NON-INTERVENTIONAL STUDY FINAL REPORT ABSTRACT

Title: A Population Based Cohort Study to Monitor the Safety and Effectiveness of Sirolimus in Patients with Sporadic Lymphangioleiomyomatosis (S-LAM)

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Rationale and background: Rapamune (sirolimus) has immunosuppressive properties that are mediated through inhibition of T-lymphocyte activation and proliferation, and antibody production by B-cells. Rapamune has been approved in the European Union (EU) since 13 March 2001 for prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant. On 04 April 2017, the Marketing Authorisation Holder (MAH) submitted an application for a Type II variation to the European Medicines Agency (EMA) for extension of the sirolimus indication to include the treatment of patients with lymphangioleiomyomatosis (LAM) based upon clinical data from the "Multicenter International LAM Efficacy and Safety of Sirolimus (MILES) trial." The MAH received approval for the S-LAM indication from the European Commission on 02 August 2018.

LAM is a rare, progressive, cystic lung disease. The condition arises almost exclusively in women (mean age of diagnosis is 35 years) and occurs either as sporadic LAM (S-LAM) or in association with tuberous sclerosis complex (TSC-LAM). This study is designed to present additional long-term safety and effectiveness data in patients with S-LAM treated with sirolimus derived from observational studies in the United Kingdom (UK) and the United States (US).

This non-interventional (NI) study is designated as a Category 3 Post-Authorisation Safety Study (PASS) and is a commitment to the EMA.

Research question and objectives: To describe the long-term safety and effectiveness of sirolimus among S-LAM patients, data within each of the UK and US data sources were used to:

1. Estimate the incidence proportion of adverse events among S-LAM patients treated with sirolimus.

2. Evaluate the selected effectiveness endpoints among S-LAM patients treated with sirolimus.

Study design and setting: This is a descriptive study using data from observational studies in the UK and the US. For this final report, both safety and effectiveness data (Objectives 1 and 2) are presented.

Patients and study size, including dropouts:

UK: The UK data were derived from the observational study entitled the "Comprehensive Cohort Study of UK patients with LAM." The inclusion criteria for this cohort are: 1) receiving care at the National Centre for LAM, Nottingham University NHS Trust and 2) a signed and dated informed consent form. The exclusion criteria are: 1) inability to give informed consent. The observation period was from 01 April 2011 to 03 February 2021. For the purposes of evaluation of safety and effectiveness events presented in this final report, the follow up period was calculated from the date of when sirolimus was first initiated.

US: The US data are derived from a prospective observational study entitled the "Multicenter International Durability and Safety of Sirolimus in LAM Trial (MIDAS)." MIDAS is a real-world observational registry that enrolled patients with LAM across 20 LAM clinics in the US. All adult patients with LAM, regardless of treatment status were eligible to enroll in MIDAS. Patients who were unable or unwilling to attend LAM clinic visits, to perform pulmonary function tests (PFTs) or to sign informed consent were excluded. Baseline data including demographic and key clinical information pertaining to LAM were collected on all patients, as well as longitudinal data including PFTs, health related quality of life questionnaires, stored blood samples for future use, as well as information regarding adverse effects from mammalian target of rapamycin (mTOR) inhibitor use. MIDAS was funded by the National Institutes of Health (NIH)/National Center for Accelerating Translational Sciences (NCATS). The observation period was from 27 March 2015 to 03 February 2021. For the purposes of this report, data analysis was limited to patients with S-LAM treated with sirolimus.

Variables and data sources:
Variables: Variables include demographic, concomitant medications, and clinical characteristics (histories of chylothorax and pneumothorax; presence of lymphatic disease), and all documented safety events and effectiveness endpoints.

Data Sources:
UK: "Comprehensive Cohort Study of UK Patients with LAM"
This ongoing observational cohort study was initiated in 2011 and is used for multiple research projects on LAM. The data collection for the study is conducted at the National Centre for LAM at Nottingham University Hospitals National Health Service (NHS) Trust.

US: "Multicenter International Durability and Safety of Sirolimus in LAM Trial (MIDAS)"
MIDAS is a real world, long-term, prospective, observational registry of patients with LAM or women at risk for development of LAM. This study evaluates the natural history of LAM in a general population-based cohort, determines the natural history of LAM development in adult women with TSC and characterises the long-term safety and efficacy of mTOR inhibitor treatment. There are 20 participating clinics in MIDAS, including the University of Cincinnati and 19 of the 35 US Rare Lung Diseases Consortium (RLDC) Sites.

Results

The results derived from these two data sources are presented and interpreted separately. As specified in the protocol, no attempt is made to pool data or compare and contrast results.

