Sponsor

Novartis Farmacéutica S.A. Spain

Generic Drug Name

Enteric-coated mycophenolate sodium

Therapeutic Area of Trial

Renal transplantation

Approved Indication

Mycophenolate sodium is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in adult patients receiving allogeneic renal transplants.

Study Number

CERL080AES06

Title

A multicentre, randomised, open-label, 12-week study to assess the effect of treatment with EC-MPS in quality-of-life terms in patients with gastrointestinal (GI) symptoms under treatment with mycophenolate mofetil (MMF) after kidney transplantation.

Phase of Development

Phase IV

Study Start/End Dates

07 Jul 2006 to 16 Sep 2008

Study Design/Methodology

This was a 12-week, phase IV, multicentre, open-label, randomised, controlled, parallel group study in patients treated with MMF with GI symptoms after renal transplantation. The patients were enrolled in the study and randomly assigned in a 1:1 ratio, to the study medication (EC-MPS) or the standard treatment (MMF) groups The standard treatment group included patients who continued treatment with MMF according to regular practice, with a possible dose reduction or increase at Visit 1 or 2, or at another time during the study if clinically indicated. The dose adjustments were done to establish and maintain the patient at the maximum tolerated dose of MMF, up to 1 g bid. The study medication treatment group included patients who were converted to EC-MPS at an equimolar dose of mycophenolic acid (MPA) (i.e. MMF 500 mg and EC-MPS 720 mg) at visit 2 (V2). Dose adjustments were made between weeks 2 and 6 of the study in order to establish and maintain the patient at the maximum tolerated dose of EC-MPS, up to 720

mg bid.

Centers

19 centers in 2 countries : Spain (15) , Portugal (4)

Publication

Objectives

Primary objective(s)

- To determine the effect of the use of EC-MPS on the quality of life of patients requiring MMF dose reduction due to gastrointestinal symptoms caused by said medication.

Secondary objective(s)

- To determine whether EC-MPS enables the administration of higher doses with good tolerability, compared with standard MMF treatment, in patients with shown susceptibility to undesirable GI effects;
- To measure health-related quality of life (HRQOL) through the GI quality of life index (GIQLI) and the psychological general well-being index (PGWB);
- To determine the severity of the GI symptoms through the GI symptom rating scale (GSRS);
- To evaluate the overall treatment effect (OTE) on GI symptoms and HRQOL.

Test Product (s), Dose(s), and Mode(s) of Administration

EC-MPS: Enteric-coated 180 mg and 360 mg tablets of mycophenolate sodium, packed in bottles of 140 tablets.

The total daily dose of EC-MPS was up to 1440 mg split in two equal doses taken orally. The tablets were to be taken whole with a large glass of water.

Reference Product(s), Dose(s), and Mode(s) of Administration

MMF: 250 mg tablets or 500 mg tablets.

The total daily dose of MMF was up to 2 g split in two equal doses taken orally. The tablets were to be taken whole with a large glass of water.

Criteria for Evaluation

Primary variables

- Total GI quality of life index (GIQLI) score per treatment group

Secondary variables

- Calculation of percentage of dose (administered dose/maximum dose) at visit 3 for all patients and proportion of patients at final visit (V3) with a greater dose of EC-MPS than at the baseline visit (V1).
- Severity of the GI symptoms by means of the GSRS and subscales.
- HRQOL by means of the PGWB.
- OTE according to patient and clinical staff per treatment group for GI symptoms and HRQOL.

Safety and tolerability

- Frequency of all the safety variables, including GI disorders, adverse events, severity, duration, analytical parameters, renal function and rejection episodes.

Pharmacology

- Not applicable

Other

- Not applicable

Statistical Methods

Analyzed populations:

Intention to treat population (ITT): This population included all the randomised patients who took at least one dose of medication post-randomization and completed the GIQLI scale at the baseline visit and at least once after the start of the treatment.

Per protocol population (PP): It comprised all the ITT patients who did not commit major violations of the protocol and for which the GIQLI scale was available from the baseline and final (Visit 3 – week 12) visits**.**

Analysis:

The primary efficacy analysis was performed on the intention to treat and per protocol populations. The secondary objective efficacy analysis was performed on the intention to treat population.

