European Reference Network | Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET)

CHU LILLE

Sclérodermie systémique: Les essais thérapeutiques négatifs 2018-2019

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Centre de Référence des Maladies Auto-immunes Systémiques Rares du Nord et Nord-Ouest de France (CeRAINO)
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Journée de la SSc , Hôpital Cochin 29 Novembre 2019

CeRAiNO
Centre de référence des maladies auto-immunes systémiques rares du Nord et Nord-Ouest

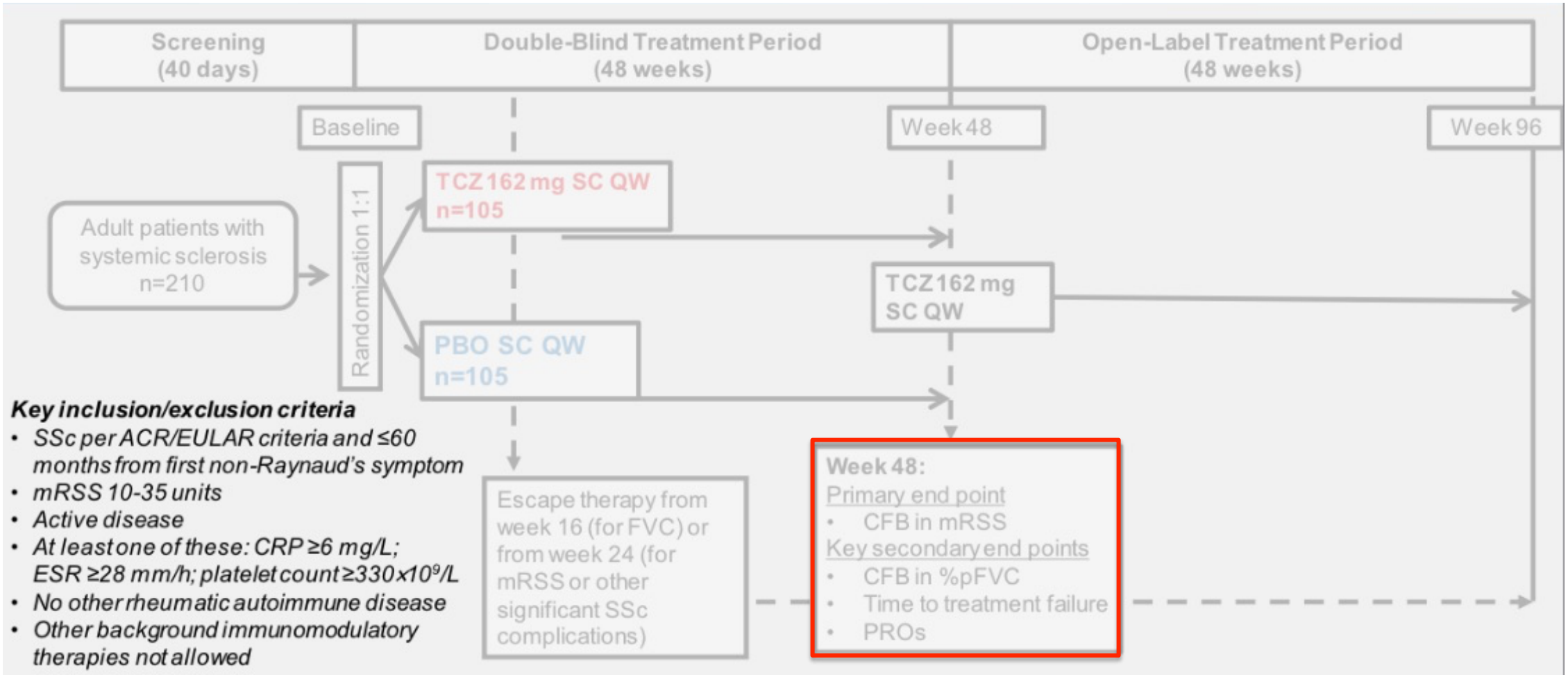
Université de Lille | FACULTÉ DE MÉDECINE Henri Warembourg

fai2r

Conflits d'Intérêt

- Investigator for clinical trials: Roche, HGS, Astra-Zeneca, Merck Serono, Neovasc, UCB, Pfizer, GENZYME, GSK, Actelion,
- Advise: Roche, GSK, HGS, Boehringer, Astra-Zeneca
- Lectures: Abbott, Roche, Pfizer, GSK, ACTELION, GENZYME, NOVARTIS, SOBI
- Meeting guest: Abbott, Actelion, Roche-Chugaï, GSK, HGS, Pfizer, Roche, Wyeth, LFB, GENZYME, NOVARTIS, SOBI
- Grant: Sanofi-Genzyme, Pfizer, GSK, Actelion, SHIRE, MSD, LFB

TCZ et SSc : résultats d'un essai randomisé, de phase 3



Khanna D ACR 2018 ***abstract*** *898*

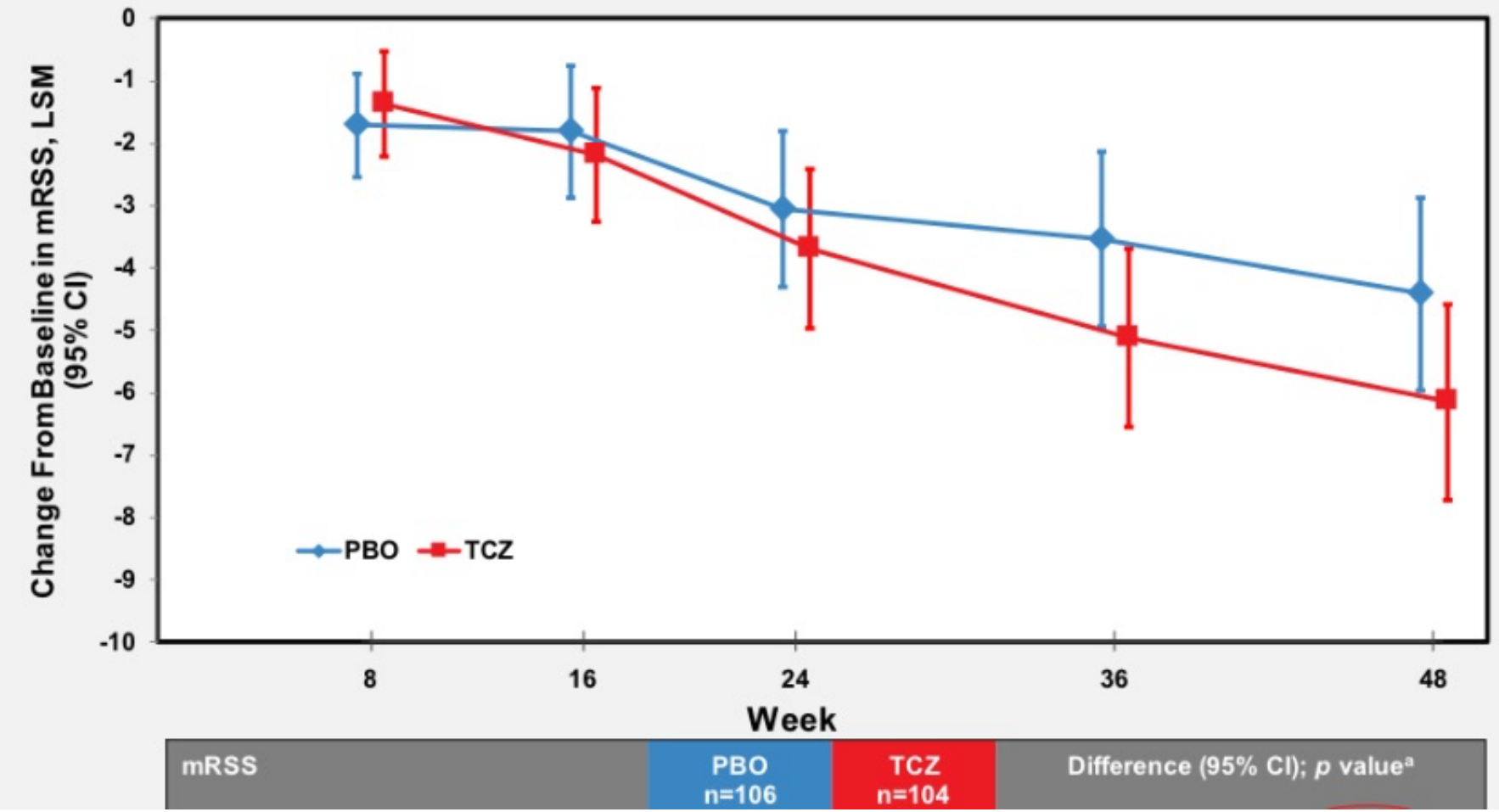
TCZ et SSc : résultats d'un essai randomisé, de phase 3

	PBO n=106	TCZ n=104	All Patients N=210
Females, %	85	78	81
Age, years	49.3 (12.6)	47.0 (12.2)	48.2 (12.4)
Duration of SSc, months	**23.1 (17.0)**	**22.2 (16.0)**	**22.6 (16.5)**
Total mRSS	**20.4 (7.0)**	**20.3 (6.7)**	**20.4 (6.8)**
%pFVC	**83.9 (15.0)**	**80.3 (14.4)**	**82.1 (14.8)**
%pDLco	76.8 (18.6)	74.4 (19.2)	75.6 (18.9)
HAQ-DI	**1.3 (0.7)**	**1.1 (0.8)**	**1.2 (0.7)**
Patient VAS	59.3 (21.3)	54.3 (24.3)	56.8 (22.9)
CRP, mg/L	7.0 (11.1)	8.9 (14.8)	7.9 (13.1)
ESR, mm/h	34.7 (18.5)	34.8 (16.3)	34.8 (17.4)
Platelet count, 10^9/L	298.7 (96.0)	311.1 (88.2)	304.9 (92.2)
Previous or concurrent ILD, %	26	37	31
ANA positive, %	92	93	92
Anti-topoisomerase positive, %	**49**	**52**	**51**
Anti-RNA polymerase positive, %	**16**	**19**	**18**
Anti-centromere positive, %	9	8	9

ANA, anti-nuclear antibody; HAQ-DI, Health Assessment Questionnaire–Disability Index; ILD, interstitial lung disease; %pDLco, percent predicted diffusing capacity for carbon monoxide; RNA, ribonucleic acid; SD, standard deviation; VAS, visual analog scale.
All data are mean (SD) unless stated otherwise.

