SAFETY REPORT ADVERSE EVENTS

PROTOCOL MYCUV-IIT02

Title: MYFORTIC (ENTERIC-COATED MYCOPHENOLATE SODIUM) FOR THE TREATMENT OF NON-INFECTIOUS INTERMEDIATE UVEITIS – A PROSPECTIVE, CONTROLLED, RANDOMIZED MULTICENTER TRIAL

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Investigational Product: Myfortic® (enteric-coated mycophenolate sodium)
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TABLE OF CONTENTS

SYNOPSIS

TITLE	Myfortic (enteric-coated mycophenolate sodium) for the treatment of non-infectious intermediate uveitis - a prospective, controlled, randomized multicenter trial
PROTOCOL NUMBER	MYCUV-IIT02
EUDRACT NUMBER	2009-009998-10
SPONSOR	Centre for Ophthalmology, University of Tübingen
FINANCIAL SUPPORT	Novartis Pharma GmbH, Nürnberg
PRINCIPAL INVESTIGATOR	Christoph Deuter, MD
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MONITORING	STZ *eyetrial* at the Centre for Ophthalmology, University of Tübingen
OBJECTIVES	To evaluate the efficacy, safety and tolerability of enteric-coated mycophenolate sodium in combination with low-dose corticosteroids compared to a monotherapy with low-dose corticosteroids in subjects with non-infectious intermediate uveitis
ELIGIBILITY CRITERIA	Inclusion criteria: • Subjects with a documented at least 6 months history of unilateral or bilateral intermediate uveitis either idiopathic or due to non-infectious systemic disease (e.g. sarcoidosis, multiple sclerosis) • Uveitis has to be considered to be active at the timepoint of enrollment according to at least one of the following criteria: o Grade 2+ or higher for vitreous haze o Grade 2+ or higher for anterior chamber cells o Presence of cystoid macular edema in OCT o Presence of retinal vessel leakage in FA • Considered by the investigator to require systemic treatment. • At least 18 years of age • Not planning to undergo elective ocular surgery during the study • Capable of understanding the purposes and risks of the study, able to give informed consent and to comply with the study requirements • Subjects of both gender with reproductive potential who are sexually active agree to use contraception throughout the course of the study and for at least 3 months after completion of their study participation. • Women of childbearing potential have to use a highly effective method of birth control defined as one which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, hormonal IUDs combined with barrier methods (e.g. condom, diaphragm or spermicide), sexual abstinence or vasectomised partner. • Women of childbearing age must have a negative urine

	pregnancy test (UPT) within 48 hours prior to starting study drug and at the end of the trial and must not be lactating. Female subjects of non-childbearing potential must meet at least one of the following criteria: 1. Postmenopausal females, defined as: a. Females over the age of 60 years. b. Females who are 45 to 60 years of age must be amenorrheic for at least 2 years. 2. Females who had a hysterectomy and/or bilateral oophorectomy. Exclusion criteria: • Uveitis of infectious etiology • Signs of tuberculosis in chest x-ray during the past 12 months prior to study entry • Clinically suspected or confirmed central nervous system or ocular lymphoma • Primary diagnosis of anterior or posterior uveitis • Uncontrolled glaucoma or known steroid response • Subjects who received treatment with a systemic immunosuppressive drug, a monoclonal antibody or any other biologic therapy within 90 days prior study entry • Treatment with mycophenolate mofetil or mycophenolate sodium in the past • Treatment with a periocular steroid injection within 6 weeks prior to study entry • Presence of absolute contraindications for Decortin H and/or Myfortic as mentioned in the product informations (Appendix 1 and 2) • Presence of relative contraindications for Decortin H and/or Myfortic as mentioned in the product information (Appendix 1 and 2) if the disorder leading to the relative contraindication can not sufficiently managed by concomitant medication. • Recipients of a solid organ transplant • Subjects with lens opacities or obscured ocular media upon enrolment making unable evaluation of the posterior eye segment • Subjects with a history of herpes zoster or varicella infection within 3 months before enrolment • Active, extraocular infection requiring the prolonged or chronic use of antimicrobial agents or the history of active hepatitis A, B or C • Seropositivity for human immunodeficiency virus (HIV) • Alanine transaminase (ALT), aspartate transaminase (AST), or gamma-glutamyl transferase (GGT) ≥ 2x upper limit of normal (ULN) • Severe anemia (hemoglobin < 8 g/dL), leukopenia (white blood

