28 June 2018
EMA/493416/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rapamune

International non-proprietary name: sirolimus

Procedure No. EMEA/H/C/000273/II/0164

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
AMLs	Angiomyolipomas
BTDR	Breakthrough Therapy Designation Request
CAST	Cincinnati Angiomyolipoma Sirolimus Trial
CCHMC	Cincinnati Children's Hospital Medical Center
CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse Events
CT	Computed tomography
CSR	Clinical study report
DLco	Diffusing capacity for carbon monoxide
DSMB	Data Safety Monitoring Board
EU	European Union
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FITC	Fluorescein isothiocyanate
FPI	Functional Performance Inventory
FVC	Forced vital capacity
GGO	Ground glass opacities
GWB	General Well-Being Scale
HDL	High density lipoprotein
HRCT	High-resolution computed tomography
LAM	Lymphangioleiomyomatosis
LDL	Low density lipoprotein
LOH	Loss of heterozygosity
MC	Medically confirmed
MedDRA	Medical Dictionary for Regulatory Activities
MILES	Multicenter International LAM Efficacy and Safety of Sirolimus Study
mTOR	Mammalian target of rapamycin
NIH	National Institutes of Health

Abbreviation	Definition
NMC	Not medically confirmed
PI	Principle Investigator
PE	Phycoerythrin
PT	Preferred Term
EUQOL	European Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumours
RLDC	Rare Lung Diseases Consortium
RMP	Risk Management Plan
SAE	Serious adverse events
SEGAs	Subependymal Giant Cell Astrocytomas
SD	Standard deviation
S-ILD	Sirolimus-associated interstitial lung disease
S-LAM	Sporadic LAM
sNDA	Supplemental New Drug Application
SGRQ	St. George's Respiratory Questionnaire
SmPC	Summary of Product Characteristics
SRL	Sirolimus
SSCP	Single-strand conformation polymorphism
TRTO	Translational Research Trials Office
TSC	Tuberous sclerosis complex
WBC	White blood cell
UK	United Kingdom
US	United States
VAS	Visual Analog Scale
VEGF-D	Vascular Endothelial Growth Factor D

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Limited submitted to the European Medicines Agency on 4 April 2017 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include the treatment of patients with lymphangioleiomyomatosis. As a consequence section 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 6.0) are updated in accordance. In addition the MAH took the opportunity to make very minor formatting changes in the Labelling.

The variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products. However, during the application review, the CHMP noted that approximately 30-40% of women with tuberous sclerosis complex (TSC) have cystic pulmonary changes consistent with LAM. Since there is an authorised orphan medicinal product designated for “Tuberous sclerosis complex (TSC)”, everolimus (Votubia), a similarity assessment against this products is considered warranted, as the proposed therapeutic indication for Rapamune can be considered as being related to the condition of an authorised orphan medicinal product.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: N/A

Timetable	Planned dates
Start of procedure:	22 April 2017
CHMP Rapporteur Assessment Report	19 June 2017
PRAC Rapporteur Assessment Report	19 June 2017
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	6 July 2017
CHMP members comments	10 July 2017
Updated CHMP Rapporteur Assessment Report	13 July 2017
Request for supplementary information	20 July 2017
Submission deadline	22 November 2017
Re-start	27 November 2017
CHMP Rapporteur Assessment Report	21 December 2017
PRAC Rapporteur Assessment Report	21 December 2017
PRAC members comments	4 January 2018
Updated PRAC Rapporteur Assessment Report	5 January 2018
PRAC Outcome	12 January 2018
CHMP members comments	15 January 2018
Updated CHMP Rapporteur Assessment Report	18 January 2018
2nd Request for supplementary information	25 January 2018
Revised 2nd Request for supplementary information	27 February 2018
Submission deadline	26 March 2018
Re-start	28 March 2018
CHMP Rapporteur Assessment Report	12 April 2018
PRAC Rapporteur Assessment Report	4 April 2018
PRAC members comments	4 April 2018
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	12 April 2018
CHMP members comments	16 April 2018
Updated CHMP Rapporteur Assessment Report	20 April 2018
3rd Request for supplementary information	26 April 2018
Submission deadline	29 May 2018
Re-start	30 May 2018
CHMP Rapporteur Assessment Report	12 June
PRAC Rapporteur Assessment Report	8 June 2018
PRAC members comments	6 June 2018
Updated PRAC Rapporteur Assessment Report	19 June 2018
PRAC Outcome	14 June 2018
CHMP members comments	18 June 2018

Timetable	Planned dates
Updated CHMP Rapporteur Assessment Report	19 June 2018
Opinion	28 June 2018

2. Scientific discussion

2.1. Introduction

Rapamune (sirolimus) has been approved in the EU since March 13, 2001, for the use for prophylaxis of organ transplant rejection in adult patients at low to moderate immunological risk receiving a renal transplant. Sirolimus is a fermentation product of Streptomyces hygroscopicus, anactinomycete that was isolated in the seventies from a soil sample collected from Rapa Nui, commonly known as Easter Island (Seghal et al 1975 J of antibiotics).

Lymphangioleiomyomatosis (LAM) is a rare, progressive, frequently fatal cystic lung disease that predominantly affects young women of childbearing age. The clinical course of LAM is typically marked by the inexorable progressive loss of lung function, with resulting exercise intolerance and disability. Although recent studies suggest that there is variability in the rate of progression, LAM typically results in death or lung transplantation within 10 to 15 years. In 2014, the LAM Foundation has estimated that 3-8 per million women are affected with non-heritable LAM or sporadic LAM (S-LAM) (15,000-23,000 globally), and that approximately 30-40% of women with tuberous sclerosis complex (TSC) have cystic pulmonary changes consistent with LAM. LAM is caused by mutations in either the TSC1 or the TSC2 genes that encode for hamartin and tuberin proteins in the Akt/mTOR signaling pathway, which are critical for control of cell growth, survival and motility (van Slegtenharst et al 1997, Science, European Chromosome 16 Tuberous Sclerosis Consortium, 1992, Cell). The knowledge that deficiency or dysfunction of hamartin or tuberin results in the constitutive activation of mTOR kinase and S6 kinase (S6K), and is associated with inappropriate cellular proliferation, suggests that the mTOR inhibitor sirolimus may represent a novel, mechanism-guided, approach to therapy.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

The MAH calculates a PECSW value for the now applied orphan indication sporadic lymphangioleimyomatosis, 0.00001 µg/l. The applicant states that this is substantially below the trigger value of 0.01 µg/l and a Phase II environmental fata and effects analysis is not considered necessary.

The estimated log Kow value for sirolimus is 5.2 (OECD TG117 HPLC study 260C-187) and thus above the trigger for a PBT assessment. However, since sirolimus is naturally occurring, extensively metabolized (> 93%) and hydrolytically unstable, and given the very low prevalence rate of LAM, the applicant argues that sirolimus is not expected to present an environmental risk following patient use.

The CHMP considered that for the calculation of Fpen and PECSW, the full use for the product should be taken into account, not only the indication now applied for. In response, the MAH provided updated calculation and showed that the PECsw is below the trigger value also in this case. The MAH also concluded that a PBT assessment is not warranted and this is agreed by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1 Tabular listing of study 5702 (MILES study)

Protocol No. (Country)	Study Design and Objective	Treatment Groups	No. of Subjects (by Treatment Group, Optional)	Demographics (by Treatment Group, Optional) (No. of Subjects)	Duration of Treatment	Study Start/Status	Study Report Location
Efficacy and Safety Study Report							
5702 (United States, Japan, Canada)	The primary objective of this phase 3, randomised, double-blind, placebo controlled, investigator-initiated research study was to determine the safety and efficacy of sirolimus in subjects with LAM. The primary outcome measure was the difference over the one year treatment period between placebo and sirolimus groups in FEV1 response, which was assessed as the rate of change in FEV1 (FEV1 slope) in milliliters per month. Female subjects age 18 years or older, and diagnosed with LAM, were enrolled, treated for 12 months, and monitored for an additional 12 months (untreated).	Sirolimus (2 mg/day, PO as unmarked white triangular tablet); dose-adjusted to maintain a trough sirolimus blood level between 5-15 ng/mL measured by HPLC/mass spec based assay). Placebo (unmarked white triangular tablet).	Planned: 120 subjects were planned to be enrolled: Randomised: 89 subjects were randomised 1:1 to either the placebo group (43 subjects) or the sirolimus group (46 subjects). Completed: 75 subjects completed 12 months treatment phase (34 placebo group and 41 sirolimus group); 27 subjects completed the additional 12 month observation phase (13 placebo group and 14 sirolimus group).	Sex: all subjects were female. Mean/Median Age (min/max): 45.9/45 years (25 – 65) placebo group; 45.0/44.5 years (23 – 63) sirolimus group Race: White/Asian/Other: 30 (70%)/ 12 (28%)/ 1 (2%) subjects in the placebo group; 29 (63%)/ 15 (33%)/ 2 (4%) subjects in sirolimus group.	Treatment duration was 12 months (a non-treatment observation period of 12 months followed treatment).	Study start/completed: December 14, 2006 to September 2010. CSR completed 14 November 2014.	Module 5.3.5.1

The MILES Study (Study 5702) was a phase 3, multicenter, randomised, double-blind, placebo-controlled, safety and efficacy study to study the effect of sirolimus on lymphangioleiomyomatosis (LAM). Please refer to section Clinical Efficacy for details.

2.4. Clinical efficacy

2.4.1. Main study

Title of Study

The MILES study 5702: A phase 3, multicenter, randomised, double-blind, placebo-controlled, safety and efficacy study to study the effect of sirolimus on lymphangioleiomyomatosis (LAM).

Methods

Study participants

The MILES Trial began enrolment in December 2006 at the Cincinnati Children's Hospital Medical Center and concluded enrolment in August 2009. The 13 MILES Trial sites in the United States (10), Canada (1), and Japan (2) completed the final phase of study conduct with the close of study visits in September 2010.

Inclusion Criteria	• Female, age 18 or over • Signed and dated informed consent • Diagnosis of LAM as determined by a. biopsy (lung, abdominal mass, lymph node or kidney or cytology from thoracic or abdominal sources revealing HMB45+ staining of spindled/epithelioid cells), and chest CT scan findings compatible with LAM; or b. compatible chest CT scan findings in the setting of tuberous sclerosis, angiomyolipomata (diagnosed by CT, MRI by the site radiologist or biopsy) or chylous pleural effusion (verified by tap) or c. Chest CT scan findings compatible with LAM (confirmed by the two MILES core radiologists) and a VEGF-D level ≥ 800 pg/mL. d. Post-bronchodilator forced expiratory volume in one second of ≤70% of predicted during baseline visit
Exclusion Criteria	a. History of myocardial infarction, angina or stroke related to atherosclerosis b. Pregnant, breast feeding, or plan to become pregnant within the next 2 years c. Inadequate contraception d. Significant hematologic or hepatic abnormality (i.e. transaminase levels > three times the upper limit of normal range, HCT <30%, platelets < 80,000/cumm, adjusted absolute neutrophil count <1000/cumm, total WBC < 3000/cumm)
	e. Intercurrent infection at initiation of study drug f. Recent surgery (involving entry into a body cavity or requiring 3 or more sutures) within eight weeks of initiation of study drug g. Use of an investigational drug within the 30 days prior to randomization h. Uncontrolled hyperlipidemia i. Previous lung transplantation or active on transplant list j. Inability to attend scheduled clinic visits k. Inability to give informed consent l. Inability to perform pulmonary function testing m. Creatinine > 2.5 mg/dl n. Chylous ascites sufficient to affect diaphragmatic function based on the opinion of the site investigator o. Pleural effusion sufficient to affect pulmonary function based on the opinion of the Site Investigator (generally > 500cc) p. Acute pneumothorax within the past 8 weeks q. History of malignancy in the past 2 years, other than squamous or basal cell skin cancer r. Use of estrogen containing medications within the 30 days prior to randomization s. Known allergy to sirolimus

Treatments

This was a phase III treatment, multi-centre, randomized, double-blind, placebo-controlled, safety/efficacy study to assess sirolimus treatment in subjects with LAM disease. One hundred and twenty subjects were randomized in a 1:1 ratio, to receive oral sirolimus, at an initial dose of 2 mg per day, or matched placebo. Sirolimus levels were measured at each follow-up visit; the results of these measurements were revealed only to an independent medical monitor, who made dosing recommendations to maintain sirolimus trough levels between 5 and 15 ng per millilitre, as well as corresponding sham dose adjustments in the placebo group. The study design included a screening visit and a 12-month, double-blind, placebo-controlled treatment period, followed by a 12-month observation period during which no patients received a study drug and all patients remained unaware of their treatment assignment.

Objectives

The experimental plan had two specific aims:

1. Developed and implemented a double-blind, placebo-controlled, 'intention to treat' based multi-centre protocol for the determination of the safety and efficacy of sirolimus in subjects with LAM. The primary end point was FEV1 response at one year, defined as the difference between groups in the rate of change in FEV1 (FEV1 slope). The secondary endpoints were response in FVC, diffusing capacity for carbon monoxide, lung volume measurements, distance walked in six minutes, volumetric CT estimate of lung cyst size and mass of tissue in the chest, and biomarker analyses such as VEGF-D. Planned safety endpoints included analysis of severity-graded adverse events, and number and severity of chylous effusions, pneumothoraxes, haemorrhagic renal episodes, and all cause mortality.

2. Determined the relationship between changes in lung function and questionnaire-based assessments of dyspnoea, quality of life, fatigue, and degree of health impairment in LAM trial subjects who are taking sirolimus or placebo.

Outcomes/endpoints

For the primary efficacy measure, the rate of change in each outcome over the first year in the sirolimus group was compared with that in placebo group. The primary outcome was FEV1 response, which was assessed as the rate of change in FEV1 (FEV1 slope) in millilitres per month, over the 12 month treatment period.