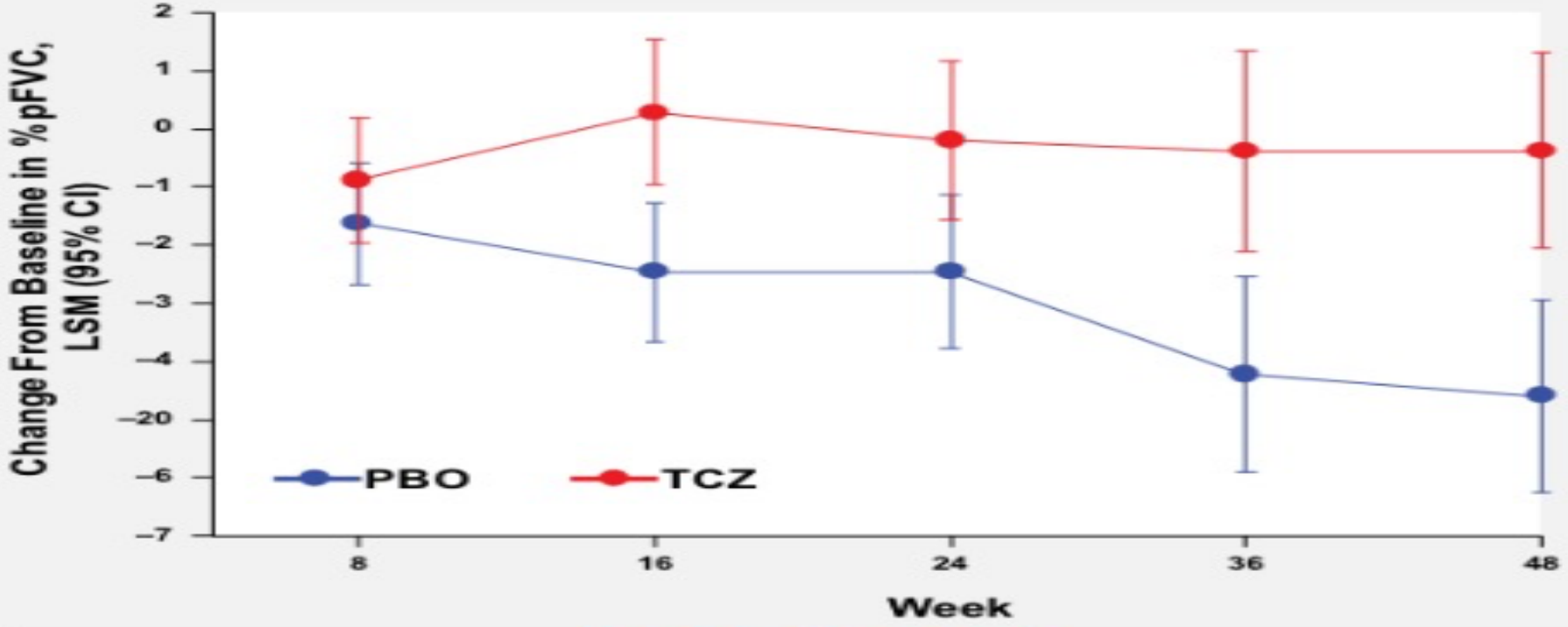
Khanna D ACR 2018 ***abstract*** *898*

TCZ et SSc : résultats d'un essai randomisé, de phase 3



Khanna D ACR 2018 ***abstract*** *898*

TCZ et SSc : résultats d'un essai randomisé, de phase 3

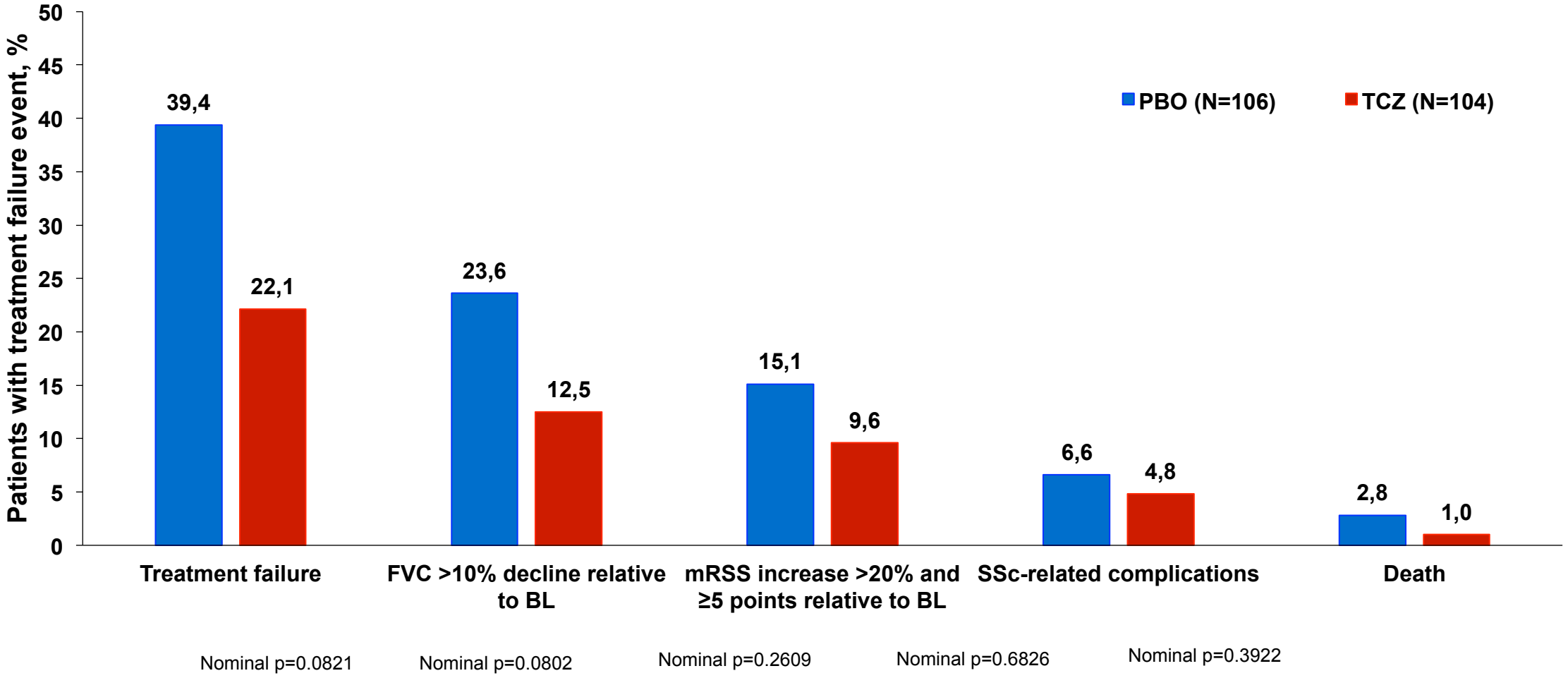


% pFVC	PBO n=106	TCZ n=104	Difference (95% CI); nominal *p* value
LSM change from BL at week 48	-4.6	-0.4	4.2 (2.0, 6.4); $p = 0.0002$
Absolute change in FVC, mL	-190	-24	167 (83, 250); $p = 0.0001$