	cell count [WBC] < 2500 mm^3), thrombocytopenia (platelet count < 80,000 mm^3) • Current malignancy or a history of malignancy within the previous 5 years • Pregnant or lactating women • Known allergy for fluorescein natrium • Currently participating in another clinical trial with an investigational agent in the 30 days prior to study participation and/or has not recovered from any reversible effects or side effects of prior investigational agent • Subjects with non-ocular, medically significant co-morbid conditions that impair normal activities, require systemic corticosteroids or immunosuppressives, or any medical condition that would likely have an impact on the participant´s ability to comply with the study visit schedule • Any current or history of substance abuse, psychiatric disorder or a condition that, in the opinion of the investigator, may invalidate communication
STUDY DESIGN	A phase 3 open, prospective, controlled, randomized, multicenter trial of mycophenolate sodium in the treatment of non-infectious intermediate uveitis
PRIMARY ENDPOINT	To evaluate whether a Myfortic based regimen will be able to reduce the probability of a relapse compared to steroid therapy alone. The primary endpoint of the study is defined as the time from study entry to the first relapse. Definition of relapse: • Deterioration of BCVA ≥ 3 lines compared to best BCVA from baseline. • At least 2-step increase of vitreous haze compared to lowest grade of vitreous haze from baseline or increase from 3+ to 4+. • At least 2-step increase of anterior chamber cells compared to lowest grade of anterior chamber cells from baseline or increase from 3+ to 4+. • New onset or worsening of preexisting cystoid macular edema, proven by Optical Coherence Tomography (OCT) • New onset or worsening of retinal vasculitis (sheating and/or leakage of retinal vessels), proven by fluorescein angiography (FA).
SECONDARY ENDPOINTS	To test whether a Myfortic based therapy provides superiority compared to a steroid regimen in terms of: • Time to relapse before and after switch from control arm to treatment arm • Dose of steroids at the timepoint of relapse before and after switch from control arm to treatment arm • Change from baseline in Best Corrected Visual Acuity (BCVA) according to the SUN-Criteria using the Early Treatment Diabetic Retinopathy Study (ETDRS) method • Change from baseline in foveal thickness, measured by Optical Coherence Tomography (OCT)

	• Change from baseline in retinal vessel leakage, measured by Fluoresceine Angiography (FA) • Number and severity of adverse events • Ratio of patients with need of dose reduction for mycophenolatesodium due to side effects
NUMBER OF CENTERS AND PATIENTS	6 centers in Germany; 144 patients in total; 1:1 randomization
DURATION OF STUDY	Enrollment period: 21 months Treatment period: 15 months Overall duration: 36 months
STUDY DRUG	Investigational drug: Mycophenolate sodium (Myfortic®) Reference therapy: Prednisolone (Decortin H®) Subjects will be randomized to one of the following treatment arms in a 1:1 ratio: • **Treatment arm:** Oral Decortin H at an initial dose of 1 mg/kg body weight; Dose reduction: 25 mg/week until 50 mg/d 10 mg/week until 30 mg/d 5 mg/week until 20 mg/d 2,5 mg/week until maintenance dose Maintenance dose: 5 mg/d Myfortic 360 mg BID (during week 1) Myfortic 720 mg BID (from week 2 on) • **Control arm:** Oral Decortin H at an initial dose of 1 mg/kg body weight; Dose reduction: 25 mg/week until 50 mg/d 10 mg/week until 30 mg/d 5 mg/week until 20 mg/d 2,5 mg/week until maintenance dose Maintenance dose: 5 mg/d Patients in whom the first relapse occurs within 6 months from study entry are allowed to switch to the treatment arm. In this case the dose of Decortin H® has to be increased again to approximately 1 mg /kg bodyweight with subsequent tapering as described above. In parallel, Myfortic® will be added according to the dose regimen described for the treatment arm.

