ORIGINAL ARTICLE

A Phase 3 Trial of Brepocitinib in Dermatomyositis

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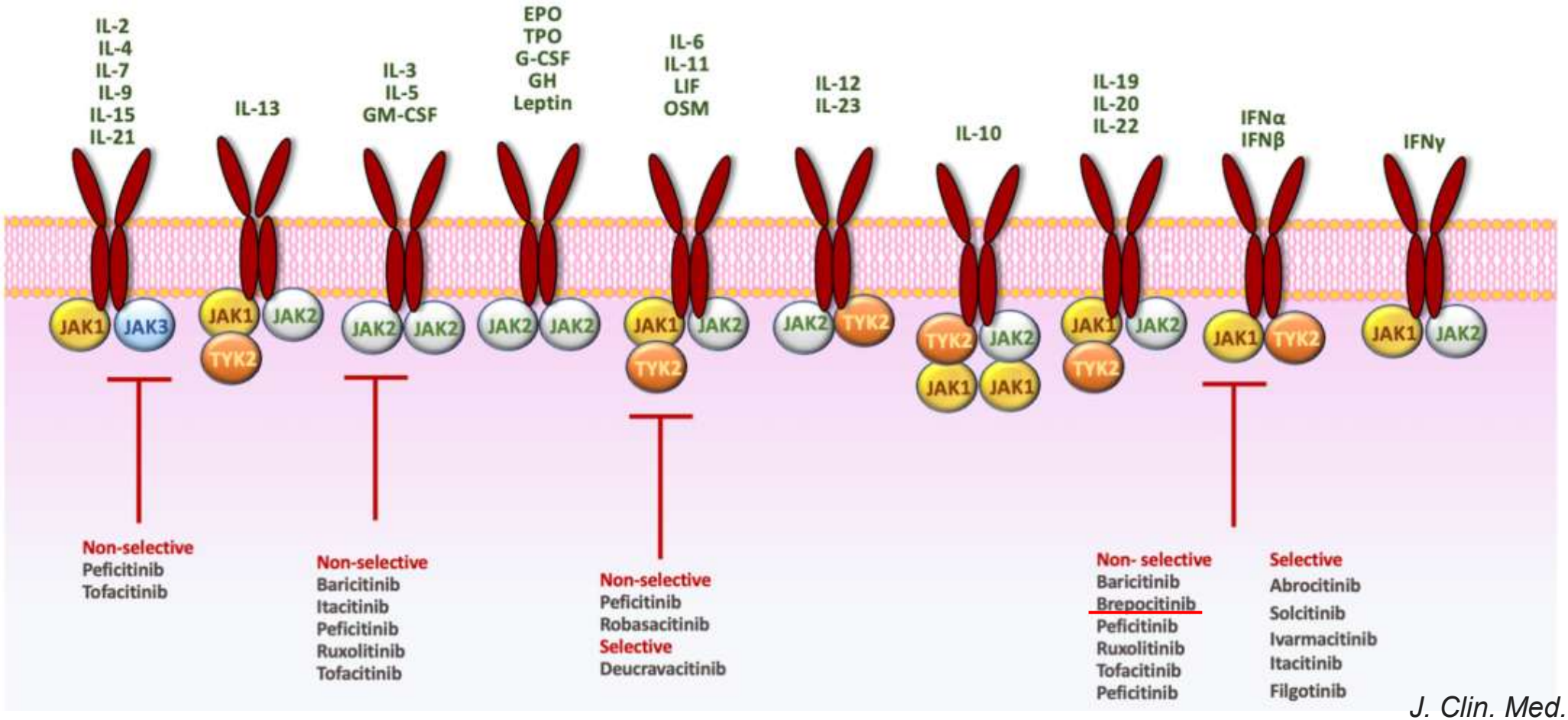
VALOR（勇気という意味）trial

Brepocitinibとは
TYK2/JAK1 inhibitor

皮膚筋炎に関連するサイトカインとして
Type I, II IFN
IL-6, 12, 23
があがっており、本治験のrational



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近年行われているIIM治験とそのEndpoint

Drug	Target	Phase	Disease	Primary Endpoint
Belimumab	BlyS	2/3	IIM	DOI & TIS at w40
GLPG-3667	Tyk2	2	DM	TIS at w24
Efgartigimod	FcRn	2/3	DM/PM/IMNM	TIS at w24, w52
Anifrolumab	INFa/b	3	IIM	TIS>40 at w52
Dazukibart	IFNb	3	IIM	TIS>40 at w24, w52
Nipocalimab	FcRn	2	IIM	TIS>20 at w52
Enpatoran	TLR-7/8	2a	PM/DM	TIS at wk24

TIS（Total Improvement Score）とは

○以下の6項目の合計で計算される*(ネットに計算機あり)

・中核指標：**MMT-8**(0-150点)

・Visual Analogue Scale(0-10点)：

Physician(PhGA)/Patient's global assessment(PtGA) of disease activity

Extra-muscular disease activity

・その他：HAQ(8項目各3点)、筋原性酵素(CK/AST/ALT/LDH/aldolase)