Two safety populations were used, comprising all the patients randomized in the study who took at least one dose of the study medication, according to whether the patients had primary endpoint data compiled with validated (Spanish sites) or unvalidated (Portuguese sites) questionnaires: safety population-1 (data of all patients, irrespective of validation; Spanish and Portuguese sites) and safety population-2 (data of patients with validated questionnaires; Spanish sites).

The clinical and demographic variables were evaluated with descriptive analyses according to the nature of the variables (discrete or continuous). Descriptive statistics were used for the analysis of the administered doses of study medication, frequency, duration of the treatment and compliance with treatment.

For the primary efficacy analysis, the difference between treatments was estimated at a 95% CI as the change in the global score on the GIQLI scale at visit 3 vs the baseline visit. An analysis of variance model was used to obtain this interval, including the global baseline score as a co variable.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Patients subject to renal transplantation
- Who were receiving an immune suppression regimen including MMF before inclusion in the study
- Who were experiencing undesirable GI effects related to the standard dose of MMF, or receiving treatment with a reduced dose of MMF to control said undesirable GI effects
- Who were 18 years of age or over
- Capable of understanding the information about the study and of granting their informed consent in writing
- Capable of fulfilling all the study requirements, including completion of the questionnaires and attending the 3 study visits

Exclusion Criteria:

- In whom it was known or assumed that the GI symptoms were not caused by treatment with MPA
- Acute rejection < 1 week before inclusion in the study
- Physically fertile women who planned to become pregnant, were pregnant and/or breastfeeding or did not wish to use effective contraception
- Presence of mental disease (such as schizophrenia, major depression) which, in the investigator's opinion, could interfere with the study requirements
- Subject to medical intervention for acute condition or hospitalised
- Any other medical condition which, in the investigator's opinion, based on memory or a review of medical records, could affect completion of the study, including, but not limited to, visual problems or cognitive deterioration
- Patients receiving an investigational drug or who had received such a drug in the 30 days prior to inclusion in the study

Number of Subjects

	MMF	EC-MPS	Total	Reasons For Exclusion	MMF	EC-MPS
Included patients [1]	66	70	137			
Safety Pop.-1	64 (100%)	70 (100%)	134 (100%)	Did not take study medication (screening fail-ure)	2 (3.0%)	
Safety Pop.-2	54 (81.8%)	59 (84.3%)	113 (82.5%)	GIQLI question-naire not vali-dated (only sites in Portugal)	12 (18.2%)	11 (15.7%)
				GIQLI question-naire incomplete and/or >20% items missing.	3 (3.5%)	2 (2.9%)
ITT population	51 (79.7%)	56 (80%)	107 (79.8%)			
				Patient not taking MMF at start of the study	0	4 (5.7%)
				GIQLI question-naire V3 with deviation of >15 days	7 (10.6%)	5 (7.1%)
PP population	44 (68.7%)	44 (62.9%)	88 (65.7%)	Non-equimolar conversion	0	6 (8.6%)
				Does not take EC-MPS at V1.	0	1 (0.7%)

[1]One patient was not randomized (screening failure): This patient is not in any of the treatment groups, but is included in the "Total" column.

Demographic and Background Characteristics

Demographic characteristics		MMF	EC-MPS
N		54	59
Age (years) (mean±SD)		49.9 (11.9)	51.8 (2.4)
Gender	Male	32 (59.3)	35 (59.3)
	Female	22 (40.7)	24 (40.7)
Race n, (%)	Caucasian	54 (100)	57 (96.6)
	African		2 (3.4)
Weight (kg) (mean±SD)		66.3 (36.2)	720.6 (12.6)
Smoker n, (%)		8 (1.8)	14 (2.4)
Education n, (%)	Unknown	1 (1.9)	1 (1.7)
	Primary	22 (40.7)	26 (44.1)
	Secondary	10 (18.5)	17 (28.8)

