Supplementary Online Content

Wataya-Kaneda M, Ohno Y, Fujita Y, et al. Sirolimus gel treatment vs placebo for facial angiofibromas in patients with tuberous sclerosis complex: a randomized clinical trial. *JAMA Dermatol*. Published online May 19, 2018. doi:10.1001/jamadermatol.2018.1408

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1-A. Rating criteria for improvements in cutaneous lesions from baseline

Rating	Angiofibromas		Size of plaques
	Size	Color*	
Markedly improved	Reduced in ≥ 75% of lesions	Improved by ≥ 3 reddishness levels in ≥ 50% of lesions	Reduced by ≥ 75%
Improved	Reduced in 50-75% of lesions	Improved by 2 reddishness levels in ≥ 50% of lesions or by ≥ 3 reddishness levels in 25-50% of lesions	Reduced by 50-75%
Slightly improved	Reduced in 25-50% of lesions	Improved by 1 reddishness level in ≥ 50% of lesions or by 2 reddishness levels in 25-50% of lesions	Reduced by 25-50%
Unchanged	Not obviously changed	Not obviously changed	Not obviously changed
Slightly aggravated	Increased or newly formed papules in 25-50% of lesions	Aggravated by 1 reddishness level in ≥ 50% of lesions or by 2 reddishness levels in 25-50% of lesions	Increased by 25-50%
Aggravated	Increased or newly formed papules in ≥ 50% of lesions	Aggravated by ≥ 2 reddishness levels in ≥ 50% of lesions or by ≥ 3 reddishness levels in 25-50% of lesions	Increased by ≥ 50%

*PANTONE® samples for the assessment of reddishness level

Level	PANTONE	Sample
1	489C	
2	486C	
3	7416C	
4	485C	
5	704C	
6		Deeper than 704C

eTable 1-B The rating criteria for composite improvement in angiofibromas based on the efficacy variables (size and color of angiofibromas)

		Improvement in the size					
		A	**B**	**C**	**D**	**E**	**F**
Improvement in the color	**A**	Aggravated	Aggravated	Aggravated	*	*	*
	B	Aggravated	Slightly aggravated	Slightly aggravated	Unchanged	*	*
	C	Aggravated	Slightly aggravated	Unchanged	Slightly improved	Slightly improved	Improved
	D	*	Unchanged	Slightly improved	Slightly improved	Improved	Improved
	E	*	*	Slightly improved	Improved	Improved	Markedly improved
	F	*	*	Improved	Improved	Markedly improved	Markedly improved

A, Aggravated; B: Slightly aggravated; C, unchanged; D, Slightly improved; E, improved; F, Markedly improved

*: Should be assessed weighting the size and color of angiofibromas.

eTable 2.A. Composite improvement in angiofibromas at week 12 of treatment

	Sirolimus		Placebo	
	% (95% CI)	n/N	% (95% CI)	n/N*
Markedly improved	17 (6-35)	5/30	0 (0-11)	0/31
Improved	43 (26-63)	13/30	0 (0-11)	0/31
Slightly improved	37 (20-56)	11/30	16 (6-34)	5/31
Unchanged	3 (0-17)	1/30	84 (66-95)	26/31

*: One patient, whose out-of-focus photograph had been rated to be "unassessable" was excluded from the denominator.

eTable 2.B. Response rates of angiofibromas

	Week 4	Week 8	Week 12	Week 4 of follow-up
Sirolimus	20 (8-39)	43 (26-63)	60 (41-77)	10 (2-27)
% (95% CI) , n/N	6/30	13/30	18/30	3/30
Placebo	0 (0-11)	0 (0-11)	0 (0-11)	0 (0-11)
% (95% CI), n/N*	0/32	0/32	0/32	0/32

*: One patient, whose out-of-focus photograph had been rated to be "unassessable" was incorporated in the denominator as nonresponder.

eTable 2.C. Response rates of cephalic plaques

	Week 4	Week 8	Week 12	Week 4 of follow-up
Sirolimus	8 (0-36)	31 (9-61)	46 (19-75)	15 (2-46)
% (95% CI) , n/N	1/13	4/13	6/13	2/13
Placebo	0 (0-21)	0 (0-21)	6 (0-30)	6 (0-30)
% (95% CI), n/N	0/15	0/16	1/16	1/16

