B. Full Novartis CTRD Template

Sponsor

Novartis

Generic Drug Name

Everolimus

Therapeutic Area of Trial

Lymphangioleiomyomatosis (LAM)

Approved Indications

United States

Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer (Advanced HR+ BC)

Advanced Neuroendocrine Tumors of Pancreatic Origin (PNET)

Advanced Renal Cell Carcinoma (RCC)

Renal Angiomyolipoma with Tuberous Sclerosis Complex (TSC)

Subependymal Giant Cell Astrocytoma (SEGA) with Tuberous Sclerosis Complex (TSC)

Protocol Number

CRAD001X2201

Title

An exploratory, open-label, non-randomized, within-patient multiple dose-escalation safety, tolerability, PK (pharmacokinetics) and efficacy trial of RAD001 (everolimus) in patients with lymphangioleiomyomatosis.

Study Phase

IIa

Study Start/End Dates

24 Jan 2010 to 16 Jun 2012

Study Design/Methodology

This was an open-label, non-randomized, within-subject dose escalation safety, tolerability, PK and efficacy study in 24 women with sporadic or TSC-associated LAM. The study consisted of a 28 day screening period, a baseline visit, a treatment period of at least 26 weeks (followed by an optional extension period wherein patients continued therapy until the last patient had completed 26 weeks of treatment) and a study completion visit performed 4-8 weeks after the last dose. All patients received a starting dose of 2.5mg/day for 4 weeks, followed by a dose of 5 mg/day for 4 weeks and finally a dose of 10mg/day for 18 weeks. Dose titration was based on tolerability. There was no was wash-out period between the different doses.

Centers

4 centers in 3 countries: United States (2), Italy (1), France (1)

Publication

NA

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

Oral tablets of everolimus 2.5mg, 5 mg and 10 mg once daily at the same time each day

Statistical Methods

All patients who received study drug were included in the safety analysis set. All patients with no major protocol deviations with impact on PK (pharmacokinetics) or PD (pharmacodynamics) were included in the respective PK and PD analysis sets.

Two-sided 95% confidence intervals for the means were provided for VEGF-D concentrations. Differences from baseline were tested for statistical significance at the two-sided 5% alpha level. VEGF-D concentrations were log transformed for analysis and results of statistical analysis back transformed to the original scale for presentation.

Change from baseline in FVC and FEV1 were compared between everolimus and historical placebo data from the MILES study (McCormack et al., 2011) due to the absence of a placebo group in the current study. These two studies had different study designs, so the change from baseline to 6 months (26 weeks) in MILES study was estimated from the publicly reported rate of change per month in order to provide a meaningful comparison.

Everolimus predose and 2-hour post-dose blood concentrations were summarized by visit and dose-level with descriptive statistics including two-sided 95% confidence intervals for the means. Everolimus concentrations were log transformed prior to the analysis and results of statistical analysis were back-transformed to the original scale for presentation.

The number and percentage of patients with adverse events was tabulated by body system and preferred term. A patient with multiple adverse events within a body system was only counted once towards the total of this body system.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Female aged >/= 18 years with a diagnosis of LAM
- Pulmonary function abnormalities as follows:
    - FEV1 of ≤ 80% of the predicted value following administration of a standard dose of a short acting β2-agonist (*200 µg Salbutamol, measured between 10 and 15 minutes of inhalation) OR
    - FEV1 < 90% of the predicted value of bronchodilator following administration of a standard dose of a short acting β2-agonist (*200 µg Salbutamol, measured between 10 and 15 minutes of inhalation) and DLco (uncorrected) <80% predicted.
- Female patients including those of childbearing potential will be included in this study.
- Negative pregnancy test at screening and baseline

Exclusion criteria

- FEV1<50% of predicted post-bronchodilator.
- Change in FVC (ml) > ± 15% of screening value at baseline visit (not less than 14d after screening visit).
- Use of any medicine containing estrogen in the 4 months prior to the screening visit and for the duration of the study
- Significant hematologic, renal, hepatic laboratory abnormality or amylase > 1.5x the upper limit of the normal range at the screening or baseline visits

- Fasting blood glucose > 126mg/dl or random blood glucose >200mg/dl at screening and/or baseline
- Recent surgery (involving entry into a body cavity or requiring sutures) within 2 months of the screening visit or any evidence of unhealed surgical wound.
- Uncontrolled hyperlipidemia (defined as persistent elevation of total cholesterol or triglycerides >6.5nM/L) or a history of clinical atherosclerotic disease including heart attack, angina, peripheral vascular disease or stroke.
- Previous organ transplantation
- Inability to give informed consent
- Inability to perform pulmonary function or 6 minute walk tests and imaging assessments