* **IMACS calculator** (https://www.niehs.nih.gov/research/resources/imacs/response_criteria/pediatric.html)

**頸部屈筋、三角筋、上腕二頭筋、手首伸筋、大殿筋、中殿筋、大腿四頭筋、足関節背屈筋

○TISの得点の評価

・0-100点で、数字が大きいほど改善。

・TIS≧20点を改善と取る(minimal improvement)。

・TIS≧40点 (moderate), TIS≧60点 (Major)。

Core Set Measure*	Level of Improvement Based on absolute percentage change	Improvement Score
Physician Global Activity	Worsening to 5% improvement	0
	>5% to 15% improvement	7.5
	>15% to 25% improvement	15
	>25% to 40% improvement	17.5
	>40% improvement	20
Patient or Parent Global Activity	Worsening to 5% improvement	0
	>5% to 15% improvement	2.5
	>15% to 25% improvement	5
	>25% to 40% improvement	7.5
	>40% improvement	10
Manual Muscle Testing or Childhood Myositis Assessment Scale	Worsening to 2% improvement	0
	>2% to 10% improvement	10
	>10% to 20% improvement	20
	>20% to 30% improvement	27.5
	>30% improvement	32.5
(Childhood) Health Assessment Questionnaire	Worsening to 5% improvement	0
	>5% to 15% improvement	5
	>15% to 25% improvement	7.5
	>25% to 40% improvement	7.5
	>40% improvement	10
Enzyme (most abnormal) or CHQ-PhS	Worsening to 5% improvement	0
	>5% to 15% improvement	2.5
	>15% to 25% improvement	5
	>25% to 40% improvement	7.5
	>40% improvement	7.5
Extramuscular Activity or Disease Activity Score	Worsening to 5% improvement	0
	>5% to 15% improvement	7.5
	>15% to 25% improvement	12.5
	>25% to 40% improvement	15
	>40% improvement	20

これを足すとmax100になる

Aggarwal R. Arthritis Rheumatol. 2017;69:898-910.
Ride G L. Arthritis Care Res. 2010;62:465-72.

2025.2.25田口先生のJC資料より拝借(少し改変)

CDASI(前半)

Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) *ver02*

Select the score in each anatomical location that describes the most severely affected dermatomyositis -associated skin lesion

Extent

	activity			damage		
Anatomical Location	Erythema	Scale	Erosion/ Ulceration	Poikiloderma (Dyspigmentation or Telangiectasia)	Calcinosis	Anatomical Location
	0-absent 1-pink; faint erythema 2-red 3-dark red	0-absent 1-scale 2-crust; lichenification	0-absent 1-present	0-absent 1-present	0-absent 1-present	
Scalp						Scalp
Malar Area						Malar Area
Periorbital						Periorbital
Rest of the face						Rest of the face
V-area neck (frontal)						V-area neck (frontal)
Posterior Neck						Posterior Neck
Upper Back & Shoulders						Upper Back & Shoulders
Rest of Back & Buttocks						Rest of Back & Buttocks
Abdomen						Abdomen
Lateral Upper Thigh						Lateral Upper Thigh
Rest of Leg & Feet						Rest of Leg & Feet
Arm						Arm
Mechanic's Hand						Mechanic's Hand
Dorsum of Hands (not over joints)						Dorsum of Hands (not over joints)
Gottron's – Not on Hands						Gottron's – Not on Hands

CDASI(後半)

Gottron's – Hands

Examine patient's hands and double score if papules are present		Ulceration	Examine patient's hands and score if damage is present	
0-absent 1-pink; faint erythema 2-red erythema 3-dark red			0-absent 1-dyspigmentation 2-scarring	

Periungual

Periungual changes (examine)			
0-absent 1-pink; red erythema/microscopic telangiectasias 2-visible telangiectasias			

Alopecia

Recent Hair loss (within last 30 days as reported by patient)			
0-absent 1-present			

Total Activity Score
(For the activity score, please add up the scores of the left side,i.e. Erythema, Scale, Excoration, Ulceration, Gottron's, Periungual, Alopecia)

Total Damage Score
(For the damage score, add up the scores of the right side, i.e. Poikiloderma, Calcinosis)

CDASI-A Max 45+30+15+6+2+1=99
(range 0-100と書いてあるが、0-99と思う)

CDASI-D Max 15+15+2=32

主なInclusion Criteria

- 18-75歳
- 2017 EULAR/ACR criteria definite/probable IIM and subclassification of DM
- Both active muscle disease (MMT8 80-142/ best 150) and

  active skin disease (CDASI-A ≧6 /worst 99)
- IR to at least one traditional therapy (GC/csDMARDs/IVIG)

