Supplementary Methods

In a prespecified analysis, changes from baseline in FVC and FEV_1 were compared between everolimus and historical placebo data from the MILES study[25] by using the following Bayesian approach. It was assumed that Y, the observed change from baseline in FVC or FEV_1, followed a normal distribution $N(\theta_i, \sigma^2)$, where the subscript i was a placeholder for the treatment arm (1: RAD001; 0: Placebo). σ=233 was for MILES placebo arm, and σ for RAD arm was estimated from data.

It was further assumed that θ_i follows a prior distribution $N(\mu_i, \sigma^2/n_{0i})$, where the parameter n_{0i} weighed the available prior information (to account for between-trial variation). The quantity of interest was the treatment effect θ_1-θ_0, and the posterior probabilities that this quantity was (a) greater than 0 mL, or (b) greater than 100 mL were estimated using Markov Chain Monte Carlo (MCMC) simulation by SAS MCMC procedure.

Assuming exchangeability among historical and concurrent placebo controls, μ_0 and σ for FVC were determined as follows:

- Based on the result in the MILES study (Table 2), -11 mL was the rate of change per month for Placebo (N=43), therefore μ_0=-66 mL was chosen for the prior mean of change from baseline to 6 months
- Based on the result of change from baseline to 12 months for Placebo (N=34) in the MILES study (Table 2), σ=233 mL was chosen for the standard deviation.

To account for between-trial heterogeneity, the sample size of n=43 from the MILES trial was downweighted to obtain an effective sample size n* according to formula (11) of Neuenschwander et al (2010)[37]

$$n^* = \frac{\sigma^2}{\frac{\sigma^2}{N} + \tau^2(1 + (1/H))} \qquad (11)$$

Assuming medium between trial heterogeneity, σ/τ=8, (Neuenschwander et al, 2010[37], Table 1) an effective sample size of n*=18 is obtained and hence used for n_{00}. Since no prior information on the effect of RAD001 on FVC was available, an "improper prior" was used for this treatment arm, that is, n_{01}=0.

The proposed proof of concept for our study was a 90% level of proof that the difference in FVC change from baseline for everolimus versus placebo was >0 mL and a 50% level of proof of a ≥100 mL difference between the treatment groups.

FEV1 was analyzed in the same fashion. Moreover, the choice of μ_0=-72(=-12x6) and σ=182 was for the prior mean of change from baseline to 6 months and standard deviation for placebo group, and σ for RAD arm was estimated from data. Assuming the same scenarios for between trial heterogeneity, the values of n_{00} and n_{01} was the same as for FVC.

