CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: : 050759

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 50,759	**Submission Date:** 9/30/97, 9/9/98
Generic Name, Strength and Formulation	Mycophenolate Mofetil 200 mg/mL Oral Suspension
Brand Name: Cellcept(R)	**Date Assigned:** 10/8/97
Applicant: Roche	**Final Review:** 9/23/98
Submission Code: 3S	**Reviewer:** Kofi A. Kumi. Ph.D.

SYNOPSIS

The applicant submitted a new drug application (NDA) for Mycophenolate Mofetil (Cellcept, MMF) oral suspension intended to be an alternate dosage form for patients who may find solid oral dosage formulations (capsules and tablets) unsuitable. MMF is currently available commercially as 250 mg capsules, 500 mg tablets and as a 500 mg powder for reconstitution for intravenous injection. MMF is approved (NDAs 50,722, 50,722SE1, 50,733, 50,758) for use in the prevention of acute allograft rejection following renal and cardiac transplantation. Information contained in original NDA is cross referenced in this application. In the Human Pharmacology and Biopharmaceutics section of this application, one pivotal bioequivalence study (MYCS 2684), one pilot supportive study (MYCS 2644) and a taste acceptability study (MYCS 2394) were submitted.

Mycophenolate Mofetil is the morpholinoethyl ester of mycophenolic acid (MPA), the pharmacologically active moiety of MMF. MPA is a potent and specific inhibitor of de novo purine synthesis which blocks the proliferation of both T and B lymphocytes. The strategy for the development of the oral suspension was to demonstrate bioequivalence between the oral suspension and the commercial capsule formulation with respect to MPA concentrations.

In the pivotal bioequivalence study (MYCS 2684), the Ln AUC and Ln Cmax after the administration of 1 gm of the oral suspension was demonstrated to be bioequivalent to 1 gm of the capsule formulation. The two formulations are bioequivalent because the 90% confidence interval (CI) for Ln AUC and Ln Cmax meet the current regulatory requirement of 80% to 125%. The mean pharmacokinetic parameters and the 90% CI for the comparison of the suspension (test formulation) and the capsule (reference formulation) is provided in the following tables

Mean MPA Pharmacokinetic Parameters

Parameter	Treatment A (N=42)	Treatment B (N=42)
AUClast (μg*h/mL)	65.9 ± 16.6	62.6 ± 15.6
AUC(0-∞)(μg*h/mL)	70.5 ± 16.5	68.9 ± 17.6
Cmax (μg/mL)	28.4 ± 7.11	27.1 ± 9.37
T ½ (h)	16.5 ± 3.61	19.2 ± 20.7
Tmax	0.67 ± 0.43	0.83 ± 0.35

A = Mycophenolate Mofetil oral suspension 1 gm (5 mL of 200 mg/mL suspension)
B = Mycophenolate Mofetil oral capsules 1 gm (4 x 250 mg capsules)

90% CI for MPA Parameters

Computed Parameter	Ratio (A/B)	90% CI	
		Lower Limit	Upper Limit
Ln AUClast	104.8%	102.0%	107.7%
Ln AUC(0-∞)	102.6%	97.9%	107.6%
Ln Cmax	106.3%	98.9%	114.3%

A = Mycophenolate Mofetil oral suspension 1 gm (5 mL of 200 mg/mL suspension)
B = Mycophenolate Mofetil oral capsules 1 gm (4 x 250 mg capsules)

Formulation: The oral suspension formulation used in the pivotal bioequivalence study is the proposed commercial formulation. The size of the lot manufactured is the same as the intended manufacturing size.

Dissolution: The following dissolution method and specification for Mycophenolate Mofetil (Cellcept) is recommended by the applicant:

Apparatus: USP Apparatus 2 (Paddle)
Speed:
Medium: 900 mL 0.1N HCL at 37° ± 0.5° C
Specification: Q

Upon review of the data, the recommendation is acceptable.

COMMENTS

1) The applicant did not evaluate the effect of food on the MMF oral suspension. The current label recommends Cellcept capsules and tablets be taken on an empty stomach and hence it will be recommended that the suspension be taken on an empty stomach. The pivotal bioequivalence study was conducted after an overnight fast.

2) The bioequivalence studies were conducted comparing 1 gm of the capsules (250 mg/cap) and suspension (200 mg/mL) formulations of MMF. The recommended dose for renal transplant patients is 1 gm of MMF twice a day (BID) and for cardiac transplant patients, it is 1.5 gm BID. The solid oral dose for renal and cardiac transplant patients is obtained by taking multiples of either 250 mg capsules or 500 mg tablets while the 1.5 gm of the suspension will be obtained by taking 7.5 mL of the suspension. It is therefore acceptable to use the suspension in situations where 1.5 gm dose is needed.