	Three-year degree	10 (18.5)	8 (13.6)
	Full degree	10 (18.5)	5 (8.5)
	Others	1 (1.9)	2 (3.4)
Dwelling n, (%)	Lives with partner or spouse	37 (68.5)	41 (69.5)
	Lives alone	7 (13.0)	7 (11.7)
	Unknown	1 (1.9)	1 (1.7)
	Others	9 (16.7)	7 (11.9)
Time since transplant	<6 months	9 (16.7)	6 (10.2)
n, (%)	6-12 months	8 (14.8)	9 (15.3)
	1-3 years	7 (13.0)	12 (20.3)
	4-6 years	11 (20.4)	16 (27.1)
	6-10 years	9 (16.7)	12 (20.3)
	>10 years	10 (18.5)	4 (6.8)
Type of transplant n, (%)	Cadaver donor	52 (96.3)	59 (100)
	Living donor	2 (3.7)	
Concomitant	Infections and infestations	50 (11.3)	66 (11.2)
diseases	Trauma injuries, intoxications	15 (3.4)	15 (2.6)
n (%)	Neoplasias (benign, malignant, others)	5 (1.1)	3 (0.5)
	Prior kidney transplant	12 (2.7)	8 (1.4)
	Cardiac disorders	18 (4.1)	24 (4.1)
	Congenital, hereditary, genetic disorders	7 (1.6)	11 (1.9)
	Skin and subcutaneous tissue disorders	6 (1.4)	6 (1.3)
	Blood and lymphatic tissue disorders	24 (5.4)	30 (5.1)
	Disorders of the reproductive system and breast	9 (2.0)	13 (2.2)
	Metabolism and nutrition disorders	53 (1.0)	69 (11.8)
	Disorders of the ear and labyrinth	1 (0.2)	4 (0.7)
	Immune system disorders	8 (1.8)	12 (2.0)
	Nervous system disorders	13 (2.9)	14 (2.4)
	Endocrine disorders	15 (3.4)	20 (3.4)
	Gastrointestinal disorders	28 (6.3)	47 (8.0)
	General disorders and alt. site of admin.	6 (1.4)	4 (0.7)
	Hepatobiliary disorders	4 (0.9)	8 (1.4)
	Musculoskeletal and conn. tissue disorders	14 (3.2)	17 (2.9)
	Ocular disorders	5 (1.1)	7 (1.2)
	Psychiatric disorders	7 (1.6)	9 (1.5)
	Renal and urinary disorders	21 (4.8)	29 (4.9)
	Respiratory, thoracic and mediastinal dis.	16 (3.6)	13 (2.2)
	Vascular disorders	52 (11.8)	62 (10.6)
	Benign, malignant and non-specif. neoplasias	0	5 (0.9)

Primary Objective Result(s)

Total Gastrointestinal Quality of Life Index (GIQLI) score

Total score and difference from baseline on GIQLI scale at baseline visit. V2 and V3 and last available measurement per treatment group (ITT)

Mean (SD)	MMF n=51	Difference from baseline	EC-MPS n=56	Difference from baseline
Baseline visit (Day 0)	89.4 (21.8)	-----	96.5 (19.3)	-----
Mean 95% CI	(83.2, 95.5)		(91.3, 101.7)	
Visit 2	98.6 (19.9)	9.8 (12.3)	109.2 (16.7)	11.6 (14.4)
Mean 95% CI	(93.0, 104.3)	(6.3, 13.3)	(104.5, 113.9)	(7.6, 15.6)
Visit 3	97.2 (24.8)	7.9 (19.4)	110.1 (18.3)	12.9 (19.3)
Mean 95% CI	(90.1, 104.3)	(2.3, 13.4)	(105.1, 115.2)	(7.6, 18.2)
Last available measure-ment	96.9 (24.4)	7.6 (19.1)	109.8 (17.9)	13.3 (19.1)
Mean 95% CI	(90.1, 103.8)	(2.2, 13.0)	(105.0, 114.6)	(8.2, 18.4)

ITT – Intent to Treat population

ANCOVA model for the difference in global GIQLI score at last available measurement relative to baseline (ITT)

GIQLI scale		MMF (n=51)	EC-MPS (n=56)	Difference between treatments
Global score at last available measurement	Adjusted means	99.2	107.8	-8.65
	p			0.014
	Standard error	2.5	2.3	

ITT – Intent to Treat population

Total score and difference from baseline on GIQLI scale at baseline visit. V2 and V3 per treatment group (Per Protocol)