Khanna D ACR 2018 ***abstract*** *898*

TCZ et SSc : résultats d'un essai randomisé, de phase 3

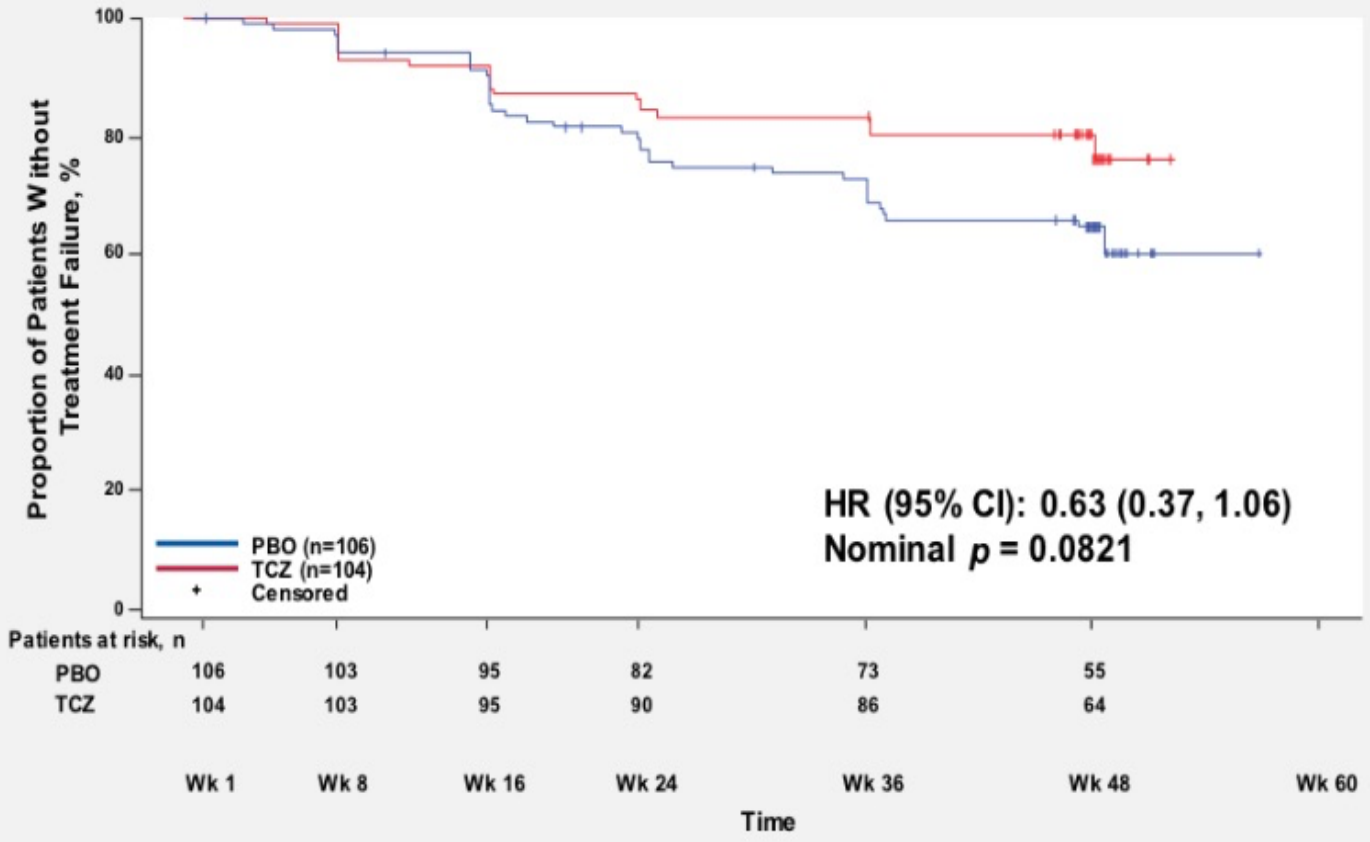
Secondary endpoint



Khanna D ACR 2018 ***abstract*** *898*

TCZ et SSc : résultats d'un essai randomisé, de phase 3

Secondary endpoint



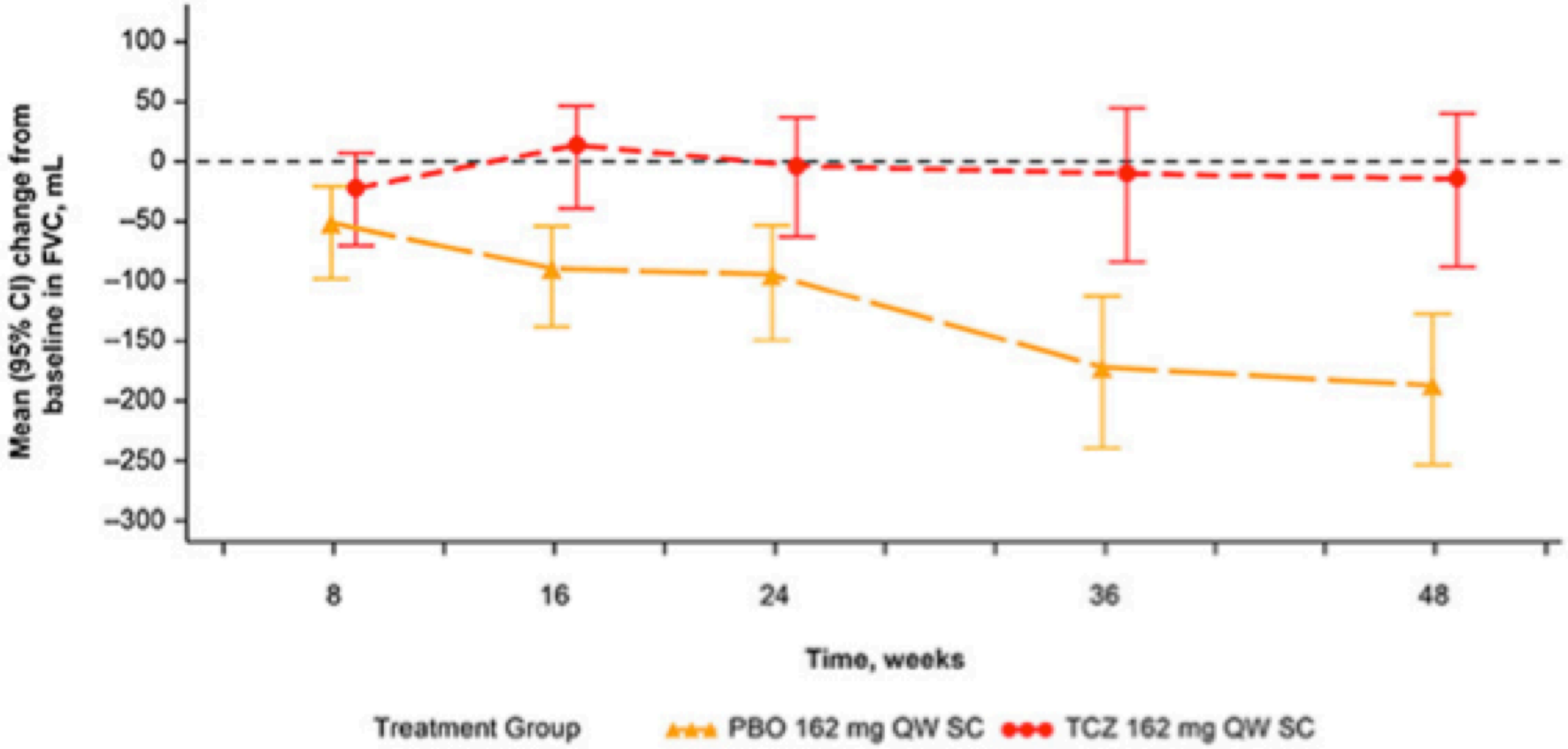
Time to treatment failure was defined as the time from the first dose of study drug to the time of first

- Death
- Decline in %pFVC >10% relative to baseline
- Increase in mRSS >20% and increase in mRSS ≥5 points relative to baseline
- Occurrence of an SSc-related complication as adjudicated by the Clinical Adjudication Committee

Khanna D ACR 2018 ***abstract*** *898*

TCZ et SSc-PID : étude de sous-groupe de la phase 3

Secondary endpoint



Sur les 106 patients placebo et 104 TCZ, 31 % avaient une PID

D. Khanna et al. Abs OP0245. EULAR 2019

TCZ et SSc : résultats d'un essai randomisé, de phase 3

Safety overview

	PBO (N=106)	TCZ (N=104)
Patients with ≥AE	82 (77.4)	89 (85.6)
Patients with ≥SAE Total SAEs, n	18 (17.0) 30	13 (12.5) 14
Patients with ≥infection and infestation AE	53 (50.0)	54 (51.9)
Patients with at ≥infection and infestation SAE	7 (6.6)	2 (1.9)
Patients who withdrew treatment because of an AE	11 (10.4)	6 (5.8)
Deaths	3 (2.8)	1 (1.0)

Khanna D ACR 2018 ***abstract*** *898*

Place du TCZ dans le traitement de fond de la PID

- Le tocilizumab : Il n'y a pas actuellement d'étude réalisée chez des malades avec PID établie. L'utilisation du tocilizumab dans cette indication ne peut être envisagée qu'après validation en RCP **(utilisation hors AMM)**.

PNDS SSc 2017 mise à jour 2019

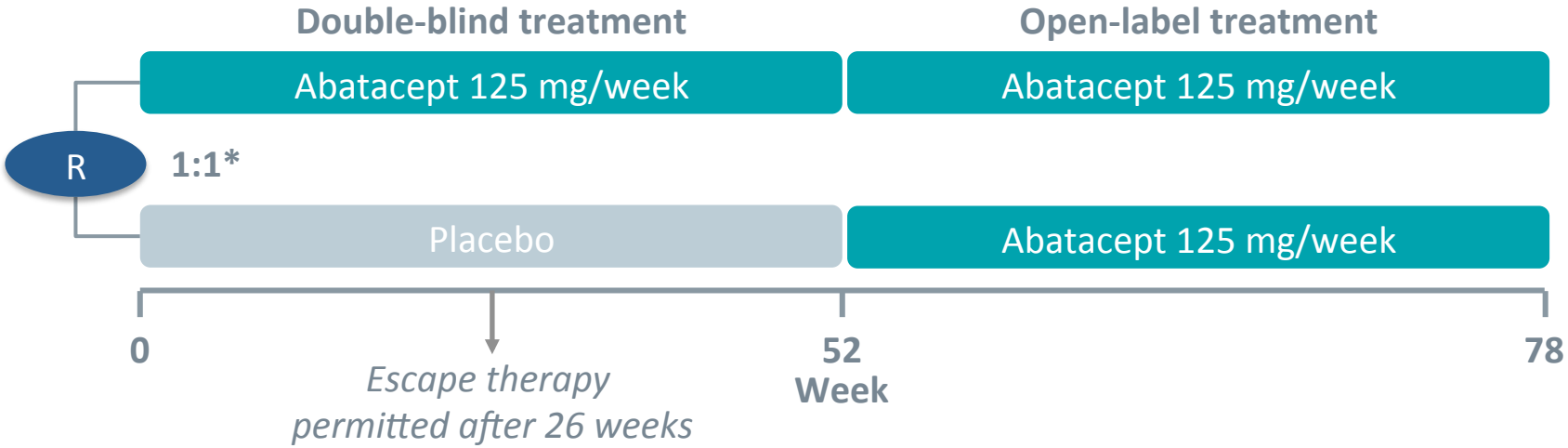
Abatacept et SSc : résultats d'un essai randomisé, de phase 2

