Public Assessment Report
Scientific discussion

Mycophenolic Acid Accord Healthcare 180 mg and 360 mg gastro-resistant tablets

Mycophenolate sodium

ES/H/0275/001-002/DC

Applicant: Accord Healthcare Limited

Registration number in Spain: 79535- 79536

This module reflects the scientific discussion for the approval of **Mycophenolic Acid Accord Healthcare 180 mg and 360 mg Gastro-resistant tablets.** The procedure was finalised on January 2015. For information on changes after this date please refer to the module ôUpdateô

INTRODUCTION

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Myfortic 180 mg and 360 mg gastro-resistant tablets by pharmaceutical form as the reference product (Novartis Pharma GmBH). Myfortic 180 mg and 360 mg gastro-resistant tablets have been registered since November 06th, 2002 via the mutual recognition procedure (NL/H/0343/001-004/MR).

The legal basis of the application is Article 10(1) of Directive 2001/83/EC.

The Concerned Member States involved in this procedure are:

- ES/H/0275/01/DC: AT, BE, BG, CY, CZ, DE, DK, FR, IS, IT, NL, NO, PL, PT, SE and UK
- ES/H/0275/02/DC: AT, BE, CY, CZ, DE, DK, FR, IS, IT, NL, NO, PL, PT, SE and UK

The efficacy and safety of mycophenolic acid (MPA) has been demonstrated in several studies conducted with the reference product as well as with its use experience after placed in the market. Mycophenolic acid Accord Healthcare 180 mg and 360 mg gastro-resistant tablets are submitted under an abridged application and no studies regarding pharmacology, pharmacokinetic, safety and efficacy has been carried out besides the bioequivalence studies against the reference product.

MPA is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in adult patients receiving allogeneic renal transplants and the treatment should be initiated and maintained by appropriately qualified transplant specialists.

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for **Mycophenolic Acid Accord Healthcare 180 mg and 360 mg gastro-resistant tablets** for Accord Healthcare Limited.

I. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

INTRODUCTION

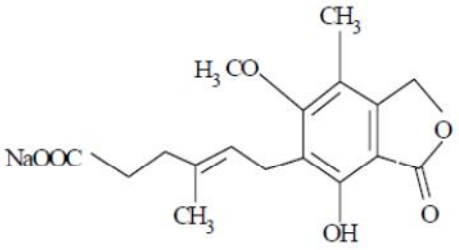
The drug product is gastro-resistant tablet. Each gastro-resistant tablet contains 180 mg and 360mg mycophenolic acid (as mycophenolate sodium) respectively, as active ingredient. IT is the sodium salt of Mycophenolic acid and is a pro drug of Mycophenolic acid.

The excipients present in the product are microcrystalline cellulose, croscarmellose sodium, povidone, talc, silica colloidal anhydrous, Magnesium stearate, water purified, isopropanol and coating suspension. The excipients used are common for the manufacture of pharmaceutical preparations. The specifications for excipients are based on the specification given in the corresponding Eur. Ph. Monographs and internal monographs.

The drug product is packed in blister packs and the blisters are placed in a suitable cardboard box with package leaflet.

Primary packaging complies with the current European regulations concerning materials in contact with food.

DRUG SUBSTANCE

INN Name	:	Mycophenolic sodium
Chemical name	:	Sodium (4E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenxofuranyl)-4-methyl-4-hexenoate.
Structure	:	
Molecular Formula	:	$C_{17}H_{19}O_6Na$
Molecular Weight	:	342.32 g/mol
Description	:	White to off white crystalline powder

The manufacture and control of Mycophenolate sodium are covered by a ASMF.

MEDICINAL PRODUCT

Gastro-resistant tablets containing 180 mg and 360 mg of mycophenolic acid (as mycophenolate sodium) respectively, similar to Myfortic® 180 mg and 360 mg gastro-resistant tablets (reference) are proposed.

The pharmaceutical development has been supported on the basis of the similarity between the reference product and the proposed formulation.

The Applicant cross-refers to the reference product Myfortic® 180 mg and 360 mg gastro-resistant tablets. Comparative studies between the proposed product and the reference product were performed and show essential similarity with respect to major physicochemical parameters.

The manufacturing process of the product is well described. Process validation data on three industrial batches have been provided. The results are satisfactory.

