Sponsor – Novartis

Generic Drug Name – Enteric-coated mycophenolic sodium

Therapeutic Area of Trial – Solid organ transplantation

Approved Indication–

EC-MPS is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute organ rejection in adult patients after kidney allotransplantation.

Study Number– CERL080ABE01

Title– Conversion trial from mycophenolate mofetil (MMF) to enteric-coated mycophenolic sodium (EC-MPS) in stable transplanted patients suffering from gastrointestinal (GI) adverse events (AEs) while on mycophenolate mofetil therapy.

Phase of Development– IV

Study Start/End dates– 8 October 2004 to 22 Aug 2006

Study Design/Methodology– Open, single arm, multicentre study

Centres– 6 centres

Objectives–

This open, single arm, explorative study investigated the evolution of GI AEs after switch from MMF to EC-MPS in organ transplanted patients suffering from GI AEs while on MMF therapy. The study population was selected after exclusion of GI AEs from infectious etiology during the screening period, due to the assumption that GI AEs are more likely related to immunosuppressive therapy when infections have been ruled out. Patients with no evidence of a GI infection entered the study and were switched to EC-MPS

Primary outcome/safety objective(s)–

- GI AEs before switch versus 3 months after switch

Secondary outcome/efficacy objective(s)–

- Biopsy proven rejection episodes
- Graft loss

Test Product, Dose, and Mode of Administration–.

After exclusion of GI infections, patients suffering from GI AEs while on MMF therapy were converted to the equimolar dose of EC-MPS. MMF 500 mg tablets equal 360 mg EC-MPS tablets. MMF 250 mg capsules equal 180 mg EC-MPS tablets. The MMF standard dose of 2 gram/day equals the standard dose of 1.44 gram/day EC-MPS. Deviations from the standard dose were at the discretion of the investigator.

Reference Product(s), Dose(s), and Mode(s) of Administration– Not applicable.

This was a single arm study. All comparisons are performed “after switch” versus “before switch”.

Criteria for Evaluation–

Primary safety:

Upper and lower GI discomfort/pain were evaluated separately by means of Visual Analogues Scales (VAS) at baseline (just before the switch from MMF to EC-MPS and at month 1 and 3 after conversion.

Secondary safety:

- Frequency of AEs, serious AEs and infections
- Blood hematology (hemoglobin, hematocrit, RBC, WBC with differential count and platelet count)
- Blood biochemistry (Sodium, potassium, magnesium, urea, creatinine, uric acid, AST, ALT, alkaline phosphatase, total bilirubin).

Secondary efficacy:

1. Time to the first biopsy-proven rejection after conversion.
2. Severity of biopsy-proven rejections after conversion.
3. Proportion of patients who had graft loss after conversion.

Statistical Methods–

Data from all centres that participated in this protocol were combined, so that an adequate number of patients were available for analysis.

Data was summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements.

The primary objective of this trial was to explore differences in GI AEs after conversion from MMF to EC-MPS in patients suffering from GI AEs while on MMF therapy.

Study population

This includes all subjects who were screened for the presence of a GI infection.

Safety population

The includes all subject who were converted from MMF to EC-MPS at baseline.

Background and demographic characteristics

Background and demographic characteristics are presented with respect to the study population defined above. Continuous variables (e.g. age) are summarized by sample size, mean, median, standard deviation, minimum and maximum. Discrete variables (e.g. gender) are summarized by frequencies and percentages.

Study medication

All dose modifications and reasons for dose modifications or interruptions are listed per patient.

Concomitant therapy

All concomitant therapy and modifications in concomitant therapy are listed per patient.

Safety evaluation

Primary safety variable

The primary safety variable is the VAS score. More specifically, for the subgroup of patients having diarrhea the number of watery bowel movements with a sense of urgency per day is also a primary safety variable. Primary safety variables were compared before conversion versus after conversion at month 3.

Other safety variables

The assessment of safety was based mainly on the frequency of AEs and on the number of laboratory values that fall outside of pre-determined ranges.

AEs were summarized by presenting the number and percentage of patients having any AE, having an AE in each body system and having each individual AE. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate.

Laboratory data was summarized by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges) and by the flagging of notable values in data listings.

Any statistical tests performed to explore the data were used only to highlight any interesting comparisons that may warrant further consideration.

Efficacy evaluation

Efficacy variables are described as follows:

1. Time to the first biopsy-proven rejection after conversion.
2. Severity of biopsy-proven rejections after conversion.
3. Proportion of patients who had graft loss after conversion.

Interim analysis

No interim analysis is foreseen in this study.

Sample size and power considerations

This explorative study is not designed for hypothesis testing. Therefore, the sample size was not based on statistical considerations.

Study Population: Inclusion/Exclusion Criteria and Demographics–

Inclusion criteria

1) Male or female patients aged 18 years and older
2) Stable kidney or liver transplant recipients
3) Patients who are currently under MMF treatment and who are currently suffering from upper or lower GI AEs.
4) Patients in a stable condition in terms of graft function (e.g. no change of immune suppressive regimen due to graft malfunction), and no known clinically significant physical and/or laboratory changes prior to enrollment.

Exclusion criteria

1) Evidence of graft rejection or treatment of acute rejection prior to Screening.
2) Pre-existing conditions that may cause GI complaints such as extensive GI surgery in the past, severe cholestatic liver dysfunction, amyloidose, diabetes mellitus, pre-terminal renal insufficiency.
3) Drug induced GI complaints with antibiotics ,NSAIDs, antacids loperamide etc.