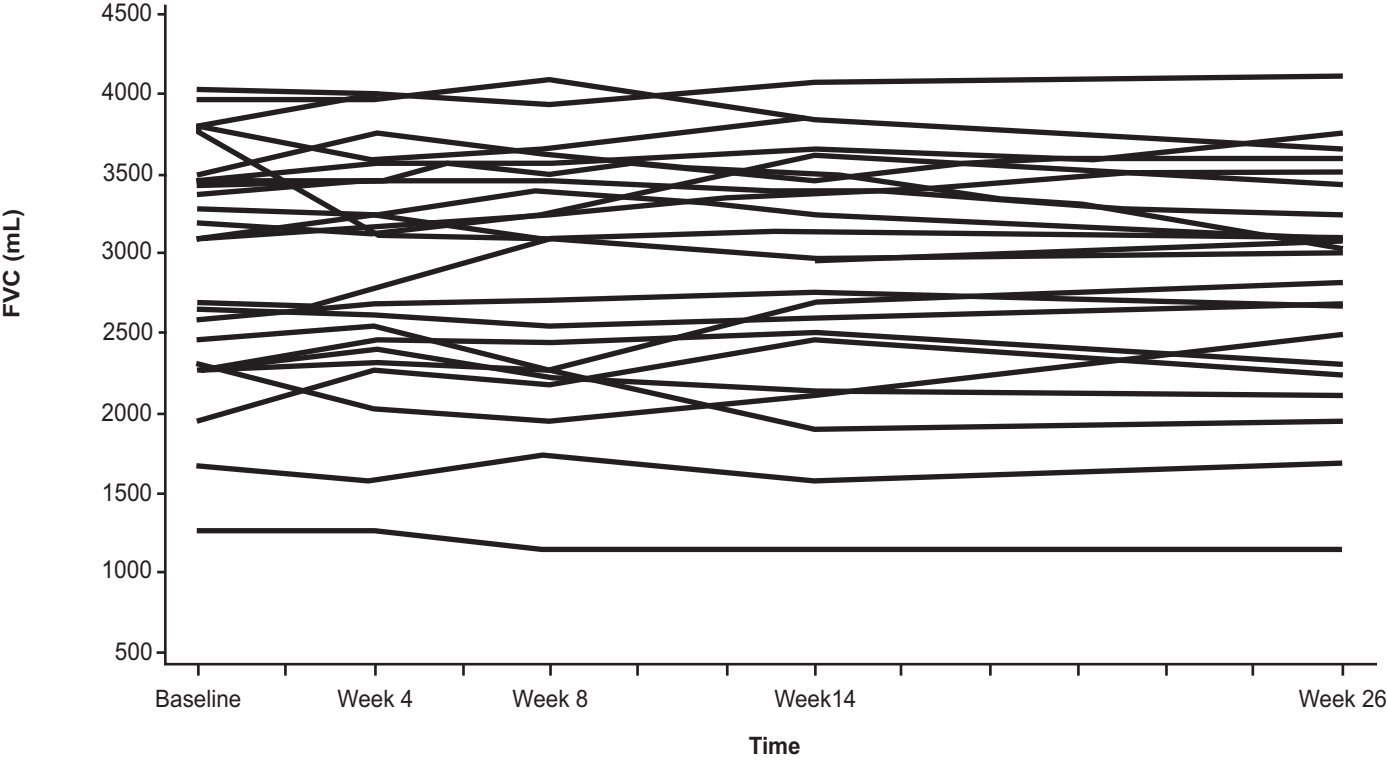
Supplementary Results

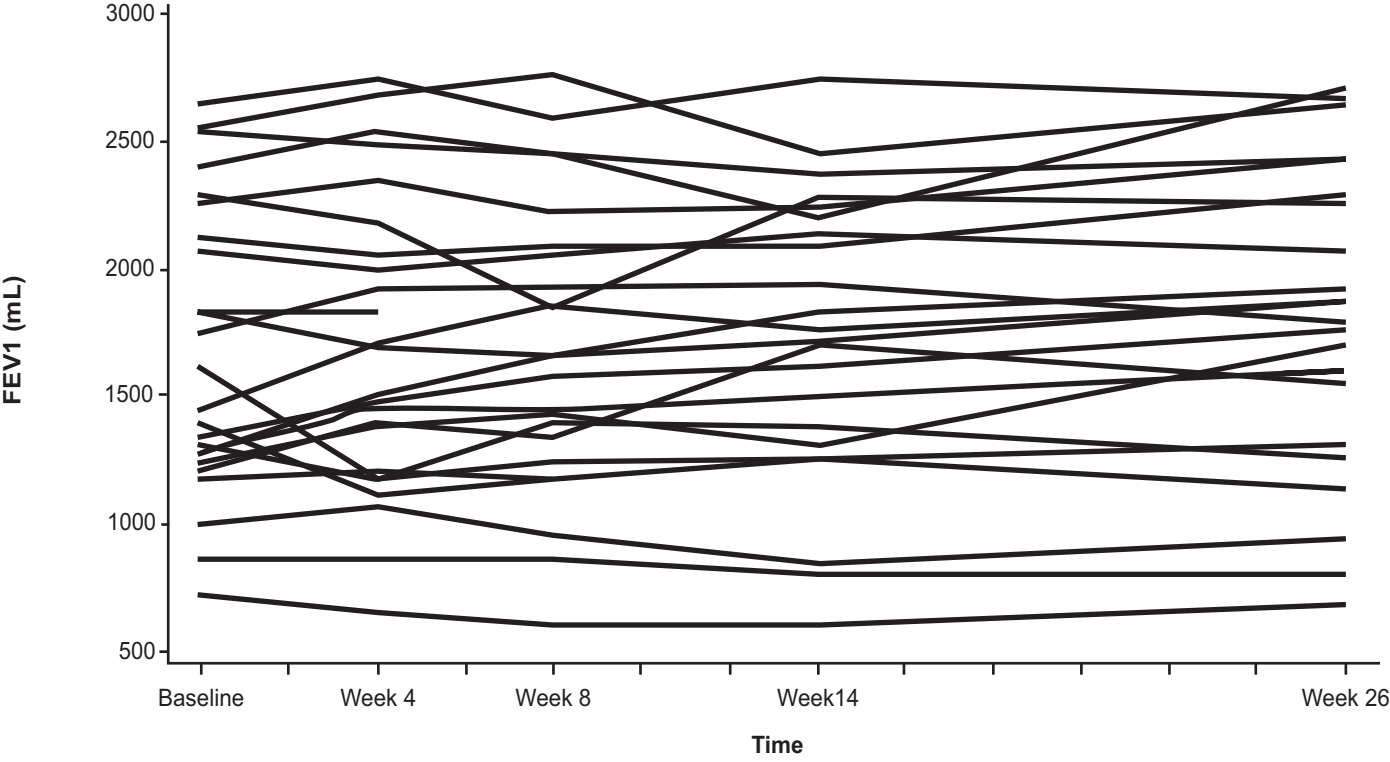
Supplemental Figure 1 shows spaghetti plots of individual patient profiles for FVC and FEV_1. After 26 weeks of treatment with everolimus, the probabilities that the placebo-corrected mean changes from baseline in FVC and FEV_1 were >0 mL and >100 mL were 85% and 38%, respectively, and 100% and 93%, respectively (**Supplemental Table 1**).