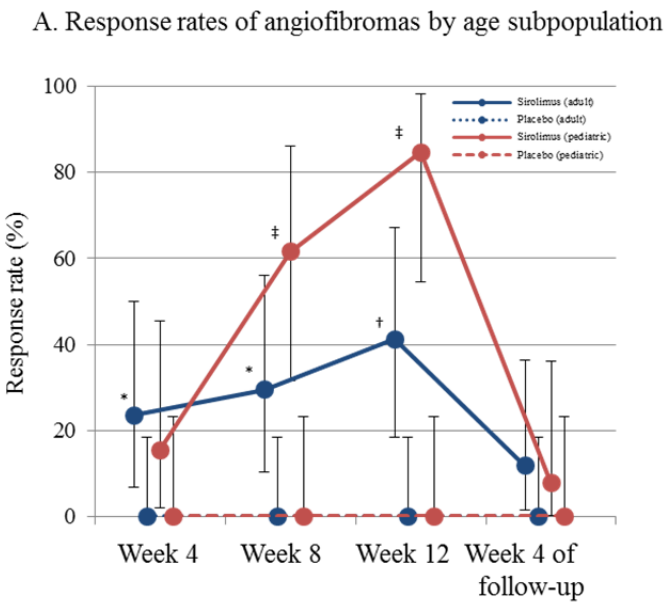
eTable 3. Adverse events

System Organ Class/ Preferred terms*	Sirolimus			Placebo		
	Total N = 30	Pediatric n = 13	Adult n = 17	Total N = 32	Pediatric n = 14	Adult n = 18
Any adverse event	27 (90%)	10 (77%)	17(100%)	22 (69%)	10 (71%)	12 (67%)
Infections and infestations						
Gastroenteritis	1 (3%)	1 (8%)	0	0	0	0
Hordeolum	1 (3%)	1 (8%)	0	0	0	0
Impetigo†	0	0	0	1 (3%)	1 (7%)	0
Influenza	3 (10%)	3 (23%)	0	0	0	0
Nasopharyngitis	1 (3%)	1 (8%)	0	3 (9%)	3 (21%)	0
Sinusitis	0	0	0	1 (3%)	0	1 (6%)
Tonsillitis	0	0	0	1 (3%)	1 (7%)	0
Vulvovaginal candidiasis	1 (3%)	0	1 (6%)	0	0	0
Oral herpes	0	0	0	1 (3%)	0	1 (6%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)						
Lymphangioma	1 (3%)	0	1 (6%)	0	0	0
Kidney angiomyolipoma	1 (3%)	0	1 (6%)	0	0	0
Immune system disorders						
Seasonal allergy	1 (3%)	0	1 (6%)	0	0	0
Psychiatric disorders						
Insomnia	0	0	0	1 (3%)	1 (7%)	0
Nervous system disorders						
Epilepsy	0	0	0	1 (3%)	1 (7%)	0
Paraesthesia	0	0	0	1 (3%)	0	1 (6%)
Eye disorders						
Eye irritation†	1 (3%)	1 (8%)	0	2 (6%)	1 (7%)	1 (6%)
Ocular hyperaemia	1 (3%)	1 (8%)	0	0	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	1 (3%)	1 (8%)	0	0	0	0
Upper respiratory tract inflammation	0	0	0	2 (6%)	1 (7%)	1 (6%)
Gastrointestinal disorders						
Abdominal pain	1 (3%)	0	1 (6%)	0	0	0
Diarrhoea	0	0	0	1 (3%)	1 (7%)	0
Enterocolitis	1 (3%)	1 (8%)	0	0	0	0
Gastric haemorrhage	1 (3%)	0	1 (6%)	0	0	0
Pancreatitis acute	1 (3%)	0	1 (6%)	0	0	0
Stomatitis	1 (3%)	0	1 (6%)	2 (6%)	0	2 (11%)
Vomiting	0	0	0	1 (3%)	1 (7%)	0
Paraesthesia oral	0	0	0	1 (3%)	0	1 (6%)
Skin and subcutaneous tissue disorders						
Acne	2 (7%)	0	2 (12%)	0	0	0
Alopecia	0	0	0	1 (3%)	0	1 (6%)
Alopecia areata	1 (3%)	1 (8%)	0	0	0	0
Dermatitis acneiform	1 (3%)	0	1 (6%)	0	0	0
Dermatitis atopic	0	0	0	1 (3%)	1 (7%)	0
Dermatitis contact	1 (3%)	0	1 (6%)	0	0	0
Dry skin	11 (37%)	4 (31%)	7 (41%)	4 (13%)	2 (14%)	2 (11%)
Erythema	1 (3%)	1 (8%)	0	0	0	0
Pruritus	7 (23%)	1 (8%)	6 (35%)	4 (13%)	2 (14%)	2 (11%)
Skin irritation	1 (3%)	0	1 (6%)	0	0	0
Asteatosis	1 (3%)	1 (8%)	0	0	0	0
Skin haemorrhage	1 (3%)	0	1 (6%)	0	0	0
Musculoskeletal and connective tissue disorders						
Back pain	1 (3%)	0	1 (6%)	0	0	0
Renal and urinary disorders	1 (3%)	0	1 (6%)	0	0	0