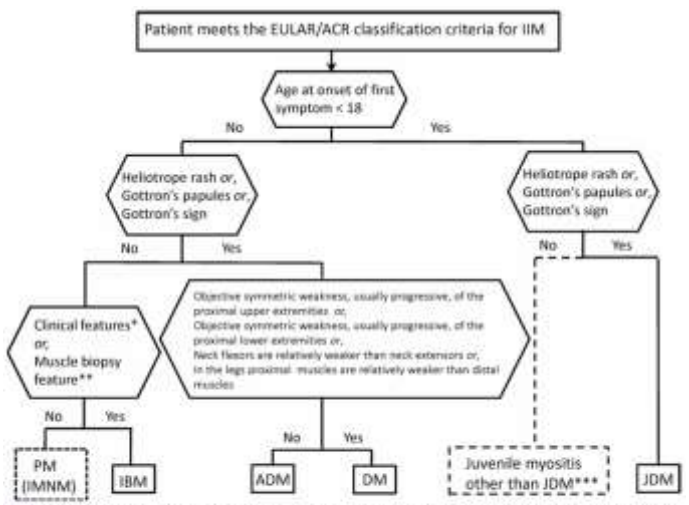


Figure 2 Classification tree for subgroups of IIM. A patient must first meet the EULAR/ACR classification criteria for IIM (probability of IIM ≥55%). The patient can then be subclassified using the classification tree. The subgroup of PM patients includes patients with IMNM. For IBM classification, one of the following, *finger flexor weakness and response to treatment: not improved, or **muscle biopsy: rimmed vacuoles, is required for classification. ***Juvenile myositis other than JDM was developed based on expert opinion. IMNM and hyperimpactic DM were too few to allow subclassification. ACR, American College of Rheumatology; ADM, amyopathic dermatomyositis; DM, dermatomyositis; EULAR, European League Against Rheumatism; IBM, inclusion body myositis; IIM, idiopathic inflammatory myopathies; IMNM, immune-mediated necrotising myopathy; JDM, juvenile dermatomyositis; PM, polymyositis.

2017 年 ACR/EULAR の IIM 分類基準 (PM/DM/ADM)

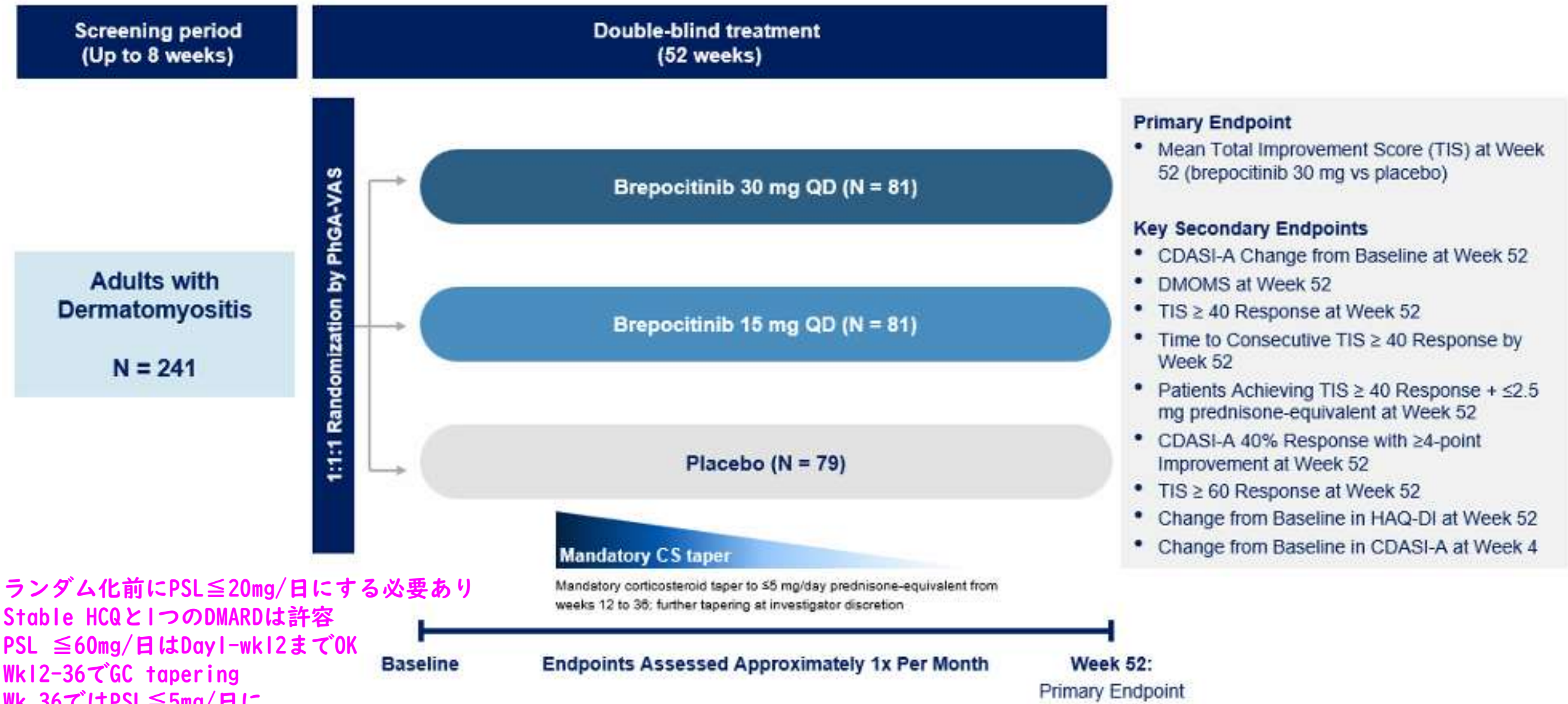
症状や徴候をよりよく説明できる疾患がない場合に、この分類基準を使用する。
筋生検なしで合計 5.5 以上（感度 87%、特異度 82%）、筋生検ありでは合計 6.7 以上(感度 93%、特異度 88%)で特発性炎症性筋疾患とされる。

