Bimekizumab in patients with psoriatic arthritis, naive to biologic treatment: a randomised, double-blind, placebo-controlled, phase 3 trial (BE OPTIMAL)

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Introduction

Method

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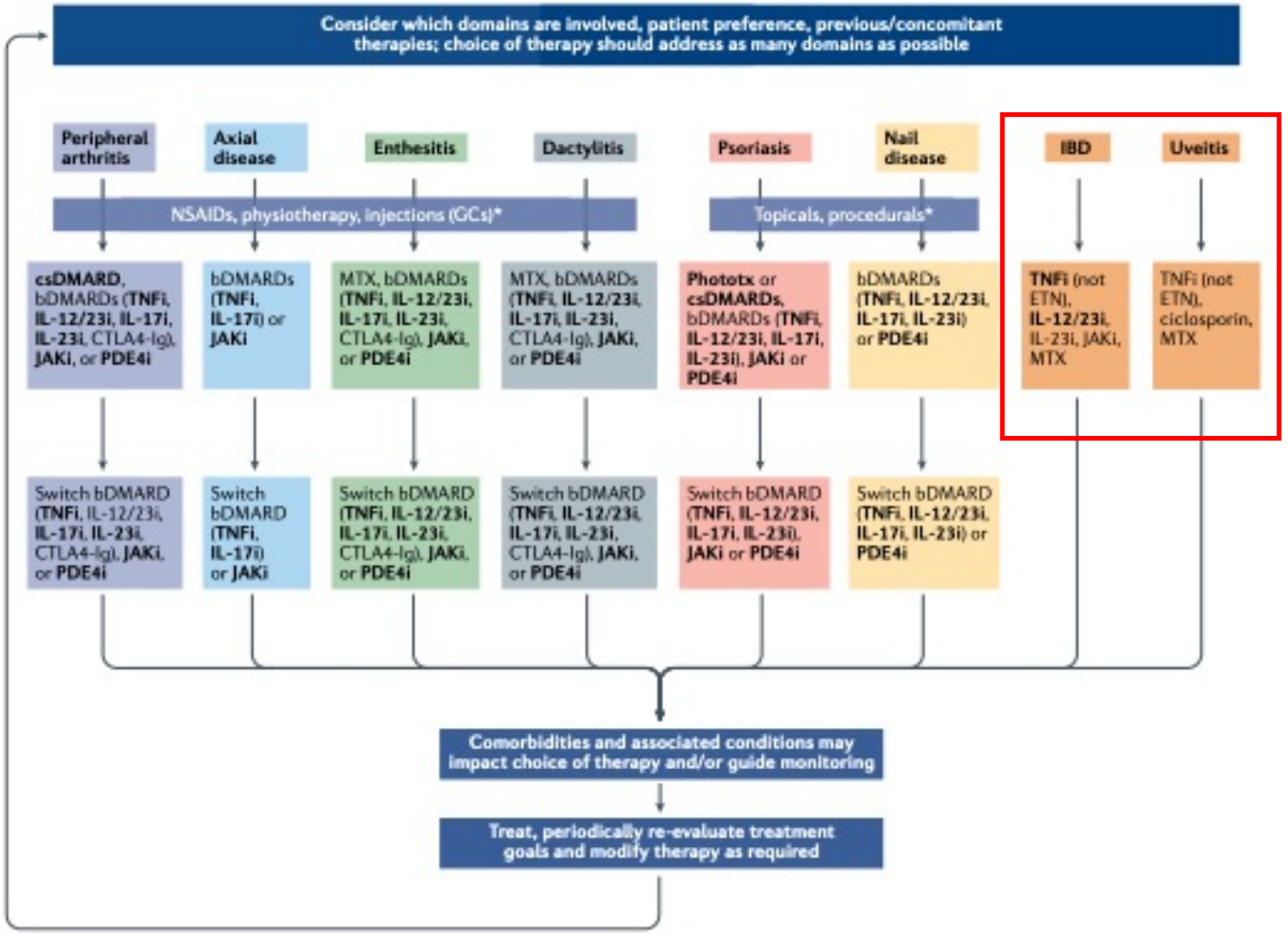
乾癬性関節炎は末梢および体軸の関節，靱帯，皮膚，爪に発現する複雑な免疫が介在する炎症性疾患である.

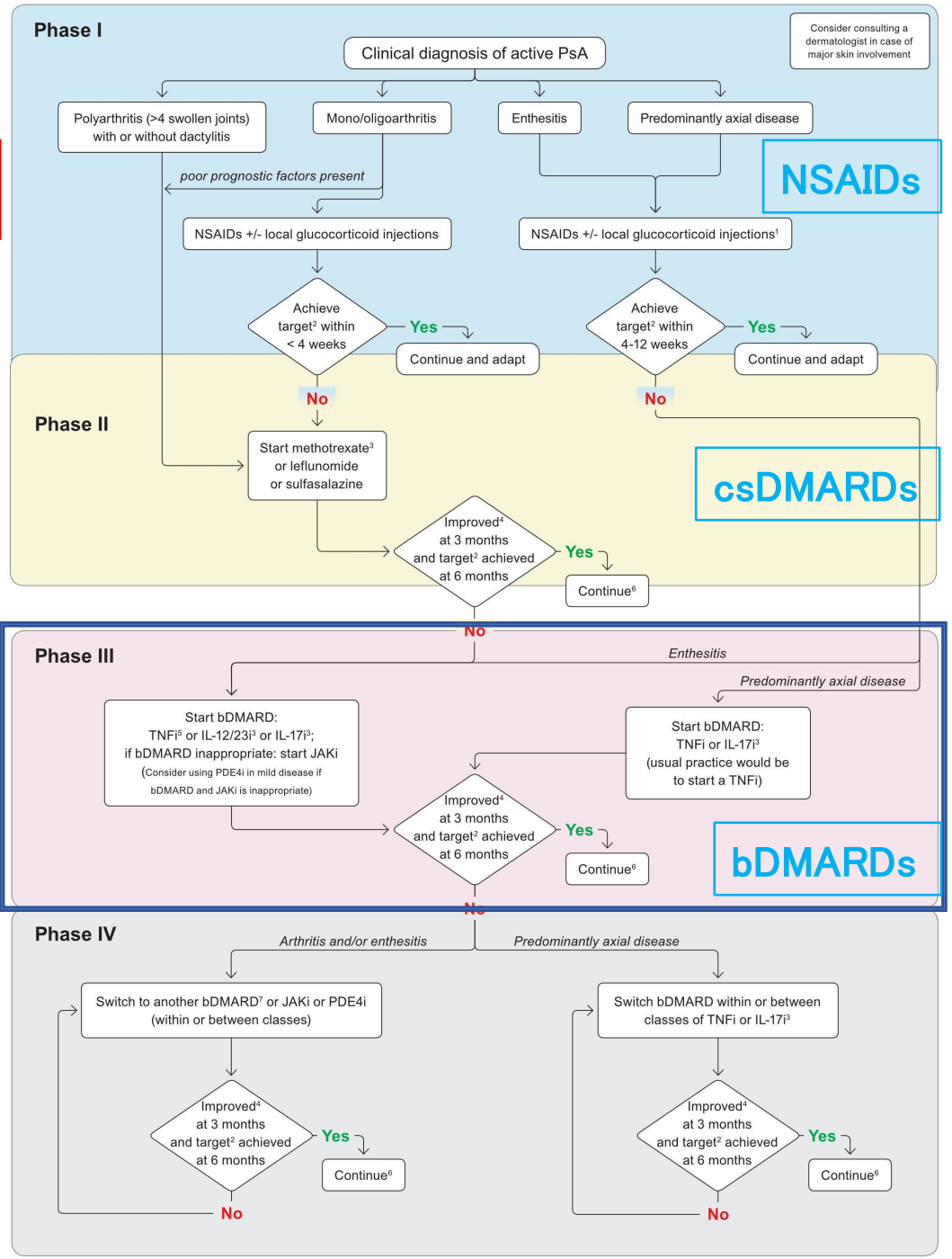
ほとんどの乾癬性関節炎患者は筋骨格系症状に，古典的合成疾患修飾性抗リウマチ薬（csDMARDs）を開始する.