System Organ Class/ Preferred terms*	Sirolimus			Placebo		
	Total N = 30	Pediatric n = 13	Adult n = 17	Total N = 32	Pediatric n = 14	Adult n = 18
Proteinuria	1 (3%)	0	1 (6%)	0	0	0
General disorders and administration site conditions						
Application site irritation	11 (37%)	4 (31%)	7 (41%)	9 (28%)	3 (21%)	6 (33%)
Feeling abnormal	0	0	0	1 (3%)	0	1 (6%)
Pyrexia	1 (3%)	1 (8%)	0	1 (3%)	0	1 (6%)
Swelling	1 (3%)	0	1 (6%)	0	0	0
Investigations						
Blood creatine phosphokinase increased	0	0	0	1 (3%)	1 (7%)	0
Blood pressure decreased	1 (3%)	1 (8%)	0	0	0	0
Blood triglycerides increased	0	0	0	1 (3%)	0	1 (6%)
Injury, poisoning and procedural complications						
Arthropod sting	1 (3%)	1 (8%)	0	0	0	0
Scratch	0	0	0	1 (3%)	0	1 (6%)
Contusion	0	0	0	1 (3%)	1 (7%)	0
Skin abrasion	0	0	0	2 (6%)	1 (7%)	1 (6%)
Skin wound	1 (3%)	0	1 (6%)	0	0	0

* MedDRA version 19.0

eFigure 1



Sirolimus (adult) % (95% CI) n/N	26 (7-50) 4/17	29 (10-56) 5/17	41 (18-67) 7/17	12 (2-36) 2/17
Placebo (adult) % (95% CI) n/N	0 (0-19) 0/18	0 (0-19) 0/18	0 (0-19) 0/18	0 (0-19) 0/18
Sirolimus (pediatric) % (95% CI) n/N	15 (2-46) 2/13	62 (32-86) 8/13	85 (55-98) 11/13	8 (0-36) 1/13
Placebo (pediatric) % (95% CI) n/N	0 (0-23) 0/14	0 (0-23) 0/14	0 (0-23) 0/14	0 (0-23) 0/14