The secondary outcomes were:

- Rate of change in FEV1 per month over the observation period
- Change of FEV1 from baseline during the treatment period and observation period
- Responses in FVC
- Diffusing capacity of the lung for carbon monoxide.
- Lung volume measurements (residual volume, functional residual capacity, and total lung capacity).
- Distance walked in a six-minute walk test.
- Volumetric CT estimate of lung cyst size and mass of tissue in the chest (Planned, but not yet completed).
- Serum VEGF-D levels.

- St. George’s Respiratory Questionnaire.
- The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36).
- The Functional Performance Inventory.
- The General Well-Being Questionnaire.
- The Euroqol Visual Analogue Scales assessing fatigue, dyspnea, and quality of life.

Sample size

One hundred and twenty patients were randomized to placebo or sirolimus groups, treated for one year and followed off of drug or placebo for one additional year. The primary endpoint will be FEV1 slope at 12 months. For efficacy, the power to test the hypothesis that there was no difference between two groups in changes of outcomes over time was calculated at a significance level α of 0.05. Assuming compound symmetry for the covariance structure of repeated measures from the same subject, the following formula was used (Diggle et al. (2003)):

$Z_{1-\beta}=[(N*m*s_x^2*d^2)/(2*\sigma^2*(1-\rho))]^{0.5}-Z_{1-\alpha/2}$, where $s_x^2=\Sigma(x_j-\text{mean}(x))^2/m$; n: the number of subjects in each group; m: the number of repeated measures; d: the difference between two slopes; σ2: the common variance of outcome; ρ: the correlation between outcomes from the same subject; β: the type II error rate.

The power was calculated assuming unit standard deviation and within-subject correlations from 0.7-0.9. The statistical powers will be less than 60% when the slope difference between two groups is 0.03 and within subject correlation smaller than 0.9. See table below.

Table 2 Power calculation for the linear mixed effects model

Within subject correlation	d	four measurements (0,3,6,12month)		Three measurements (0,6,12month)	
		n=50	n=25	n=50	n=25
0.7	0.03	0.681	0.405	0.642	0.376
	0.05	0.982	0.817	0.972	0.782
	0.07	0.999	0.980	>0.999	0.970
0.8	0.03	0.845	0.558	0.812	0.521
	0.05	0.999	0.939	0.997	0.918
	0.07	>0.999	0.998	>0.999	0.997
0.9	0.03	0.988	0.845	0.981	0.812
	0.05	>0.999	0.999	>0.999	0.997
	0.07	>0.999	>0.999	>0.999	>0.999

n: number of patients in each arm;d: slope difference between two groups

Randomisation

Participants were randomly assigned to treatment with placebo or sirolimus arm via the DMCC on-line system. Kits were prepared based on a 1:1 randomization assignment.

Blinding

The site principal investigator and all site team members were blinded to treatment assignment for the subjects. Rapamune 1mg tablets and placebo to match were supplied to site pharmacies in numbered kits. Each kit consisted of 2 boxes, Box A and Box B. To maintain blinding, for each subject in the treatment arm who underwent a dose adjustment, a subject in the placebo arm also underwent a dose adjustment.

Statistical methods

Taking into account within subject correlation of each outcome, a linear mixed effects model was planned to test whether the slope of each outcome in the sirolimus group was the same as that in the placebo group. Repeated measurements were planned to be analysed as a vector outcome. An indicator of the sirolimus group, time, and an interaction term between the indicator of sirolimus group and time were included as fixed effects. Two types of random effects models were planned: one was to include a random intercept only and the other was to include a random intercept and a random slope for each subject. Maximum likelihood estimates (MLE) were to obtain regression coefficients for fixed effects and restricted MLE for the variance component. A linear predictor was to be obtained through the estimates of random intercept and random slope to identify individuals with steeper change. To examine whether the mean FEV1 response was similar between the two treatment groups, a linear mixed-effects model was used to include the time since enrolment, the treatment assignment, and the interaction between time and treatment. The PROC MIXED procedure with the Kenward-Roger correction (SAS Institute) was used to fit the model, without imputation of missing data. Four models were examined:

- Intent-to-treat approach using all enrolled subjects
- Protocol-driven approach including subjects who were primary outcome completers (i.e., had values for 12-month FEV1
- Protocol driven approach with removal of data from subjects who had trough sirolimus levels below 5 ng/mL for at least 3 months of the study
- Protocol driven approach with removal of data from subjects who were identified as outliers to the fitted model when residual analysis was performed.

The primary statistical analysis was the intent-to-treat approach using all enrolled subjects. This model was compared for consistency with the other three models. The treatment and time interaction was found to be statistically significant in all four approaches, implying that the level of FEV1 (L) improved in the active treatment group compared to the placebo treatment group. Slope estimation showed that the FEV1 level decreased significantly over time in the placebo group, but remained stable in the sirolimus group.

A general linear model was used to compare the difference between the two groups in the mean change from baseline to 12 months, after adjustment for baseline values. A Wilcoxon signed-rank test was used to assess the difference from baseline to 12 months within each group. For categorical outcomes, the data were compared with the use of Fisher's exact test or the chi-square test, as appropriate. For continuous variables, the medians were compared with the use of the Wilcoxon rank-sum test. P values of less than 0.05 were considered to indicate statistical significance. All reported P values were two-sided, and were not adjusted for multiple testing. The analyses were performed according to the intention-to-treat principle. Since subject-specific change plots clearly suggested that slopes differed among subjects, the focus of the primary efficacy analysis was the linear mixed effects model for FEV1 with both random intercept and slope. The normality of FEV1 (L) at each visit time was examined through a Shapiro-Wilk test, and there was no significant violation of normality assumption (p-value > 0.3).

Missing data

If data were missing, the analyses were planned to be performed in several ways: First, data were to be analysed assuming missing status was completely at random. However, if the 'missingness' depended on the outcome, the parameter estimation could be biased. As a secondary analysis, investigating the missing data mechanism given observed outcomes was planned. If the 'missingness'

depended on the set of observed outcomes, a correctly specified covariance structure could accommodate the situation. But if the 'missingness' was due to a specific outcome value that should have been obtained at the time, a sensitivity analysis under various plausible assumptions concerning the 'missingness' was to proceed. Dropout was also to be considered in a monotone missing data pattern. When the dropout was completely at random or unrelated to all future outcome values, an imputation was to be incorporated to fill out the missing data. However, when the dropout depended on current and future unobserved outcomes, there would be no standard approach to accommodate this situation.

Analysis of the pattern of missing data was not completed fully as described in the planned statistical analyses. The percent change from baseline was examined for study participants with post-baseline data who withdrew before the 12 month primary efficacy time point. This examination was judged to be sufficient for concluding that the missing data were not likely to affect the study efficacy conclusion.

Interim Analyses

An interim analysis occurred using the O'Brien–Fleming stopping boundary when 40 subjects had completed the 12-month visit. A significance level of 0.002 was chosen to preserve a nominal significance level of 0.049 for efficacy at the end of the study. The analyses were planned to be performed according to the intention-to-treat principle. The primary outcome, the FEV1 response measured in liters over the course the treatment year (termed the FEV1 slope), was planned to be analysed as the difference in the FEV1 slope between the placebo group and the sirolimus group. The planned calculation was to use the spirometric data obtained at baseline and at 3, 6, 9, and 12 months during the treatment phase. A linear mixed-effects model including the time since enrolment, the treatment assignment, and the interaction between time and treatment was planned for use to evaluate the between-group and within group differences in the FEV1 slope.

Results

Participant flow

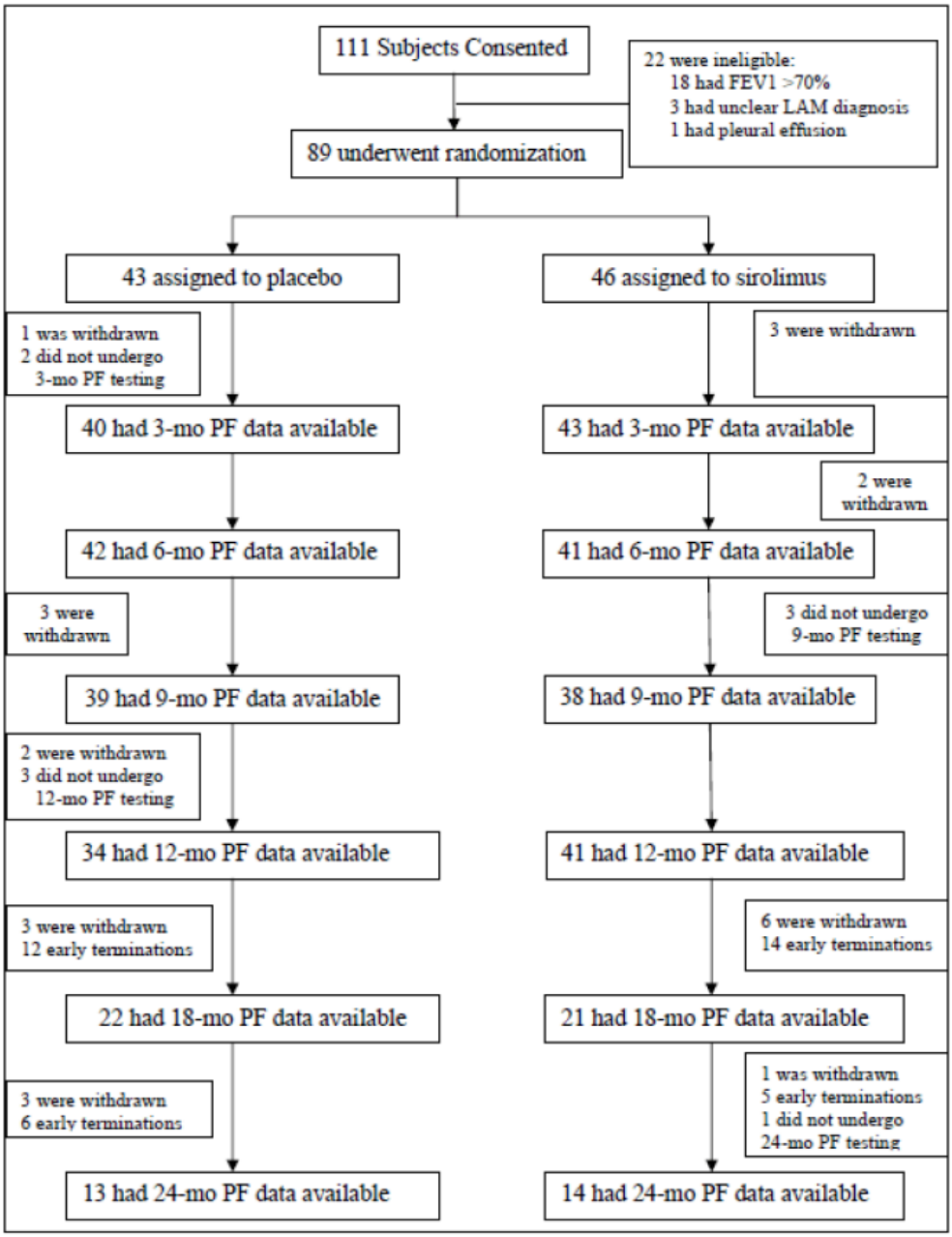

Table 3 Reasons for discontinuations

Summary:				sirolimus	placebo	% total	% total	
	8	rapamycin treatment	Withdrew to pursue rapmycin treatment	5	3	21%	13%	33%
	2	pneumothorax	Withdrawn due to pneumothorax	0	2	0%	8%	8%
	2	transplant list	Transplant list	0	2	0%	8%	8%
	6	Infection	Infection	3	3	13%	13%	25%
	1	GI and anxiety	GI and anxiety	1	0	4%	0%	4%
	1	failure to attend visits	Failure to atttend study visits	1	0	4%	0%	4%
	2	expired	Expired	0	2	0%	8%	8%
	1	Acne	Acne	1	0	4%	0%	4%
	1	Couldn't perform PFT	Couldn't perform PFT	1	0	4%	0%	4%
Total	**24**			**12**	**12**			**100%**

Recruitment

The study was conducted in the USA, Japan and Canada and patients were recruited between December 2006 and September 2010.

Conduct of the study

Although the interim stopping rule met the threshold for early termination due to a finding of efficacy in the primary endpoint, the DSMB recommended that the trial be continued until all the subjects had completed the 12-month visit. The purpose of this action was to ensure that a full complement of efficacy and safety data would be gathered. The data and safety monitoring board also endorsed an investigator-initiated proposal to truncate the observation phase of the study, owing to the impending termination of the funding period and expiration of the study drug. The treatment assignments and the deliberations of the data and safety monitoring board remained concealed until the release of the final analysis.