	• **Additional Therapy:** Following additional medication for uveitis is allowed during the study: • Oral acetazolamide (e.g. Diamox®) in a dose up to 250 mg BID. Dose has to be stable for at least 2 weeks prior to study inclusion. Tapering should be started at visit 4 (month 3) at the discretion of the investigator. • Topical prednisolone, topical non-steroidal anti-inflammatory drugs. Dose has to be stable for at least 2 weeks prior to study inclusion. Tapering should be started at visit 4 (month 3) at the discretion of the investigator. • Mydriatics
DISCONTINUATION OF SUBJECTS FROM THE STUDY	Discontinuation from the study and end of study visit has to be performed if • ocular disease shows no improvement (no change or increase of anterior chamber cells and/or vitreous haze and/or cystoid macular edema) at visit 3 (month 1) • the first relapse occurs in any eye of a patient who has been primarily randomized to the treatment arm. • the first relapse occurs more than 6 months from study in any eye of a patient who has been primarily randomized to the control arm. • a relapse occurs in any eye of a patient after switching from the control arm to the treatment arm. If a subject has to be discontinued from the study, further treatment will be initiated at the discretion of the investigator.
ASSESSMENT OF SAFETY	• Incidence and severity of adverse events (including lab AEs)
STATISTICAL ANALYSIS	• For analysing the primary endpoint, the time from study entry to the first relapse, Kaplan-Meier curves will be calculated. • A two-sided log-rank test will be used to evaluate differences between the treatment and control group at a significance level of 0.05. • The analysis will be carried out on the Intention-To-Treat population (randomised patients who received at least one dose of medication and for whom at least one post-baseline assessment is available).

1 PREVIOUS REPORTED SIDE EFFECTS

The incidence of adverse events for Myfortic® (mycophenolic acid) was determined in randomized, comparative, active-controlled, double-blind, double-dummy trials in prevention of acute rejection in de novo and maintenance kidney transplant patients.

The principal adverse reactions associated with the administration of Myfortic include constipation, nausea, and urinary tract infection in de novo patients and nausea, diarrhea and nasopharyngitis in maintenance patients.

Adverse events reported in ≥ 20% of patients receiving Myfortic or mycophenolate mofetil in the 12-month de novo renal study and maintenance renal study, when used in combination with cyclosporine, USP (MODIFIED) and corticosteroids, are listed in Table 1. Adverse event rates were similar between Myfortic and mycophenolate mofetil in both de novo and maintenance patients.

Table 1: Adverse Events (%) in Controlled de novo and Maintenance Renal Studies Reported in ≥ 20% of Patients

	de novo Renal Study		Maintenance Renal Study	
	Myfortic® 1.44 g/day (n=213)	mycophenolate mofetil 2 g/day (n=210)	Myfortic® 1.44 g/day (n=159)	mycophenolate mofetil 2 g/day (n=163)
Blood and Lymphatic System Disorders				
Anemia	21.6	21.9	-	-
Leukopenia	19.2	20.5	-	-
Constipation	38.0	39.5	-	-
Nausea	29.1	27.1	24.5	19.0
Diarrhea	23.5	24.8	21.4	24.5
Vomiting	23.0	20.0	-	-
Dyspepsia	22.5	19.0	-	-
Urinary Tract Infection	29.1	33.3	-	-
CMV Infection	20.2	18.1	-	-
Insomnia	23.5	23.8	-	-
Postoperative Pain	23.9	18.6		

Table 2 summarizes the incidence of opportunistic infections in de novo and maintenance transplant patients, which were similar in both treatment groups.

