Novartis Clinical Trials

Sponsor Novartis Pharma AG.
Generic Drug Name Enteric-coated mycophenolate sodium (ECMPS)-IEM combination product
Therapeutic Area of Trial Kidney Transplantation
Approved Indication Indicated in combination with cyclosporine and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal transplants.
Study Number CPRO400A2201
Title A 3-month, exploratory, non-randomized, multi-center, open label study to evaluate the reliability, safety and usability of the Transplantation Sensor System combined with ECMPS in adult kidney transplant patients
Phase of Development IIa

Study Start/End Dates

10 May 2011 to 18 Nov 2011

Study Design/Methodology

Multicenter, single cohort, non-randomized, open label design. Eligible patients on treatment with mycophenolate mofetil (MMF) were converted to equimolar doses of ECMPS at Visit 1 and entered a two-week run-in period prior to randomization.

At randomization patients received the first dose of ECMPS-IEM (over-encapsulated enteric coated mycophenolic acid) under direct observation by the study personnel to ensure that the Proteus Personal Monitor (PPM) was functional and to initiate the collection of data for the evaluation of the study endpoints. Patients were then treated with ECMPS-IEM as prescribed by the investigator for 12 weeks.

Centres

5 centers in Switzerland

Publication

Wüthrich R.P., Eisenberger U., Bock A., Ambühl P., Steiger J., Intondi A., Kuranoff S., Maier T., Green D., Feutren G., De Geest S. Towards a Gold Standard for Adherence Assessment in Transplantation: High Accuracy of the Proteus Raisin System (PRS) Combined with Enteric-Coated Mycophenolate Sodium (ECMPS) in Stable Kidney Transplant Recipients. [Abstract WED.CO41.01] XXIVth International Congress of The Transplantation Society (TTS 2012 Berlin Congress)

Objectives

Primary objective

To assess the reliability of the Raisin technology, defined as the accuracy and precision in detecting directly observed ingestion of ECMPS-IEM and Placebo-IEM in adult maintenance kidney transplant patients.

Secondary objective(s)

This trial also assessed:

1. Patient adherence to the prescribed ECMPS-IEM schedule with and without active feedback for two consecutive periods of 8 and 4 weeks each :
   - Taking adherence was defined as the % IEM detected divided by the number of IEM prescribed
   - Scheduling adherence was defined as the % IEM detected within the pre-set time window ± 1 hour for the morning and evening intakes divided by the number of IEM prescribed.
2. The incidence and severity of adverse events observed during the utilization of ECMPS-IEM and Placebo-IEM and the PPM.
3. The satisfaction and usability of the Transplantation Sensor System (TSS) by patients.

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

Oral capsules of ECMPS-IEM 360 mg, Placebo-IEM and ECMPS 180 mg

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

N/A

Criteria for Evaluation

Primary variables

Detection accuracy of the Raisin technology

The primary endpoint assessed the detection accuracy of the Raisin technology, defined as the proportion of ECMPS-IEM and/or Placebo-IEM detected by the PPM in relation to the total number of ECMPS-IEM and/or Placebo-IEM ingested under direct observation of the research staff at the study visits.

Secondary variables

Adherence to the prescribed ECMPS-IEM schedule

A secondary endpoint assessed patient adherence to the prescribed ECMPS-IEM schedule, defined as the percentage of ECMPS-IEM detected by the PPM in relation to the prescribed ECMPS-IEM schedule.

Satisfaction and usability of the Transplantation Sensor System

Another secondary endpoint assessed the satisfaction and usability by patients of the TSS. A self-administered questionnaire was designed to evaluate patient opinions about the elements of the TSS and the information provided back to the patient.

Safety and tolerability

Safety assessments consisted of the collection of all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, placebo, and/or the Raisin technology. Assessments included the regular monitoring of hematology (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count) and blood chemistry (creatinine, AST [SGOT], ALT [SGPT], GGT, alkaline phosphatase, total bilirubin, glucose, albumin, cholesterol, triglycerides, potassium, sodium), and GFR(MDRD formula) which were performed at a central laboratory. Regular assessments of vital signs, physical condition and body weight were made. The incidence of pregnancy as well as the number of patients experiencing biopsy proven acute rejection, graft loss or death during the study period was provided.