Baseline data

Table 4 Baseline Demographic and Clinical Characteristics of the Subjects

Characteristic	All Subjects (N=89)	Placebo Group (N=43)	Sirolimus Group (N=46)	P-Value
Age (years)				
Mean ± SD	45.4±10.6	45.9±10.3	45.0±10.9	0.74
Median (min-max)	45 (23-65)	45 (25-65)	44.5(23-63)	-
Race, n (%)[a]				
White	59 (66)	30 (70)	29 (63)	0.58 (White vs. Asian)[b]
Asian	27 (30)	12 (28)	15 (33)	-
Other	3 (3)	1 (2)	2 (4)	-
Clinical features, n (%)				
Tuberous sclerosis complex	8 (9)	4 (9)	4 (9)	1.00[c]
Post menopause	30 (34)	16 (37)	14 (30)	0.50[b]
History of angiomyolipoma	44 (49)	22 (51)	22 (48)	0.75[b]
History of pneumothorax	53 (60)	29 (67)	24 (52)	0.14[b]
Oxygen-therapy requirement				
Continuous use	28 (31)	14 (33)	14 (30)	0.83[b]
Intermittent use	52 (58)	23 (53)	29 (63)	0.36[b]
Pulmonary-function testing	-	-	-	-
FEV1				
Volume (mL)	1367±420	1378±446	1357±400	0.69
% of predicted value	48.54±13.77	47.73±14.37	49.29±13.31	0.77
FVC				
Volume (mL)	2791±692	2909±749	2682±622	0.14
% of predicted value	79.71±16.60	80.77±17.62	78.73±15.70	0.55
Ratio of FEV1 to FVC	0.50±0.15	0.48±0.15	0.52±0.16	0.35
TLC (% of predicted value)	105.21±25.63	106.70±29.45	103.83±21.71	0.61
FRC				
Volume — mL	3000±905	3175±1059	2838±710	0.20
% of predicted value	112.49±31.32	116.61±38.29	108.67±22.97	0.43
RV (% of predicted value)	141.42±59.22	147.48±69.25	135.78±48.15	0.80
DLco				
Diffusing capacity (mL/mm Hg/min)	10.23±4.61	10.42±4.82	10.05±4.47	0.52
% of predicted value	43.43±18.97	43.77±20.56	43.12±17.66	0.70
6MWD (m)	403±105	399±115	407±96	0.78

Characteristic	All Subjects (N=89)	Placebo Group (N=43)	Sirolimus Group (N=46)	P-Value
Health-related symptom scores				
EuroQOL VAS for QOL[d]	67.82±19.25	67.09±20.11	68.50±18.61	0.83
FPI[e]	2.29±0.50	2.35±0.49	2.25±0.51	0.35
General Well Being score	62.71±4.71	62.63±4.24	62.78±5.15	0.56
Serum VEGF-D concentration (pg/mL)	2029±2343	2223±2997	1848±1514	0.57

a. Race was self-reported.
b. P-value was calculated with the use of the chi-square test.
c. P-value was calculated with the use of Fisher's exact test.
d. The EuroQOL visual-analogue scale measures self-reported ratings of health status. Scores range from 0 to 100, with lower scores indicating worse functioning
e. Scores on the Functional Performance Inventory range from 1 to 4, with lower scores indicating lower health status
P-value was calculated with the use of the Wilcoxon rank-sum test
* Plus–minus values are means ±SD.
Abbreviations: N=Number of subjects; n (%)= Number and percentage of subjects; min=Minimum; max=Maximum; vs=Versus; SD=Standard deviation; FEV1=Forced Expiratory Volume in 1 Second; FVC=Forced Vital Capacity; TLC=Total Lung Capacity; FRC=Functional Residual Capacity; RV=Residual Volume; DLco=Diffusing Capacity for Carbon Monoxide; mm Hg=Millimeters of mercury; min=Minutes; 6MWD=Distance walked in 6 minute walk test; m=Metres; VAS=Visual Analogue Scale; EuroQOL=European Quality of life; FPI=Functional Performance Inventory; VEGF-D=Vascular Endothelial Growth Factor-D.

The subjects had moderately severe lung disease; the mean ± standard deviation (SD) FEV1 was 47.7±14.4% of the predicted value in the placebo group and 49.3±13.3% of the predicted value in the sirolimus group (p=0.77). There was also evidence of airflow obstruction, gas trapping, and impaired gas exchange. At baseline, most subjects had a history of a pneumothorax and/or angiomyolipoma and required oxygen therapy intermittently.

Numbers analysed

The population for the efficacy analyses included all subjects who received at least 1 dose of study drug (43 in the placebo group and 46 in the sirolimus group).

Outcomes and estimation

Primary Endpoint

In the placebo group, the $FEV1_{slope}$ ±SE from baseline to 12 months was −12±2 mL per month; the slope was significantly less than zero (p<0.0001), a finding that was consistent with declining lung function. The FEV1slope ±SE in the sirolimus group was 1±2 mL per month, which was not significantly different from zero; this was indicative of the stabilization of lung function during treatment. There was a significant difference between the two groups in the FEV1slope (p<0.0001). The mean change (±SD) in FEV1, during the treatment period in the placebo group was -134 (±182) mL, versus 19 (±124) mL in the sirolimus group. The baseline-adjusted difference in the mean change in FEV1 (sirolimus versus placebo) during the treatment periods was 151 mL (p<0.0001 for the between-group difference). A total of 12% of the subjects in the placebo group, as compared with 46% of the subjects in the sirolimus group, had FEV1 values at or above baseline values at the 12 month visit (p=0.0004). FEV1 declined in both groups during the observation year (a decline of 8±3 mL per month in the placebo group and of 14±3 mL per month in the sirolimus group). Although these slopes were both less than zero (p=0.005 and p<0.0001, respectively), the difference between them did not reach significance (p=0.08).

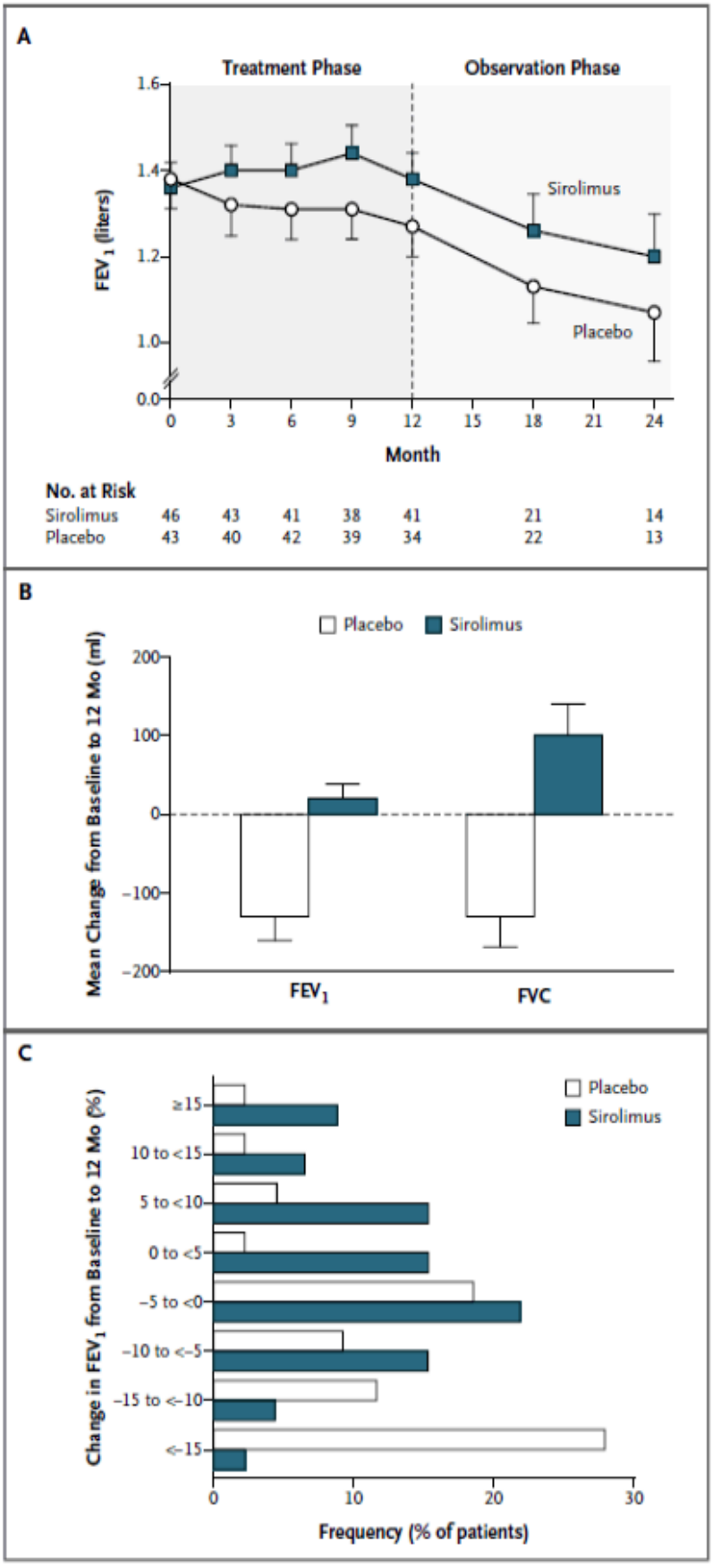
A
Treatment Phase
Observation Phase
1.6
1.4
1.2
1.0
0.0
FEV1 (liters)
Sirolimus
Placebo
0
3
6
9
12
15
18
21
24
Month
No. at Risk
Sirolimus 46 43 41 38 41 21 14
Placebo 43 40 42 39 34 22 13
B
Placebo
Sirolimus
200
100
0
−100
−200
Mean Change from Baseline to 12 Mo (ml)
FEV1
FVC
C
Placebo
Sirolimus
≥15
10 to <15
5 to <10
0 to <5
−5 to <0
−10 to <−5
−15 to <−10
<−15
Change in FEV1 from Baseline to 12 Mo (%)
0
10
20
30
Frequency (% of patients)

Figure 1 Change in Lung Function During Treatment and Observation Phases

Secondary Endpoints

The FVC slope (±standard error [SE]) during the treatment phase was −11±3 mL per month in the placebo group, as compared with 8±3 mL per month in the sirolimus group (p<0.0001). The FVC slope was significantly less than zero in the placebo group (p=0.001), which was consistent with a decline in lung function. The slope was significantly greater than zero in the sirolimus group (p=0.009), which was consistent with an improvement in lung function during treatment. The mean change (±SD) in FVC, during the treatment period in the placebo group was -129 (±233) mL, versus 97 (±260) mL in the sirolimus group. The baseline-adjusted difference in the mean change in FVC (sirolimus versus placebo) during the treatment periods was 216 mL (p=0.0005 for the between-group difference). A total of 23% of the subjects in the placebo group, and 54% of subjects in the sirolimus group, had FVC values that were at or above baseline values at the 12-month visit (p=0.003). The difference between groups in the slope for FRC during the treatment phase was also significant (p=0.049). The differences between groups in the slopes for TLC, RV, DLco, and 6MWD were not significant (Table 2).
There were significant differences in the change from baseline to 12 months in the score on the EuroQOL VAS for QOL and in the total score on the FPI. The changes in individual measures of SF-36 and SGRQ did not differ significantly between the two groups. Mean VEGF-D levels were similar in the two groups at baseline and were significantly lower at the 12 month points in the sirolimus group than in the placebo group.

Table 5 Effects of Sirolimus on Primary and Secondary Outcome Variables in the Treatment Period. (MILES Study)

	Mean at 12 months Mean ± SD		Mean change from baseline Mean ± SD			Rate of change per month Mean ± SE		
Pulmonary function	**Placebo (N =34)**	**Sirolimus (N = 41)**	**Placebo (N = 34)**	**Sirolimus (N = 41)**	**p-value[a]**	**Placebo (N = 43)**	**Sirolimus (N = 46)**	**p-value[b]**
FEV1 (ml)	1272±414	1383±394	-134±182[c]	19±124	<0.0001	-12±2[d]	1±2	<0.001
FVC (ml)	2843±668	2780±735	-129±233[c]	97±260	0.0005	-11±3[d]	8±3[d]	<0.001
TLC (ml)	5464±1217	4944±982	-7±650	94 ±504	0.648	-2±7	8±7	0.340
RV (ml)	2502±969	2112±617	-16 ±514	38±538	0.613	-3±7	4±7	0.465
FRC (ml)	3260±968	2912±660	-123±521	53±335	0.426	-11±6	6±6	0.049
DLco (ml/ mmHg/min)	9.61 ± 4.06	9.62 ± 3.92	-0.62±2.89[c]	-0.06± 1.50	0.376	-0.06±0.03[d]	-0.01±0.02	0.172
6MWD (m)	418±106	431±104	26.1±50.6[c]	23.7±59.4	0.986	1.46±0.82	1.77±0.76	0.783
VAS-QOL score	65.60±18.47[e]	73.71±18.03	-2.34±15.77	6.10±16.96	0.015	-0.21±0.20	0.39±0.19[d]	0.028
FPI-total score	2.33±0.47	2.35 ±0.49	-0.05 ±0.23	0.10±0.38	0.089	-0.009±0.004[d]	0.005±0.004	0.031

Serum VEGF-D (pg/ml)	2444±3862[e]	862±540	-14.8±1113	-1032±1301[c]	0.0006	-2.42±17.23	-88.01±16.61[d]	0.001
General Well-Being Total Score	62.71±5.00	61.88±5.40	0.34±6.02	-0.95±5.22	0.360	0.06±0.07	-0.02±0.07	0.434

a.: p-value1 General linear model p-value for placebo vs. sirolimus, after adjusting for baseline level
b.: p-value2 Linear mixed effects model p-value for no slope difference between placebo and sirolimus
c.: Wilcoxon signed rank sum 2 sided test p-value<0.05 for 0 median within placebo or sirolimus: <0.05 (FVC, 6MWD), <.01 (DLco), and <0.0001 (FEV1, VEGF-D)
d.: Linear mixed effects model p-value<0.05 for 0 slope within placebo or sirolimus: <0.05 (FPI-total score, DLco, VAS-QOL), <.01 (FVC in placebo and sirolimus), and <0.0001 (VEGF-D, FEV1)
e.: Wilcoxon rank sum 2 sided test p-value <0.05 for no median difference at 12 month between placebo and sirolimus
N Number of subjects with FEV1
Abbreviations: FEV1- Forced Expiratory Volume in 1 Second, FVC Forced Vital Capacity, TLC-total lung Capacity , RV-Residual Volume, FRC functional residual capacity, DLco Carbon Monoxide Diffusing Capacity, 6MWD-6 minute walk test, VAS Visual Analogue Scale, QOL- Quality of life, FPI- Functional Performance Inventory, VEGF-D- Vascular Endothelial Growth Factor-D.

There was no significant difference between treatment groups in the observation-year slopes or the mean changes from baseline to 24 months in FVC. The mean (±SD) serum VEGF-D levels at 24 months remained elevated in the placebo group (2108±2146 pg per millilitre in the 13 subjects for whom data were available at 24 months) and depressed in the sirolimus group (930±461 pg per millilitre in the 14 subjects for whom data were available at 24 months).VEGF-D, a lymphangiogenic growth factor implicated in the pathophysiology of LAM, were elevated at baseline in both groups and fell in the group treated with sirolimus. There were no significant differences in the slopes from 12 to 24 months or in the mean change from baseline to 24 months in any other variables measured, including lung volumes, diffusing capacity for carbon monoxide, distance covered on a 6-minute walk test, and symptoms.