Table 2: Viral and Fungal Infections (%) Reported Over 0-12 Months

	de novo Renal Study		Maintenance Renal Study	
	Myfortic® 1.44 g/day (n = 213) (%)	mycophenolate mofetil 2 g/day (n = 210) (%)	Myfortic® 1.44 g/day (n = 159) (%)	mycophenolate mofetil 2 g/day (n = 163) (%)
Any Cytomegalovirus	21.6	20.5	1.9	1.8
- Cytomegalovirus Disease	4.7	4.3	0	0.6
Herpes Simplex	8.0	6.2	1.3	2.5
Herpes Zoster	4.7	3.8	1.9	3.1
Any Fungal Infection	10.8	11.9	2.5	1.8
- Candida NOS	5.6	6.2	0	1.8
- Candida Albicans	2.3	3.8	0.6	0

The following opportunistic infections occurred rarely in the above controlled trials: aspergillus and cryptococcus.

The incidence of malignancies and lymphoma is consistent with that reported in the literature for this patient population. Lymphoma developed in 2 de novo patients (0.9%), (one diagnosed 9 days after treatment initiation) and in 2 maintenance patients (1.3%) (one was AIDS-related), receiving Myfortic with other immunosuppressive agents in the 12-month controlled clinical trials. Nonmelanoma skin carcinoma occurred in 0.9% de novo and 1.8% maintenance patients. Other types of malignancy occurred in 0.5% de novo and 0.6% maintenance patients.

The following adverse events were reported between 3% to < 20% incidence in de novo and maintenance patients treated with Myfortic in combination with cyclosporine and corticosteroids are listed in Table 3.

Table 3: Adverse Events Reported in 3% to < 20% of Patients Treated with Myfortic® in Combination with Cyclosporine* and Corticosteroids

	de novo Renal Study	Maintenance Renal Study
Blood and Lymphatic Disorders	Lymphocele, thrombocytopenia	Leukopenia, anemia
Cardiac Disorder	Tachycardia	-
Eye Disorder	Vision blurred	-
Endocrine Disorders	Cushingoid, hirsutism	-
Gastrointestinal Disorders	Abdominal pain upper, flatulence, abdominal distension, sore throat, abdominal pain lower, abdominal pain, gingival hyperplasia, loose stool	Vomiting, dyspepsia, abdominal pain, constipation, gastroesophageal reflux disease, loose stool, flatulence, abdominal pain upper

General Disorders and Administration Site Conditions	Edema, edema lower limb, pyrexia, pain, fatigue, edema peripheral, chest pain	Fatigue, pyrexia, edema, chest pain, peripheral edema
Infections and Infestations	Nasopharyngitis, herpes simplex, upper respiratory tract infection, oral candidiasis, herpes zoster, sinusitis, wound infection, implant infection, pneumonia	Nasopharyngitis, upper respiratory tract infection, urinary tract infection, influenza, sinusitis
Injury, Poisoning, and Procedural Complications	Drug toxicity	Postprocedural pain
Investigations	Blood creatinine increased hemoglobin decrease, blood pressure increased, liver function tests abnormal	Blood creatinine increase, weight increase
Metabolism and Nutrition Disorders	Hypocalcemia, hyperuricemia, hyperlipidemia, hypokalemia, hypophosphatemia hypercholesterolemia, hyperkalemia, hypomagnesemia, diabetes mellitus, hyperphosphatemia, dehydration, fluid overload, hyperglycemia, hypercalcemia	Dehydration, hypokalemia, hypercholesterolemia
Musculoskeletal and Connective Tissue Disorders	Back pain, arthralgia, pain in limb, muscle cramps, myalgia	Arthralgia, pain in limb, back pain, muscle cramps, peripheral swelling, myalgia
Nervous System Disorders	Tremor, headache, dizziness (excluding vertigo)	Headache, dizziness
Psychiatric Disorders	Anxiety	Insomnia, depression
Renal and Urinary Disorders	Renal tubular necrosis, renal impairment, dysuria, hematuria, hydronephrosis, bladder spasm, urinary retention	-
Respiratory, Thoracic and Mediastinal Disorders	Cough, dyspnea, dyspnea exertional	Cough, dyspnea, pharyngolaryngeal pain, sinus congestion
Skin and Subcutaneous Tissue Disorders	Acne, pruritus	Rash, contusion
Surgical and Medical Procedures	Complications of transplant surgery, postoperative complications, postoperative wound complication	-

