Tabular Listing of all Clinical Studies

Protocol Code	Title of Study
2006-1184	A Single-Dose, Comparative Bioavailability Study of Two Formulations of Mycophenolate mofetil 500mg Film-coated tablets under fasting conditions.
2006-1267	A Single-Dose, Comparative Bioavailability Study of Two Formulations of Mycophenolate mofetil 500mg Film-coated tablets under fed conditions.
2007-1335	A Single-Dose, Comparative Bioavailability Study of Two Formulations of Mycophenolate mofetil 500mg Film-coated tablets under fed conditions.

1.0 TITLE PAGE

Study Title:	A Single-Dose, Comparative Bioavailability Study of Two Formulations of Mycophenolate Mofetil 500 mg Tablets Under Fasting Conditions
Test Drugs:	Mycophenolate Mofetil 500 mg Tablets; Batch No.: K-36659; (Teva Pharmacuetical Industries Ltd.) CellCept® 500 mg Tablets; Lot No.: M1284; (Roche Registration Limited, UK)
Indication Studied:	N/A
Description:	An evaluation of the comparative bioavailability between Mycophenolate Mofetil 500 mg Tablets (Teva Pharmacuetical Industries Ltd.) and CellCept® 500 mg Tablets (Roche Registration Limited, UK) after a single-dose in healthy subjects under fasting conditions
Name of Sponsor:	Teva Pharmaceutical Industries Ltd. P.O. Box 353, Hashikma Street, Industrial Zone Kfar Saba, Israel 44102 Phone: 972-9-7648260 Fax: 972-9-7648636
Protocol No.:	2006-1184 Version 2
Development Phase of Study:	Bioequivalence
Study Initiation:	May 11, 2006
Study Completion:	July 17, 2006
Principal Investigator:	Xueyu (Eric) Chen, M.D., Ph.D., FRCP(C) Pharma Medica Research Inc.
Sponsor Signatory:	Dr. Zeev Elkoshi Biopharmaceutics Manager Teva Pharmaceutical Industries Ltd.
GCP Compliance:	PMRI study number 2006-1184 was performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.
Date of Report:	September, 2006

PHARMA MEDICA
RESEARCH INC.

A Single-Dose, Comparative Bioavailability Study of Two Formulations of Mycophenolate Mofetil 500 mg Tablets Under Fasting Conditions

Study Report
Protocol No.: 2006-1184 Version 2
PMRI Study No.: 2006-1184

Sponsor:
Teva Pharmaceutical Industries Ltd.
P.O. Box 353, Hashikma Street, Industrial Zone
Kfar Saba, Israel
44102

Principal Investigator:	Xueyu (Eric) Chen, M.D., Ph.D., FRCP(C)	Sep 21, 2006 Date (mmm-dd-yyyy)
Study Director:	Latifa Yamlahi, M.Sc.	Sep 22, 2006 Date (mmm-dd-yyyy)
Vice President Scientific Affairs:	for Radu Pop, Ph.D.	SEPT 21, 2006 Date (mmm-dd-yyyy)

HEAD OFFICE: 966 Pantera Dr., Unit 31, Mississauga, Ontario L4W 2S1 Telephone 905-624-9115 Fax 905-624-4433
PHASE I CLINIC: 1410 Warden Ave., Scarborough, Ontario M1R 5A3 Telephone 416-759-4111 Fax 416-759-2869
Internet: www.pharmamedica.com

2.0 SYNOPSIS

Name of Sponsor/Company: Teva Pharmaceutical Industries Ltd.	Volume:	(For National Authority Use only)
Name of Finished Product: Mycophenolate Mofetil 500 mg Tablets		
Name of Active Ingredient: Mycophenolate Mofetil	Page:	

Title of Study:
A Single-Dose, Comparative Bioavailability Study of Two Formulations of Mycophenolate Mofetil 500 mg Tablets Under Fasting Conditions

Investigators:
Xueyu (Eric) Chen, M.D., Ph.D., FRCP(C)
Andrea S. Gershon, M.D., FRCP(C)
Tomislav Buconjic, M.D., M.Sc., CCFP
Carol Townsley, M.D.
Robert C. Wu, M.D., FRCP (C), M.Sc

Study Centre(s):

Clinical Facility:	Pharma Medica Research Inc. 1410 Warden Avenue Toronto, Ontario, Canada, M1R 5A3
Clinical Laboratory:	Gamma-Dynacare Medical Laboratories 115 Midair Court Brampton, Ontario, Canada, L6T 5M3
Analytical, Pharmacokinetics, Statistical and Report Issuing Facility:	Pharma Medica Research Inc. 966 Pantera Drive, Unit 31 Mississauga, Ontario, Canada, L4W 2S1

Study Period: **Group I** **Period 1:** May 11, 2006 **Period 2:** May 18, 2006 **Group II** **Period 1:** July 08, 2006 **Period 2:** July 15, 2006	**Phase of Development:** Bioequivalence

Objective:
The objective of this study is to evaluate the comparative bioavailability between Mycophenolate Mofetil 500 mg Tablets (Teva Pharmacuetical Industries Ltd.) and CellCept® 500 mg Tablets (Roche Registration Limited, UK) after a single-dose in healthy subjects under fasting conditions.

Name of Sponsor/Company: Teva Pharmaceutical Industries Ltd.	Volume:	(For National Authority Use only)
Name of Finished Product: Mycophenolate Mofetil 500 mg Tablets		
Name of Active Ingredient: Mycophenolate Mofetil	Page:	

Methodology:

- This is an open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study designed to evaluate the comparative bioavailability of two formulations of Mycophenolate Mofetil 500 mg Tablets administered to healthy male and post-menopausal or surgically sterile female subjects under fasting conditions.
- Subjects were divided into two groups of approximately 40 subjects each. In each group subjects were randomly assigned to one of the two dosing sequences AB or BA under fasting conditions.
- Concentrations of Mycophenolic Acid were measured from the plasma samples collected over a 48-hour interval after dosing in each period.
- Pharmacokinetic parameters: AUCt, AUCinf, Cmax, Tmax, Kel and Thalf were estimated based on Mycophenolic Acid plasma levels for each subject included in the statistical analysis.

Number of subjects (planned and analyzed):

Group I

- Thirty four (34) subjects were dosed in Period 1.
- Thirty two (32) subjects completed Group I of the study.

Group II

- Forty six (46) subjects were dosed in Period 1.
- Forty five (45) subjects completed Group II of the study.

A total of 77 subjects completed the entire study.

Name of Sponsor/Company: Teva Pharmaceutical Industries Ltd.	Volume:	(For National Authority Use only)
Name of Finished Product: Mycophenolate Mofetil 500 mg Tablets		
Name of Active Ingredient: Mycophenolate Mofetil	Page:	

Diagnosis and main criteria for inclusion:
Subjects met all of the following inclusion criteria within 21 days prior to first drug administration.

1) • Healthy, non-smoking male subjects 18 to 55 years of age (inclusive).
   • Healthy, non-smoking post-menopausal or surgically sterile females 18 to 55 years of age
2) BMI $\geq$ 19 and $\leq$ 30.
3) Negative for:
   • HIV.
   • Hepatitis B surface antigen and Hepatitis C antibody.
   • Urine drugs of abuse test (marijuana, amphetamines, barbiturates, cocaine, opiates, benzodiazepines and methadone).
   • Urine cotinine test
   • Serum HCG consistent with pregnancy (females only).
4) No significant diseases or clinically significant findings in a physical examination.
5) No clinically significant abnormal laboratory values.
6) No clinically significant findings in the 12-lead electrocardiogram (ECG).
7) No clinically significant findings from the vital signs measurement.
8) Be informed of the nature of the study and given written consent prior to receiving any study procedure.
9) Females who participate in this study must be unable to have children:
   • Post-menopausal for at least 1 year – no menstrual cycle for 12 months and LH and FSH levels judged by a physician to be consistent with post-menopausal status. OR
   • Proof of surgical sterility (full hysterectomy only).
10) Females who participate in this study are not pregnant and/or non-lactating.

Test Product (A): Mycophenolate Mofetil 500 mg Tablets (Teva Pharmacuetical Industries Ltd.);
Batch No.: K-36659; Manufacturing Date: MAR 27, 2006
Dose: 500 mg
Mode of Administration: Oral under fasting conditions

1 006

Name of Sponsor/Company: Teva Pharmaceutical Industries Ltd.	Volume:	(For National Authority Use only)
Name of Finished Product: Mycophenolate Mofetil 500 mg Tablets		
Name of Active Ingredient: Mycophenolate Mofetil	Page:	

Reference Product (B): CellCept® 500 mg Tablets (Roche Registration Limited, UK);
Lot No.: M1284; Expiration Date: 10 2007
Dose: 500 mg
Mode of Administration: Oral under fasting conditions.

Duration of treatment:
Single-Dose treatment

Criteria for Evaluation:
Efficacy:
Based on the log-transformed parameters, the following criteria were used to evaluate the bioequivalence between the test and reference products:
The 90% confidence intervals of the relative mean AUCs and C_{max} of the test to reference products should be between 80% and 125%.[1]

Safety:
Safety was assessed based on vital signs measurements and on the severity and causality of adverse events experienced by subjects who underwent drug administration.

Statistical Methods:
Descriptive statistics were calculated by treatments for the estimated pharmacokinetic parameters. Analysis of Variance (ANOVA) was also carried out on the natural log-transformed AUCt, AUCinf, and Cmax data, and on the untransformed Kel, and Thalf data. Values for the Tmax parameter were analyzed by a non-parametric approach. The following results are included:

- Geometric and arithmetic means of AUCs and Cmax for the test product and reference product.
- Ratios of geometric means of the test product versus the reference product for AUCs and Cmax.
- 90% confidence intervals of the above ratios.

PHARMA MEDICA RESEARCH INC.
Study Report, Mycophenolate Mofetil 500 mg Tablets – Single-Dose, Fasting
Protocol No.: 2006-1184 Version 2
PMRI Study No.: 2006-1184

Name of Sponsor/Company: Teva Pharmaceutical Industries Ltd.	Volume:	(For National Authority Use only)
Name of Finished Product: Mycophenolate Mofetil 500 mg Tablets		
Name of Active Ingredient: Mycophenolate Mofetil	Page:	

Summary-Conclusions:
Efficacy Results:

[redacted]

Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
	Treatment A	Treatment B			
AUCt (µg *h/mL)	25.3659 26.2858 (28)	25.8229 26.8275 (29)	98.23	95.47 - 101.7	10
AUCinf (µg *h/mL)	27.5778 28.2125 (29)	28.0102 29.1255 (29)	98.46	95.59 - 101.41	10
Cmax (µg/mL)	11.6002 13.3396 (48)	11.6831 13.2049 (44)	99.29	87.40 - 112.80	49
Tmax[a] (h)	0.81 (77)	0.75 (52)	-	-	-
Kel[a] (1/h)	0.0592 (32)	0.0589 (36)	-	-	-
Thalf[a] (h)	13.30 (44)	13.49 (41)	-	-	-

[a]Presented as arithmetic mean (CV%) only.