The lack of a significant between-group difference in the distance covered on a 6-minute walk test suggested that improvement in lung function was not accompanied by an increase in exercise capacity, though a treatment effect might have been obscured by the relatively high baseline exercise tolerance of the subjects or limitations in the performance characteristics of the test.

Ancillary analyses

Measurements of Treatment Compliance: Trough sirolimus levels were drawn at each study visit beginning on study visit 2. The levels of sirolimus in the placebo group were below the detection limit throughout the study. Other than brief out-of-range excursions, the sirolimus trough levels in the active-treatment group were maintained between 5 and 15 ng/mL, except in the case of four subjects in whom levels were intentionally kept below 5 ng/mL for 3 months or more in order to control side effects.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 6 Summary of Efficacy for trial MILES

Title: Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus Trial (The MILES Trial)			
Study identifier	5702		
Design	12-month treatment period, followed by a 12-month observation period during which no patients received a study drug and all patients remained unaware of their treatment assignment.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12-month treatment period, followed by a 12-month observation period during which no patients received a study drug and all patients remained unaware of their treatment assignment. not applicable not applicable
Hypothesis	Superiority vs placebo		
Treatments groups	Sirolimus		Treatment 2 mg/day (unmarked, white, triangular tablet) PO, dose-adjusted to maintain a trough sirolimus blood level between 5-15 ng/mL. Duration 1 year Number randomised 46
	Placebo		Treatment Matching placebo (unmarked, white, triangular tablet) Duration 1 year Number randomised 43
Endpoints and definitions	Primary endpoint	FEV1 response at one year.	Defined as the difference between groups in the rate of change per month in FEV1 (FEV1 slope).
	Secondary endpoints	Response in FVC, diffusing capacity for carbon monoxide, lung volume measurements, distance walked in six minutes, at a subset of sites volumetric CT estimate of lung cyst size and mass of tissue in the chest, and biomarker analyses such as VEGF-D.	Secondary outcome measures included responses in forced vital capacity (FVC), measured as changes from baseline to 12 months; lung volumes (residual volume, functional residual capacity, and total lung capacity); the distance covered on a 6-minute walk test; diffusing capacity of the lung for carbon monoxide; serum VEGF-D levels; and scores on the St. George's Respiratory Questionnaire; the Medical Outcomes Study 36-Item Short- Form Health Survey (SF-36); the Functional Performance Inventory; the General Well-Being Questionnaire and the EuroQOL Visual Analogue Scales assessing fatigue, dyspnoea, and quality of life. Measurements of these parameters were variably obtained at visits that occurred at baseline, at 3 weeks, and at 3, 6, 9, 12, 18, and 24 months. Analysis of volumetric estimate of lung cyst size and mass of tissue in the chest was planned, but not completed.
Database lock	**6th January 2011**		
Results and Analysis			

Analysis description	**Primary Analysis** FEV1 response measured in mL per month over the course of 1 year (termed the FEV1 slope) was analysed using a linear mixed-effects model (with time since enrolment, treatment, and the interaction between time and treatment as fixed effects, and time-slope and intercept for each patient as random effects).			
Analysis population and time point description	Analysis population: Intention-to-treat approach using all enrolled subjects Analysis time points: FEV1 from baseline to month 12. Data collected at the baseline, 3, 6, 9, and 12 month timepoints are included in the slope model.			
Descriptive statistics and estimate variability	Treatment group	Sirolimus	Placebo	Treatment group
	Number of subject	46	43	Number of subject
	FEV1 rate of change per month (mL/month) Mean	1	-12	FEV1 rate of change per month (mL/month) Mean
	SE	2	2	SE

Effect estimate per comparison	FEV1 rate of change per month (mL/month)	Comparison groups	Treatment difference (sirolimus minus placebo)
		mean	13
		SE	3
		P-value	<0.001

Analysis description	**Secondary Analysis:** FVC response measured in mL per month over the course of 1 year (termed the FVC slope) was analysed using a linear mixed-effects model (with time since enrolment, treatment, and the interaction between time and treatment as fixed effects, and time-slope and intercept for each patient as random effects).		
Analysis population and time point description	Analysis population: Intention-to-treat approach using all enrolled subjects Analysis time points: FVC from baseline to month 12. Data collected at the baseline, 3, 6, 9, and 12 month timepoints are included in the slope model.		
Descriptive statistics and estimate variability	Treatment group	Sirolimus	Placebo
	Number of subject	46	43
	FVC rate of change per month (mL/month) Mean	8	-11
	SE	3	3

Effect estimate per comparison	FVC rate of change per month (mL/month)	Comparison groups	Treatment difference (sirolimus minus placebo)
		mean	20
		SE	5
		P-value	<0.001

Analysis description	**Secondary Analysis:** DLCO response measured in mL/mmHg/min per month over the course of 1 year (termed the DLCO slope) was analysed using a linear mixed-effects model (with time since enrolment, treatment, and the interaction between time and treatment as fixed effects, and time-slope and intercept for each patient as random effects).
Analysis population and time point description	Analysis population: Intention-to-treat approach using all enrolled subjects Analysis time points: DLCO from baseline to month 12. Data collected at the baseline, 3, 6, and 12 month timepoints are included in the slope model.

Descriptive statistics and estimate variability	Treatment group	Sirolimus	Placebo
	Number of subject	46	43
	DLCO rate of change per month (mL/mmHg/min/month) Mean	-0.01	-0.06
	SE	0.02	0.03

Effect estimate per comparison	DLCO rate of change per month (mL/mmHg/min/month) Mean	Comparison groups	Treatment difference (sirolimus minus placebo)
		mean	0.05
		SE	0.04

		P-value	0.172

Analysis description	**Secondary Analysis:** 6MWD response measured in metres per month over the course of 1 year (termed the 6MWD slope) was analysed using a linear mixed-effects model (with time since enrolment, treatment, and the interaction between time and treatment as fixed effects, and time-slope and intercept for each patient as random effects).
Analysis population and time point description	Analysis population: Intention-to-treat approach using all enrolled subjects Analysis time points: 6MWD from baseline to month 12. Data collected at the baseline, 3, 6, and 12 month timepoints are included in the slope model.

Descriptive statistics and estimate variability	Treatment group	Sirolimus	Placebo
	Number of subject	46	43
	6MWD rate of change per month (metres/month) Mean	1.77	1.46
	SE	0.76	0.82

Effect estimate per comparison	6MWD rate of change per month (metres/month) Mean	Comparison groups	Treatment difference (sirolimus minus placebo)
		mean	0.31
		SE	1.11
		P-value	0.783

Analysis description	**Secondary Analysis:** VAS-QOL rate of change per month over the course of 1 year (termed the VAS-QOL slope) was analysed using a linear mixed-effects model (with time since enrolment, treatment assignment, and the interaction between time and treatment as fixed effects, and time-slope and

	intercept for each patient as random effects).		
Analysis population and time point description	Analysis population: Intention-to-treat approach using all enrolled subjects Analysis time points: VAS-QOL from baseline to month 12. Data collected at the baseline, 3, 6, 9, and 12 month timepoints are included in the slope model.		
Descriptive statistics and estimate variability	Treatment group	Sirolimus	Placebo
	Number of subject	46	43
	VAS-QOL rate of change per month Mean	0.39	-0.21
	SE	0.19	0.20
Effect estimate per comparison	VAS-QOL rate of change per month Mean	Comparison groups	Treatment difference (sirolimus minus placebo)
		mean	0.60
		SE	0.27
		P-value	0.028

Analysis description	**Secondary Analysis:** FPI-total score rate of change per month over the course of 1 year (termed the FPI-total score slope) was analysed using a linear mixed-effects model (with time since enrolment, treatment, and the interaction between time and treatment as fixed effects, and time-slope and intercept for each patient as random effects).		
Analysis population and time point description	Analysis population: Intention-to-treat approach using all enrolled subjects Analysis time points: FPI-total score from baseline to month 12. Data collected at the baseline, 3, 6, 9, and 12 month timepoints are included in the slope model.		
Descriptive statistics and	Treatment group	Sirolimus	Placebo

estimate variability			
	Number of subject	46	43
	FPI-total score rate of change per month Mean	0.005	-0.009
	SE	0.004	0.004

Effect estimate per comparison	FPI-total score rate of change per month Mean	Comparison groups	Treatment difference (sirolimus minus placebo)
		mean	0.013
		SE	0.006
		P-value	0.031

Analysis description	**Secondary Analysis:** VEGF rate of change in pg/mL per month over the course of 1 year (termed the VEGF slope) was analysed using a linear mixed-effects model (with time since enrolment, treatment, and the interaction between time and treatment as fixed effects, and time-slope and intercept for each patient as random effects).
Analysis population and time point description	Analysis population: Intention-to-treat approach using all enrolled subjects Analysis time points: VEGF from baseline to month 12. Data collected at the baseline, 6, and 12 month timepoints are included in the slope model.

Descriptive statistics and estimate variability	Treatment group	Sirolimus	Placebo
	Number of subject	46	43
	VEGF rate of change per month (pg/mL/month) Mean	-88.01	-2.42

	SE	16.61	17.23

Effect estimate per comparison	VEGF rate of change per month (pg/mL/month) Mean	Comparison groups	Treatment difference (sirolimus minus placebo)
		mean	-85.60
		SE	23.93
		P-value	0.001

Analysis description	**Secondary Analysis:** General Well Being total score was measured per month over the course of 1 year (termed the General Well Being total score slope) was analysed using a linear mixed-effects model (with time since enrolment, treatment, and the interaction between time and treatment as fixed effects, and time-slope and intercept for each patient as random effects).
Analysis population and time point description	Analysis population: Intention-to-treat approach using all enrolled subjects Analysis time points: General Well Being total score from baseline to month 12. Data collected at the baseline, 3, 6, 9, and 12 month timepoints are included in the slope model.

Descriptive statistics and estimate variability	Treatment group	Sirolimus	Placebo
	Number of subject	46	43
	General Well Being total score Mean	-0.02	0.06
	SE	0.07	0.07

Effect estimate per comparison	General Well Being total score	Comparison groups	Treatment difference (sirolimus minus placebo)

	Mean		
		mean	-0.08
		SE	0.10
		P-value	0.434

Analysis description	**Secondary Analysis:** FEV1 change from baseline to Month 12 (mL) was analysed using a general linear model (with treatment, and baseline covariate)
Analysis population and time point description	Analysis population: Intention-to-treat approach using all enrolled subjects Analysis time points: FEV1 baseline and at 12 months on treatment phase.

Descriptive statistics and estimate variability	Treatment group	Sirolimus	Placebo
	Number of subject	41	34
	FEV1 change from baseline to Month 12 (mL) Mean	19	-134
	SD	124	182

Effect estimate per comparison	FEV1 change from baseline to Month 12 (mL)	Comparison groups	Baseline-adjusted Treatment difference (sirolimus minus placebo)
		mean	151
		SE	35
		P-value	<0.0001

Analysis description	**Secondary Analysis:** FVC change from baseline to Month 12 (mL) was analysed using a general linear model (with treatment, and baseline covariate)
Analysis population and time point description	Analysis population: Intention-to-treat approach using all enrolled subjects Analysis time points: FVC baseline and at 12 months on treatment phase.

Descriptive statistics and estimate variability	Treatment group	Sirolimus	Placebo
	Number of subject	41	34
	FVC change from baseline to Month 12 (mL) Mean	97	-129
	SD	260	233

Effect estimate per comparison	FVC change from baseline to Month 12 (mL)	Comparison groups	Baseline-adjusted Treatment difference (sirolimus minus placebo)
		mean	216
		SE	59
		P-value	0.0005

Analysis description	**Secondary Analysis:** DLCO change from baseline to Month 12 (mL/mmHg/min) was analysed using a general linear model (with treatment, and baseline covariate)
Analysis population and time point description	Analysis population: Intention-to-treat approach using all enrolled subjects Analysis time points: DLCO baseline and at 12 months on treatment

	phase.

Descriptive statistics and estimate variability	Treatment group	Sirolimus	Placebo
	Number of subject	41	32
	DLCO change from baseline to Month 12 (mL/mmHg/min) Mean	-0.06	-0.62
	SD	1.50	2.89

Effect estimate per comparison	DLCO change from baseline to Month 12 (mL/mmHg/min) Mean	Comparison groups	Baseline-adjusted Treatment difference (sirolimus minus placebo)
		mean	0.43
		SE	0.48
		P-value	0.376

Analysis description	**Secondary Analysis:** 6MWD change from baseline to Month 12 (metres) was analysed using a general linear model (with treatment, and baseline covariate)
Analysis population and time point description	Analysis population: Intention-to-treat approach using all enrolled subjects Analysis time points: 6MWD at baseline and at 12 months on treatment phase.

Descriptive statistics and estimate variability	Treatment group	Sirolimus	Placebo
	Number of subject	41	34
	6MWD change from	23.7	26.1

	baseline to Month 12 (metres) Mean		
	SD	59.4	50.6

Effect estimate per comparison	6MWD change from baseline to Month 12 (metres) Mean	Comparison groups	Baseline-adjusted Treatment difference (sirolimus minus placebo)
		mean	0.22
		SE	12.34
		P-value	0.986

Analysis description	**Secondary Analysis:** VAS-QOL change from baseline to Month 12 was analysed using a general linear model (with treatment, and baseline covariate)
Analysis population and time point description	Analysis population: Intention-to-treat approach using all enrolled subjects Analysis time points: VAS-QOL baseline and at 12 months on treatment phase.

Descriptive statistics and estimate variability	Treatment group	Sirolimus	Placebo
	Number of subject	41	35
	VAS-QOL change from baseline to Month 12 Mean	6.10	-2.34
	SD	16.96	15.77

Effect estimate per	VAS-QOL change from	Comparison	Baseline-adjusted

comparison	baseline to Month 12 Mean	groups	Treatment difference (sirolimus minus placebo)
		mean	8.30
		SE	3.34
		P-value	0.015

Analysis description	**Secondary Analysis:** FPI-total score change from baseline to Month 12 was analysed using a general linear model (with treatment, and baseline covariate)
Analysis population and time point description	Analysis population: Intention-to-treat approach using all enrolled subjects Analysis time points: FPI-total score baseline and at 12 months on treatment phase.

