NOVARTIS

CERL080ATW12 Study Results Abstract for Public Disclosure

Title

Evaluating the Safety of Myfortic (Mycophenolate sodium) in Patients With Lupus Nephritis: a 12 Month, Single-arm, Observational Study in Taiwan population

Keywords

Lupus nephritis, Post Approval Commitment study, Mycophenolate Sodium, Taiwanese population

Rationale and background

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that may affect the skin, joints, kidneys, lungs, heart, serous membranes, nervous system or other organs. Lupus nephritis (LN) is one of the common clinical manifestations of SLE that affects the kidneys. The incidence of LN is higher in the Asian population (21% to 65% diagnosis and 40% to 82% at follow-up) compared with the Caucasian population.

Traditionally, intravenous cyclophosphamide in combination with corticosteroid (CS) has been used to induce remission of proliferative LN. However, this treatment can lead to significant toxicity, infection, malignancies and infertility. As an alternative, mycophenolic acid (MPA) administered as mycophenolate mofetil (MMF) has been used in the induction and maintenance treatment of LN patients. MPA is a potent, selective and reversible inhibitor of inosine monophosphate dehydrogenase that inhibits the de-novo pathway of guanosine nucleotide synthesis

Another formulation with MPA has become available as enteric-coated mycophenolate sodium (EC-MPS) to reduce the gastrointestinal toxicity. EC-MPS is absorbed in the small intestine and metabolized into its active drug form, MPA. The therapeutic equivalence for 2 g/d of MMF and 1440 mg/d of EC-MPS has been confirmed in previous studies. A randomized multi-center, parallel, open-label study (CERL080A2420) found out that the patients with complete remission who received EC-MPS in combination with standard-dose CS compared with patients with complete remission on reduced-dose CS was similar (19.0% vs. 20.5%) ($p = 0.098$). The proportion of patients with partial remission at Week 24 was higher in the standard dose CS group than in the reduced dose CS group (47.6% vs. 35.9%), however, the difference was not statistically significant.

Recently, the Taiwan Health Authority granted the indication of both the induction and maintenance usage of EC-MPS (trade name “Myfortic®”) in LN patients and requested a post-approval commitment (PAC) study especially to evaluate safety. As few studies have been conducted on the safety of EC-MPS in the Taiwanese population, the current proposed PAC study was designed to bridge this knowledge gap. This study aimed to provide further data on the safety of EC-MPS for the treatment of LN patients in Taiwan.

Research question and objectives

Primary objective

- The primary objective of this study was to describe the safety profile of EC-MPS on LN patients.

Secondary objective

- To describe the reasons for study drug (EC-MPS) discontinuation during the 12-month period.
- To investigate the efficacy of EC-MPS in LN patients, including renal function changes and the proportion of complete or partial responses during the 12-month period.

Study design

This was an open-label, prospective, single-arm, observational post-authorization safety study (PASS) in LN patients who newly received treatment of EC-MPS (either received the first dose within 30 days prior to informed consent form [ICF] signing date or received the first dose after study enrollment). Patients who switched from another treatment to EC-MPS were included in this study.

If patients received the first dose of EC-MPS within 30 days prior to ICF signing, Day 1 could be the day of first administration of EC-MPS. If patients received the first dose of EC-MPS after study enrollment, Day 1 could be the patient's baseline visit.

All patients were required to provide written informed consent and screened for eligibility prior to enrollment. It was planned that at least 64 patients would be enrolled in the study to reach an 80.2% probability of detecting adverse events (AEs) with an incidence rate of 2.5% in one or more patients. The study consisted of a 12-month follow-up period.

All AEs, serious adverse events (SAEs), and deaths were recorded over the 12-month follow up period, up to 30 days after the end of study (EoS). The reasons for study drug (EC-MPS) discontinuation were also recorded. In addition, the efficacy of the study drug at 6 months and 12 months was recorded. Baseline patient laboratory data were established upon enrollment and used for safety and efficacy comparison at the end of the study. The clinical diagnosis of LN was defined in the inclusion criteria; all patients could be diagnosed before baseline. The dose of EC-MPS was recorded throughout the study, and any changes in dose/treatment were at the clinician's discretion. Concomitant medications and non-drug information (surgical procedures) were also recorded.