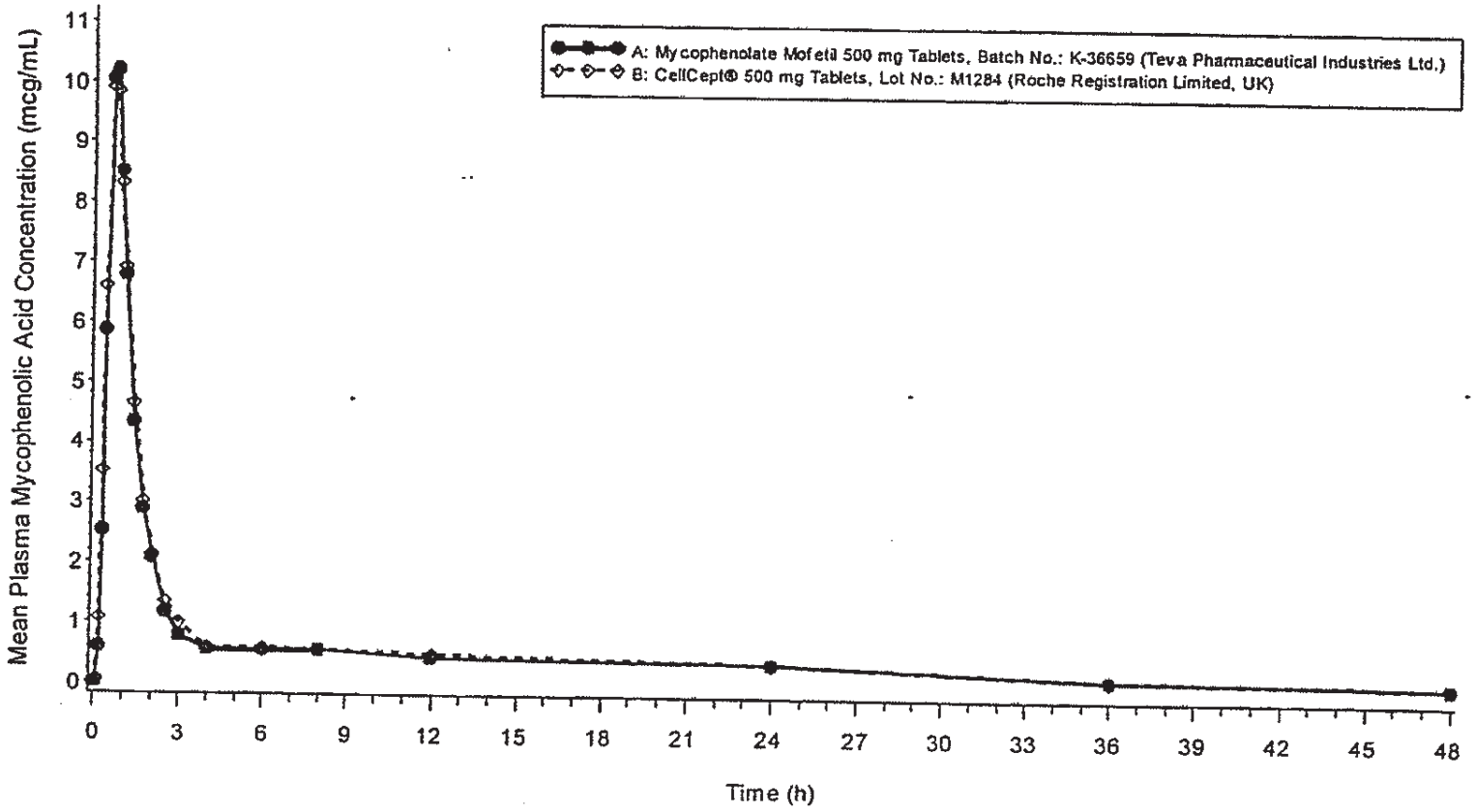
Safety Results:
No serious AEs were reported during the conduct of this study.
None of the AEs had a significant impact on the safety of the subjects or on the integrity of the study results.

Conclusions:
The 90% confidence intervals of the relative mean AUCt, AUCinf and Cmax of the test to reference product for measured data are within the 80-125% range.

Therefore, Mycophenolate Mofetil 500 mg Tablets (Teva Pharmacuetical Industries Ltd.) exhibited equivalent rate and extent of absorption to CellCept® 500 mg Tablets (Roche Registration Limited, UK) in healthy subjects after an oral single-dose, under fasting conditions. These are bioequivalent drug products.

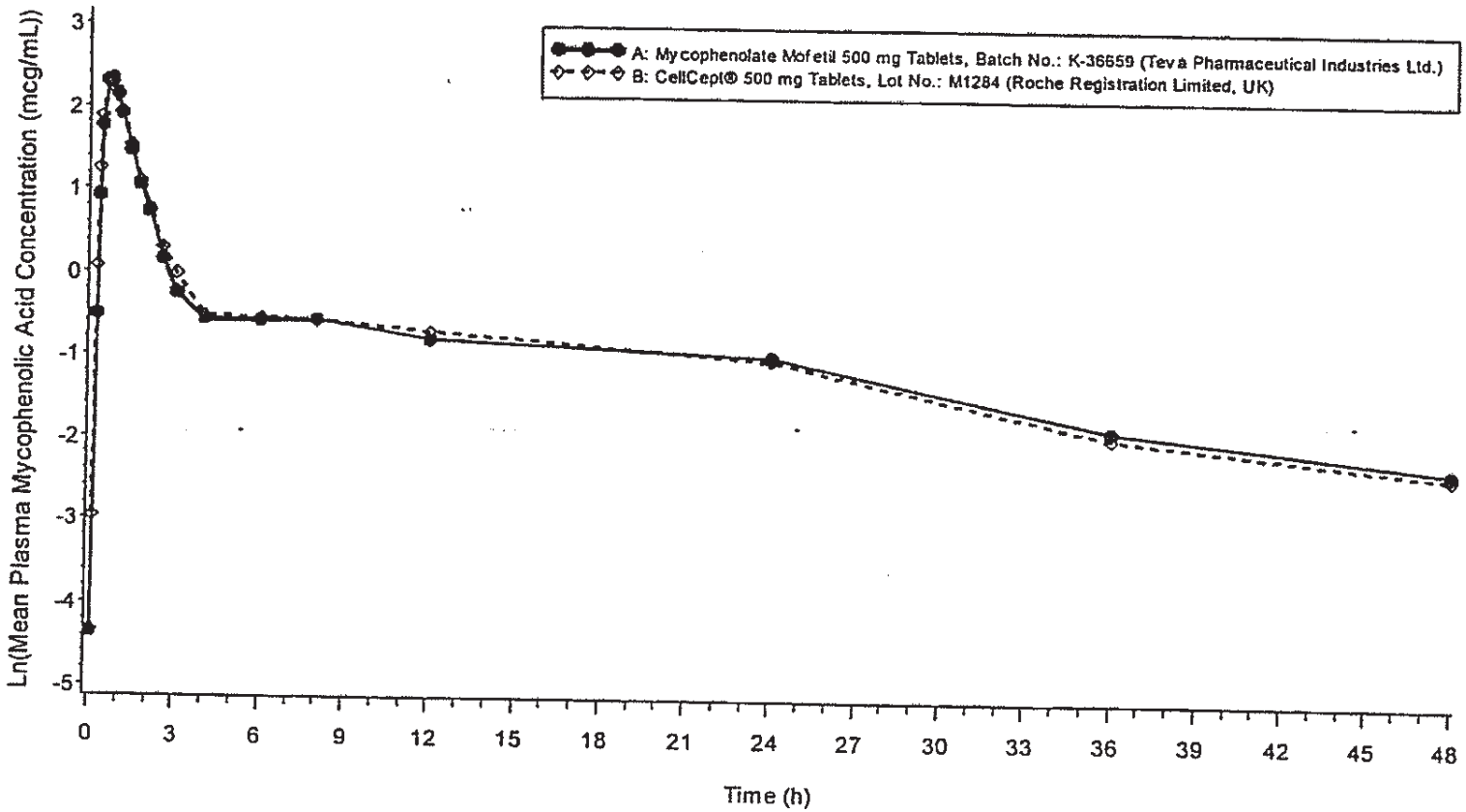
Date of Report: September, 2006

STUDY No.: 2006-1184
MEAN PLASMA MYCOPHENOLIC ACID CONCENTRATION VERSUS TIME CURVES
N=77



1 008

STUDY No.: 2006-1184
LOG MEAN PLASMA MYCOPHENOLIC ACID CONCENTRATION VERSUS TIME CURVES
N=77



1 009

3.0 TABLE OF CONTENTS

4.0 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Ab:	Antibody
AE:	Adverse Event
BP:	Blood Pressure
CI:	Confidence Interval
CRF:	Case Report Form
Ct:	The measured analyte concentration at the time of the last measurable plasma concentration
CV:	Coefficient of Variation
ECG:	Electrocardiogram
ERB:	Ethics Review Board
EMEA:	European Agency for the Evaluation of Medicinal Products (Evaluation of Medicines for Human Use)
GLM:	General Linear Model
ICF:	Informed Consent Form
ICH:	International Conference on Harmonization
LOQ:	Limit of Quantitation
LQCT:	Last Quantifiable Concentration Time
LSM:	Least Squares Mean
N/A:	Not Applicable, Not Available
NCS:	Not Clinically Significant
PC:	Post Clinical
PI:	Principal Investigator
PMRI:	Pharma Medica Research Inc.
R:	Correlation Coefficient
SC:	Screening Clinical
SD or STD:	Standard Deviation
SEQ:	Sequence
TLIN:	Start Time Point for Linear Regression
TRT:	Treatment
VCF:	Volunteer Consent Form
WNL:	Within Normal Limits

5.0 ETHICS

5.1 Ethics Review Board (ERB)

On April 13, 2006 the Ethics Review Board (ERB), Optimum Clinical Research Inc., approved:

- Protocol No.: 2006-1184 Version 2 Date: April 04, 2006
- Informed Consent Form (ICF), Version Date: April 13, 2006.

At the request of the Sponsor, the sample size was changed from 60 subjects to 80 subjects, resulting in changes to the protocol and ICF.

On April 20, 2006 the Ethics Review Board (ERB), Optimum Clinical Research Inc., approved:

- Protocol No.: 2006-1184 Version 2 Date: April 18, 2006
- Informed Consent Form (ICF), Version Date: April 18, 2006.

The subject fee was subsequently changed for this study creating Amendment No.1 which was approved by the ERB on May 04, 2006.

5.2 Ethical Conduct Of The Study

This study was conducted in accordance with the current EMEA guidance documents[1], Good Clinical Practice, as established by the International Conference on Harmonization (ICH), the basic principles defined in the U.S. Code of Federal Regulations (21 CFR Part 312), and the principles enunciated in the World Medical Association Declaration of Helsinki (Edinburgh, Scotland, 2000).

A description of the clinical procedures followed in this study may be found in the protocol provided in section *16.1.1 Protocol and Consent Forms.*

5.3 Subject Information And Consent

A Volunteer Consent Form (VCF) for pre-study testing was approved by the ERB on December 22, 2005.

All subjects signed a VCF for pre-study testing prior to any medical procedures.

All subjects signed an ICF prior to study initiation.

A sample of the protocol, the ICF and the VCF are provided in section *16.1.1 Protocol and Consent Forms.* The ERB approval documentation

and the list of ERB members in attendance at the approval meetings are provided in section *16.1.3 Ethics Review Board.*

6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Principal Investigator:	Xueyu (Eric) Chen, M.D., Ph.D., FRCP(C)
Sub-Investigators:	Tomislav Buconjic, M.D., M.Sc., CCFP
	Andrea S. Gershon, M.D., FRCP(C)
	Carol Townsley, M.D.
	Robert C. Wu, M.D., FRCP (C), M.Sc.
Study Director:	Latifa Yamlahi, M.Sc.
Assistant Study Director:	Robert Lepage, M.Sc., C.C.R.P.
Study Coordinator:	Marianna Screnci, B.Sc.
Vice President Laboratory Operations:	Mohammed Bouhajib, M.Sc.
Vice President Scientific Affairs:	Radu Pop, Ph.D.
Pharmacokinetics/Statistics:	Robert Lepage, M.Sc., C.C.R.P.
Report Writer:	Celine D'Souza, Ph.D.
Ethics Review Board:	Optimum Clinical Research Inc. 231 King Street East Oshawa, Ontario, Canada L1H 1C5 Tel: 905-723-4694; Fax: 905-723-7590
Clinical Facility:	Pharma Medica Research Inc. 1410 Warden Avenue Toronto, Ontario, Canada M1R 5A3 Tel: 416-759-4111; Fax: 416-759-2869
Clinical Laboratory:	Gamma-Dynacare Medical Laboratories 115 Midair Court Brampton, Ontario, Canada L6T 5M3 Tel: 905-790-3000; Fax: 905-790-0473
Analytical, Pharmacokinetics, Statistical, and Report Issuing Facility:	Pharma Medica Research Inc. 966 Pantera Drive, Unit 31 Mississauga, Ontario, Canada L4W 2S1 Tel: 905-624-9115; Fax: 905-624-4433

Refer to section *16.1.4 List and Description of Investigators* for documents related to investigators (e.g. Investigator Statements, CVs), and section *16.1.5 Signature Pages* for staff signature pages.