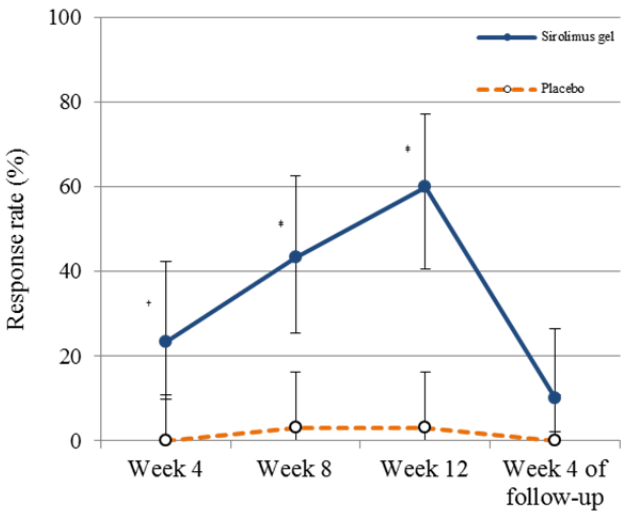
eFigure 1

The response rates of angiofibromas by age subpopulation (A); response rates of the size of angiofibromas in all populations (B); response rates of the size of angiofibromas by age subpopulation (C); response rates of the color of angiofibromas in all populations (D); response rates of the color of angiofibromas by age subpopulation (E); and response rates of plaques by age subpopulation (F). The response rate was defined as the proportion of patients rated to “Markedly improved” and “Improved.” The upper and lower 95% confidence intervals (95% CI) are shown as error bars. Fisher’s exact test was conducted for comparisons.

*, $P < .05$; †, $P < .01$; ‡, $P < .001$ (vs. placebo)

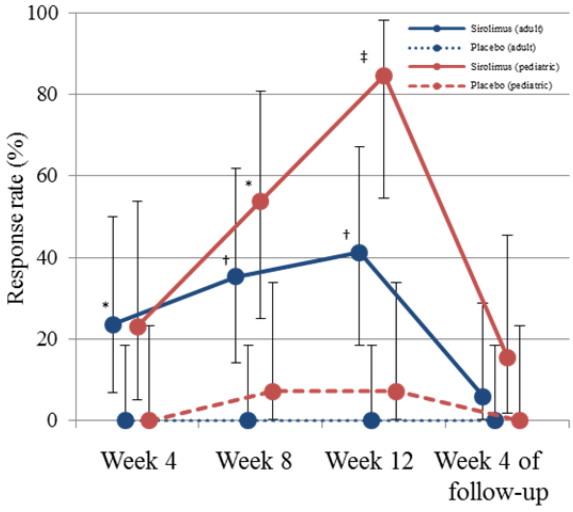
eFigure 1

B. Response rates of the size of angiofibromas in all populations



Sirolimus % (95% CI) n/N	23 (10-42) 7/30	43 (26-63) 13/30	60 (41-77) 18/30	10 (2-27) 3/30
Placebo % (95% CI) n/N	0 (0-11) 0/32	3 (0-16) 1/32	3 (0-16) 1/32	0 (0-11) 0/32

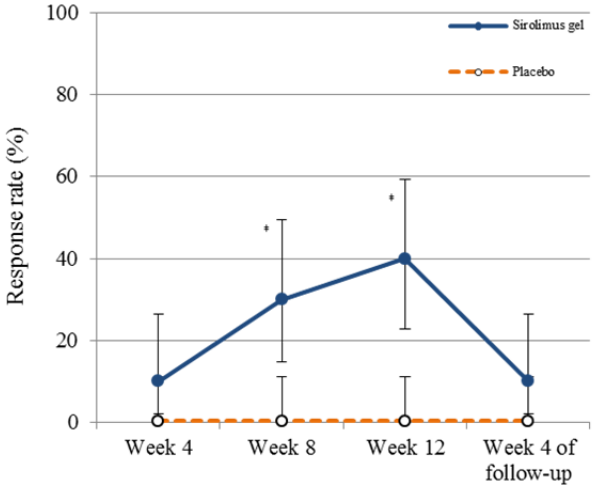
C. Response rates of the size of angiofibromas by age subpopulation



Sirolimus (adult) % (95% CI) n/N	24 (7-50) 4/17	35 (14-62) 6/17	41 (18-67) 7/17	6 (0-29) 1/17
Placebo (adult) % (95% CI) n/N	0 (0-19) 0/18	0 (0-19) 0/18	0 (0-19) 0/18	0 (0-19) 0/18
Sirolimus (pediatric) % (95% CI) n/N	23 (5-54) 3/13	54 (25-81) 7/13	85 (55-98) 11/13	15 (2-46) 2/13
Placebo (paediatirc) % (95% CI) n/N	0 (0-23) 0/14	7 (0-34) 1/14	7 (0-34) 1/14	0 (0-23) 0/14