3) The pivotal bioequivalence studies were conducted with the capsule not the tablet formulation. The tablet has been demonstrated to be bioequivalent to the capsule; hence, it is acceptable to infer that the suspension would be bioequivalent to the tablet formulation.

RECOMMENDATION

The Bioequivalent Studies submitted to the Human Pharmacokinetics and Bioavailability Section of NDA 50,759 are acceptable and support a recommendation for approval.

/S/ 9/23/98

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Concurrence: /S/ 9/23/98

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APPEARS THIS WAY
ON ORIGINAL

CC: HFD-590
HFD-340
HFD-880
CDR

NDA 50,758 (original)
Division Files
/MO/JKorvick
/SMO/MCavalle-Coll
/PM/MDempsey
/Viswanathan
/TLDPEIII/FAjayi
/DPEIII/KKumi
/DPEIII Drug Files ✓
/Attn. B Murphy ✓

File:wpfiles/data/kumiwp/cellcept/susp/overall
draft 1: 9/14/98

APPEARS THIS WAY
ON ORIGINAL

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REVIEW

Background: The applicant submitted a new drug application (NDA) for Mycophenolate Mofetil (Cellcept, MMF) oral suspension intended to be an alternate dosage form for patients who solid oral dosage formulations (capsules and tablets) may be unsuitable. MMF is currently available commercially as 250 mg capsules, 500 mg tablets and as a 500 mg powder for reconstitution for intravenous infusion. MMF is approved (NDAs 50,722, 50,722SE1, 50,733, 50,758) for use in the prevention of acute allograft rejection following renal and cardiac transplantation. In the Human Pharmacology and Biopharmaceutics section of this application, one pivotal bioequivalence study (MYCS 2684), one pilot bioequivalence study (MYCS 2644) and a taste acceptability study (MYCS 2394) were submitted.

MMF is the morpholino-ethyl ester pro-drug for mycophenolic acid (MPA). MMF is hydrolyzed to MPA, which is a selective, noncompetitive and reversible inhibitor of inosine monophosphate, a critical enzyme in the *de novo* pathway for purine biosynthesis which blocks the proliferation of both T and B lymphocytes. MPA was demonstrated to be an effective immunosuppressive agent for the prevention of acute rejection in renal and cardiac allografts in a variety of species. From the original oral application (NDA 50,722), the mean absolute bioavailability after oral administration is reported to be 94%. MPA undergoes conversion to an inactive glucuronide (MPAG) which is eventually excreted in urine. MPAG is excreted in bile and is believed to be deglucuronidated in the colon and thereby undergoes enterohepatic recycling (as MPA). This finding was based on the observation of a secondary peak 6-12 hours post administration and a 40% reduction in the AUC of MPA when MMF was coadministered with cholestyramine. Orally administered MMF resulted in complete recovery of the administered dose (93% in the urine and 6% in feces). Most of an administered dose is excreted in the urine as MPAG; less than 1% is reported excreted in the urine as MPA. MMF is reported not to be detected in the plasma after oral administration. MPA and MPAG are extensively bound (97% for MPA and 82% for MPAG) to plasma proteins, mainly serum albumin. In renal transplant patients, it was observed that AUC and Cmax were approximately 50% lower in the immediate post transplant period (≤ 40 days) compared to stable renal transplant period (≥ 3 months) or in healthy patients.

Formulation: The oral suspension formulation used in the pivotal bioequivalence study is the proposed commercial one. The size of the lot manufactured is the same as the intended manufacturing size. The details of the formulation is provided in the table on the following page.

Dissolution: The following dissolution method and specification for Mycophenolate Mofetil (Cellcept) is recommended by the applicant:

Apparatus: USP Apparatus 2 (Paddle)
Speed:
Medium: 900 mL 0.1N HCL at 37° ± 0.5° C
Specification: Q

The dissolution method recommended is similar to the USP method for MMF capsule formulation.. Upon review of the clinical and stability lot data provided in section 6 of the application, the recommendation is acceptable. The dissolution data is provided in the Appendix.

1 page
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Confidential
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OVERVIEW OF PHARMACOKINETIC STUDIES

Study MYCS2684: A Two-Way Crossover Bioequivalence Study of Mycophenolate Mofetil Oral Suspension Formulation and Capsule Formulation in Healthy Subjects (Volume 13 page 1)

Introduction: Mycophenolate Mofetil (Cellcept, MMF) is approved for use following renal and cardiac organ transplantation. Currently, the dosage forms approved for this indication are capsules, tablets and an intravenous formulation. An oral suspension has been developed to provide a dosing form for patient populations who have difficulty swallowing capsules or tablets. The sponsor is seeking approval based on the ability to demonstrate the suspension is bioequivalent to the capsules with respect to MPA AUC and Cmax. This study is the pivotal bioequivalence study submitted for this application.

