pivotal or supportive; four of which were chosen because of their inclusion in a meta-analysis of Zhu *et al*. The fifth study report was relatively recent (2009). All studies were open-label.

Three induction studies compared MMF to IVC: Appel, Ginzler, Ong. One induction study compared MMF to oral cyclophosphamide (Chan 2000). The WHO classes enrolled include: Appel and Ginzer class III, IV and V; Ong enrolled class III and IV and Chan enrolled class IV.

The planned doses of MMF and IVC were similar. IVC was administered in monthly pulses. Oral cyclophosphamide was administered daily. Each study included use of corticosteroid.

No common primary endpoint or statistical approach was employed. The result of the primary analysis of Appel, Ong and Chan demonstrated no significant difference between groups. However, lack of finding of significant difference is not the same as proving non-inferiority or equivalence, and does not exclude the possibility that a statistically significant difference may be present. The Study of Ginzler reported that having met the criteria for non-inferiority, the results were sufficient to allow the conclusion of superiority of MMF compared to IVC.

The main concerns with each of the studies were:

- Ginzler: Assessment of progress at 12 weeks with treatment cross-over for some, but not all of the patients who met the criteria for cross-over. The IVC group's response rate was exceptionally low.
- Ong: Exclusion after randomization of over 27% of patients in the MMF treatment arm, based on reassessment of renal biopsies.
- Chan: randomisation and allocation concealment not discussed. Wide confidence intervals reflect the small study numbers and made the result difficult to interpret.

The two maintenance studies, Chan 2005 and Contreras, compared MMF with AZA; the Contreras study also included an IVC group. Both used survival statistics. There was no statistical difference in primary objective results of serial serum creatinine documented in the study of Chan. Compared to the IVC group the event free survival was statistically higher in the azathioprine ($p = 0.009$) and MMF groups ($p = 0.05$).

The main concerns with each of the studies were:

- Chan: the extension component of the study was considered observational.

- Contreras: the timing of statistical analysis was not stated. The numbers at risk dropped rapidly and to very low numbers, and information on disposition and censoring was lacking.

In conclusion, with regard to direct evidence in support of use of Myfortic in treatment of lupus nephritis, the level of evidence presented is not considered sufficiently free from potential bias to be wholeheartedly endorsed. However, it would seem that EC-MPS has some efficacy in treatment of this condition.

With regard to pharmacokinetic equivalence of Myfortic and MMF, it is accepted that MPA exposure is generally similar for EC-MPS and MMF in the study population including stable renal transplant patients, however, two small studies documented higher exposure following exposure to EC-MPS. There appears to be considerable inter-individual variation in results and the results of studies with small sample size are readily influence by outliers. It appears that there may be a sub-population of patients who metabolise EC-MPS more slowly than the majority of patients. In stable renal transplant patients, it appears that Cmax is lower for EC-MPS and that C_0 is likely to be higher, and possibly considerably higher. The results of these studies done on renal transplant patients are likely to have been influenced by co-medication with cyclosporine which is said to potentiate enterohepatic recirculation of MPA. Cyclosporine is used by some medical practitioners in treatment of lupus nephritis, but not commonly it would appear. The results of the study of Czock *et al* (reference 30), including small numbers of patients with IgA nephritis, indicate that confounding by indication is a possibility.

Therapeutic equivalence of MMF and Myfortic was shown according to the pre-determined criteria in renal transplant patients. However, the result reported was based on the ITT population, whereas the per-protocol population is generally preferred for equivalence studies; the ITT analysis has the capacity to be biased towards equivalence. In addition, as with all studies included in the submission, the endpoint is composite with the potential to add variance which is an undesirable property in equivalence testing.[12]

In the safety study undertaken in renal transplant patients, there was no statistically significant difference detected between the MMF and EC-MPS groups with respect to nausea, dyspepsia, upper abdominal pain, gastro oesophageal reflux, gastritis, anorexia or diarrhoea, nor for neutropenia or for efficacy failure.

The studies submitted in support of equivalence of efficacy and safety of EC-MPS and MMF were undertaken in transplant patients co-medicated with cyclosporine, predominantly including Caucasians and males. While equivalence of efficacy and similarity of safety profiles were reported, there was appears no clear cut reason for preferring one formulation over the other. Furthermore, external validity is considered a problem.

With respect to the efficacy of MMF in treatment of lupus nephritis, lack of consistency of individual study designs, and some serious problems with conduct of studies, made assessment difficult, and contributed to weakness in the meta-analysis. The studies included patients who were designated Black, Hispanic, Asian and White. Efficacy and safety in the Australian Aboriginal population have not been studied.

Efficacy beyond 10 years of treatment has been demonstrated only for cyclophosphamide based regimens. And it remains to be proved whether MMF will ultimately be as effective as cyclophosphamide in pre-empting ESRD. .. The two most common choices for maintenance therapy are MMF and AZA... (however) premature declaration of superiority or rushing into discrediting old treatments that have served patients well need to be avoided in the editorial opinion of Boumpas *et al*.[13]

[12] Points to consider on multiplicity issues in clinical trials CPMP/EWP/908/99

[13] Boumpas DT, Bertsias GK, Balow JE. Editorial A decade of mycophenolate mofetil for lupus nephritis: is the glass half-empty or half-full? *Ann Theum Dis* 2010; 69 (12) 2059 - 2061

With regard to safety, no collation of data was presented in Module 2 and the evaluator did not attempt such an assemblage. In general, the adverse events reported were in keeping with the known safety profile of each product. No new safety issues were indentified, and each study independently was not powered to assess significance of differences or to identify uncommon or rare drug related adverse events.

Two Novartis funded, non-randomised, open label studies [14, 15] were included in the submission, with the aim to show that gastrointestinal symptoms attributed to use of MMF were improved by switching to EC-MPS. Not only was the potential for bias considered significant, the low level of initial symptoms, and the relatively small improvement were considered of borderline clinical significance.

The renal transplant safety study did not show difference between MMF and EC-MPS in gastrointestinal symptoms. Considering that the underlying mechanism of gastrointestinal damage is thought likely to be apoptosis caused by MPA[16], it seems possible that enteric coating may delay the onset, rather than ameliorate the problem.

7. First round benefit-risk assessment

7.1. Benefits

Lupus nephritis is a condition with potential to cause significant morbidity and mortality. There is no argument that proliferative lupus nephritis requires affordable, safe, effective treatment.

Myfortic has been demonstrated to have short term (6 – 12 month) efficacy in treatment of lupus nephritis in observational studies undertaken in small numbers of Asian patients and utilising surrogate endpoints. In support of the findings there is evidence of equivalence of MMF and EC-MPS MPA exposure, safety and efficacy albeit in post-transplant patients. In addition, efficacy of MMF in treatment of lupus nephritis has been documented.

Oral medication is likely to be better tolerated than intravenous medication and orally administered medication does not require skilled staff with sterile conditions and equipment for administration.

7.2. Risks

The evidence submitted for efficacy and safety of EC-MPS in treatment of lupus is considered tortuous and indirect. Much of the data was collected in renal transplant patients rather than lupus nephritis patients, in patients with differing racial characteristic from those common in the Australian setting, in male patients and in compliant patients. This chain of evidence is considered the basis of hypothesis rather than proof of concept. The treatment would potentially be required for protracted periods of time as lupus nephritis is chronic and subject to flares of increased activity, thus solid evidence of efficacy and safety is considered a basic requirement.

The superiority of EC-MPS over MMF with regard to gastrointestinal symptoms is not considered proven, and neither is superiority of MMF over cyclophosphamide and azathioprine

[14]Chan L *et al*. Patient-reported gastrointestinal symptom burden and health related quality of life following conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium. *Transplantation* 2006;81: 1290 - 1297

[15] Bolin *et al*. Improvement in 3-month patient reported gastrointestinal symptoms after conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in renal transplant patients. *Transplantation* 2007; 84: 1443 - 1451

[16] Nguyen T, *et al* Mycophenolic acid (cellcept and myfortic) induced injury of the upper GI tract. *Am J Surg Pathol* 2009; 33(9): 1355 - 63

with regard to overall safety and efficacy in treatment of lupus nephritis. In addition long-term efficacy of MMF or EC-MPS, in preventing end stage renal disease has not been proven beyond doubt.

The known safety profile of EC-MPS includes the following concerns

- Myfortic is contraindicated in pregnancy; use of MMF has been associated with increase rate of congenital malformation and pregnancy loss. The lupus nephritis patient population is predominantly female, of child bearing age.
- EC-MPS is not recommended for use in lactation.
- Increased risk of malignancy including skin cancer. The advice to avoid exposure to sunlight and UV light to limit potential for skin cancer would be problematic for patients living in Australia.
- Susceptibility to infection. There is a disproportionate disease burden in remote Aboriginal communities compared with the general Australian population. Communicable diseases of particular importance to Indigenous people include: tuberculosis; hepatitis (A, B, and C); sexually transmitted infections; HIV/AIDS; Haemophilus influenzae type b (Hib); pneumococcal disease, and meningococcal disease[17] Australian Aboriginals have been reported to have incidence of blood stream infection amongst the highest in the world.[18]
- Reduced effectiveness of vaccination.
- Gastrointestinal toxicity including ulceration, haemorrhage and perforation.
- Blood dyscrasias – weekly, progressing to monthly blood counts are advised for the first year.
- Increased blood creatinine.
- Progressive multifocal leukoencephalopathy.

In considering the risks, it is acknowledged that lupus nephritis affects more non-Aboriginal Australians than Aboriginal Australians. However, the request for registration with a view to inclusion of Myfortic on the PBS, was made on behalf of the Expert Advisory Panel on Aboriginal and Torres Strait Islander Medicines. Thus special consideration is given to the risks in the Aboriginal population.

Aboriginal health workers have reported occurrence of inappropriate use of medication and non-compliance. In addition, Consumer medicine information is often considered difficult to understand, culturally inappropriate and unlikely to be used.[19]. Sharing of medication has been reported to occur.[20] Storage difficulties are also prevalent in rural Aboriginal communities; storage is often inadequate and unsafe.[21] Myfortic needs to be stored below 30 degrees C, protected from light and moisture.

7.3. Balance

In pragmatic terms, it is accepted that the medications used in the treatment of lupus nephritis would share many of the risks outlined above. It is accepted that affordable treatment is a priority. It is also accepted that despite the lack of clinical trial evidence, EC-MPS is being used off-label to treat patients with lupus nephritis. However, the balance at this point in time would seem to be heavily weighted to risk.

[17] <http://archive.healthinfonet.ecu.edu.au/html/html_overviews/overviews_our_communicable.htm>
[18] <http://www.mja.com.au/public/issues/192_10_170510/ein10732_fm.html>
[19] <http://www.rrh.org.au/articles/subviewnew.asp?ArticleID=557>
[20] <http://caepr.anu.edu.au/Publications/briefs/1997IB17.php>
[21] <http://www.australianprescriber.com/magazine/28/5/123/5/>

8. First round recommendation regarding authorisation

Registration of Myfortic for the proposed INDICATION is not recommended.

If this recommendation is rejected following expert consultation and negotiation, the following conditions based on the perceived need to conscientiously manage all components of risk outlined above are recommended.

- Detail of the register to which the Sponsor has committed should be submitted to the TGA for evaluation prior to registration.
- It is recommended that a Risk Management Plan is formulated, with particular considered attention given to prevention of each of the following risk factors detailed above.

In the event of registration, it is recommended that the draft Product Information and Consumer Medicine Information documents should be revised.

The issues relating to the Product Information are:

Clinical trials: the proposed wording is considered to imply that small randomised trials may have been done.

Indication: The studies submitted for evaluation were undertaken in predominantly adult patient populations, with predominantly WHO Class IV nephritis. It is considered that the indication should reflect this.

Dosage and Administration: The support for the indication is based heavily on the assumption that MMF and EC-MPS are equivalent. It is recommended that the existing advice that the two formulations are not interchangeable should be removed.

The issue relating to the Consumer Medicine Information is that it is considered likely to be culturally inappropriate for the remote community Australian Aboriginal and Torres Straight Islanders. It is recommended that this issue is addressed in the Risk Management Plan.

9. Clinical questions

The sponsor was requested to address matters raised in this clinical evaluation report.

10. References – First round evaluation

1. Novartis' Application for Orphan Drug Designation, submitted 1 December 2009
2. Kitiyakara C *et al*. Treatment of lupus nephritis and primary glomerulonephritis with enteric-coated mycophenolate sodium. *Clinical nephrology* 2008;69:90-101
3. Mak S-K *et al*. Efficacy of enteric-coated mycophenolate sodium in patients with active lupus nephritis. *Nephrology* 2008; 13: 331 – 336
4. Traitanon O *et al*. Efficacy of enteric-coated mycophenolate sodium in patients with resistant-type lupus nephritis: a prospective study. *Lupus* 2008; 17: 774 – 751
5. Kreuter A *et al*. Mycophenolate sodium for subacute cutaneous lupus erythematosus resistant to standard therapy. British Journal of Dermatology 2007; 156: 1321 – 1327
6. WHO classification of LN (summarised in Table 1)
7. Explanatory note: references 15-19 were not included in the submission dossier.
8. Shipkova M, Armstrong VW, Weber L, *et al*: Pharmacokinetics and protein adduct formation of the pharmacologically active acyl glucuronide metabolite of mycophenolic acid in pediatric renal transplant recipients. *Ther Drug Monit* 24:390, 2002. Reference not included in the submission
9. Pumford NR, Halmes NC, Hinson JA: Covalent binding of xenobiotics to specific proteins in the liver. *Drug Metab Rev* 29:39, 1997. [Reference was not included in the submission]
10. Jadad AR, *et al*. assessing the quality of reports of randomised clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1 - 12
11. Pumford NR, Halmes NC, Hinson JA: Covalent binding of xenobiotics to specific proteins in the liver. *Drug Metab Rev* 29:39, 1997. Reference not included in the submission.
12. Joy MS *et al*. Pharmacokinetics of mycophenolic acid in patients with lupus nephritis. *Pharmacotherapy* 2009; 29 (1): 7 – 16 [not submitted for evaluation]
13. Points to consider on multiplicity issues in clinical trials CPMP/EWP/908/99
14. Boumpas DT, Bertsias GK, Balow JE. Editorial A decade of mycophenolate mofetil for lupus nephritis: is the glass half-empty or half-full? *Ann Theum Dis* 2010; 69 (12) 2059 - 2061
15. Chan L *et al*. Patient-reported gastrointestinal symptom burden and health related quality of life following conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium. *Transplantation* 2006;81: 1290 - 1297
16. Bolin *et al*. Improvement in 3-month patient reported gastrointestinal symptoms after conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in renal transplant patients. *Transplantation* 2007; 84: 1443 – 1451
17. Nguyen T, *et al* Mycophenolic acid (cellcept and myfortic) induced injury of the upper GI tract. *Am J Surg Pathol* 2009; 33(9): 1355 – 63
18. <http://archive.healthinfonet.ecu.edu.au/html/html_overviews/overviews_our_communicable.htm>
19. <http://www.mja.com.au/public/issues/192_10_170510/ein10732_fm.html>
20. <http://www.rrh.org.au/articles/subviewnew.asp?ArticleID=557>
21. <http://caepr.anu.edu.au/Publications/briefs/1997IB17.php>
22. <http://www.aihw.gov.au/publications/phe/phe-112-10704/phe-112-10704-c09.pdf>