Setting

The study population consisted of male and female patients diagnosed with LN between 20 and 75 years of age. This study was designed for a target population of 64 patients in Taiwan.

Inclusion criteria:

Patients eligible for inclusion in this study must have met **all** of the following criteria:

1. Aged ≥ 20 years and ≤ 75 years.
2. Patients with written ICF.
3. Male or female diagnosed with SLE.
4. Patients with a confirmed diagnosis of LN by physician and eligible for EC-MPS treatment according to the package insert. Diagnosis of LN was defined as:
    - Kidney biopsy with confirmed histological diagnosis of LN (class III/IV/V); or
    - Laboratory evidence of active nephritis: spot urine protein creatinine ratio (UPCR) 0.5, and/or proteinuria > 0.5 g/24 hours, and/or greater than 3+ by dipstick, and/or cellular casts (> 5 red blood cells [RBCs] and > 5 white blood cells [WBCs] per high-power field [hpf] and/or cellular casts where none previously existed).
5. Patients with LN who received EC-MPS for the first time (either received the first dose within 30 days prior to ICF signing date or received the first dose after study enrollment). Patients who switched from another treatment to EC-MPS could be included in this study.
6. Male patients must use effective contraception methods during therapy and for 13 weeks after their last dose of EC-MPS.
7. Women of childbearing potential must have used effective contraception before beginning EC-MPS therapy, during therapy, and for six weeks after their last dose of EC-MPS.

Exclusion criteria:

Patients meeting any of the following criteria were not eligible for inclusion in this study:

1. Previous or planned kidney transplant.
2. Patients who were receiving continuous dialysis at the time of the study or had a glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2 within 3 months prior to the start of study.
3. Patients with active serious digestive system disease, including infrequent cases of gastrointestinal tract ulceration with hemorrhage or perforation.
4. Patients with life threatening conditions including malignancies, or severe infection in recent 6 months prior to start of study.

Patients and study size, including dropouts

This study was designed for a target population of 64 patients in Taiwan. Initially, interim analysis (IA) was conducted when approximately 50% (32 patients) reached Month 6. Early discontinued patients who did not complete the Month 6 visit were also included in the analysis.

Early discontinued patients - Study discontinuation was defined as the time when patients stopped receiving EC-MPS and follow-up for any reason or switched from EC-MPS to another drug prior to the planned EoS. The investigator could discontinue the study for a given patient if, on balance, he/she believed that continuation would negatively impact the wellbeing of the patient. Data of early discontinuation could be collected on the last/EoS visit (if available). All AEs, SAEs, and deaths were recorded until 30 calendar days after the patient discontinued EC-MPS during the study conduct.

Variables and data sources

Primary endpoints:

- The primary endpoint was the safety of EC-MPS in LN patients over the 12-month study period, which was assessed via the AEs, SAEs, and deaths.

Secondary endpoints:

- The reasons for study drug (EC-MPS) discontinuation in the 12-month period including poor response, loss to follow-up, etc.
- The proportion of patients with a complete response, after 6 months and 12 months of treatment.
- The proportion of patients with a partial response after 6 months and 12 months of treatment.
- The proportion of patients achieving renal response in eGFR at 6 months and 12 months (estimated glomerular filtration rate [eGFR] within the normal range, or no less than 85% of baseline)
- The proportion of patients achieving inactive urinary sediment (no cellular casts) at 6 months and 12 months

Patient demographics and other baseline characteristics

The following variables were collected at baseline:

- Patient demographics (sex and age)
- Height and weight
- Medical history of SLE (date of diagnosis for LN, kidney biopsy or laboratory results of active nephritis)
- Relevant medical history/current medical conditions
- Treatment history of LN

Treatment information of EC-MPS: The treatment information of EC-MPS was recorded throughout the study, and any changes in dose/treatment were at the clinician's discretion.

