THE LANCET
Rheumatology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Chung L, Spino C, McLain R, et al. Safety and efficacy of abatacept in early diffuse cutaneous systemic sclerosis (ASSET): open-label extension of a phase 2, double-blind randomised trial. *Lancet Rheumatol* 2020; published online Oct 19. https://doi.org/10.1016/S2665-9913(20)30237-X.

Supplemental Table 1: Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
1. Signed Written Informed Consent 2. Diagnosis of SSc, as defined using the 2013 American College of Rheumatology/ European Union League Against Rheumatism classification of SSc 3. dcSSc as defined by LeRoy and Medsger 4. Disease duration of ≤ 36 months (defined as time from the first non−Raynaud phenomenon manifestation) For disease duration of ≤ 18 months • ≥ 10 and ≤ 35 mRSS units at the screening visit For disease duration of >18-36 months • ≥ 15 and ≤ 45 mRSS units at the screening visit **and** one of the following: 1. Increase ≥ 3 in mRSS units compared with the last visit within previous 1–6 months 2. Involvement of one new body area with ≥ 2 mRSS units compared with the last visit within the previous 1–6 months 3. Involvement of two new body areas with ≥ 1 mRSS units compared with the last visit within the previous 1–6 months 4. Presence of 1 or more Tendon Friction Rub 5. Age ≥ 18 years at the screening visit 6. If female of childbearing potential (see 4.2.3), the patient must have a negative pregnancy test at screening and baseline visits 7. Oral corticosteroids (≤ 10 mg/day of prednisone or equivalent) and NSAIDs are permitted if the patient is on a stable dose regimen for ≥ 2 weeks prior to and including the baseline visit 8. ACE inhibitors, calcium-channel blockers, proton-pump inhibitors, and/or oral vasodilators are permitted if the patient is on a stable dose for ≥ 2 weeks prior to and including the baseline visit	1. Rheumatic disease other than dcSSc; it is acceptable to include patients with fibromyalgia and scleroderma-associated myopathy 2. Limited cutaneous SSc or sine scleroderma at the screening visit 3. Major surgery (including joint surgery) within 8 weeks prior to screening visit 4. Any infected ulcer prior to randomization 5. Treatment with any investigational agent within ≤ 4 weeks (or 5 half-lives of the investigational drug, whichever is longer) of the baseline visit 6. Severe (MRSS 3+) skin on the inner aspects of thighs, upper arms, and abdomen 7. Previous treatment with cell-depleting therapies, including investigational agents, including but not limited to, CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19, and ABA 8. Anti-CD20, and cyclophosphamide within 12 months prior to baseline visit 9. Use of Intravenous Immunoglobulin (IVIG) within12 weeks prior to baseline visit 10. Previous treatment with chlorambucil, bone marrow transplantation, or total lymphoid irradiation 11. Immunization with a live/attenuated vaccine within ≤ 4 weeks prior to the baseline visit 12. Treatment with methotrexate, hydroxychloroquine, cyclosporine A, azathioprine, mycophenolate mofetil rapamycin, colchicine, D-penicillamine, within ≤ 4 weeks prior to the baseline visit 13. Treatment with etanercept within ≤ 2 weeks, infliximab, certolizumab, golimumab, ABA or adalimumab within ≤ 8 weeks, anakinra within ≤ 1 week prior to the baseline visit 14. Pulmonary disease with FVC ≤ 50% of predicted, or DLCO (uncorrected for hemoglobin) ≤ 40% of predicted at the screening visit 15. Pulmonary arterial hypertension (PAH) as determined by right heart catheterization or on PAH approved medications for PAH. It is acceptable to use PDE-5 inhibitors for Raynaud's and digital ulcers. 16. Subjects at risk for tuberculosis (TB). Specifically excluded from this study will be participants with a history of active TB within the last 3 years, even if it was treated; a history of active TB greater than 3 years ago, unless there is documentation that the prior anti-TB treatment was appropriate in duration and type; current clinical, radiographic, or laboratory evidence of active TB; and latent TB that was not successfully treated (≥ 4 weeks).