23. Kitiyakara C *et al*. Treatment of lupus nephritis and primary glomerulonephritis with enteric-coated mycophenolate sodium. *Clinical nephrology* 2008;69:90-101

24. Mak S-K *et al*. Efficacy of enteric-coated mycophenolate sodium in patients with active lupus nephritis. *Nephrology* 2008; 13: 331 – 336

25. Traitanon O *et al*. Efficacy of enteric-coated mycophenolate sodium in patients with resistant-type lupus nephritis: a prospective study. *Lupus* 2008; 17: 774 – 751

26. Kreuter A *et al*. Mycophenolate sodium for subacute cutaneous lupus erythematosus resistant to standard therapy. *British Journal of Dermatology* 2007; 156: 1321 – 1327

27. Arms *et al*. Enteric-coated mycophenolate sodium delivers bioequivalent MPA exposure compared with mycophenolate mofetil. *Clin Tranplant* 2005; 19: 199 – 206

28. 28. Budde K *et al*. Pharmacokinetic and pharmacodynamic comparison of enteric-coated mycophenolate sodium and mycophenolate mofetil in maintenance renal transplant patients. *American Journal of Transplantation* 2007; 7: 888 – 898

29. Budde *et al*. Enteric-Coated Mycophenolate Sodium Provides Higher Mycophenolic Acid Predose Levels Compared With Mycophenolate Mofetil: Implications for Therapeutic Drug Monitoring. Short communication. *Ther Drug Monit* 2007; 29 (3): 381 - 384

30. Czock D *et al*. Pharmacolinetics and pharmacodynamics of mycophenolic acid after enteric-coated mycophenolate versus mycophenolate mofetil in patients with progressive IgA nephritis. *J Clin Pharmacol*. 2007; 47: 850 - 859

31. Granger DK Enteric-coated mycophenolate sodium: results of two pivotal global multicentre trials. *Transplantion proceedings* 2001; 33: 3241 – 3244

32. 32. Tedesco-Silva H *et al*. Mycophenolic acid metabolite profile in renal transplant patients receiving enteric-coated mycophenolate sodium or mycophenolate mofetil. *Transplantation Proceedings* 2005; 37: 852 – 855

33. Arms *et al*. Enteric-coated mycophenolate sodium delivers bioequivalent MPA exposure compared with mycophenolate mofetil. *Clin Tranplant* 2005; 19: 199 – 206

34. Johnston A, He X, Holt DW. Bioequivalence of enteric-coated mycophenolate sodium and mycophenolate mofetil? A meta-analysis of three studies in stable renal transplant recipients. *Transplantation* 2006; 82 (11): 1413 – 1418

35. Salvadori M *et al*. Enteric-coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in *de novo* renal transplant patients. *American Journal of Transplantation* 2003; 4: 231–236

36. Budd K *et al*. Enteric-coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: results of a 1-year study. *American Journal of Transplantation* 2003; 4: 237 – 243

37. Granger DK Enteric-coated mycophenolate sodium: results of two pivotal global multicentre trials. *Transplantion proceedings* 2001; 33: 3241 – 3244

38. Granger DK Enteric-coated mycophenolate sodium: results of two pivotal global multicentre trials. *Transplantion proceedings* 2001; 33: 3241 – 3244

39. Ciancio G *et al*. Randomised trial of mycophenolate mofetil versus enteric-coated mycophenolate sodium in primary renal transplant recipients given tacrolimus and daclizumab/thymoglobulin: one year follow-up. *Transplantation* 2008; 86: 67 - 74

40. Kobashigawa J *et al*. Similar efficacy and safety of enteric-coated mycophenolate sodium (EC-MPS, Myfortic) compared with mycophenolate mofetic (MMF) in de novo heart

transplant recipients: results of a 12-month single-blind, randomised, parallel-group multicentre study. *The Journal of Heart and Lung Transplantation* 2006; 25(8): 935 – 941

41. Segovia J *et al*. Impact of dose reductions on efficacy outcome in heart transplant patients receiving enteric-coated mycophenolate sodium or mycophenolate mofetil at 12 months transplantation. *Clin Transplant* 2008: 22: 809–814
42. Ginzler *et al* Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005;353:2219-28
43. Ong LM *et al*. Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. *Nephrology* 2005; 10: 504 – 510
44. Chan TM *et al*. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. *NEJM* 2000; 343 (16) 139 - 145
45. Chan T-M *et al* Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis*. J Am Soc Nephrol* 2005 16: 1076-1084
46. Contreras G *et al*. Sequential therapies for proliferative lupus nephritis. *N Engl J Med* 2004;350:971-80
47. Appel GB *et al*. Mycophenolate Mofetil versus Cyclophosphamide for Induction Treatment of Lupus Nephritis*. J Am Soc Nephrol* 20: 1103–1112, 2009
48. Bao H*et al* Successful treatment of Class V + IV lupus nephritis with multitarget therapy. *J Am Soc Nephrol* 19: 2001–2010, 2008
49. Wang J *et al*. Induction therapies for class IV lupus nephritis with non-inflammatory necrotizing vasculopathy: mycophenolate mofetil or intravenous cyclophosphamide. *Lupus* (2007) 16, 707–712
50. Hu W *et al*. Mycophenolate mofetil vs. Cyclophosphamide therapy for patients with diffuse proliferative lupus nephritis. *Chinese Medical Journal* 2002; 115 (5) 705 – 709 (Not included in the submission – included in the meta-analysis of Walsh *et al*
51. Lin YK, Liu D, Wei G: A comparison of response between mycophenolate mofetil and cyclophosphamide therapy for lupus nephritis. *J Clin Derm* 31: 636–638, 2002
52. Florez-Suarez L, Villa A: Open, randomised trial comaring mycophenolate mofetil (MMF) vs. Intravenous Cyclophosphamide (IC-CYC) as Induction Therapy for Severe Lupus Nephritis (LN) *J Am Soc Nephrol* 15: PO257, 2004
53. Tedesco-Silva H *et al*. Mycophenolic acid metabolite profile in renal transplant patients receiving enteric-coated myophenolate sodium or mycophenolate mofetil. *Transplant Proc*. 2005; 37: 852 - 855

11. Supplementary Clinical Evaluation Report

11.1. Introduction

Novartis Pharmaceuticals Pty Ltd submitted a literature based, orphan, Type C, submission to extend the INDICATION for Myfortic 180 mg and 360 mg enteric coated tablets to include induction and maintenance treatment of lupus nephritis. Following assessment of the original Clinical Evaluation Report (above), and after meeting with the TGA on 2 June 2011, Novartis has submitted supplementary data in support of the application.

The applicant proposes to change the requested additional indication from *"Myfortic is indicated for induction and maintenance treatment of lupus nephritis"* to:

> *Myfortic is indication for the induction and maintenance treatment of adult patients with WHO Class III, IV or V lupus nephritis*

11.2. Scope of the clinical dossier

The supplementary data consisted of the following:

Module 1

- Novartis' response to the Clinical Evaluation Report
- Protocol for the patient registry
- Revised Product Information
- Revised Consumer Information
- Details of an updated literature search
- Australian Risk Management Plan

Module 2

- Clinical Overview of supplementary data
- Clinical Summary of supplementary data
- Module 5
- Clinical Study Report of Novartis sponsored study A2420
- Literature references identified in the updated literature search
- Copies of other references cited in Novartis' response to the Clinical Evaluation Report[22]
- [Information redacted]

Novartis gave assurance that apart from the inclusion of additional Individual Patient Data for Study A2420 in the electronic copy of the submission, the hard copy and the electronic copy of the dossier are identical.

[22] Note that reference numbers have recommenced from 1 in the Supplementary Clinical Evaluation and are listed in Section 14.

11.3. Clinical efficacy – supplementary data

11.3.1. Study A2420

11.3.1.1. Design

Study A2420 was an randomised, multicenter, open-label, 6-month, non-inferiority study of efficacy and safety of enteric coated mycophenolate sodium (EC-MPS) in combination with two corticosteroid regimens for the treatment of lupus nephritis flares. The study was conducted in 16 centres across 9 countries and included 81 patients.[23]

The primary objective of the study was to assess efficacy of the low dose corticosteroid regimen compared to the standard dose in terms of the proportion of patients in complete remission after 24 weeks of treatment.

There were multiple secondary objectives, including assessment of the proportion of patients with partial remission, assessment of overall disease activity and assessments of safety including treatment failure.

Complete remission was defined as proteinuria < 0.5 g/24h, normalised urine sediment, and serum creatinine within 10% of normal value. Partial remission was defined as proteinuria ≤ 50% from baseline and serum creatinine within 10% of baseline value or improved. Study definitions and the assessment schedule were provided.

The enrolled participants were male or non-pregnant female patients aged ≥18 year with proliferative lupus nephritis ISN/RPS class III or IV and with proteinuria defined as > 0.5gram urine protein per gram urine creatinine, serum creatinine > 88.4 µmol/L and > 5 red cells per high power field and presence of cellular casts on urine microscopy.

11.3.1.2. Study therapy

All patients were treated with Myfortic at a daily dose of 2160 mg daily after an initial 2 weeks on 1440 mg per day. All patients received a bolus of 0.5 g IV methylprednisone for 3 consecutive days before oral corticosteroid therapy.

On day 4, patients commended oral prednisone or prednisolone (PRED). Patients were randomly assigned to Group I, standard dose or Group II, half dose.

- Group I: Starting dose PRED 1 mg/kg/day [24]
- Group II: Starting dose PRED 0.5 mg/kg/day

The dose for both groups was reduced progressively over the course of the study by reducing the daily dose according to patient's weight as specified in the protocol to 2.5 mg/day in patients weighing ≤65 kg and 5 mg/day in those weighing >65 kg. Study medication was taken until Week 24. Treatment thereafter was according to local practice.

Concomitant non-lupus diseases were treated with the appropriate medication. The use of hydroxychloroquine, Angiotensin Converting Enzyme inhibitors or Angiotensin Receptor Blockers was allowed only if the patient was already on treatment at the screening visit. Use of the following treatments was not allowed after the start of study drug:

- Any other investigational drugs
- All other immunosuppressive drugs other than those specified by the protocol
- Intravenous Polyvalent Immunoglobulin (IvIg) and plasmapheresis
- Drugs known to interfere with Myfortic

[23] Colombia, Germany, Greece, Taiwan, United Kingdom, Hungary, Spain, France and Italy
[24] Dose according to Ginzler EM, Dooley MA, Aranow C, *et al* (2005). Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med*; 353:2219-28.

11.3.1.3. Statistics

With a sample size of 40 patients per arm, a non-inferiority margin difference of 10% (Ginzler *et al*., 2005) and using a one-sided 97.5% normal confidence interval based approach, a non-inferiority of Group II to Group I had calculated power of 28%.

The primary analysis was based on the intent-to-treat (ITT) population using all observed data values after having compared patients' discontinuation rate in both groups. Supportive analysis was to be done on the Per Protocol (PP) population.

An interim analysis was performed when 50% of randomized patients had completed the first12 weeks of the study and was done both on the pooled data for both Groups and per Group. The interim analysis focused on the safety parameters: the proportion of patients with no therapeutic response after 12 weeks of treatment, incidence of AEs/ SAEs/ infection and serum creatinine.

11.3.1.4. Randomisation

The randomisation list was undertaken by Novartis Drug Supply Management using a validated automatic system generating randomisation numbers in the specified ratio. The investigator entered the randomisation number on the case report form (CRF) and scratched off the cover revealing the treatment arm for that patient.

11.3.1.5. Study populations

The Intention-To-Treat (ITT) population consisted of all patients as randomised who received at least one dose of study drug and have at least one post-baseline assessment of the primary efficacy variable. Patients were analysed according to the treatment they were assigned at randomisation.

The Per Protocol (PP) population consisted of all patients in ITT population who did not experience any protocol deviation.

The Safety Population included all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. Patients were analysed according to treatment received.

11.3.1.6. Missing data

The handling of missing data was largely not prospectively defined.

11.3.1.7. Conduct of the study

There were six protocol amendments which did not generally appear to have affected interpretation of the study. One major change relating to precautions in pregnancy was based on safety data not available at the commencement of the study. According to protocol version 6 issued 14 months after study initiation in accordance with the new labelling order to strengthen the prevention of pregnancy in the following terms:

> "Females capable of becoming pregnant must have had a negative serum β-HCG pregnancy test at BL and were required to practice two approved methods of birth control for the duration of the study and for a period of six weeks following discontinuation of study medication. For the baseline visit, a serum pregnancy test was mandatory. Serum pregnancy test was also performed at week 24 (visit 7). Serum pregnancy tests were evaluated in the local laboratory. Patients who were determined to be post-menopausal and were not of child bearing potential before or during the study were not required to get subsequent pregnancy testing. Women were considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or 6 months of spontaneous amenorrhea with serum follicle stimulating hormone levels > 40 mIU/ml and oestradiol < 20 pg/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) at least

six weeks prior. In the case of oophorectomy alone, only when the reproductive status of the woman had been confirmed by follow up hormone level assessment."

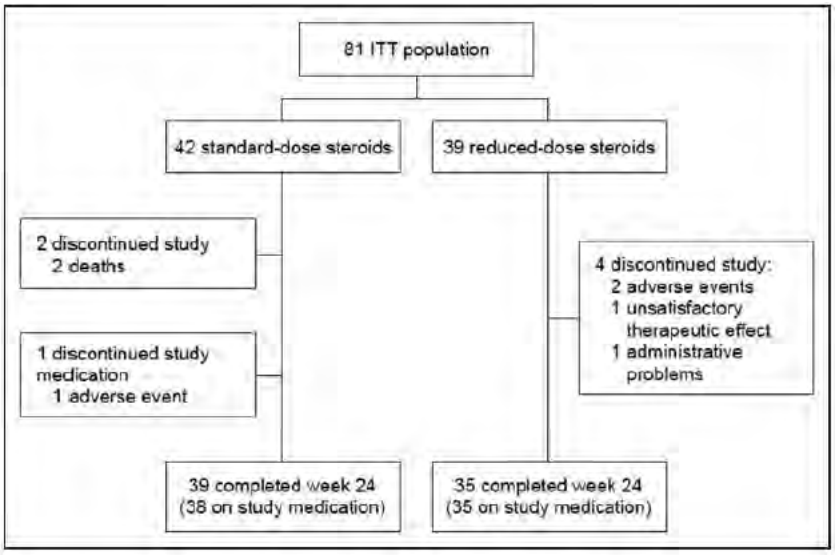
The study protocol and all amendments were reviewed by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for each centre. The study was conducted according to the ethical principles of the Declaration of Helsinki. Informed consent was obtained from each patient in writing before randomization.