国際的なガイドラインではcsDMARDsの効果が不十分な場合は，疾患活動性をできる限り低下させることを目的に，生物学的DMARDs(bDMARDs)に切り替える，または追加することが推奨されている.

Supplement

TNFi > IL17i





Coates LC, et al. Nat Rev Rheumatol. 2022 ;18:465.

Gossec L, et al. Ann Rheum Dis. 2020 ;79:700.

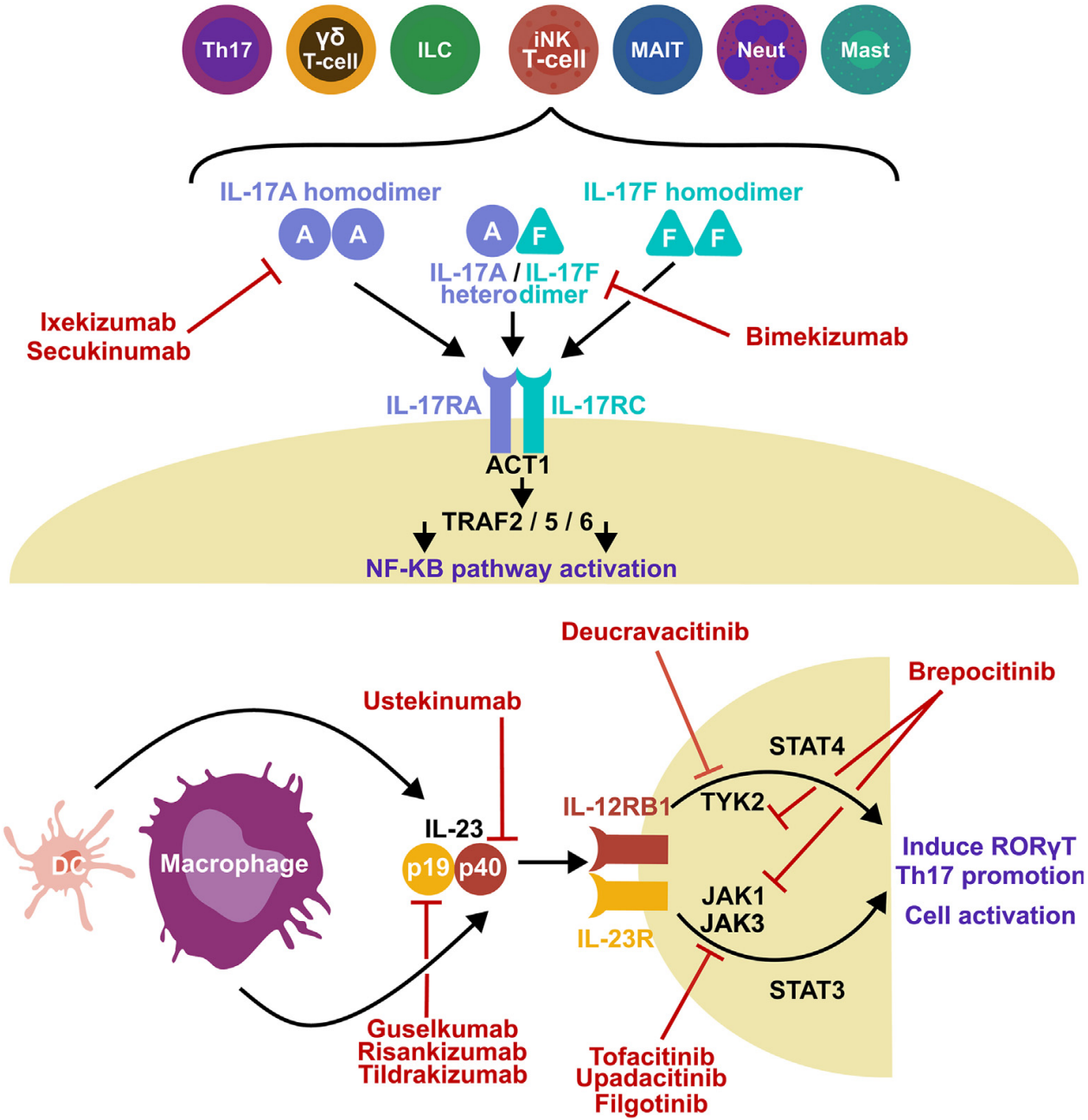
Introduction

インターロイキン（IL）-17ファミリーのサイトカインは乾癬性関節炎の病因に関与していると考えられ，いくつかの二量体アイソフォームから構成されている.

特にIL-17AとIL-17Fは50%の相同性を有し，炎症促進活性が重複しているため，ホモダイマーやヘテロダイマーを形成する.