- Dosage of EC-MPS (mg)
- Frequency of EC-MPS

Safety variables: The occurrence of all AEs, SAEs, and deaths from baseline until EoS (up-to 30 days) were collected. The safety profile of previous studies were used as a reference. The safety profiles referenced included LN patients under EC-MPS treatment and LN patients under MMF treatment.

Efficacy variables:

Reasons for study drug discontinuation: The reasons for study drug (EC-MPS) discontinuation were collected throughout the 12-month period. Any change in medication that resulted in termination of EC-MPS use was considered as discontinuation.

Clinical response

Complete response: Patients were reported to have a complete response if their proteinuria was < 0.5 g/24 hours; or UPCR ≤ 0.5.

The proportion of patients with a complete response after 6 months and 12 months of treatment could be determined.

Partial response:

Patients were reported to have a partial response if they experienced any one criterion as follows:

- At least 50% decrease from baseline in proteinuria. Note: patients with a baseline proteinuria of > 3.5 g/24 hours, must have had a proteinuria < 3 g/24 hours;
- Red blood cells per high power field (RBCs/hpf) ≤ 50% above baseline and no cellular casts;
- At least 50% decrease in UPCR or to < 1.0 (if 1.0 ≤ baseline ≤ 3.0) or to ≤ 3.0 (if baseline was > 3.0).

The proportion of patients with a partial response after 6 months and 12 months of treatment were determined.

Renal function assessments:

eGFR: The proportion of patients achieving renal response of eGFR (within normal range or no less than 85% of baseline) at 6 months and 12 months were determined.

Urinary sediment: The proportion of patients achieving inactive urinary sediment (no cellular casts) at 6 months and 12 months were determined.

UPCR: The UPCR measured by urine test. At Month 6 and Month 12, the proportion of patients achieving a ≥ 50% decrease in UPCR or to < 1.0 (if 1.0 ≤ baseline ≤ 3.0) or to ≤ 3.0 (if baseline was > 3.0) were determined.

Data sources and measurement: This was an observational study. Patients were treated and followed according to routine medical practice in terms of visit frequency and type of assessment performed. Only endpoint related data were collected as part of the study. Sites were requested to record the available data corresponding to the closest visit. Limited information (i.e., date and reason of ICF withdrawal) was collected for the patients at the time point when withdrawal of ICF.

If the baseline laboratory data were not available during the baseline visit, data could be collected retrospectively (within 90 days prior to the baseline). In order to understand patients' treatment information that might confound safety evaluation in study period, including concomitant medication or non-drug therapy (surgical procedure), therefore, data could be collected.

Statistical methods

All analyses were performed by Novartis GBS. Data from study centers in Taiwan that participated in this study were merged for data analysis. Analysis datasets and statistical outputs were produced using the SAS® Version 9.4 or above (SAS Institute Inc., Cary, NC, USA) and stored in Novartis global programming & statistical environment (GPS II).

No statistical hypothesis testing was performed in this study. All data analyses were descriptive in nature.

In general, all continuous variables were summarized with number of non-missing values, mean, standard deviation (SD), minimum, first quartile (Q1), median, third quartile (Q3) and maximum. The following number of decimal places were used for mean, median, Q1 and Q3 values: for mean and median: 1 more decimal place than the raw data; for minimum and maximum values: same number of decimal places as the raw data; for SD: 2 more decimal places than the raw data. Categorical variables were summarized with counts and percentages. Missing category was included if a non-zero count of missing values were present. Summaries with estimates and corresponding 95% confidence intervals were presented as appropriate. Missing values were not to be imputed.