Participant Flow

	RAD001 N=24 n (%)
Exposed	24 (100)
Completed	17 (71)
Discontinued	7 (29)
Main reason for discontinuation	
Adverse event	6 (25)
Subject withdrew consent	1 (4)

Baseline Characteristics

Demographic summary by treatment sequence

		RAD001 N=24	MILES placebo group N=43
Age (years)	Mean (SD)	44 (13.4)	46 (10.3)
	Range	18 – 69	25 – 65
Gender – n (%)	Female	24 (100%)	43 (100%)
Weight (kg)	Mean(SD)	66.3 (14.85)	
	Range	47.0 – 107.4	
Height (cm)	Mean(SD)	163 (7.2)	
	Range	144 -173	
Predominant Race	Caucasian	22 (92%)	30 (70%)
n (%)	Black	1 (4%)	0
	Asian	0	12 (28%)
	Other	1 (4%)	1 (2%)
BMI (kg/m^2)	Mean (SD)	25.1 (6.50)	
	Range	16.3 – 41.5	

BMI = body mass index

Summary of baseline pulmonary function tests

		Everolimus N=24	MILES placebo group N=43
FVC (L)*	Mean (SD)	2.92 (0.751)	2.91 (0.749)
	Range	1.27 – 4.01	

		Everolimus N=24	MILES placebo group N=43
FEV_1 (L)*	Mean(SD)	1.67 (0.569)	1.38 (0.446)
	Range	0.71 – 2.64	
Predicted FEV_1 (%)*	Mean(SD)	60.4 (14.59)	47.7 (14.37)
	Range	40.4 - 87.1	
TLC (L)	Mean(SD)	5.16 (0.864)	5.27 (1.463)
	Range	3.68, 6.83	
TGV (L) / FRC (L)**	Mean(SD)	3.62 (1.029)	3.18 (1.059)
	Range	1.33, 5.49	
RV (L)	Mean (SD)	2.33 (0.776)	2.41 (1.029)
	Range	1.11, 4.40	
Actual DL_{CO} (ml/min/mmHg)	Mean (SD)	10.28 (3.479)	10.42 (4.82)
	Range	4.46, 18.70	
Predicted DL_{CO} (%)	Mean (SD)	39.6 (13.75)	43.8 (20.56)
	Range	17.0, 71.0	
VEGF-D (pg/mL)	Mean (SD)	2870 (2567.5)	2223 (2997)
	Range	362, 8510	

* post-bronchodilator results for everolimus, **TGV measured in current study TGV or FRC in MILES study

Outcome Measures

Primary Outcome Result(s)

Change from baseline in VEGF-D concentrations

			VEGF-D (pg/mL)
			RAD001
Dose Level	Visit	Statistics	(Everolimus)
2.5 mg	Week 4	n	21
		Mean (SD)	-464.3 (745.23)
		95% CI	(-803.51, -125.06)
		CV (%)	-160.5
		25th percentile	-670.0
		Median	-296.0
		75th percentile	-35.0
		Minimum, Maximum	-2360, 740
5 mg	Week 4	n	3
		Mean (SD)	-807.0 (1103.99)
		95% CI	(-3549.46, 1935.46)
		CV (%)	-136.8
		25th percentile	-2020.0
		Median	-540.0
		75th percentile	139.0
		Minimum, Maximum	-2020, 139
	Week 8	n	22
		Mean (SD)	-1113.2 (1468.98)

Dose Level	Visit	Statistics	VEGF-D (pg/mL) RAD001 (Everolimus)
		95% CI	(-1764.49, -461.87)
		CV (%)	-132.0
		25th percentile	-1610.0
		Median	-672.0
		75th percentile	-336.0
		Minimum, Maximum	-6220, 785
10 mg	Week 14	n	22
		Mean (SD)	-1563.4 (1920.37)
		95% CI	(-2414.81, -711.92)
		CV (%)	-122.8
		25th percentile	-2050.0
		Median	-800.0
		75th percentile	-398.0
		Minimum, Maximum	-6750, 490
10 mg	Week 26	n	22
		Mean (SD)	-1771.7 (2091.60)
		95% CI	(-2699.04, -844.32)
		CV (%)	-118.1
		25th percentile	-2280.0
		Median	-937.0
		75th percentile	-400.0
		Minimum, Maximum	-7310, -25