ビメキズマブはヒト化モノクローナルIgG1抗体でIL-17AとIL-17Fの分子上の類似部位に結合し，ホモダイマーとヘテロダイマーの両方を選択的に阻害する.

Supplement



Th17，γδT細胞，ILC，好中球などからIL-17AとIL-17Fがホモおよびヘテロ二量体として産生される．

IL-17RAとIL-17RCの2つのサブユニットからなるIL-17受容体に結合し，ACT1→TRAF2/5/6をリクルートし，NF-κb経路を活性化させる．

Hutton J, et al.
Best Pract Res Clin Rheumatol.2022 :101809.

Introduction

中等度から重度の尋常性乾癬患者では, ビメキズマブは第3b相 BE RADIANT試験で
セクキヌマブと比較し統計的に有意な優れた皮膚反応を示した.

また, その臨床効果および忍容性は第3相BE SURE/BE VIVID試験でも示された.

中等度から重度の乾癬性関節患者を対象とした第2b相BE ACTIVE試験でも, ビメキズマブ
の臨床的有効性と忍容性が示され, オープンラベル延長試験でも3年まで改善が持続する
ことが示された.

Introduction

ビメキズマブの有効性と安全性を2つの多国籍多施設第3相の臨床試験で並行し評価した.
その1つのBE OPTIMAL試験の主要解析結果を報告する.

本試験は16週間の二重盲検プラセボ比較期間と36週間の治療盲検期間で構成されている.
またベネフィット・リスク・プロファイルの参考とするためにアダリムマブ群を設定した.
ただ, ビメキズマブ群またはプラセボ群とアダリムマブ群の統計的比較のための検出力は
算出されていない.

Review of bimekizumab in the treatment of psoriasis

Table 1. Efficacy results from phase II and III clinical trials.

Trial	Primary Endpoint	Treatment Duration	Treatment Groups (% Achieving)		
Phase IIb (BE ABLE)			Bimekizumab Q4W	Placebo Q4W	
	PASI 90	12 weeks	64 mg: 46.2% 160 mg: 67.4% 160 mg with 320 mg loading dose: 75% 320 mg: 79.1% 480 mg: 72.1%	0%	
Phase III (BE VIVID)			Bimekizumab Q4W	Placebo	Ustekinumab Q12W
	PASI90	16 weeks	320 mg: 85%	15%	45 mg or 90 mg (based on weight): 50%
	IGA 0/1	16 weeks	320 mg: 84%	5%	45 mg or 90 mg (based on weight): 53%
Phase III (BE READY)			Bimekizumab Q4W	Placebo	
	PASI90	16 weeks	320 mg: 91%	1%	
	IGA 0/1	16 weeks	320 mg: 93%	1%	
Phase III (BE SURE)			Bimekizumab Q4W	Adalimumab Q2W	
	PASI90	16 weeks	320 mg: 86.2%;	40 mg: 47.2%	
	IGA0/1	16 weeks	320 mg: 85.3%	40 mg: 57.2%	
Phase III (BE RADIANT)			Bimekizumab Q4W	Secukinumab Q1W(until week 4) then Q4W	
	PASI90	16 weeks	320 mg: 61.7%	300 mg: 48.9%	
	PASI100	48 weeks	320 mg: 67.0%	300 mg: 46.2%	

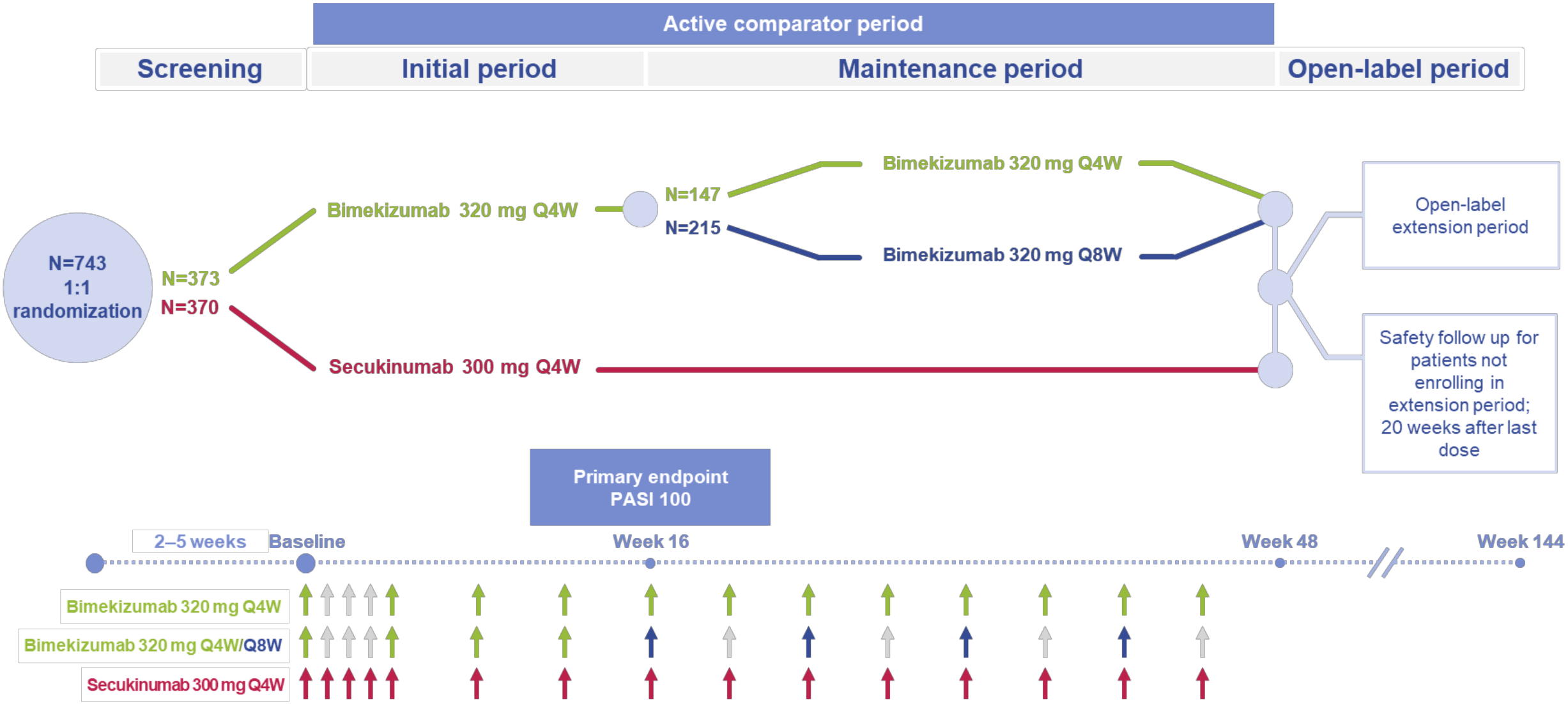
Koppu S, et al. Hum Vaccin Immunother. 2022 ;18 :2119767.