Objective: To evaluate an oral suspension formulation of Mycophenolate Mofetil (MMF) as compared with capsule formulation of MMF for bioequivalence, based on plasma AUC and Cmax values of MPA, in healthy subjects.

Design: This was a single-center, open-label, randomized, single-dose, two-period crossover pharmacokinetic study in 44 healthy adult subjects with a mean age and weight of 34.4 ± 10.3 years and 70.4 ± 13.9 kg, respectively. Forty-two patients were evaluable; two volunteers were withdrawn from the study for noncompliance. The study consisted of 2 periods with 2 formulations (either a suspension or capsule). The volunteers were randomized to receive either the suspension or capsule in period 1 and the other formulation during period 2. Each dose (1gm) was administered after an overnight fast and separated by a 7-day washout period. Blood samples for analysis of MPA and MPAG concentrations were taken at 0 (immediately prior to dosing), 20, 30, 40, 50, 60, 75 and 90 mins and at 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after dosing. The plasma samples were assayed for MPA and MPAG using a . The limit of quantitation for MPA and MPAG in plasma were 0.1 µg/mL and 4 µg/mL, respectively. MPAG values were converted to MPA equivalent units by multiplying by the ratio of the molecular weight of MPA to MPAG (0.594). The analytical method is acceptable. The test formulation was a 200 mg/mL suspension of MMF (Formulation # F61443-051, Lot #: 1501951); this is the to be marketed formulation. The reference formulation was the commercial 250 mg MMF capsule (Formulation # F61443-114 and Lot # 1179631).

Data Analysis: The computed pharmacokinetic parameters were examined using an ANOVA model with terms for sequence, subject within sequence, period and treatment.

Results: The mean plasma concentration time profiles for MPA and MPAG are provided in the figures on the following pages. The mean computed pharmacokinetic parameters for MPA and MPAG after administration of MMF capsules and suspensions are provided on the following pages; individual pharmacokinetic parameters are provided in the appendix.