7.0 INTRODUCTION

Mycophenolate mofetil is an immunosuppressive agent which is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. The usual recommended dose ranges between 1 g and 1.5 g given twice daily (total daily dose of 2 g to 3 g).

Mycophenolate mofetil is rapidly absorbed and hydrolysed to form mycophenolic acid (MPA) which is the active metabolite. MPA is a potent, selective, uncompetitive and reversible inhibitor of ionisine monophosphate dehydrogenase (IMPDH) and, therefore, inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA.

MPA has potent cytostatic effects on lymphocytes and also suppresses antibody formation by B-lymphocytes. MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in the intercellular adhesion to endothelial cells and may inhibit recruitment of leukocytes into sites of inflammation and graft rejection.

The mean absolute bioavailability of mycophenolate mofetil is 94%. When orally administered to healthy volunteers, peak plasma concentrations for MPA were observed approximately 1 hour post-dose (T_{max}). Secondary peaks in the plasma MPA concentration-time profile are usually observed 6 to 12 hours following administration.

Food had no effect on the extent of absorption of mycophenolate mofetil (based on MPA AUC) when administered at does of 1.5 g twice daily in renal transplant patients. The peak plasma concentration (C_{max}) of MPA is decreased by 40% in the presence of food.

Following oral administration, mycophenolate mofetil undergoes rapid and complete metabolism to MPA. The metabolism of MPA occurs presystemically: it is metabolized mainly by glucuronyl transferase to form its phenolic glucuronide, MPAG, which is not pharmacologically active. *In vivo*, MPAG is converted to MPA via enterohepatic recirculation. At clinically relevant concentrations, MPA is 97% bound to plasma albumin.

The mean apparent half-life of MPA is approximately 18 hours (±7 hours). Negligible amounts of the initial dose (less than 1%) are excreted as MPA in the urine, while 87% of the dose is excreted as MPAG. Ninety-three percent (93%) of a radiolabeled dose was recovered in the urine and 6% was recovered in the feces.[2,3]

8.0 STUDY OBJECTIVES

The objective of this study is to evaluate the comparative bioavailability between Mycophenolate Mofetil 500 mg Tablets (Teva Pharmacuetical Industries Ltd.) and CellCept® 500 mg Tablets (Roche Registration Limited, UK) after a single-dose in healthy subjects under fasting conditions.

9.0 INVESTIGATIONAL PLAN

9.1 Overall Study Design And Plan – Description

This is an open-label, single-dose, two-period, two-sequence, two-treatment, comparative bioavailability study. The two products were studied using a randomized crossover design with 77 healthy, non-smoking, male and post-menopausal or surgically sterile female subjects. The test and reference formulations were administered as a single 500 mg oral dose under fasting conditions.

The study was performed in two phases, with approximately 40 subjects being dosed in each phase. The decision to continue the study with the second phase was taken based on the results from the first phase.

Under no circumstances will results of the first phase only, be submitted.

9.2 Discussion Of Study Design

This bioequivalence study involved a single 500 mg dose of Mycophenolate Mofetil 500 mg Tablets (Teva Pharmacuetical Industries Ltd.) and CellCept® 500 mg Tablets (Roche Registration Limited, UK). The study was performed under fasting conditions.

According to the plan defined in the protocol, subjects were dosed in two groups of approximately 40 subjects each. Based on the favourable results of the first group the decision was taken to continue with the second group.

Seventy seven (77) male and post-menopausal or surgically sterile female subjects completed both of the study periods.

9.3 Selection Of Study Population

9.3.1 Inclusion Criteria

Subjects met all of the following inclusion criteria within 21 days prior to the first drug administration.

1)
- Healthy, non-smoking male subjects 18 to 55 years of age (inclusive).
- Healthy, non-smoking post-menopausal or surgically sterile females 18 to 55 years of age (inclusive).

2) BMI $\geq$ 19 and $\leq$ 30.

3) Negative for:
- HIV.
- Hepatitis B surface antigen and Hepatitis C antibody.
- Urine drugs of abuse test (marijuana, amphetamines, barbiturates, cocaine, opiates, benzodiazepines and methadone).
- Urine cotinine test
- Serum HCG consistent with pregnancy (females only).

4) No significant diseases or clinically significant findings in a physical examination.

5) No clinically significant abnormal laboratory values.

6) No clinically significant findings in the 12-lead electrocardiogram (ECG).

7) No clinically significant findings from the vital signs measurement.

8) Be informed of the nature of the study and given written consent prior to receiving any study procedure.

9) Females who participate in this study must be unable to have children:
   - Post-menopausal for at least 1 year – no menstrual cycle for 12 months and LH and FSH levels judged by a physician to be consistent with post-menopausal status. OR
   - Proof of surgical sterility (full hysterectomy only).

10) Females who participate in this study are not pregnant and/or non-lactating.

9.3.2 Exclusion Criteria

Subjects who fulfilled any of the following criteria were excluded from the study.

1) Known history or presence of any clinically significant medical condition.

2) Known or suspected carcinoma.

3) **Known or suspected increased susceptibility to infection.**

4) Known history or presence of:
   - Hypersensitivity or idiosyncratic reaction to mycophenolate . mofetil and/or any other drug substances with similar activity.
   - Alcoholism within the last 12 months.
   - Drug dependence and/or substance abuse.
   - Use of tobacco or nicotine-containing products, within the last 6 months.

5) On a special diet within 4 weeks prior to drug administration (e.g. liquid, protein, raw food diet).

6) Participated in another clinical trial or received an investigational product within 30 days prior to drug administration.

7) Donated up to 250 mL of blood within the previous 30 days
OR
Donated from 251 to 499 mL of blood in the previous 45 days OR
Donated more than 499 mL of blood in the previous 56 days (based on the Canadian Blood Services guideline for blood donation).

8) Females taking oral or transdermal hormonal contraceptives within 14 days preceding period 1 dosing.
OR
Females having taken implanted or injected hormonal contraceptives within 6 months prior to period 1 dosing.

9) Requirement of any non-topical medication, (prescription and/or over-the-counter, with systemic absorption) on a routine basis.

10) Difficulty fasting or consuming the standard meals.

11) Do not tolerate venipuncture.

12) Unable to read or sign the ICF.

9.3.3 Removal Of Subjects From Therapy Or Assessment

Subject 11 withdrew during Period 1 of the study due to adverse events. Subject 17 was dismissed during Period 2 check-in due to ongoing adverse events. Subject 79 withdrew from the study prior to Period 2 check-in due to health reasons.

The protocol requires that samples from subjects who withdrew or were dismissed due to adverse events also be assayed. Plasma concentration data and the concentration versus time curve(s) for Subjects 11, 17 and 79 are provided, refer to section *16.2.1 Discontinued Subjects*. Case Report Forms for these subjects are in section *16.3.1 CRFs for Deaths, Other Serious Adverse Events and Withdrawals for Adverse Events*.

9.4 Treatments

9.4.1 Treatments Administered

Treatment A (Test):	Mycophenolate Mofetil 500 mg Tablets (Teva Pharmacuetical Industries Ltd.); Batch No.: K-36659; [500 mg tablet administered after an overnight fast of at least 10 hours]
Treatment B (Reference):	CellCept® 500 mg Tablets (Roche Registration Limited, UK); Lot No.: M1284; [500 mg tablet administered after an overnight fast of at least 10 hours]

Study drugs were dispensed in unit dose packages according to the randomization scheme prior to each study period.

Study drugs were administered according to the Randomization Scheme.

The washout interval between successive drug administrations was 7 days. Subject 12 was dosed one minute earlier than the scheduled dosing time. Refer to section *16.2.2 protocol Deviations.*

Study drugs were administered with 240 mL of room temperature potable water. Refer to section *16.3.2.3 Drug Administration* for drug administration records.

9.4.2 Identity Of Investigational Product

The following drug products were used in this study:

Test:	Mycophenolate Mofetil 500 mg Tablets (Teva Pharmacuetical Industries Ltd.); Batch No.: K-36659; Manufacturing Date: MAR 27, 2006

Reference: CellCept® 500 mg Tablets (Roche Registration Limited, UK);
Lot No.: M1284;
Expiration Date: 10 2007
Manufactured by: Roche S.p.A., Italy

Refer to section *16.3.2.1 Pharmacy Records* for documentation regarding the study drug products.

9.4.3 Method Of Assigning Subjects To Treatment Groups

The randomization scheme was generated by a computer program (SAS® Version 8.2) producing a balanced random allocation of subjects into treatment sequences. Subjects were assigned consecutive subject numbers in an ascending order. This number identified the subject and determined the treatment sequence the subject would undergo, as described in the randomization scheme. Refer to section *16.1.7 Randomization Scheme* for the randomization scheme.

9.4.4 Selection Of Doses In The Study

The 500 mg dose was used for this bioequivalence study.

9.4.5 Selection And Timing Of Dose For Each Subject

Study drugs for each period within each group were administered on the following dates, according to the randomization scheme:

- May 11, 2006, and May 18, 2006, for Group I
- July 08, 2006, and July 15, 2006, for Group II .

For each period, dosing commenced at 08:01 and subjects were dosed at one-minute intervals. Drug administration records are located in section *16.3.2.3 Drug Administration.*

9.4.6 Blinding

The analytical personnel were blinded from the treatment sequence throughout the analytical process. After completion of the analytical phase, the randomization scheme was made

available in order to provide a description of the dosage regimen within the report.

9.4.7 Prior And Concomitant Therapy

Prescription or over-the-counter medications (with the exception of topically applied products or occasional use of common analgesics), herbal/natural products and nutritional supplements were restricted for 14 days preceding the first drug administration until completion of the entire study.

Subjects abstained from ingesting products containing grapefruit, alcohol, caffeine, or xanthine for 48 hours prior to each drug administration until after the last sample collection in the period.

At check-in of each study period, adherence to the above restrictions was confirmed and recorded for each subject.

Items that are restricted in the clinic were confiscated during check-in for each study period.

9.4.8 Treatment Compliance

Treatment compliance was assured by administration of the test and reference products in the presence of the Investigator at the time of dosing. The Investigator was present prior to each drug administration and for at least 4 hours after the first subject was dosed.

A mouth check was done immediately after drug administration to ensure that the drug was swallowed.

Qualified clinic staff ensured that all study drugs were administered according to the protocol. Subjects were confined to the clinical facility and their activities were monitored by the clinic staff throughout the confinement period. Subjects refrained from strenuous activity and remained seated or in a semi-reclined position for 4 hours following drug administration, unless required to ambulate for study specific procedures. They were allowed to resume normal activity thereafter.

Subjects were confined to the PMRI clinical facility from at least 10 hours prior to each drug administration until after the 36-hour blood sample was collected.

In each period, an optional pre-study snack was provided to each subject after check-in and prior to fasting. Subjects fasted overnight for at least 10 hours prior to drug administration and for at least 4 hours following drug administration.

Standardized xanthine-free meals with caffeine-free beverages were provided to subjects at least 4 hours after drug administration in each period. Other standardized meals were served throughout the remainder of the confinement period. Other than the optional pre-study snack and the protocol specified meals, subjects were not allowed any other food or drink while confined in the clinic. The same menu was followed for both periods of the study.

With the exception of the water ingested during drug administration, water was not allowed from 1 hour prior to drug administration, until 1 hour post-dose.

Refer to section *16.3.2.2 Meal Records*, section *16.3.2.4 Study Restrictions* and section *16.3.2.8 Memos to File* for study specific documentation.

9.5 Efficacy And Safety Variables

9.5.1 Efficacy And Safety Measurements Assessed

Vital signs (blood pressure and pulse rate) were measured pre-dose and at 1 and 3 hours (±30 min) post-dose in each period of the study and at study exit.

All vital signs were within normal range or returned to normal after repeat measurement.

Subject 17 had hypertension which started approximately an hour after dosing in Period 1. The subject's blood pressure was still out of range when he checked-in for Period 2 dosing and was dismissed from the study. Subject was advised to see his GP regarding his blood pressure and follow up with the clinic, but could not be contacted. The Subject is now considered lost to follow up.