項目		筋生検なし	筋生検あり
発症年齢	最初の症状の発現年齢が 18 歳以上 40 歳未満	1.3	1.5
	症状の発現年齢が 40 歳以上	2.1	2.2
筋力低下	進行性の上肢近位筋の客観的な対称性筋力低下	0.7	0.7
	進行性の下肢近位筋の客観的な対称性筋力低下	0.8	0.5
	頸部伸筋より頸部屈筋が相対的に低下	1.9	1.6
	下肢遠位筋より下肢近位筋が相対的に低下	0.9	1.2
皮膚症状	ヘリオトロープ疹	3.1	3.2
	ゴットロン丘疹	2.1	2.7
	ゴットロン徴候	3.3	3.7
臨床症状	嚥下障害または食道運動障害	0.7	0.6
検査所見	抗 Jo-1 抗体陽性	3.9	3.8
	血清 CK，LDH，AST，ALT などの正常上限以上の上昇	1.3	1.4
筋生検	筋繊維内には侵入しない筋繊維周囲の単核球の浸潤	–	1.7
	筋周囲あるいは血管周囲の単核球の浸潤	–	1.2
	筋束周辺部の萎縮	–	1.9
	縁取り空胞	–	3.1

筋生検なしで 7.5 以上，筋生検ありで 8.7 以上では確率 90%以上に相当し，definite IIM.
筋生検なしで 5.5 以上，筋生検ありで 6.7 以上では確率 55%以上に相当し，probable IIM.
筋生検なしで 5.3 以上 5.5 未満，筋生検ありで 6.5 以上 6.7 未満では確率 50%以上 55%未満に相当し，possible IIM.

Lundberg IE, et al. Ann Rheum Dis 2017;76:1955–1964

Figure S1. VALOR Phase 3 Study Design Through Week 52



ランダム化前にPSL≦20mg/日にする必要あり
Stable HCQと1つのDMARDは許容
PSL ≦60mg/日はDay1-wk12までOK
Wk12-36でGC tapering
Wk 36ではPSL≦5mg/日に

患者背景

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Brepocitinib, 30 mg (N=81)	Brepocitinib, 15 mg (N=81)	Placebo (N=79)
Mean age (range) — yr	50 (21–77)	51 (23–72)	51 (20–74)
Female sex — no. (%)	65 (80)	67 (83)	55 (70)
Race or ethnic group — no. (%)†			
White	55 (68)	57 (70)	61 (77)
Asian	6 (7)	11 (14)	7 (9)
Black	6 (7)	6 (7)	4 (5)
Hispanic or Latino	23 (28)	13 (16)	21 (27)
Medical history — no. (%)			
Interstitial lung disease	19 (24)	17 (21)	11 (14)
Previous benign or malignant neoplasm	14 (17)	9 (11)	11 (14)
Atherosclerotic cardiovascular disease	5 (6)	0	2 (3)
Hypertension	27 (33)	23 (28)	23 (29)
Hyperlipidemia	13 (16)	16 (20)	17 (22)
Diabetes mellitus	10 (12)	10 (12)	11 (14)
Obesity	26 (32)	25 (31)	25 (32)
Current tobacco use	7 (9)	7 (9)	8 (10)
Testing scores			
PhGA-VAS‡	5.3±1.6	5.5±1.7	5.6±1.7
CDASI-A§	18.7±11.3	19.5±11.3	21.1±12.0
MMT-8¶	121.7±16.4	124.5±14.2	121.6±17.0
Dermatomyositis background therapy — no. (%)			
Oral glucocorticoids — no. (%)	60 (74)	58 (72)	64 (81)
Daily prednisone-equivalent dose — mg	12.2±5.7	10.7±6.2	11.3±5.9
DMARDs — no. (%)	55 (68)	57 (70)	61 (77)
≥2 Dermatomyositis-directed therapies	64 (79)	66 (82)	66 (84)
History of intravenous immune globulin or rituximab	25 (31)	24 (30)	25 (32)