ASSET

Phase II, investigator-initiated, randomised placebo-controlled trial of abatacept in patients with early dcSSc, followed by open-label treatment

Key inclusion criteria:

- dcSSc for ≤36 months
- mRSS ≥10 and ≤35 units for patients with disease duration ≤18 months
- mRSS ≥15 and ≤45 units with evidence of active disease for patients with disease duration >18 months
- No background immunomodulatory therapy



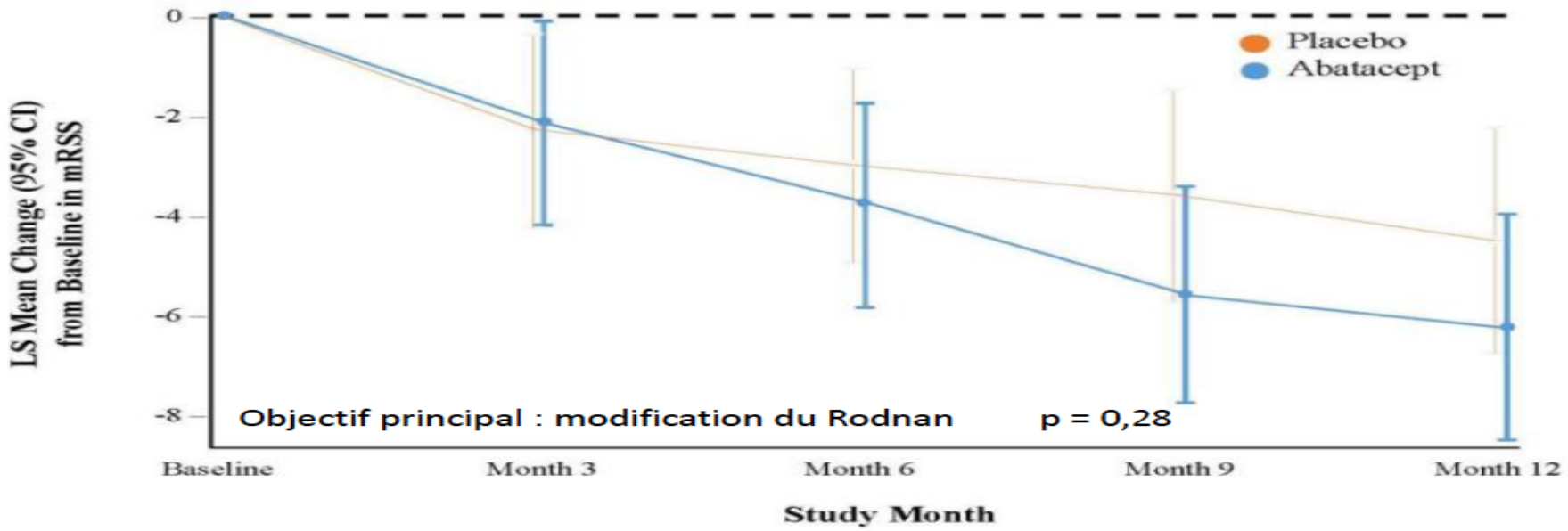
Primary endpoint:

- Change from baseline in mRSS at week 52

Abatacept et SSc : résultats d'un essai randomisé, de phase 2

ASSET

primary outcome: mRSS at week 52



	Placebo (N=44)	Abatacept (N=44)	Difference
LS mean (SE)	-4.49 (1.14)	-6.24 (1.14)	-1.75 (1.61)
95% CI	-6.75, -2.23	-8.50, -3.98	-4.93, 1.43
p-value			0.28

Khanna D. abstract 900 ACR 2018

Abatacept et SSc : résultats d'un essai randomisé, de phase 2

ASSET

secondary endpoints at week 52

	Placebo (N=44)	Abatacept (N=44)	Difference vs. placebo	p-value
Patient global assessment, LS mean (SE)	-0.09 (0.46)	-0.31 (0.42)	-0.22	0.73
Physician global assessment, LS mean (SE)	-0.35 (0.32)	-1.30 (0.29)	-0.95	0.03
FVC % predicted, LS mean (SE)	-4.13 (1.2)	-1.34 (1.2)	2.79	0.11
HAQ-DI, LS mean (SE)	0.11 (0.07)	-0.17 (0.07)	-0.28	0.005
CRISS, median (IQR)	0.01 (0.86)	0.68 (1.00)		0.003

Khanna D. abstract 900 ACR 2018

Box 2 Combined Response Index for Systemic Sclerosis (CRISS)

Step 1

Subjects who develop new or worsening cardiopulmonary and/or renal involvement due to SSc are considered as NOT IMPROVED (irrespective of improvement in other core items). Specific definitions include:

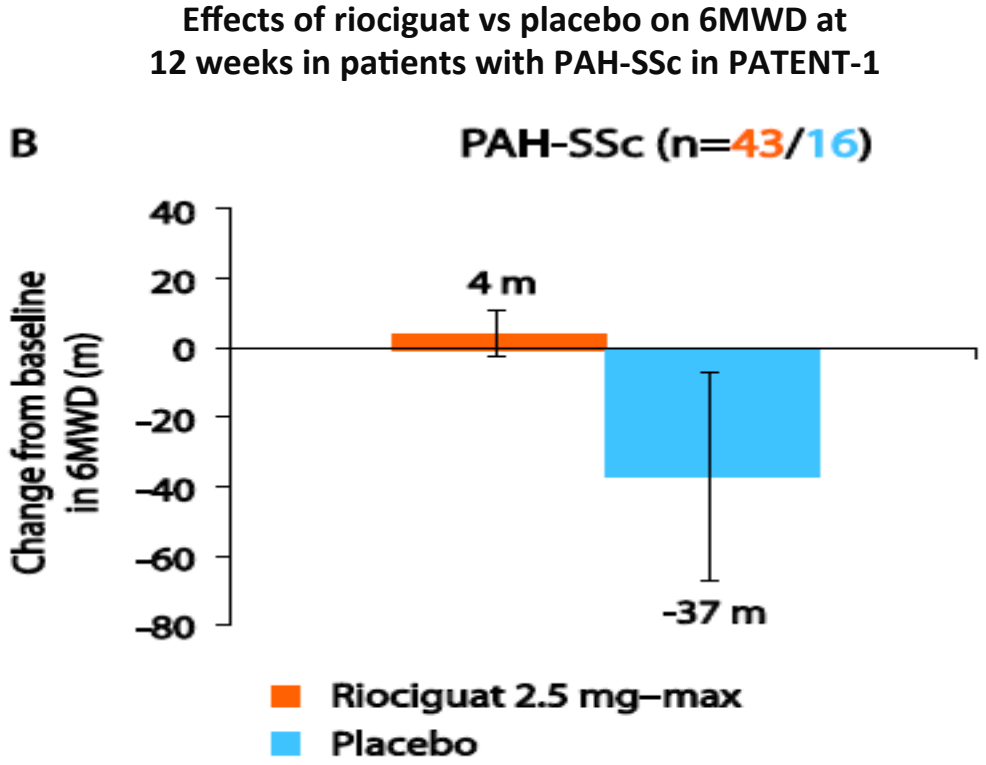
- New scleroderma renal crisis.
- Decline in FVC% predicted > (relative) confirmed by another FVC test within a month. HRCT to confirm ILD (if previous HRCT of chest did not show ILD) and FVC <80% of predicted.
- New onset of left ventricular failure (defined as left ventricular ejection fraction <45%) requiring treatment.
- New onset of PAH on right heart catheterisation requiring treatment.

Step 2

- Change in modified Rodnan Skin Score.
- Change in FVC.
- Change in HAQ-DI.
- Change in Patient Global Assessment.
- Change in Physician Global Assessment.