Pharmacology

N/A

Other

N/A

Statistical Methods

All analyses were descriptive. Qualitative variables were summarized by the number and percentage per category, quantitative variables by number of patients, mean, standard deviation, median, minimum and maximum.

The mean, median and quartiles were displayed to 1 decimal place more than the data collected, and the standard deviation to 2 decimal places more. The minimum and maximum were displayed with no additional decimals. Unless otherwise stated, summary tables/figures/listings on all patients were included in the population under consideration. SAS® Version 9.1 (or higher) was used to perform all statistical analyses.

Patient disposition was summarized for the Full Analysis Set (FAS) by summarizing the number and percentage of patients who completed, prematurely discontinued study drug, and prematurely discontinued the study. The primary reason for premature drug or study discontinuation was provided.

Analysis of the Primary Endpoint

The detection accuracy of the Raisin technology was defined as the proportion of IEM detected by the PPM out of the directly observed IEM ingested (DOI).

At the study visits, preferably in the morning, patients were asked to take their dose of Myfortic at the study center. Patients on treatment with the Myfortic dose of 720 mg b.i.d. ingested two ECMPS-IEM under direct observation of the research staff at study Visits 2 to 6. Patients on doses lower than 720 mg b.i.d. of Myfortic, i.e., those taking one ECMPS-IEM b.i.d., ingested one Placebo-IEM at the same time.

ECMPS-IEM and Placebo-IEM ingested as described above constituted the directly observed ingestions, whereas ECMPS-IEM capsules ingested at home in the evenings of the study visits and between visits were not considered directly observed ingestions.

Detection accuracy of direct observed ingestions was derived for ECMPS-IEM only, placebo IEM only, ECMPS-IEM and placebo IEM combined. The detection accuracy was defined as the number of ingestions detected divided by the number of directly observed ingestions.

A 95% confidence interval (CI) for the detection accuracy was calculated using the binomial distribution. A 95% CI for the detection accuracy was calculated for all ingestions across all the patients, assuming all ingestions were independent. It was also calculated for ECMPS-IEM and placebo IEM combined, ECMPS-IEM only and placebo IEM only.

Summaries by patient across 5 visits were provided.

The above analysis was performed for all DOIs and also for the subset of DOIs that occurred when patch adherence to the skin was satisfactory, as measured by skin impedance <4 000 Ω for the sessions immediately prior to and following the ingestion. The detection accuracy for the directly observed ingestions was determined for each patient separately by pooling the counts from the 5 study visits.

The patient adherence to the prescribed ECMPS-IEM schedule was derived as the percentage of ECMPS-IEM detected by the PPM out of the prescribed ECMPS-IEM schedule. The adherence by week, the visit interval, the 8 and 4 week intervals and the overall study was calculated for each patient. Summary statistics were also provided. Analyses of adherence were conducted for

the entire treatment periods and also for periods when PPMs had satisfactory skin contact (impedance <4000 Ω) since PPM can detect IEM ingestion only when it is properly adherent to the body, and for daily adherence assessments, all daily impedance measurements (one about every 20 minutes) by the PPM had to be <4000 Ω. Endpoints were defined as follows:

- Taking adherence = number of IEM detected divided by the number of IEM-ECMPS prescribed during the study period.
- Scheduling (timing) adherence = number of IEM detected within the time window preset by the patient divided by the number of IEM-ECMPS capsules prescribed. A two-hour time window for drug ingestion was defined at time of inclusion by each patient for morning and evening intakes; this time window could not be modified thereafter. The magnitude of time deviations from the target window was also reported for the subset of ingestions occurring outside that window.

The proportion of patients demonstrating an adherence ≥85%, ≥90% or ≥95% was also reported.

The patient adherence based on drug accountability was assessed as a proportion of the dosage taken based on the dispense and return CRFs out of the prescribed schedule. The dosage taken was calculated as the difference between the dosage dispensed and returned (unused) as recorded in the drug dispensing log. The adherence of ECMPS-IEM and commercial Myfortic 180mg was assessed separately, by the visit interval and the overall study.

The two approaches compared side-by-side tabulations of the adherence of ECMPS-IEM by visit interval, 8 and 4 week intervals and the overall study.

Satisfaction and usability of the TSS

To assess satisfaction and usability of the TSS by the patients, frequency tables were provided for the responses to each of the questions of the questionnaire, by visit as applicable.