Supplemental Figure Title and Legend

Supplemental Figure 1. Individual spaghetti plots of postbrochodilator A) FVC and B) FEV_1 over 26 weeks of treatment with everolimus (PD analysis set)

FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; PD: pharmacodynamic.


4500
4000
3500
3000
2500
2000
1500
1000
500
FVC (mL)
Baseline
Week 4
Week 8
Week14
Week 26
Time


3000
2500
2000
1500
1000
500
FEV1 (mL)
Baseline
Week 4
Week 8
Week14
Week 26
Time

Supplemental Table 1. Summary of change from baseline in FVC and FEV_1 over time (pharmacodynamics analysis set)

	Everolimus		MILES placebo[b]	Difference of everolimus and MILES placebo		
	N[a]	Mean (95% CI)	Mean (95% CI)	Mean (5th–95th percentile range)	P (difference >0 mL)	P (difference >100 mL)
FVC, mL						
Week 4	24	13 (–71–97)	–11 (–109–87)	23 (–96–147)	62%	15%
Week 8	22	8 (–96–112)	–22 (–128–84)	30 (–94–152)	65%	18%
Week 14	23	31 (–58–121)	–33 (–139–73)	63 (–58–184)	81%	31%
Week 26	23	10 (–111–132)	–66 (–181–49)	76 (–45–196)	85%	38%
Week 38	14	100 (–73–273)				
Week 50	11	148 (–45–341)				
Week 62	4	50				

		(−227–327)				
End of study[c]	16	84 (−122–290)				
FEV_1, mL						
Week 4	24	16 (−52–84)	−12 (−88–64)	27 (−65–122)	68%	10%
Week 8	22	22 (−60–104)	−24 (−106–58)	46 (−50–140)	78%	18%
Week 14	23	41 (−49–131)	−36 (−118–46)	76 (−19–173)	90%	34%
Week 26	23	114 (11–217)	−72 (−162–18)	186 (93–279)	100%	93%
Week 38	14	124 (−23–272)				
Week 50	11	150 (−24–324)				
Week 62	4	−3 (−254–249)				
End of study[c]	16	56 (−59–170)				

[a]Number of patients in everolimus treatment group at each visit.

[b]Number of patients in MILES placebo group assumed as 18 based on historical data. Mean values derived from Bayesian posterior distribution assuming an FVC decline of 11 mL/month with SD 233 mL and an FEV_1 decline of

12 mL/month with SD 182 mL.

[c]4–8 weeks after the last dose of study drug.

Abbreviations: CI, confidence interval; FEV_1, forced expiration volume in 1 second; FVC, forced vital capacity; N, number of patients; P, probability.

Supplemental Reference

(37) Neuenschwander B, Capkun-Niggli G, Branson M, Spiegelhalter DJ. Summarizing historical information on controls in clinical trials. *Clin Trials*. 2010;7(1):5-18.