The finished product specifications are considered acceptable. The analytical procedures have been described and are considered suitably validated. The analytical batch data results confirm the satisfactory uniformity of the product and indicate the manufacturing process is under control.

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 36 months with the storage condition ñStore in the original package in order to protect from lightò is authorized.

II-2 Non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology of the active substance has been provided, which is based on up-to-date and adequate scientific literature.

The submitted application concerns gastro-resistant tablets with the active substances in the same form as the reference product.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate and the Member States agreed that no further non-clinical studies are required.

Environmental Risk Assessment (ERA)

No ERA was submitted. The medicinal product has the same quantitative and qualitative composition in active substances and a similar pharmaceutical form to the reference product. The introduction on the market of this medicinal product will not mean an increased exposure to the environment, since the generic medicinal product is intended to substitute the reference medicinal product as well as other generic products in the market.

In accordance with the Guideline on the Environmental Risk Assessment for medicinal products for human use (CPMP/SWP/4447/00), the absence of this Environmental Risk Assessment is therefore justified.

II.3 Clinical aspects

Introduction

Mycophenolic acid is a well-known drug with established efficacy and safety.

No new clinical efficacy or safety studies were conducted, which is acceptable for this abridged application. A clinical overview has been provided, which is based on scientific literature. The Member States agreed that no further clinical studies are required.

For this generic application, the MAH has submitted three bioequivalence studies, which are discussed below.

Biowaiver

The criteria regarding manufacture process, qualitative composition, ratio between amounts of active substance and excipients, dissolution profile and the proportionality of gastro-resistant coating with respect to the surface area (not to core weight) to have the same gastro-resistance (mg/cm^2) are fulfilled.

Based on the proportionality proved for gastro-resistant coating with respect to the surface area (mg/cm^2), the BE study in fed condition with the lower strength of 180 mg could be waived.

Bioequivalence

To support the application, the Applicant has submitted three bioequivalence studies:

- ñAn open label, balanced, randomized, two-treatment, three-period, three-sequence, single oral dose, reference replicated crossover bioequivalence study of two

formulations of Mycophenolic Acid Gastro-resistant Tablets 360 mg in normal, healthy, adult, human subjects under fasting conditions.ò

- ñAn open label, balanced, randomized, two-treatment, three-period, three-sequence, single oral dose, reference replicated crossover bioequivalence study of two formulations of Mycophenolic Acid Gastro-resistant Tablets 360 mg in normal, healthy, adult, human subjects under fed conditions.ò
- ñA pivotal open label, balanced, randomized, two-treatment, three-period, three-sequence, single oral dose, reference replicated crossover bioequivalence study of two formulations of Mycophenolic acid gastro-resistant tablets 180 mg in normal, healthy, adult, human subjects under fasting conditionsò.

The application concerns a gastro-resistant tablet (single unit) formulation and in accordance to section 5.2 Delayed release formulations of the Note for Guidance on Modified Release Oral and Transdermal Dosage Forms (CPMP/EWP/280/96), in gastro-resistant or enteric products bioequivalence should be demonstrated not only in a single dose study in fasted conditions, but also in a single dose study under fed conditions.

As this application concern a modified release single unit formulation extrapolation of evidence of bioequivalence obtained in the fasted and fed state with the highest strength cannot be performed simply based on dissolution studies. A BE study in fasted state (since according to de SmPC of the reference product can be taken with or without food) is also necessary for the lowest strength even where the manufacturing process is the same, the qualitative composition is the same, the quantitative composition is proportional and the dissolution profiles are similar.

In addition, as described in the reference SmPC, mycophenolic acid pharmacokinetics is dose proportional and linear over the dose range of 180 to 2,160 mg.

For these reasons, the Applicant has submitted three BE studies, two under fasting condition at both strengths and other under fed condition at the highest strength.

A multiple dose study is not necessary because this modified release product is of delayed release.

Bioequivalence study I (Project No.: 736-10)

The Clinical facility, Bio-analytical, Pharmacokinetic, Bio-statistics & Programming, Quality Assurance and In-house Clinical Laboratory Services were performed at Lambda Therapeutic Research Ltd., Plot No. 38, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-380 061, Gujarat, India and the principal investigator was Dr. Rakesh Patel M.D.