Subjects were observed and/or questioned at regular intervals throughout the study by qualified personnel to monitor adverse events. All adverse events were documented. The Investigator judged the relationship of the adverse events to the study drugs. The severity of each adverse event was assessed as either mild, moderate or severe as defined in the protocol.

Post-clinical laboratory tests for hematology, serum chemistry, and urinalysis and a post-study physical examination (including vital signs measurements), were performed.

Refer to section *16.3.2.9 Subject CRFs* for individual records.

9.5.2 Appropriateness Of Measurements

According to the EMEA guidance, the determination of bioavailability is dependent on the reliable, precise and accurate measurement of the concentration levels of the active ingredient of the drug product in blood, plasma, serum or other biological matrices. In this study, plasma samples were assayed for mycophenolic acid using a validated analytical method with a calibration range of 0.0200 – 20.0 µg/mL. Based on these concentration levels, the pharmacokinetic parameters AUCt, AUCinf, Cmax and Tmax were estimated in order to characterize the extent and rate of absorption of the study drugs.

9.5.3 Primary Efficacy Variables (N/A)

Not Applicable

9.5.4 Drug Concentration Measurements

In each period, 22 blood samples from 21 time points were obtained from an arm vein of each subject by direct venipuncture or from an indwelling cannula. Post-dose blood sampling deviations are presented in a table in section *16.2.2 Protocol Deviations*. All other blood samples were collected prior to drug administration and at 0.083, 0.167, 0.25, 0.33, 0.5, 0.667, 0.833, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48 hours following drug administration in pre-chilled, labeled 6 mL Vacutainers® containing K_2EDTA as the anticoagulant. The time of each sample collection was recorded. Refer to section *16.3.2.5 Blood Sample Collection.* Approximately 290 mL of blood was collected from each subject over the course of the study, including the samples collected for screening and post-study tests.

Blood samples were centrifuged at 3000 rpm for 10 minutes at 4°C, within 30 minutes of collection. Each plasma sample was subdivided into 2 approximately equal aliquots and placed in labeled polypropylene tubes. Refer to section *16.3.2.6 Sample*

Processing & Storage for documentation regarding sample processing and storage. All samples were stored at -20°C ± 5°C or colder pending shipment. The stored samples were then transferred to the bioanalytical facility.

All samples were maintained in an ice bath or chilled from the time they were collected until transferred into the freezer.

Plasma samples from Group I were shipped to the bioanalytical facility on May 23, 2006 and May 24, 2006 (Aliquots 1 and 2, respectively) and were received within 24 hours of shipment. Plasma samples from Group II were shipped on July 18, 2006 and July 20, 2006 (Aliquots 1 and 2, respectively) and were received within 24 hours of shipment. All plasma samples were shipped by courier, frozen in dry ice, and were received frozen and in good condition. Refer to section *16.3.2.7 Analytical Sample Shipment/Receipt*.

9.6 Data Quality Assurance

Quality Assurance (QA) audits were performed throughout the study. After an audit of the final report, a QA statement was issued. The Quality Assurance Statement is provided in section *16.1.8 Audit Certificate*.

9.7 Statistical Methods Planned In The Protocol And Determination Of Sample Size

9.7.1 Statistical And Analytical Plans

The following pharmacokinetic parameters were obtained using a non-compartmental approach:

AUC_t: The area under the plasma concentration versus time curve, from time zero (0) to the time of the last measurable plasma concentration (t) as calculated by the linear trapezoidal method.

AUC_{inf}: The area under the plasma concentration versus time curve from time zero (0 hour) to infinity. AUCinf was calculated as the sum of AUCt + Ct/Kel, where Ct is the measured plasma concentration at the time of the last measurable plasma concentration and Kel is the apparent

first order elimination rate constant.

AUC_t/AUC_{inf}: The ratio of AUC_t to AUC_{inf}.

C_{max}: Maximum measured plasma concentration over the sampling period.

T_{max}: Time of the maximum measured plasma concentration over the sampling period.

K_{el} (λ): The apparent first-order elimination rate constant.

T_{half} ($t^1/_2$): The apparent elimination half-life.

K_{el}, T_{half} and AUC_{inf} parameters were not estimated for plasma concentration-time profiles where the terminal linear phase is not clearly defined.

Statistical analysis were applied to quality assured data from all subjects in the data set, with unbalanced groups if necessary. The PROC GLM procedure from SAS® was used.

Analysis of variance (ANOVA) was applied to log-transformed AUC_t, AUC_{inf}, C_{max} and to untransformed K_{el} and T_{half} parameters.

The least square means, the differences between the treatments least square means and the corresponding standard errors of these differences were estimated for log-transformed AUCs and Cmax parameters. Based on these statistics the ratios of the geometric means for treatments and their 90% confidence intervals were calculated.

Values for the T_{max} parameter were analyzed by a non-parametric approach.

Based on the log-transformed parameters, the following criteria were used to evaluate the bioequivalence between the test and reference products:

- The 90% confidence intervals of the relative mean AUCs and C_{max} of the test to reference products should be between 80% and 125%.[1]

9.7.2 Determination Of Sample Size

As per the sponsor's request, eighty (80) subjects were enrolled into the study. Additional volunteers were not recruited or dosed to replace subjects who withdraw or dropout.

Subjects were assigned consecutive subject numbers in an ascending order. This number identified the subject and determined the sequence of drug product administration according to the randomization scheme

9.8 Changes In The Conduct Of The Study Or Planned Analyses

The entire study was conducted as described in the protocol, except for those actions presented as protocol deviations (refer to section *16.2.2 Protocol Deviations*).

The protocol states 40 subjects will be dosed in each phase of the study. Thirty four (34) subjects were dosed in Group I and 46 subjects were dosed in Group II of the study. No other changes were made in the conduct of the study or the planned analyses of the samples.

10.0 STUDY SUBJECTS

Refer to section *16.1.2 Sample Case Report Form* for a blank sample case report form. Refer to section *16.3.2.9 Subject CRFs* for the case report forms used in this study.

10.1 Disposition Of Subjects

Subjects who were selected for the study met the inclusion criteria and did not fulfill any of the exclusion criteria described in the study protocol.

In Group I, 34 healthy, non-smoking male and post-menopausal or surgically sterile female subjects were dosed in Period 1 on May 11, 2006. Subject 11 withdrew from the study during Period 1 due to adverse events and Subject 17 was dismissed from the study during Period 2 check-in, due to ongoing adverse events. Thirty two subjects were dosed in Period 2 on May 18, 2006 and completed this phase of the study.

In Group II, 46 healthy, non-smoking male and post-menopausal or surgically sterile female subjects were dosed in Period 1 on July 08, 2006. Subject 79 withdrew prior to Period 2 check-in due to health reasons. Forty five subjects were dosed in Group II Period 2 on July 15, 2006 and completed this phase of the study.

Therefore, a total of 77 subjects completed the entire study.

The dosage regimen for the study is presented as follows:

Group I:

Subject No.	Tentative No.	Subject Identification No.	Sequence	Group I Period 1 May 11, 2006	Group I Period 2 May 18, 2006
01	T01	CC120667	BA	B	A
02	T02	GI111878	AB	A	B
03	T03	HS115096	AB	A	B
04	T04	UL123720	BA	B	A
05	T36	PA122392	BA	B	A
06	T06	BR3106	BA	B	A
07	T07	CA124007	AB	A	B
08	T08	AL120553	AB	A	B
09	T09	BH643	AB	A	B
10	T10	BM30928	BA	B	A
11	T11	ST123939	BA	B	-
12	T12	GC122190	AB	A	B
13	T13	TN116698	BA	B	A
14	T14	CC118568	AB	A	B
15	T35	RL124107	BA	B	A
16	T16	AO119613	AB	A	B
17	T17	ER116337	BA	B	-
18	T18	NG118204	AB	A	B
19	T19	SB118274	AB	A	B
20	T20	CG114270	BA	B	A
21	T21	BD122837	AB	A	B
22	T22	DS115755	BA	B	A
23	T23	WR26376	AB	A	B
24	T24	NV122132	BA	B	A
25	T25	CD111800	BA	B	A
26	T26	VJ116010	BA	B	A
27	T27	RD117543	AB	A	B
28	T28	ZT122165	AB	A	B
29	T29	RJ24397	BA	B	A
30	T30	TR114024	BA	B	A
31	T31	VE121655	AB	A	B
32	T32	SM122887	AB	A	B
33	T33	YH22561	AB	A	B
34	T34	MO119450	BA	B	A

Group II:

Subject No.	Tentative No.	Subject Identification No.	Sequence	Group II Period 1 July 08, 2006	Group II Period 2 July 15, 2006
35	T35a	MJ112049	AB	A	B
36	T84a	HM119903	BA	B	A
37	T37a	DR120803	BA	B	A
38	T38a	CH114616	AB	A	B
39	T39a	SR123029	AB	A	B
40	T40a	CA119736	BA	B	A
41	T41a	NJ1128	AB	A	B
42	T42a	CD110132	AB	A	B
43	T43a	AS88940	BA	B	A
44	T44a	HD114601	BA	B	A
45	T45a	MB115182	BA	B	A
46	T82a	GJ124469	AB	A	B
47	T47a	CL122206	BA	B	A
48	T48a	NS56009	AB	A	B
49	T49a	FA78072	BA	B	A
50	T50a	GP6521	BA	B	A
51	T51a	BM237	AB	A	B
52	T52a	BJ24954	AB	A	B
53	T53a	KR110267	AB	A	B
54	T83a	SW123890	AB	A	B
55	T55a	BA110718	BA	B	A
56	T56a	KB119876	BA	B	A
57	T57a	CG21178	BA	B	A
58	T58a	JI110990	AB	A	B
59	T59a	SP21530	AB	A	B
60	T60a	SM119855	BA	B	A
61	T61a	MB115616	BA	B	A
62	T62a	MM117978	AB	A	B
63	T63a	OJ114596	BA	B	A
64	T64a	PA114815	AB	A	B
65	T65a	PR123436	BA	B	A
66	T66a	HS110765	BA	B	A
67	T67a	CP114411	AB	A	B
68	T68a	HC115429	AB	A	B
69	T69a	MD114896	AB	A	B
70	T70a	MD834	BA	B	A
71	T71a	HS115096	AB	A	B
72	T72a	MS50343	BA	B	A
73	T73a	KP112076	AB	A	B
74	T85a	SK123849	BA	B	A
75	T75a	BY123558	AB	A	B
76	T76a	HO114403	BA	B	A

Subject No.	Tentative No.	Subject Identification No.	Sequence	Group II Period 1 July 08, 2006	Group II Period 2 July 15, 2006
77	T77a	BD114677	BA	B	A
78	T78a	RD121468	AB	A	B
79	T79a	CC122561	AB	A	-
80	T80a	BJ116144	BA	B	A

10.2 Protocol Deviations

Post-dose blood sampling deviations greater than or equal to 1 minute and a summary of all other protocol deviations are presented in a table in section *16.2.2 Protocol Deviations*.

Deviations from the scheduled sampling time were all accounted for in the pharmacokinetic calculations since the actual sampling times were used.

None of the protocol deviations had a significant impact on the safety of the subjects or on the integrity of the study results.

11.0 EFFICACY EVALUATION

11.1 Data Sets Analyzed

The protocol requires that data from all subjects who complete the study should be included in the final data set and used in the pharmacokinetic and statistical analysis. Hence data from 77 subjects (01-10, 12-16, 18-78, and 80) were included in the pharmacokinetic and statistical analysis.

11.2 Demographic And Other Baseline Characteristics

The mean, standard deviation and range of the demographic data for the 77 subjects who were included in the data set, were as follows, mean ± SD (range):

- Age: 36 ± 8 yrs (22 – 54 yrs)
- Height: 173.0 ± 8.2 cm (150.5 – 187.5 cm)
- Weight: 77.0 ± 10.5 kg (57.3 – 100.1 kg)
- BMI: 25.7 ± 2.3 (19.3 – 29.9)

Of the 77 subjects who were included in the data analysis, 60 were caucasian, 12 were black and 5 were asian. Seventy one (71) were male

and 6 were female. Subject demographic data are presented in section *16.2.4 Demographic Data.*

Subjects enrolled in the study were healthy based upon a medical history, physical examination (including vital signs), a 12-lead ECG, and clinical laboratory tests which were performed during screening.