Mean (SD)	MMF n=44	Difference from baseline	EC-MPS n=44	Difference from baseline
Baseline visit (Day 0)	88.2 (22.3)	-----	96.5 (19.7)	-----
Mean 95% CI	(81.4, 95.0)		(90.5, 102.4)	
Visit 2	98.4 (20.3)	10.8 (12.2)	110.9 (16.8)	13.0 (12.7)
Mean 95% CI	(92.1, 104.6)	(7.1, 14.6)	(105.5, 116.4)	(8.9, 17.2)
Visit 3	97.1 (25.0)	8.9 (19.0)	109.2 (18.8	12.8 (19.7)
Mean 95% CI	(89.5, 104.7)	(3.2, 14.7)	(103.5, 114.9)	(6.8, 18.8)

ANCOVA model for the difference in global GIQLI score at Visit 3 relative to baseline (Per Protocol)

GIQLI scale		MMF (n=44)	EC-MPS (n=44)	Difference between treatments
Global score at V3	Adjusted means	99.7	106.6	-6.9
	p			0.078
	Standard error	2.7	2.7	

Secondary Objective Result(s)

Tolerability of high doses of mycophenolic acid in both treatment groups

Administered doses of study treatment at the start of each visit, by treatment group (ITT).

	MMF (N=51)					EC-MPS (N=56)					
n (%)	500 mg	750 mg	1000 mg	1500 mg	2000 mg	360 mg	540 mg	720 mg	900 mg	1080 mg	1440 mg
Base-line visit (Day 0)	11 (21.6%)	6 (11.8%)	19 (37.3%)	11 (21.6%)	4 (7.8%)	10 (17.9%)	7 (12.5%)	29 (51.8%)	0 (0.0%)	5 (8.9%)	3 (5.4%)
Visit 2 (week 2)	12 (23.5%)	5 (9.8%)	18 (35.3%)	10 (19.6%)	6 (11.8%)	9 (16.1%)	4 (7.1%)	28 (50.0%)	0 (0.0%)	10 (17.9%)	5 (8.9%)
Visit 3 (week 12)	12 (23.6%)	7 (13.7%)	14 (27.5%)	11 (21.6%)	6 (11.8%)	5 (8.9%)	1 (1.8%)	31 (55.4%)	1 (1.8%)	13 (23.2%)	5 (8.9%)

Visit 2: dose at the start of visit 2
Visit 3: dose before ceasing to take the study medication (before visit 3)
ITT – Intent to Treat population

Percentage of administered dose of EC-MPS and MMF (ITT)

			MMF (N=51)	EC-MPS (N=56)	Total (N=107)
Baseline visit (Day 0)	Percentage of dose[1]	0.50	1 (2.0%)	15 (26.8%)	16 (15.0%)
		0.67	9 (17.7%)	7 (12.5%)	16 (14.9%)
		0.75	3 (5.9%)	3 (5.4%)	6 (5.6%)
		0.83		0 (0.0%)	0 (0.0%)
		1.00	38 (74.5%)	30 (53.6%)	68 (63.6%)

	N	51	55	106
	Mean (SD)	0.92 (0.2)	0.81 (0.22)	0.86 (0.2)
	P-value Student's T-test	**0.004**		

(1) Dose administered at start of visit/maximum dose reached.
ITT – Intent to Treat population

ANCOVA model including SITE for global GIQLI score at last available measurement (ITT)

GIQLI (ITT) scale including SITE		MMF (n=51)	EC-MPS (n=56)	Difference between treatments
Global score at last available measurement	Adjusted means	101.2	110.3	-9.2
	Standard error	3.4	3.3	
	p			0.012

ITT – Intent to Treat population

Overall treatment effect (OTE) scale for GI symptoms according to the patient and clinical personnel and for HRQOL according to the patient, at V3, by treatment group (ITT)