The study was carried out from July 20th, 2011 to August 14th, 2011 and the study periods are described below:

- Period-I: July 20th, 2011 to July 25th, 2011
- Period-II: July 30th, 2011 to August 04th, 2011
- Period-III: August 09th, 2011 to August 14th, 2011

The analytical portion was conducted at Lambda Therapeutic Research Ltd., Ahmedabad, India from August 17th, 2011 to August 30th, 2011.

The trial has been conducted in compliance with GCP requirements. Monitoring reports have been submitted. QA statement of audits assuring compliance to GCP was issued by Head-QA. The clinical, the analytical, the pharmacokinetic and the statistical sites were inspected by Regulatory Authorities of the European Union without critical findings.

Design

The study was an open label, balanced, randomized, two-treatment, three-period, three sequence, single oral dose, reference replicated crossover bioequivalence study in healthy, adult, human subjects under fasting conditions with 10 days washout period, with a screening period of 28 days prior to first dose of Investigational Medicinal Product (IMP) administration.

The application concerns a gastro-resistant tablet formulation and in accordance to section 5.2 Delayed release formulations of the Note for Guidance on Modified Release Oral and Transdermal Dosage Forms (CPMP/EWP/280/96), in gastro-resistant or enteric products bioequivalence should be demonstrated in a single dose study in fasted conditions and fed conditions, Thus, this study investigated the bioequivalence in fasted conditions for the highest strength.

The wash-out period of 10 days is considered adequate since the drug has a half-life of approximately 12 hours and no pre-dose level was detected.

Considering the expected time to peak concentration (1.5-2.0 hours) and the elimination half-life of Mycophenolic acid, the sampling schedule and the sampling time period of 96 hours seems long enough to estimate PK parameters (please refer to result section). In fact, sampling up to 72 hours could have been enough.

Sampling is reasonably frequent over the first 3.00 hours and should be sufficient to allow an accurate measurement of t_{max}.

Test product: Mycophenolic acid 360 mg gastro-resistant tablets manufactured by Intas Pharmaceuticals Limited, India. Batch number: M03447. Batch size: 97,692 tablets. Expiry date: March 2013. Assay (content): 98.3% of label claim.

Reference product: Myfortic 360 mg gastro-resistant tablets manufactured by Novartis Pharma GmBH, 90327 Nürnberg from the German market. Batch number: S0025A. Expiry date: February 2013. Assay (content): 100.7% of label claim.

After an overnight fast of at least 10 hours, the subjects were administered a single oral dose of either the test or the reference product with 240 mL of water.

The selection of the 360 mg dose to establish bioequivalence is adequate for a generic application as Mycophenolic acid pharmacokinetic is dose proportional and linear over the studied range of 180 to 2,160 mg. An additional study with the lowest strength in fasted state is submitted since this is a single unit delayed release formulation.

Both batches were tested before expiry date and the CoA shows a similar content. Therefore, content correction is not necessary.

In this study, a total of 47 subjects (no female were enrolled), including two additional subjects in order to account for any dropouts prior to dosing in period I (Subject Nos. 1001-1045, X-1 & X-2), were enrolled and checked-in for the trial. Hence, as per the protocol, 45 subjects (Subject Nos. 1001-1008, 2009, 1010-1045) were dosed in Period-I of the trial.

In all, 41 subjects (Subject Nos. 1001-1008, 2009, 1010-1013, 1015-1018, 1020, 1022-1037, 1039-1045) completed the clinical phase of the study successfully. Subject Nos. 1019 & 1021 (withdrawn on their own accord) and Subject Nos.1014 & 1038 (withdrawn on grounds of protocol non-compliance).

Analytical methods

The analytical method has been adequately validated before the conduct of the study and during the analysis of the subject samples. Therefore, the analytical method is considered acceptable for analysis of the plasma samples.

Pharmacokinetic data analysis

Pharmacokinetic parameters were calculated using a non-compartmental method with acceptable software. AUC was calculated by the trapezoidal rule. The methods used in this study for the pharmacokinetic calculations are considered acceptable.

Statistical analysis

The pharmacokinetic data were analysed by the statistical package integrated in the PROC GLM SAS® version 9.2 using the analysis of variance (ANOVA) of the logarithmically transformed kinetic parameters AUC and C_{max} and the application of 90% confidence intervals. This ANOVA takes 4 factors into account: sequence, subjects (sequence), period and formulation.