	17. Positive for hepatitis B surface antigen prior to the baseline visit 18. Positive for hepatitis C antibody, if the presence of hepatitis C virus was also shown with polymerase chain reaction or recombinant immunoblot assay prior to baseline visit 19. Any of the following prior to the baseline visit: • Hemoglobin <8.5 g/dL; • WBC < 3,000/mm3 (<3 x 109/L); • Platelets < 100,000/mm3 (<3 x 109/L); • Serum creatinine > 2 x ULN; or • Serum ALT or AST > 2 x ULN 20. Any other laboratory test results that, in the opinion of the investigator, might place a participant at unacceptable risk for participation in the study. 21. The following medical history and concurrent diseases: • Subjects who are impaired, incapacitated, or incapable of completing study-related assessments. • Subjects with active vasculitis of a major organ system. • Subjects with current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, pulmonary, cardiac, neurologic, or cerebral disease, whether or not related to SSc and which, in the opinion of the investigator, might place a participant at unacceptable risk for participation in the study. • Subjects with a history of cancer in the last 5 years, other than non-melanoma skin cell cancers cured by local resection or carcinoma in situ. Existing non-melanoma skin cell cancers should be removed, the lesion site healed, and residual cancer ruled out before administration of the study drug. • Subjects who currently abuse drugs or alcohol. • Subjects with evidence (as assessed by the investigator) of active or latent bacterial or viral infections at the time of potential enrollment, including participants with evidence of human immunodeficiency virus (HIV) detected during screening. • Subjects with herpes zoster or cytomegalovirus (CMV) that resolved less than 2 months prior to screening. • Subjects with any serious bacterial infection within the last 3 months, unless treated and resolved with antibiotics, or any chronic bacterial infection (e.g., chronic pyelonephritis, osteomyelitis, or bronchiectasis). **22.** Patients with a history of anaphylaxis to abatacept

Supplemental Table 2: Responder analysis for improvement

		Double-Blind Period Month 12		Open-Label Period Month 18	
	Response Criteria	**Placebo (N=44)**	**Abatacept (N=44)**	**Pbo-Aba (N=34)**	**Aba-Aba (N=33)**
mRSS, n/N (%)	Decrease ≥5 units	19/38 (50)	23/34 (68)	20/31 (65)	23/32 (72)
% pFVC, n/N (%)	Increase >3 units	6/37 (16)	6/32 (19)	8/29 (28)	9/30 (30)
	Increase ≥5 units *	3/37 (8)	6/32 (19)	4/29 (14)	6/30 (20)
	Increase ≥10 units*	1/37 (3)	2/32 (6)	1/29 (3)	5/30 (17)
	Between -5 and 5±	19/37 (51)	18/32 (56)	20/29 (69)	18/30 (60)
HAQ-DI, n/N (%)	Decrease >0.14 units	24/36 (67)	26/33 (79)	19/28 (68)	24/32 (75)
CRISS, n/N (%)	Score ≥0.60	13/36 (36)	18/33 (55)	13/26 (50)	19/29 (66)
Multi-Component Responder, n/N (%)	mRSS ≤ 10, HAQ-DI ≤ 0.75 and Patient Global Assessment ≤ 3	6/38 (16)	5/34 (15)	4/31 (13)	10/32 (31)

Pbo= Placebo; Aba= Abatacept; mRSS= modified Rodnan skin score; pFVC= Predicted Forced Vital Capacity; HAQ-DI=Health assessment questionnaire disability index; CRISS=composite response index in dcSSc

*Improvement; ± Stable

Supplemental Table 3: Summary of escape therapy during double blind and open-label period. Safety Population.

	Double-Blind Period Month 12		Open-Label Period Month 18	
Variable Statistic or Category	**Placebo (N=44)**	**Abatacept (N=44)**	**Pbo-Aba (N=34)**	**Aba-Aba (N=33)**
Participant using escape therapy [1], n (%)				
Started ≤ 3 months	0 (0)	1 (2)	0 (0)	0 (0)
Started > 3 months and ≤ 6 months	3 (7)	2 (5)	3 (9)	1 (3)
Started > 6 months and ≤ 12 months	13 (30)	4 (9)	9 (26)	4 (12)
Started > 12 months and ≤ 15 months	..	..	1 (3)	1 (3)
Started > 15 months and ≤ 18 months	..	..	0 (0)	0 (0)

[1] Escape therapy included methotrexate, mycophenolate mofetil, cyclophosphamide, hydroxychloroquine, azathioprine or intravenous immunoglobulin. Other biologic therapies were not acceptable as escape therapy. Safety population includes all of the randomized participants who received at least one dose of study medication.