			MMF (N=51)	**EC-MPS (N=56)**
OTE for symptoms according to patient	1. Changes in GI symptoms since baseline visit	They have got worse	9 (18.0%)	3 (5.7%)
		They have improved	22 (44.0%)	37 (69.8%)
		NA	1 (2.0%)	2 (3.8%)
		There has been no change	18 (36.0%)	11 (20.8%)
		P-value chi-square test	0.015	
	2. To what extent have the GI symptoms got worse since the baseline visit	1. They are hardly worse	1 (11.1%)	0 (0.0%)
		2. They are a little worse	4 (44.4%)	0 (0.0%)
		3. They are slightly worse	0 (0.0%)	1 (33.3%)
		4. They are moderately worse	1 (11.1%)	2 (66.7%)
		5. They are considerably worse	2 (22.2%)	0 (0.0%)
		6. They are much worse	1 (11.1%)	0 (0.0%)
		7. They are a lot worse	0 (0.0%)	0 (0.0%)
		NA	0 (0.0%)	0 (0.0%)
	3. To what extent have the GI symptoms improved since the baseline visit	1. They are hardly better	0 (0.0%)	1 (2.7%)
		2. They are a little better	1 (4.6%)	1 (2.7%)

		3. They are slightly better	2 (9.1%)	3 (8.1%)
		4. They are moderately better	3 (13.6%)	6 (16.2%)
		5. They are considerably better	11 (50.0%)	11 (29.7%)
		6. They are much better	2 (9.1%)	7 (18.9%)
		7. They are a lot better	3 (13.6%)	8 (21.6%)
		NA	0 (0.0%)	0 (0.0%)
OTE for GI symptoms according to clinical per-sonnel	1. Changes in GI symptoms since baseline visit	They have got worse	9 (17.7%)	2 (3.6%)
		They have improved	20 (39.2%)	42 (75.0%)
		NA	0 (0.0%)	0 (0.0%)
		There has been no change	22 (43.1%)	12 (21.4%)
		P-value chi-square test	0.0006	
	2. To what extent have the GI symptoms got worse since the baseline visit	1. They are hardly worse	1 (11.1%)	0 (0.0%)
		2. They are a little worse	3 (33.3%)	0 (0.0%)
		3. They are slightly worse	0 (0.0%)	1 (50.0%)
		4. They are moderately worse	2 (22.2%)	1 (50.0%)
		5. They are considerably worse	2 (22.2%)	0 (0.0%)
		6. They are much worse	1 (11.1%)	0 (0.0%)
		7. They are a lot worse	0 (0.0%)	0 (0.0%)
		NC	0 (0.0%)	0 (0.0%)
	3. To what extent have the GI symptoms improved since the baseline visit	1. They are hardly better	2 (10.0%)	1 (2.4%)
		2. They are a little better	2 (10.0%)	7 (16.7%)
		3. They are slightly better	2 (10.0%)	0 (0.0%)
		4. They are moderately better	4 (20.0%)	9 (21.4%)
		5. They are considerably better	8 (40.0%)	11 (26.2%)
		6. They are much better	2 (10.00%)	6 (14.3%)
		7. They are a lot better	0 (0.0%)	8 (19.1%)
		NA	0 (.0%)	0 (0.0%)
OTE for HRQOL according to patient	1.Changes in general state of health since baseline visit	It has got worse	8 (16.3%)	3 (6.0%)
		It has improved	22 (44.9%)	29 (58.0%)
		NA	1 (2.0%)	4 (8.0%)
		No change	18 (36.7%)	14 (28.0%)

	P-value chi-square test	0.158	
2.To what extent has your general state of health got worse since the baseline visit	1. It has hardly got worse	0 (0.0%)	0 (0.0%)
	2. It has got a little worse	4 (50.0%)	1 (33.3%)
	3. It has got slightly worse	0 (0.0%)	1 (33.3%)
	4. It has got moderately worse	2 (25.0%)	1 (33.3%)
	5. It has got considerably worse	2 (25.0%)	0 (0.0%)
	6. It has got much worse	0 (0.0%)	0 (0.0%)
	7. It has got a lot worse	0 (0.0%)	0 (0.0%)
	NA	0 (0.0%)	0 (0.0%)
	1. It is hardly better	0 (0.0%)	1 (3.5%)
	2. It is a little better	3 (13.6%)	2 (6.9%)
	3. It is slightly better	3 (13.7%)	3 (10.4%)
	4. It is moderately better	2 (9.1%)	2 (6.9%)
	5. It is considerably better	11 (50.0%)	6 (20.7%)
	6. It is much better	2 (9.1%)	9 (31.0%)
	7. It is a lot better	1 (4.6%)	6 (20.7%)
	NA	0 (0.0%)	0 (0.0%)