Bioequivalence of Test Product-A vs. Reference Product-B was concluded, if the 90% confidence interval fell within the acceptance range as defined below for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-Ð}$ for Mycophenolic Acid.

For AUC_{0-t} and $AUC_{0-Ð}$:

If the 90% confidence interval falls within the acceptance range of 80.00ï 125.00% for ln-transformed pharmacokinetic parameter AUC_{0-t} and $AUC_{0-Ð}$ for Mycophenolic Acid.

For C_{max}

Bioequivalence of the test product with that of the reference product under fasting condition was concluded for C_{max}.

- If the 90% confidence interval for ln-transformed data of C_{max} falls within the newly widen range [U, L] = exp [$\pm k \cdot S_{WR}$].
- If the geometric least square mean ratio of test and reference for C_{max} falls within the acceptance range of 80.00ï 125.00%.

Results

The 90% confidence intervals mean treatment T/R ratios are shown in the following table (N=41):

Parameters	Ln-transformed Geometric Least Squares Mean			90% CI	Acceptance range
	Test Product	Reference product	Ratio (A/B)%		
C_{max} (ng/mL)	16530.654	15064.108	109.7	96.25-125.11%	73.31-136.42%
AUC_{0-t} (ng.h/mL	28157.831	28484.951	98.9	95.04-102.81%	80.00-125.00%
$AUC_{0-Ð}$ (ng.h/mL)	30665.888	30866.243	99.4	95.48-103.38&	80.00-125.00%

As it is shown in the re-calculated analysis using PROC GLM, BE is concluded for AUC_{0-t} and $AUC_{0-Ð}$. With regard to C_{max} the 90% CI is slightly outside of 80.00-125.00%. However as the within-reference intra-subject CV of ln-transformed C_{max} > 30% (42.6%), hence C_{max} limits were widen to 73.31-136.42% using scaled-average-bioequivalence.

Bioequivalence study Project No.: 737-10

The Clinical facility, Bio-analytical, Pharmacokinetic, Bio-statistics & Programming, Quality Assurance and In-house Clinical Laboratory Services were performed at Lambda Therapeutic Research Ltd., Plot No. 38, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-380 061, Gujarat, India and the principal investigator was Dr. Pankaj Kumar Jha, MD.

The study was carried out from May 16th, 2011 to June 10th, 2011 and the study periods are described below:

- Period-I: May 16th, 2011 to May 21st, 2011
- Period-II: May 26th, 2011 to May 31st, 2011
- Period-III: June 05th, 2011 to June 10th, 2011

The analytical portion was conducted at Lambda Therapeutic Research Ltd., Ahmedabad, India from June 13th, 2011 to June 29th, 2011.

The trial has been conducted in compliance with GCP requirements. Monitoring reports have been submitted. QA statement of audits assuring compliance to GCP was issued by Head-QA. The clinical, the analytical, the pharmacokinetic and the statistical sites were inspected by Regulatory Authorities of the European Union without critical findings.

Design

The study was an open label, balanced, randomized, two-treatment, three-period, three sequence, single oral dose, reference-replicated crossover bioequivalence study in healthy, adult, human subjects under fed conditions with 10 days washout period, with a screening period of 28 days prior to first dose of IMP administration.

The application concerns a gastro-resistant tablet formulation and in accordance to section 5.2 Delayed release formulations of the Note for Guidance on Modified Release Oral and Transdermal Dosage Forms (CPMP/EWP/280/96), in gastro-resistant or enteric products bioequivalence should be also demonstrated in a single dose study in fed conditions.

The wash-out period of 10 days is considered adequate since the drug has a half-life of approximately 12 hours and no pre-dose level was detected.

The sampling schedule and the sampling time period of 96 hours seems long enough to estimate PK parameters (as indicated in the reference SmPC a high fat meal decrease C_{max} in a 33% and moreover the t_{max} were on average 3-5 hours delayed with several patients having a t_{max} of >15 h)

Test product: Mycophenolic acid 360 mg gastro-resistant tablets manufactured by Intas Pharmaceuticals Limited, India. Batch number: M03447. Batch size: 97,692 tablets. Expiry date: March 2013. Assay (content): 98.3% of label claim.