Figure 1A Mean Plasma Concentrations of MPA versus Time

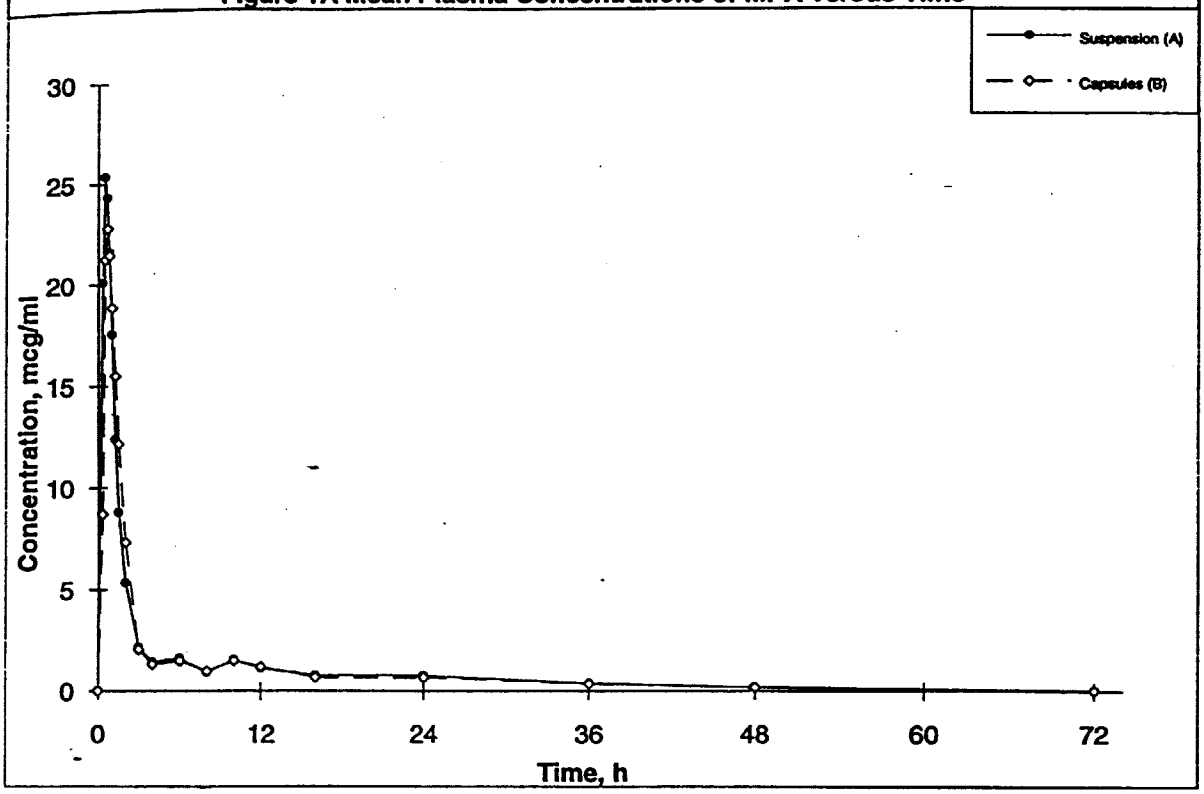
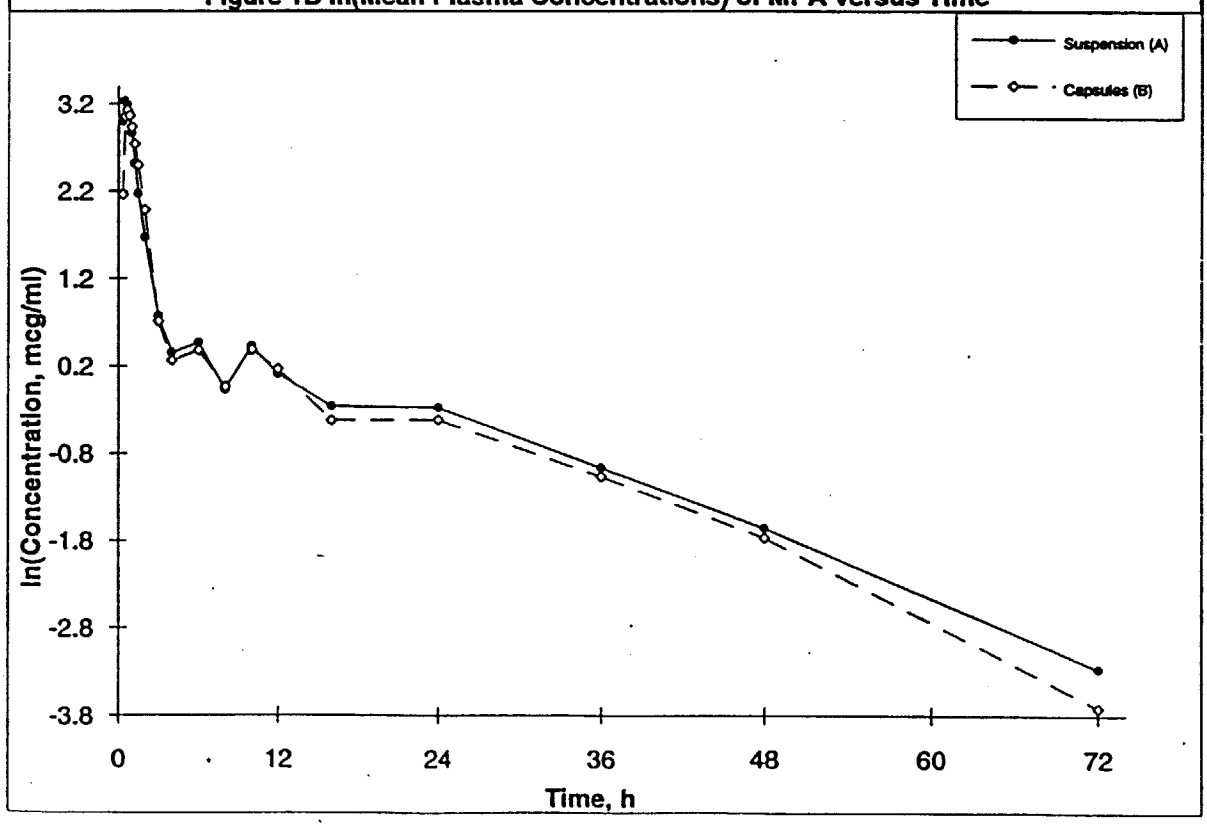