Bimekizumab versus Secukinumab in Plaque Psoriasis

多国籍 多施設共同 盲検 無作為化試験 (優越性・非劣性)

- Patients: CASPER分類基準を満たす18歳以上の乾癬性関節炎患者
- Exposure: ビメキズマブ群 (ビメキズマブ 320mg 4週間毎 皮下注射)
- Comparison: セクキヌマブ群(セクキヌマブ 300mg 4週間毎 皮下注射)
- Outcome: 16週目でのPASI 100%低下した患者の割合

Reich K, et al. N Engl J Med. 2021 ;385:142.



Reich K, et al. N Engl J Med. 2021 ;385:142.

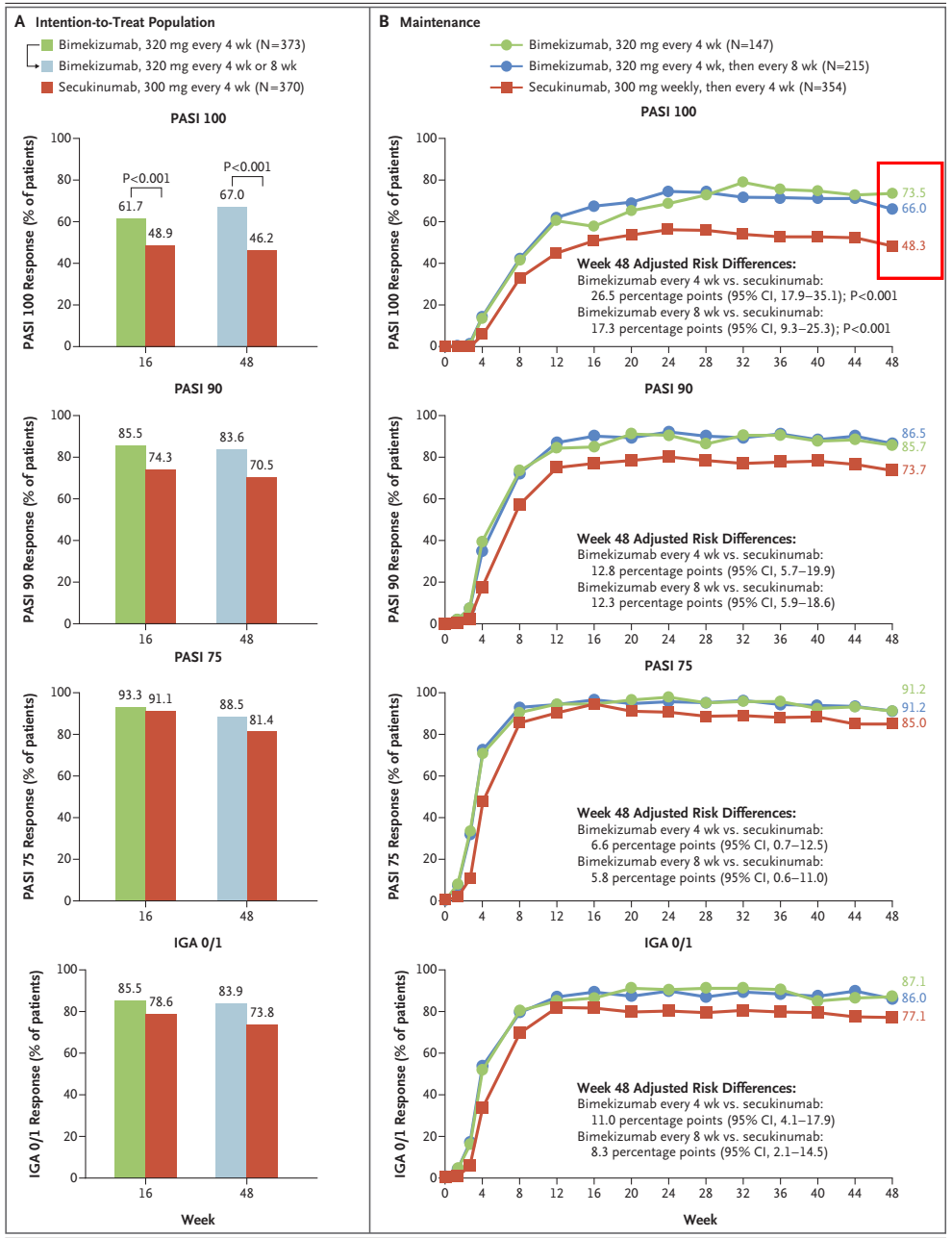


Table 3. Adverse Events Occurring during the Treatment Period.*

Event	Weeks 0–48†		Weeks 16–48‡	
	Bimekizumab (N=373)	Secukinumab (N=370)	Bimekizumab every 4 wk (N=147)	Bimekizumab every 8 wk (N=215)
	number of patients (percent)			
Any adverse event	321 (86.1)	301 (81.4)	119 (81.0)	162 (75.3)
Serious adverse event	22 (5.9)	21 (5.7)	4 (2.7)	9 (4.2)
Discontinuation of treatment due to adverse event	13 (3.5)	10 (2.7)	3 (2.0)	1 (0.5)
Drug-related adverse event	160 (42.9)	117 (31.6)	46 (31.3)	72 (33.5)
Severe adverse event	26 (7.0)	15 (4.1)	5 (3.4)	11 (5.1)
Death	1 (0.3)	1 (0.3)	0	1 (0.5)
Most common adverse events§				
Upper respiratory tract infections¶	145 (38.9)	154 (41.6)	35 (23.8)	62 (28.8)
Oral candidiasis	72 (19.3)	11 (3.0)	19 (12.9)	36 (16.7)
Urinary tract infection	25 (6.7)	22 (5.9)	11 (7.5)	10 (4.7)
Adverse events of interest				
Serious infection	8 (2.1)	8 (2.2)	1 (0.7)	6 (2.8)
Active tuberculosis	0	0	0	0
Latent tuberculosis	5 (1.3)	4 (1.1)	4 (2.7)	1 (0.5)
Inflammatory bowel disease	1 (0.3)	1 (0.3)	0	0
Ulcerative colitis	1 (0.3)	1 (0.3)	0	0
Candida infections	79 (21.2)	17 (4.6)	21 (14.3)	38 (17.7)
Genital candidiasis‖	3 (0.8)	5 (1.4)	0	2 (0.9)
Oral candidiasis	72 (19.3)	11 (3.0)	19 (12.9)	36 (16.7)
Oropharyngeal candidiasis	2 (0.5)	1 (0.3)	1 (0.7)	0
Skin candida	4 (1.1)	2 (0.5)	1 (0.7)	1 (0.5)
Adjudicated suicidal ideation and behavior	1 (0.3)	0	0	0
Suicide attempt	1 (0.3)	0	0	0
Cancer**	5 (1.3)	3 (0.8)	1 (0.7)	2 (0.9)
Nonmelanoma skin cancer	3 (0.8)	3 (0.8)	1 (0.7)	1 (0.5)
Serious hypersensitivity reactions	0	0	0	0
Adjudicated MACE	0	2 (0.5)	0	0
Elevated liver enzymes††	21 (5.6)	19 (5.1)	3 (2.0)	7 (3.3)

