Sponsor

Novartis

Generic Drug Name

Mycophenolate Sodium

Therapeutic Area of Trial

Renal Transplantation

Approved Indication

Prophylaxis of organ rejection in patients receiving allogenic renal transplants, administered in combination with cyclosporine and corticosteroids.

Enteric-coated mycophenolate sodium is approved in:

Albania, Argentina, Aruba, Australia, Austria, Bahrain, Bangladesh, Belarus, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Curacao, Cyprus, Czech Republic, Denmark, Dominican Republic, Ecuador, Egypt, El Salvador, Estonia, Finland, France, Germany, Greece, Guatemala, Honduras, Hong Kong, Hungary, Iceland, India, Indonesia, Iraq ,Ireland, Israel, Italy, Jamaica, Jordan, Kazakhstan, Kuwait, Latvia, Lebanon, Libya, Lithuania, Luxembourg, Macedonia, Malaysia, Malta, Mexico, Netherlands, New Zealand, Nicaragua, Norway, Oman, Pakistan, Palestine, Panama, Peru, Philippines, Poland, Portugal, Qatar, Russia, Saudi Arabia, Serbia & Montenegro, Singapore, Slovakia, Slovenia, South Korea, Spain, Sudan, Sweden, Switzerland, Syria, Taiwan, Thailand, Trinidad & Tobago, Turkey, United Kingdom, United Arab Emirates, Ukraine, Uruguay, United States, Venezuela, Yemen, Yugoslavia

Study Number

CERL080A2404E1

Title

A 24-month extension to a 12-month, randomized, multicenter, open-label study to investigate the clinical outcomes of two immunosuppressive regimens of mycophenolate sodium (EC-MPS) with short-term steroid use or free of steroids compared with a regimen of mycophenolate sodium with standard steroids in de novo kidney recipients - FREEDOM Study

Phase of Development

Phase IV

Study Start/End Dates

16-Mar-2004 to15-May 2006

Study Design/Methodology

This was a multicenter, open-label extension study to core study CERL080A2404 and was designed to collect long-term safety and tolerability data of EC-MPS. All patients of the core study who completed the treatment phase and were interested of being treated with EC-MPS could have been included in this extension study.

Visits were performed every 6 months (Visit 12, 13, 14 and 15). At each of these visits, vital signs, incidence and severity of adverse events (AEs) (including malignancies and infections), patient survival, graft survival, chronic rejection, acute rejection, renal function (serum creatinine), hematology parameters, blood chemistry (glucose and total cholesterol) and cyclosporine C-2 blood levels were reported.

Basic immunosuppression was Cyclosporine microemulsion – CsA-ME (C-2 monitored). There were optional visits every 3 months for drug dispensing purposes only.

Centres

12 centers in 6 countries: Canada (6), Italy (1), Malaysia (1), New Zealand (1), Spain (2), United States (1)

Publication

Objectives

Primary objective(s)

- Long-term safety and tolerability data of mycophenolate sodium on the patients who completed the core study and consented to participation in the extension study until drug was commercially available in specific countries

Secondary objective(s)

- Biopsy proven acute rejection (BPAR), graft loss and death

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

All patients enrolled in the extension study received mycophenolate sodium 720mg (2 enteric coated tablets of 360mg) b.i.d., 12 hours apart (unless the dose was adjusted for clinical reasons) with or without steroid therapy according to the treatment given at the end of the core study treatment:

- Group A: mycophenolate sodium 720mg b.i.d. without any steroids
- Group B: mycophenolate sodium 720mg b.i.d. with a short-term steroids use in the core study (Day 1-3: methylprednisolone i.v., Day 4-7: oral prednisone).

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

Group C (reference): mycophenolate sodium 720mg b.i.d. with standard steroid therapy.

Criteria for Evaluation

Primary variables

Adverse events & Serious Adverse events

Secondary variables

BPAR, graft loss and death

Safety and tolerability

See primary variables above

Pharmacology

None

Other

None

Statistical Methods

Data from all patients participating in the extension phase were summarized with respect to demographic and baseline characteristics, and to efficacy and safety observations and measurements. The descriptive efficacy and safety analyses followed those described in the core protocol.

Study Population: Inclusion/Exclusion Criteria and Demographics

All patients who completed core study CERL080A2404, still receiving the study drug who were willing to continue treatment, and from whom written informed consent had been obtained

The main Inclusion/Exclusion criteria for the core studies were:

Inclusion criteria

- Males or females, 18 to 75 years old
- Recipient of first, heart-beating, cadaveric, living unrelated or living related non-HLA identical donor kidney transplant treated with Basiliximab and cyclosporine microemulsion
- For females capable of becoming pregnant, negative pregnancy test prior to entry into trial and effective birth control during trial and at least 4 months after randomization, even when there has been a history of infertility

Exclusion criteria

- Second or subsequent kidney transplant or multi-organ recipients
- Recipients from a non-heart-beating donor or HLA identical living related donors
- Known hypersensitivity to Mycophenolic acid or other components of formulation
- HIV positive or Hepatitis B surface antigen or Hepatitis C positive with advanced liver disease or with clinical or pathological diagnosis of cirrhosis
- History of malignancy (past 5 years)
- Pregnancy or planned pregnancy, Lactating, or unwillingness to use effective contraception.
- Evidence of severe liver disease