Figure 1B ln(Mean Plasma Concentrations) of MPA versus Time



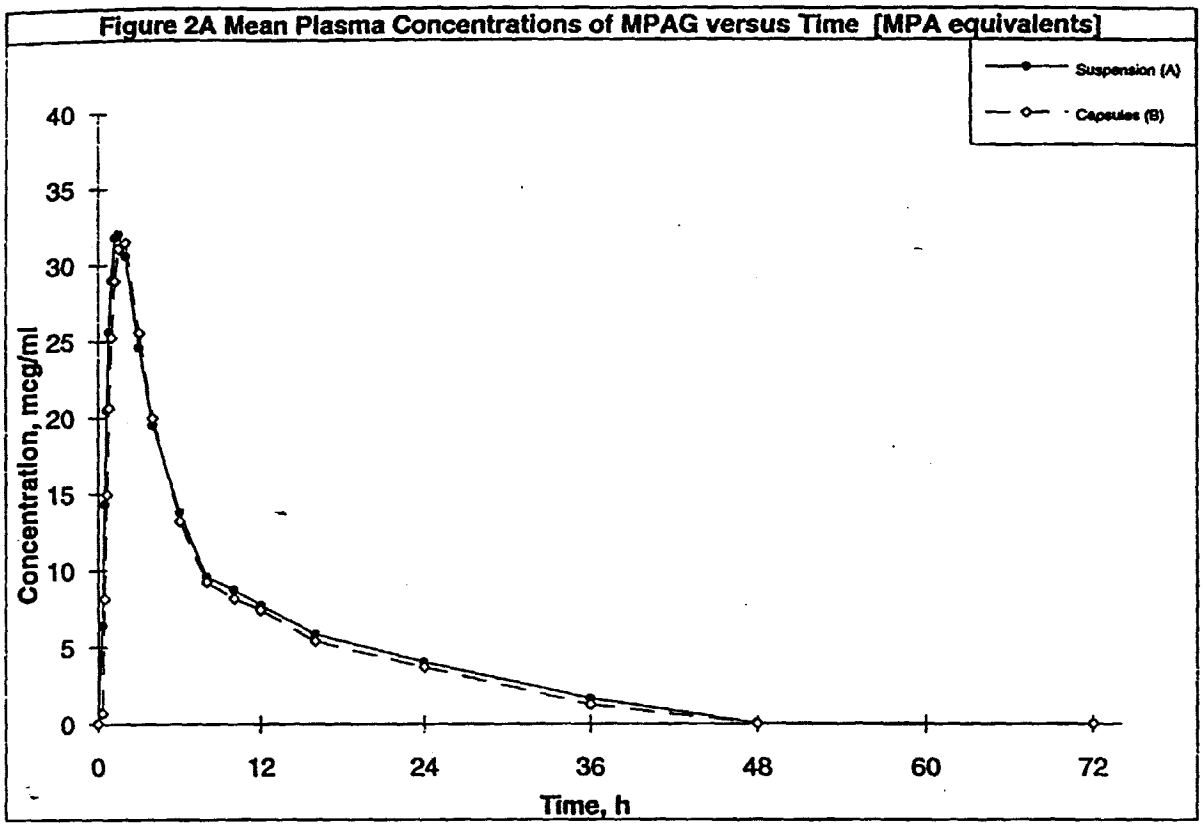


Figure 2A Mean Plasma Concentrations of MPAG versus Time [MPA equivalents]
Suspension (A)
Capsules (B)
Concentration, mcg/ml
0
5
10
15
20
25
30
35
40
0
12
24
36
48
60
72
Time, h