Goal setting

Goals were set regarding the time windows for ingestion of ECMPS-IEM doses, step counts per day and hours of sleep. Differences to the actual values achieved were expressed in percent and summarized.

Safety

Vital signs and laboratory measurements were summarized at the study visits.

Adverse events occurring during the study were coded according to the MedDRA dictionary and summarized. The same type of tabulation was provided for events which were, according to investigator judgment, suspected to be related to the study medication (ECMPS-IEM, Placebo-IEM, Myfortic 180 mg and 360 mg tablets) and also for events related to the PPM.

In addition, GFR was estimated by the 4-variable MDRD formula below and summarized at the study visits.

$eGFR = 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times [1.21 \text{ if black}] \times [0.742 \text{ if female}]$, where serum creatinine is expressed in mg/dL and age in years,

The number of patients experiencing biopsy proven acute rejection, graft loss or death during the study period was provided.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

Patients had to fulfill all of the following criteria to be eligible for inclusion in the study:

1. Male or female kidney transplant recipients aged 18 years or older
2. Patients at least 6 months post-transplantation and in stable clinical condition
3. Treatment with ECMPS doses between 720 mg/day and 1440 mg/day or MMF doses between1000 mg/day and 2000 mg/day, divided in two equal doses 12 hours apart and with no dose titrations planned for the duration of the trial
4. Ability to independently take medication
5. Successfully ingest a Placebo-IEM capsule with no difficulty
6. Ability to read and understand the instructions for the study and the printed weekly periodic reports provided by the study center
7. Patients who were willing and able to participate in the study and from whom a written informed consent form (ICF) was obtained

Exclusion criteria

Patients were excluded from study entry due to:

1. The inability to use the mobile phone provided for use in the clinical trial
2. Any episodes of acute rejection in the previous 3 months
3. Presence of cognitive impairment
4. Active alcohol or drug abuse
5. History of dysphagia, or inflammatory bowel disease, or gastrointestinal conditions or surgery that had modified the normal luminal flow of the gastrointestinal tract (e.g. Whipple procedure, bariatric surgery or Roux-en-Y)
6. Known allergies, including history of skin reactions to patches, that could have precluded safe participation in the study
7. Use of other investigational drugs or a non-protocol immunosuppressant within 30 days or 5 half-lives (whichever was longer) prior to, or at the time of inclusion into the study
8. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes
9. Patients with thrombocytopenia (platelets <100,000/mm^3), with an absolute neutrophil count of <1,500/mm^3 or leucopenia (leucocytes <2,500/mm^3), or hemoglobin <6 g/dL
10. Patients with a history of malignancy during the last five years, except squamous or basal cell carcinoma of the skin
11. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL)
12. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precluded intercourse with a male partner and women whose partners had been sterilized by vasectomy or other means, UNLESS they were using two birth control methods. The two methods could be

a double barrier method or a barrier method plus a hormonal method.

Number of Subjects

Disposition Reason	ECMPS-IEM N=20 n (%)
Screened	20
FAS	20 (100.0)
Completed	14 (70.0)
Prematurely discontinued study drug	8 (40.0)
Primary reason for discontinuation	
Adverse event(s)	4 (20.0)
Subject withdrew consent	3 (15.0)
Administrative problems	1 (5.0)
Abnormal laboratory value(s)	0
Abnormal test procedure result(s)	0
Death	0
Graft loss	0
Lost to follow-up	0
Protocol Violation	0
Subject's condition no longer requires study drug	0
Unsatisfactory therapeutic effect	0
Prematurely Discontinued study	6 (30.0)
Primary reason for discontinuation	
Subject withdrew consent	6 (30.0)
Death	0
Lost to follow-up	0

Demographic and Background Characteristics

Description	ECMPS-IEM N=20
Age (years)	
n	20
Mean	51.7
SD	8.75
Median	51.0
Minimum	35
Maximum	68
Gender – n (%)	
Male	15 (75.0)
Female	5 (25.0)
Race – n (%)	
Caucasian	19 (95.0)
Asian	1 (5.0)

Primary Objective Result(s)

Positive Detection Accuracy (PDA) of IEM ingestions was 100% (95% CI – 89.7-100) in the 34 DOI events performed when skin contact of the patch was satisfactory (impedance <4000 ohms). Of these 34, 8 were IEM-placebo ingestions.