During screening, laboratory tests for hematology, serum chemistry, urinalysis, HIV, Hepatitis B surface antigen and Hepatitis C antibody and serum HCG tests (females only) were performed within 21 days prior to the first drug administration. Urine tests for drugs of abuse (marijuana, amphetamines, barbiturates, cocaine, opiates, benzodiazepines, methadone) and cotinine were performed in-house during screening. All test results at screening for drugs of abuse, cotinine and serum HCG were negative.

All clinically significant laboratory results outside of normal range are presented in section *16.2.8 Clinically Significant Laboratory Results Outside of Normal Range.* During screening these tests were repeated and the results were within normal range or were deemed by a study investigator to be not clinically significant (NCS).

Individual records for clinical laboratory tests, urine drug tests, serum HCG and cotinine tests are provided in the subjects' CRFs in section *16.3.2.9 Subject CRFs.*

11.3 Measurements Of Treatment Compliance (N/A)

Not Applicable

11.4 Efficacy Results And Tabulations Of Individual Subject Data

11.4.1 Analysis Of Efficacy

The analytical and statistical analyses were conducted at Pharma Medica Research Inc. (PMRI).

11.4.2 Statistical/Analytical Issues

Refer to section *16.2.5 Compliance and Drug Concentration Data*, section *16.2.6 Individual Efficacy Response Data*, and section *16.1.9 Documentation of Statistical Methods.*

11.4.2.1 Adjustments for Covariates (N/A)

Not Applicable

11.4.2.2 Handling of Dropouts or Missing Data

Dropouts were not replaced. The analysis was performed on data from available subjects. Refer to section *16.2.1 Discontinued Subjects.*

11.4.2.3 Interim Analysis and Data Monitoring

In order to prevent the unnecessary dosing of excess subjects, the protocol for this study specified an interim analysis after the completion of the first phase.

The protocol specifically indicates that the study will be conducted in two separate groups of 40 subjects and that *"Based on the results of the first phase of the study, the sponsor will decide if the second phase of the study will be conducted. The results from one phase only cannot be the subject of a regulatory submission."*

The first phase of the study dosed 34 subjects (short panel) and 32 completed this phase.

Upon completion of the first 32 dosed subjects (Subjects 01-10, 12-16, 18-32), samples were assayed and analyzed. Evaluation of the results of the analysis indicated that the remaining protocol required subjects could be dosed with a likelihood that the test product was acceptable.

Results from the interim analysis:

	Ratio	90% Confidence Interval
AUCt	98.86	95.34 - 102.51
AUCinf	98.18	94.34 - 102.17
Cmax	105.40	88.46 - 125.60

The second phase of the study dosed 48 subject and 47 of those subject completed the study.

The data was pooled and GROUP was added to the statistical analysis to determine if there was a

significant group effect. The model for the ANOVA of the pooled data is as follows:

- Group
- Sequence
- Subject (Group*Seq)
- Period (Group)
- Treatment
- Group by Treatment

The *group, group by treatment, treatment and Period(group)* analysis were not significant for all pharmacokinetic parameters (AUCt, AUCinf, Cmax, Kel and Thalf).

This indicates that the data is not statistically different between groups or treatments and that the data may therefore be pooled.

Final statistical analysis was conducted with the above mentioned model.

11.4.2.4 Multicentre Studies (N/A)

Not Applicable

11.4.2.5 Multiple Comparison/Multiplicity (N/A)

Not Applicable

11.4.2.6 Use of an "Efficacy Subset" of Subjects (N/A)

Not Applicable

11.4.2.7 Active-Control Studies Intended to Show Equivalence (N/A)

Not Applicable

11.4.2.8 Examination of Subgroups (N/A)

Not Applicable

11.4.3 Tabulation Of Individual Response Data

Individual pharmacokinetic parameters are presented in section *16.2.6 Individual Efficacy Response Data.*

11.4.4 Drug Dose, Drug Concentration, And Relationships To Response (N/A)

Not Applicable

11.4.5 Drug-Drug And Drug-Disease Interaction (N/A)

Not Applicable

11.4.6 By-Subject Displays (N/A)

Not Applicable

11.4.7 Efficacy Conclusions

Mycophenolic Acid

The ratios of geometric means and the corresponding 90% confidence intervals (test versus reference) for AUCt, AUCinf and Cmax were as follows [mean (CI)]:

- AUCt: 98.23% (95.47 - 101.7%)
- AUCinf: 98.46% (95.59 - 101.41%)
- Cmax: 99.29% (87.40 - 112.80%)

The arithmetic means of Tmax were 0.81 hours 0.75 hours for the test and reference products, respectively.

ANOVA did not detect a significant difference in any of the pharmacokinetic parameters.

12.0 SAFETY EVALUATION

12.1 Extent Of Exposure (N/A)

Not Applicable

12.2 Adverse Events (AEs)

12.2.1 Brief Summary Of Adverse Events

There were 75 adverse events involving 39 subjects in the study.

	Severity			Relation to the Drug				Intervention	
Treatment Group	Mild	Mod	Severe	Unrelated	Unlikely	Possible	Probable	Required Drug Therapy	Required Non-Drug Therapy
A	35	1	0	20	4	11	1	2	0
B	39	0	0	22	5	10	2	1	2
Total	74	1	0	42	9	21	3	3	2

Adverse event forms pertaining to the above AEs can be found in section *16.3.2.9 Subject CRFs*, and all AEs are summarized in section *16.2.7 Adverse Event Listings*.

No serious AEs were reported during the conduct of this study.

None of the AEs had a significant impact on the safety of the subjects or on the integrity of the study results.

Treatment A

There were 36 AEs associated with Treatment A, which consisted of:

- Bradycardia (4)
- Diarrhea (3)
- Urin Abnorm (3)
- Acne (3)
- Creatinine Inc (3)
- Dizziness (2)
- Headache (2)
- Pharyngitis (2)
- Pain Abdo (2)
- Fever (1)
- Ecchymosis (1)
- Hypertens (1)
- Hematuria (1)
- SGPT Inc (1)
- Thrombocytopenia (1)
- Neutropenia (1)

- SGOT Inc (1)
- Dry Mouth(1)
- Hypotens (1)
- Pain Back (1)
- Pain Neck (1)

Subject 79 suffered from sore throat on July 11, 3 days after dosing in Period 1. On July 14, Subject started gargling with 0.15% Benzydamine once daily, and started taking Apo-Pen VK 300 mg tablets, four times a day, for 10 days. Subject withdrew from the study.

Treatment B

There were 39 AEs associated with Treatment B, which consisted of:

- Urin Abnorm (9)
- Dizziness (4)
- Rhinitis (3)
- Hypertens (3)
- Diarrhea (2)
- Nausea(2)
- Amblyopia (2)
- Hematuria (2)
- Rash (1)
- Headache (1)
- Hyperglycem (1)
- Cough Inc (1)
- SGPT Inc (1)
- Bun Inc (1)
- Constip (1)
- Bradycardia (1)
- Sweat (1)
- Pain Ear (1)
- Tachycardia (1)
- Applicat Site React (1)

Subject 53 had pimples on the neck on July 12, 4 days after dosing in Period 1 and red spots on the calf and lower leg approximately 10 hours after dosing in Period 2 (July 15). Subject started using Bactroban cream, once a day, from July 17 to July 19. Subject completed the entire study.

12.2.2 Display Of Adverse Events

Refer to section *12.2.1 Brief Summary Of Adverse Events.*

12.2.3 Analysis Of Adverse Events (N/A)

Not Applicable

12.2.4 Listing Of Adverse Events By Subject

Refer to section *16.2.7 Adverse Event Listings.*

12.3 Deaths, Other Serious Adverse Events, And Other Significant Adverse Events

There were no deaths or other serious or significant adverse events reported during this study.

12.3.1 Listing Of Deaths, Other Serious Adverse Events And Other Significant Adverse Events (N/A)

Not Applicable

12.3.1.1 Deaths (N/A)

Not Applicable

12.3.1.2 Other Serious Adverse Events (N/A)

Not Applicable

12.3.1.3 Other Significant Adverse Events (N/A)

Not Applicable

12.3.2 Narratives Of Deaths, Other Serious Adverse Events And Certain Other Significant Adverse Events (N/A)

Not Applicable

12.3.3 Analysis And Discussion Of Deaths, Other Serious Adverse Events And Other Significant Adverse Events (N/A)

Not Applicable

12.4 Clinical Laboratory Evaluation

All subjects underwent urine tests for drugs of abuse, urine cotinine tests and HCG tests (female subjects only) at check-in for both periods. All test results at check-in for drugs of abuse, cotinine and HCG were negative.

The clinical laboratory tests (hematology, serum chemistry and urinalysis) were repeated prior to discharge at the end of the study or after termination of a subject from the study.

12.4.1 Abnormal Laboratory Value(s)

Clinically significant laboratory results outside of normal range are presented in section *16.2.8 Clinically Significant Laboratory Results Outside of Normal Range*. These tests were repeated with results which were within normal range or were deemed by a study investigator to be not clinically significant (NCS). Subject 20 had elevated serum creatinine level at the end of the study. The test was repeated four times with results that were out of range. The subject failed to return to the clinic for another repeat test and is now considered lost to follow up. Subject 16 had bacteria in urine during post study laboratory tests and did not return to the clinic to repeat the urinalysis. The subject is now considered lost to follow up.

12.4.2 Evaluation Of Each Laboratory Parameter (N/A)

Not Applicable

12.4.2.1 Laboratory Values Over Time (N/A)

Not Applicable

12.4.2.2 Individual Subject Changes (N/A)

Not Applicable

12.4.2.3 Individual Clinically Significant Abnormalities (N/A)

Not Applicable

12.5 Vital Signs, Physical Findings And Other Observations Related To Safety

Refer to section *9.5.1 Efficacy and Safety Measurements Assessed.*

12.6 Safety Conclusions

No serious adverse events were reported during the conduct of this study.

None of the adverse events had a significant impact on the safety of the subjects or on the integrity of the study results.

13.0 DISCUSSION AND OVERALL CONCLUSIONS

The 90% confidence intervals of the relative mean AUCt, AUCinf and Cmax of the test to reference product for measured data are within the 80-125% range.

Therefore, Mycophenolate Mofetil 500 mg Tablets (Teva Pharmacuetical Industries Ltd.) exhibited equivalent rate and extent of absorption to CellCept® 500 mg Tablets (Roche Registration Limited, UK) in healthy subjects after an oral single-dose, under fasting conditions. These are bioequivalent drug products.

14.0 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data

Refer to section *16.2.4 Demographic Data.*

14.2 Efficacy Data

Refer to section *16.2.5 Compliance and Drug Concentration Data* and section *16.2.6 Individual Efficacy Response Data.*

14.3 Safety Data

14.3.1 Displays Of Adverse Events

Refer to section *16.2.7 Adverse Event Listings.*

14.3.2 Listings Of Deaths, Other Serious And Significant Adverse Events (N/A)

Not Applicable

14.3.3 Narratives Of Deaths, Other Serious And Certain Other Significant Adverse Events (N/A)

Not Applicable

14.3.4 Abnormal Laboratory Value Listing

Refer to section *16.2.8 Clinically Significant Laboratory Results Outside of Normal Range.*

15.0 REFERENCE LIST

1. Note for Guidance on the Investigation of Bioavailability and Bioequivalence. Committee for Proprietary Medicinal Products (CPMP), The European Agency for the Evaluation of Medicinal Products (Evaluation of Medicines for Human Use), July 2001.
2. Compendium of Pharmaceuticals and Specialties (CPS), 2004.
3. Physicians Desk Reference (PDR), 2004

16.0 APPENDICES

16.1 Study Information

16.1.1 Protocol and Consent Forms

Protocol: 2006-1184
Version: 2

A Single-Dose, Comparative Bioavailability Study of Two Formulations of Mycophenolate Mofetil 500 mg Tablets Under Fasting Conditions

Pharma Medica Research Inc.
966 Pantera Drive, Unit 31
Mississauga, Ontario, Canada
L4W 2S1

For

Teva Pharmaceutical Industries Ltd.
P.O. Box 353, Hashikma Street, Industrial Zone
Kfar Saba, Israel
44102

Phone: 972-9-7648260
Fax: 972-9-7648636

April 18, 2006

AMENDMENT 1 - Dated May 04, 2006

This amendment affects:
Protocol: 2006-1184 Version 2 Dated April 18, 2006
ICF Dated April 18, 2006

The following change has been made to the above mentioned protocol.