Reich K, et al. N Engl J Med. 2021 ;385:142.

Bimekizumab in patients with active psoriatic arthritis: results from a 48-week, randomised, double-blind, placebo-controlled, dose-ranging phase 2b trial

多国籍 多施設共同 盲検 無作為化試験

- Patients: CASPER分類基準を満たす18歳以上の乾癬性関節炎患
- Exposure:

16mg ビメキズマブ群 (ビメキズマブ 16mg 4週間毎 皮下注射)

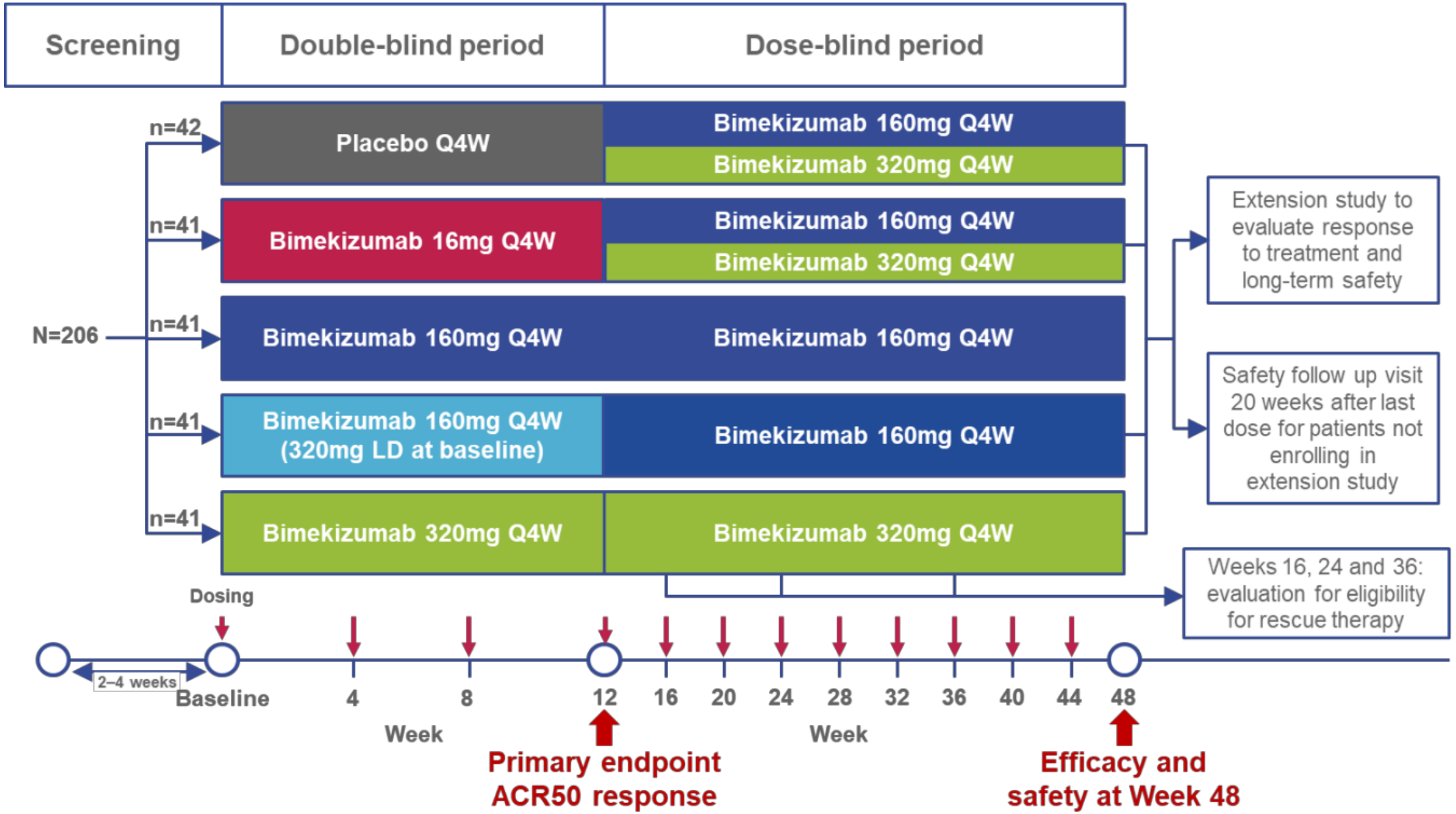
160mg ビメキズマブ群 (ビメキズマブ 160mg 4週間毎 皮下注射)

160mg loading ビメキズマブ群 (ビメキズマブ 320mg→160mg 4週間毎 皮下注射)