Descriptive statistics and estimate variability	Treatment group	Sirolimus	Placebo
	Number of subject	41	35
	FPI-total score change from baseline to Month12 Mean	0.10	-0.05
	SD	0.38	0.23

Effect estimate per comparison	FPI-total score change from baseline to Month 12 Mean	Comparison groups	Baseline-adjusted Treatment difference (sirolimus minus placebo)
		mean	0.12
		SE	0.07
		P-value	0.089

Analysis description	**Secondary Analysis:** VEGF change from baseline to Month 12 (pg/mL) was analysed using a general linear model (with treatment, and baseline covariate)
Analysis population and time point description	Analysis population: Intention-to-treat approach using all enrolled subjects Analysis time points: VEGF at baseline and at 12 months on treatment phase.

Descriptive statistics and estimate variability	Treatment group	Sirolimus	Placebo
	Number of subject	38	33
	VEGF change from baseline to Month 12 (pg/mL) Mean	-1032	-14.8
	SD	1301	1113

Effect estimate per comparison	VEGF change from baseline (pg/mL) Mean	Comparison groups	Baseline-adjusted Treatment difference (sirolimus minus placebo)
		mean	-1052
		SE	291
		P-value	0.0006

Analysis description	**Secondary Analysis:** General Well Being total change from baseline to Month 12 was analysed using a general linear model (with treatment, and baseline covariate)
Analysis population and time point description	Analysis population: Intention-to-treat approach using all enrolled subjects Analysis time points: General Well Being total score at baseline and at

	12 months on treatment phase.		
Descriptive statistics and estimate variability	Treatment group	Sirolimus	Placebo
	Number of subject	41	35
	General Well Being total score Mean	-0.95	0.34
	SD	5.22	6.02
Effect estimate per comparison	General Well Being total score Mean	Comparison groups	Baseline-adjusted Treatment difference (sirolimus minus placebo)
		mean	-1.03
		SE	1.11
		P-value	0.360

Supportive studies

A search of the PubMed database was conducted to identify reports on the efficacy and safety of sirolimus in subjects with LAM, cumulatively through 6 February 2017. A summary of 11 relevant references obtained from this search are presented below and are considered supportive of the safety and effectiveness of mTOR inhibition for the treatment of LAM.

- Taille et al (2007); case report
- Bissler et al(2008); open label non-randomised study in 25 subject with angiomyolipoma and LAM.
- Davies et al, (2008, 2011) open label non-randomised phase 2 study in 16 subjects with angiomyolipoma.
- Dabora et al (2011); phase 1 in 36 adults with TSC or TSC/LAM.
- Taveira-DaSilva et al (2011); observational study of 19 patients with rapidly progressing LAM or LAM
- Taveira-DaSilva and Moss (2012) – Review

- Cai et al (2014) a study conducted to determine the effect of sirolimus on circulating LAM cells
- Yao et al (2014) a study conducted to determine whether the effects of sirolimus are associated with reduction of lung function decline in 38 LAM patients.
- Argula et al (2014) Argula et al reported in a conference abstract that the MILES trial demonstrated that sirolimus stabilised lung function and improved measures of functional performance and quality of life when compared to the placebo group.
- Sugimoto et al (2016) reported in a poster presentation, a retrospective review of LAM treatment in 55 cases with sirolimus from April 2007 to April 2016.
- Takada et al (2016) reported that in a randomised, controlled clinical trial sirolimus stabilised lung function in subjects with LAM treated for a 12-month period, however pretreatment decline in lung function after the drug was discontinued indicated that continued exposure is required to suppress disease progression. The authors therefore conducted a single-arm, open-label, investigator initiated safety and efficacy study of sirolimus in 63 women with LAM at 9 sites in Japan to determine the durability and tolerability of long-term sirolimus treatment in Asian subjects with LAM. The subjects received sirolimus for 2 years at doses adjusted to maintain a trough blood level of 5-15 ng/ml. Results show 52 subjects (82.5%) completed the trial with mean drug compliance of more than 80% overall during the study. The number of AEs was greatest during the initial 6 months of therapy, but they continued to occur with declining frequency throughout the 2-year study period. Of the 1,549 AEs reported, 27 were classified as serious, including reversible sirolimus pneumonitis in 3 subjects. New hypercholesterolaemia occurred in 30 subjects (48%); microcytosis in 10 subjects; loss of body weight in 33 subjects; and an increase in blood pressure that required treatment in 5 subjects. The FEV1, FVC, and quality-of-life parameters were stable in the overall study cohort during the study period, but baseline to 2-year improvements in lung function occurred in the subset of subjects with a prior history of chylothorax.

  The authors conclude although long-term sirolimus treatment of Asian subjects with LAM was associated with a large number of AEs, including three episodes of pneumonitis, most subjects completed the 2-year course of medication with good drug compliance and stable quality of life and lung function.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The MILES trial was a phase III treatment, randomized, double-blind, placebo-controlled, safety/efficacy study to assess sirolimus treatment in subjects with LAM disease; the majority of patients were diagnosed with sporadic LAM, presenting the pulmonary manifestations. One hundred and twenty subjects were randomized in a 1:1 ratio, to receive oral sirolimus, at an initial dose of 2 mg per day, or matched placebo. Sirolimus levels were measured at each follow-up visit; the results of these measurements were revealed only to an independent medical monitor, who made dosing recommendations to maintain sirolimus trough levels between 5 and 15 ng per millilitre, as well as corresponding sham dose adjustments in the placebo group. The study design included a screening visit and a 12-month, double-blind, placebo-controlled treatment period, followed by a 12-month observation period during which no patients received a study drug and all patients remained unaware of their treatment assignment. The design is considered appropriate but the CHMP requested further information on the chosen dosing strategy. More specifically, for sirolimus a single loading dose of 6 mg is recommended for (i.e. directly after) renal transplantation (and 2 mg as maintenance, or the

dose in steady state, respectively). The applicant justified why a loading dose is not needed or recommended for the treatment of LAM, i.e. treatment of LAM with sirolimus does not require immediate attainment of the target concentration range. In the case of renal transplantation a loading dose is recommended in order to quickly achieve an efficacious concentration in order to reduce the risk of rejection, while for the LAM indication there is no such risk.

It is acknowledged that the study is performed outside the EU, but it is acceptable to extrapolate the MILES data to an EU patient population considering that the disease and treatment is expected to be similar.

Efficacy data and additional analyses

The MILES trial showed a statistical significance for the primary endpoint with a preserved pulmonary function with treatment with sirolimus for 1 year and determined by the change in FEV1. It was shown that the FEV1slope (±SE) from baseline to 12 months was 1±2 mL per month in the sirolimus group, which was not significantly different from zero. This was not the case in the placebo group were the FEV1slope (±SE) was −12±2 mL per month and the slope was significantly less than zero ($p<0.0001$), a finding that was consistent with declining lung function. The mean change from baseline in FEV1 after 12 months treatment was 19±124 in the sirolimus group and -134±182 in the placebo group ($p<0.0001$). The baseline-adjusted difference in the mean change in FEV1 (sirolimus versus placebo) during the treatment periods was 151 mL ($p<0.0001$ for the between-group difference). A total of 46% of the subjects in the sirolimus group, as compared with 12% of the subjects in the placebo group, had FEV1 values at or above baseline values at the 12 month visit ($p=0.0004$).

In addition, effect was shown in several secondary endpoints. A difference in FVC was shown with a baseline-adjusted difference in the mean change in FVC (sirolimus versus placebo) during the treatment periods of 216 mL ($p=0.0005$ for the between-group difference). A total of 54% of subjects in the sirolimus group and 23% of the subjects in the placebo group, had FVC values that were at or above baseline values at the 12-month visit ($p=0.003$). In addition, an effect on VEGF-D (Vascular Endothelial Growth Factor D) was shown with lower levels in the active treatment group ($p = 0.001$). For the quality of life parameters the results was significant in two of the investigated 4 different scores. There were significant differences in the change from baseline to 12 months in the score on the EuroQOL VAS for QOL and in the total score on the FPI. The changes in individual measures of SF-36 and SGRQ did not differ significantly between the two groups. Even though many of the comparisons to placebo reached statistical significance, the clinical relevance of the magnitude of the differences is difficult to evaluate considering the rarity of the condition. In addition, no effects were observed on the diffusing capacity of the lung for carbon monoxide or on exercise tolerance and the positive effects on airflow vanished after sirolimus was discontinued.

The CHMP requested the MAH to further discuss the clinical relevance of the effect and the choice of study endpoints. Namely, the treatment with Rapamune has been shown to stabilize FEV1 during the treatment period of one year, whereas FEV1 declined in the placebo group in patients with LAM and FEV1≤ 70%. However, the clinical relevance of the data needs further justification, especially as with respect to the FEV1 as the primary endpoint for the patient population with LAM, which is a heterogeneous population including patients with normal lung function and different progression rates. Furthermore, the CHMP requested details on the clinical relevance of the effect on FEV1 for the target population. Discussion on the potential impact on long term outcomes like respiratory insufficiency and lung transplantation was requested, as well as that on the lack of effect on CO diffusion and exercise tolerance.

In response to these requests, the MAH argued that the loss of spirometry-derived lung function parameters (e.g. FVC and FEV1) are established features of LAM in combination with cystic lung

destruction and refers among other sources to the clinical guidelines in the US and Japan. This is accepted by the CHMP. If the explanation for lack of effect on DLCO is that DLCO may fluctuate for reasons unrelated to LAM disease, this should have equal impact in both the active treatment group and the placebo group. However, it is acknowledged that there were numerical trends with effect on DLCO in sirolimus treated patients. Considering the six minute walk test (6MWT) the MAH argued that the patients in the MILES study had a preserved walking distance related to the relatively young age of the patients. This is agreed by the CHMP.

The supportive evidence for the long term effect of sirolimus on lung function and the potential impact on long term outcomes was supplied by literature references. In Taveira-DaSilva et al (2011), a mean decrease of FEV1 of approximately 100 ml /year was seen before sirolimus therapy. When the subject was treated with sirolimus there was seen an increase in FEV1 of approximately 50 ml/year. The same pattern is shown in Yao et al (2014). In Takada et al, improvements were seen only in subjects with prior history of chylothorax, and the authors discussed if this may be useful for candidate selection and predictive biomarker and the concluded that long-term sirolimus treatment of Asian patients with LAM was associated with a large number of adverse events, including three episodes of pneumonitis, most patients completed the 2-year course of medication with good drug compliance and stable quality of life and lung function. In Taveira-DaSilva (2017) it was reported stabilization of lung function values compared to the predicted values without treatment with a longer study duration compared to the MILES trial.

However, the CHMP also considered that in order to truly reflect the trial population in the new indication of Rapamune, the choice of the pulmonary primary endpoint and the fact that most subjects had moderate disease and all included patients had FEV1≤70%, it was requested to describe the treated patients in the indication as: patients with moderate lung disease or declining lung function. This was agreed by the applicant.

Furthermore, the CHMP also assessed the similarity between sirolimus and the authorised orphan product Votubia (everolimus) and reflected on the potential extend of overlap of the target population for Rapamune with the target population of Votubia (everolimus) . The full, currently approved indication of Votubia is:

Renal angiomyolipoma associated with tuberous sclerosis complex (TSC)

Votubia is indicated for the treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC) who are at risk of complications (based on factors such as tumour size or presence of aneurysm, or presence of multiple or bilateral tumours) but who do not require immediate surgery.

The evidence is based on analysis of change in sum of angiomyolipoma volume.

Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC)

Votubia is indicated for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery.

The evidence is based on analysis of change in SEGA volume. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated.

Thus, the CHMP asked the applicant to provide a concrete estimate calculation of the extent of the overlap of patients who have Tuberous Sclerosis Complex (TSC)-LAM and who could meet clinical criteria for treatment with Rapamune and with Votubia. After careful consideration regarding further quantifying the extent of the potential overlap of patients who have Tuberous Sclerosis Complex (TSC)-LAM and who meet clinical criteria for treatment with Rapamune and with Votubia, the applicant

was not able to provide a clear estimate and argued thatpublished data are limited and do not enable a concrete quantification of the overlap. Further to this, data captured in the registries are not sufficiently granular to understand whether patients with co-existing angiomyolipomas and subependymal giant cell astrocytomas (SEGAs) would meet the criteria for treatment with Votubia, and therefore do not provide insight for the degree of potential overlap. Therefore to address the CHMP's major objection as related to the potential overlap of patients, the MAH proposed a narrowed indication for patients with S-LAM only, as follows:

Treatment of patients with sporadic lymphangioleiomyomatosis with moderate lung disease or declining lung function.

This indication also better reflects the studied population, i.e. the MILES study enrolled 89 subjects of which 81 subjects had S-LAM.

Efficacy of sirolimus for the treatment of LAM in the subset of subjects with S-LAM is consistent with the findings in the overall LAM population included in the MILES study, as presented in the table below. The primary outcome, the FEV1 response measured in millilitres per month over the course of 1 year (termed the FEV1 slope), was significantly better in the sirolimus group, p<0.001. These data demonstrated stabilisation of lung function in the sirolimus group, compared with declining lung function in the placebo group. These findings are also supported by a significant difference observed in FVC, quality of life and functional performance measures. Changes in serum VEGF-D (pg/ml) also reflected treatment response.