11.3.1.8. Results

11.3.1.8.1. Disposition

Of the 90 patients who were screened, 81 patients were randomized to treatment (42 patients in the standard dose group, 39 patients in the low dose group) The proportions completing 24 weeks were 92.9% and 89.7%, respectively. Of the 7 patients who discontinued before week 24, 5 were for safety reasons while one low-dose patient discontinued due to administrative problems and one low-dose patient due to unsatisfactory therapeutic effect (Figure 3).

Figure 3. Study A2420 Patient disposition



Major protocol deviations resulting in exclusion of patients from the PP population occurred in 11 (26%) patients in the standard dose group and 15 (38%) patients in the low dose group. The most common protocol deviations were that the patient did not receive Myfortic on Day 1 or the patient did not receive correct Myfortic dose as per protocol or there was either no renal clinical activity or missing pregnancy test/positive test at week 24.

11.3.1.8.2. Demographics

Demographic characteristics were comparable for the two groups. The mean age of the ITT population was 32.2 years for the standard dose and 34.2 years for the low dose group. Most of the patients were female (standard dose: 88.1%, low dose: 74.4%) and Caucasian (standard dose: 64.3%, low dose: 64.1%) or Asian (standard dose: 16.7%, low dose: 15.4%).

Median time between most recent renal biopsy and Day 1 were comparable for the two treatment groups but median time between diagnosis and screening visit was higher in the standard dose group (39.5 months vs. 21.0 months). Overall, the classification of Lupus Nephritis was comparable between groups. Most patients had a histological diagnosis of Class IV lupus nephritis.

Previous flares were reported by14/42 (33.3%) of the Standard Dose group and 16/39 (41%) of the Low Dose group. Baseline results relevant to renal disease could not be located in the

dossier. Baseline creatinine, creatinine clearance, glomerular filtration rate and urine protein to creatinine ratio are shown in the data though not all patients are included.

11.3.1.9. Efficacy

The median cumulative dose of prednisone equivalent corticosteroids at Week 24 was 116.7 mg/kg/day in the standard dose group and 74.4 mg/kg/day in the low dose group.

Complete remission of a lupus nephritis flare after 24 weeks of treatment was achieved in 19.0% of the patients of the standard dose group and 20.5% of the low dose group. Non-inferiority was not shown in the ITT population and therefore analysis using the PP population was not undertaken (Table 5).

The proportion of patients with partial remission at week 24 was 20/42 (47.6%) in the standard dose group and 14/39 (35.9%) in the low dose group (Table 6).

Table 5. Study A2420 Proportion of patients with complete remission after 24 weeks of Treatment

Complete remission	Standard dose n (%)	Low dose n (%)	one-sided 97.5% CI for the difference in proportions	Test Statistic$	one-sided p-value	Chi-square p-value
ITT population						
yes	8 (19.0)	8 (20.5)	(-15.9%,infinity)	1.29	0.098	0.869
no	34 (81.0)	31 (79.5)				
PP population						
yes	6 (19.4)	4 (16.7)	(-23.1%,infinity)	0.70	0.241	0.798
no	25 (80.6)	20 (83.3)				

Complete remission = urine protein / urine creatinine ratio is <0.5, urine sediment is normalized, and serum creatinine is within 10% of normal value.

$: Non-inferiority test, delta=10%

Table 6. Study A2420 Proportion with partial remission after 12 and 24 weeks of treatment (ITT population)

Visit	Partial remission	Standard dose n (%)	Low dose n (%)	Chi-square p-value
Week 12	yes	16 (38.1)	11 (28.2)	0.345
	no	26 (61.9)	28 (71.8)	
Week 24	yes	20 (47.6)	14 (35.9)	0.285
	no	22 (52.4)	25 (64.1)	

- Partial remission=urine protein / creatinine ratio is reduced by at least 50% from baseline and if serum creatinine is stable (within 10% of baseline value) or improved.

One patient in the standard dose group reported a moderate to severe SLE flare after the 24 weeks of study therapy. Results relating to disease activity were provided according to BILAG score and SLEDAI score.

For patients with paired results at study time points, mean creatinine and mean creatinine clearance were in the normal range and changes throughout the 24 weeks of the study were minor. Mean glomerular filtration rate was at the lower limit of normal at baseline. At Week 24 there was an increase in mean glomerular filtration rate in the standard dose group of 8 mL/min/1.73m^2 and in the low dose group of 15.2 mL/min/1.73 m^2. Mean urine protein to creatinine ratio was 1.9 in both dosage groups at baseline At 6 months, the urine protein to creatinine ratio had decreased by 1.1 in the standard dose group and by 0.8 in the low dose group. In the urine protein to creatinine ration data there were two results with p-values < 0.05; however, multiplicity was not discussed in the protocol and chance could not be precluded.

11.3.1.10. Safety

Exposure to study medication is summarised in Table 7 below. Concomitant medications initiated after the start of the study medication and during the treatment period up to week 24

were most commonly used for acid related disorders (including proton pump inhibitors): 33.3% in the standard dose group and 43.6% in the low dose group. Mineral supplements e.g. calcium (28.6% in standard dose group and 35.9% in low dose group), ophthalmological products (40.5% in standard dose group and 17.9% in low dose group) and analgesics (35.7% in standard dose group and 23.1% in low dose group) were the other common concomitant medications used. Two patients in the standard dose group and one in the low dose group were administered corticosteroids for systemic use.

Table 7. Study A2420 Overall exposure (Safety population)

Variable	Statistic/Category	Standard dose (N=42)	Low dose (N=39)
Total duration of exposure (days)	n (%)	42 (100.0)	39 (100.0)
	Mean	164.5	157.7
	SD	24.87	41.15
	Min	28	2
	Q1	166.0	168.0
	Median	168.0	169.0
	Q3	174.0	174.0
	Max	184	188
Total exposure categories, n (%)	>= 1 day	42 (100.0)	39 (100.0)
	>= 7 days	42 (100.0)	38 (97.4)
	>= 14 days	42 (100.0)	38 (97.4)
	>= 28 days	42 (100.0)	38 (97.4)
	>= 60 days	41 (97.6)	36 (92.3)
	>= 90 days	41 (97.6)	35 (89.7)
	>= 180 days	2 (4.8)	3 (7.7)

- Duration of exposure was calculated as date of last Myfortic dose - date of first Myfortic dose + 1.
- Periods of temporary treatment interruptions are included.

The overall incidence of adverse events (AEs) was 83.3% in the standard dose group vs. 76.9% in the low dose group. The frequency of notable (sic) AEs was higher in the standard steroid group (21.4% vs 12.8%), and GI events (42.9% vs 33.3%), infections (59.5% vs 35.9%), and general disorders (33.3% vs 20.5%) were more frequently reported in the standard steroid group.

The incidence of adverse events reported to 24 weeks is summarised in Table 8 below. Diarrhoea was the most common AE reported in both groups: 23.8% in standard dose and 20.5% in low dose group (Table 9).

Table 8. Study A2420 Incidence of adverse events up until Week 24 (Safety population)

	Standard dose (N=42)		Low dose (N=39)	
	n	(%)	n	(%)
At Least One Adverse Event(1)	35	(83.3)	30	(76.9)
Any Severe(2) Adverse Event(1)	7	(16.7)	3	(7.7)
Any Drug Related(3) Adverse Event(1)	18	(42.9)	16	(41.0)
Any Serious(2) Adverse Event(1)	8	(19.0)	4	(10.3)
Any Infection	25	(59.5)	17	(43.6)
Any Severe(2) Infection	3	(7.1)	1	(2.6)
Any Drug Related(3) Infection	10	(23.8)	6	(15.4)
Any Serious(2) Infection	4	(9.5)	1	(2.6)

- Incidence refers to number of patients who experienced the event.
- (1) Adverse Events also include infections.
- (2) As reported on Adverse Events/Infections CRF page by the investigator.
- (3) Drug-related Adverse Events are those reported as being suspected to be drug related.

Table 9. Study A2420 Adverse events (>10% in any group) up until Week 24 (Safety population)

Preferred term	Standard dose (N=42) n (%)	Low dose (N=39) n (%)
At least one AE/infection	35 (83.3)	30 (76.9)
Diarrhea	10 (23.8)	8 (20.5)
Herpes zoster	7 (16.7)	0 (0.0)
Edema peripheral	5 (11.9)	5 (12.8)
Vomiting	4 (9.5)	4 (10.3)
Arthralgia	4 (9.5)	5 (12.8)
Insomnia	4 (9.5)	4 (10.3)

- AEs/infections are presented in descending frequency in the Standard dose group
- A patient with multiple adverse events/infections within a SOC is counted only once in the total row of this SOC.

During the period to week 24, two patients in the standard dose group died, one from unknown cause; one from multi-organ failure). No deaths were reported in the low dose group.

Serious adverse events were reported by 8/42 (19.0%) patients in the standard dose group and 4/39 (10.3%) patients in the low dose group up to week 24. No SAE was reported for more than one patient in either dose group.

Adverse events leading to discontinuation were reported for 3/42 patients in the standard dose group and 2/39 patients in the low dose group In the standard dose group, in addition to the two patients who died, one patient in the standard dose group was discontinued from the study medication due to gastroenteritis. In the low dose group one patient discontinued study medication due to gastroenteritis and one discontinued due to rash. There were no discontinuations due to laboratory abnormalities.

Treatment failure was defined as lack of therapeutic response (without complete or partial remission) or premature discontinuation of study medication for any reason except complete or partial remission. Treatment failure was reported by 21/42 (50.0%) in the standard dose group and 22/39 (56.4%) in the low dose group.

Clinically notable elevations in creatinine values were reported in a higher number of patients in the low dose group (18.4%) than in the standard dose group (10.0%). Urine protein/creatinine ratio was noted to be ≤0.1 in equal number of patients in both the dose groups. However, a rise of ≥50% above baseline was observed in a higher number of patients in the low dose group (standard dose group: 19.5%, low dose group: 26.5%).

11.3.1.11. Discussion

11.3.1.11.1. Investigator

Non-inferiority in the primary efficacy endpoint was not shown in this study with a low sample size and a low power. However, the results of this exploratory study suggest that a regimen of Myfortic with corticosteroids is a viable therapy for active lupus nephritis. The findings indicate that reduced corticosteroid dosing in the presence of concomitant Myfortic may offer tolerability benefits versus a standard corticosteroid regimen while maintaining efficacy in the management of lupus nephritis flare. These findings merit examination in a larger-scale study.

11.3.1.11.2. Evaluator

The study design assumed efficacy in treatment of LN with Myfortic that has not been systematically studied in trials comparing Myfortic with standard care. The incidence of complete remission in this study in comparison to the study reports included in this submission cannot be easily compared when the definition of remission is composite and literature definitions inconsistent and also with different inclusion/exclusion criteria.

Baseline disease characteristics in terms of creatinine clearance, glomerular filtration rate and urine microscopic changes for all patients could not be located in the dossier for all participants.

While the apparent reduction of adverse events is desirable, and the complete response rate in terms of the primary analysis was numerically similar, the partial response rate was numerically higher in the high dose group, clinically notable elevations in creatinine values were reported in a higher number of patients in the low dose group than in the standard dose group and a rise in urine protein/creatinine ratio of ≥ 50% above baseline was observed in a higher number of patients in the low dose group than the standard dose group.

Summary of this study is proposed for inclusion in the Product Information. This is considered acceptable with qualification. It is recommended that the incidence of partial remission for both groups (currently reported overall), the numbers (%) with treatment failure, with change in protein/urine creatinine ratio increase of ≥50% from baseline and with elevation in creatinine values are included. It is not considered appropriate to state that there was no significant difference in partial remission, serum creatinine etc when the differences were not subjected to hypothesis testing. The findings of this exploratory study are considered hypothesis generating and not definitive.

11.4. Additional literature

The studies listed in Table 10 below were identified by Novartis following a literature search. If a submitted article referenced a separate protocol which was not submitted, the article was assessed purely on the reference supplied in the dossier. Each article has been individually evaluated (Sections 11.4.1, 11.4.2, 11.4.3, 11.4.4).

Table 10. Additional literature

Single study reports	Systematic Review/Meta-analysis
El-Shafey *et al* 2010 (reference 1). LN induction study MMF vs. IVC	Kamanamool *et al*. (reference 2)
Radhakrishnan (reference 3). LN induction MMF vs. IVC	Lee *et al* (reference 4)
Li (reference 5). LN Induction MMF vs. IVC vs. tacrolimus	[Information redacted, reference 6]
Isenberg (reference 7). LN response by race/ethnicity/region	Mak *et al* (reference 8)
Dooley (reference 9). LN maintenance study MMF vs. AZA	Mohan *et al* (reference 10)
Houssiau (reference 11). LN maintenance study MMV vs. AZA	Swan *et al* (reference 12)
Rupprecht (reference 13). PK study	Touma *et al* (reference 14)
Tedesco-Silva (reference 15). PK study	
Zeher (reference 16). LN Study A2420 EC-MPS, evaluated above	

11.4.1. Induction therapy

11.4.1.1. El-Shafey et al 2010 – MMF vs. IVC - Jadad score 2

Methods	Country: Egypt Setting: Unclear Trial design: randomized 1:1, open-label, controlled trial to determine whether MMF is superior to pulse IVC in induction treatment of LN Blinding: No ITT: Yes
Participants	Patients with newly diagnosed active proliferative class III or IV lupus nephritis and aged ≥15 years. Females 95%
Interventions	Six months treatment with • MMF 1.0 g twice daily (N = 24) • IVC 0.5 – 1.0 g/m^2/month (N = 23) Prednisolone 60 mg/day reducing to between 5 – 10 mg/day
Outcomes	Primary outcome: Combined partial and complete remission at 6 months. Complete remission: Normal serum creatinine concentration, reduction in proteinuria to less than 0.5 g/day and urinary RBC of less than 5 per HPF, without red cell cast. Partial remission: Improvement of 50% in all abnormal renal measurements, without deterioration (within 20%) of any measurement. Secondary outcomes: change Systemic Lupus Activity Measure (SLAM) score, sIL-2R concentration, complement concentration, death and commencement of permanent dialysis or renal transplantation.
Notes	The introductory text specifying testing of superiority, however, under the "statistical analysis" heading, non-inferiority was specified. There was no detail regarding equivalence margin, sample size calculation, power, and significance level. In non-inferiority testing the PP population analysis is considered to have equal weight with the ITT analysis and both should be reported but were not. The ITT analysis in non-inferiority testing "is generally not conservative and its role should be considered carefully."[25]
Random sequence generation (selection bias)	Details not included

[25] Points to consider on switching between superiority and non-inferiority CPMP/EWP/482/99 July 2000

Allocation concealment (selection bias)	Details not included
Blinding (performance bias and detection bias) Self-reported outcomes	Details not included
Blinding (performance and detection bias) Objective outcomes	Details not included
Incomplete outcome data (attrition bias)	ITT analysis
Selective reporting (reporting bias)	Unclear
Other bias (include funding)	The conflict of interest statement discussed the open label plan but not conflict of interest with regard to the investigators, nor was there any statement regarding funding.
Ethics and GCP	Ethics committee approval was obtained, and all patients gave written informed consent.
Results	Patients generally well matched for baseline characteristics. Remission occurred in 14 patients (58.33%) in the MMF group and 12 (52.17%) in the IVC group. Odds ratio (OR) 1.1; 95% CI (0.67, 1.88). Complete remission: 6/24 (25%) in the MMF group compared with 5/23 (21.74%) of 23 in the IVC group. OR 1.15, 95% CI (0.41, 3.25). Partial remission: 8 patients (33.33%) in the MMF group and 7 (30.93%) in the IVC group. OR 1.1; 95% CI (0.47, 2.53). Treatment failure: 10 (41.67%)in the MMF group vs. 11 (47.83%) in the IVC group. OR 0.87; 95% CI (0.46, 1.65). Diarrhoea MMF 5 patients, IVC 2 patients; leucopenia MMF 16.67%; IVC 13.04%.
Evaluator conclusion	The study included a small number of patients with short duration of treatment. There was no evidence of significant difference in efficacy in the defined terms which is not to say that significant difference has been ruled out. Statistical approach was neither superiority nor non-inferiority in design begging the question, was the approach decided post-hoc. The inclusion of the word superiority in the title is considered misleading.