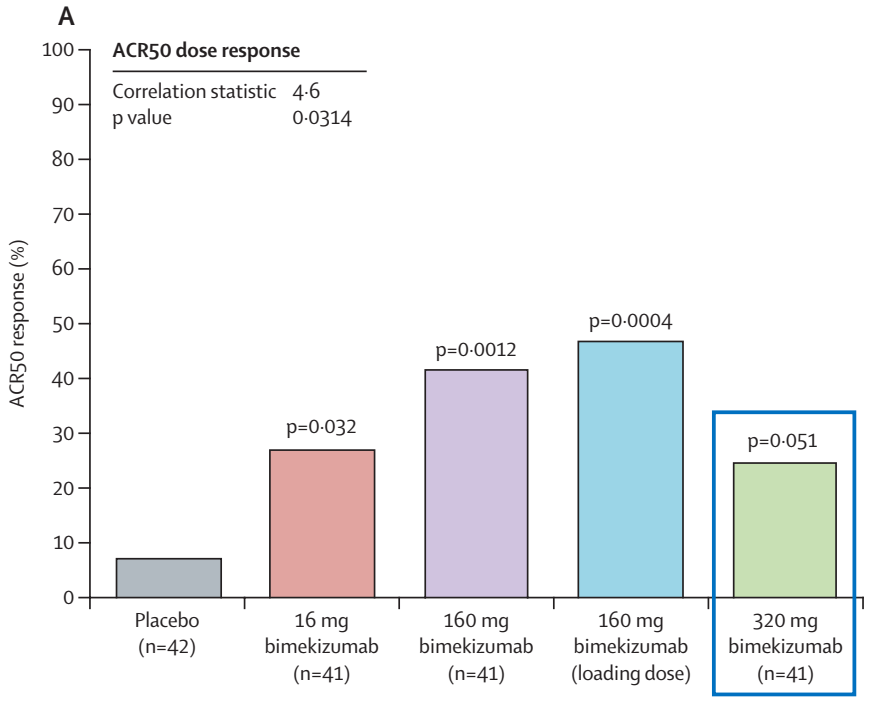
320mg ビメキズマブ群 (ビメキズマブ 320mg 4週間毎 皮下注射)

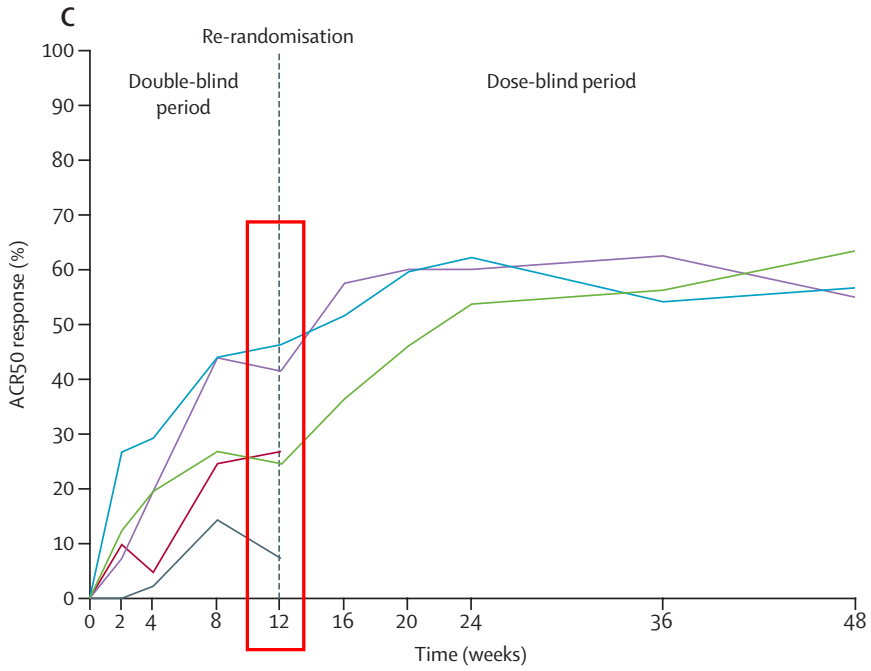
- Comparison: プラセボ群
- Outcome: 12週目でのACR50を満たす患者の割合

Ritchlin CT, et al. Lancet. 2020 ;395 :427.



Ritchlin CT, et al. Lancet. 2020 ;395 :427.