白人が7割
アジア人は約10%

ILD合併は14-24%

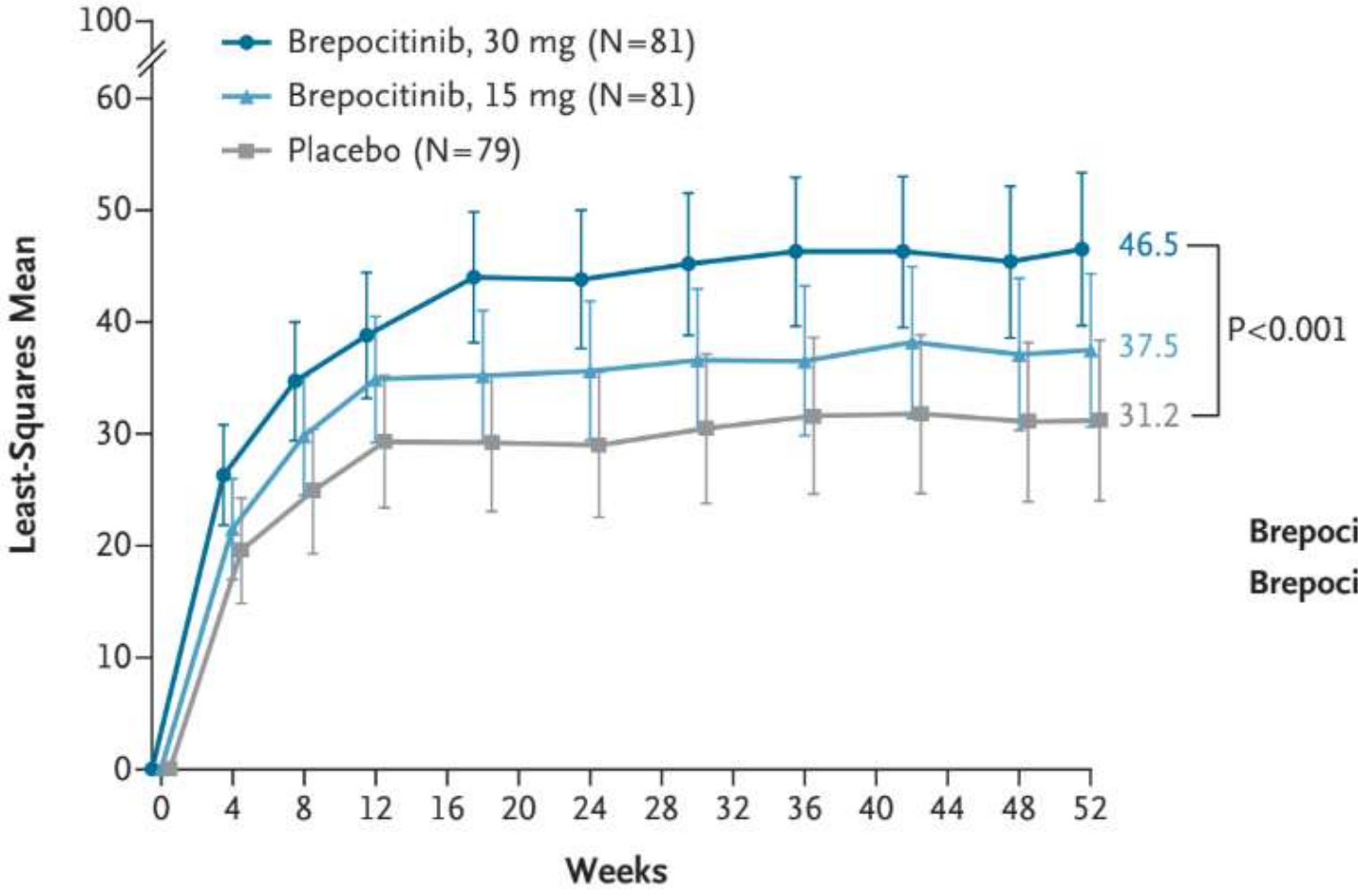
皮疹は中程度

筋力低下は軽度から中等度

GC (-)も20-30%
PSL は平均10-12mg/d程度

主要評価項目：TIS平均 at 52週

A Total Improvement Score (TIS) and Glucocorticoid Reduction

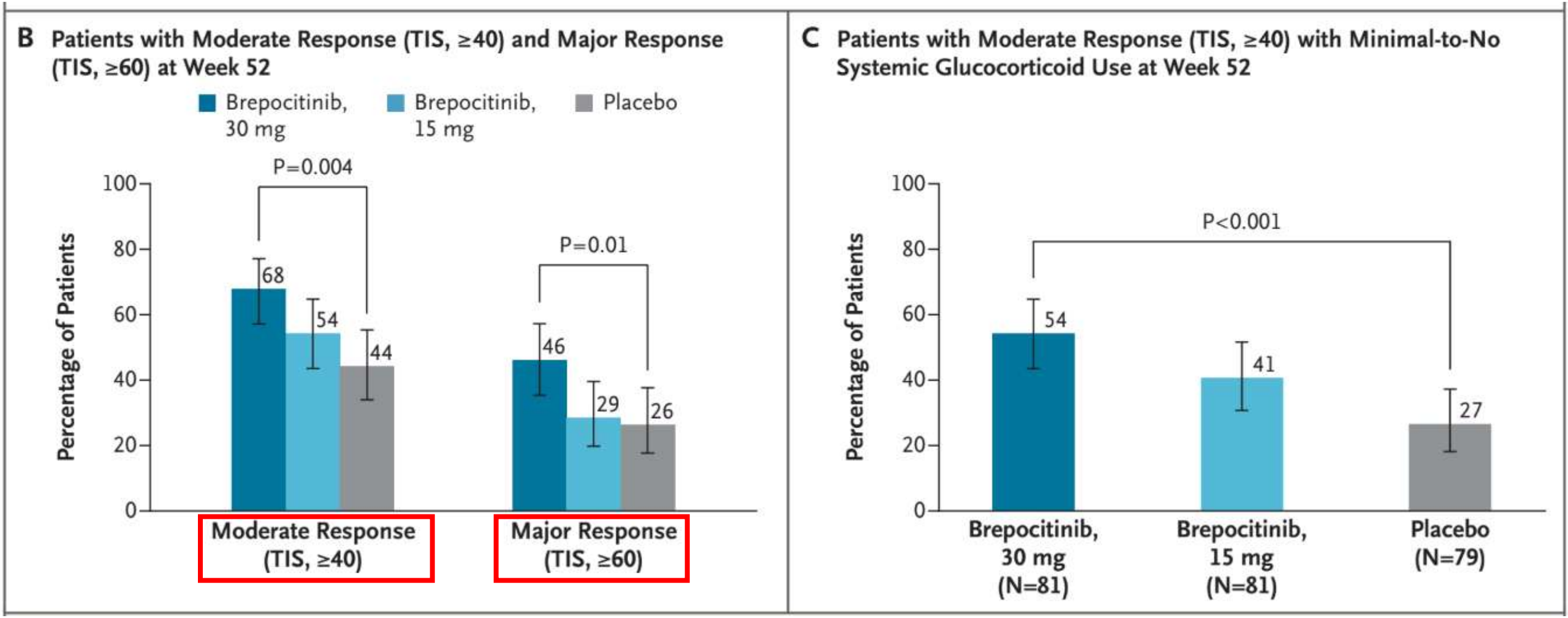


Glucocorticoid Reduction Outcomes (prednisone-equivalent dose)