1) The subject fee has **increased** from $1200 to **$1400**

The above mentioned change has been made to the above mentioned ICF. The amended ICF is dated May 04, 2006.

Bill Wilson
Chair
Optimum Research Ethics Board

Date (MMM-DD-YYYY)

Xueyu (Eric) Chen, M.D., Ph.D., FRCP(C)
Principal Investigator
Pharma Medica Research Inc.

May 07, 2006
Date (MMM-DD-YYYY)

Latifa Yamlahi, M.Sc. or Robert Lepage, M.Sc. CCRP
Study Director Assistant Study Director
Pharma Medica Research Inc. Pharma Medica Research Inc.

May 05, 2006
Date (MMM-DD-YYYY)

Zeev Elkoshi, Ph.D.
Biopharmaceutics Manager
Teva Pharmaceutical Industries Ltd.

Date (MMM-DD-YYYY)

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PHASE I CLINIC: 1410 Warden Ave., Scarborough, Ontario M1R 5A3 **Telephone** 416-759-4111 **Fax** 416-759-2869
Internet: www.pharmamedica.com

AMENDMENT 1 - Dated May 04, 2006

This amendment affects:
Protocol: 2006-1184 Version 2 Dated April 18, 2006
ICF Dated April 18, 2006

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Bill Wilson
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May 04, 2006
Date
(MMM-DD-YYYY)

Xueyu (Eric) Chen, M.D., Ph.D., FRCP(C)
Principal Investigator
Pharma Medica Research Inc.

Date
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Latifa Yamlahi, M.Sc.
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or

Robert Lepage, M.Sc. CCRP
Assistant Study Director
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Date
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Zeev Elkoshi, Ph.D.
Biopharmaceutics Manager
Teva Pharmaceutical Industries Ltd.

Date
(MMM-DD-YYYY)

PHARMA MEDICA
RESEARCH INC.

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Bill Wilson Chair Optimum Research Ethics Board	Date (MMM-DD-YYYY)
Xueyu (Eric) Chen, M.D., Ph.D., FRCP(C) Principal Investigator Pharma Medica Research Inc.	Date (MMM-DD-YYYY)
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PHARMA MEDICA
RESEARCH INC.

A Single-Dose, Comparative Bioavailability Study of Two Formulations of Mycophenolate Mofetil 500 mg Tablets Under Fasting Conditions

Protocol: 2006-1184
Version: 2

Pharma Medica Research Inc.
966 Pantera Drive, Unit 31
Mississauga, Ontario, Canada
L4W 2S1

For

Teva Pharmaceutical Industries Ltd.
P.O. Box 353, Hashikma Street, Industrial Zone
Kfar Saba, Israel
44102

I am aware of the current version of this protocol and informed consent form (ICF) listed below and I agree that I will comply fully with the provisions of the current protocol and informed consent form (ICF) provided:

- Protocol: 2006-1184 Version: 2
- ICF: April 18, 2006

PMRI Representatives:

Xueyu (Eric) Chen, M.D., Ph.D., FRCP(C)
Principal Investigator
Pharma Medica Research Inc.

April 26, 2006
Date
(MMM-DD-YYYY)

Radu Pop, Ph.D.
Vice President, Scientific Affairs
Pharma Medica Research Inc.

Apr 25, 2006
Date
(MMM-DD-YYYY)

Latifa Yamlahi, M.Sc.
Study Director
Pharma Medica Research Inc.

or

Robert Lepage, M.Sc. CCRP
Assistant Study Director
Pharma Medica Research Inc.

Apr 25, 2006
Date
(MMM-DD-YYYY)

ERB Approved - April 20, 2006

PHARMA MEDICA RESEARCH INC.

A Single-Dose, Comparative Bioavailability Study of Two Formulations of Mycophenolate Mofetil 500 mg Tablets Under Fasting Conditions

Protocol: 2006-1184
Version: 2

Pharma Medica Research Inc.
966 Pantera Drive, Unit 31
Mississauga, Ontario, Canada
L4W 2S1

For

Teva Pharmaceutical Industries Ltd.
P.O. Box 353, Hashikma Street, Industrial Zone
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I am aware of the current version of this protocol and informed consent form (ICF) listed below and I agree that I will comply fully with the provisions of the current protocol and informed consent form (ICF) provided:

- Protocol: 2006-1184 Version: 2
- ICF: April 18, 2006

Sponsor Representative: Ariel Shavis
Project coordinator
Teva Pharmaceutical Industries

p.p. Zeev Elkoshi, Ph.D.
Biopharmaceutics Manager
Teva Pharmaceutical Industries Ltd.

April 25th, 2006
Date
(MMM-DD-YYYY)

ERB Approved - April 20, 2006

2.0 Synopsis

Title:	A Single-Dose, Comparative Bioavailability Study of Two Formulations of Mycophenolate Mofetil 500 mg Tablets Under Fasting Conditions
Protocol Number:	2006-1184 Version: 2
Objective:	To evaluate the comparative bioavailability between: • mycophenolate mofetil 500 mg tablets (Teva Pharmaceutical Industries Ltd.) and • CellCept® 500 mg tablets (Roche, Italy), after a single-dose in healthy subjects under fasting conditions.
Study Type:	Open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover. The study will be performed in two phases consisting of 40 subjects in each phase. The decision to continue the study with the second phase will be taken based on the results from the first phase. Under no circumstances will results of the first phase only be submitted.
Clinical Phase:	Bioequivalence
Sample Size:	Eighty (80) subjects
Subject Population:	Healthy, non-smoking, male subjects (18 to 55 years of age, inclusive) and post-menopausal or surgically sterile female subjects
Test Product:	Mycophenolate Mofetil 500 mg tablets (Teva Pharmaceutical Industries Ltd.)
Reference Product:	CellCept® 500 mg tablets (Roche, Italy)
Dosage:	A single 500 mg dose (1 tablet)
Drug Administration:	Oral, single dose with 240 mL of water
Meals:	Standardized meal after 4 hours post-dose Other standardized meals will be served throughout the remainder of the confinement period
Clinic Confinement:	At least 10 hours pre-dose until 36 hours post-dose
Washout Period:	At least 7 days between drug administrations

Safety Monitoring:	• ECG monitoring is not required • Vital signs measurements (blood pressure and pulse rate) will be obtained prior to dosing and at 1 and 3 hours post-dose. • Health monitoring will be conducted throughout the study • Adverse events will be monitored throughout the study • Investigator monitoring - 2 hours (on call for entire study)
Sampling Schedule:	2x 6 mL pre-dose 1x 6 mL 0.083, 0.167, 0.25, 0.33, 0.5, 0.667, 0.833, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 12, 24, 36 and 48 (21 time points)
Total Blood Volume:	≈290 mL of blood (including ≈25 mL for pre- and post-study clinical lab tests)
Sample Collection, Processing & Storage:	• K2EDTA Vacutainers® • Within 30 minutes, centrifuged for 10 min • ≈4°C • 3000 rpm. • Plasma will be separated into polypropylene tubes and stored at -20±5°C or colder pending assay
Analytical:	Plasma concentrations of mycophenolic acid will be measured by a validated analytical method
Statistical Analysis:	ANOVA (PROC GLM) for log-transformed AUCs and C_{max}, and untransformed K_{el} and T_{half}. Based on log-transformed data, ratios of the geometric means for treatments and the corresponding 90% confidence intervals will be calculated for AUC_t, AUC_{inf} and C_{max}. Values for T_{max} parameter will be analyzed by a non-parametric approach
Bioequivalence Criteria:	The 90% confidence intervals of the relative mean AUCs and C_{max} of the test to reference products should be between 80-125%

3.0 Table of Contents

4.0 Investigators and Facilities

Principal Investigator:	Xueyu (Eric) Chen, M.D., Ph.D., FRCP (C) Pharma Medica Research Inc. 1410 Warden Avenue Toronto, Ontario, Canada M1R 5A3
Study Director:	Latifa Yamlahi, M.Sc. Pharma Medica Research Inc. 1410 Warden Avenue Toronto, Ontario, Canada M1R 5A3
Clinical Facility	Pharma Medica Research Inc. 1410 Warden Avenue Toronto, Ontario, Canada M1R 5A3 Phone (416) 759-4111 Fax (416) 759-2869
Clinical Laboratory:	CML HealthCare Inc. 6560 Kennedy Road Mississauga, Ontario, Canada, L5T 2X4 Phone (905) 565-0433 Fax (905) 565-6704 and or Gamma-Dynacare Medical Laboratories 115 Midair Court Brampton, Ontario, Canada, L6T 5M3 Phone: (905) 790-3000 Toll Free: (800) 668-2714 Fax: 905-790-0473
Analytical Laboratory:	Pharma Medica Research Inc. 966 Pantera Drive, Unit 31 Mississauga, Ontario, Canada L4W 2S1 Phone (905) 624-9115 Fax (905) 624-4433
Pharmacokinetic & Statistical Analysis:	Pharma Medica Research Inc. 966 Pantera Drive, Unit 31 Mississauga, Ontario, Canada L4W 2S1 Phone (905) 624-9115 Fax (905) 624-4433
Institutional Review Board:	Optimum Clinical Research Inc. 231 King Street East Oshawa, Ontario, Canada L1H 1C5 Phone (905) 723-4694 Fax (905) 723-7590

5.0 Objective

The objective of this study is to evaluate the comparative bioavailability between:

- mycophenolate mofetil 500 mg tablets (Teva Pharmaceutical Industries Ltd.) and
- CellCept® 500 mg tablets (Roche, Italy),

after a single-dose in healthy subjects under fasting conditions.

6.0 Background and Pharmacokinetics

Mycophenolate mofetil is an immunosuppressive agent which is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. The usual recommended dose ranges between 1 g and 1.5 g given twice daily (total daily dose of 2 g to 3 g).

Mycophenolate mofetil is rapidly absorbed and hydrolysed to form mycophenolic acid (MPA) which is the active metabolite. MPA is a potent, selective, uncompetitive and reversible inhibitor of ionisine monophosphate dehydrogenase (IMPDH) and, therefore, inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA.

MPA has potent cytostatic effects on lymphocytes and also suppresses antibody formation by B-lymphocytes. MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in the intercellular adhesion to endothelial cells and may inhibit recruitment of leukocytes into sites of inflammation and graft rejection.

The mean absolute bioavailability of mycophenolate mofetil is 94%. When orally administered to healthy volunteers, peak plasma concentrations for MPA were observed approximately 1 hour post-dose (T_{max}). Secondary peaks in the plasma MPA concentration-time profile are usually observed 6 to 12 hours following administration.

Food had no effect on the extent of absorption of mycophenolate mofetil (based on MPA AUC) when administered at does of 1.5 g twice daily in renal transplant patients. The peak plasma concentration (C_{max}) of MPA is decreased by 40% in the presence of food.

Following oral administration, mycophenolate mofetil undergoes rapid and complete metabolism to MPA. The metabolism of MPA occurs presystemically: it is metabolized mainly by glucuronyl transferase to form its phenolic glucuronide, MPAG, which is not pharmacologically active. *In vivo*, MPAG is converted to MPA via enterohepatic recirculation. At clinically relevant concentrations, MPA is 97% bound to plasma albumin.

The mean apparent half-life of MPA is approximately 18 hours (±7 hours). Negligible amounts of the initial dose (less than 1%) are excreted as MPA in the urine, while 87% of the dose is excreted as MPAG. Ninety-three percent (93%) of a radiolabeled dose was recovered in the urine and 6% was recovered in the feces.[1,2]

7.0 Study Design

7.1 Design

This is an open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover comparative bioavailability study.