11.4.1.2. Li et al 2011 – MMF vs. tacrolimus vs. IVC - Jadad score 1

Methods	Country: China Setting: Not specified Trial design: Randomised controlled trial Blinding: No ITT: Yes
Participants	60 patients aged between 16 – 64 years in three groups of 20 participants 87% female. Classes III, IV, V or combination and chronic index ≤ 3 with urinary protein excretion ≥1.0 g/24 h and/or a recent deterioration in renal function.
Interventions	• MMF: 1.5g – 2g/day • Tacrolimus: 0.08 – 01 mg/kg/day • IVC: 0.5 – 0.75 g/m^2/ month Prednisolone 0.8 – 1 mg/kg/day to max 60 mg reducing to minimum 10 mg/day over 4 months
Outcomes	Assessed at 24 weeks *Primary outcome*: Complete remission or partial remission *Complete remission*: Urinary protein excretion < 0.3 g/24 h, with normal urine sediment, serum albumin concentration of > 35 g/L and stabilization (±15%) or improvement in serum creatinine at 24 weeks. *Partial remission:* Urinary protein excretion between 0.3 and 2.9 g/24h, having decreased by ≥50% from baseline values, with serum albumin concentration ≥30 g/L and stabilization (±30%) in serum creatinine.
Notes	Imbalance of baseline demographics noted with MMF group including patients with lower median age, lower median serum creatinine, higher creatinine clearance and higher serum albumen.
Random sequence generation (selection bias)	No details
Allocation concealment (selection bias)	No details
Blinding (performance bias and detection bias) Self-reported outcomes	No details

Blinding (performance and detection bias Objective outcomes	No details
Incomplete outcome data (attrition bias)	Unlikely
Selective reporting (reporting bias)	Unlikely
Other bias (include funding)	Funded by Shanghai Institutes of Health and Chinese National Natural Science Foundation (81170671). Conflict of interest: none declared.
Ethics and GCP	Patients gave informed consent. The study was approved by the institutional Ethics Committees. Chinese Clinical Trial Registry number ChiCTR-TRC-10000896.
Results	Complete or partial remission: MMF 14/20: tacrolimus 15/20: IVC 12/20 Complete remission: MMF: 9/20: Tacrolimus 9/20: IVC 6/20 Partial remission: MMF 6/20: Tacrolimus 6/20: IVC 6/20
Evaluator conclusion	Small study of short duration in which selection bias, performance and detection bias could not be excluded.

11.4.1.3. Radhakrishnan et al 2010 – MMF vs. IVC - Jadad score 0

Methods	Country: International Setting: Multi-centre Trial design: Retrospective comparative sub-analysis of two pooled studies examining treatment of class V LN Blinding: No ITT: No
Participants	84 patients with Class V LN
Interventions	24 weeks induction MMF (33 patients) IVC (31 patients)
Outcomes	Percentage change in proteinuria and serum creatinine as end points. Complete remission was defined as urine protein less than 300 mg/day at 24 weeks, whereas partial remission was defined as urine protein less than 3.5 g/day at 24 weeks plus a 50% reduction from the baseline values.

Notes	The study is considered observational, data mining.
Conflict of interest	E.M. Ginzler is a consultant to Aspreva and investigator in ALMS in the ALMS trial. Neil Solomons is an employee of Aspreva pharmaceuticals. Gerald B. Appel has received honoraria for lectures and consultant for Genentech, LaJolla Pharmaceuticals and Aspreva Roche. The remaining authors declared no competing interests. This work was supported in part by The Glomerular Center at Columbia University and by 'Zo's Fund for Life.' Funding in full is left unsaid.
Ethics and GCP	Institutional review boards at each centre approved the study. All individuals gave written informed consent before randomisation.
Results	Weighted mean difference in percent change in proteinuria - 3.49 (95% CI -26.88, 19.9) moderate heterogeneity reported I^2 46% Weighted mean difference in percent change in serum creatinine - 2.55 (95% CI -18.49, 13.38) (heterogeneity not specified) Odds ratio for partial remission between MMF and IVC 1.19 (95% CI 0.29, 4.91) Ten of 17 patients treated with MMF and 14 of 23 treated with IVC achieved partial remission One of 17 patients treated with MMF achieved complete remission while none of 23 IVC treated patients did so.
Evaluator conclusion	The study was post-hoc and observational and of short duration, with unblinded original study and hence with inherent possibility of bias which appeared to have occurred in the reporting. Results suggest but not prove that MMF is as effective as IVC in Class V LN for the outcomes specified, the clinical significance of which is debateable. Complete remission in response to either treatment was a rarity.

11.4.1.4. Isenberg et al 2010 – Influence of race - Jadad score 0

This study of the influence of race/ethnicity on response to lupus nephritis treatment was based on the ALMS study reported previously by Appel *et al*. (reference 20) in which a total of 370 patients with active Class III–V LN received MMF (target dose 3.0 g/day) or IVC (0.5-1.0 g/m^2/month), plus tapered prednisone, for 24 weeks. The primary efficacy outcome was the proportion of patients with response to induction therapy at Week 24. Response was defined as a decrease in urine protein/creatinine ratio (P/Cr), measured over 24 hours to < 3 in patients with baseline nephrotic range P/Cr (≥3 at baseline), or by ≥50% in patients with sub-nephrotic baseline P/Cr (<3) and stabilization (±25%) or improvement in serum creatinine levels.

For the primary endpoint, there were pre-specified interactions between treatment and race (p = 0.047) and treatment and region (P = 0.069). The sub-analysis results were: MMF and IVC response rates were similar for Asians (53.2 vs 63.9%; P = 0.24) and Whites (56.0 vs 54.2%; P = 0.83), but differed in the combined 'Other' and Black group (60.4 vs 38.5%; P = 0.03). Fewer patients in the Black (40 vs 53.9%; P = 0.39) and Hispanic (38.8 vs 60.9%; P = 0.011) groups responded to IVC. Latin American patients had lower response to IVC (32 vs. 60.7%; P = 0.003). Baseline disease characteristics were not predictive of response.

Evaluator conclusion: In this observational study the analysis was at least in part post-hoc and multiplicity was not addressed. The results are considered hypothesis generating rather than definitive and the evaluator agrees with the authors' final statement that "it is difficult to draw firm conclusions about the importance of the results". In addition the study was funded by Roche, the statistics were done by and employee of Aspreva Pharmaceuticals (now called Vifor Pharma Ltd.) and a number of the authors disclosed payments by industry. It is of concern that the abstract selectively reported "more Black and Hispanic patients responded to MMF than IVC", a statement which is considered promotional when such a conclusion is considered to require pre-planned specific hypothesis testing.

11.4.2. Maintenance therapy

11.4.2.1. Dooley et al. 2011– MMF vs. AZA - Jadad score 5

Methods	Country: Asia, Latin America, North America, Europe, South Africa and Australia Setting: Multicentre Trial design: 36 month, randomised 1:1, double-blind, double dummy, phase 3 study comparing oral mycophenolate mofetil 2 g per day and oral azathioprine 2 mg/kg per day plus placebo in each group, in patient who met response criteria during a 6-month induction trial with either MMF or cyclophosphamide. Blinding: Double blind, double dummy ITT: Yes
Participants	227 patients with active class III, IV, or V LN, aged between 12 to 75 years, approximately 86% female were randomly assigned to maintenance treatment (116 to mycophenolate mofetil and 111 to azathioprine).
Interventions	• MMF 1g twice daily • Azathioprine 2 mg/kg/day ±prednisolone or equivalent to max 10 gm/day
Outcomes	The primary efficacy end point was the time to treatment failure, measured as the time until the first event and defined as death, end-stage renal disease, sustained doubling of the serum creatinine level, renal flare, or the need for rescue therapy, compared using Kaplan–Meier survival estimates for the time to treatment failure, with censoring of data for patients who withdrew before the end of the study. Between-group differences in survival curves were assessed with the use of a logrank test. The magnitude of the treatment effect was estimated by means of the hazard ratio obtained from an unadjusted Cox model. Hazard ratios were also estimated in subgroups stratified according to induction therapy, race, and geographic region. Proteinuric renal flare was defined as a doubling of the urinary protein/creatinine ratio and proteinuria (≥1 g of protein per 24 hours in patients with urinary protein clearance of ≤0.5 g per 24 hours at the end of induction, and ≥2 g per 24 hours in patients with urinary protein clearance of > 0.5 g per 24 hours at the end of

	induction). Nephritic renal flare was defined as an increase of 25% or more in the lowest serum creatinine level during the period from screening to the end of induction, plus one or more of the following findings: simultaneous doubling of urinary protein clearance, reaching a minimum of 2 g per 24 hours (or the urinary protein/creatinine ratio equivalent); new or increased hematuria (>5 red cells per high-power field or .2+ on a dipstick test for blood); or the appearance of cellular casts.
Notes	The protocol was made available at NEJM.org but was not submitted with this application. A supplementary appendix was also referenced in the submitted article but could not be found in the submission dossier.
Random sequence generation (selection bias)	No evidence of bias
Allocation concealment (selection bias)	Not specified in the submitted article.
Blinding (performance bias and detection bias) Self-reported outcomes	Blinding was adequate
Blinding (performance and detection bias Objective outcomes)	Not specified in the submitted article
Incomplete outcome data (attrition bias)	Unlikely
Selective reporting (reporting bias)	Generally no evidence of significant bias though with some exceptions: e.g. with respect to the sub-analysis of the primary outcome the following was stated: “The superiority of mycophenolate mofetil was consistent, regardless of induction therapy, race, and geographic region”. However, in these analysis, the HR included 1 with wide confidence intervals, most likely because of limited numbers. In such circumstances it is not possible to claim better effect for one drug or the other. Another example is inclusion of p-values for safety results which suggest significance but without apparent consideration of multiplicity.

Other bias (include funding)	The study was funded by Vifor Pharma (formerly Aspreva Pharmaceuticals) as part of the Roche–Aspreva rare diseases collaboration. All the investigators have confidentiality agreements with Vifor Pharma. Seven of the academic authors and two authors who are employees of the sponsor conceived of and designed the study, seven of the academic authors collected the data, and all the authors analysed and interpreted the data. The manuscript was drafted initially by medical writers from Caudex Medical (Oxford, United Kingdom), with funding from Vifor Pharma and in line with guidance from all the authors. It was then amended substantially, critically reviewed, and edited by all the authors, who approved the final version, made the decision to submit the manuscript for publication, and vouch for the completeness and accuracy of the reported data.
Ethics and Good Clinical Practice	Institutional review boards at the participating centres approved the protocol, and all patients or their representatives provided written informed consent. The study was conducted in accordance with the protocol and all amendments.
Results	The hazard ratio for treatment failure, 0.44; 95% CI(0.25, 0.77); P = 0.003 favouring MMF. Overall observed rates of treatment failure were 16.4% (19 of 116 patients) in the MMF group and 32.4% (36 of 111) in the AZA group. The finding was consistent for sub analysis of results based on induction treatment with IVC, but the HR for MMF induction included one, as did sub analyses based on race, and geographic region. Infections were the most common adverse events: 79.1% (91/115) for MMF and 78.4% (87/111) for AZA . Serious infections: 9.6% (11/115 patients) for MMF, 11.7% (13/111) for AZA. Events leading to withdrawal: 25.2% (29/115) for MMF vs. 39.6% (44/111) with AZA. At least one serious adverse event: 23.5% (27/115) for MMF vs. 33.3% (37/111) for AZA. During the study, one death occurred in the AZA group (traffic accident). One case of cancer (uterine carcinoma in situ) was diagnosed in the AZA group.
Evaluator conclusion	Regarding the primary outcome, time to treatment failure, the result for MMF was demonstrated to be significantly better than for AZA. This study design and report were considered of high quality. Based solely on the submitted article it was not possible to exclude bias related to allocation concealment or bias relating to blinding of objective and subjective outcomes. There might have been more detail publically available but not submitted. The enrolment only of patients who had responded to induction therapy potentially limits external validity. From reports of other studies of maintenance therapy submitted by the applicant, prior response appears not a requirement for transition from induction to maintenance treatment.

11.4.2.2. Houssiau et al. 2010 –MMF vs. AZA - Jadad score 2[26]

Methods	Country: Europe Setting: Multicentre Trial design: randomised, controlled trial testing superiority of mycophenolate mofetil (MMF) vs. azathioprine as maintenance treatment. Blinding: No ITT: Yes
Participants	105 patients aged ≥14 years WHO class III, IV, Vc or Vd LN. 92% female in both groups. Patients in the MMF group had longer history of LN than the AZA group 18 vs. 13 years respectively, had greater mean 24 hour proteinuria, 3.63 vs. 2.29 g, lower mean serum albumin 2.97 vs. 3.01 g/dL and lower serum C3 49 vs 55 g/dL.
Interventions	• MMF 2 g/day (N = 53) • AZA 2mg/kg/day (N = 52) Prednisolone tapered to 7.5 mg/day at week 24 and to 5 mg/day at week 52. From week 76 onwards, it was strongly advised to taper the steroids further and to stop if possible.
Outcomes	Primary: Time to renal flare, analysed by Kaplan Meier survival curves. Follow-up 48 weeks Renal flare was defined as: • Recurrence of nephrotic syndrome • ≥33% increase in serum creatinine within a 1-month period • Threefold increase in 24 hour proteinuria within a 3-month period with microscopic haematuria and ≥33% reduction of serum C3 level within a 3-month period applicable to those patients with low-grade baseline 24 h proteinuria (≥0.5 g and < 1 g)
Notes	With regard to the following assessments of study report quality, the judgement was made on the text submitted for evaluation. A detailed treatment protocol was provided in the supplementary material but that was not submitted for evaluation. Of note, renal remission was not a prerequisite to enrolment.
Random sequence generation (selection bias)	Central, using minimisation; undertaken at baseline however detail of method unclear in the submitted report.