Reference product: Myfortic 360 mg gastro-resistant tablets manufactured by Novartis Pharma GmBH, 90327 Nürnberg from the German market. Batch number: S0025A. Expiry date: February 2013. Assay (content): 100.7% of label claim.

After an overnight fast of at least 10 hours, the subjects were administered a single oral dose of either the test or the reference product at 30 ± 02 minutes after serving of the high fat & high calorie vegetarian breakfast (please see below table), with 240 ± 02 mL of water, and with the subjects in the sitting posture.

The composition of the meal is according with the bioequivalence Guideline requirements (approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively).

The selection of the 360 mg dose to establish bioequivalence is adequate for a generic application (see comment on this topic in the previous study in fasted state).

Both batches were tested before expiry date and the CoA shows a similar content. Therefore, content correction is not necessary.

A total of 48 subjects including two additional subjects & one extra subject with ASN 50 in order to account for any dropouts prior to dosing in period I (Subject Nos. 1001-1045, X-1 & X-2) were enrolled and checked-in for the trial.

Hence, as per the protocol, 45 subjects (Subject Nos. 1001-1024, 2025 & 1026-1045) were dosed in Period-I of the trial.

In all, 41 subjects (Subject Nos. 1001-1005, 1007, 1009-1020, 1022-1024, 2025, 1026-1037 and 1039-1045) completed the clinical phase of the study successfully.

*Analytical methods*The analytical method has been adequately validated before the conduct of the study and during the analysis of the subject samples. Therefore, the analytical method is considered acceptable for analysis of the plasma samples.

Pharmacokinetic data analysis

Pharmacokinetic parameters were calculated using a non-compartmental method with acceptable software. AUC was calculated by the trapezoidal rule. The methods used in this study for the pharmacokinetic calculations are considered acceptable.

Statistical analysis

The pharmacokinetic data were analysed by the statistical package integrated in the PROC GLM SAS® version 9.2 using the analysis of variance (ANOVA) of the logarithmically transformed kinetic parameters AUC and C_{max} and the application of 90% confidence intervals. This ANOVA takes 4 factors into account: sequence, subjects (sequence), period and formulation.

Bioequivalence of Test Product-A vs. Reference Product-B was concluded, if the 90% confidence interval fell within the acceptance range as defined below for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-Ð}$ for Mycophenolic Acid.

For AUC_{0-t} and $AUC_{0-Ð}$:

If the 90% confidence interval falls within the acceptance range of 80.00ï 125.00% for ln-transformed pharmacokinetic parameter AUC_{0-t} and $AUC_{0-Ð}$ for Mycophenolic Acid.

For C_{max}

Bioequivalence of the test product with that of the reference product under fasting condition was concluded for C_{max}.

- If the 90% confidence interval for ln-transformed data of C_{max} falls within the newly widen range [U, L] = exp [$\pm k \cdot S_{WR}$].
- If the geometric least square mean ratio of test and reference for C_{max} falls within the acceptance range of 80.00ï 125.00%.

Results

The 90% confidence intervals mean treatment T/R ratios are shown in the following table (N=41):

Parameters	Ln-transformed Geometric Least Squares Mean			90% CI	Acceptance range
	Test Product	Reference product	Ratio (A/B)%		
C_{max} (ng/mL)	7573.520	8092.133	93.6	75.67-115.76%	69.84-143.19%
AUC_{0-t} (ng.h/mL	23570.707	25527.420	92.3	85.40-99.83%	80.00-125.00%
$AUC_{0-Ð}$ (ng.h/mL)	24454.154	26406.578	92.6	85.92-99.82%	80.00-125.00%

As it is shown in the re-calculated analysis using PROC GLM, BE is still concluded. With regard to C_{max} the 90% CI is outside of 80.00-125.00%. However as the within-reference intra-

subject CV of ln-transformed C_{max} > 30% (79.2%), hence C_{max} limits were widen to 69.84-143.19% using scaled-average-bioequivalence.

Bioequivalence study Project No.: 534-12

The Clinical facility, Bio-analytical, Pharmacokinetic, Bio-statistics & Programming, Quality Assurance and In-house Clinical Laboratory Services were performed at Lambda Therapeutic Research Ltd., Plot No. 38, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-380 061, Gujarat, India and the principal investigator was Dr. Ketul Modi, MBBS.
The study was carried out from December 27th, 2012 to January 11th, 2013 and the study periods are described below:

- Period-I: December 27th, 2012 to December 30th, 2012
- Period-II: January 02nd, 2013 to January 05th, 2013
- Period-III: January 08th, 2013 to January 11th, 2013

The analytical portion was conducted at Lambda Therapeutic Research Ltd., Ahmedabad, India from January 12th, 2013 to January 26th, 2013.