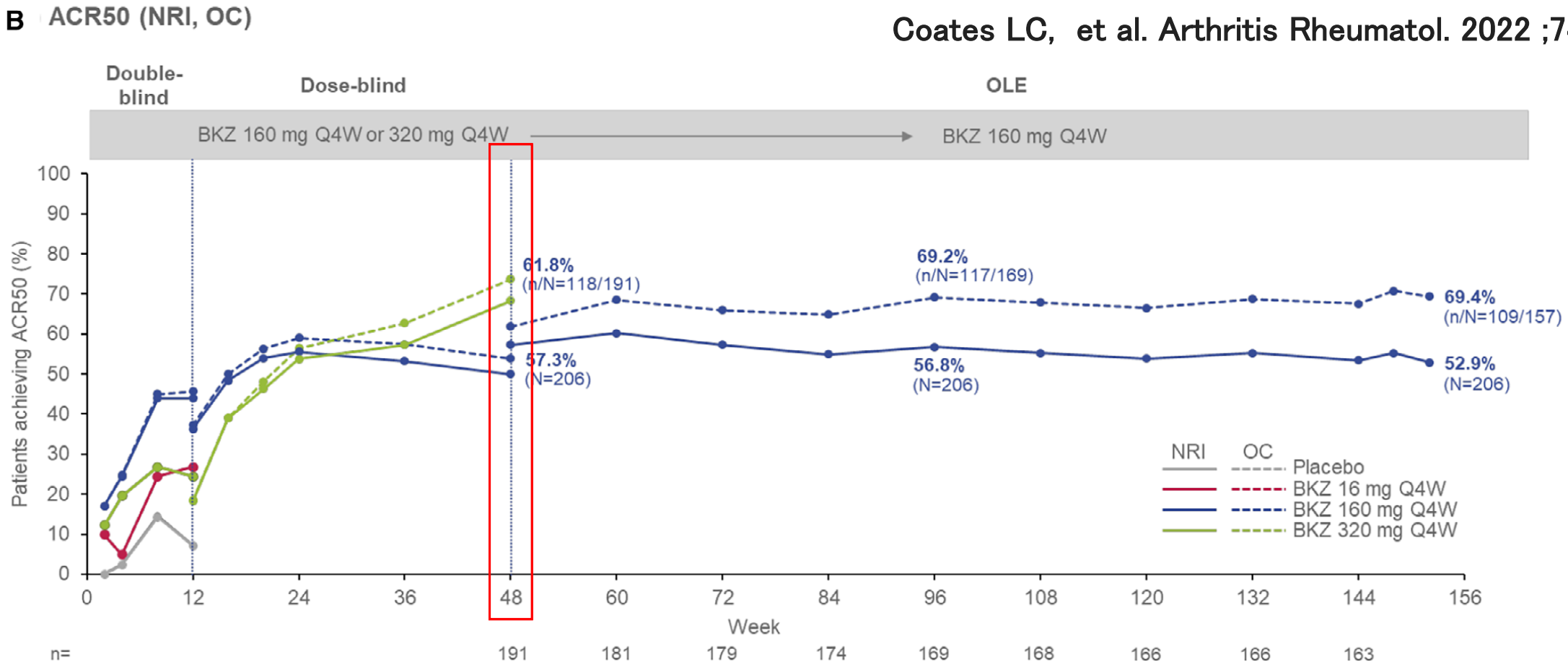


	Placebo group	16 mg bimekizumab group	160 mg bimekizumab group	160 mg bimekizumab (loading dose) group	320 mg bimekizumab group
ACR20*					
Response	8/42 (19%)	22/41 (54%)	30/41 (73%)	25/41 (61%)	21/41 (51%)
OR (95% CI); p value	..	4·6 (1·7–12·4); 0·0023	11·0 (3·9–31·0); <0·0001	6·2 (2·3–16·8); 0·0003	4·2 (1·6–11·4); 0·0040
ACR50 (primary outcome)*					
Response	3/42 (7%)	11/41 (27%)	17/41 (41%)	19/41 (46%)	10/41 (24%)
OR (95% CI); p value	..	4·2 (1·1–15·2); 0·032	8·1 (2·3–28·7); 0·0012	9·7 (2·7–34·3); 0·0004	3·7 (1·0–13·7); 0·051
ACR70*					
Response	2/42 (5%)	5/41 (12%)	8/41 (20%)	13/41 (32%)	6/41 (15%)
OR (95% CI); p value	..	2·4 (0·5–11·3); 0·28	4·1 (0·9–17·9); 0·065	7·5 (1·8–31·3); 0·0061	2·9 (0·6–13·4); 0·17
PASI75*					
Response	2/28 (7%)	13/29 (45%)	18/28 (64%)	20/26 (77%)	19/26 (73%)
OR (95% CI); p value	..	8·8 (1·9–39·8); 0·0048	21·6 (4·6–101·6); 0·0001	34·7 (7·0–173·3); <0·0001	27·1 (5·6–131·1); <0·0001
PASI90*					
Response	2/28 (7%)	6/29 (21%)	13/28 (46%)	14/26 (54%)	14/26 (54%)
OR (95% CI); p value	..	2·9 (0·6–14·3); 0·19	11·2 (2·4–52·3); 0·0020	12·9 (2·8–60·5); 0·0011	12·1 (2·6–56·2); 0·0014
PASI100†	2/28 (7%)	5/29 (17%)	10/28 (36%)	13/26 (50%)	10/26 (38%)
Minimal disease activity	6/42 (14%)	13/41 (32%)	19/41 (46%)	17/41 (41%)	12/41 (29%)
MASES‡					
n	20	19	23	22	23
Mean change	−0·4 (3·5)	−2·3 (3·3)	−1·6 (2·3)	−3·1 (2·8)	−1·0 (3·8)
Health Assessment Questionnaire—Disability Index					
n	42	41	41	41	41
Change from baseline	−0·1 (0·5)	−0·2 (0·4)	−0·4 (0·5)	−0·4 (0·5)	−0·4 (0·5)
Short-Form 36-item Health Survey					
n	42	41	41	41	41
Mean change (physical component score)	2·7 (8·4)	5·7 (7·8)	7·6 (8·9)	7·5 (7·7)	6·5 (8·4)
Mean change (mental component store)	−1·2 (7·2)	−0·5 (7·7)	2·5 (6·9)	−1·1 (7·0)	1·7 (8·4)
Psoriatic Arthritis Impact of Disease—9 score ≤3	12/42 (29%)	21/41 (51%)	30/41 (73%)	30/41 (73%)	22/41 (54%)

Ritchlin CT, et al. Lancet. 2020 ;395 :427.

Safety and Efficacy of Bimekizumab in Patients With Active Psoriatic Arthritis: Three-Year Results From a Phase IIb Randomized Controlled Trial and Its Open-Label Extension Study

Coates LC, et al. Arthritis Rheumatol. 2022 ;74:1959.



Safety and Efficacy of Bimekizumab in Patients With Active Psoriatic Arthritis: Three-Year Results From a Phase IIb Randomized Controlled Trial and Its Open-Label Extension Study