Everolimus trough and peak concentrations by dose level

Dose level	Statistic	C0,ss (ng/ml)	C2,ss (ng/ml)
2.5 mg/day	N	13	13
	Mean (SD)	3.1 (1.33)	12.1 (3.56)
5 mg/day	N	14	16
	Mean (SD)	5.8 (3.02)	22.6 (7.22)
10 mg/day	N	11	10
	Mean (SD)	11.0 (3.45)	45.7 (12.52)

Note: Summarized over all visits with each patient only included once at a given dose level.
Values are mean (SD)

Secondary Outcome Result(s)

Summary of change from baseline in FVC (mL) by week

	RAD001		MILES placebo**	Difference: RAD001 minus MILES**		
Week	N*	Mean (95% CI)	Mean (95% CI)	Mean (95^{th} %ile range)	P(Diff >0)	P (Diff>100)
4	24	13 (-71, 97)	-11 (-109, 87)	23 (-96, 147)	62%	15%
8	22	8 (-96, 112)	-22 (-128, 84)	30 (-94, 152)	65%	18%
14	23	31 (-58, 121)	-33 (-139, 73)	63 (-58, 184)	81%	31%
26	23	10 (-111, 132)	-66 (-181, 49)	76 (-45, 196)	85%	38%
38	14	100 (-73, 273)				

	RAD001	MILES placebo**	Difference: RAD001 minus MILES**		
Week	N*	Mean (95% CI)	Mean (95% CI)	Mean (95^{th} %ile range)	P(Diff >0)	P (Diff>100)
50	11	148 (-45, 341)				
62	4	50 (-227, 327)				
EOS	16	84 (-122, 290)				

* N = the number of patients in RAD001 group at each visit; for placebo group, the prior sample size was always assumed as 18 based on historical data from MILES study.

** Derived from posterior distribution assuming an FVC decline of 11mL/month in MILES placebo group with SD=233 mL; %ile = percentile; P(x) Probability of x; EOS = End of study

Summary of change from baseline in FEV1 (mL) by week

	Everolimus	MILES placebo**	Difference: Everolimus minus MILES*		
Week	N*	Mean (95% CI)	Mean (95% CI)	Mean (95^{th} %ile range)	P(Diff >0)	P (Diff>100)
4	24	16 (-52, 84)	-12 (-88, 64)	27 (-65, 122)	68%	10%
8	22	22 (-60, 104)	-24 (-106, 58)	46 (-50, 140)	78%	18%
14	23	41 (-49, 131)	-36 (-118, 46)	76 (-19, 173)	90%	34%
26	23	114 (11, 217)	-72 (-162, 18)	186 (93, 279)	100%	93%
38	14	124 (-23, 272)				
50	11	150 (-24, 324)				
62	4	-3 (-254, 249)				
EOS	16	56 (-59, 170)				

* N = the number of patients in everolimus group at each visit; for placebo group, the prior sample size is always assumed as 18 based on historical data from MILES study.

** Derived from posterior distribution assuming an FVC decline of 12mL/month in MILES placebo group with SD=182 mL; %ile = percentile; P(x) Probability of x; EOS = End of study

Summary of DLco, TLC, TGV and RV

Visit	Time point	Statistics	DLco (ml/min/mmHg)	TLC (L)	TGV (L)	RV (L)
BAS		n	22	22	22	22
		Mean	10.340	5.038	3.513	2.310
		SD	3.5550	0.7943	0.9863	0.8027
		Minimum	4.46	3.68	1.33	1.11
		Median	9.855	4.975	3.735	2.085
		Maximum	18.70	6.65	5.26	4.40
		95% CI	(8.764,11.917)	(4.686, 5.390)	(3.075, 3.950)	(1.954, 2.666)
W26	Pre-dose	n	22	22	22	22
		Mean	9.559	5.237	3.780	2.479
		SD	3.1764	1.2930	1.3763	1.4138
		Minimum	5.65	3.55	2.28	0.97

Median	8.915	5.120	3.425	2.150
Maximum	18.00	9.09	8.61	7.76
95% CI	(8.150,10.967)	(4.664, 5.811)	(3.170, 4.390)	(1.852, 3.105)

Note: 1. Baseline is defined as the last non-missing measurement prior to the first dose.

2. 95% CI is the 95% confidence intervals for the mean.