The trial has been conducted in compliance with GCP requirements. Monitoring reports have been submitted. QA statement of audits assuring compliance to GCP was issued by Head-QA. The clinical, the analytical, the pharmacokinetic and the statistical sites were inspected by Regulatory Authorities of the European Union without critical findings.

Design
This study was an open label, balanced, randomized, two-treatment, three-period, three sequence, single oral dose, reference replicated crossover bioequivalence study in healthy, adult, human subjects under fasting conditions with a 6 days washout with a screening period of 28 days prior to first dose of IMP administration.

The application concerns a gastro-resistant tablet formulation and in accordance to section 5.2 Delayed release formulations of the Note for Guidance on Modified Release Oral and Transdermal Dosage Forms (CPMP/EWP/280/96), in gastro-resistant or enteric products bioequivalence should be also demonstrated in a single dose study in fasting condition with the lowest strength.

The wash-out period of 6 days is considered adequate since the drug has a half-life of approximately 12 hours and no pre-dose level was detected.

Considering the expected time to peak concentration (1.5-2.0 hours) and the elimination half-life of Mycophenolic acid, the sampling schedule and the sampling time period of 48 hours seems long enough to estimate PK parameters.

Sampling is reasonably frequent over the first 3.00 hours and should be sufficient to allow an accurate measurement of T_{max}.

Test product: Mycophenolic acid 180 mg gastro-resistant tablets manufactured by Intas Pharmaceuticals Limited, India. Batch number: M03446. Batch size: 98,462 tablets. Expiry date: March 2013. Assay (content): 97.1% of label claim.

Reference product: Myfortic 180 mg gastro-resistant tablets manufactured by Novartis Pharma GmBH, 90327 Nürnberg from the German market. Batch number: S0001B. Expiry date: January 2013. Assay (content): 101.0 % of label claim.

The selection of the 180 mg dose is adequate for a generic application as the formulations are single unit prolonged release and bioequivalence should be demonstrated with both strengths in fasting state even if dissolution profiles are similar and composition is proportional.

Both batches were tested before expiry date and the CoA shows a similar content. Therefore, content correction is not necessary.

After an overnight fast of at least 10 hours, the subjects were administered a single oral dose of either the test or the reference product with 240 mL of water.

A total of 47 subjects including two extra subjects (Subject Nos. 1001-1020, 2021, 1022-1031, 2032 & 1033-1045, X-1 & X-2) were checked in for the study.

As per the protocol, 45 subjects were dosed in Period-I of the study.

Subject No. 1028 was withdrawn from the study on the grounds of emesis in Period-I.

Subject Nos. 1009 & 1019 discontinued on their own accord in Period-III.

In all, 42 subjects (Subject Nos. 1001-1008, 1010-1018, 1020, 2021, 1022-1027, 1029-1031, 2032 & 1033-1045) completed the clinical phase of the study successfully.

Analytical methods

The analytical method has been adequately validated before the conduct of the study and during the analysis of the subject samples. Therefore, the analytical method is considered acceptable for analysis of the plasma samples.

Pharmacokinetic data analysis

Pharmacokinetic parameters were calculated using a non-compartmental method with acceptable software. AUC was calculated by the trapezoidal rule. The methods used in this study for the pharmacokinetic calculations are considered acceptable.

Statistical analysis

The pharmacokinetic data were analysed by the statistical package integrated in the PROC GLM SAS® version 9.2 using the analysis of variance (ANOVA) of the logarithmically transformed kinetic parameters AUC and C_{max} and the application of 90% confidence intervals. This ANOVA takes 4 factors into account: sequence, subjects (sequence), period and formulation.

Bioequivalence of Test Product-A vs. Reference Product-B was concluded, if the 90% confidence interval fell within the acceptance range as defined below for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-Ð}$ for Mycophenolic Acid.

For AUC_{0-t} and $AUC_{0-Ð}$:

If the 90% confidence interval falls within the acceptance range of 80.00ï 125.00% for ln-transformed pharmacokinetic parameter AUC_{0-t} and $AUC_{0-Ð}$ for Mycophenolic Acid.