[26] Based on the submitted article. It was stated that the protocol was also available.

Note	Regarding minimisation, a form of randomisation not commonly reported, the following is taken from CONSORT:[27] "Minimisation ensures balance between intervention groups for several selected patient factors (such as age). The first patient is truly randomly allocated; for each subsequent participant, the treatment allocation that minimises the imbalance on the selected factors between groups at that time is identified. That allocation may then be used, or a choice may be made at random with a heavy weighting in favour of the intervention that would minimise imbalance (for example, with a probability of 0.8). The use of a random component is generally preferable. Minimisation has the advantage of making small groups closely similar in terms of participant characteristics at all stages of the trial. Minimisation offers the only acceptable alternative to randomisation, and some have argued that it is superior. On the other hand, minimisation lacks the theoretical basis for eliminating bias on all known and unknown factors. Nevertheless, in general, trials that use minimisation are considered methodologically equivalent to randomised trials, even when a random element is not incorporated."
Allocation concealment (selection bias)	Unclear in the submitted report
Blinding (performance bias and detection bias) Self-reported outcomes	Unclear
Blinding (performance and detection bias Objective outcomes	Unclear
Incomplete outcome data (attrition bias)	Attrition bias not detected
Selective reporting (reporting bias)	Not detected
Other bias (include funding)	Investigator-initiated study, no external funding
Ethics and GCP	The study was registered at http://ClinicalTrials.gov (NCT00204022) and approved by the ethics committees of all participating hospitals. Written informed consent was obtained and the trial was conducted according to the Good Clinical Practice guidelines of the European Medicines Agency.

[27]The CONSORT Statement 2010 is available at: <http://www.consort-statement.org/consort-statement/further-explanations/box2_randomisation_minimisation/>

Results	Kaplan-Meier probability of renal flare: Hazard ratio 0.75 (0.33, 1.71) p = 0.486 One patients from each group developed end stage renal failure. Two patients died, both in the MMF group, one of legionella pheumophilia sepsis after renal flare and one with severe systemic flare. There were no statistically significant differences in the comprehensive list of safety outcomes examined.
Evaluator conclusion	The Jadad of 2 based only on the submitted article without consideration of the supplementary material, not submitted, which possibly may have increased this number. Superiority was not shown. There was no statistically significant difference in outcomes for MMF and AZA. This study differs from that of Dooley *et al*. in lacking the requirement for prior remission in response to induction therapy. Outcomes of studies continue to differ which complicates comparison between studies. Interpretation of composite outcomes is challenging and the composite outcome definitions for this study were complicated and differed for differing baseline disease. The authors comment: Serum measures of the active metabolites of AZA ... or of MMF ... were not routinely performed, leaving open the possibility that patients who failed on one or the other drug were actually under dosed or non-adherent to the medication. This hypothesis might not be too farfetched based on the recent finding that patients who have undergone kidney transplant had a lower rejection rate if MMF doses were titrated according to serum MPA titres instead of fixed. (Le Meur Y, Büchler M, Thierry A, *et al*. Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. *Am J Transplant* 2007; 7: 2496 – 503).

11.4.3. Pharmacokinetic studies

11.4.3.1. Rupprecht et al. 2009– PK interaction study

Methods	Country: Germany Setting: Not specified Trial design: Single dose open, block-wise randomised, cross-over pharmacokinetic study , comparing the influence of pantoprazole 40 mg twice daily on the bioavailability of a single dose of mycophenolate mofetil 1000 mg or enteric-coated mycophenolate sodium 720 mg Blinding: No
Participants	Healthy volunteers: 6 men, 6 women
Interventions	Part A: MMF 100 mg with and without pantoprazole 40 mg Part B: EC-MPS 720 mg with and without pantoprazole 40 mg

Outcomes	Plasma concentrations of MPA and MPA-G were determined by an established high-performance liquid chromatography (HPLC)
Notes	Biases unlikely
Financial disclosure	This work was supported in part by a grant from Novartis Pharma, Nuremberg, Germany. L Faerber and W Fischer are employees of Novartis Pharma, Nuremberg and Basel, respectively. All other authors have no financial interest to disclose.
Ethics and GCP	The study protocol (EudraCT-No 2008-001970-34) was approved by the ethics committee at the University Hospital Regensburg. Written informed consent was obtained from all volunteers.
Results	The point estimate and 90% CIs were not included in the text. The result was illustrated in a figure showing the ratio (point estimate and 90% confidence interval) of Cmax and AUC following administration of MMF 1000 mg or EC-MPS with and without co administered pantoprazole.
Evaluator conclusion	AUC_{∞} and AUC_{t} for both products and Cmax for EC-MPS appear to be within bioequivalence limits. $AUC_{12\,h}$ is below bioequivalence limits for MMF as is Cmax. This represents an advantage for EC-MPS for patients requiring concomitant treatment with pantoprazole. From the data submitted with Study A2420, it seems that use of proton pump inhibitor use is relatively common. Acid related treatments were used by one third of patients in that study; perhaps due to the gastrointestinal effects of steroids and EC-MPS. Although variability in results was mentioned, there were no objective results included.

11.4.3.2. Tedesco-Silva et al. 2010 PK variability study

Methods	Country: Brazil/US Setting: Single centre Brazil Trial design: Randomized, open-label, two-period, two treatment, multiple-dose, crossover study comparing the inter- and intra-subject variability of MPA pre-dose levels from EC-MPS and MMF, each with cyclosporine. Blinding: No
Participants	24 clinically stable, maintenance renal transplant patients; between 18 and 65 years of age, two thirds male

Interventions	Treatment sequences (A-B or B-A). Treatment A: EC-MPS 720 mg 12 hour for 21 days. Treatment B MMF 1000 mg 12 hourly for 21 days. Drugs were administered one hour before meals. Cyclosporine and prednisone doses were kept constant over the course of the study and were taken concomitantly with the study medication, whereas other co medications were ingested four hours apart. Drug administration prior to PK testing drugs was after a 12 hour fast.
Outcomes	MPA plasma levels were measured over the final seven consecutive days at 1, 0, 1, 2, and 3 h after the morning MPA dose using validated high performance liquid chromatography method.
Random sequence generation (selection bias)	Unclear
Allocation concealment (selection bias)	Unclear
Blinding (performance bias and detection bias) Self-reported outcomes	Unclear
Blinding (performance and detection bias) Objective outcomes	Unlikely
Incomplete outcome data (attrition bias)	Unlikely
Selective reporting (reporting bias)	No for PK. Possibly for AEs
Other bias (include funding)	Novartis study
Ethics and GCP	The trial was performed in accordance with the amended Declaration of Helsinki.

Results	Inter-individual coefficients of variation (% CV) for MPA troughs were 47.5% (95% CI, 34.1, 80.3) and 54.4% (40.0, 86.8) for EC-MPS and MMF, respectively. Intra-individual % CVs were 62.7% (55.1, 72.9) and 42.8% (37.9, 49.2). High MPA C0 h levels >10 µg/mL were observed for EC-MPS (1.8%) and MMF (0.6%). The only drug-related AE was diarrhoea reported by three patients – relatedness to formulation was not specified.
Evaluator conclusion	Based on p-value < 0.0001, intra-subject variability for C0, Cmax and AUC_{0-3h} was significantly greater for EC-MPH than for MMF. Inter-individual variability was numerically higher for the EC-MPS but not shown to be significantly different, though not possible to rule out a significant difference if larger numbers of patients had been studied. With regard to external validity, patients were predominantly male, the indication and co-medications differ from those for the proposed indication and variability is likely to be greater in real world use in which timing of drug administration in relation to food may be more variable. The variability is a concern and, while not discussed, the formulation itself may play a significant part.

11.4.4. Systematic reviews and meta-analyses

11.4.4.1. Z Touma et al. 2011

Mycophenolate Mofetil for Induction Treatment of Lupus Nephritis: A Systematic Review and Metaanalysis. J Rheumatol 2011;38;69-78. (reference 14)

Articles Included (reference No.)	• Ginzler 2005 (17) • Chan 2005 (18) • Ong 2005 (19) • Appel 2009 (20)
Results: Induction	MMF vs. IVC: RR (95% CI) • Partial remission: 0.94 (0.80, 1.12) • Complete remission: 0.67 (0.35, 1.28) • Overall remission: 0.89 (0.71, 1.10)
Results: Maintenance	NA

Results: Safety	RR (95% CI): • Leucopenia 1.29 (0.35, 4.70) NS • Infections 1.56 (0.66, 3.69) NS • Gastrointestinal (0.74 (0.54, 1.02) NS • Herpes zoster 0.88 (0.43, 1.80) NS • Amenorrhoea 6.64 (2.00, 22.07) • Alopecia 5.77 (1.56, 21.38) • ESRD RR 1.29, 95% CI 0.22 to 7.63 • Death 1.15 (0.47, 2.82) 1.07, 95% CI 0.14, 8.03
Evaluator comments	• Ginzler Jadad 3 • Chan 2005 Jadad 1 • Ong Jadad 3 • Appel Jadad 3 Risk ratio for complete and partial remission includes one. Risk ratios for leucopenia, infections, gastrointestinal AEs, herpes zoster and death included one. The incidence of amenorrhoea and alopecia was higher in the IVC groups. The authors state that estimates of alopecia and amenorrhea appear unstable given the width of the CI and this should be interpreted with caution. Conclusion: Risk ratios including one indicate that the results for each treatment regimen appear similar but it is not possible to exclude the possibility that one of the treatments may be better or worse than the other. If results included in a meta-analysis are to be relied upon, unbiased and rigorous collection of data is required and, particularly in unblinded studies, this can be a concern. The method and rigor of collection of safety data could not be located in the Ginzler article nor the Chan article; the other 2 articles submitted in the original application were not revisited for the purpose of this commentary.

11.4.4.2. N Kamanamool et al. 2010

Efficacy and Adverse Events of Mycophenolate Mofetil Versus Cyclophosphamide for Induction Therapy of Lupus Nephritis. Systematic Review and Meta-Analysis: Medicine Volume 89, Number 4, July 2010. (reference 2).

Articles Included (reference No.)	• Appel 2009 (20) • Ginzler 2005 (17) • Ong 2005 (19) • Wang 2007 (21) • Chan 2005 (18)
Results: Induction	MMF vs. cyclophosphamide RR (95% CI) • Complete remission: 1.6 (0.87, 2.93) • Complete/partial remission: 1.2 (0.97, 1.48)
Results: Maintenance	NA
Results: Safety	RR (95% CI) • Leucopoenia 0.65 (0.44, 0.96) • Infection 0.77 (0.39, 1.49) • GI symptoms 1.09 (0.74, 1.60)
Evaluator comments	• Appel Jadad 3 • Ginzler Jadad 3 • Ong Jadad 3 • Wang Jadad 2 • Chan 2005 Jadad 1 The RR for complete remission, and overall remission, infection and GI symptoms include one. While the RR for leucopenia which excludes one suggest that this AE is less likely to occur with MMF than with cyclophosphamide. It is noted that in table 3 of the article: *Risk of bias of included trials*: all trials are said to have been blinded which is just not true for any of the trials. It is noted that the authors of this meta-analysis defined partial remission for the Appel study while the report on the Appel study did not include such a definition and the authors of the meta-analysis stated that there was no contact with original authors. Such problems in reporting are considered to compromise confidence in the conclusions made by the authors.

11.4.4.3. Lee YH et al. 2010

Induction and maintenance therapy for lupus nephritis: a systematic review and meta-analysis Lupus 2010 19: 703 – 710 (reference 4).

Articles Included (reference No.)	Induction: • Appel (20) • Ginzler (17) • Ong (19) • Chan (18) • Hu (22) • Wang (21) Maintenance • Sahin (23) • Contreras (24)
Results: Induction	MMF vs. cyclophosphamide RR (95% CI) • Complete remission: 1.613 (0.908, 2.863) • Partial remission: 1.03 (0.678, 1.5670)
Results: Maintenance	MMF vs. AZA RR (95% CI) • Response 1.623 (0.369 – 7.146) • Development of ESRD 1.3620 (0.236, 7.828)
Results: Safety	MMF vs cyclophosphamide RR included 1 for amenorrhoea, leukopenia, infection, herpes zoster, ESRD, Death

Evaluator comments	Induction • Appel Jadad 3 • Ginzler Jadad 3 • Ong: Jadad 3 • Chan: Jadad 1 • Hu: Jadad 1* (as rated by Lee *et al.*) • Wang Jadad 2 *Re Hu *et al*, considered to rate a Jadad score of 0; the study was not randomised and met no other criteria. Maintenance • Sahin*: Jadad 1 as rated by the authors • Contreras: Jadad 2 • Houssiau: Jadad 2 • Sabry: Jadad 2 *The study of Sahin *et al* was retrospective, observational thus Jadad score 0 is considered appropriate. Studies designed such a way that bias cannot be ruled out are not considered ideal for inclusion in a meta-analysis.

11.4.4.4. [Information redacted]

11.4.4.5. A Mak et al. 2009

Mycophenolate mofetil is as efficacious as, but safer than, cyclophosphamide in the treatment of proliferative lupus nephritis: a meta-analysis and meta-regression Rheumatology 2009;48:944–952. (reference 8).

Articles Included (reference No.)	• Chan 2000 (26) • Ong 2005 (19) • Ginzler 2005 (17) • Chan 2005 (18) • Wang 2007 (21) • Flores-Suarez 2004 (30; abstract) Funded by Roche • Mulic-Bacic 2008 (27; abstract) Funding and conflict of interest not disclosed • Isenberg 2008 (31) (abstract)
Results: Induction	Complete and partial remission: RR(95% CI) 1.052 (0.950, 1.166)
Results: Maintenance	NA

Results: Safety	RR (95% CI): • Death 0.709 (0.373, 1.347) • ESRD 0.453 (0.183, 1.121) • Amenorrhoea 0.212 (0.094, 0.479) • Leucopenia 0.473 (0.269, 0.832) • Herpes (sic) 0.7 (0.391, 1.251) • Diarrhoea 2.078 (0.982, 4.397) • Pneumonia 0.565 (0.235, 1.360)
Evaluator comments	• Chan 2000 Jadad 1 • Chan 2005 Jadad 1 • Ong 2005 Jadad 3 • Wang 2007 Jadad 2 • Flores-Suarez 2004 Jadad 1 • Mulic-Bacic 2008 Jadad 1 • Isenberg 2008 Jadad 1 (NB, this abstract reported the ALMS results which would be reported in full by Appel et al.) It was stated that "The authors of correspondence were contacted for obtaining information essential for this meta-analysis which was lacking in the published articles." It is generally usual to state which authors were contacted. Implicit in the statement is that all authors were contacted but is this so? C.S.L. was a member of the Aspreva Asia Pacific Advisory Board between 2004 and 2006 and has received an unrestricted grant from Aspreva for research. In the meta-analysis for complete and partial remission, the Chan studies appear twice and are give relative weights of 18.94 and 30.15, the highest and third highest rating; however there was only one study – the 2005 report is of an extension of the 2000 study.