Riociguat

- Riociguat a sGC stimulator: vasoactive, anti-inflammatory, antiproliferative, and antifibrotic effects in vivo and in vitro



Riociguat et SSc : résultats d'un essai randomisé, de phase 2

RISE

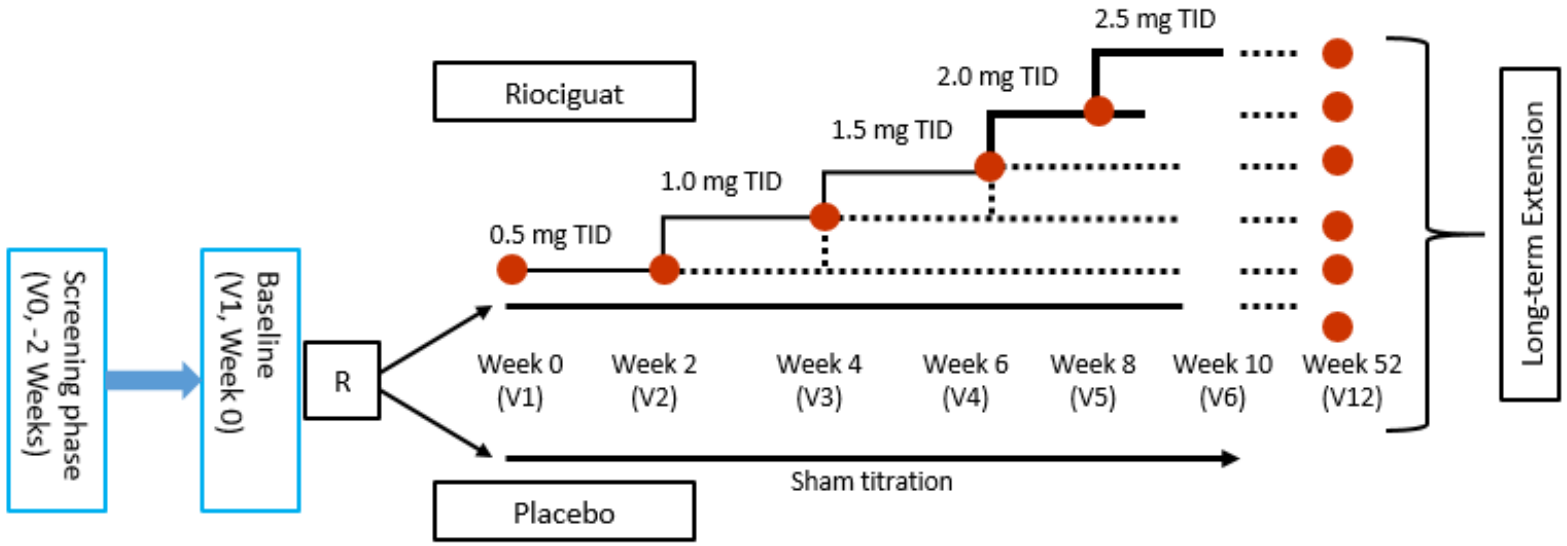
primary outcome: mRSS at week 52

Inclusion criteria were:

- Diagnosis of SSc by ACR/EULAR criteria
- Diffuse cutaneous involvement
- Disease duration ≤18 months

mRSS ≥10 and ≤22 units

Main treatment phase design



Abbreviations: V = visit; R = randomization; TID = 3 times a day.

Study design was based on data from the EUSTAR cohort

Riociguat et SSc : résultats d'un essai randomisé, de phase 2

RISE

primary outcome: mRSS at week 52

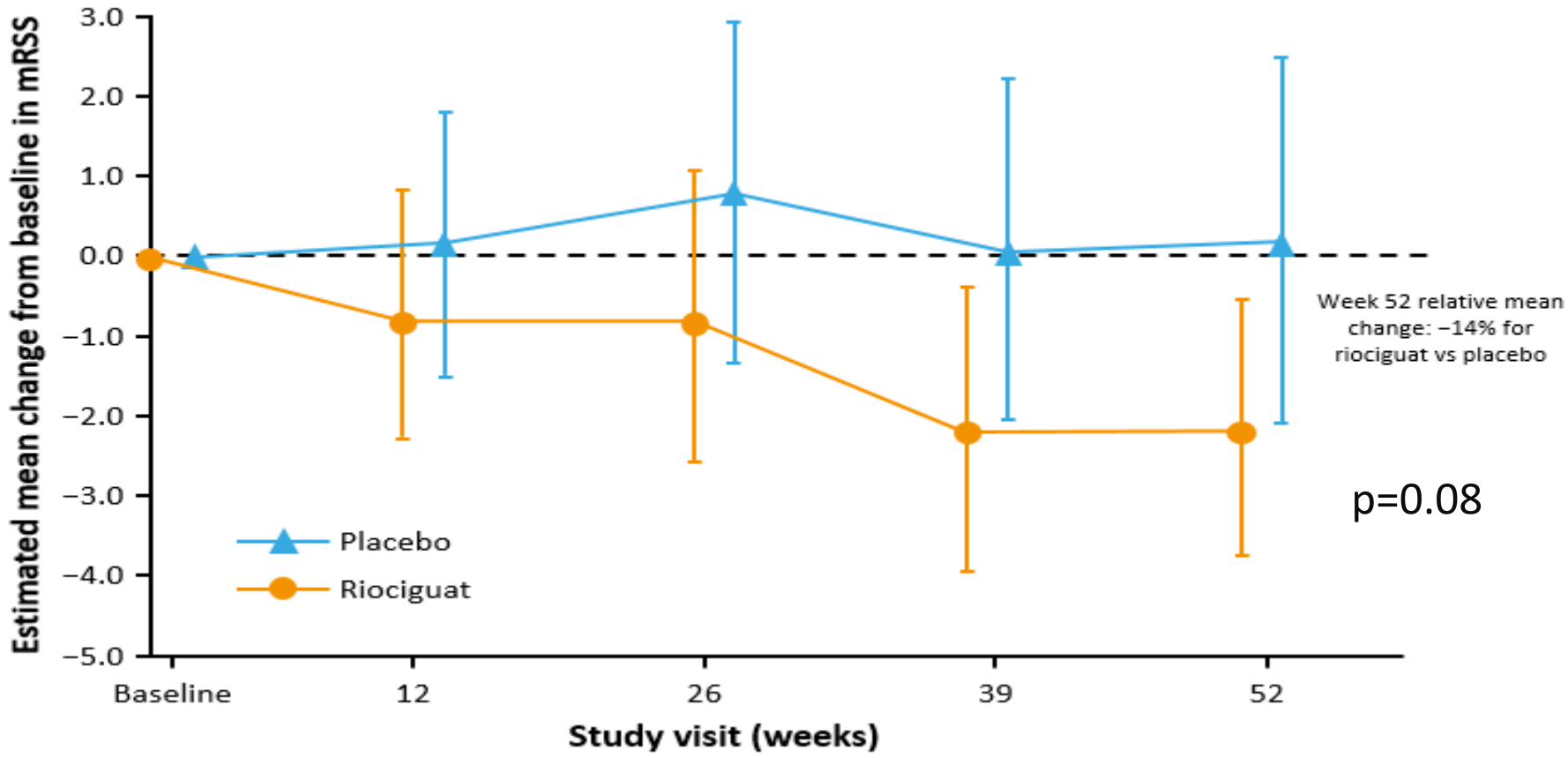
Baseline characteristics

	Riociguat (n=60)	Placebo (n=61)
Age, years	52 (11.5)	50 (12.9)
Female, n (%)	47 (78)	45 (74)
Disease duration, months	9.5 (7.0)	8.6 (5.8)
mRSS	17 (3.4)	17 (4.1)
Percent predicted FVC	91 (19)	95 (17)
Percent predicted DL_{CO} (Hb corr)	76 (20)	77 (17)
Digital ulcer count ≥1, n (%)	9 (15)	6 (10)
Digital ulcer count	0.3 (0.7)	0.4 (1.4)
Digital ulcer count in patients with ulcers	1.7 (1.0)	3.7 (3.2)
Anti-RNA polymerase III positive, n (%)	10 (17)	16 (26)
Anti-Scl-70 (anti-topoisomerase 1) positive, n (%)	26 (43)	23 (38)