UK:

During the observation period (01 April 2011 to 03 February 2021), the study database included 438 patients with cystic lung disease, of whom 64 were diagnosed with TSC-LAM and 313 with S-LAM. Of the 313 patients with S-LAM, 225 were excluded as they had no reported treatment with sirolimus. Data presented in this final report were compiled from the remaining 88 patients. Before sirolimus treatment of the 88 patients, 27.3%, 9.1% and 47.7% of the patients with S-LAM had lymphatic disease (lymphadenopathy masses or lymphangiomyomas), history of chylothorax or pneumothorax, respectively. The median age at diagnosis was 39.8 years (range 18.6 to 67.2 years). Sirolimus was initiated at a median age of 43.9 years. The median sirolimus dose was 1.53 mg/day with a trough sirolimus whole blood concentration of 4.49 ng/ml. The median follow-up of patients was 5.16 years; median sirolimus treatment duration was 4.63 years. Seven out of 88 (8.0%) discontinued sirolimus treatment during the observation period, of which 1 (1.1%) was due to side effects. Safety events frequently reported by sirolimus-treated patients with S-LAM included aphthous ulcers (37.5%); diarrhoea (25.0%); headache (14.8%); acne (13.6%); and nausea (12.5%). Three patients died during the observation period. One of these patients, who had very advanced disease and was undergoing workup for lung transplant assessment, was still being treated with sirolimus. One patient died from breast cancer; no other malignancies were reported. In this UK cohort, 1 subject received a lung transplant 23 years after LAM diagnosis; the duration of sirolimus treatment from study start (01 April 2011) to transplant was 78.7 months.

Patients with S-LAM treated with sirolimus had a mean increase in forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) of 0.06 and 0.14 L respectively over the first year of treatment although there was a wide range of variation between patients. Although numbers were small, those with a history of chylothorax tended to have the greatest improvements in spirometry values. Lung diffusion of carbon monoxide (DL_{CO}) remained stable over the first year of treatment. In 52 patients, where data were available for longer than 2 years, this stability in FEV_1, tended to be sustained over a mean of 69 months of treatment with an annual change of 0.04 L.

US:

During the study period (27 March 2015 – 03 February 2021), a total of 415 LAM patients were enrolled in MIDAS. After excluding patients with missing data, TSC-LAM, or patients who did not receive treatment with sirolimus, data from 175 patients with S-LAM who were prescribed sirolimus are summarized in this report. Before sirolimus exposure, 14.9% and 36.0% of the patients with S-LAM had a history of chylothorax and pneumothorax, respectively. The median age at diagnosis was 42 years (range 24 to 64 years). Sirolimus was initiated at a median age of 45 years. The median sirolimus dose was 1.5 mg/day with a trough sirolimus whole blood concentration of 4.9 ng/ml. The median follow-up of patients was 3.6 years in the study; median sirolimus treatment duration was 1.83 years. Eleven out of

175 (6.3%) discontinued sirolimus treatment during the observation period, of which 4 (2.3%) were due to side effects/intolerance. The most frequent side effects related to sirolimus use were consistent with the known side effect profile of mTOR inhibitors and included headache (25.1%), aphthous ulcers (22.9%), fatigue (20.0%), hypercholesterolemia/elevated lipids (19.4%) skin rash/acne (18.9%), diarrhoea/loose stools (16.6%), and swelling/oedema (16.6%). No lung transplants or deaths were reported during the study period. One participant reported a diagnosis of calcaneal melanoma after 96 months on sirolimus and discontinued drug. As an isolated incidence, it remains unclear whether this complication was related to drug exposure.

Treatment with sirolimus resulted in durable stability in the rate of disease progression. The rate of changes (slope) in FEV_1, FVC, and DL_{CO} among the S-LAM patients treated with sirolimus were -0.004 L/year, 0.012 L/year, and 0.12 ml/min/mmHg/year, respectively.

Discussion:

UK:
Sirolimus treatment in 88 patients with S-LAM was associated with stable lung function, with mean FEV_1 generally unchanged over the duration of the study period. The patients studied were a range of ages, disease duration and severity and are representative of the spectrum of LAM patients requiring disease modifying therapy. Sirolimus side effects were frequent, with the majority of patients experiencing at least one, with aphthous ulcers, diarrhoea, headache, acne and nausea particularly frequent. The nature and frequency of these side effects were consistent with other reports of sirolimus treatment for LAM. Despite the frequency of side effects, only one patient (1.1% of those treated) discontinued treatment because of them. In this real-world cohort, sirolimus was generally safe and well tolerated, and associated with a preservation of lung function associated with stabilization of decline over the median duration of sirolimus treatment (4.63 years).

US:
Sirolimus treatment in 175 patients with S-LAM was associated with durable stability of pulmonary function across a mean 4.1 years of follow up in this cohort of S-LAM patients based on the slope estimates of FEV_1, FVC, and DL_{CO} over the study period. The most frequently reported safety events in MIDAS were consistent with the known safety profile of sirolimus and included headache, aphthous ulcers, fatigue, hypercholesterolemia/elevated lipids, skin rash/acne, diarrhoea/loose stools, and swelling/oedema. Some of the reported safety events in MIDAS are likely disease related (shortness of breath, chest pain, chyle or pleural effusion). Although safety events are frequently reported by patients taking sirolimus, they infrequently led to drug discontinuation in this study. Overall, these analyses demonstrate that treatment with sirolimus is generally safe and well-tolerated and is associated with stabilised lung function decline over the median duration of sirolimus treatment (1.83 years).

Marketing Authorisation Holder(s): Pfizer Europe MA EEIG

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