Table 7 Sporadic LAM: Effects of Sirolimus on Primary and Secondary Outcome Variables in the Treatment Period (MILES Study)

	Mean at 12 Months Mean ±SD		Mean Change from Baseline Mean ±SD		p-value[a]	Mean (95% CI)	Rate of Change per Month Mean ±SE		p-value[b]	Mean (95% CI)
Primary Function	Placebo N=31	Sirolimus N=38	Placebo N=31	Sirolimus N=38		Placebo-Sirolimus	Placebo N=39	Sirolimus (N=42)		Placebo-Sirolimus
FEV1 (mL)	1317±402	1378±405	-140±189[c]	12±119	0.0002	-152 (-229,-75)	-12±2[d]	0.3±2	<0.001	-12.72 (-18.66, -6.78)
FVC (mL)	2937±621	2732±709	-132±242[e]	76±253[e]	0.0041	-207 (-324,-90)	-12±3[d]	7±3[d]	<0.001	-18.31 (-27.84, -8.78)
TLC (mL)	5525±1246[e]	4885±975	28±673	98 ±512	0.438	-71 (-365, 223)	0.4±8	7±7	0.512	-7.05 (-28.39,14.29)
RV (mL)	2467±996	2102±639	4±536	47±547	0.621	-43 (-305, 218)	-2±8	6±7	0.458	-7.76 (-28.48,12.96)
FRC (mL)	3314±995	2866±643	-44±394	62±342	0.666	-106 (-301, 89)	-4±6	6±5	0.149	-10.76 (-25.46,3.93)
DLCO (mL/mmHg/min)	9.58±4.17	9.36±3.63	-0.60±3.03[e]	-0.18±1.44	0.629	-0.42 (-1.61, 0.77)	-0.06 ±0.03[d]	-0.02±0.03	0.355	-0.04 (-0.11, 0.04)
6MWD (m)	421±110	423±102	23.1±50.3[e]	22.5±61.5[e]	0.995	0.54 (-25.85,26.92)	1.22±0.88	1.67±0.81[d]	0.711	-0.44 (-2.80, 1.91)
VAS-QOL score	64.9± 19.4	72.9±18.3	- 3.26±15.61	6.18±17.37[e]	0.016	-9.44 (-17.23,-1.65)	-0.28±0.21	0.39±0.20	0.022	-0.67 (-1.23, -0.10)
FPI-total score	2.33±0.46	2.33±0.50	-0.03±0.22	0.10±0.39	0.203	-0.13 (-0.27, 0.02)	-0.009±0.005[d]	0.004± 0.004	0.044	-0.01 (-0.03, -0.00)
Serum VEGF-D (pg/ml)	1750±1484[e]	848±553	-146±574	-1021±1354[e]	<0.0001	875 (380, 1370)	-8.61±15.19	-85.34 ±14.19[d]	<0.001	76.73 (35.28, 118.19)
General Well Being total score	62.68±4.46	61.76±5.54	-0.19±4.84	-1.03±5.32	0.423	0.83 (-1.57, 3.23)	0.03±0.07	-0.04±0.07	0.483	0.07 (-0.13,0.27)

a. P-value1 General linear model p-value for placebo vs. sirolimus, after adjusting for baseline level
b. P-value2 Linear mixed effects model p-value for no slope difference between placebo and sirolimus
c. Wilcoxon signed rank sum 2 sided test p-value<0.05 for 0 median within placebo or sirolimus: <0.05 (FVC in sirolimus, 6MWD in placebo and sirolimus, VAS-QOL), <.01 (FEV1,FVC in placebo, DLCO), and <0.0001 (VEGF-D)
d. Linear mixed effects model p-value<0.05 for 0 slope within placebo or sirolimus: <0.05 (FVC in sirolimus, FPI-total score, DLCO, 6MWD), <.01 (FVC in placebo), and <0.0001 (VEGF-D, FEV1)
e. Wilcoxon rank sum 2 sided test p-value <0.05 for no median difference at 12 month between placebo and sirolimus: <0.05 (TLC), <.01 (VEGF-D)
N Number of subjects with FEV1
1. It was obtained assuming (m1-m2) follows the normal distribution, where m1is the mean of the placebo group and m2 is the mean of the sirolimus group: m1~ Normal(μ1, σ12/N1) and m2 ~ Normal(μ2, σ22/N2), N1=number of observations in the placebo group and N2=number of observations in the sirolimus group
2. It was obtained assuming t-distribution for the slope difference from the linear mixed effects model

Abbreviations: LAM=lymphangioleiomyomastosis; SD=standard deviation; SE=standard error; FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; mL=millilitre; TLC=total lung capacity; RV=residual volume; FRC=functional residual capacity; DLCO=diffusion capacity of lung for carbon monoxide; 6MWD=six minute walk test; VAS-QOL=Visual Analogue Score-Quality of Life; FPI=Functional Performance Inventory; VEGF-D= vascular endothelial growth factor D

Within the S-LAM subset, all subjects across both treatment groups reported at least 1 adverse event (AE) during the 12 month treatment period. Reported AEs were consistent with the known safety

profile of sirolimus, except for the addition of weight decreased (as previously described for the overall study population). There were 9 subjects (23%) in the placebo group reporting at least 1 serious adverse event (SAE) during the 12 month treatment period, and 8 subjects (19%) in the sirolimus group. Overall, the safety of sirolimus in patients with S- LAM was similar to the safety profile observed for all sirolimus treated subjects in the study.

The applicant's proposal was accepted by the CHMP.

2.4.3. Conclusions on the clinical efficacy

In conclusion, the analysis of the key efficacy results such as FEV1 and FVC of S-LAM subjects in the MILES study of the difference in mean change from baseline to the end of the treatment period between the sirolimus and the placebo treatment groups of the S-LAM subset show that the efficacy of sirolimus for the treatment of LAM in the subset of subjects with S-LAM is consistent with the findings in the overall LAM population included in the MILES Study. The patient population and the clinical data from the pivotal study support the indication to patients with sporadic lymphangioleiomyomatosis with moderate lung disease or declining lung function and this is agreed by the CHMP.

2.5. Clinical safety

Introduction

The most commonly reported adverse reactions as described in the SmPC 4.8 (occurring in <10% of patients) are thrombocytopaenia, anaemia, pyrexia, hypertension, hypokalaemia, hypophosphataemia, urinary tract infection, hypercholesterolaemia, hyperglycaemia, hypertriglyceridaemia, abdominal pain, lymphocoele, peripheral oedema, arthralgia, acne, diarrhoea, pain, constipation, nausea, headache, increased blood creatinine, and increased blood lactate dehydrogenase (LDH).

Since sirolimus is an immunosuppressant the patients under treatment are vulnerable to opportunistic infections and reactivation of viral diseases, such as herpes and CMV. Moreover, immunosuppressive treatment increases the susceptibility to the development of lymphoma and other malignancies, particularly of the skin. Cases of BK virus-associated nephropathy, as well as cases of JC virus-associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including sirolimus. Hepatoxicity has been reported. The risk may increase as the trough sirolimus level increases. Rare reports of fatal hepatic necrosis have been reported with elevated trough sirolimus levels. Cases of interstitial lung disease (including pneumonitis and infrequently bronchiolitis obliterans organising pneumonia (BOOP) and pulmonary fibrosis), some fatal, with no identified infectious aetiology have occurred in patients receiving immunosuppressive regimens including sirolimus.

Patient exposure

The MILES study included 46 subjects enrolled in the active treatment group. Subjects were given 2 mg sirolimus per day by mouth initially. The dose was adjusted throughout the study to maintain a trough sirolimus level between 5-15 ng/mL.

Adverse events

The safety population was comprised of subjects who received at least 1 dose of study drug (43 in the placebo group and 46 in the sirolimus group). Safety-related data were summarised using tables and graphical presentations, subject listings, and complete narrative descriptions of subjects who experienced serious AEs (SAEs). Results of the safety-related data analysis are expressed as counts or

medians (or means). AEs were entered as CTCAE version 3 codes. AEs were converted to MedDRA v16.1. Safety was assessed based on all-cause mortality within the sirolimus or placebo group. The following safety assessments were performed; physical exams, vital signs, levels of electrolytes, blood urea nitrogen, creatinine, fasting glucose, hepatic enzymes, urine protein and albumin to creatinine ratio, bilirubin, fasting serum lipids, and sirolimus level were performed at every visit. Chest radiographs were done at baseline and at the end of study visit.

During the study, all subjects who received study drug reported AEs. A total of 1911 AEs were reported: 43 subjects in the placebo group reported 817 AEs, and 46 subjects in the sirolimus group reported 1094 AEs (see table below).

Table 8 reported Any Adverse Events by Category (CTCAEv3)

AE Category[a]	Frequency (by Treatment)		
	Placebo	Sirolimus	Total
Allergy/Immunology	14	12	26
Auditory/Ear	2	5	7
Blood/Bone Marrow	5	12	17
Cardiac Arrhythmia	0	4	4
Cardiac General	15	17	32
Constitutional Symptoms	42	53	95
Death not associated with event	1	0	1
Dermatology/Skin	49	117	166
Endocrine	5	2	7
Gastrointestinal	193	295	488
Hemorrhage/Bleeding	17	18	35
Hepatobiliary/Pancreas	2	0	2
Infection	94	102	196
Lymphatics	14	15	29
Metabolic/Laboratory	27	62	89
Musculoskeletal/Soft Tissue	23	39	62
Neurology	31	40	71
Ocular/Visual	4	10	14
Pain	124	143	267
Pulmonary/Upper Respiratory	138	129	267
Renal/Genitourinary	8	13	21
Sexual/Reproductive Function	8	5	13
Vascular	1	1	2
Total	817	1094	1911

a. AEs and SAEs by MedDRA term are available in Appendix 16.8.3. There were 31 events not included in the MedDRA analysis, as they were later determined to be duplicates (14) or data entry error (17). All but one AE were non-serious and there was no specific clustering.

The number of subjects with all causality AEs >5% in the sirolimus group during the Treatment Period, based on MedDRA v16.1., is presented below. The most common AEs during the treatment period for subjects receiving sirolimus were stomatitis, diarrhoea, acne, headache, nasopharyngitis, upper respiratory tract infection, cough, and nausea (MedDRA v16.1 terms).

Table 9 Adverse Events Reported by >5% of Subjects in the Sirolimus Treatment Group

			Treatment							
			Placebo				Sirolimus			
			TRT Period (N=43)		OBS Period (N=34)		TRT Period (N=46)		OBS Period (N=41)	
			N	%	N	%	N	%	N	%
Number of Subjects reporting one or more AEs			43	100	20	59	46	100	22	54
System Organ Class	High Level Group Term	Preferred Term	N	%	N	%	N	%	N	%
Blood and lymphatic system disorders	White blood cell disorders	Leukopenia	--	--	--	--	4	8.70	--	--
		Lymphopenia	--	--	--	--	3	6.52	--	--
Cardiac disorders	Pericardial disorders	Pericardial effusion	1	2.33	1	2.94	3	6.52	--	--
Gastrointestinal disorders	Gastrointestinal motility and defecation conditions	Constipation	1	2.33	--	--	3	6.52	--	--
		Diarrhea	15	34.88	--	--	29	63.04	--	--
	Gastrointestinal signs and Symptoms	Abdominal pain	3	6.98	1	2.94	9	19.57	1	2.44
		Dyspepsia	4	9.30	--	--	5	10.87	--	--
		Nausea	10	23.26	1	2.94	17	36.96	1	2.44
		Vomiting	3	6.98	2	5.88	4	8.70	2	4.88
	Gastrointestinal vascular conditions	Hemorrhoids	--	--	--	--	3	6.52	--	--
	Oral soft tissue conditions	Stomatitis	27	62.79	--	--	31	67.39	--	--
	Salivary gland conditions	Dry mouth	2	4.65	--	--	3	6.52	--	--
General disorders and administration site conditions	Body temperature conditions	Pyrexia	3	6.98	1	2.94	4	8.70	2	4.88
	General system disorders NEC	Chest pain	11	25.58	2	5.88	13	28.26	2	4.88
		Chills	2	4.65	1	2.94	4	8.70	--	--
		Fatigue	13	30.23	--	--	13	28.26	--	--
		Edema peripheral	4	9.30	4	11.76	12	26.09	--	--
Infections and infestations	Infections-pathogen unspecified	Otitis media	1	2.33	--	--	4	8.70	1	2.44
		Upper respiratory tract infection	14	32.56	--	--	18	39.13	5	12.20
	Viral infectious disorders	Influenza	2	4.65	1	2.94	3	6.52	1	2.44
Investigations	Hepatobiliary investigations	Alanine aminotransferase increased	1	2.33	--	--	4	8.70	--	--
		Aspartate aminotransferase increased	3	6.98	--	--	6	13.04	--	--

			Treatment							
			Placebo				Sirolimus			
			TRT Period (N=43)		OBS Period (N=34)		TRT Period (N=46)		OBS Period (N=41)	
			N	%	N	%	N	%	N	%
Number of Subjects reporting one or more AEs			**43**	**100**	**20**	**59**	**46**	**100**	**22**	**54**
System Organ Class	**High Level Group Term**	**Preferred Term**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
	Physical examination and organ system status topics	Weight decreased	1	2.33	1	2.94	5	10.87	--	--
Metabolism and nutrition disorders	Appetite and general nutritional disorders	Decreased appetite	2	4.65	--	--	3	6.52	--	--
	Lipid metabolism disorders	Hypercholesterolemia	5	11.63	1	2.94	9	19.57	--	--
		Hypertriglyceridemia	2	4.65	--	--	4	8.70	--	--
Musculoskeletal and connective tissue disorders	Joint disorders	Arthralgia	4	9.30	--	--	6	13.04	--	--
	Muscle disorders	Muscle spasms	6	13.95	--	--	3	6.52	--	--
		Myalgia	4	9.30	--	--	9	19.57	--	--
	Musculoskeletal and connective tissue disorders NEC	Back pain	5	11.63	3	8.82	4	8.70	--	--
		Pain in extremity	6	13.95	--	--	3	6.52	--	--
Nervous system disorders	Headaches	Headache	16	37.21	--	--	21	45.65	--	--
	Neurological disorders NEC	Dizziness	7	16.28	3	8.82	10	21.74	--	--
Psychiatric disorders	Depressed mood disorders and disturbances	Depression	4	9.30	--	--	4	8.70	--	--
	Sleep disorders and disturbances	Insomnia	5	11.63	--	--	7	15.22	--	--
Renal and urinary disorders	Urinary tract signs and symptoms	Proteinuria	1	2.33	--	--	4	8.70	--	--
Reproductive system and breast disorders	Menstrual cycle and uterine bleeding disorders	Menorrhagia	2	4.65	--	--	4	8.70	--	--
	Vulvovaginal disorders (excluding infections and inflammations)	Vaginal hemorrhage	--	--	--	--	3	6.52	--	--
Respiratory, thoracic and mediastinal disorders	Bronchial disorders (excluding neoplasms)	Bronchospasm	5	11.63	--	--	3	6.52	--	--