11.4.4.6. Mohan S, Radhakrishnan J 2011

Geographical variation in the response of lupus nephritis to mycophenolate mofetil induction therapy. Clinical Nephrology, Vol. 75 – No. 3/2011 (233-241). (reference 3).

Articles Included (reference No.)	• Hu 2008 (22) • Duncan 2003 (32) • Chan 2005 (18) • Ginzler 2005 (17) • Ong 2005 (19) • Flores-Suarez 2006 (33) • Choi 2007 (34) • Wang 2007 (21) • Tang 2008 (35) • Traitanon 2008 (38) • Appel 2009 (20)
Results: Induction	Complete remission overall including studies of Chan, Ginzler Ong, Choi, Appel, Wang: 1.41 (0.87, 2.30) Sub analyses Complete remission Asian (Chan, Ong, Choi, Appel, Wang): 1.06 (0.79, 1.42) Complete remission Other (Flores-Suarez, Ginzler, Appel): 1.85 (1.04, 3.29)
Results: Maintenance	NA
Results Safety	NA

Evaluator comments	• Hu Jadad 0 • Duncan Jadad 0 • Ginzler Jadad 3 • Ong Jadad 3 • Flores-Suarez Jadad 0 • Choi Jadad 0 • Tang Retrospective controlled trial Jadad 0 • Wang Jadad 2 • Traitanon EC-MPS study with historical controls Jadad 0 • Appel Jadad 3 The analysis of efficacy was done on reports of randomised controlled trials. The non-randomised studies were included in the safety analysis. However, in all studies, especially those with retrospective component, it is impossible to determine the rigor with which safety was reported and therefore the results are not included in this summary. The article by Duncan appears to apply to nephrotic syndrome. The Mohan article references Flores-Suarez 2006 which documents a case series of 7 patients, two of whom did not have renal biopsies. However the complete remission result is stated to include results for Flores-Suarez 2004, discussed in the original CER. Flores-Suarez 2004 did not appear in the list of references at the end of the Mohan article. The analysis by race is considered observational and the basis of hypothesis. Conflict of interest statement was not included.

11.4.4.7. Swan et al. 2011

Systematic Review and Meta-Analysis of Immunosuppressant Therapy Clinical Trials in Membranous Lupus Nephritis. Journal of Investigative Medicine & Volume 59, Number 2, February 2011. (reference 12).

Articles Included	Twenty-four studies with 34 groups of patient (sparse) data. Owing to the variable quality of articles regarding MLN, no assessment of validity was made for qualifying studies. Compared were at least one nonsteroid immunosuppressant therapy(NSIT) including AZA, MMF, EC-MPS chlorambucil, cyclophosphamide, cyclosporine A and tacrolimus vs. Steroid only immunosuppressant therapy (SOIT).

Results: Induction	Response rate : NSIT 81%; SOIT 60% significant heterogeneity (P < 0.0001 for both results) Complete remission: NSIT 42%; SOIT 39% Sub-analyses: Response: AZA 88%, Cyclophosphamide 75%, MMF 82%, Cyclosporine A 84%
Results: Maintenance	NA
Results: Safety	NA
Evaluator comments	Included studies ranged from retrospective chart reviews to a randomized controlled trial evaluating pharmacological therapy in patients with class V MLN. The patients used for this analysis were generally subpopulations of the original article. The authors noted publication bias based on the appearance of the funnel plots and statistically significant Egger weighted regression p-values. The main limitation of this analysis was the design variability and heterogeneity of the trials included. Data available for this paper were not sufficient for analysis of relapse, flare, or adverse events.

11.5. Novartis' response to the Clinical Evaluation Report

The Novartis response to the original CER is summarised below under the headings included in the response.

11.5.1. Myfortic

1 The findings from the three studies directly investigating the efficacy of Myfortic in patients with lupus nephritis were largely dismissed by the evaluator. The findings from these studies in Asian patients were considered by the applicant to be relevant to a significant proportion of the Australian population (approximately 9% of Australians have Asian ancestry). In these studies

- There were no reports of patients reaching end-stage renal disease when treated with Myfortic.
- In the two retrospective studies (references 36 and 37), a complete or partial response was achieved in 86.2% (25/28) of patients.
- In the study that compared Myfortic treatment to intravenous cyclophosphamide (reference 38) the combined response rates were 56.3% (9/16 patients) for Myfortic versus 33.3% (5/15 patients) for cyclophosphamide. The lower response rate for Myfortic in the latter study may have been because the patients included in this study were selected on the basis that they were non-responsive to cyclophosphamide induction treatment.

2. Nephrologists, who treat patients undergoing renal transplant and patients with lupus nephritis, are already familiar with Myfortic.

3. Substantial off label use of Myfortic in lupus nephritis in Australia has not identified any change in the overall risk-benefit profile. The applicant estimates that approximately 45% and 53% of lupus nephritis patients in Australia were prescribed either Myfortic or

CellCept (mycophenolate mofetil, MMF) for induction or maintenance therapy respectively (Source: 2011 IMS survey commissioned by Novartis).

4. Greater weight should be placed on the benefits afforded by Myfortic oral therapy particularly for remote communities where administration of intravenous medication can be challenging.

5. The evaluator placed disproportionate emphasis on the known risks associated with Myfortic and provides a simplified notion of the inherent risks in Aboriginal patients and failed to acknowledge the risks associated with cyclophosphamide treatment.

6. Pregnancy can be prevented with adequate education and contraception which is provided as part of clinical practice by nephrologists prescribing Myfortic. Azathioprine should not be administered to patients who are pregnant because of reports of premature birth and low birth weight, and cyclophosphamide should not be used in pregnancy (or lactation) as it can cross the placenta (and is expressed in breast milk) and cause foetal toxicity.

7. The Myfortic Product Information has been updated during the evaluation to strengthen the information on the prevention of pregnancy particularly with regard to male partners treated with Myfortic (ref. SRN submitted 31 August 2011; Sub. No. PM-2011-02868-3-2).

8. Novartis does not claim superiority of Myfortic over MMF with regard to gastrointestinal symptoms and considers that for the specific indication of lupus nephritis, superiority of Myfortic or MMF over cyclophosphamide and azathioprine should not be a pre-requisite to approval for use in lupus nephritis.

11.5.2. MMF

1. Therapeutic equivalency of Myfortic and MMF in renal transplant is well established. There is no apparent reason to expect these medicines not to be therapeutically equivalent in lupus nephritis patients based on the active ingredient common to the two products.

2. MMF Studies showing that mycophenolate drugs are effective over 2 to 6 years in the treatment of lupus nephritis include results of 2 studies evaluated in the original CER: Contreras *et al.* (reference 39) and Chan *et al* (reference 18).

11.5.3. Other drugs

1. Myfortic, cyclophosphamide and azathioprine have similar efficacy in the treatment of lupus nephritis. The current standard of care (cyclophosphamide) has more risks associated with its use. Cyclophosphamide should not be considered an acceptable standard of care because of the side effect profile. With respect to azathioprine, approximately 20 to 40% of azathioprine treated patients require a dose reduction or are unable to tolerate azathioprine, and azathioprine is not effective as induction therapy.

11.5.4. Aboriginal patients

1. There is no evidence to suggest that the safety profile of Myfortic will be different in Aboriginal and Torres Strait Islander populations compared with the general population.

2. The Panel was concerned with the level of stereotyping of ATSI people that was present in the evaluation report and noted that the evaluation should focus solely on the medicine and its use for lupus nephritis, regardless of cultural and ethnic issues.

3. Novartis argues that the majority of the evaluator's concerns are not relevant to the application since they are associated with socioeconomic factors that affect access to, and quality use of, all medicines by the Aboriginal community. Several national programs are in place to address these medicine-related issues, including programs established by NACCHO (QUMAX). Novartis considers that the evaluator has placed undue emphasis on broader issues that would be relevant to the supply of any medication to indigenous patients. These

issues should have no bearing on the approvability of our application to register Myfortic in lupus nephritis.

4. Novartis commits to having culturally appropriate material (such as a patient brochure) developed specifically for this population. This will be done in collaboration with researchers in an academic institution who have expertise in the field of medical communication and with peak groups and specialists in the field of ATSI health. This material will use pictograms and/or suitable language for low literacy groups to instruct patients on the recommended dose and risks associated with use of Myfortic in lupus nephritis (e.g. signs and symptoms to watch out for and what to do). It will be part of a range of interventions, including education. There are many examples of successful medical education programs for Aboriginal communities, including for diabetes, HIV / AIDS, and sexually transmitted infections.
5. The evaluator noted concern regarding the equivalence of doses of Myfortic and MMF, raising the possibility of therapeutic drug monitoring, which has been suggested as an alternative method of determining the dose of mycophenolic acid. Such an approach is not favoured by clinicians for the following reasons: data on the use of mycophenolate levels are discordant; therapeutic drug monitoring has not been validated in large-scale randomised controlled trials; no drug target levels have been established; and correlation between mycophenolate levels and clinical outcome has not been validated in large-scale trials. In addition, such an approach is impractical, particularly in remote communities, due to difficulties in accessing infrastructure needed to determine mycophenolate blood levels. Clinicians advocate that treatment of patients with lupus nephritis should be guided by clinical response, disease activity, and patient well-being, rather than drug levels (Novartis Renal Expert Advisory Board Meeting 21st February 2011).

11.5.5. Risk management plan

Evaluation of the Risk Management Plan is the province of the Office of Product Review. The risks identified by Novartis, including pregnancy are all to be dealt with by:

- Routine pharmacovigilance including cumulative analysis in PSUR.
- Study CERL080AAU06, a Phase IV study also called LUNAR, the Lupus Nephritis Australian Registry.
- Physician, non-indigenous and indigenous patient educational material.
- Risk addressed in the Australian Product Information Precautions and Adverse Events section.
- Health Care professional educational letters.

11.6. Summary and discussion

Novartis submitted 45 publications in the initial application. A further 43 articles have been submitted in the supplementary data, seventeen of which were identified for evaluation. The evidence is summarised below and discussed under the following headings.

- Comments on the applicant's response to the CER
- Efficacy and safety of EC-MPS in treatment of LN
- Pharmacokinetic comparison of EC-MPS and MMF
- Equivalence of efficacy and safety of EC-MPS vs. MMF renal transplantation
- Efficacy and safety of MMF in treatment of LN

11.6.1. Novartis' response to the Clinical Evaluation Report

The applicant has not included evidence regarding the off-label use of Myfortic in Australia including documentation of the safety of off-label use.

The risks associated with cyclophosphamide are accepted. However, the application is to register Myfortic and therefore primarily the risks of Myfortic are relevant to the evaluation.

It is agreed that the Aboriginal and Torres Strait Islander and non-ASTI populations are similarly at risk of the known safety concerns of Myfortic. The extent to which they are susceptible to the risks has not been studied. A major concern with regard to Myfortic is the teratogenic potential. If use of Myfortic results in birth of infants with congenital abnormalities such as congenital diaphragmatic hernia, anomalies of the distal limbs and heart, oesophagus and kidney, then the parents and the community will not be considered well served.

The applicant has been advised to provide adequate, culturally appropriate educational material but has not yet done so. In Study A2420, participants were required to use 2 effective methods of contraception once it became clear from post-market surveillance that significant birth defects were occurring in women using MMF in pregnancy. The FDA considers the risk sufficiently worrying to have mandated the following boxed warning unlike either cyclophosphamide or azathioprine.

> WARNING
>
> ... Female users of childbearing potential must use contraception. Use of Myfortic during pregnancy is associated with increased risks of pregnancy loss and congenital malformations.

With respect to contraception the revised A2420 protocol specified: "The two methods can be a double barrier method or a barrier method plus a hormonal method. Adequate barrier methods of contraception include: diaphragm, condom (by the partner), intrauterine device (copper or hormonal), sponge or spermicide. Hormonal contraceptives include any marketed contraceptive agent that includes an estrogens and/or a progestational agent. Patients should be aware that Myfortic reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness. Reliable contraception should start 4 weeks prior to beginning Myfortic".

It is considered that if this was a requirement for the study, it should be a requirement for each treated woman of child bearing potential and that patients should be adequately informed of the risk and the requirements for prevention.

11.6.1.1. The Lupus Nephritis Australian Registry

In the initial letter of application Novartis stated the intention to develop a registry. Instead, a Phase IV observational study, the Lupus Nephritis Australian Registry (LUNAR), is now proposed. This evaluator considers the proposal to call the study a registry, semantically incorrect and the effect in practical terms is to undermine active surveillance. This matter is to be evaluated by the Office of Product Review.

11.6.2. Direct evidence for EC-MPS

In direct support of the proposed INDICATION, three articles were submitted in the initial application dossier, each reporting results of EC-MPS treatment of selected Asian patients, predominantly female, aged 14 to 50 years with WHO Class III, IV and V lupus nephritis (references 36, 37, 38). Included were two cohort studies and one prospective study in which patients treated with MMF were compared with historical controls treated with monthly intravenous cyclophosphamide. The studies were considered observational.

A total of 45 patients were treated in these non-randomised, non blinded trials. One patient was maintained in remission following change in treatment from MMF to EC-MPS. Of the remainder, 16/44 achieved complete remission and 17/44 achieved partial remission.

Each of these exploratory studies presented as direct evidence for efficacy and safety of EC-MPS in treatment of LN is considered to have significant methodological inadequacies for regulatory purposes.

Included in the supplementary data was a summary of observational Study A2420, a randomised, multicenter, open-label, 6-month non-inferiority study of efficacy and safety of either standard dose or low dose corticosteroid regimens co-administered with EC-MPS for treatment of Class III or IV lupus nephritis flares. The primary objective was to assess efficacy of the low dose corticosteroid regimen compared to the standard dose in terms of the proportion of patients in complete remission after 24 weeks of treatment. A total of 81 patients were randomized to treatment: 42 patients in the standard dose group, 39 patients in the low dose group. Complete remission was achieved by 19.0% of the patients of the standard steroid dose group and 20.5% of the low dose group. Non-inferiority was not shown in the ITT population; the study was underpowered. The proportion of patients with partial remission at week 24 was 20/42 (47.6%) in the standard dose group and 14/39 (35.9%) in the low dose group.

11.6.3. Pharmacokinetic equivalence of EC-MPS and MMF

In the initial application dossier; one single dose study, two multiple dose studies and one pre-dose study undertaken in stable adult renal transplant patients examined pharmacokinetic of EC-MPS compared to MMF. All studies reported longer time to tmax for the enteric coated formulation as would be expected. All studies reported considerable inter-individual and intra-individual variation.