ITT – Intent to Treat population

Safety Results

Summary of reported AEs, by treatment group (SP-2)

	MMF n=54		EC-MPS n=59		TOTAL n=113	
	AEs n	No. patients n (%)	AEs n	No. patients n (%)	AEs n	No. patient n (%)
Total AEs	69	26 (48.2)	104	29 (49.2)	173	55 (48.7)
Total severe AEs	8	5 (9.3)	23	5 (8.5)	31	10 (8.9)
Total related AEs	25	12 (22.2)	24	12 (20.3)	49	24 (21.2)
Total severe related AEs	6	3 (5.6)	5	1 (1.7)	11	4 (3.5)
Total AEs causing suspension	0	0	2	1 (1.69)	2	1 (0.88)
No. patients with at least 1 AE		36 (66.7)		43 (72.9)		79 (73.8)
Intensity: Mild	42	(60.9%)	60	(57.7%)	102	(59.0%)
Moderate	18	(26.1%)	30	(28.9%)	48	(27.8%)
Severe	9	(13.0%)	14	(13.5%)	23	(13.3%)

SP-2:Safety population 2

Most commonly reported AEs (SP-2)

AEs n (%)	MMF n=54			EC-MPS n=59		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Oedema	2 (3.7)	0	0	2 (3.7)	1 (1.7)	0
Periph. oedema	3 (5.6)	1 (1.9)	0	0	1 (1.7)	0
Anaemia	4 (7.4)	2 (3.7)	0	1 (1.7)	2 (3.4)	1 (1.7)
Dyslipidaemia	0	0	0	3 (5.1)	1 (1.7)	0
High creatinine	2 (3.7)	0	0	2 (3.4)	0	0
Headache	0	0	0	2 (3.4)	0	0
Hypertension	1 (1.9)	1 (1.9)	0	2 (3.4)	1 (1.7)	0

SP-2:Safety population 2

Adverse Events by System Organ Class

Number of patients and number of AEs: Relationship to study treatment and treatment group (SP-2)

	MMF (n=54)		EC-MPS (n=59)	
	Not suspected	Suspected	Not suspected	Suspected
Number of AEs	44 (63.8%)	25 (36.2%)	80 (76.9%)	24 (23.1%)
Number of patients **with at least 1 AE**	22 (40.7%)	12 (22.2%)	25 (42.4%)	12 (20.3%)

SP-2 – Safety Population 2

Number of AEs by SOC, action taken, treatment group and equimolar dose, from baseline to Visit 2 (SP-2)

Number of AEs by SOC	No action		Dose adjusted/ temporarily suspended		Concomitant medication		Alternative therapy (no medication)		Hospitalization	
Disorders	MMF n=54	EC-MPS n=59	MMF n=54	EC-MPS n=59	MMF n=54	EC-MPS n=59	MMF n=54	EC-MPS n=59	MMF n=54	EC-MPS n=59
1	1	5	1	0	0	2	0	0	0	1
2	0	1	0	0	0	2	0	0	0	1
3	0	8	0	0	1	1	0	0	0	0
4	0	1	0	0	0	2	0	0	0	0
5	0	0	1	0	1	3	0	0	1	0
6	0	1	0	1	1	1	0	0	0	0
7	0	4	1	0	0	0	0	0	1	0
8	0	0	0	0	1	1	1	0	0	1
9										
10	0	1	0	0	0	0	0	0	0	0
11										
12	0	0	0	0	0	0	0	0	0	0
13										
14										
15	0	1	0	0	0	0	0	0	0	0
16	0	0	1	0	0	0	0	0	0	0
17										
18										
Total AEs	1	22	4	1	4	12	1	0	2	3
No. patients with at least 1 AE n (%)	1 (1.9)	13 (22.0)	3 (5.6)	1 (1.7)	3 5.7)	6 (10.2)	1 (1.9)	0	1 (1.9)	1 (1.7)

SOCs: Disorders 1: Renal and urinary; 2: Infections and infestations; 3: General and administration site alterations: 4:

Blood and lymphatic system; 5: Metabolism and nutrition; 6: Gastrointestinal; 7: Supplementary examinations; 8: Reproductive system and breast; 9: Musculoskeletal and connective tissue; 10: Nervous system; 11: Respiratory, thoracic and mediastinal; 12: Vascular; 13: Trauma, intoxications and complications from therapeutic procedures; 14: Psychiatric; 15: Neoplasias; 16: Skin and subcutaneous tissue; 17: Ocular; 18: Medical and surgical procedures.