The study will be performed in two phases, with 40 subjects dosed in each phase. The same protocol requirements and procedures will be followed within each phase.

Based on the results of the first phase of the study, the sponsor will decide if the second phase of the study will be conducted.

The results from one phase only cannot be the subject of a regulatory submission.

7.2 Interval Between Doses

The washout period between each drug administration will be at least 7 days.

7.3 Randomization

Subjects will receive one of two treatments (TRT), A or B, during each period of study:

Treatment A:	Mycophenolate Mofetil 500 mg tablet (Teva Pharmaceutical Industries Ltd.) [500 mg after an overnight fast of at least 10 hours]
Treatment B:	CellCept® 500 mg tablet (Roche, Italy) [500 mg after an overnight fast of at least 10 hours]

Subjects will be randomly assigned to one of the following dosing sequences according to a predetermined computer-generated randomization scheme.

	Treatment	
Sequence	Period 1	Period 2
AB	A	B
BA	B	A

8.0 Subject Selection

8.1 Study Population

The study population will consist of healthy, non-smoking, male and post-menopausal or surgically sterile female subjects. All subjects will meet all subject selection criteria within 21 days prior to first drug administration.

8.2 Sample Size

As per the sponsor's request, eighty (80) subjects may be enrolled into the study. Additional volunteers will not be recruited or dosed to replace subjects who withdraw or dropout.

Forty (40) subjects will be dosed in each phase of the study. Recruiting for the second phase of the study will not begin until confirmation from the sponsor has been received that the second phase will be conducted.

Subjects will be assigned consecutive subject numbers in an ascending order. This number will identify the subject and determine the sequence of drug product administration according to the randomization scheme.

8.3 Inclusion/Exclusion Criteria

8.3.1 Inclusion Criteria

Subjects will meet all of the following inclusion criteria within 21 days prior to first drug administration.

1)
   - Healthy, non-smoking male subjects 18 to 55 years of age (inclusive).
   - Healthy, non-smoking post-menopausal or surgically sterile females 18 to 55 years of age (inclusive).

2) BMI $\geq$ 19 and $\leq$ 30.

3) Negative for:
   - HIV.
   - Hepatitis B surface antigen and Hepatitis C antibody.
   - Urine drugs of abuse test (marijuana, amphetamines, barbiturates, cocaine, opiates, benzodiazepines and methadone).
   - Urine cotinine test
   - Serum HCG consistent with pregnancy (females only).

4) No significant diseases or clinically significant findings in a physical examination.

5) No clinically significant abnormal laboratory values.

6) No clinically significant findings in the 12-lead electrocardiogram (ECG).

7) No clinically significant findings from the vital signs measurement.

8) Be informed of the nature of the study and given written consent prior to receiving any study procedure.

9) Females who participate in this study must be unable to have children:
   - Post-menopausal for at least 1 year – no menstrual cycle for 12 months and LH and FSH levels judged by a physician to be consistent with post-menopausal status.
     OR
   - Proof of surgical sterility (full hysterectomy only).

10) Females who participate in this study are not pregnant and/or non-lactating.

8.3.2 Exclusion Criteria

Subject fulfilling any of the following criteria will be excluded from the study.

1) Known history or presence of any clinically significant medical condition.

2) Known or suspected carcinoma.

3) **Known or suspected increased susceptibility to infection.**

4) Known history or presence of:
   - Hypersensitivity or idiosyncratic reaction to mycophenolate mofetil and/or any other drug substances with similar activity.
   - Alcoholism within the last 12 months.
   - Drug dependence and/or substance abuse.
   - Use of tobacco or nicotine-containing products, within the last 6 months.

5) On a special diet within 4 weeks prior to drug administration (e.g. liquid, protein, raw food diet).

6) Participated in another clinical trial or received an investigational product within 30 days prior to drug administration.

7) Donated up to 250 mL of blood within the previous 30 days OR Donated from 251 to 499 mL of blood in the previous 45 days OR Donated more than 499 mL of blood in the previous 56 days (based on the Canadian Blood Services guideline for blood donation).

8) Females taking oral or transdermal hormonal contraceptives within 14 days preceding period 1 dosing.
   OR
   Females having taken implanted or injected hormonal contraceptives within 6 months prior to period 1 dosing.

9) Requirement of any non-topical medication, (prescription and/or over-the-counter, with systemic absorption) on a routine basis.

10) Difficulty fasting or consuming the standard meals.

11) Do not tolerate venipuncture.

12) Unable to read or sign the ICF.

8.4 Dropout and Withdrawal/Termination

Additional volunteers will not be recruited or dosed to replace subjects who withdraw or dropout.

Subjects who are dismissed by the Investigator or sub-investigator as a result of an adverse event or medical condition will be considered as incomplete cases and will not be replaced.

If a subject's participation is terminated prematurely, the cause for the early termination and the total dose consumed will be documented on the case report form and in the final study report.

Subjects will be free to withdraw at any time, for any reason, or they may be dismissed, if necessary, to protect their health or the integrity of the study.

Whenever possible, all safety data normally required at the completion of the study will be obtained after a subject withdraws or is dismissed from the study. All details available will be reported and recorded.

9.0 Drug Products

9.1 Drug Products

Test Product:	Mycophenolate Mofetil 500 mg tablets (Teva Pharmaceutical Industries Ltd.)
Reference Product:	CellCept® 500 mg tablets (Roche, Italy)

9.2 Drug Administration

A single 500 mg dose (1 tablet) of the assigned formulation will be administered according to the randomization scheme with 240 mL of room temperature potable water, after an overnight fast of at least 10 hours. A mouth check will be performed immediately after drug administration to ensure that the study drug has been swallowed.

Subjects will be instructed not to chew, break or touch the study drug. If a subject chews or breaks the study drug, that subject will be removed from the study.

The study drug will be provided in unit-dose packages.

9.3 Drug Accountability

The sponsor will supply a sufficient quantity of the study drugs to allow for completion of this study and for sample retention.

The designated clinical staff will be responsible for monitoring the receipt, storage, dispensing and accounting of all study medications according to Good Clinical Practice (GCP).

The product name, strength, the manufacturer's name and lot/batch number will be identified on each container. The reference product will also include an expiry date. The study drug will be placed under appropriate storage conditions in an area with controlled access.

At the completion of the study, all unused study drug(s) will be retained at Pharma Medica Research Inc. (PMRI), as per the regulatory agency directives for drug retention.

10.0 Study Procedures

10.1 Clinical Laboratory Assessment

10.1.1 Pre-Study Screening Tests

The following tests will be performed within 21 days prior to the first drug administration:

Serum Chemistry:
Glucose
Urea
Creatinine
LH
FSH
Calcium
Total bilirubin
Alkaline phosphatase
AST (SGOT) & ALT (SGPT)
Gamma glutamyl transpeptidase (GGT)
Lactate dehydrogenase (LD)
Electrolytes (sodium, potassium & chloride).

Urinalysis:
Specific gravity
pH
Protein
Glucose
Ketones
Blood
Nitrite
Leukocyte esterase
Microscopic examination.

Hematology:
Hemoglobin
Hematocrit
RBC, WBC and Differential
Platelet count

Serology:
HIV
Hepatitis B surface antigen
Hepatitis C antibody

Other Tests:

- Urine tests for drugs of abuse (marijuana, amphetamines, barbiturates, cocaine, opiates, benzodiazepines and methadone)
- Cotinine.
- Serum HCG test (females only).

10.1.2 Tests at each Study Period Check-in

Subjects will undergo the following tests at the check-in of each period:

- urine cotinine test.
- urine drugs of abuse test (marijuana, amphetamines, barbiturates, cocaine, opiates, benzodiazepines and methadone).
- urine HCG test (females only).

Clinical study personnel reserve the right to conduct additional testing as they deem necessary (e.g. urine cotinine test, breath alcohol test, serum HCG test) at the check-in of each period or anytime throughout the study.

10.1.3 Post-Study Tests

Clinical laboratory tests (hematology, serum chemistry and urinalysis as per section 10.1.1) will be repeated prior to discharge at the end of the study or after termination of a subject from the study.

10.2 Prohibitions

At check-in of each study period, adherence to the following restrictions will be confirmed and recorded for each subject:

- The following items are restricted for the 14 days preceding drug administration until completion of the entire study:
  - All medications (prescription or over-the-counter) including the use of common analgesics.
  - **Hormonal contraceptives (oral and transdermal)**
  - Herbal/natural products
  - Nutritional supplements

  Note: Topically applied products (prescription or otherwise) are allowed.
- No consumption of grapefruit-, alcohol-, caffeine- and/or xanthine-containing products for 48 hours prior to each study period and until after the last sample from each period is collected.

If drug therapy other than that specified in the protocol is required during the study, the decision whether to continue or discontinue the subject's participation in the study will be made by the Investigator/Study Director and the sponsor will be informed.

10.3 Housing

Subjects will be confined in-house for at least 10 hours prior to each drug administration until 36 hours post-dose.

10.4 Administration of Food and Fluid

All subjects will fast for at least 10 hours prior to each drug administration.and for at least 4 hours following drug administration.

A standardized meal will be provided at least 4 hours after drug administration in each period. Other standardized meals will be served throughout the remainder of the confinement period.

The menu will be identical for all periods.

With the exception of the water ingested during drug administration, water will be restricted from 1 hour prior to each drug administration, until 1 hour following drug administration.

10.5 Vital Signs Measurements

Vital signs measurements (blood pressure and pulse rate) will be obtained prior to dosing, and at 1 and 3 hours (±30 minutes) post-dose.

If a vital signs measurement conflicts with a blood sample time, the blood sample will take precedence, however, the time frame for the former will be respected so that the 30 minute window will not be exceeded.

Additional measurements will be performed if deemed necessary by the investigator.

10.6 ECG Monitoring

ECG measurements are not required during this study unless deemed necessary by the investigator.

10.7 Health Status Monitoring

Subjects will be questioned regarding their health status throughout the study.

An exit physical examination (including blood pressure, pulse rate, temperature and respiration rate) will be conducted at the end of the study or after termination of a subject from the study.

10.8 Posture and Physical Activity

Subjects will:

- remain seated or in a semi-reclined position for 4 hours following drug administration (unless required to ambulate for study specific procedures) and may resume normal activity thereafter.
- not engage in any strenuous activity during the confinement period.
- be permitted to lie down if they experience drowsiness, dizziness, lightheadedness or other adverse events requiring such a position.

10.9 Sampling Schedule

In each period, 22 blood samples from 21 time points will be obtained. Blood samples will be collected:

2x 6 mL: Pre-dose (before drug administration)
1x 6 mL: 0.083, 0.167, 0.25, 0.33, 0.5, 0.667, 0.833, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 12, 24, 36 and 48 hours after dosing
Subjects will be required to return to the clinic for the 48-hour sample.

≈290 mL of blood from each subject will be drawn over the entire study, including ≈25 mL for pre- and post-study clinical laboratory tests.

10.10 Sample Collection, Processing and Storage

Blood samples will be collected at the times specified under Sampling Schedule (section 10.9) in pre-chilled, labeled 6 mL Vacutainers® containing K2EDTA as anticoagulant. The actual clock time of each sample collection will be recorded.

Blood samples will be collected by direct venipuncture or from an indwelling cannula, which will be placed in an arm vein of the subject. If the catheter becomes unusable, a new catheter will be re-inserted into the arm or the remaining samples will be collected by direct venipuncture.

Within 30 minutes of collection, the blood samples will be centrifuged at approximately 4°C for 10 minutes at 3000 rpm. The separated plasma will be divided in 2 approximately equal aliquots and placed in labeled polypropylene tubes. Samples that are disturbed during the separation process will be re-spun under the same conditions in an attempt to obtain the maximum amount of plasma from each sample.

Throughout sample collection and following centrifugation, the samples will be maintained in an ice bath.

The aliquots will be stored at -20±5°C or colder pending assay.

10.11 Sample Shipment

Samples collected within each phase of the study will be shipped separately.

The first set of aliquots will be packed in dry ice and delivered to the analytical facility at the completion of the clinical portion of the study. The second set of aliquots will be shipped only after written confirmation that the first set has been received.