			Treatment							
			Placebo				Sirolimus			
			TRT Period (N=43)		OBS Period (N=34)		TRT Period (N=46)		OBS Period (N=41)	
			N	%	N	%	N	%	N	%
Number of Subjects reporting one or more AEs			43	100	20	59	46	100	22	54
System Organ Class	High Level Group Term	Preferred Term	N	%	N	%	N	%	N	%
	Respiratory disorders NEC	Oropharyngeal pain	3	6.98	--	--	4	8.70	--	--
		Chest pain	1	2.33	1	2.94	3	6.52	--	--
		Cough	16	37.21	1	2.94	17	36.96	2	4.88
		Dyspnea	15	34.88	2	5.88	9	19.57	3	7.32
		Hypoxia	2	4.65	--	--	3	6.52	2	4.88
		Laryngeal pain	4	9.30	--	--	3	6.52	1	2.44
		Productive cough	3	6.98	1	2.94	3	6.52	1	2.44
	Respiratory tract infections	Bronchitis	7	16.28	--	--	7	15.22	2	4.88
		Nasopharyngitis	16	37.21	2	5.88	20	43.48	1	2.44
		Sinusitis	2	4.65	1	2.94	3	6.52	2	4.88
	Upper respiratory tract disorders (excluding infections)	Epistaxis	7	16.28	--	--	7	15.22	--	--
		Rhinitis allergic	3	6.98	--	--	5	10.87	--	--
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Dermatitis exfoliative	6	13.95	1	2.94	5	10.87	1	2.44
		Rash	1	2.33	--	--	3	6.52	2	4.88
	Skin appendage conditions	Acne	5	11.63	--	--	23	50.00	--	--
		Hyperhidrosis	2	4.65	--	--	4	8.70	--	--
	Skin vascular abnormalities	Ecchymosis	4	9.30	--	--	5	10.87	--	--
Vascular disorders	Vascular hypertensive disorders	Hypertension	4	9.30	1	2.94	3	6.52	1	2.44

Abbreviations: N=Number of subjects; NEC=Not Elsewhere Classified; OBS=Observational; TRT=Treatment.
Source: CSR-5702 Appendix 16.8.3 and Clinical Overview Table 3

Serious adverse event / deaths / other significant events

Deaths: There were two deaths, both in the placebo group. Neither of the deaths was considered to be study related. One participant died as a result of a brain haemorrhage. The death was unexpected and determined to be probably not related to the study participation as per the review by the medical review officer. The participant had been off the study drug (placebo) for a period of nine months prior to the fatal event. The second participant died in a house fire. The cause of death was inhalation of combustion products. This death was determined to be definitely not related to study participation by the medical review officer.

Other Serious Adverse Events: Among the 47 SAEs recorded during the study (treatment and observation phase combined), there were 23 SAE reports from 13 subjects in the placebo group and 24 SAE reports from 8 subjects in the sirolimus group. There was no significant difference in the proportion of SAE reports between the two groups (p=0.39). A total of 15 SAEs were not related, while another 8 were possibly related, please see table below for further details.

Table 10 Total Serious Adverse Event Causality, by Reviewer[a]

Causality	Frequency (by Treatment)		
	Placebo	Sirolimus	Total
Definitely not related	3	12	15
Possibly related	5	3	8
Probably not related	11	7	18
Probably related	4	2	6

a. Causality was determined by the Data Management Coordinating Center Medical Review Officer.
Source: CSR-5702 Table 14

Serious adverse cardiac events occurred only in the sirolimus group and included five events: pericarditis/pericardial effusion and pericarditis/pericardial effusion with bradytachyarrhythmia (2 events in 1 subject); tachycardia and fluid overload after embolisation of an angiomyolipoma (2 events in 1 subject); and chest pain. Serious adverse pulmonary or upper respiratory events occurred only during the treatment period and were reported more frequently among subjects receiving placebo than among those receiving sirolimus. There were 13 reports of pulmonary infiltrates from 6 placebo subjects and 2 reports from sirolimus subjects. During the observation year, considerably fewer AEs (both overall and per subject) occurred in both groups, but SAEs occurred more frequently in the placebo group than in the sirolimus group.

Table 11 Serious Adverse Events Reported in the Study

			Treatment							
			Placebo				Sirolimus			
			TRT Period (N=43)		OBS Period (N=34)		TRT Period (N=46)		OBS Period (N=41)	
			N	%	N	%	N	%	N	%
Number of Subjects reporting one or more SAEs			9	21	5	15	8	17	1	2
System Organ Class	High Level Group Term	Preferred Term	N	%	N	%	N	%	N	%
Cardiac disorders	Cardiac arrhythmias	Tachycardia	--	--	--	--	1	2.17	--	--
	Heart failures	Pulmonary edema	--	--	--	--	1	2.17	--	--
	Pericardial disorders	Pericardial effusion	--	--	--	--	1	2.17	--	--
Endocrine disorders	Hypothalamus and pituitary gland disorders	Pituitary cyst	--	--	1	2.94	--	--	--	--
Gastrointestinal disorders	Gastrointestinal signs and symptoms	Abdominal pain	--	--	--	--	3	6.52	--	--
		Dyspepsia	--	--	--	--	1	2.17	--	--
		Nausea	--	--	--	--	1	2.17	--	--
		Vomiting	1	2.33	--	--	--	--	--	--
General disorders and administration site conditions	Fatal outcomes	Accidental death	--	--	1	2.94	--	--	--	--
	General system disorders NEC	Chest discomfort	--	--	--	--	1	2.17	--	--
Hepatobiliary disorders	Gallbladder disorders	Cholecystitis	--	--	1	2.94	--	--	--	--
Infections and infestations	Infections - pathogen unspecified	Bronchitis	1	2.33	--	--	--	--	--	--
		Pneumonia	1	2.33	1	2.94	1	2.17	--	--
		Upper respiratory tract infection	1	2.33	--	--	--	--	--	--
Investigations	Hematology investigations (including blood groups)	Hemoglobin	--	--	--	--	1	2.17	--	--
Metabolism and nutrition disorders	Acid-base disorders	Acidosis	--	--	--	--	1	2.17	--	--
Musculoskeletal and connective tissue disorders	Joint disorders	Arthralgia	1	2.33	--	--	--	--	--	--
	Musculoskeletal and connective tissue disorders NEC	Musculoskeletal pain	--	--	--	--	1	2.17	--	--
Nervous system disorders	Central nervous system vascular disorders	Hemorrhagic stroke	--	--	1	2.94	--	--	--	--
	Neurological disorders NEC	Neuralgia	--	--	--	--	1	2.17	--	--
Respiratory, thoracic and mediastinal disorders	Bronchial disorders (excluding neoplasms)	Bronchospasm	1	2.33	--	--	--	--	--	--

			Treatment							
			Placebo				Sirolimus			
			TRT Period (N=43)		OBS Period (N=34)		TRT Period (N=46)		OBS Period (N=41)	
			N	%	N	%	N	%	N	%
Number of Subjects reporting one or more SAEs			9	21	5	15	8	17	1	2
System Organ Class	High Level Group Term	Preferred Term	N	%	N	%	N	%	N	%
	Pleural disorders	Pneumothorax	4	9.30	--	--	--	--	--	--
	Respiratory disorders NEC	Aspiration	--	--	--	--	1	2.17	--	--
		Dyspnea	2	4.65	--	--	1	2.17	--	--
		Hypoxia	1	2.33	--	--	--	--	--	--
	Respiratory tract infections	Nasopharyngitis	--	--	--	--	1	2.17	--	--
Surgical and medical procedures	Therapeutic procedures and supportive care NEC	Surgery	--	--	--	--	--	--	1	2.44
Vascular disorders	Embolism and thrombosis	Pulmonary embolism	1	2.33	--	--	--	--	--	--
		Thrombosis	--	--	--	--	1	2.17	--	--

Abbreviations: N=Number of subjects; NEC=Not Elsewhere Classified; OBS=Observational; TRT=Treatment.
Source: Clinical Overview Table 4

Serious Cardiac Adverse Events: Review of the CTCAEv3-coded serious cardiac AEs showed that these events occurred only in the sirolimus group. Three cases describing 5 events which included pericarditis/ pericardial effusion and pericarditis/pericardial effusion with brady-tachyarrhythmia (2 events in 1 subject); tachycardia and fluid overload after embolization of an angiomyolipoma (2 events in 1 subject); and chest pain. One case described 2 events of pericardial effusion (within 8 days of each other) which were attributed to viral pericarditis in a subject with an elevated viral Coxsackie titer. The events resolved with treatment. The second cardiac case described the events of tachycardia and fluid overload, which occurred in the setting of an elective embolization of the subject's preexisting angiomyolipoma. These events were deemed "definitely not related" to therapy by both investigator and the medical monitor. The events also resolved with treatment. The remaining case described chest pain which was considered to be non-ischemic in nature, and related to a pre-existing hypertrophic cardiomyopathy. The outcome was not reported.

Serious Pulmonary Adverse Events: Review of the CTCAEv3-coded serious adverse pulmonary or upper respiratory events showed that these events occurred only during the treatment period and were reported more frequently among subjects receiving placebo than among those receiving sirolimus. There were 13 reports of pulmonary infiltrates from 6 placebo treated subjects and 2 reports from sirolimus treated subjects. During the observation year, considerably fewer AEs (both overall and per subject) occurred in both groups, and SAEs occurred more frequently in the placebo group than in the sirolimus group.

Laboratory findings

Laboratory values including haemoglobin and cholesterol were evaluated for subjects who were assessed for the primary outcome (FEV1). There was no significant difference in haemoglobin between the placebo group and sirolimus group. There were no significant differences in baseline total cholesterol, triglycerides, low density lipoprotein (LDL), or high density lipoprotein (HDL) between the placebo and sirolimus groups. During the treatment period, total cholesterol and triglycerides were increased in the sirolimus group (p=0.025 and 0.006, respectively), but not in the placebo group. At 12 months, median total cholesterol, triglycerides, and LDL levels were higher in the sirolimus group as compared to the placebo group (p=0.028, 0.002 and 0.037, respectively). There were no significant

differences in other labs analysed (HDL, white blood cell [WBC] count, platelet count and urinary albumin/creatinine ratio.

Discontinuation due to adverse events

Of the eighty nine subjects enrolled, 12 subjects, including 7 subjects in the placebo group and 5 subjects in the sirolimus group, were discontinued from the study due to AEs (see table below). AEs leading to permanent discontinuation included pneumothorax (2 subjects in the placebo group, and 1 in the sirolimus group), infection/intercurrent illness (3 subjects in the placebo group, and 2 in the sirolimus group), dermatological (1 subject in the sirolimus group), gastrointestinal (1 subject in the sirolimus group), and death (2 in the placebo group: 1 due to brain haemorrhage, and 1 in a house fire).

Table 12 Adverse Events Leading to Permanent Discontinuation From Study, by Treatment Group

Number of Participants	Reason by PI	Sirolimus	Placebo
3	Pneumothorax	1	2
5	Infection/Intercurrent Illness	2	3
1	Gastrointestinal	1	0
2	Death	0	2
1	Dermatologic	1	0
12	Total	5	7

Abbreviations: PI=Principal Investigator.
Source: CSR-5702 Table 9

Post marketing experience

A cumulative search of the safety database through 14 September 2016 was conducted for sirolimus cases that reported either an indication of the use of sirolimus for patients with LAM, a medical history of LAM or where LAM was utilised as string text in the case narrative. MILES trial cases were excluded, as these cases are discussed in this application. This cumulative search identified 150 cases reporting 342 events. Of these cases, there were 26 cases from non-MAH interventional trials reporting 37 events, and 124 cases from nonclinical sources reporting 305 events. Please see Table 13 for a breakdown of the number of cases and events reported by year.

Table 13 Number of Case and Events of LAM Reported by Year

Year	Number of Cases (Number of Events)	
	Clinical Trials	Post-Marketing
2006	3 (5)	-
2007	2 (4)	1 (1)
2008	1 (2)	9 (17)
2009	-	3 (9)
2010	-	-
2011	-	4 (5)
2012	2 (3)	7 (26)
2013	13 (18)	8 (27)
2014	5 (5)	3 (4)
2015	-	63 (143)
2016	-	26 (73)

Abbreviation: LAM=Lymphangioleiomyomatosis

Clinical Trial Data: There were 26 cases reporting 37 events from non-MAH sponsored interventional clinical trials. Selected characteristics of the sirolimus non-MAH sponsored interventional clinical cases reported through 14 September 2016 are presented in table below.

Table 14Selected Characteristics of Sirolimus Non MAH Sponsored Clinical Cases

Characteristic		(N=26) Number (%)
Sex	Female	22 (84.6%)
	Unknown	4 (15.4%)
Age (years) Min = 36 , Max = 62 Mean = 45.8 Median = 45.5 N = 22	31-50 years	18 (69.2%)
	51-64 years	4 (15.4%)
	Unknown	4 (15.4%)
Case Outcome	Fatal	1 (3.2%)
	Recovered/Resolved	23 (88.5%)
	Recovering/Resolving	1 (3.8%)
	Unknown	1 (3.8%)
Country Where Event Occurred Top 10 Case Count	Japan	20 (77.0%)
	United Kingdom	4 (15.4%)
	United States	2 (7.7%)
Source	Clinical Study	26 (100%)
Medical History	Present	22 (84.6%)
Most Commonly Reported Medical Histories (PT) (≥ 3%)	LAM	17 (65.4%)
	Angiomyolipoma	5 (19.2%)
	Hyperlipidaemia	5 (19.2%)
	Uterine leiomyoma	5 (19.2%)
	Hypertension	4 (15.4%)
	Constipation	4 (15.4%)
	Anxiety disorder	2 (7.7%)
Concomitant medications	Present	22 (84.6%)
	Unknown	4 (15.4%)

Characteristic		(N=26) Number (%)
Co-Suspect	Present	1 (3.8%) (Atorvastatin)
	None	25 (96.2%)
Most Commonly Reported Concomitant medications (≥ 4)	Atorvastatin, herbal extract/preparation NOS (6 each), tiotropium bromide, loxoprofen sodium, carbocisteine, (5 each), ambroxol, diclofenac (4 each)	

Abbreviations: MAH=Marketing Authorisation Holder; N=Number of subjects; US=United States; UK=United Kingdom; LAM=Lymphangioleiomyomatosis; PT=Preferred Term; NOS=Not otherwise specified.