Secondary Objective Result(s)

The following efficacy conclusions are drawn from this study:

DOI and taking adherence

Of the 4136 IEM-ECMPS prescribed ingestions, 2824 (68%) took place while patch impedance was documented to be satisfactory (<4000 ohms for a 24-hr period). The difference is due mostly to instances where patients decided not to wear the patch during vacation periods while taking IEM-ECMPS, or waited for several hours between patch replacements, or discontinued patch use a few days before they discontinued the study.

When the patch was worn as intended (impedance <4000 ohms), taking adherence rate was 99.4% over 2824 prescribed ECMPS-IEM ingestions (95% CI – 99.0-99.6).

All patients had a taking adherence ≥95%. Of interest, adherence assessed by the pill count recorded on drug disposition log showed values ≥95% in only 62% of patients. The difference between taking adherence by ISS and by the drug disposition log is mostly explained by drug accounting inaccuracies.

Scheduling adherence

Scheduling adherence rate was 84.5% (95% CI: 83.1-85.8) (corrected for patch impedance <4000 ohms), with no significant change over time: 85.5%, 82.6% and 85.2% over the first, second and third months respectively (p=NS). Scheduling adherence was lower during mornings than evenings (82.7% vs. 86.3%, p=0.0093). Mean deviation from the time window preset for drug intake was 42±50 minutes (median 20 min, range 0.1-180). Only 59% of patients had ≥95% adherence to the prescribed time for study drug ingestion. These data demonstrate the variability in the timing of drug intake even in a highly adherent population and illustrates the power of Proteus technology for adherence monitoring.

Averages of 1.8 to 2.8 SMS messages per patient per week were sent out. All patients received at least two SMS reminders for patch replacement and 15 patients (88.2%) received more than 10 SMS messages. Dose adherence SMS reminders were sent to 8 of the 13 patients who entered the week 8-12 study period, two of whom received more than five messages.

Safety Results

Incidence of adverse events regardless of study treatment relationship by primary system organ class, preferred term and maximum severity (Safety Set)

	ECMPS-IEM N = 19				
Primary System Organ Class Preferred Term	**Asymptomatic n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Total n (%)**
Any Primary SOC	0 (0.0)	7 (36.8)	5 (26.3)	0 (0.0)	12 (63.2)
Ear & labyrinth disorders	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	1 (5.3)
Ear Pain	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	1 (5.3)
Gastrointestinal disorders	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	1 (5.3)
Diarrhoea	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	1 (5.3)
General disorders and admin-istration site conditions	1 (5.3)	2 (10.5)	4 (21.1)	0 (0.0)	7 (36.8)
Application site erythema	1 (5.3)	1 (5.3)	2 (10.5)	0 (0.0)	4 (21.1)
Application site rash	0 (0.0)	1 (5.3)	1 (5.3)	0 (0.0)	2 (10.5)
Application site reaction	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	1 (5.3)
Oedema peripheral	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	1 (5.3)
Infections & infestations	0 (0.0)	3 (15.8)	1 (5.3)	0 (0.0)	4 (21.1)
Nasopharyngitis	0 (0.0)	1 (5.3)	1 (5.3)	0 (0.0)	2 (10.5)
Application site folliculitis	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	1 (5.3)
Cystitis	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	1 (5.3)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	1 (5.3)
Foot fracture	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	1 (5.3)
Investigations	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Blood creatinine increased	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	1 (5.3)
Back pain	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	1 (5.3)
Psychiatric disorders	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	1 (5.3)
Sleep disorder	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	1 (5.3)
Respiratory, thoracic and medi-astinal disorders	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	1 (5.3)
Cough	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	1 (5.3)
Oropharyngeal pain	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	1 (5.3)

Serious Adverse Events and Deaths (Safety Set)

	ECMPS-IEM N = 19 n (%)
Any AEs	12 (63.2)
Death	0 (0.0)
SAEs	0 (0.0)
AEs leading to discontinuation of study drug*	3 (15.8)
AEs leading to discontinuation of device	0 (0.0)

NB : Two AEs leading to discontinuation of device are captured under AEs leading to discontinuation of study drug in the first instance.

Other Relevant Findings

None

Date of Clinical Trial Report

30 March 2012

Date Inclusion on Novartis Clinical Trial Results Database

20 September 2012

Date of Latest Update

27 Aug 2012