Patient disposition (eligible extension population)

	EC-MPS without steroids	EC-MPS + short-term steroids	EC-MPS + standard steroids	Total
Total no. of patients – n (%)				
Eligible for extension study	84	82	89	255
Entered extension study	22 (100.0)	30 (100.0)	27 (100.0)	79 (100.0)
Completed	20 (90.9)	22 (73.3)	24 (88.9)	66 (83.5)
Discontinued treatment prematurely – n (%)				
Total	2 (9.1)	8 (26.7)	3 (11.1)	13 (16.5)
Administrative problems	1 (4.5)	3 (10.0)	2 (7.4)	6 (7.6)
Adverse event(s)	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.3)
Abnormal laboratory value(s)	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.3)
Unsatisfactory therapeutic effect	0 (0.0)	0 (0.0)	1 (3.7)	1 (1.3)
Protocol violation	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.3)
Subject withdrew consent	1 (4.5)	0 (0.0)	0 (0.0)	1 (1.3)
Death	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.3)
Graft loss	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.3)

EC-MPS without steroids: EC-MPS 720 mg + Cyclosporine ME + Basiliximab
EC-MPS + short-term steroids: EC-MPS 720 mg + Cyclosporine ME + Basiliximab+ short-term steroids
EC-MPS + standard steroids: EC-MPS 720 mg + Cyclosporine ME + Basiliximab+ standard steroids
Treatment allocation as from the core study.

Demographic and Background Characteristics

	EC-MPS without steroids (N=22)	EC-MPS + short-term steroids (N=30)	EC-MPS + standard steroids (N=27)	Total (N=79)
Patient's age (yr) at extension start				
Mean (SD)	46.0 (15.08)	43.8 (11.87)	45.8 (14.85)	45.1 (13.72)
Median (range)	47.5 (20 – 71)	44.0 (19 – 67)	46.0 (18 – 68)	46.0 (18 – 71)
18-60 yr – n (%)	18 (81.8)	27 (90.0)	22 (81.5)	67 (84.8)
>60 yr – n (%)	4 (18.2)	3 (10.0)	5 (18.5)	12 (15.2)
Patient's sex – n (%)				
Male	13 (59.1)	19 (63.3)	15 (55.6)	47 (59.5)
Female	9 (40.9)	11 (36.7)	12 (44.4)	32 (40.5)
Patient's race – n (%)				
Caucasian	21 (95.5)	22 (73.3)	17 (63.0)	60 (75.9)
Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oriental	0 (0.0)	4 (13.3)	5 (18.5)	9 (11.4)
Other	1 (4.5)	4 (13.3)	5 (18.5)	10 (12.7)

Primary Objective Result(s)

See Adverse events and Serious Adverse event tables

Secondary Objective Result(s)

Population Endpoint	EC-MPS without steroids (N=22) n = %	EC-MPS + short-term steroids (N=30) n = %	EC-MPS + standard steroids (N=27) n = %
Biopsy proven acute rejection	2 (9.1)	0	2 (7.4)
Chronic Nephropathy	0	2 (6.7)	1
Graft loss	0	1	0
Death	0	1	0
Treatment failure*	2 (9.1)	2 (6.7)	2 (7.4)

* Treatment failure defined as BPAR, graft loss or death

Safety Results

Adverse Events by System Organ Class

MedDRA primary system organ class Preferred term	EC-MPS without steroids (N=22) n (%)	EC-MPS + short-term steroids (N=30) n (%)	EC-MPS + standard steroids (N=27) n (%)
Any adverse event	18 (81.8)	23 (76.7)	22 (81.5)
Infections and infestations	6 (27.3)	10 (33.3)	15 (55.6)
Upper respiratory tract infection	2 (9.1)	2 (6.7)	4 (14.8)
Urinary tract infection	1 (4.5)	3 (10.0)	3 (11.1)
Herpes zoster	0	2 (6.7)	3 (11.1)
Bronchitis	0	0	3 (11.1)
General disorders & admin. site cond.	8 (36.4)	10 (33.3)	9 (33.3)
Oedema peripheral	3 (13.6)	4 (13.3)	3 (11.1)
Pyrexia	3 (13.6)	4 (13.3)	1 (3.7)
Fatigue	1 (4.5)	1 (3.3)	3 (11.1)
Gastrointestinal disorders	6 (27.3)	8 (26.7)	10 (37.0)
Diarrhea	1 (4.5)	3 (10.0)	3 (11.1)
Vomiting	0	4 (13.3)	0
Nervous system disorders	5 (22.7)	8 (26.7)	9 (33.3)
Headache	4 (18.2)	2 (6.7)	5 (18.5)
Dizziness	2 (9.1)	3 (10.0)	1 (3.7)
Musculoskeletal & conn. tissue dis.	6 (27.3)	8 (26.7)	7 (25.9)
Arthralgia	1 (4.5)	4 (13.3)	2 (7.4)
Muscle spasms	3 (13.6)	1 (3.3)	1 (3.7)
Pain in extremity	1 (4.5)	1 (3.3)	3 (11.1)
Respiratory, thoracic & mediastinal dis.	4 (18.2)	2 (6.7)	10 (37.0)
Cough	2 (9.1)	1 (3.3)	3 (11.1)
Nasal congestion	1 (4.5)	0	3 (11.1)
Metabolism and nutrition disorders	6 (27.3)	4 (13.3)	4 (14.8)
Renal and urinary disorders	5 (22.7)	2 (6.7)	7 (25.9)