The following analysis sets were used for all the analyses:

- Full Analysis Set (FAS): The FAS included all correctly enrolled patients who received at least one dose of the study drug. Patients enrolled but who did not meet the inclusion and exclusion criteria, which was discovered after enrollment in the study were not included in the FAS.
- Safety Set (SAF): The SAF included all patients who received at least one dose of the study drug.
- Per-protocol Set (PPS): The PPS included all FAS patients who completed the study without any protocol deviations.

Participant demographics and other baseline characteristics of patients were summarized using counts and percentages for categorical variables and number of non-missing values, mean, SD, minimum, first quartile, median, third quartile, and maximum for continuous variables. The summaries were reported for all analysis sets.

Results

Patient disposition

The FAS and SAF each consisted of 69 patients, while the PPS included 64 patients.

In the FAS, 21 patients (30.4%) discontinued from the study, while in the PPS, 16 patients (25.0%) discontinued.

The FAS and SAF included the same patients so the data has been presented for FAS.

The reasons for discontinuation across FAS and PPS were AEs (7 patients [10.1% for FAS and 10.9% for PPS]), lost to follow up (4 patients [5.8% for FAS and 6.3% for PPS]), physician decisions (3 patients [4.3% for FAS and 3.1% for PPS]), protocol deviations (FAS: 3 patients [4.3%], PPS: 0 patient), death (FAS: 2 patients [2.9%], PPS: 1 patient [1.6%]), new therapy for study indication (1 patient [1.4% for FAS and 1.6% for PPS]), and unsatisfactory therapeutic effect (1 patient [1.4% for FAS and 1.6% for PPS]).

Protocol deviations

A total of 69 patients were included in the FAS. Among these, 5 patients (7.2%) had protocol deviations, all these patients had deviation from inclusion criteria (LN patients were not EC-MPS treatment naive at the time of study entry or were not newly starting EC-MPS).

Analysis set

A total of 69 patients were included in the FAS. A total of 64 patients (92.8%) in PPS included all FAS patients who completed the study without any protocol deviations.

Demographics and baseline characteristics

- The mean age was 41.1 years (SD: 13.26), with patients ranging from 22 to 72 years. The majority were females (61 patients, 88.4%). All patients were of Asian race (69 patients, 100%). The mean weight reported was 60.16 kg (SD: 17.799), and the mean body mass index (BMI) was 22.85 kg/m^2 (SD: 5.387). Sixty-eight patients (98.6%) were diagnosed with SLE and LN respectively. One patient (1.4%) had missing data due to protocol deviation was identified, after which the case report form (CRF) data were no longer updated. Based on the diagnosis of LN criteria reported, the majority were spot UPCR > 0.5 g/g and renal biopsy (32 patients, 46.4% in each criterion). Based on renal biopsy results, Class IV Diffuse (proliferative) LN was the predominant classification reported (18 patients, 26.1%).
- In the PPS, the mean age was 40.2 years (SD: 12.99). The majority of patients were females (56 patients, 87.5%). All patients were Asian (64 patients, 100%). The mean weight was 60.54 kg (SD: 17.806), and the mean BMI was 22.92 kg/m^2 (SD: 5.281). All 64 patients (100%) were diagnosed with SLE and LN. Based on the diagnosis of LN criteria; the majority were spot UPCR > 0.5 g/g (31 patients, 48.4%) followed by renal biopsy (30 patients, 46.9%). Based on renal biopsy results, Class IV Diffuse (proliferative) LN was the predominant SLE class reported (17 patients, 26.6%).

Medical history

A total of 68 patients (98.6%) experienced at least one event. The most frequently reported events by system organ class (SOC) included Musculoskeletal And Connective Tissue (67 patients [97.1%]), Blood And Lymphatic System Disorders (39 patients [56.5%]), Gastrointestinal Disorders (35 patients [50.7%]), and Infections And Infestations (34 patients [49.3%]). The most commonly reported events by preferred terms (PTs) were SLE (67 patients [97.1%]), Anemia (18 patients [26.1%]), Hyperlipidemia (14 patients [20.3%]), Hypertension (17 patients [24.6%]), urinary tract infection (UTI) and Essential hypertension (10 patients each [14.5%]).