Safety Results

Incidence of AEs by primary system organ class (SOC), preferred term and dose for events experienced by at least two patients

	Everolimus			
Primary system organ class **Preferred term**	**2.5 mg** **N=24** **n (%)**	**5 mg** **N=24** **n (%)**	**10 mg** **N=24** **n (%)**	**All doses** **N=24** **n (%)**
Patients with at least one AE	21 (88)	20 (83)	24 (100)	24 (100)
Gastrointestinal disorders	**12 (50)**	**11 (46)**	**20 (83)**	**22 (92)**
Mouth ulceration	5 (21)	5 (21)	5 (21)	11 (46)
Diarrhoea	3 (13)	1 (4)	3 (13)	7 (29)
Nausea	2 (8)	1 (4)	5 (21)	7 (29)
Stomatitis	1 (4)	3 (13)	6 (25)	7 (29)
Aphthous stomatitis	2 (8)	2 (8)	3 (13)	5 (21)

	Everolimus			
Primary system organ class Preferred term	2.5 mg N=24 n (%)	5 mg N=24 n (%)	10 mg N=24 n (%)	All doses N=24 n (%)
Vomiting	1 (4)	1 (4)	2 (8)	4 (17)
Haemorrhoids	1 (4)	0	2(8)	3 (13)
Abdominal pain upper	0	1 (4)	1 (4)	2 (8)
Constipation	1 (4)	0	1 (4)	2 (8)
Respiratory, thoracic and mediastinal disorders	**3 (13)**	**4 (17)**	**13 (54)**	**18 (75)**
Cough	0	3 (13)	4 (17)	7 (29)
Oropharyngeal pain	1 (4)	1 (4)	5 (20)	7 (29)
Nasal congestion	1 (4)	0	3 (13)	4 (17)
Dyspnoea	1 (4)	0	2 (8)	3 (13)
Upper airway cough syndrome	0	0	2 (8)	2 (8)
General disorders & administration site conditions	**5 (21)**	**4 (17)**	**15 (63)**	**17 (71)**
Oedema peripheral	1 (4)	0	7 (29)	8 (33)
Fatigue	2 (8)	2 (8)	7 (29)	7 (29)
Non-cardiac chest pain	2 (8)	1 (4)	4 (17)	6 (25)
Pyrexia	0	1 (4)	3 (13)	3 (13)
Skin & subcutaneous tissue disorders	**1 (4)**	**5 (21)**	**11 (46)**	**17 (71)**
Acne	0	2 (8)	3 (13)	5 (21)
Pruritus	1 (4)	0	2 (8)	3 (13)
Rash	0	2 (8)	1 (4)	3 (13)
Dry skin	0	1 (4)	1 (4)	2 (8)
Infections and infestations	**4 (17)**	**3 (13)**	**15 (63)**	**15 (63)**
Nasopharyngitis	0	1 (4)	3 (13)	4 (17)

	Everolimus			
Primary system organ class **Preferred term**	**2.5 mg** **N=24** **n (%)**	**5 mg** **N=24** **n (%)**	**10 mg** **N=24** **n (%)**	**All doses** **N=24** **n (%)**
Upper respiratory tract infection	0	0	3 (13)	3 (13)
Bronchitis	0	0	2 (8)	2 (8)
Ear infection	0	0	2 (8)	2 (8)
Furuncle	0	1 (4)	2 (8)	2 (8)
Influenza	0	0	2 (8)	2 (8)
Oral herpes	0	2 (8)	1 (4)	2 (8)
Urinary tract infection	2 (8)	0	2 (8)	2 (8)
Vulvovaginal mycotic infection	0	0	2 (8)	2 (8)
Nervous system disorders	**6 (25)**	**4 (17)**	**6 (25)**	**12 (50)**
Headache	4 (17)	3 (13)	4 (17)	9 (38)
Muscoloskeletal & connective tissue disorders	**4 (17)**	**3 (13)**	**7 (29)**	**10 (42)**
Arthralgia	0	2 (4)	2 (4)	4 (17)
Muscle spasms	2 (8)	0	2 (8)	3 (13)
Back pain	0	0	2 (8)	2 (8)
Flank pain	1 (4)	0	1 (4)	2 (8)
Myalgia	0	1 (4)	1 (4)	2 (8)
Reproductive system & breast disorders	**2 (8)**	**3 (13)**	**7 (29)**	**10 (42)**
Dysmenorrhoea	2 (8)	0	0	2 (8)
Menorrhagia	0	0	2 (8)	2 (8)
Menometorrhagia	0	0	2 (8)	2 (8)
Pelvic pain	1 (4)	1 (4)	0	2 (8)
Investigations	**1 (4)**	**4 (17)**	**6 (25)**	**8 (33)**