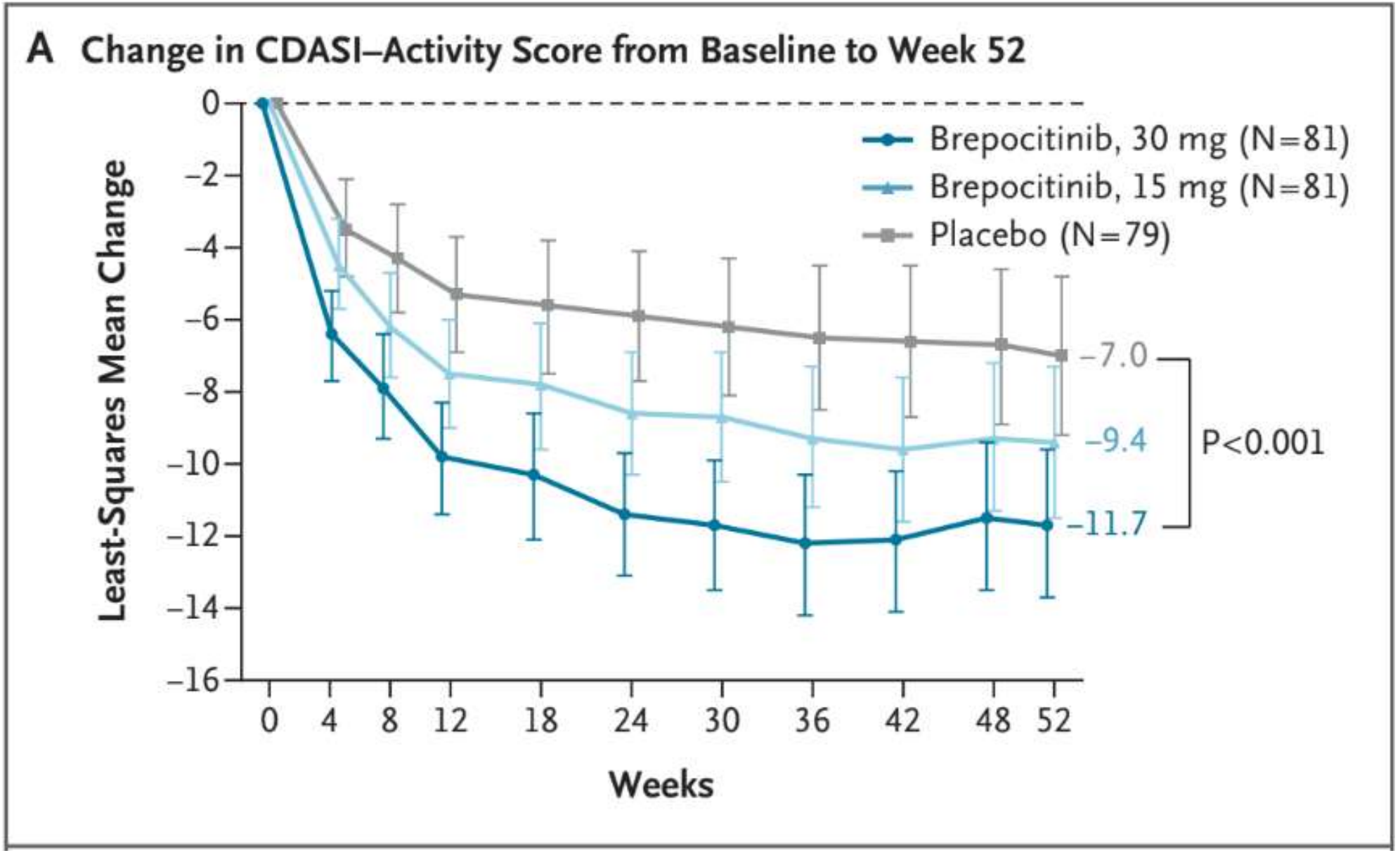
	No. of patients at baseline	Dose at baseline	Percentage with ≤2.5 mg/day by weeks 48–52	Percentage with 0 mg/day by weeks 48–52
		mg/day (±SD)		
Brepocitinib, 30 mg	60	12.2±5.7	62	42
Brepocitinib, 15 mg	58	10.7±6.2	41	31
Placebo	64	11.3±5.9	34	23