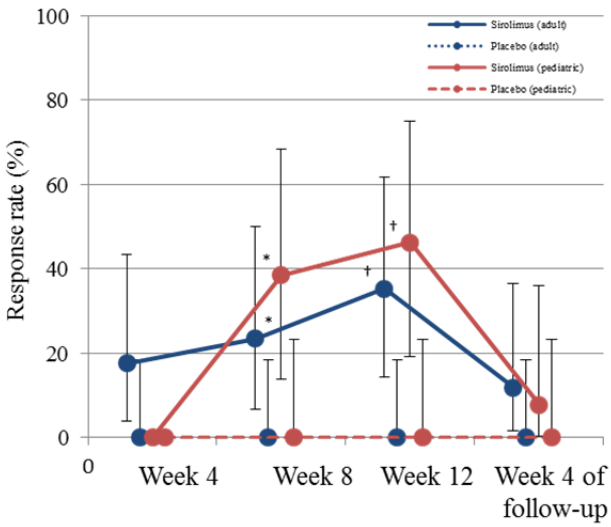
eFigure 1

D. Response rates of the color of angiofibromas in all populations



Sirolimus % (95% CI) n/N	10 (2-27) 3/30	30 (15-49) 9/30	40 (23-59) 12/30	10 (2-27) 3/30
Placebo % (95% CI) n/N	0 (0-11) 0/32	0 (0-11) 0/32	0 (0-11) 0/32	0 (0-11) 0/32

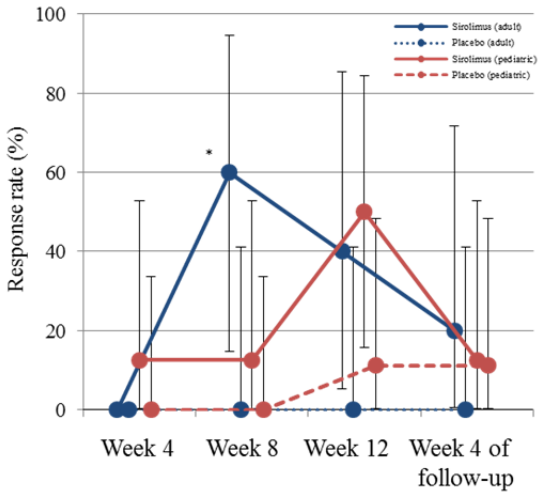
E. Response rates of the color of angiofibromas by age subpopulation



Sirolimus (adult) % (95% CI) n/N	18 (4-43) 3/17	24 (7-50) 4/17	35 (14-62) 6/17	12 (2-36) 2/17
Placebo (adult) % (95% CI) n/N	0 (0-19) 0/18	0 (0-19) 0/18	0 (0-19) 0/18	0 (0-19) 0/18
Sirolimus (pediatric) % (95% CI) n/N	0 (N.A.) 0/13	39 (14-68) 5/13	46 (19-75) 6/13	8 (0-36) 1/13
Placebo (pediatric) % (95% CI) n/N	0 (N.A.) 0/14	0 (0-23) 0/14	0 (0-23) 0/14	0 (0-23) 0/14