4) Patients with thrombocytopenia (<75,000/mm^3), with an absolute neutrophil count of <1,500/mm^3 and/or leukocytopenia (<2,500/mm^3), and/or hemoglobin <9.0 g/dL prior to enrollment.

5) Females of childbearing potential who are planning to become pregnant, who are pregnant and/or lactating, who are unwilling to use effective means of contraception

Number of Subjects	EC-MPS
Planned N	200
Randomised n	27
Completed n (%)	21 (78%)
Withdrawn n (%)	6 (22%)
Withdrawn due to AEs n (%)	4 (15%)
Withdrawn due to lack of efficacy n (%)	1 (4%)
Withdrawn for other reasons n (%)	1 (4%)
Demographic and Background Characteristics	
N (ITT)	27
Females: males	13:14
Mean age, years (SD)	55.1 (12.17)
Mean weight, kg (SD)	72.37 (14.246)
Race White n (%) Oriental n (%)	 25 (93%) 2 (7%)
Organ transplant Kidney n (%) Liver n (%) Kidney and liver n (%)	 17 (63%) 9 (33%) 1 (4%)
Transplantation First transplantation n (%) Re-transplantation n (%) Missing Value n (%)	 21 (78%) 5 (18%) 1 (4%)
Primary Efficacy and Safety Result(s) – intent to treat population	
Upper and lower GI discomfort/pain by means of Visual Analogue Scales	EC-MPS
Baseline Lower GI: Mean ± Standard Deviation Median Minimum - Maximum	94.8 ± 159.37 72.0 1 - 780
Baseline Upper GI: Mean ± Standard Deviation Median Minimum - Maximum	45.8 ± 29.4 55.0 1 - 90
Month 1 Lower GI: Mean ± Standard Deviation Median Minimum – Maximum p-value (baseline – month1)	43.6 ± 31.52 50.0 2 – 88 0.2441
Month 1 Upper GI: Mean ± Standard Deviation Median Minimum – Maximum	28.9 ± 19.93 24.5 3 – 53

p-value (baseline – month1)	0.0206
Month 3 Lower GI: Mean ± Standard Deviation	25.4 ± 26.38
Median	10.5
Minimum – Maximum	2 - 81
p-value (baseline – month3)	0.2251
Month 3 Upper GI: Mean ± Standard Deviation	31.3 ± 26.21
Median	29
Minimum – Maximum	3 – 70
p-value (baseline – month3)	0.1228
Secondary Efficacy Result(s)–intent to treat population	
Primary reason of discontinuation:	
N (discontinuation)	6
Due to: AE(s) n (%)	4 (66%)
Abnormal lab value(s) n (%)	0
Abnormal test procedure result(s) n (%)	0
Lack of efficacy n (%)	1 (17%)
Patient's condition no longer requires study Medication n (%)	0
Protocol violation n (%)	0
Subject withdrew consent n (%)	1 (17%)
Lost to follow-up n (%)	0
Administrative problems n (%)	0
Graft loss n (%)	0
Death n (%)	0
There were no suspected and biopsy proven rejections, and no graft loss	
AEs by System Organ Class	
Patients studied	27
Patients with AE	14 (52 %)
Patients with drug-related AE	3 (11%)
Drug-related AEs by primary system organ class	
Nervous system disorders n (%)	1 (1 %)
Insomnia	1
GI disorders n (%)	3 (4 %)
Nausea	2
Ulcerative terminal ileitis	1
Skin and subcutaneous tissue disorders n (%)	3 (4 %)
Dry skin hands	1
Pruritis	1
Erythema of the hands	1

10 Most Frequently Reported AEs Overall by Preferred Term: Headache Hypertension Pruritus Fatigue Dyspnea Influenza Fever Nausea Sore throat Rhinitis Shoulder pain	 3 (6 %) 3 (6 %) 2 (4 %) 2 (4 %) 2 (4 %) 2 (4 %) 2 (4 %) 2 (4 %) 2 (4 %) 2 (4 %) 2 (4 %)
Secondary Safety Result(s)	
N of subjects studied N (%) of subjects with AEs	27 14 (52%)
Number of AEs Mild n (%) Moderate n (%) Severe n (%) Missing Value n (%)	50 38 (76%) 10 (20%) 1 (2%) 1 (2%)
AEs – Relationship to drug Not suspected n (%) Suspected n (%) Missing Value n (%)	 41 (82%) 7 (14%) 2 (4%)
AEs – Still Continuing No Yes	 32 (64%) 18 (36%)
AEs – Action taken Concomitant medication taken No action taken Study drug dosage adjusted/temporarily Interrupted Study drug permanently discontinued due To this AE Other Missing Value	 10 (20%) 21 (42%) 3 (6%) 6 (12%) 4 (8%) 6 (12%)
Serious AEs N SAE of AE No n (%) Yes n (%) 1 Cerebrovascular accident 1 Pancytopenia 1 Crohn-like syndrome 1 Eye bleeding (Left) with reduced vision – Headache - Dyspnea and pressure bithoracal 1 Esophageal cancer	 45 (90 %) 5 (10%) No suspected relation to study drug Suspected relation to study drug Suspected relation to study drug No suspected relation to study drug No suspected relation to study drug
Infections There was one infection reported, it concerns a mild dental infection. There was no suspected relationship to the study medication	

Date of Clinical Trial Report	Dec19 2007
Date Inclusion of Registry	February 8, 2008
Date of Latest Update	19 Dec 2007