BREPO群でよりGC減量できた

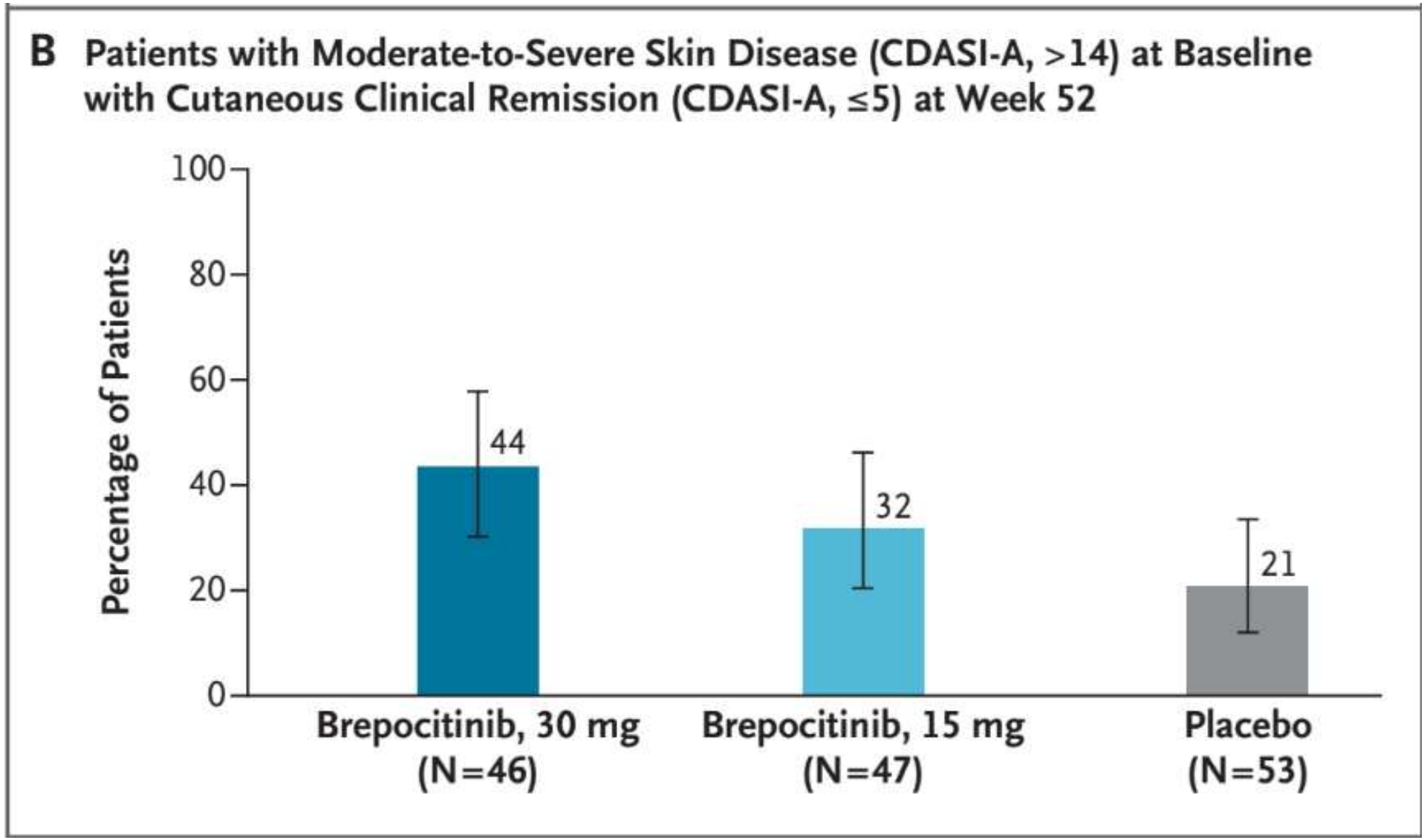
副次評価項目：TIS≧40，TIS≧60割合 at 52週



副次評価項目：CDASI-A改善の平均値 at 52週



CDASI-A 中等度以上（>14）＝＞ 寛解(≦5)の割合



まとめ：すべての評価項目で有意な改善（30mg群vsプラセボ）

Table 2. Primary and Secondary End Points.*

End Point	Brepocitinib, 30 mg (N=81)			Brepocitinib, 15 mg (N=81)		Placebo (N=79)
	Value	Difference from Placebo†	P Value	Value	Difference from Placebo†	Value
Primary end point						
Mean Total Improvement Score at wk 52 (95% CI)‡	46.5 (39.7 to 53.4)	15.3 (6.7 to 24.0)	<0.001	37.5 (30.6 to 44.3)	6.3 (−2.4 to 14.9)	31.2 (24.0 to 38.4)
Key secondary end points						
Change in CDASI-A from baseline at wk 52 (95% CI)§	−11.7 (−13.7 to −9.6)	−4.6 (−7.3 to −2.0)	<0.001	−9.4 (−11.5 to −7.3)	−2.4 (−5.0 to 0.2)	−7.0 (−9.2 to −4.9)
DMOMS at wk 52 (95% CI)¶	57.9 (49.5 to 66.2)	17.3 (6.8 to 27.9)	0.001	48.9 (40.5 to 57.2)	8.3 (−2.2 to 18.9)	40.5 (31.8 to 49.3)
Patients with Total Improvement Score of ≥40 at wk 52 — % (95% CI)	68 (57 to 77)	22 (7 to 37)	0.004	54 (44 to 65)	12 (−4 to 27)	44 (34 to 55)
Median time to consecutive Total Improvement Score of ≥40 — days (95% CI)‖	85 (57 to 127)	Hazard ratio, 1.60 (1.09 to 2.33)	0.02	169 (85 to 297)	Hazard ratio, 0.99 (0.66 to 1.48)	168 (85 to 254)
Patients with Total Improvement Score of ≥40 at wk 52 with minimal-to-no oral glucocorticoid use — % (95% CI)**	54 (44 to 65)	26 (11 to 40)	<0.001	41 (31 to 52)	13 (−2 to 28)	27 (18 to 37)
Patients with CDASI-A of ≥40% and ≥4-point improvement at wk 52 — % (95% CI)	62 (51 to 72)	17 (1 to 32)	0.04	59 (48 to 69)	16 (<1 to 31)	44 (34 to 55)