Proteinuria	3 (13.6)	0	1 (3.7)
Investigations	4 (18.2)	3 (10.0)	6 (22.2)
Psychiatric disorders	4 (18.2)	4 (13.3)	4 (14.8)
Blood & lymphatic system disorders	3 (13.6)	2 (6.7)	5 (18.5)
Anemia	1 (4.5)	2 (6.7)	3 (11.1)
Eye disorders	4 (18.2)	1 (3.3)	3 (11.1)
Injury, poisoning & proc. complications	1 (4.5)	3 (10.0)	4 (14.8)
Skin & subcutan. tissue disorders	2 (9.1)	3 (10.0)	2 (7.4)
Immune system disorders	0	0	3 (11.1)
Neoplasms benign, malignant and unspecified (incl. cysts)	2 (9.1)	1 (3.3)	3 (11.1)

Only AEs which started or worsened between first and last EC-MPS extension dose + 7 days were analyzed.

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

MedDRA primary system organ class Preferred term	EC-MPS without steroids (N=22) n (%)	EC-MPS + short-term steroids (N=30) n (%)	EC-MPS + standard steroids (N=27) n (%)
Upper respiratory tract infection	2 (9.1)	2 (6.7)	4 (14.8)
Urinary tract infection	1 (4.5)	3 (10.0)	3 (11.1)
Oedema peripheral	3 (13.6)	4 (13.3)	3 (11.1)
Pyrexia	3 (13.6)	4 (13.3)	1 (3.7)
Diarrhea	1 (4.5)	3 (10.0)	3 (11.1)
Headache	4 (18.2)	2 (6.7)	5 (18.5)
Dizziness	2 (9.1)	3 (10.0)	1 (3.7)
Arthralgia	1 (4.5)	4 (13.3)	2 (7.4)
Cough	2 (9.1)	1 (3.3)	3 (11.1)
Anemia	1 (4.5)	2 (6.7)	3 (11.1)

Serious Adverse Events and Deaths

	EC-MPS without steroids	EC-MPS + short-term steroids	EC-MPS + standard steroids
No. (%) of subjects studied	22	30	27
No. (%) of subjects with AE(s)			
Number (%) of subjects with serious or other significant events	n (%)	n (%)	n (%)
Death	0	1(3.3)	0
SAE(s)	2 (9.1)	4(13.3)	8 (29.6)
Discontinued due to SAE(s)	0	1(3.3)	0

MedDRA primary system organ class Preferred term	EC-MPS without steroids (N=22) n (%)	EC-MPS + short-term steroids (N=30) n (%)	EC-MPS + standard steroids (N=27) n (%)
Any serious AE / infection	2 (9.1)	4 (13.3)	8 (29.6)
Infections and infestations	2 (9.1)	0	5 (18.5)
Pneumonia	0	0	2 (7.4)
Enterococcal bacteremia	1 (4.5)	0	0
Escherichia bacteremia	0	0	1 (3.7)
Gastroenteritis	1 (4.5)	0	0
Herpes zoster	0	0	1 (3.7)
Human polyomavirus infection	0	0	1 (3.7)
Sepsis	0	0	1 (3.7)
Cardiac disorder	0	2 (6.7)	0
Atrial fibrillation	0	1 (3.3)	0
Cardiac arrest	0	1 (3.3)	0
General disorders & admin. site conditions	2 (9.1)	0	0
Pyrexia	2 (9.1)	0	0
Neoplasms benign, malign. & unspecified	1 (4.5)	0	1 (3.7)
Basal cell carcinoma	0	0	1 (3.7)
Thyroid cancer	1 (4.5)	0	0
Nervous system disorder	0	1 (3.3)	1 (3.7)
Dizziness	0	1 (3.3)	0
Hypoglycemic coma	0	0	1 (3.7)
Renal and urinary disorders	1 (4.5)	0	1 (3.7)
Nephrolithiasis	0	0	1 (3.7)
Ureteric stenosis	1 (4.5)	0	0
Endocrine disorders	1 (4.5)	0	0
Hyperparathyroidism	1 (4.5)	0	0
Gastrointestinal disorders	0	1 (3.3)	0
Diarrhea	0	1 (3.3)	0
Vascular disorders	0	0	1 (3.7)
Hypertensive crisis	0	0	1 (3.7)

Other Relevant Findings

None

Date of Clinical Trial Report 03-Aug-2007
Date Inclusion on Novartis Clinical Trial Results Database 5-Sept-2007
Date of Latest Update