Riociguat et SSc : résultats d'un essai randomisé, de phase 2

RISE

primary outcome: mRSS at week 52

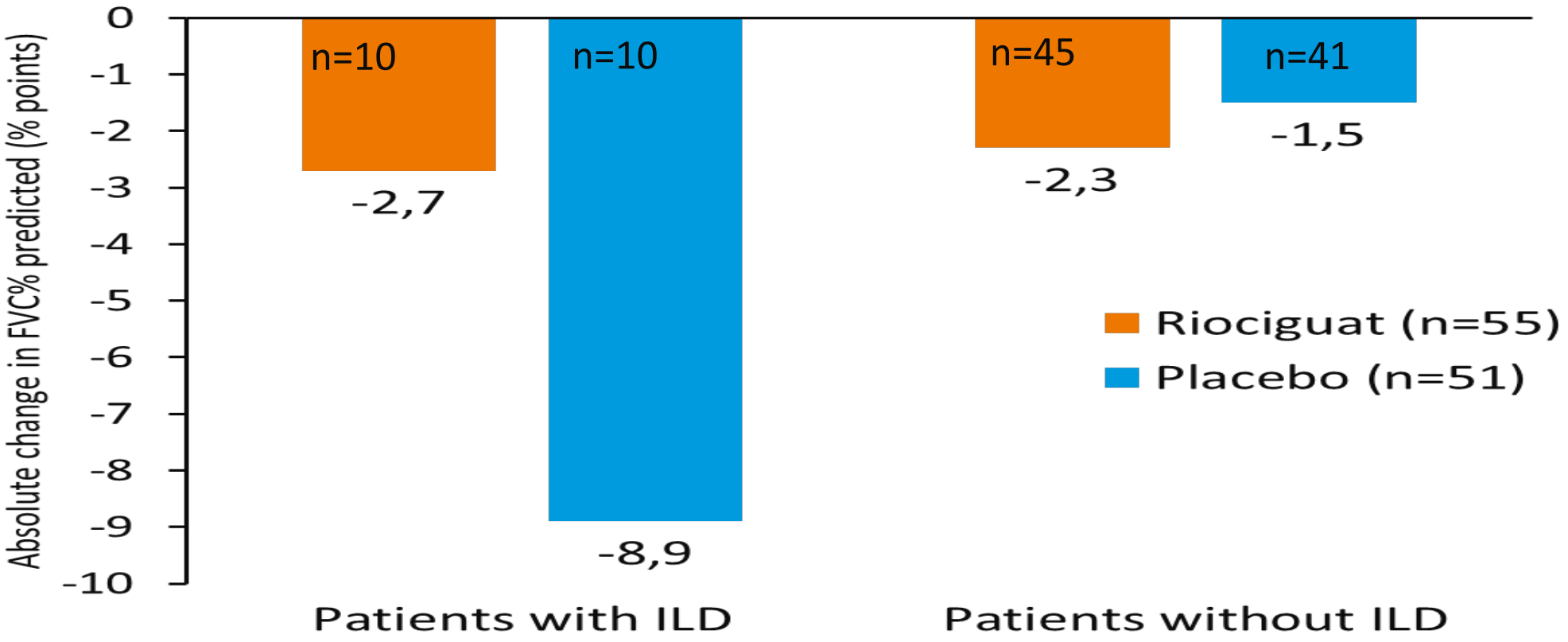


Riociguat et SSc : résultats d'un essai randomisé, de phase 2

RISE

Secondary outcomes

Changes in FVC% predicted in patients with vs without ILD at Week 52



Riociguat et SSc : résultats d'un essai randomisé, de phase 2

RISE

Secondary outcomes

Endpoint	Mantel-Haenszel estimate of difference (95% CI)	Nominal p-value
CRISS (improver rate)	0.20% (–13.68 to 14.09)	0.977
HAQ-DI	–0.07 (–0.23 to 0.08)	0.353
Patient's Global Assessment	0.79 (–0.12 to 1.69)	0.089*
Physician's Global Assessment	**0.83 (0.11 to 1.54)**	**0.024†**
Percent predicted FVC	–0.20 (–3.40 to 3.00)	0.901

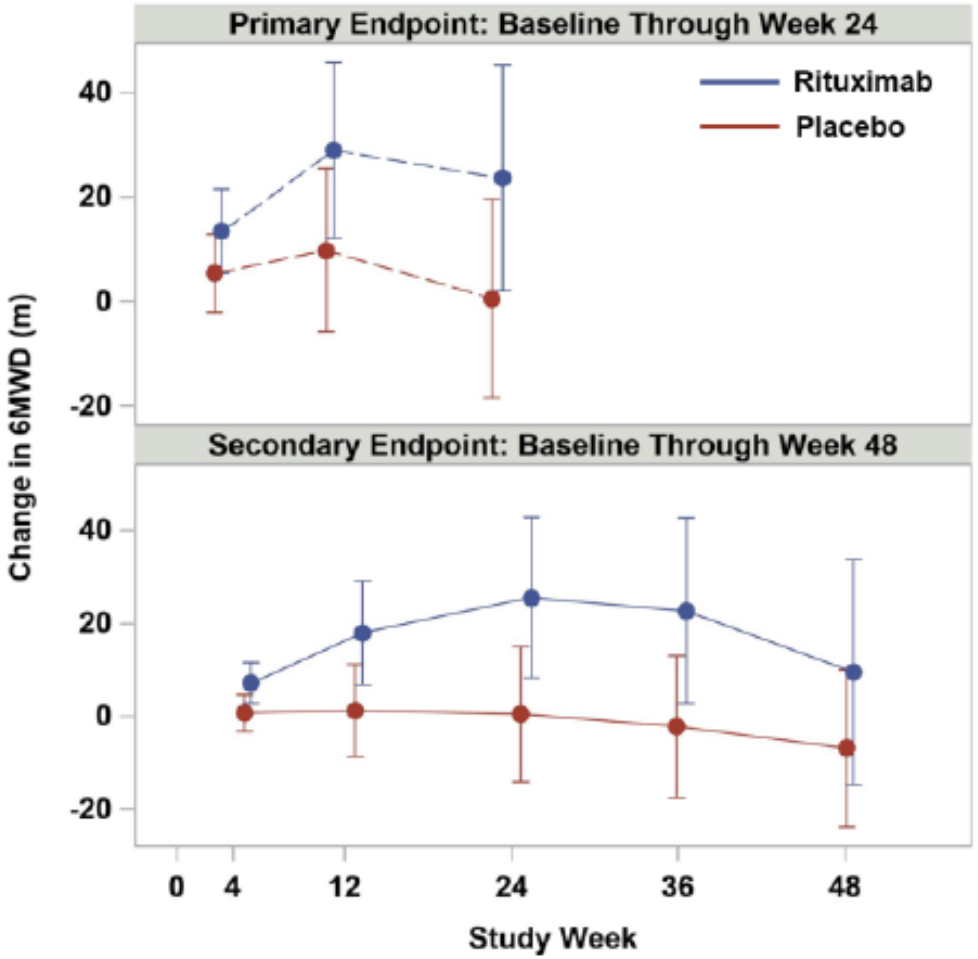
Riociguat et SSc : résultats d'un essai randomisé, de phase 2

RISE

Safety

Event, n (%)	Riociguat (n=60)	Placebo (n=61)
Any AE	58 (97)	55 (90)
Any study drug-related AE	40 (67)	29 (48)
Any AE related to procedures required by the protocol	4 (7)	2 (3)
Any serious AE	**9 (15)**	**15 (25)**
Any study drug-related serious AE	**0**	**2 (3)**
Discontinuation of study drug due to AE	11 (18)	11 (18)
Discontinuation of study drug due to serious AE	**2 (3)**	**7 (11)**
Deaths	**1 (2)**	**1 (2)**

RTX et SSc-PAH : résultats d'un essai de phase 2



	Rituximab (n=27)	Placebo (n=27)	p-value
Primary Endpoint			
Change in 6MWD (m) at:			
Week 24	23.6 (11.05)	0.5 (9.71)	0.12
Secondary Endpoints			
Change 6MWD (m) at:			
Week 24	25.5 (8.79)	0.4 (7.43)	0.03
Week 48	9.5 (12.35)	-7.0 (8.63)	0.28

All data represent Least Squares Mean and SEM

Change in 6MWD from baseline in the modified Intent-to-Treat cohort. A repeated measures random effect model was fit to distance walked as a function of treatment, visit week, a treatment by visit week interaction, and a quadratic term for visit. Dashed lines represent the primary endpoint model using all data to Week 24. Solid lines represent secondary analysis including all data out to Week 48. Whiskers represent 95% confidence interval

Zamanian R. ACR 2019

HHS Public Access

Author manuscript

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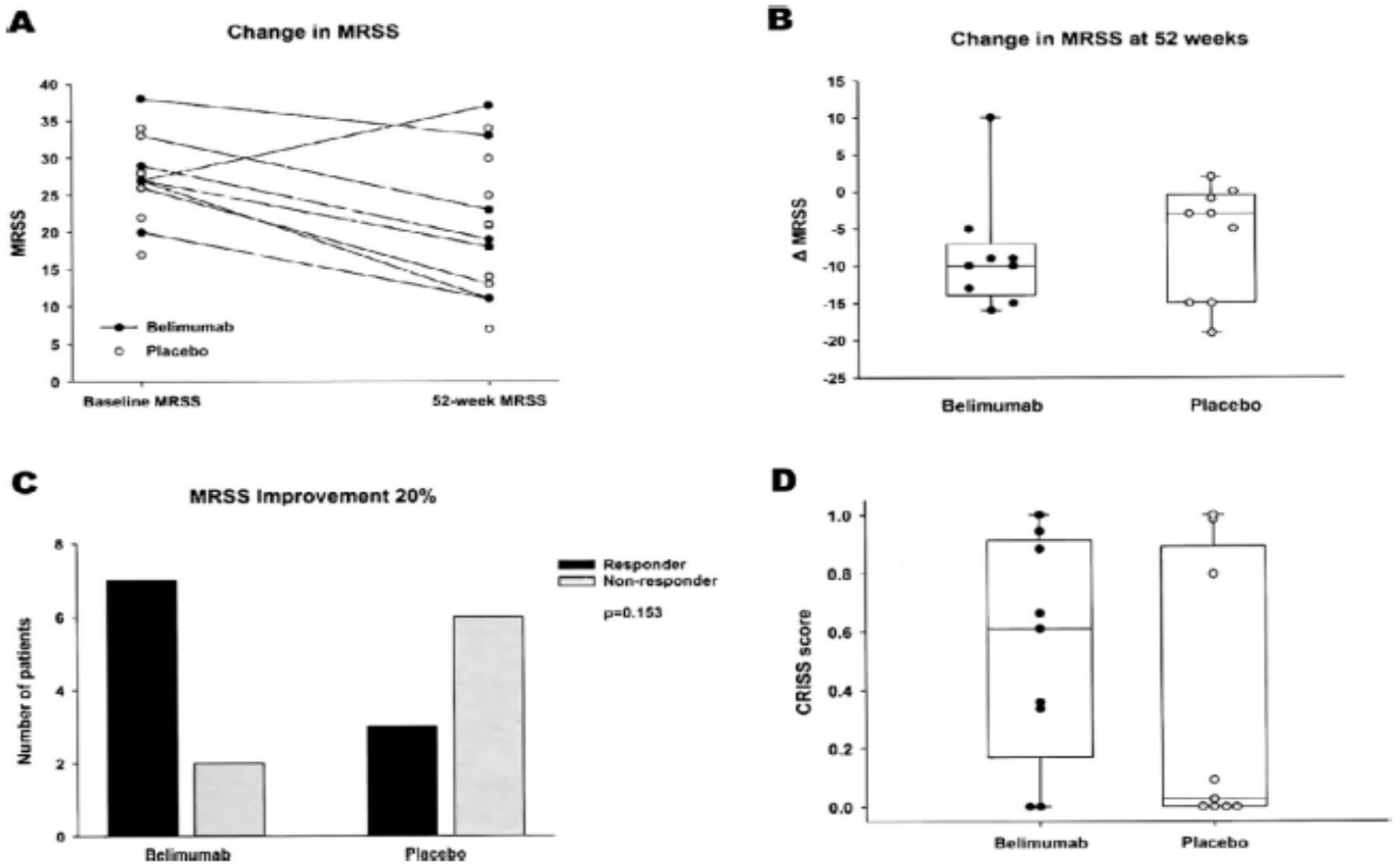
Belimumab for the Treatment of Early Diffuse Systemic Sclerosis:

Results of a Randomized, Double-Blind, Placebo-Controlled, Pilot Trial

Jessica K. Gordon[1], **Viktor Martyanov**[2], **Jennifer M. Franks**[2], **Elana J. Bernstein**[3], **Jackie Szymonifka**[3], **Cynthia Magro**[4], **Horatio F. Wildman**[4], **Tammara A. Wood**[2], **Michael L. Whitfield**[2], and **Robert F. Spiera**[1]

Bélimumab et SSc : résultats d'un essai de phase 2



Pan-PPAR agonist (IVA 337) et SSc : résultats d'un essai de phase 2

The FASST trial

Primary endpoint

Inventiva press release 18-Feb-2019:

	800mg lanifibranor	1200mg lanifibranor	Placebo
Number of patients	49	48	48
Mean baseline mRSS (SD[1])	18.2 (3.8)	17.8 (3.9)	17.1 (-3.7)
Mean absolute change of mRSS from baseline to week 48 (SD[3])	-3.7 (4.2)	-4.3 (5.0)	-4.9 (4.6)

Pan-PPAR agonist (IVA 337) et SSc : résultats d'un essai de phase 2

The FASST trial

Primary endpoint

Inventiva press release 18-Feb-2019:

	800mg lanifibranor	1200mg lanifibranor	Placebo
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Mean absolute change of mRSS from baseline to week 48 (SD[3])	-3.7 (4.2)	-4.3 (5.0)	-4.9 (4.6)

- STOP

ARTHRITIS & RHEUMATOLOGY
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DOI 10.1002/art.40547
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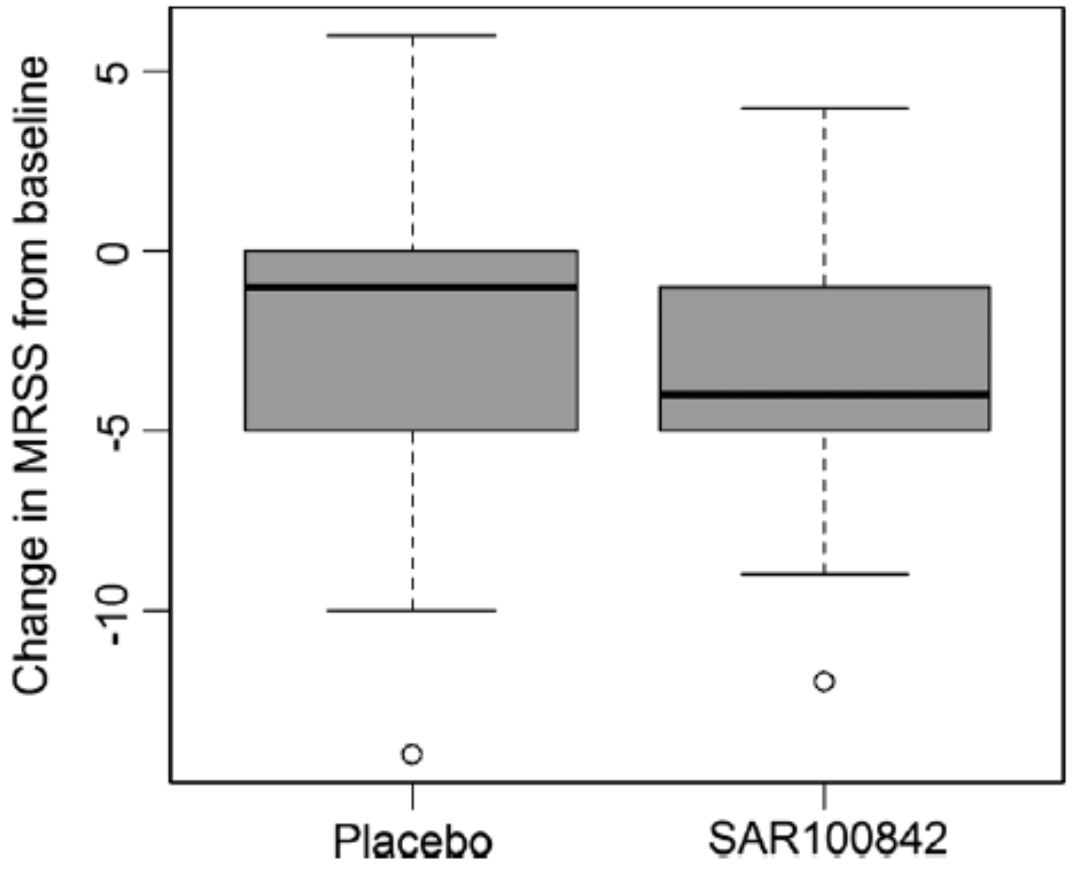
Lysophosphatidic Acid Receptor 1 Antagonist SAR100842 for Patients With Diffuse Cutaneous Systemic Sclerosis

A Double-Blind, Randomized, Eight-Week Placebo-Controlled Study Followed by a Sixteen-Week Open-Label Extension Study

Yannick Allanore,[1] Oliver Distler,[2] Alexandre Jagerschmidt,[3] Stephane Illiano,[3] Laetitia Ledein,[3] Eric Boitier,[4] Inoncent Agueusop,[5] Christopher P. Denton,[6] and Dinesh Khanna[7]

LPA1 Récepteur antagoniste et SSc : résultats d'un essai de phase 2

SAR100842 is a potent selective LPA1 receptor antagonist. In vivo, SAR100842 reversed dermal thickening and significantly inhibited myofibroblast differentiation and reduced collagen content in a mouse model of skin fibrosis



***Results*. Seventeen of 32 patients were randomly assigned to receive placebo and 15 to receive SAR100842;**

ARTHRITIS & RHEUMATOLOGY
Vol. 69, No. 12, December 2017, pp 2370–2379
DOI 10.1002/art.40242
© 2017, The Authors. *Arthritis & Rheumatology* published by Wiley Periodicals, Inc. on behalf of American College of Rheumatology
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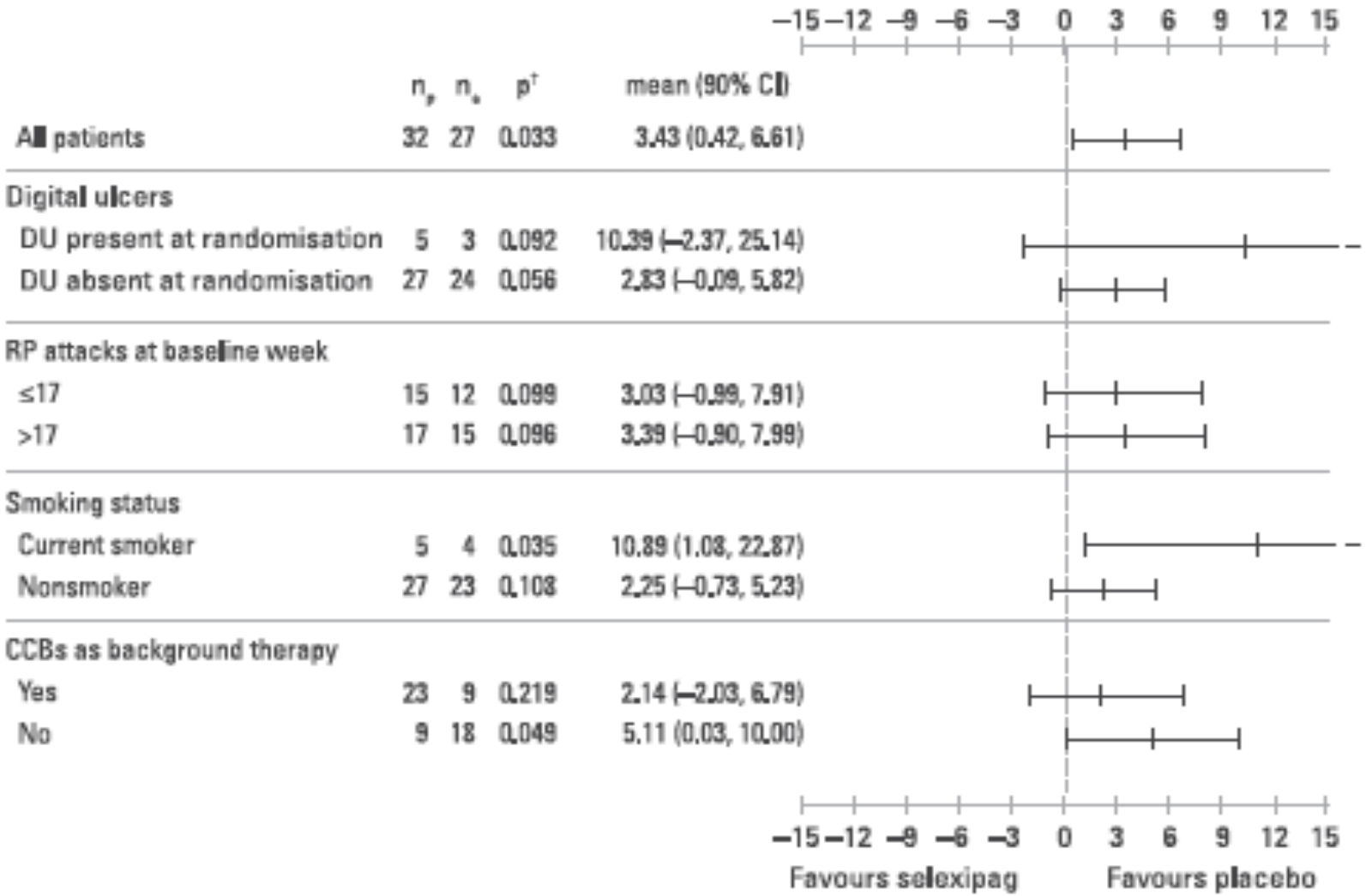
Efficacy and Safety of Selexipag in Adults With Raynaud's Phenomenon Secondary to Systemic Sclerosis