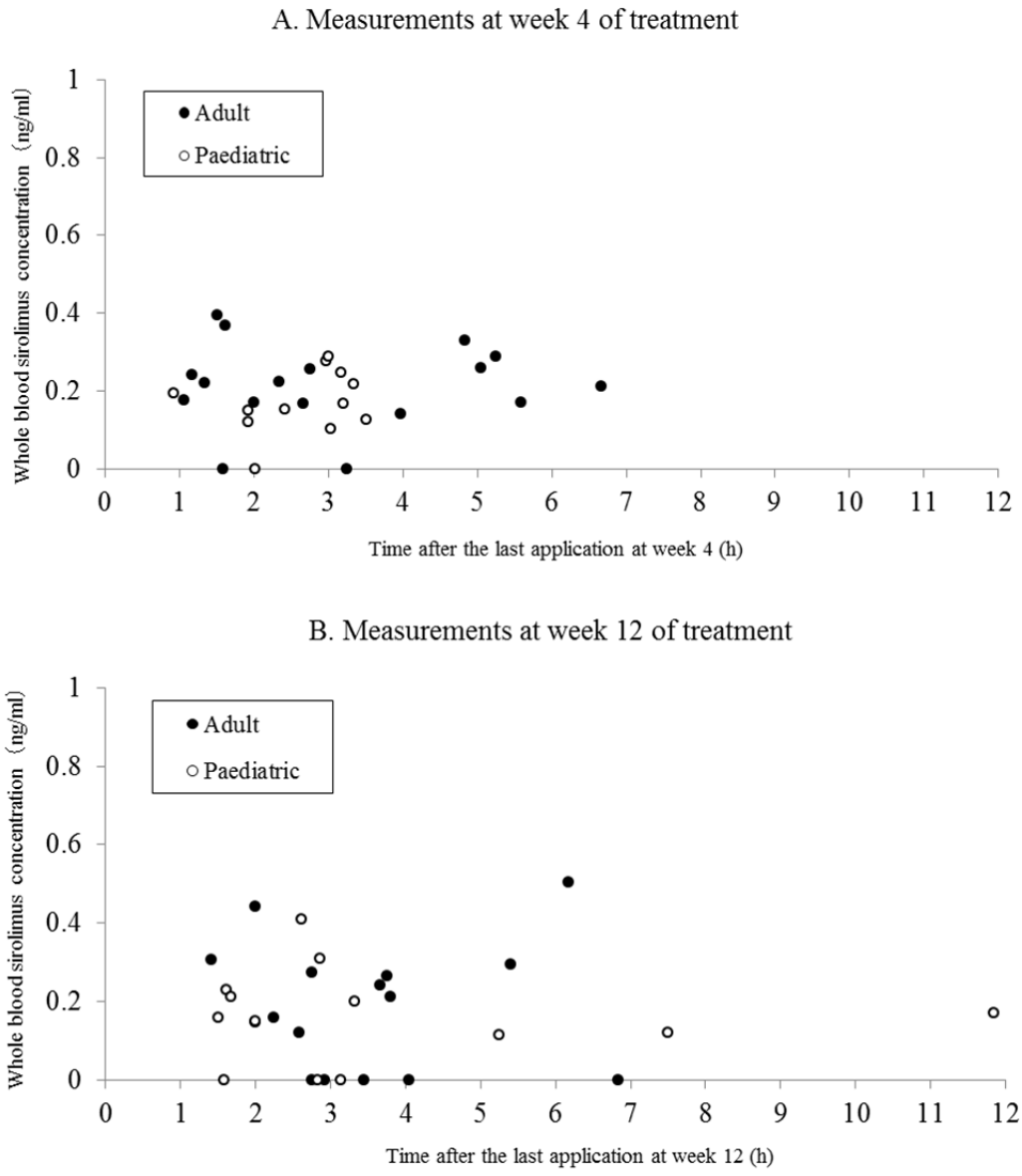
eFigure 1

F. Response rates of plaques by age subpopulation



Sirolimus (adult) % (95% CI) n/N	0 (N.A.) 0/5	60 (15-95) 3/5	40 (5-85) 2/5	20 (1-72) 1/5
Placebo (adult) % (95% CI) n/N	0 (N.A.) 0/7	0 (0-41) 0/7	0 (0-41) 0/7	0 (0-41) 0/7
Sirolimus (pediatric) % (95% CI) n/N	13 (0-53) 1/8	13 (0-53) 1/8	50 (16-84) 4/8	13 (0-53) 1/8
Placebo (pediatric) % (95% CI) n/N	0 (0-34) 0/8	0 (0-34) 0/9	11 (0-48) 1/9	11 (0-48) 1/9

eFigure 2



eFigure 2

Plots of whole blood sirolimus concentrations measured by LC/MS/MS in patients after the last application at weeks 4 (Panel A) and 12 (Panel B) of treatment. Values below the detection limit (0.1 ng/mL) are expressed as 0 ng/ml. Twenty-seven (90%) of 30 samples were measurable at week 4 (Panel A), and 21 (70%) at week 12 (Panel B). Means ± SD at weeks 4 and 12 of treatment were 0.2 ± 0.1 ng/mL each, with the maximum levels of 0.4 and 0.5 ng/mL, respectively. LC/MS/MS, liquid chromatography/mass spectrometry.