The single dose study of Arns *et al* (reference 40) reported that doses of EC-MPS 640 and 720 mg to be bioequivalent to 1000 mg MMF for MPA $AUC0_{-\infty}$. Tmax was delayed for EC-MPS compared to MMF, and Cmax was lower for EC-MPS that for MMF, and was lower for the 720 mg dose than for the 640mg dose, with 90% confidence intervals outside the accepted bioequivalence levels; well outside those limits for the 720 dose. Based on the result of this study the two formulations cannot be considered truly bioequivalent.

The multiple dose study of Budde *et al* (reference 41) reported the finding of bioequivalence with regard to AUC in general agreement with the findings of the single dose study reported by Arns *et al*. (40). The MPA Cmax result for 720 mg EC-MPS was less than that of MMF 1000 mg; the EC-MPS MPA tmax was delayed as it was in the single dose study and in keeping with the enteric coating of the EC-MPS formulation. With repeated doses, the EC-MPS, MPA Cmin averaged approximately twice that of MMF. Again, overall, the two formulations could not be considered bioequivalent.

The single dose study of Arns (40) reported bioequivalent MPAG Cmax and AUC while the multiple dose study of Budde (41) reported IMPDH AUC 14% lower for EC-MPS than for MMF.

In a further report Budde *et al* (42) undertook a systematic review of results of three multiple dose studies and found that MPA C0 values were consistently higher for EC-MPS than for MMF. This report also documented a number of outliers with relatively high values.

The multiple dose study of Tedesco-Silva (43) reported results for the metabolite AcMPAG, thought to be an active metabolite. The MPA AUC and Cmax results in this study differed from those of Budde *et al* and are summarised thus:

- The ratio of MPA AUCs and Cmax was outside the bioequivalence range: 125% 90% CI (108 – 129), and 116% 90% CI (94 – 142) respectively.
- The MPA Cmin results were similar between groups.

- Inactive metabolite MPAG AUC and Cmax were estimated to be 22% higher for EC-MPS than for MMF with 90% CI outside the bioequivalence range.
- For potentially active metabolite AcMPAG, both AUC and Cmax were within bioequivalence range.

The study of Tedesco-Silva *et al* (43) reported that the AcMPAG had slower clearance than MPA. This is of interest because this metabolite has been shown to have some IMPDH-II inhibitory activity, although not as potent as MPA, and because it may undergo hydrolysis, molecular rearrangement and covalent binding to proteins and nucleic acids. The formation of such stable products has been suggested to play a role in the manifestation of drug toxicities, either through direct disruption of the function of critical proteins or through antigen formation with subsequent hyper- sensitivity and other immune reactions.

The submitted PSUR included summary of a study by Joy *et al* (44) in which pharmacokinetics of mycophenolic acid were examined in lupus nephritis. Both creatinine clearance and serum albumin level were identified as primary contributors to mycophenolic acid exposure and should be considered when evaluating dosages. The author concluded: Clinicians need to be mindful of clinical changes that occur throughout the course of lupus nephritis in order to maintain efficacy and reduce toxicity from mycophenolic acid therapy.

The conclusion drawn following evaluation of these study reports was that MPA AUC is generally similar for EC-MPS and MMF in stable renal transplant patients, however, two small studies documented higher AUC exposure for EC-MPS compared to MMF. There appeared to be considerable inter-individual variation in results and the results of studies with small sample size are readily influence by outliers. It appeared that there may be a sub-population of patients who metabolise EC-MPS more slowly than the majority of patients. In stable renal transplant patients, it appears that Cmax is lower for EC-MPS and that C0 is likely to be higher, and possibly considerably higher. The results of these studies done on renal transplant patients are likely to have been influenced by co-medication with cyclosporine which potentiates enterohepatic recirculation of MPA.

In the supplementary data, two further PK studies were submitted. The study of Rupprect *et al*. (reference 13) compared the influence of pantoprazole 40 mg twice daily on the bioavailability of a single dose of mycophenolate mofetil 1000 mg or enteric-coated mycophenolate sodium 720 mg and demonstrated little effect on PK parameters of EC-MPS in comparison to marked reduction in PK results for MMF.

The Novartis study of Tedesco-Silva *et al* (15), a multiple-dose, crossover study compared the inter- and intra-subject variability of MPA pre-dose levels from EC-MPS and MMF, each with cyclosporine in clinical stable renal transplant patients, two thirds of whom were male. The results indicated that intra-subject variability for C0h, Cmax and AUC_{0-3h} was significantly greater for EC-MPS than for MMF. Inter-individual variability was numerically higher for the EC-MPS than for MMF.

The authors of this article use the results to state in the abstract that “In conclusion, pre doseMPA trough level monitoring appears of limited value during EC-MPS and MMF therapy given the large intra-subject variability in MPA C0 h levels with both treatments”, whereas in the discussion the authors state that the findings raised questions about the value of therapeutic drug monitoring.

Tedesco-Silva *et al* also state it was suggested that outside clinical studies, variability might be even higher because of a more unreliable drug intake. While in de novo patients, time dependent changes of MPA pharmacokinetics is a main contributor to the high intra-subject variability in pre dose levels, this does not apply to the maintenance transplant population. In this setting, day-to-day fluctuations in the enterohepatic recirculation of MPA may explain a

significant portion of the observed intra subject variability; genetic factors have been reported as possible determinants for the high between-subject variability.

The evaluator agrees that genetic determinants could well play a part in inter individual variation. The authors of this Novartis study have not theorised that problems with the formulation may play a part in intra-subject variability. Rather than being an argument against TDM, the variability could well be the basis of an argument for TDM. Furthermore the greater variability reported for EC-MPS compared to MMF is considered a potential problem relating to reliance on the product for therapeutic safety and efficacy.

Houssiau *et al*. (11) in discussion of their study testing superiority of MMF vs AZA in maintenance therapy discuss the possibility that patients who failed on one or the other drug may actually have been under dosed or non-adherent to the medication. They state that this hypothesis might not be too farfetched based on the recent finding that patients who have undergone kidney transplant had a lower rejection rate if MMF doses were titrated according to serum MPA titres instead of fixed (dose).They state that individualized mycophenolate mofetil dosing based on drug exposure has been shown to significantly improves patient outcomes after renal transplantation.

11.6.4. Efficacy and safety of EC-MPS vs, MMF in renal transplantation

Two study reports included in the initial dossier were considered pivotal, one for efficacy and one for safety. Each of these included renal transplant patients co-administered cyclosporine with or without corticosteroid.

The study of Salvadori *et al* (45) was rated NHMRC level II and Jadad score 5. The study evaluated statistical equivalence of treatment with EC-MPS compared to MMF. The primary outcome was efficacy failure based on the incidence of biopsy-proven acute rejection, graft loss, death or loss to follow-up at 6 months. There were 213 patients in the EC-MPS group and 210 in the MMF group. The patient population was predominantly Caucasian and male.

Within the first 6 months post-transplant, on the basis of ITT analysis, the incidence of efficacy failure, defined as the incidence of BPAR, graft loss, death or loss to follow up, was similar for EC-MPS and MMF (25.8% and 26.2%, respectively). The 95% CI for efficacy failure was [−8.7, +8.0], indicating equivalence according to pre-specified criteria.

The study of Budd *et al* (reference 46) also rated NHMRC level II, Jadad score 5. The aim was to investigate whether renal transplant patients could be safely converted from treatment with MMF to EC-MPS. The primary objective was to assess safety with respect to gastrointestinal adverse events and neutropenia at 3 months. Efficacy was a secondary objective and was assessed as for the study or Salvadori *et al* above. There were 159 patients in the EC-MPS group and 163 patients in the MMF group. The patient population was predominantly Caucasian and approximately two thirds of patients were male.

There was no statistically significant difference detected between the two groups with respect to nausea, dyspepsia, upper abdominal pain, gastro oesophageal reflux, gastritis, anorexia or diarrhoea, nor for neutropenia or for efficacy failure. There was no sample size calculation and the study numbers may have been too small to detect statistically significant differences.

While accepting the findings of these two studies, the evaluator considers that it is not sound logic to accept non-inferiority of efficacy in treatment of one condition as proof of non-inferiority of efficacy in another unrelated condition.

11.6.5. MMF treatment of lupus nephritis

11.6.5.1. Reports of single studies

In the initial evaluation, five study reports were considered pivotal or supportive. All studies were open-label.

Three induction studies compared MMF to IVC: Appel (20), Ginzler (17), Ong (19). One induction study compared MMF to oral cyclophosphamide (Chan 2000 (26)). The WHO classes enrolled include: Appel and Ginzer class III, IV and V; Ong enrolled class III and IV and Chan enrolled class IV.

The planned doses of MMF and IVC were similar. IVC was administered in monthly pulses. Oral cyclophosphamide was administered daily. Each study included use of corticosteroid.

No common primary endpoint or statistical approach was employed. The result of the primary analysis of Appel, Ong and Chan demonstrated no significant difference between groups. However, lack of finding of significant difference is not the same as proving non-inferiority or equivalence, and does not exclude the possibility that a statistically significant difference may be present. The Study of Ginzler reported that having met the criteria for non-inferiority, the results were sufficient to allow the conclusion of superiority of MMF compared to IVC.

The main concerns with each of the studies were:

- Ginzler: Assessment of progress at 12 weeks with treatment cross-over for some, but not all of the patients who met the criteria for cross-over. The IVC group's response rate was exceptionally low.
- Ong: Exclusion after randomization of over 27% of patients in the MMF treatment arm, based on reassessment of renal biopsies.
- Chan: randomisation and allocation concealment not discussed. Wide confidence intervals reflect the small study numbers and made the result difficult to interpret.

The two maintenance studies, Chan 2005 (18) and Contreras (24), compared MMF with AZA; the Contreras study also included an IVC group. Both used survival statistics. There was no statistical difference in primary objective results of serial serum creatinine documented in the study of Chan. Compared to the IVC group the event free survival was statistically higher in the azathioprine ($p = 0.009$) and MMF groups ($p = 0.05$).

The main concerns with each of the studies were:

- Chan: the extension component of the study was a post-hoc, add-on considered observational and therefore hypothesis generating.
- Contreras: the timing of statistical analysis was not stated. The numbers at risk dropped rapidly and to very low numbers, and information on disposition and censoring was lacking.

The supplementary data included two reports of small studies of induction therapy limited to 6 months, one from Egypt (El-Shafey *et al* (1)) and from China (Li *et al* (5)). These studies had different definitions of complete remission which was the primary outcome in each. Both reported similar response rates for MMF vs, IVC, and in the study of Li *et al*, similar response to tacrolimus.

Two studies of maintenance therapy were included. The study of Dooley *et al* (9) was considered a stand out in design and reporting and was rated a Jadad score of 5. This 36 month, randomised 1:1, double-blind, double dummy, phase 3 study compared oral mycophenolate mofetil 2 g per day and oral azathioprine 2 mg/kg per day plus placebo in each group, in patient who met the response criteria during a 6-month induction trial with either MMF or cyclophosphamide. The primary efficacy end point was the time to treatment failure, measured as the time until the first event and defined as death, end-stage renal disease, sustained doubling of the serum creatinine level, renal flare, or the need for rescue therapy. The hazard ratio for treatment failure, 0.44 [95% [CI, 0.25 to 0.77]; P = 0.003) favouring MMF. Overall observed rates of treatment failure were 16.4% (19 of 116 patients) in the MMF group and 32.4% (36 of 111) in the AZA group. The finding was consistent, for sub-analysis of results

based on induction treatment with IVC, but the HR for MMF induction included one, as did sub-analyses based on race, and geographic region.

The study of Houssiau *et al* (11) was a multicentre, randomised, controlled, unblinded 48 week trial testing superiority of mycophenolate mofetil (MMF) vs. azathioprine as maintenance treatment. Included were 105 patients aged ≥ 14 years WHO class III, IV, Vc or Vd LN. There were some discrepancies in baseline characteristics. The Kaplan-Meier probability of renal flare: Hazard ratio 0.75 (0.33, 1.71) p = 0.486. Superiority was not demonstrated.

11.6.5.2. Systematic reviews and meta-analyses

One meta-analysis was evaluated in the original CER (Zhu *et al*) (reference 47) and a further six systematic reviews/meta-analyses addressing efficacy and safety of induction therapy with MMF vs. cyclophosphamide were evaluated for this report. The study reports included in the meta-analyses were rated Jadad scores between zero and 3. The studies of Ginzler (17), Ong (19) and Chan (18) were included in all meta-analysis. The ALMS study reported by Appel *et al* (20) was included in all except the meta-analysis of Mak *et al* (8); however, results of the ALMS study were included in abstract form in the meta-analysis of Mak *et al*. Two meta-analyses, [information redacted] (6) and the analysis by Lee *et al* (4), also assessed maintenance therapy comparing MMF with AZA. A seventh review compared response of class V membranous LN with steroid therapy alone in comparison to treatment with a variety of non steroid immunosuppressant therapies.

With respect to induction therapy, complete remission, partial remission and overall remission risk ratios included one for each of the meta-analysis reports. The risk of amenorrhea following treatment with cyclophosphamide was found to be greater than with MMF by Touma *et al* (14), Kamanamool *et al* (2), Mak *et al*. (8) and [information redacted] (6). Leucopenia risk from treatment with cyclophosphamide was determined to be greater by Kamanamool *et al* (2) and Mak *et al* (8). Alopecia less likely to occur with MMF use than with IVC according to Touma *et al* (14) [information redacted]. There appeared to be no difference in rates of infection, death or ESRD. [information redacted]

Regarding maintenance therapy the RR included one for response and development of ESRD in the analysis of Lee *et al* (4), but the

[information redacted]. This is in keeping with the report of Dooley *et al* (9) of a randomised, double-blind, double-dummy study comparing MMF with AZA in maintenance treatment of patients who had previously responded to induction therapy. The single trial report of Houssiau *et al* (11) tested but failed to show superiority of MMF vs. AZA; however, the numbers included in the study were small.

The meta-analysis of Mohan *et al* (10) concluded that complete remission with MMR was more likely in patients outside Asia while Isenberg *et al* (7) in their report of sub-analysis of a single trial, concluded that response for Asian and white patients was similar while Black and Hispanic patients were less responsive to IVC than to MMF.

The review of Swan *et al* (12) comparing non steroid immunosuppressant therapy with steroid only therapy for Class V LN concluded with the recommendation that non steroid immunosuppressants in combination with steroids are to be recommended in view of their finding of better overall response to combined therapy. The report of Radhakrishnan *et al*, of post-hoc analysis of results of a single trial suggested that MMF is as effective as IVC in treatment of Class V LN, but that neither treatment is very effective.