Clinic personnel will notify the bioanalytical laboratory prior to shipment.

All shipments will be accompanied by an inventory list with appropriate documents and delivered to the following address:

Bioanalytical Laboratory
Pharma Medica Research Inc.
966 Pantera Drive, Unit 31
Mississauga, Ontario, Canada L4W 2S1
Phone: (905) 624-9115 Fax: (905) 624-4433

11.0 Adverse Events

Pharma Medica Research Inc. has established standard operating procedures (SOPs) in conformity with regulatory requirements to ensure the timely, accurate and complete reporting of safety information. These SOPs will be followed during the conduct of this study.

11.1 Adverse Event Definition and Classification

11.1.1 Adverse Event

An adverse event (AE) is defined as - any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An AE can, therefore, be any unfavourable and unintended sign (including abnormal laboratory finding), symptom or disease temporarily associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

11.1.2 Serious Adverse Event

A serious adverse event is defined as - any experience expected, unexpected or unwanted, which is reported during a study occurring at any dose that results in any of the following outcomes: death, a life threatening adverse experience, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, and a congenital anomaly/birth defect.

Important medical events are those, which may not be immediately life threatening, but may jeopardize the subject and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization. These adverse events will normally be considered serious by this criterion.

11.1.3 Severity

Adverse events will be classified according to the following severity scale:

Mild - The adverse event is easily tolerated and does not interfere with daily activity.

Moderate - The adverse event interferes with daily activity, but the subject is still able to function.

Severe - The adverse event is incapacitating and requires medical intervention.

11.1.4 Relationship to Study Drug

Adverse events will be assessed for the relationship of the drug (causality) according to the following scale:

Unrelated - The event is independent of the study drug.

Unlikely - The event may or may not follow a reasonable temporal sequence from drug administration and can plausibly be explained and/or attributed to something other than the study drug.

Possible - The event follows a reasonable temporal sequence from drug administration, follows a clinically reasonable response on withdrawal and is unlikely to be attributed to something other than the study drug.

Probable - The event follows a reasonable temporal sequence from drug administration, follows a clinically reasonable response on withdrawal and cannot be reasonably explained by something other than the study drug.

11.2 Procedures for Collecting Adverse Event Information

The Investigator will be present prior to each drug administration and for 2 hours after the first subject is dosed on each study day. The Investigator will remain on-call until the end of the study.

Prior to subsequent drug administration(s), subjects will be questioned concerning unusual symptoms that may have occurred since the previous administration of the study drug(s).

Any adverse events, whether serious or non-serious, will be monitored throughout the study and followed to resolution, when possible, regardless of whether the subject is still participating in the study.

11.3 Procedures for Reporting Adverse Events

Subjects will be instructed to inform clinic personnel of adverse events that may arise during the course of the study. Treatment of any adverse events will be administered under the direction of a physician, either at Pharma Medica Research Inc. (PMRI) or at a nearby hospital emergency room.

All symptoms will be recorded and will be reviewed by the Investigator prior to any subsequent drug administration.

When appropriate, medical tests and examinations will be performed to document resolution of the event(s).

Adverse events will be classified according to COSTART (Coding Symbols for a Thesaurus of Adverse Reaction Terms) and reported with respect to severity, duration, relationship to study medication(s) and action taken.

All serious adverse experiences, whether deemed drug-related or not, will be reported to the sponsor by telephone immediately after the occurrence, followed by a written report within 48 hours. The sponsor will be responsible for notifying the regulatory agencies, if applicable.

The following sponsor contact person is to be contacted immediately following the occurrence of a serious adverse event:

Dr. Zeev Elkoshi
Biopharmaceutics Manager
Teva Pharmaceuticals Industries Ltd., Israel
Phone (972) 9-7648260 Fax (972) 9-7648636

In parallel any serious adverse event that occurs after the start of the study, whether considered related to the drug product or not, will be reported to Teva Pharmacovigilance Unit within 48 hours:

Pharmacovigilance Unit (USA)
Teva Neuroscience, Horsham, PA, USA
Phone (215) 293-6351 Fax (215) 293-6398
e-mail: drug.safety@tevaneuro.com

These SAE reports will contain the following information:

- Study name/number
- Study Drug
- Investigator detail (name, phone, fax, e-mail)
- Subject number
- Subject demographics
- Clinical event
  - Description
  - Date of onset
  - Treatment drug, dose, dosage form
  - Relationship to study drug
  - Action taken regarding study drug
- If the AE was fatal of life-threatening
  - Cause of death (whether or not the death was related to the study drug)
  - Autopsy findings (if available)

12.0 Data Evaluation

The pharmacokinetic and statistical analysis will initially be performed on the data set resulting from the first phase of the study.

Based on the results from the first group of subjects (Phase 1), the sponsor will determine whether the second group of subjects (Phase 2) will be dosed. The data from the second group of subjects will be analyzed together with data from the first group in order to obtain the final study results.

If the study will be stopped after the first phase, the available results will be presented in a Summary Report.

The results from one phase only cannot be the subject of a regulatory submission.

12.1 Definition of Data Set

Subjects for whom all samples were obtained will be included in the data set.

Additionally, subjects whose missed samples that may not affect the estimation of the pharmacokinetic parameters, will also be included in the data set.

Subjects, whose missed samples that may affect the estimation of the pharmacokinetic parameters, will not be included in the data set. Decision to exclude these subjects will be made as soon as the determination of the effect of missed sample(s) is evaluated.

12.2 Analytical Procedures

12.2.1 Analyte(s) in Biological Matrix

Plasma samples will be assayed for mycophenolic acid using a validated analytical method according to the principles of Good Laboratory Practice.[3]

12.2.2 Samples to be Analyzed

The assay of the analyte in the samples will be carried out separately for the two phases of the study.

Within each phase of the study:

- Samples from subjects included in the data set will be assayed.
- Samples from those subjects who withdraw or are dismissed, due to adverse events will also be assayed.

12.3 Analysis of Data

Analyte concentration values from samples of subjects who were withdrawn or/and are dismissed due to AEs will be reported but they will not be included in the pharmacokinetic and statistical analysis.

12.3.1 Pharmacokinetic Analysis

The following pharmacokinetic parameters will be obtained using a non-compartmental approach:

AUC_t:	The area under the plasma concentration versus time curve, from time zero (0) to the time of the last measurable plasma concentration (t) as calculated by the linear trapezoidal method.
AUC_{inf}:	The area under the concentration versus time curve from time zero to infinity.
AUC_t/AUC_{inf}:	The ratio of AUC_t to AUC_{inf}.
C_{max}:	Maximum measured plasma concentration over the sampling period.
T_{max}:	Time of the maximum measured plasma concentration over the sampling period.
K_{el} (λ):	The apparent first-order elimination rate constant.
T_{half} ($t^1/_2$):	The apparent elimination half-life.

K_{el}, T_{half} and AUC_{inf} parameters will not be estimated for plasma concentration-time profiles where the terminal linear phase is not clearly defined.

12.3.2 Statistical Analysis

Statistical analysis will be applied to quality assured data from all subjects in the data set, with unbalanced groups if necessary. The PROC GLM procedure from SAS® will be used.

Analysis of variance (ANOVA) will be applied to log-transformed AUC_t, AUC_{inf}, C_{max} and to untransformed K_{el} and T_{half} parameters.

The least square means, the differences between the treatments least square means and the corresponding standard errors of these differences will be estimated for log-transformed AUCs and Cmax parameters. Based on these statistics the ratios of the geometric means for treatments and their 90% confidence intervals will be calculated.

Values for the T_{max} parameter will be analyzed by a non-parametric approach.

Based on the log-transformed parameters, the following criteria will be used to evaluate the bioequivalence between the test and reference products:

- The 90% confidence intervals of the relative mean AUCs and C_{max} of the test to reference products should be between 80% and 125%.[4]

Subjects exhibiting pre-dose levels higher than 5% of Cmax will be excluded from the statistical analysis. Subjects that exhibit non-zero pre-

dose levels ≤5% of Cmax will be included in the statistical analysis with no baseline correction.

13.0 Ethical Considerations

13.1 Basic Principles

This research will be carried out in accordance with Good Clinical Practice as set out by the International Conference on Harmonization, the basic principles defined in the U.S. Code of Federal Regulations (21 CFR Part 312) and the principles enunciated in the World Medical Association Declaration of Helsinki (Edinburgh, Scotland, 2000). The Clinical Trial Application for the study will be approved by Health Canada.

13.2 Investigator Responsibilities

The Principal Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, the current revision of the Declaration of Helsinki, current International Conference on Harmonization (ICH), Good Clinical Practice (GCP) guidelines and applicable regulatory requirements.

13.3 Ethical Review

A study will not be initiated by PMRI without prior written approval from the Institutional Review Board (IRB). This protocol, the Informed Consent Form (ICF), and any amendments to the protocol, will be reviewed and approved by the IRB prior to the initiation of the study. A copy of the IRB's approval documentation will be included in the final report.

The IRB is constituted and operates in accordance with the principles and requirements described in the U.S. 21 CFR Part 56.

13.4 Informed Consent Form

A copy of the ICF will be approved by the IRB and will be provided with the final report. The ICF will be signed by each subject prior to any study procedure. Each subject will be provided with verbal and written information, in non-technical terms, which describes the nature and duration of the study. Prior to signing the ICF, subjects will be allowed adequate time to consider the potential benefits and risks associated with their participation in the study. Signed and dated ICFs will be retained with the study records.

13.5 Confidentiality

All documentation collected by the sponsor or by Pharma Medica Research Inc. will be kept confidential. The name and identity of the subjects will remain confidential. If documents containing the subjects' names are photocopied, the name will be omitted from the photocopied version.

If results of this study are published, only a number or symbol will identify the subjects. If photographs are required and published, the identity of the subjects will be protected.

13.6 Amendments and Protocol Revisions

Amendments to the protocol or the ICF that change the manner in which the study is to be conducted or that have an impact on the subjects' well being or their safety, will be submitted to the IRB for approval. Minor changes to the protocol that are administrative changes will be reported to the IRB but will not require IRB approval.

For amendments to the protocol that alter the study design after initiation of the study, the Principal Investigator and/or the sponsor will decide whether the subjects' consent to continue participation will be needed. If an alteration is required in the ICF, then IRB approval is necessary for the new ICF. Subjects will be required to sign the revised ICF at their next visit to PMRI.

It is the sponsor's responsibility to submit, or to assign responsibility to submit, all amendments to the appropriate regulatory authorities when necessary.

13.7 Study Completion/Termination

PMRI and the sponsor reserve the right to terminate the study at any time.

13.8 Monitoring of the Study

13.8.1 On-Site Audits/Inspections

Representatives of the sponsor may visit the clinical research facility to carry out an audit of the study in compliance with the regulatory guidelines and company policy. Such audits will require access to all study records, study medication and source documents (CRFs) for inspection and comparison. The sponsor will provide sufficient notice to the Investigator prior to the visit to adequately prepare for the audit.

Internal audits will be conducted at pivotal times by PMRI Quality Assurance staff.

Similar inspection procedures may also be conducted by agents of any regulatory body reviewing the results of this study in support of a Licensing Application. Pharma Medica Research Inc. will immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

13.8.2 Monitoring

The sponsor or representative(s) of the sponsor may visit the study site to monitor the conduct of the study. The staff of PMRI will be available to assist the sponsor in answering any inquiries.

During these monitoring visits, the subjects' medical records, source documentation (CRFs) and other study related documents, including drug accountability records and study medications, will be made available for review.

14.0 Archives/Record Retention

All study related documents and retained test and reference products will be archived by PMRI as required by the applicable regulatory requirements.

15.0 References

[1] Compendium of Pharmaceutical and Specialties (CPS), 2004.
[2] Physicians Desk Reference (PDR), 2004.
[3] Food and Drug Administration: Good Laboratory Practice 21 CFR Part 58
[4] Note for Guidance on the Investigation of Bioavailability and Bioequivalence. Committee for Proprietary Medicinal Products (CPMP), The European Agency for the Evaluation of Medicinal Products (Evaluation of Medicines for Human Use). July 2001.