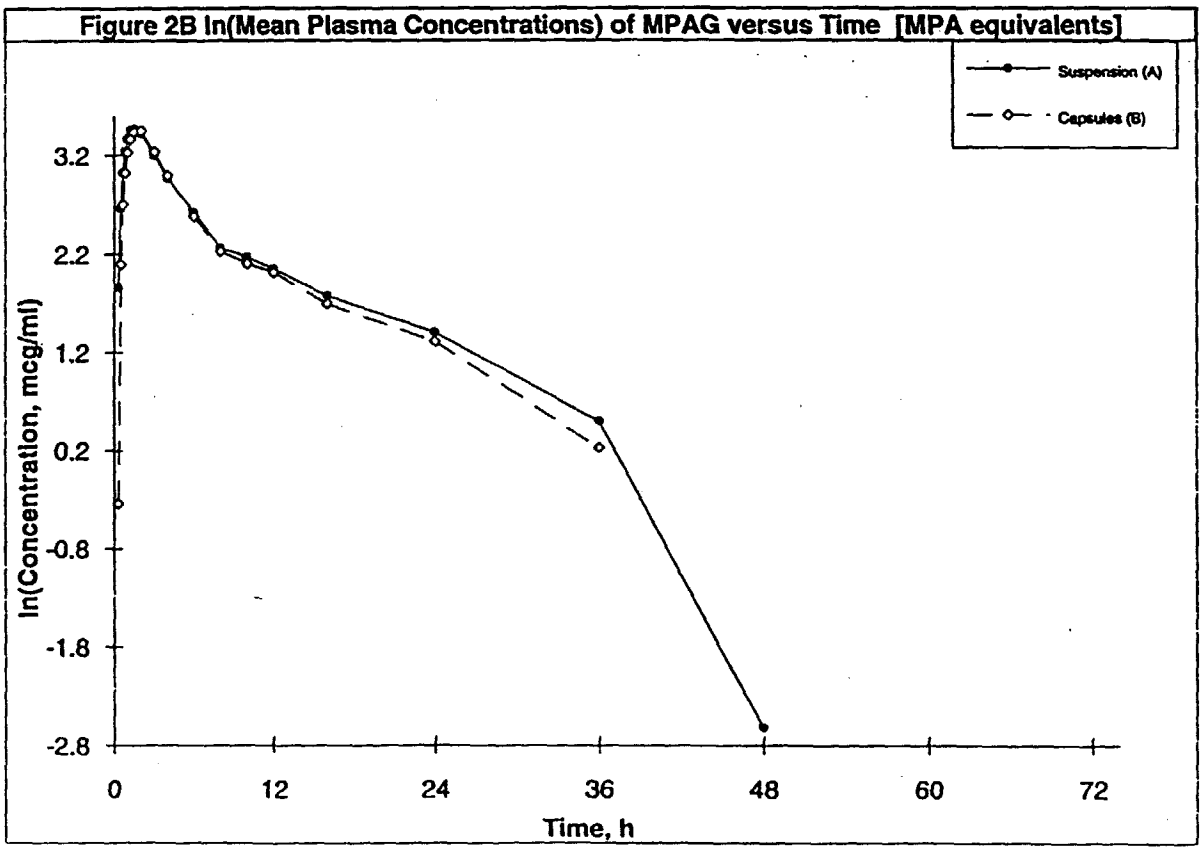


Figure 2B ln(Mean Plasma Concentrations) of MPAG versus Time [MPA equivalents]
Suspension (A)
Capsules (B)
ln(Concentration, mcg/ml)
-2.8
-1.8
-0.8
0.2
1.2
2.2
3.2
0
12
24
36
48
60
72
Time, h

Mean MPA Pharmacokinetic Parameters

Parameter	Treatment A (N=42)	Treatment B (N=42)
AUClast (μg*h/mL)	65.9 ± 16.6	62.6 ± 15.6
AUC(0-∞)(μg*h/mL)	70.5 ± 16.5	68.87 ± 17.6
Cmax (μg/mL)	28.4 ± 7.11	27.1 ± 9.37
T ½ (h)	16.5 ± 3.61	19.2 ± 20.7
Tmax	0.67 ± 0.43	0.83 ± 0.35

A = Mycophenolate Mofetil oral suspension 1 gm (5 mL of 200 mg/mL suspension)
B = Mycophenolate Mofetil oral capsules 1 gm (4 x 250 mg capsules)

Mean MPAG Pharmacokinetic Parameters

Parameter	Treatment A	Treatment B
AUClast (μg*h/mL)	278 ± 67.5	260 ± 67.4
AUC(0-∞)(μg*h/mL)	372 ± 107	335 ± 81.6
Cmax (μg/mL)	34.6 ± 7.90	33.9 ± 7.13
T ½ (h)	17.9 ± 11.6	16.5 ± 10.8
Tmax	1.53 ± 0.42	1.75 ± 0.48

A = Mycophenolate Mofetil oral suspension 1 gm (5 mL of 200 mg/mL suspension)
B = Mycophenolate Mofetil oral capsules 1 gm (4 x 250 mg capsules)

90% CI for MPA Parameters

Computed Parameter	Ratio (A/B)	90% CI	
		Lower Limit	Upper Limit
Ln AUClast	104.8%	102.0%	107.7%
Ln AUC(0-∞)	102.6%	97.9%	107.6%
Ln Cmax	106.3%	98.9%	114.3%

90% CI for MPAG Parameters

Computed Parameter	Ratio (A/B)	90% CI	
		Lower Limit	Upper Limit
Ln AUClast	107.8%	103.6%	112.2%
Ln AUC(0-∞)	107.6%	100.6%	115.0%
Ln Cmax	101.8%	96.9%	107.0%

The regulatory criteria for two formulations to be bioequivalent require that the 90% confidence interval (CI) for the log transformed Cmax and AUC(0-∞) be between 80% to 125%. The 90% CI calculation indicates Ln AUC(0-∞) and Ln Cmax for MPA and MPAG meet the regulatory criteria for bioequivalence. Therefore, 1 gm Mycophenolate Mofetil suspension is bioequivalent to 1 gm of the capsule formulation. The sponsor reported that no serious adverse events occurred in the study.

Conclusion: The oral Mycophenolate Mofetil suspension was demonstrated to be bioequivalent to the capsule formulation.

Study MYCS 2644: A Bioequivalence of Two Mycophenolate Mofetil Oral Suspension Formulations With Different Dissolution Rates and a Capsule Formulation in Healthy Subjects (Vol. 16 page 1)

Background: This was a pilot study to evaluate whether two Mycophenolate Mofetil suspensions were bioequivalent to the commercial capsule formulation. The results of this study was intended to help select a formulation for further commercial development.

Objectives: The primary objective was to demonstrate bioequivalence, based on plasma AUC values of MPA, of two MMF oral suspension formulations and the MMF capsule formulation in healthy subjects.