A Randomized, Placebo-Controlled, Phase II Study

Christopher P. Denton,[1] Éric Hachulla,[2] Gabriela Riemekasten,[3] Andreas Schwarting,[4] Jean-Marie Frenoux,[5] Aline Frey,[5] Franck-Olivier Le Brun,[5] and Ariane L. Herrick,[6] on behalf of the Raynaud Study Investigators

Selexipag et SSc : résultats d'un essai de phase 2



Pomalidomide in Patients with Interstitial Lung Disease due to Systemic Sclerosis: A Phase II, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study

Vivien M. Hsu, Christopher P. Denton, Robyn T. Domsic, Daniel E. Furst, Maureen Rischmueller, Marina Stanislav, Virginia D. Steen, Jörg H.W. Distler, Shimon Korish, Alyse Cooper, Suktae Choi, Peter H. Schafer, Gerald Horan and Douglas R. Hough

The Journal of Rheumatology March 2018, 45 (3) 405-410; DOI: https://doi.org/10.3899/jrheum.161040

for SSc (18) and had dcSSc (19). Patients were included if they were age >18 years, had disease duration of <3 years since the first SSc-related symptom other than Raynaud's phenomenon (RP), and had a baseline MRSS of ≥16. Patients were excluded if their

Results. Mean change at Week 52 from baseline in predicted FVC% −5.2 and −2.8; mRSS −2.7 and −3.7; and UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract (SCTC GIT 2.0) score 0.1 and 0.0, with POM and PBO, respectively. Statistical significance was not achieved for any of these 3 primary endpoints at 52 weeks.

HHS Public Access

Author manuscript

Arthritis Rheumatol. Author manuscript; available in PMC 2018 August 01.

Published in final edited form as:

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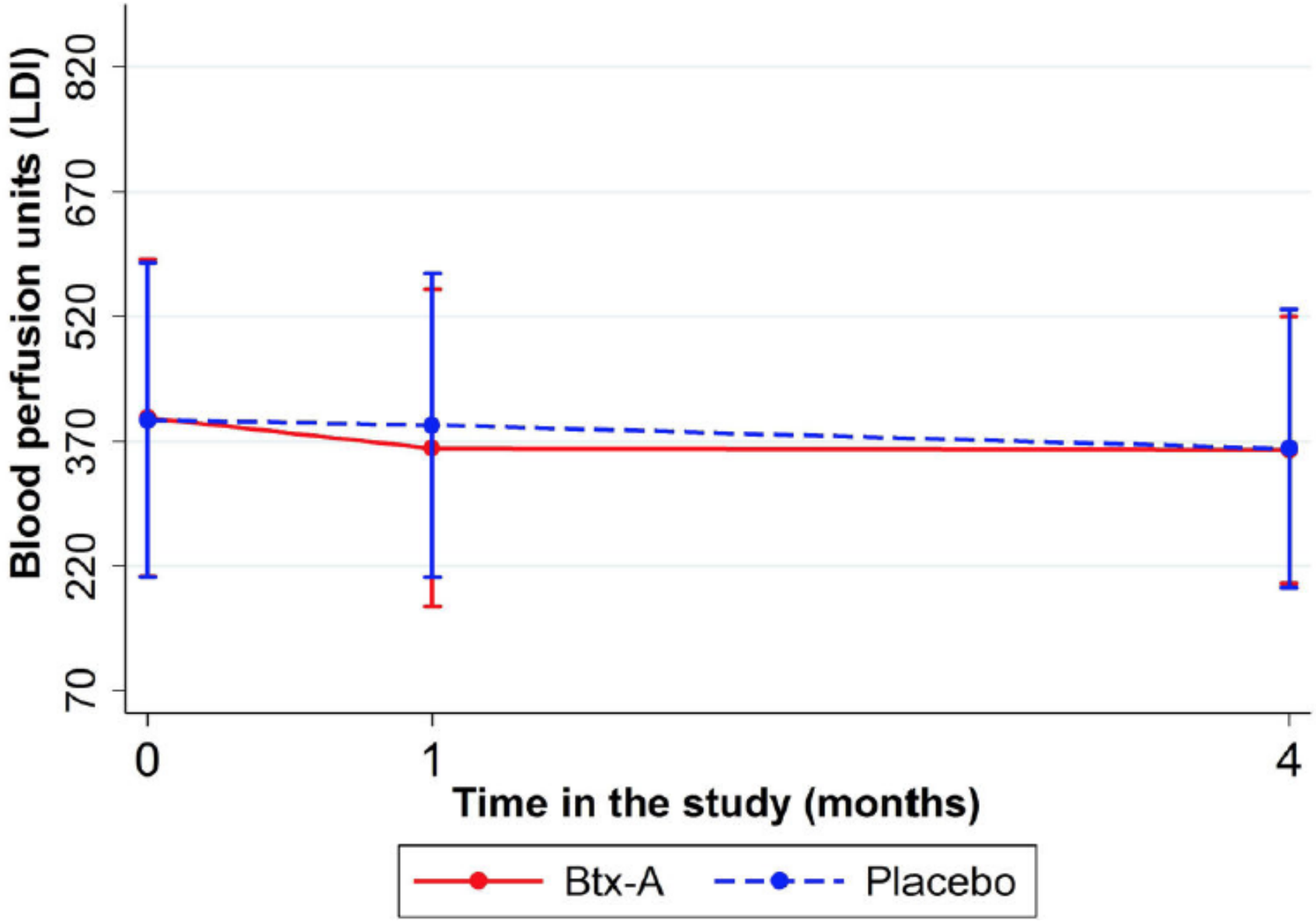
The Therapeutic Efficacy of Botulinum Toxin in Treating Scleroderma-Associated Raynaud's Phenomenon:

A Randomized, Double-Blind, Placebo-Controlled Clinical Trial Assessing

Ricardo J. Bello, MD, MPH[1], Carisa M. Cooney, MPH[1], Eitan Melamed, MD[1], Keith Follmar, MD[1], Gayane Yenokyan, MD, MPH, PhD[2], Gwendolyn Leatherman, RN, MS[3], Ami A. Shah, MD, MHS[3], Fredrick M. Wigley, MD[3], Laura K. Hummers, MD, ScM[3,*], and Scott D. Lifchez, MD[1,*]


Blood perfusion units (LDI)
820
670
520
370
220
70
0
1
4
Time in the study (months)
Btx-A
Placebo

Quel critère principal: CVF, CRISS?

Box 2 Combined Response Index for Systemic Sclerosis (CRISS)

Step 1

Subjects who develop new or worsening cardiopulmonary and/or renal involvement due to SSc are considered as NOT IMPROVED (irrespective of improvement in other core items). Specific definitions include:

- New scleroderma renal crisis.
- Decline in FVC% predicted > (relative) confirmed by another FVC test within a month. HRCT to confirm ILD (if previous HRCT of chest did not show ILD) and FVC <80% of predicted.
- New onset of left ventricular failure (defined as left ventricular ejection fraction <45%) requiring treatment.
- New onset of PAH on right heart catheterisation requiring treatment.

Step 2

- Change in modified Rodnan Skin Score.
- Change in FVC.
- Change in HAQ-DI.
- Change in Patient Global Assessment.
- Change in Physician Global Assessment.

Quel critère principal?

Time to treatment failure was defined as the time from the first dose of study drug to the time of first

- Death
- Decline in %pFVC >10% relative to baseline
- Increase in mRSS >20% and increase in mRSS ≥5 points relative to baseline
- Occurrence of an SSc-related complication as adjudicated by the Clinical Adjudication Committee

Traitement de la SSc: de nombreux candidats

Candidate therapy	Target pathway	
• Macitentan	ET_A/ET_B receptor	Vascular
• Zibotentan	ET_A receptor	
• Selexipag	IP receptor agonist	
• Riociguat	Guanylate cyclase agonist	
• Rituximab	CD20	Inflammatory
• Basiliximab	IL-2Ra	
• Tocilizumab	IL-6R	
• Abatacept	CTLA4	
• Rilanocept	IL-1 ligand	
• Pomalidomide	anti-inflammatory	
• Hyperimmune caprine serum	anti-inflammatory	
• Dasatinib, Nilotinib	c-Abl, c-Kit, PDGF	Fibrotic
• GC-1008	TGF-β1, -β2, -β3	
• FG-3019	CTGF ligand	
• P144	TGF-β ligand (topical)	
• BIBF1120	VEGF, bFGF, PDGF	
• Anti-integrin antibodies	Blocking α_v integrin activation of TGF-β	
• LPA1 antagonists	Inhibit myofibroblast differentiation	
• Cannabinoid receptor blockade	Attenuate CB2 mediated fibrosis	
• Terguride	Serotonin (5HT) receptor inhibition	
• Riociguat	Guanylate cyclase agonist	

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