Treatment history of LN

Among patients diagnosed with LN, 34 patients (49.3%) received at least one medication that was started and discontinued before receiving their first EC-MPS. The most frequently administered medication was MMF, received by 14 patients (20.3%), followed by azathioprine in 13 patients (18.8%), and hydroxychloroquine sulfate in 11 patients (15.9%).

Among the patients with LN who received at least one medication, 28 patients (40.6%) were treated orally, 12 patients (17.4%) were treated intravenously, and 1 patient (1.4%) received an intramuscular treatment.

Duration of exposure to EC-MPS

A total of 69 FAS and 64 PPS patients received EC-MPS. The mean (SD) duration of treatment exposure was 40.1 weeks (18.18) for FAS and 42.3 weeks (16.63) for PPS. Median exposure was 50.1 weeks for both analysis sets. The Q1-Q3 exposure ranged from 32.3 to 52.1 weeks for FAS and 36.6 to 52.1 weeks for PPS. At Week 24, 55 patients (79.7%) in the FAS and 54 patients (84.4%) in the PPS were exposed to EC-MPS. At Week 48, 42 patients (60.9%) in the FAS and 42 patients (65.6%) in the PPS were exposed to EC-MPS. At Week 52, 18 patients (26.1%) in the FAS and 18 patients (28.1%) in the PPS remained exposed to EC-MPS.

Discussion

Overview of safety profile of the study treatment:

The safety profile of study drug EC-MPS in LN patients over the study period, which was assessed through the AEs, SAEs, and deaths.

- Overall, 59 patients (85.5%) experienced AEs, with majority of mild severity (43 patients, 62.3%). Of these, treatment-related AEs were reported in 17 patients (24.6%); with 12 patients (17.4%) having mild severity events, while the remaining 5 patients (7.2%) had moderate severity events.

- Overall, 14 patients (20.3%) experienced SAEs. 7 patients (10.1) reported severe SAEs; 6 patients (8.7%) reported SAEs with moderate severity, and 1 patient (1.4%) reported a mild SAE. Of these patients, 3 patients (4.3%) experienced treatment-related SAEs.
- Two patients (2.9%) experienced fatal SAEs, which were not related to study treatment.
- Overall, 15 patients (21.7%) experienced AEs that required a dose adjustment or interruption; most of these events were mild (11 patients, 15.9%), while moderate and severe AEs occurred in 3 patients (4.3%) and 1 patient (1.4%), respectively. Treatment-related AEs were reported in 6 patients (8.7%) with mild severity, while the remaining 2 patients (2.9%) experienced events of moderate severity that required dose adjustment or interruption.
- Forty-six patients (66.7%) experienced AEs requiring additional therapy, in which the majority reported in mild (33 patients, 47.8%), moderate (6 patients, 8.7%), and severe (7 patients, 10.1%) categories. Among them, 6 patients (8.7%) experienced mild treatment-related AEs that required additional therapy, while 2 patients (2.9%) had moderate treatment-related events.
- Seven patients (10.1%) experienced AEs leading to study discontinuation, in which the majority reported were mild (4 patients, 5.8%) while 2 patients (2.9%) experienced moderate AEs, and 1 patient (1.4%) experienced severe AEs. Treatment-related AEs leading to study discontinuation were reported in 6 patients (8.7%); of these 4 patients (5.8%) had mild AEs and the remaining 2 patients (2.9%) had moderate AEs.
- Seventeen patients (24.6%) experienced at least one AE related to EC-MPS. Among them, 12 patients (17.4%) had mild events, 5 patients (7.2%) had moderate events, and no severe events were reported. The most frequently reported AEs related to EC-MPS by PT were leukopenia (5 patients, 7.2%) and abdominal discomfort (3 patients, 4.3%), followed by diarrhoea and alopecia (2 patients, 2.9% each). For all other AEs related to EC-MPS by PT, only one patient (1.4%) was reported in each category.
- A total of 3 patients (4.3%) experienced at least one SAE related to EC-MPS. Among them, 1 patient (1.4%) had mild events, 2 patients (2.9%) had moderate events, no severe events were reported. No single SAE related to EC-MPS by PT was reported in more than one patient (1.4%).
- For the exposure-adjusted event rate in AE episodes, categorized by PT, arthralgia was reported with an exposure adjusted event rate of 0.3 per patient-years followed by diarrhoea, herpes zoster, pyrexia, UTI, and cough reported with an exposure adjusted event rate of 0.2 per patient-years. The remaining AEs identified by PT were reported at a rate of 0.1 per patient-year.
- The exposure-adjusted serious event rates in SAE episodes, categorized by PT, reported with SLE and acute kidney injury SAEs showed an exposure-adjusted serious event rate of 0.1 per patient-year.