The consistency in results of the meta-analyses of induction therapy is in part due to inclusion of much the same data in each analysis. It is considered that observational, non-randomised studies and studies with a retrospective component are of questionable value in a meta-analysis and may serve to bias the result. In addition, while well conducted meta-analyses examining

results of high quality studies are considered high level evidence, meta-analyses are all considered observational.

Studies with differing primary objectives and with differing definitions of response add confusion. In general the authors of meta-analyses must accept the definitions included in the primary reports. Studies which are not blinded increase the possibility of bias, though with objective outcomes based on laboratory findings it may be argued that risk of bias reduced. However, non-blinded studies with composite endpoints, even if the individual elements of the endpoint are objective, may be subject to bias when some components are consistent with response and others are borderline or inconsistent with response. In addition, all studies relied on surrogate endpoints.

With respect to safety, reliability of results depends on which adverse events are reported, how they are recorded during the study and the manner in which they are interpreted by the original investigators. Safety was not the primary outcome of any of the studies included in the meta-analysis. The original articles of Appel (20), Ginzler (17) , Chan (18) and Ong (19) did not discuss the method of reporting or recording of adverse events nor the completeness of the data reported. Other original texts were not revisited for this information. It was also not apparent in the meta-analyses whether the AEs reported were required to have been determined to be treatment related or otherwise.

12. Second round benefit-risk assessment

12.1. Benefits

- There is a clear need for effective, safe and affordable treatment for lupus nephritis, a condition with potential to cause significant morbidity or mortality.
- Treatment with oral medication has advantages of being non painful, oral treatment does not require specialised medical assistance or sterile equipments.
- Induction treatment with MMF has been shown in randomised, controlled, unblinded trials and meta-analyses to have similar efficacy to IVC. Maintenance treatment for 36 weeks with MMF has been shown in a randomised, controlled, double blind, double dummy study (9) to have significantly better results than AZA in patients who have responded to induction therapy, [information redacted].
- Observational studies have documented response in patients treated with EC-MPS.
- Registration of Myfortic may be followed by inclusion of Myfortic on the Pharmaceutical Benefit Scheme resulting in more affordable treatment for patients with lupus nephritis. Presently there is no medication registered for this indication and thus no other treatment eligible for subsidisation.
- The pharmacokinetics of EC-MPS are not substantially altered by co-administration of the proton pump inhibitor pantoprazole.

12.2. Risks

- Systemic Lupus Erythematosus predominantly affects women of child bearing age. MPA has been demonstrated to be teratogenic and to increase the probability of spontaneous abortion. The congenital abnormalities reported in relation to MMF use have potential to cause death or significant disability and this adverse event would impact most on a person other than the one requiring treatment. The registration of a teratogenic drug for use in this population is considered of great concern.

- Direct evidence for efficacy of Myfortic efficacy in treatment of lupus nephritis is limited to observational studies.
- Evidence presented in the report of observational Study A2420 demonstrated that the primary outcome, complete remission, was only recorded for approximately 20% of patients after 6 months of treatment.
- There is no long term evidence to support Myfortic use.
- The bulk of evidence submitted in support of the application was based on literature reports of studies using MMF. In addition, there are problems with many of the study designs and literature reports of efficacy and safety of MMF in treatment of LN as discussed comprehensively the evaluation reports.
- Therapeutic bioequivalence of MMF and EC-MPS has not been studied in treatment of LN.
- For regulatory purposes, therapeutic equivalence of MMF and EC-MPS in renal transplantation is not considered sufficient evidence for therapeutic equivalence in lupus nephritis.
- EC-MPS has demonstrated considerable inter-individual and intra-individual PK variation which may impact both safety and efficacy.
- Neither Myforic nor CellCept are registered for the requested indication anywhere else in the world.

12.3. Balance

Subject to the delegate's approval of the risk management plan, the recommendation is for approval of the use of Myfortic for patients with lupus nephritis. This recommendation has been found very difficult to determine despite the acknowledged need.

13. Second round recommendation regarding authorisation

Prior to registration it is required that the applicant justifies the proposed dosage of 1440 mg daily which differs from that used in Study A2420 in which it was stated that all patients were treated with Myfortic at a daily dose of 2160 mg daily after an initial 2 weeks treatment with 1440 mg per day.

Should the extension of indication be registered it is recommended that further changes to the Product Information are made as follows:

- Strengthened warning relating to the use of Myfortic in pregnancy including a black box warning is recommended for both the Product Information and the Consumer Medicine Information.
- Clinical trials: Revision of the proposed summary of study A2420 is required.
- Indication: It is recommended that the following statement or similar is included. Evidence for this indication is based on literature reports of studies of treatment with mycophenolate mofetil in patients with LN, the majority of whom were in ISN/RPS (2003) Class IV. The evidence for efficacy was based on surrogate endpoints.
- Contraindications: It is recommended that the reason Myfortic is contraindicated in pregnancy is included under this heading, i.e. Use of Myfortic during pregnancy is associated with increased risks of pregnancy loss and congenital malformations.

- Precautions: It is recommended that the order of headings in this section is revised and that precautions relating to use in pregnancy are strengthened. In addition it is recommended that two types of reliable contraception are specified in line with the requirements of Study A2420.
- Dosage and Administration: Justification for the proposed dosage is required before a recommendation can be finalised.

14. References - Supplementary evaluation

1. El-Shafey E *et al* Is mycophenolate mofetil superior to pulse intravenous cyclophosphamide for induction therapy of proliferative lupus nephritis in Egyptian patients? *Clin Exp Nephrol* (2010) 14:214–221
2. Kamanamool N, McEvoy M, Attia J, *et al* Efficacy and adverse events of mycophenolate mofetil versus cyclophosphamide for induction therapy of lupus nephritis: systematic review and meta-analysis. *Medicine (Baltimore)* 2010;89(4):227-35
3. Radhakrishnan J *et al* Mycophenolate mofetil and intravenous cyclophosphamide are similar as induction therapy for class V lupus nephritis. *Kidney International* (2010) 77, 152–160
4. Lee YH *et al* Induction and maintenance therapy for lupus nephritis: a systematic review and meta-analysis *Lupus* 2010 19: 703 - 710
5. Li X *et al* Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis *Nephrol Dial Transplant* (2011) 0: 1–6
6. [Information redacted]
7. Isenberg d *et al* Influence of race/ethnicity on response to lupus nephritis treatment: the ALMS study *Rheumatology* 2010;49:128–140
8. Mak A *et al* Mycophenolate mofetil is as efficacious as, but safer than, cyclophosphamide in the treatment of proliferative lupus nephritis: a meta-analysis and meta-regression *Rheumatology* 2009;48:944–952
9. Dooley MA *et al* Mycophenolate versus Azathioprine as Maintenance Therapy for Lupus Nephritis. *N Engl J Med* 2011;365:1886-95
10. Mohan S, Radhakrishnan J. Geographical variation in the response of lupus nephritis to mycophenolate mofetil induction therapy. *Clinical Nephrology*, Vol. 75 – No. 3/2011 (233-241)
11. Houssiau F *et al* Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial *Ann Rheum Dis* 2010 69: 2083-2089
12. Swan J *et al* Systematic Review and Meta-Analysis of Immunosuppressant Therapy Clinical Trials in Membranous Lupus Nephritis. *Journal of Investigative Medicine* Volume 59, Number 2, February 2011
13. Rupprecht K *et al* Bioavailability of Mycophenolate Mofetil and Enteric-Coated Mycophenolate Sodium Is Differentially Affected by Pantoprazole in Healthy Volunteers *J Clin Pharmacol* 2009 49: 1196
14. Touma Z *et al* Mycophenolate mofetil for induction treatment of lupus nephritis: A systematic review and metaanalysis. *The Journal of Rheumatology* 2011; 38; 69 - 78
15. Tedesco-Silva H *et al* Randomized crossover study to assess the inter- and intrasubject variability of morning mycophenolic acid concentrations from enteric-coated mycophenolate sodium and mycophenolate mofetil in stable renal transplant recipients. *Clin Transplant* 2010: 24: E116–E123
16. Zeher M *et al* Efficacy and safety of enteric-coated mycophenolate sodium in combination with two glucocorticoid regimens for the treatment of active lupus nephritis *Lupus* (2011) 0, 1–10

17. Ginzler EM, Dooley MA, Aranow C, Kim MY, Buyon J, Merrill JT *et al* Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005;353:2219-28

18. Chan TM, Tse KC, Tang CS, Mok MY, Li FK; Hong Kong Nephrology Study Group. Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. *J Am Soc Nephrol* 2005;16:1076-84

19. Ong LM, Hooi LS, Lim TO, Goh BL, Ahmad G, Ghazalli R, *et al*. Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. *Nephrology* 2005;10:504-10

20. Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, *et al* Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol* 2009; 20:1103-12

21. Wang J, Hu W, Xie H, Zhang H, Chen H, Zeng C, Liu Z, Li L. Induction therapies for class IV lupus nephritis with non-inflammatory necrotizing vasculopathy: mycophenolate mofetil or intravenous cyclophosphamide. *Lupus*. 2007; 16:707Y712

22. Hu W, Liu Z, Chen H, *et al* Mycophenolate mofetil vs cyclophosphamide therapy for patients with diffuse proliferative lupus nephritis. *Chin Med J (Engl)* 2002; 115: 705–709

23. Sahin GM, Sahin S, Kiziltas S, Masatlioglu S, Oguz F, Ergin H. Mycophenolate mofetil versus azathioprine in the maintenance therapy of lupus nephritis. *Ren Fail* 2008; 30: 865–869

24. Contreras G, Tozman E, Nahar N, Metz D. Maintenance therapies for proliferative lupus nephritis: mycophenolate mofetil, azathioprine and intravenous cyclophosphamide. *Lupus* 2005; 14(Suppl 1): s33–s38

25. Bao H, Liu ZH, Xie HL, Hu WX, Zhang HT, Li LS. Successful treatment of class V+IV lupus nephritis with multitarget therapy. *Journal of the American Society of Nephrology* 2008; 19(10):2001-10

26. Chan TM, Li FK, Tang CS, Wong RW, Fang GX, Ji YL, *et al* Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. *New England Journal of Medicine* 2000; 343(16):1156-62

27. Mulic-Bacic S, Antic D, Krizic M, Hajdarovic A, Mulic E. Mycophenolate mofetil or intravenous cyclophosphamide in treatment of lupus nephritis [abstract no: FRI0201]. *Annals of the Rheumatic Diseases* 2008; 67(Suppl II):349

28. Sundel RP, Lisk L. Mycophenolate mofetil compared with intravenous cyclophosphamide as induction treatment for pediatric lupus nephritis: a randomized trial [abstract no: 1247]. In: *American College of Rheumatology Annual Scientific Meeting*, Oct 24-29, 2008, San Francisco, CL. 2008

29. Moroni G, Doria A, Mosca M, Alberighi O, Ferraccioli G, Todesco S, *et al* A randomized pilot trial comparing cyclosporine and azathioprine for maintenance therapy in diffuse lupus nephritis over four years. *Clinical Journal of the American Society of Nephrology*: CJASN 2006; 1(5):925-32

30. Flores-Suarez LF, Villa AR. Preliminary results of an open label randomized clinical trial comparing mycophenolate mofetil (MMF) vs intravenous cyclophosphamide as induction therapy for severe lupus nephritis. *Arthritis Rheum* 2004; 50(Suppl. 1):S1029

31. Isenberg D, Appel G, Dooley MA *et al* Mycophenolate mofetil compared with intravenous cyclophosphamide as induction for lupus nephritis. *Ann Rheum Dis* 2008; 67(Suppl. II):S53

32. Duncan N, Cairns T, Griffith M, McLean A, Palmer A, Taube D. Mycophenolate mofetil as treatment for the nephrotic syndrome caused by lupus nephritis. *J Am Soc Nephrol.* 2003; 14: 379.

33. Flores-Suarez LF. Remission of severe relapsing or persistent lupus nephritis using mycophenolate mofetil. *Arch Med Res*. 2006; 37: 68-73.

34. Choi KH, Moon S, Han S, Lee J, Kim D, Kim B, Kang S, Han D, Lee H. The comparison study between mycophenolate mofetil and cyclophosphamide for treatment of proliferative lupus nephritis. *J Am Soc Nephrol*. 2007; 18: 566.

35. Tang Z, Yang G, Yu C, Yu Y,Wang J, HuW, Zeng C, Chen H, Liu Z, Li L. Effects of mycophenolate mofetil for patients with crescentic lupus nephritis. *Nephrology* (Carlton). 2008; 13: 702-707

36. Kitiyakara C, Ophascharoensuk V, Changsirikulchai S, *et al* Treatment of lupus nephritis and primary glomerulonephritis with enteric-coated mycophenolate sodium. *Clin Nephrol* 2008; 69(2):90-101

37. Mak SK, Lo KY, Lo MW, *et al* Efficacy of enteric-coated mycophenolate sodium in patients with active lupus nephritis. *Nephrology* (Carlton) 2008; 13(4):331-6.

38. Traitanon O, Avihingsanon Y, Kittikovit V, *et al* Efficacy of enteric-coated mycophenolate sodium in patients with resistanttype lupus nephritis: a prospective study. *Lupus* 2008; 17(8):744- 51.

39. Contreras G, Pardo V, Leclercq B, *et al* Sequential therapies for proliferative lupus nephritis. *N Engl J Med* 2004; 350(10):971-80

40. Arns W, Breuer S, Choudhury S, *et al* Enteric-coated mycophenolate sodium delivers bioequivalent MPA exposure compared with mycophenolate mofetil. *Clin Transplant* 2005; 19(2):199-206

41. Budde K *et al* Pharmacokinetic and pharmacodynamic comparison of enteric-coated mycophenolate sodium and mycophenolate mofetil in maintenance renal transplant patients. *American Journal of Transplantation* 2007; 7: 888 – 898

42. Budde *et al* Enteric-Coated Mycophenolate Sodium Provides Higher Mycophenolic Acid Predose Levels Compared With Mycophenolate Mofetil: Implications for Therapeutic Drug Monitoring. Short communication. *Ther Drug Monit* 2007; 29 (3): 381 – 384

43. Tedesco-Silva H *et al* Mycophenolic acid metabolite profile in renal transplant patients receiving enteric-coated mycophenolate sodium or mycophenolate mofetil. *Transplantation Proceedings* 2005; 37: 852 – 855

44. Joy MS *et al* Pharmacokinetics of mycophenolic acid in patients with lupus nephritis. *Pharmacotherapy* 2009; 29 (1): 7 – 16 (not submitted for evaluation)

45. Salvadori M *et al* Enteric-coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in de novo renal transplant patients. *American Journal of Transplantation* 2003; 4: 231–236

46. Budde K *et al* Enteric-coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: results of a 1-year study. *American Journal of Transplantation* 2003; 4: 237 – 243

47. Zhu B *et al* Mycophenolate mofetil in induction and maintenance therapy of severe lupus nephritis: a meta-analysis of randomized controlled trials. *Nephrol Dial Transplant* (2007) 22: 1933–1942

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au