Primary system organ class Preferred term	Everolimus 2.5 mg N=24 n (%)	 5 mg N=24 n (%)	 10 mg N=24 n (%)	 All doses N=24 n (%)
GGT increased	0	2 (8)	1 (4)	2 (8)
Metabolism & nutrition disorders	**1 (4)**	**2 (8)**	**6 (25)**	**7 (29)**
Decreased appetite	1 (4)	1 (4)	1 (4)	3 (13)
Hypercholesterolaemia	0	1 (4)	1 (4)	2 (8)
Hypokalaemia	0	0	2 (8)	2 (8)
Injury, poisoning & procedural complications	**1 (4)**	**1 (4)**	**3 (13)**	**5 (21)**
Post traumatic pain	1 (4)	0	1 (4)	2 (8)
Immune system disorders*	**0**	**1 (4)**	**3 (13)**	**4 (17)**
Psychiatric disorders	**1 (4)**	**0**	**3 (13)**	**4 (17)**
Insomnia	1 (4)	0	2 (8)	3 (13)
Blood & lymphatic system disorders*	**0**	**0**	**3 (13)**	**3 (13)**
Vascular disorders	**0**	**0**	**3 (13)**	**3 (13)**
Hypertension	0	0	2 (8)	2 (8)
Cardiac disorders*	**0**	**1 (4)**	**1 (4)**	**2 (8)**
Renal and urinary disorders*	**1 (4)**	**2 (8)**	**1 (4)**	**2 (8)**

* All events within this system were experienced by only one patient per event

Note: 3 AEs have been miscoded. Patient 5104 had an AE of increase in creatinine kinase on Day 263 that was coded as Blood creatinine increased instead of Blood creatine phosphokinase increased. The previous incidence was correctly coded for this patient. Patients 5110 and 5125 had an AE of prolonged menstrual bleeding/cycle which was wrongly coded as Oligomenorrhoea and should have been coded as menometorrhagia for both patients

Incidence of SAEs

Primary system organ class Preferred term	RAD001 (Everolimus) 2.5 mg N=24 n (%)	 5 mg N=24 n (%)	 10 mg N=24 n (%)	 All doses N=24 n (%)
Patients with at least one SAE	1 (4)	2 (8)	5 (21)	8 (33)
General disorders & administration site conditions	**1 (4)**	**0**	**3 (13)**	**4 (17)**
Oedema peripheral	0	0	2 (8)	2 (8)
Non-cardiac chest pain	1 (4)	0	0	1 (4)
Pyrexia	0	0	1 (4)	1 (4)
Infections and infestations	**0**	**0**	**3 (13)**	**3 (13)**
Bronchitis	0	0	1 (4)	1 (4)
Pneumocystis jiroveci infection	0	0	1 (4)	1 (4)
Pneumonia	0	0	1 (4)	1 (4)
Cardiac disorders	**0**	**1 (4)**	**1 (4)**	**2 (8)**
Cardiac failure	0	0	1 (4)	1 (4)
Pericarditis	0	1 (4)	0	1 (4)
Tachycardia	0	0	1 (4)	1 (4)
Renal and urinary disorders	**0**	**1 (4)**	**0**	**1 (4)**
Nephrolithiasis	0	1 (4)	0	1 (4)
Respiratory, thoracic and mediastinal disorders	**1 (4)**	**0**	**0**	**1 (4)**
Dyspnoea	1 (4)	0	0	1 (4)

Number of patients who experienced serious or adverse events that led to withdrawal

	RAD001 (Everolimus)			
Patients with serious or significant AEs	2.5 mg N=24 n (%)	5 mg N=24 n (%)	10 mg N=24 n (%)	All doses N=24 n (%)
Death	0	0	0	0
SAEs	1 (4)	2 (8)	5 (21)	8 (33)
Discontinued due to AEs	0	0	6 (25)	6 (25)
Discontinued due to SAEs	0	0	1 (4)	1 (4)
Discontinued due to non-serious AEs	0	0	5 (21)	5 (21)

Summary of severe, non-serious adverse events

Patient	Dose (mg)	Day	Adverse event	Related to study drug
5113	10	114	Apthous stomatitis	Suspected
5114	10	291	Diabetes mellitus	Not suspected
5116	10	189	Gamma GT increased*	Suspected
5122	10	168	Mouth ulcer	Suspected
		309	Dyspnea	Suspected
5123	5	49	Nasopharyngitis	Not suspected
5134	10	245	Oedema peripheral	Suspected

* led to withdrawal

There were no relevant changes in routine laboratory variables and few abnormalities noted in laboratory values of interest.

There were no clinically relevant differences in ECG parameters including QTcF interval and heart rate.

Date of Clinical Trial Report

13 June 2013

Date Inclusion on Novartis Clinical Trial Results Database

13 June 2013

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Date of Latest Update