Design: This was a single-center, open-label, randomized, single-dose, three-period crossover pharmacokinetic study in 24 healthy men; twenty-three volunteers provided data for the pharmacokinetic evaluation. The mean age and weight of the volunteers were 32.7 years (range 22 - 54) and 82.3 kg (range, 64.9 - 103), respectively. The study was balanced, complete block design. In each dosing period, each subject were administered one of three treatments: Treatment A consisted of four 250 mg capsules of MMF (Formulation No. F61443-052, Lot No. 61443-000-11886); Treatment B consisted of a suspension of MMF (200 mg/mL) of one formulation (Formulation # F61443-103, Lot No. 61443-000-1369021) and Treatment C consisted of a suspension of MMF (200 mg/mL) of a (Formulation No. F61443-108 Lot No. 61443-000-1369041). Each dose was taken orally and contained 1 gm of MMF. Each dose was separated by a 7 day washout period. Blood samples were collected at 0 (pre-dose), 20, 30, 40, 50, 60,75, and 90 minutes and 2,3,4,6,8,10,12,16,24,36, and 48 hours.

Analytical Method: The plasma samples were analyzed using a . The quantitation limit of the assay for MPA and MPAG were 0.1 μg/mL and 4 μg/mL, respectively. For all calculations, the MPAG concentration was converted to MPA equivalents by multiplying the value by the ratio of the molecular weights of MPA and MPAG (320.35/539.42 = 0.594). The quantitation limit of the assay for MPAG expressed in MPA equivalents is

Data Analysis: The pharmacokinetic parameters were examined using an analysis of variance (ANOVA) model for a three-period crossover study; the model included terms for subject, subjects(sequence), period and treatment. Two MMF formulations were considered to be bioequivalent with respect to a given parameter for an analyte if the 90% confidence interval (CI) for the ratio of the parameter values fell entirely within the 80% to 125% range for log-transformed parameters.

Results: The mean plasma concentration time profile are provided in the appendix. The mean ± SD values for MPA and MPAG are provided in the following tables

Pharmacokinetic Parameters for MPA

Computed Parameter	Treatment A (capsules) (N=23)	Treatment B (Fast Dissolving Susp.) (N=23)	Treatment C (Slow-Dissolving Susp) (N=23)
Cmax (μg/mL)	19.8 ± 5.65	21.6 ± 6.30	20.0 ±4.85
Tmax (hr)	0.80 ± 0.39	0.54 ± 0.27	0.53 ± 21.7
Half-life (h)	28.0 ± 22.7	28.9± 32.2	28.0 ± 17.9
AUClast (μg*h/mL)	42.9 ± 7.29	42.8 ± 9.12	41.2 ± 7.61
AUC∞ (μg*h/mL)	53.9 ± 18.0	58.1 ± 39.6	53.6 ± 21.7

Pharmacokinetic Parameters for MPAG

Computed Parameter	Treatment A (capsules) (N=23)	Treatment B (Fast Dissolving Susp) (N=23)	Treatment C (Slow-Dissolving Susp) (N=23)
Cmax (μg/mL)	24.8 ± 5.69	24.6 ± 5.31	24.0 ±4.18
Tmax (hr)	1.58 ± 1.61	1.21 ± 0.32	1.27 ±0.27
Half-life (h)	19.6 ± 9.6	17.0± 9.85	19.4 ± 10.5
AUClast (μg*h/mL)	209 ± 50.4	196 ± 44.3	194 ± 44.5
AUC∞ (μg*h/mL)	295 ± 65.5	272 ± 56.8	284 ± 59.9

The ratio of the parameters and 90% confidence intervals (CI) for the log-transformed Cmax and AUC of MPA are provided in the following tables

90% CI for MPA Parameters

Parameter	Ratio B/A	Lower Limit	Upper Limit
Ln AUClast	99.2%	94.3%	104.3%
Ln AUC∞	101.2%	94.3%	108.7%
Cmax	109.1%	98.3%	121.0%

A = Mycophenolate Mofetil 250 mg x 4 capsules, B = Mycophenolate Mofetil 200 mg/mL suspension with similar in vitro dissolution to the capsule

90% CI for MPA Parameters

Parameter	Ratio C/A	Lower Limit	Upper Limit
Ln AUClast	96.0%	91.3%	101%
Ln AUC∞	99.9%	92.9%	107.4%
Cmax	102.4%	92.3%	113.6%

A= Mycophenolate Mofetil 250 mg X 4 capsules, C = Mycophenolate Mofetil 200 mg/mL suspension with slower in vitro dissolution than the capsule

90% CI for MPA Parameters

Parameter	Ratio C/B	Lower Limit	Upper Limit
Ln AUClast	96.8%	92%	101.8%
Ln AUC∞	98.7%	91.8%	106.1%
Cmax	93.9%	84.6%	104.2%

B= Mycophenolate Mofetil 200 mg/mL suspension with similar in vitro dissolution to the capsule
C= Mycophenolate Mofetil 200 mg/mL suspension with slower in vitro dissolution than the capsule

The 90% CI for the comparison of the fast dissolving suspension (Treatment B) to the capsule (Treatment A) with respect to Ln AUC, Ln Cmax met the regulatory requirement for bioequivalence; therefore, the two formulations are bioequivalent. Similarly, the slow dissolving capsules (Treatment C) was demonstrated to be bioequivalent to the capsules. Comparison of the two suspension formulations using Treatment B as the reference, demonstrated the suspension formulations were also bioequivalent. 90% CI for Ln AUC, Ln Cmax for MPAG (Tables in Appendix) also demonstrated that both suspensions were bioequivalent to the capsules and to each other with respect to MPAG.
The sponsor reported that no serious adverse events occurred in the study and none of the patients withdrew from the study due to adverse events.