No. of patients = No. of patients with at least 1 AE by SOC ; SP-2 – Safety Population 2

Serious Adverse Events and Deaths

Number of patients and number of serious AEs (SAEs), by intensity, SOC, relationship with the drug, action taken and treatment group (SP-2)

	MMF n=54			EC-MPS n=59		
Number of SAEs	8 (14.8%)			23 (39%)		
No. of patients with at least 1 SAE	5 (9.3%)			6 (10.2%)		
Intensity	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
No. of SAEs	0	0	8	3	8	12
No. patients with at least 1 SAE n (%)	0	0	5 (9.3)	1 (1.7)	2 (3.4)	3 (5.1)
SOC	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
No. of SAEs	0	0	8	3	8	12
Infec. + infestations	0	0	2	2	0	2
Renal and urin. dis.	0	0	3	0	1	2
Blood and lymph. dis.	0	0	0	0	1	4
Metab and nut. dis.	0	0	1	0	1	0
GI disorders	0	0	1	1	0	0
General dis.	0	0	0	0	1	2
Resp. thor. dis.	0	0	0	0	2	0
Supp. exams	0	0	1	0	0	0
Trauma inj, intox.	0	0	0	0	1	0
Med. and surg. proc.	0	0	0	0	0	1
Reprod. system and breast	0	0	0	0	0	1
Vascular dis.	0	0	0	0	1	0
Relationship with drug	**Not suspected**		**Suspected**	**Not suspected**		**Suspected**
No. of SAEs	2		6	18		5
No. patients with at least 1 SAE, n (%)	2 (3.7)		3 (5.6)	4 (6.8)		1 (1.7)
Action taken	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**

No. of SAEs	5	0	3	0	8	2	2	23	2	14
No. patients with at least 1 SAE, n (%)	3 (5.6)	0	2 (3.7)	0	5 (9.3)	1 (1.7)	1 (1.7)	5 (8.5)	1 (1.7)	4 (6.8)

Action taken: 1: No action; 2: Dose adjusted/temporarily suspended; 3: Dose permanently suspended; 4: Concomitant medication; 5: Hospitalization.

SP-2 – Safety Population 2

GI disorders during the study by type of disorder and treatment group (SP-2)

		MMF (N=54)	Mycophenolate Sodium (N=59)	P-value chi-square test
Number of GI disorders		108	86	
Number of patients with at least one GI disorder		47 (87.0%)	40 (67.8%)	**0.015**
Diarrhea	Disorders	47	33	
	Persists at end of study	19	6	
	Patients	33 (61.1%)	25 (42.4%)	**0.046**
Constipation	Disorders	3	2	
	Persists at end of study	3	0	
	Patients	3 (5.6%)	2 (3.4%)	0.576
Dyspepsia	Disorders	15	12	
	Persists at end of study	12	5	
	Patients	15 (27.8%)	12 (20.4%)	0.354
Reflux	Disorders	5	5	
	Persists at end of study	3	4	
	Patients	5 (9.6%)	5 (8.5%)	0.882
Nausea	Disorders	7	3	
	Persists at end of study	3	1	
	Patients	7 (13.0%)	3 (5.1%)	0.141
Vomiting	Disorders	7	3	
	Persists at end of study	2	1	
	Patients	7 (13.0%)	3 (5.1%)	0.141
Abdominal pain/swelling	Disorders	20	25	
	Persists at end of study	13	14	
	Patients	19 (35.2%)	25 (42.4%)	0.434
Others	Disorders	4	3	
	Persists at end of study	2	1	
	Patients	4 (7.4%)	3 (5.1%)	0.609

SP-2 – Safety Population 2

Date of Clinical Trial Report 25 Aug 2009
Date Inclusion on Novartis Clinical Trial Results Database 27 May 2010
Date of Latest Update