The mean age was 45.8 years (n=22) and the most common age group was 31-50 years. The country of origin for the majority of cases was Japan. For cases that reported outcomes, the case outcome was reported as resolved/resolving in 92.3%. There was 1 case that reported a fatal outcome: it involved a female patient (unknown age) with a history of end stage lung disease due to LAM who had been turned down for a lung transplant by two lung transplant centres. The patient had recurrent chest infections and each infection caused a further acute deterioration in lung function. The patient died from an acute exacerbation of chronic respiratory failure and a chest infection. According to the patient's physician, there was no clinical or radiological evidence of sirolimus induced pneumonitis. Although starting sirolimus did not result in any objective improvement in lung function tests the subject reported a “subjective benefit”. No other information was provided.

Non clinical study sources: There were 124 cases reporting 305 events from post-marketing sources. The mean age was 43.0 years (n=68) and the most common age group was 31-50 years. The country of origin for the majority of cases was Japan. For cases that reported outcomes, the case outcome was reported as resolved/resolving in 25.8% and not resolved in 13.7 %. There were 2 events (1.6 %) that resulted in a fatal outcome. The first case described a 45-year-old female patient with a history of LAM developed a right pneumothorax with a rapid deterioration of respiratory function requiring lung transplantation. After the transplantation, the patient experienced bilateral chylothorax. Rapamycin was initiated (2 months post-transplant). Infective pyrexia appeared within 3 months from a Pseudomonas aeruginosa urinary tract infection. Thereafter, a MRSA pleural effusion was noted. Treatment was rendered and pyrexia subsided. However, pyrexia accompanied by neutropenia

recurred within a month. Pseudomonas aeruginosa was detected again from the “airway secretions”. Candida parapsilosis was detected from the pleural effusion and on a blood culture. Despite various therapies, the patient succumbed to Candida pleurisy within 7 months of the transplant.

The second fatal case reported a 61-year-old female patient with a history of LAM, lymphoedema, renal surgery, uterine cancer, and uterine leiomyoma developed pneumonia. Rapalimus was discontinued and the patient recovered. The patient succumbed to respiratory failure 4 months later. The reporting physician assessed the death from respiratory failure as related to the primary disease of LAM.

2.5.1. Discussion on clinical safety

In the MILES trial, sirolimus was associated with a greater number of AEs as compared with placebo, although the rates of SAEs were similar in the two study groups. According to the MAH, the most common AEs during the treatment period for subjects receiving sirolimus were stomatitis, diarrhoea, acne, headache, nasopharyngitis, upper respiratory tract infection, cough, and nausea, which are consistent with the known safety profile of sirolimus. The MAH noted that weight decrease was reported with a greater incidence with sirolimus when compared to placebo during the treatment period, and therefore proposed to add this as an adverse drug reaction in the sirolimus SmPC section 4.8. The MAH argue that weight decrease should only be included for the LAM population. The clinical trials and publications on this matter in renal transplant patients’ point towards less weight gain for sirolimus treated patients but not weight loss per se. This may be explained by the concomitant medication in the transplant setting such as corticosteroids but does not preclude that the reason for less weight gain in transplant patients is mediated by the same mechanism as weight loss in LAM patients. Therefore the influence on weight might be less pronounced. The MAH included a description of safety in LAM patients in the SmPC. The adverse drug reactions observed in this study were consistent with the known safety profile of the product for the indication prophylaxis of organ rejection in renal transplantation with the addition of weight decreased, which was reported in the study at a greater incidence with Rapamune when compared to that observed with placebo (very common, 10.9% vs. common, 2.3%). These changes were considered acceptable to the CHMP.

Overall, the safety pool of sirolimus in LAM consists of 46 patients, which is rather limited and that and the characteristics of proposed indication LAM differs from the authorized indication renal transplant it has been discussed whether some kind of registry study would be feasible to collect long term safety data in this population. As discussed in sections 2.6 and 3.4, the applicant has provided a feasibility report in cooperation with existing registries and a protocol submission is expected by October 2018. In case it is deemed that the study is not feasible after protocol review, the need for an alternative proposal for collecting long term safety in this population will be re-discussed.

2.5.2. Conclusions on clinical safety

In general, the safety profile seems to be consistent with the known safety profile of sirolimus. The applicant sufficiently described the implications of the known safety profile in the claimed indication although that it is recognised that due to the small population of subjects investigated in the MILES trial, the assessment with relation to the totality of safety data has its limitations. Therefore the applicant will explore how to best monitor long term safety in post-authorisation phase either via existing registries or any other alternative ways. The proposed changes in the SmPC are acceptable.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set

out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance activities
Malignancy	Routine risk minimisation measures: 4.4 Special warnings and precautions for use 4.8 Undesirable effects Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
Long term safety in patients with sporadic LAM	Routine risk minimisation measures: 4.2 Posology and method of administration 4.8 Undesirable effects Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: A population-based cohort study to monitor the safety and effectiveness of sirolimus use among patients with sporadic lymphangioleiomyomatosis (LAM). Protocol to be submitted by October 2018.

LAM - lymphangioleiomyomatosis

The PRAC and the CHMP considered that the risk management plan version 6.4 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition the MAH took the opportunity to make very minor formatting changes in the Labelling.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Lymphangioleiomyomatosis is a rare, progressive, frequently fatal cystic lung disease that predominantly affects young women of childbearing age. The clinical course of LAM is typically marked by the inexorable progressive loss of lung function, with resulting exercise intolerance and disability. Although recent studies suggest that there is variability in the rate of progression, LAM typically results in death or lung transplantation within 10 to 15 years. In 2014, the LAM Foundation has estimated that 3-8 per million women are affected with non-heritable LAM or sporadic LAM (S-LAM) (15,000-23,000 globally), and that approximately 30-40% of women with tuberous sclerosis complex have cystic pulmonary changes consistent with LAM.

3.1.2. Available therapies and unmet medical need

There is no approved medicinal product for the treatment of LAM.

3.1.3. Main clinical studies

The MILES Study (Study 5702) was a phase III treatment, randomized, double-blind, placebo-controlled, safety/efficacy study to assess sirolimus treatment in subjects (n=89) with LAM disease, of these 81 had spontaneous, S-LAM disease.

3.2. Favourable effects

The MILES trial showed a statistical significance for the primary endpoint with a preserved pulmonary function with treatment with sirolimus for 1 year and determined by the change in FEV1. It was shown that the FEV1slope (±SE) from baseline to 12 months was 1±2 mL per month in the sirolimus group, which was not significantly different from zero. This was not the case in the placebo group were the FEV1slope (±SE) was −12±2 mL per month and the slope was significantly less than zero ($p<0.0001$), a finding that was consistent with declining lung function. The mean change from baseline in FEV1 after 12 months treatment was 19±124 in the sirolimus group and -134±182 in the placebo group ($p<0.0001$). The baseline-adjusted difference in the mean change in FEV1 (sirolimus versus placebo) during the treatment periods was 151 mL ($p<0.0001$ for the between-group difference in LAM). A total of 46% of the subjects in the sirolimus group, as compared with 12% of the subjects in the placebo group, had FEV1 values at or above baseline values at the 12 month visit ($p=0.0004$).

Furthermore, a significant effect was seen on some important secondary endpoint such as FVC and VAS-QOL score.

Although the applicant provided additional scientific arguments for the validity of the chosen endpoints for the proposed indication, the wording of the indication was proposed by the applicant to be narrowed in order to precisely reflect the population in the MILES trial and to avoid a potential overlap in the treated population between Rapamune and the orphan medicinal product Votubia (see section 2.4).

> *Rapamune is indicated for the treatment of patients with sporadic lymphangioleiomyomatosis with moderate lung disease or declining lung function (see sections 4.2 and 5.1).*

3.3. Uncertainties and limitations about favourable effects

For the quality of life parameters the results was significant in two of the investigated 4 different scores. There were significant differences in the change from baseline to 12 months in the score on the EuroQOL VAS for QOL and in the total score on the FPI. The changes in individual measures of SF-36 and SGRQ did not differ significantly between the two groups. No effects were observed on the diffusing capacity of the lung for carbon monoxide or on exercise tolerance and the positive effects on airflow vanished after sirolimus was discontinued. However, one explanation for this might be that sirolimus in LAM seems to stabilise pulmonary function and thereby decrease the progression of the disease. Therefore, patients may not notice any quality of life change in this relatively short duration of treatment and no advantage towards the placebo population can be seen. The inclusion criteria did not differentiate between S-LAM and LAM secondary to TCS.

3.4. Unfavourable effects

The most important common AEs with sirolimus are infections including opportunistic infections and reactivation of viral diseases. In addition to this, cases of interstitial lung disease (including pneumonitis and infrequently bronchiolitis obliterans organising pneumonia (BOOP) and pulmonary fibrosis), some fatal, with no identified infectious aetiology have occurred in patients receiving immunosuppressive regimens including sirolimus. In the MILES trial weight decrease was seen in the LAM population in the active treatment group. This observation was reflected in the SmPC.

While the risks with sirolimus treatment are well known in the renal transplant patients, the long-term risk in the LAM population is not fully known. Thus, for evaluation of long term safety a registry was initially proposed but the applicant was of the opinion that this was not required because the overall safety profile of sirolimus is well-known since it has been approved for use in the post-transplant setting since 2001. Whilst this acknowledged, the applicant will elaborate on the possibilities of collaboration with the available clinical registries that is ongoing in the UK (English registry for lymphangioleiomyomatosis) and the US (NHLBI lymphangioleiomyomatosis registry). The MAH has contacted these registries and performed a feasibility assessment which is accepted with some remarks. In conclusion, the proposed plan to receive long-term data in this indication is considered acceptable pending further details to be provided in the draft protocol in the post-authorisation phase.

3.5. Uncertainties and limitations about unfavourable effects

Since this is a small trial in a rare disease some unfavourable effects in the safety profile in this population may not have been detected. Furthermore, long-term safety will be evaluation post-authorisation as the current data set is limited.

3.6. Effects Table

Table 15 Effects Table for Rapamune in the LAM indication.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Pulmonary function Primary endpoint	FEV1slope	ml/month	Sirolimus 1±2	Placebo −12±2	p<0.0001 Effect disappears after stopping treatment	Figure 1 P 23
Pulmonary function Primary endpoint	mean change (±SD) in FEV1 during treatment period	ml	Sirolimus 19 (±124)	Placebo -134 (±182)	Mean change in FEV1 (sirolimus versus placebo) during the treatment periods 151 mL (p<0.0001 for the between - group difference).	Figure 1 P 23
Pulmonary function Secondary endpoint	Change in FEV1 from baseline to 12 months	%	Sirolimus 46% of the subjects in the sirolimus group, had FEV1 values at or above baseline values at the 12 month visit	placebo 12% of the subjects in the placebo group, had FEV1 values at or above baseline values at the 12 month visit	p=0.0004.	Figure 1 P 23
Pulmonary function Secondary endpoint	FVC slope	ml/month	Sirolimus 8±3	Placebo −11±3	p=0.001	Table 2 P25
	mean change (±SD) in FVC	ml	Sirolimus 97 (±260)	Placebo -129 (±233)	p=0.0005	Table 2 P25
Unfavourable Effects						
Weight decreased	Physical signs		Sirolimus' n=46 5 (10.87%)	Placebo n=34 1 (2.33%)		Table 3 p31
Serious adverse cardiac events	pericarditis/pericardial effusion bradytachyarrhythmia tachycardia fluid overload, chest pain		Sirolimus 3 (2.17%)	Placebo 0		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The stabilisation of lung function in this severely ill patient population is considered important. The primary endpoint and most of the secondary endpoints showed a beneficial effect although some of the secondary endpoints such as CO diffusion and exercise tolerance did not reach significant level.

The scientific base for the clinical relevance of using FEV1 as a primary endpoint was supported by the applicant by an in-depth description of published data both on the endpoint and on clinical relevance of the results with sirolimus treatment. In addition to this, a discussion on the results of long term treatment from different published references with treatment up to 3.5 years was provided. The CHMP concluded that the applicant adequately justified the use of FEV1 as the primary endpoint and described literature data on long term results and the clinical relevance of the results. However, based on the patient population in the trial, the indication was subsequently limited to S-LAM diagnosis only.

3.7.2. Balance of benefits and risks

The benefit-risk balance for Rapamune used in the restricted sporadic LAM indication is considered positive by the CHMP.

3.8. Conclusions

The overall B/R of Rapamune in the treatment of patients with sporadic lymphangioleiomyomatosis with moderate lung disease or declining lung function is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include the treatment of patients with sporadic lymphangioleiomyomatosis with moderate lung disease or declining lung function. As a consequence section 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 6.4) are updated in accordance. In addition the MAH took the opportunity to make very minor formatting changes in the Labelling.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Rapamune is not similar to Votubia within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*Steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include the treatment of patients with sporadic lymphangioleiomyomatosis

with moderate lung disease or declining lung function. As a consequence section 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 6.4) are updated in accordance. In addition the MAH took the opportunity to make very minor formatting changes in the Labelling.

Summary

Please refer to Scientific Discussion: Rapamune-H-C-273-II-0164