Conclusion: Both suspensions were demonstrated to be bioequivalent to the commercial capsules in accordance to the current regulatory standards. Hence, the two suspensions are bioequivalent to the commercial capsule formulation. The sponsor elected to further develop the slow dissolving suspension because according to them it provided a better match with the pharmacokinetic parameters obtained after administration of the capsule.

A graphical representation of the 90% CI for the bioequivalence studies is provided in the figures on the following two pages.

Study MYCS 2394: Comparative Acceptability Study of Four Formulations of Mycophenolate Mofetil Oral Suspension in Healthy Adults (Volume 18 page 1)

Objectives: The primary objective of this study was to evaluate the degree of acceptability (for further clinical development) of each of four flavor formulations of Mycophenolate Mofetil (MMF) oral suspension with respect to the perceived degree of overall like/dislike of each formulation. The secondary objective was to ascertain a relative comparison of the four flavor formulations for overall acceptability with respect to appearance, aroma, flavor, texture and after taste.

Design: This was a single center, open-label, randomized study of incomplete block design, involving four flavor formulations and 12 serving rotations (sequences). Twenty four subjects (mean ± SD age and weight were 35.1 ± 9.7 years and 72.4 ± 16.3 kg, respectively) enrolled in the study, but 20 subjects completed the evaluations per protocol. Each subject was to evaluate 3 of the 4 four flavor formulations; however, the 4 subjects that were withdrawn from the study evaluated only 2 dosing flavors and were included in the analysis. The 4 different MMF formulations were identical except for their color, aroma, and flavor. The four flavors of MMF oral suspension evaluated were: Orange (Formulation No. F61443-088), Mixed Fruit (Formulation # F61443-089), Mint (Formulation # F61443-090) and Berry (Formulation No. F61443-091). Each volunteer received 1 gm of MMF suspension orally. All the doses were administered at least 7 days apart. The Berry formulation was evaluated by 16 subjects, Mixed fruits and orange formulations by 17 subjects and the Mint Formulation by 18 subjects.

Each formulation was evaluated with respect to its appearance and aroma before administration; flavor and texture during and immediately after administration; and flavor and after taste 4, 7, and 10 minutes after administration. Each of the parameters was evaluated on unstructured visual analog scale from dislike extremely to like extremely. The acceptability of each formulation was evaluated on a five-point categorical scale (unacceptable, slightly acceptable, moderately acceptable, very acceptable, extremely acceptable).

Statistical Analysis: The volunteer responses were analyzed using an analysis of variance (ANOVA) model for a balanced incomplete block design; the model included terms for sequence, subject, period, period by formulation and formulation. Statistical testing was done at the 0.05 level of significance.

Results: The following are the results as reported by the applicant. The subjects order of preference with respect to each evaluated parameter is provided below:

Appearance	Mixed Fruit > Orange > Berry > Mint
Aroma	Mixed Fruit > Orange > Berry > Mint
Flavor	Mixed Fruit > Orange > Berry > Mint
Texture	Mixed Fruit = Orange > Berry > Mint
4-min Aftertaste	Orange > Mixed Fruit > Berry > Mint
7-min Aftertaste	Orange > Mixed Fruit > Berry > Mint
10-min Aftertaste	Orange > Mixed Fruit > Berry > Mint
Overall Like/Dislike	Mixed Fruit > Orange > Berry > Mint
Acceptability	Orange > Mixed Fruit > Berry > Mint

The subjects rated Mixed Fruit and Orange first or second for all parameters evaluated. They rated Mint lower than the other three formulations and Berry third. From the statistical analysis, significant formulation effects were found for appearance, aroma, and overall like/dislike. Orange flavor did not differ statistically from Mixed fruit or Berry, Orange and Mixed Fruit differed significantly from Mint with respect to appearance, aroma, and 10-minute aftertaste, overall like /dislike and acceptance and Mixed Fruit differed significantly from Berry only with respect to appearance. The applicant reported no serious adverse event. However, four volunteers were withdrawn from the study due to adverse events. This was brought to the attention of the reviewing medical officer.

Conclusions: The applicant concluded that except for the Mint formulation, all the other flavors were acceptable. The commercial formulation contains the mixed fruit flavor. This study did not evaluate acceptance of the flavors in children who may be the likely population to use this formulation.