Vascular Disorders	Hypertension, hypertension aggravated, hypotension	Hypertension

*USP (MODIFIED)

The following additional adverse reactions have been associated with the exposure to MPA when administered as a sodium salt or as mofetil ester:

Gastrointestinal: Colitis (sometimes caused by CMV), pancreatitis, esophagitis, intestinal perforation, gastrointestinal hemorrhage, gastric ulcers, duodenal ulcers, and ileus.

Resistance Mechanism Disorders: Serious life-threatening infections such as meningitis and infectious endocarditis have been reported occasionally and there is evidence of a higher frequency of certain types of serious infections such as tuberculosis and atypical mycobacterial infection.

Respiratory: Interstitial lung disorders, including fatal pulmonary fibrosis, have been reported rarely with MPA administration and should be considered in the differential diagnosis of pulmonary symptoms ranging from dyspnea to respiratory failure in posttransplant patients receiving MPA derivatives.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Myfortic. Because these reactions are reported voluntarily from a population of uncertain size, reliably estimating their frequency or establishing a causal relationship to drug exposure is not always possible.

Congenital disorder: Embryofetal toxicity: Congenital malformations and an increased incidence of first trimester pregnancy loss have been reported following exposure to mycophenolate mofetil (MMF) during pregnancy.

Infections: Polyomavirus associated nephropathy (PVAN), especially due to BK virus infection, has been observed in patients receiving immunosuppressants, including Myfortic. This infection is associated with serious outcomes, including deteriorating renal function and renal graft loss. Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with MPA derivatives.

Hematologic: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA derivatives in combination with other immunosuppressive agents.

Dermatologic: Cases of rash have been reported in patients treated with MPA derivatives.

2.0 REPORTED SERIOUS ADVERSE EVENTS IN MYCUV-IIT02

Center	Subject No	Event No	SAE_ Report_ Date	SAE_ Description	SAE_ Start_Date [DD.MM.JJ]	SAE_ End_Date [DD.MM.JJ]
1	101	1	31 May 10	Pneumonia	01. May 10	01. Jun 10
4	403	1	27. Jun 11	Gastrointestinal inflammation/ Gastroenteritis	21. Jun 11	24. Jun 11
1	107	2	17. Jun 11	Urolithiasis left side	05. Jun 11	01. Jul 11
4	403	7	28. Dec. 10	Obstipation	22. Dec 10	27. Dec 10

Center	Subject No	SAE_ Outcome	SAE_ Frequency	SAE_ Intensity	SAE_ Relation to Study_Medication	SAE_ Action taken	SAE_ Concomitant Therapy
1	101	completely recovered	unk	severe	not suspected	study-medication ongoing	antibiotics iv, unk
4	003	completely recovered	unk	mild	suspected	study-medication ongoing	ciprofloxacin
1	107	completely recovered	unk	severe	not suspected	no study-medication	extraction of stone
4	403	completely recovered	unk	severe	suspected	study medication ongoing	purgatives (Practo Clyss, Laxans)

Only two reported SAE (Center 4, Event-No 1 and Event-No 7) seem to be suspected to have a relationship to the study medication. Diarrhea or gastroenteritis is a wellknown side effect of Myfortic and because patient completely recovered under study medication, no other action was taken. Of note, since the last safety report one SAE was reported and documented.