For C_{max}

Bioequivalence of the test product with that of the reference product under fasting condition was concluded for C_{max}.

- If the 90% confidence interval for ln-transformed data of C_{max} falls within the newly widen range [U, L] = exp [$\pm k \cdot S_{WR}$].
- If the geometric least square mean ratio of test and reference for C_{max} falls within the acceptance range of 80.00ï 125.00%.

Results

The 90% confidence intervals mean treatment T/R ratios are shown in the following table (N=42):

Parameters	Geometric Least Squares Means			90% Confidence Interval	Acceptance Range	Power (%)
	Test Product-T**	Reference Product-R#	Ratio (T / R)%			
lnC_{max}	7701.802	7930.063	97.1	87.24 – 108.12	72.83 – 137.31	100.0
$lnAUC_{0-t}$	13676.225	13701.872	99.8	96.81 – 102.90	80.00-125.00%	100.0
$lnAUC_{0-\infty}$	14366.323	14600.156	98.4	95.08 – 101.83	80.00-125.00%	100.0

** represents 42 observations in Test Product-T and # represents 84 observations in Reference Product-R.

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference with respect to the extent and rate of absorption/exposure as the 90% confidence intervals for the ln-transformed AUC_{0-t} and AUC_{0-D} are within the acceptance range of 80-125% and in accordance with Guideline on the investigation of bioequivalence, section 4.1.10 as the within reference intra-subject CV% of ln-transformed was 43.6% larger than 30%, the acceptance criteria for C_{max} was widened to the acceptance range of 72.83-137.31%. This new acceptance interval is acceptable. The 90% CI of C_{max} is inside of this widened acceptance range. In any case, the 90% CI for C_{max} is also within the acceptance range of 80-125% and the widening of the acceptance range is not necessary.

Risk Management Plan

The MAH has submitted a risk management plan , in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Mycophenolic acid Accord.

Summary table of safety concerns as approved in RMP (version 3, final sign-off 21 Jul 2014)

Important identified risks
Congenital malformations and spontaneous abortions (related to exposure during pregnancy)
Serious bacterial, fungal, protozoal, and viral (including BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML)) infections and sepsis.
GI ulcerative and haemorrhage
Malignancies (lymphomas and other malignancies, particularly of the skin)
Blood and lymphatic system disorders including pure red cell aplasia (PRCA)
Important potential risks
Serious adverse reactions in breast-fed babies (related to exposure during breastfeeding)
Missing Information
Paediatric population
Interaction with other immunosuppressants (e.g. tacrolimus and azathioprine)

For all safety concerns, the applicant will performed routine pharmacovigilance activities. No additional pharmacovigilance activities or efficacy studies are proposed.
In addition, routine risk minimisation measures are considered sufficient to monitor the benefit-risk profile of the product. No additional risk minimisation activities are proposed.

Discussion on the clinical aspects

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference product.

Efficacy and safety of the active substances mycophenolic acid are well documented for the reference medicinal product. The design of the submitted bioequivalence study is adequate and the results allow us to conclude bioequivalence with the reference.

III OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the submitted bioequivalence studies, Mycophenolic acid Accord Healthcare 360 mg and 180 mg gastro-resistant tablets, Intas Pharmaceuticals, India, when compared with the Reference Product Myfortic 360 mg and 180 mg gastro-resistant tablets, Novartis Pharma, GmBH, German, meet the bioequivalence criteria with respect to the C_{max} and AUC_{0-t} and $AUC_{0-Ð}$

The results of the fed study 737-10 with 360 mg formulation can be waived to the lower strength of 180 mg since the criteria regarding manufacture process, qualitative composition, ratio between amounts of active substance and excipients, dissolution profile and the proportionality of gastro-resistant coating with respect to the surface area (mg/cm^2; not to core weight) are fulfilled.

Both strengths could be approved.

The SmPC, PIL and labelling are considered satisfactory and consistent with the information for the reference medicinal product. The user testing of the Package Information Leaflet has been tested in accordance with Article 59(3) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

The benefit/risk balance was considered to be positive.

Agreement between Member States was reached during the procedure. The decentralised procedure was finalised with a positive outcome in January 2015.