Overview of efficacy analysis at 6 months and 12 months:

- **Reasons for study drug discontinuation:** AEs (7 patients [10.1%] each), lost to follow up (4 patients [5.8% for FAS and 6.3% for PPS]), physician decisions (3 patients [4.3% for FAS and 3.1% for PPS]), protocol deviations (FAS: 3 patients [4.3%], PPS: 0 patient), death (FAS: 2 [2.9%], PPS: 1 patient [1.6%]), new therapy for study indication (1 patient [1.4% for FAS and 1.6% for PPS]), and unsatisfactory therapeutic effect (1 patient [1.4% for FAS and 1.6% for PPS]).
- **Clinical response:** At Month 6, among the 53 evaluable patients in the FAS, 12 patients (22.6%) achieved a complete response, and 26 patients (49.1%) achieved a partial response. The remaining 15 patients showed no response. Among the 52 evaluable patients in the PPS,12 patients (23.1%) experienced a complete response, and 26 patients (50.0%) had a partial response, while the remaining 14 patients exhibited no response.

- **Renal response in eGFR:** At Month 6, an equivalent number of patients exhibited renal response in eGFR within both FAS and PPS, with 45 patients (84.9% and 86.5%). The remaining 8 patients (15.1%) in FAS and 7 patients (13.5%) in PPS did not exhibit renal response. At Month 12, a similar proportion of patients exhibited renal response in eGFR in both FAS and PPS, with 40 patients (88.9%). The remaining 5 patients (11.1%) in each set exhibited no response.
- **Inactive urinary sediment response:** At Month 6, among the 38 evaluable patients in the FAS, 35 patients (92.1%) achieved an inactive urinary sediment response. Similarly, of the 37 evaluable patients in the PPS, 34 patients (91.9%) had achieved inactive urinary sediment response, while the remaining 3 patients in each set did not achieve inactive urinary sediment response. At Month 12, all 33 patients (100%) achieved an inactive urinary sediment response in both FAS or PPS.
- **Urine protein creatinine ratio:** At Month 6, among the 53 evaluable patients in the FAS, 25 patients (47.2%) achieved meaningful UPCR reduction. Similarly, of the 52 evaluable patients in the PPS, 25 patients (48.1%) achieved UPCR reduction, while 25 patients (47.2%) in FAS and 24 patients (46.2%) in PPS did not achieve meaningful UPCR reduction. The remaining 3 patients in each set reported as missing. At Month 12, the same proportion of patients achieved the meaningful UPCR reduction, with 33 patients (75.0%) in both the FAS and PPS. In each set, 10 patients (22.7%) did not achieve meaningful UPCR reduction, while one patient in each set reported as missing.

Conclusion

This prospective, single-arm, observational PASS provided evidence using data and insights into the preliminary safety profile of mycophenolate sodium (EC-MPS) for the treatment of LN patients in Taiwan.

The overall safety profile was consistent with other previous mycophenolate sodium studies conducted during clinical development.