3.0 REPORTED ADVERSE EVENTS IN MYCUV-IIT02

From beginning of the study up to October 2012, 170 adverse events were documented in 44 patients. The number of 256 AEs reported in the previous safety report resulted in a counting error that occurred because of double data entry into the database.
Please note that in this safety report all AEs from point of screening visit are listed, i.e. AEs that occurred before randomization were also included.

The causality of AEs was described as follows:

Causality related to study medication	
related	17
Probably / possibly related	86
not related	67
sum	**170**

Previous and actually AE descriptions found in **Blood and Lymphatic System**:

	Previous study	MYCUV-IIT02 N (%)
	%	
Anemia	21.6	1 (0,58)
Leukopenia	19.2	0
Hypokalemia		1 (0,58)
Hypocalcaemia		1 (0,58)
GPT /GGT elevation		2 (1,17)

Previous and actually AE descriptions found in **Intestinal System**:

	Previous study	MYCUV-IIT02 N (%)
	%	
Gastrointestinal disturbances		9 (5,3)
Diarrhea	23,5	6 (3,5)
Constipation / Meteorism		4 (2,4)
Nausea	29,1	2 (1,2)
Vomiting	23,0	0
Dyspepsia	22,5	3 (1,8)
Weight increase		3 (1,8)

Previous and actually AE descriptions found as **viral** / **bacterial infections**:

	Previous study (%)	MYCUV-IIT02 N (%)
Any Cytomegalovirus	21,6	0
Herpes Simplex	8,0	5 (2,9)
Herpes Zoster	4,7	1 (0,6)
Any Fungal Infection	10,8	0
Upper respiratory tract infection (common cold)		23 (13,5)
Urinary Tract Infection	29.1	2 (1,2)
Lower respiratory tract infection (Bronchitis)		4 (2,4)
Pneumonia		1 (0,6)

Other AE descriptions found in **ophthalmologic system**:

	Previous study (%)	MYCUV-IIT02 N (%)
Hordeolum		1 (0,6)
Metamorphopsia		1 (0,6)
Blepharitis / Konjuntivitis		7 (4,1)
Hyposphagma		1 (0,6)
Photophobia		2 (1,2)
Cataract		1 (0,6)
Epiretinal Gliosis		1 (0,6)
Sicca		3 (1,8)
Macular edema		3 (1,8)
other		4 (2,4)

Other AE descriptions found in **different organ systems**:

	Previous study (%)	MYCUV-IIT02 N (%)
Parodonditis		1 (0,6)
Diabetes manifestation		2 (1,2)
Arthralgia		6 (3,5)
Insomnia	23.5	3 (1,8)
Postoperative Pain	23.9	0
Alopecia		4 (2,4)
Muscle cramps / pain		7 (4,1)
Skin alterations		9 (5,3)
Vertigo		5 (2,9)
Urolithiasis		1 (0,6)
Alleries		2 (1,2)
Loss of appetite		3 (1,8)

Venous insufficiency		3 (1,8)
Hypertension		1 (0,6)
Headache		8 (4,7)
Cardiac arrhythmia		2 (1,2)
Depression or fatigue		10 (5,9)
Mood disorder		4 (2,4)
disorientation		1 (0,6)
Cysts		1 (0,6)
other		5 (2,9)

Out of the 170 reported AEs in 44 patients, 103 AEs seemed to be suspected to have a relationship to the study medication, 86 AEs seemed probably or possably related to the study medication. All AE descriptions are well known side effect of Myfortic and because patients completely recovered under study medication, no further action was taken.

4.0 APPRAISAL OF THE RISK-TO-BENEFIT RATIO

There is no change in the risk-to benefit ratio to the MYCUV-IIT02 trial.

5.0 RECENT INFORMATION BY THE MANUFACTURER OF CELLCEPT

Recently, the manufacturer of CellCept® informed the regulatory and health authorities about the risk of hypogammaglobulinemia and bronchiectasia if Mycophenolatmofetil is combined with other immunosuppressants. This is based on observations in recent clinical trials and case reports.

Date: 30.06.2016
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