Patients with Total Improvement Score of ≥60 at wk 52 — % (95% CI)	46 (35 to 57)	20 (4 to 35)	0.01	29 (20 to 40)	6 (−8 to 20)	26 (18 to 38)
Change in HAQ-DI from baseline at wk 52 (95% CI)††	−0.34 (−0.49 to −0.18)	−0.30 (−0.49 to −0.10)	0.004	−0.17 (−0.32 to −0.01)	−0.13 (−0.32 to 0.07)	−0.04 (−0.21 to 0.12)
Change in CDASI-A from baseline at wk 4 (95% CI)	−6.4 (−7.7 to −5.2)	−3.0 (−4.6 to −1.4)	<0.001	−4.5 (−5.7 to −3.2)	−1.0 (−2.6 to 0.6)	−3.5 (−4.8 to −2.1)

安全性評価：SAEは差がないが、重篤感染症は多いかも

Table 3. Safety during the 52-Week Treatment Period.*

Adverse Events	Brepocitinib, 30 mg (N=81)	Brepocitinib, 15 mg (N=81)	Placebo (N=79)
		number of patients (percent)	
Any adverse event	73 (90)	70 (86)	72 (91)
Serious adverse event			
Any serious event	13 (16)	7 (9)	10 (13)
Infection	8 (10)	2 (2)	1 (1)
Leading to discontinuation of brepocitinib or placebo	5 (6)	6 (7)	9 (11)
Leading to trial discontinuation	3 (4)	4 (5)	3 (4)
Adverse events of special interest†	6 (7)	4 (5)	10 (13)
Cardiovascular	1 (1)	0	2 (3)
Thromboembolic	0	0	1 (1)
Viral reactivation	4 (5)	2 (2)	4 (5)
New or recurrent cancer	0	0	2 (3)
Increase in ALT or AST level‡	1 (1)	2 (2)	1 (1)

Discussion

（ほとんど、結果の繰り返しでdiscussionされていない）

・DM P3治験において、BREPO 30mg/dがプラセボに対して52週でのTISスコアを有意に改善した
・68%がmoderate改善（TIS>40)、46%がmajor改善(TIS>60)（プラセボはそれぞれ44%, 26%)
・筋肉・皮膚活動性、GC sparing, moderate改善の維持、QOLすべてにおいて有意に改善した
・2倍以上の患者がPSL≦2.5mg/dを達成した
・AEはほぼ群間で変わらなかったが、serious infectionは多かった。ただ、ほとんどの患者はBREPOを継続した。
・Limitationは盲検期間中に改善している患者においても背景のDMARD治療を変えていないこと(?)
・BREPO 30mg（15mgではなく）がプラセボに比してDM治療の優位性を示した。
・4週後くらいから効果が出始め、52週継続した。