	Weeks 0–48†		Weeks 48–152	Weeks 0–152‡
	160 mg BKZ every 4 weeks (n = 126; 113.2 patient-years)	320 mg BKZ every 4 weeks (n = 80; 72.9 patient-years)	Total BKZ (N = 183; 392.7 patient-years)	Total BKZ (N = 206; 570.1 patient-years)
Any TEAE	94 (74.6) (177.6)	57 (71.3) (165.9)	148 (80.9) (94.3)	184 (89.3) (126.4)
Serious TEAEs	8 (6.3) (7.9)	0	14 (7.7) (3.8)	22 (10.7) (4.1)
Severe TEAEs	5 (4.0) (4.6)	2 (2.5) (2.9)	8 (4.4) (2.1)	14 (6.8) (2.5)
Withdrawal due to TEAEs	6 (4.8) (5.9)	2 (2.5) (3.1)	9 (4.9) (2.3)	17 (8.3) (3.0)
Drug-related TEAEs	43 (34.1) (52.7)	29 (36.3) (57.0)	60 (32.8) (20.0)	97 (47.1) (26.4)
Deaths	0	0	0	0
Most frequently reported TEAEs (≥5%) by MedDRA preferred term				
Nasopharyngitis	12 (9.5) (12.0)	11 (13.8) (18.4)	19 (10.4) (5.2)	37 (18.0) (7.6)
Upper respiratory tract infection	12 (9.5) (12.0)	8 (10.0) (13.2)	20 (10.9) (5.5)	34 (16.5) (6.8)
Bronchitis	7 (5.6) (6.9)	3 (3.8) (4.8)	11 (6.0) (2.9)	19 (9.2) (3.5)
Oral candidiasis	6 (4.8) (6.0)	4 (5.0) (6.4)	13 (7.1) (3.5)	19 (9.2) (3.5)
Pharyngitis	4 (3.2) (3.9)	7 (8.8) (11.6)	10 (5.5) (2.7)	17 (8.3) (3.2)
Sinusitis	6 (4.8) (5.9)	4 (5.0) (6.5)	10 (5.5) (2.6)	17 (8.3) (3.2)
Psoriasis	2 (1.6) (1.9)	2 (2.5) (3.1)	14 (7.7) (3.7)	16 (7.8) (2.9)
Psoriatic arthropathy	2 (1.6) (1.9)	1 (1.3) (1.6)	12 (6.6) (3.1)	16 (7.8) (2.9)
Respiratory tract infection	8 (6.3) (8.0)	2 (2.5) (3.2)	4 (2.2) (1.0)	15 (7.3) (2.8)
Oral fungal infection	3 (2.4) (2.9)	3 (3.8) (4.7)	9 (4.9) (2.4)	14 (6.8) (2.6)
Tonsillitis	6 (4.8) (5.9)	2 (2.5) (3.2)	6 (3.3) (1.6)	14 (6.8) (2.6)
ALT increased	6 (4.8) (6.0)	3 (3.8) (4.7)	6 (3.3) (1.6)	13 (6.3) (2.4)
Safety topics of interest				
Serious infections	3 (2.4) (2.9)	0	1 (0.5) (0.3)	4 (1.9) (0.7)
Fungal infections	17 (13.5) (17.8)	10 (12.5) (16.7)	32 (17.5) (9.2)	47 (22.8) (9.7)
Candida infections	9 (7.1) (9.1)	5 (6.3) (8.1)	16 (8.7) (4.3)	24 (11.7) (4.6)
Oral candidiasis	6 (4.8) (6.0)	4 (5.0) (6.4)	13 (7.1) (3.5)	19 (9.2) (3.5)
Skin candidiasis	1 (0.8) (1.0)	0	1 (0.5) (0.3)	2 (1.0) (0.4)
Vulvovaginal candidiasis	0	0	1 (0.5) (0.3)	1 (0.5) (0.2)
Genital candidiasis	1 (0.8) (1.0)	0	1 (0.5) (0.3)	1 (0.5) (0.2)
Oropharyngeal candidiasis	1 (0.8) (1.0)	0	0	1 (0.5) (0.2)
Fungal infections NEC	9 (7.1) (9.0)	4 (5.0) (6.3)	17 (9.3) (4.6)	25 (12.1) (4.7)
Oral fungal infection	3 (2.4) (2.9)	3 (3.8) (4.7)	9 (4.9) (2.4)	14 (6.8) (2.6)
Tongue fungal infection	3 (2.4) (2.9)	0	4 (2.2) (1.0)	5 (2.4) (0.9)
Fungal skin infection	0	1 (1.3) (1.6)	3 (1.6) (0.8)	4 (1.9) (0.7)
Fungal esophagitis	1 (0.8) (1.0)	1 (1.3) (1.6)	1 (0.5) (0.3)	3 (1.5) (0.5)
Vulvovaginal mycotic infection	2 (1.6) (1.9)	0	0	2 (1.0) (0.4)
Onochomycosis	0	0	2 (1.1) (0.5)	2 (1.0) (0.4)
Fungal pharyngitis	0	0	1 (0.5) (0.3)	1 (0.5) (0.2)
Tinea infections	0	1 (1.3) (1.6)	1 (0.5) (0.3)	2 (1.0) (0.4)
Tinea pedis	0	1 (1.3) (1.6)	0	1 (0.5) (0.2)
Tineas cruris	0	0	1 (0.5) (0.3)	1 (0.5) (0.2)
Serious hypersensitivity reactions	0	0	0	0
Opportunistic infections	1 (0.8) (1.0)	1 (1.3) (1.6)	1 (0.5) (0.3)	3 (1.5) (0.5)
Active tuberculosis	0	0	0	0
Liver enzyme elevation				
ALT increased	6 (4.8) (6.0)	3 (3.8) (4.7)	6 (3.3) (1.6)	13 (6.3) (2.4)
AST increased	4 (3.2) (4.0)	2 (2.5) (3.1)	6 (3.3) (1.6)	10 (4.9) (1.8)
Hepatic enzymes increased	2 (1.6) (1.9)	1 (1.3) (1.6)	1 (0.5) (0.3)	4 (1.9) (0.7)
MACE	0	0	0	0
Malignancies	1 (0.8) (1.0)	0	0	1 (0.5) (0.2)
IBD	0	0	1 (0.5) (0.3)	1 (0.5) (0.2)
Microscopic colitis	0	0	1 (0.5) (0.3)	1 (0.5) (0.2)
Anterior uveitis	0	0	0	0
Neutropenia	0	1 (1.3) (1.6)	5 (2.7) (1.3)	6 (2.9) (1.1)
Drug hypersensitivity	2 (1.6) (1.9)	0	1 (0.5) (0.3)	3 (1.5) (0.5)

	Weeks 0–48†		Weeks 48–152	Weeks 0–152‡
	160 mg BKZ every 4 weeks (n = 126; 113.2 patient-years)	320 mg BKZ every 4 weeks (n = 80; 72.9 patient-years)	Total BKZ (N = 183; 392.7 patient-years)	Total BKZ (N = 206; 570.1 patient-years)
Injection site reactions	0	3 (3.8) (4.9)	0	3 (1.5) (0.5)
SIB	1 (0.8) (1.0)	0	0	1 (0.5) (0.2)
Depression	1 (0.8) (1.0)	1 (1.3) (1.6)	2 (1.1) (0.5)	4 (1.9) (0.7)

152週までに206例中184例（89.3%）に1回以上の有害事象（126.4/100人年）が発生し，206例中22例（10.7%）が1回以上の重症の有害事象（4.1/100人年）を経験した.

Coates LC, et al. Arthritis Rheumatol. 2022 ;74:1959.

Bimekizumab in patients with psoriatic arthritis, naive to biologic treatment: a randomised, double-blind, placebo-controlled, phase 3 trial (BE OPTIMAL)

Introduction

Method

Result

Discussion

Method: Study design

BE OPTIMAL試験は52週間の第3相無作為化二重盲検プラセボ比較試験である.

本試験は14カ国（オーストラリア, ベルギー, カナダ, チェコ共和国, フランス, ドイツ, ハンガリー, イタリア, 日本, ポーランド, ロシア, スペイン, イギリス, アメリカ）の病院, 診療所, 医院, 研究センターなどの135施設で行われた.

Method: Study design

本試験は2～5週間のスクリーニング期間，16週間のプラセボ対照二重盲検治療期間，36週間の積極的治療盲検治療期間で構成された.

52週目を終了し，適格基準を満たした患者はオープンラベル延長試験に登録することができ，前治療にかかわらず4週間ごとにビメキズマブ160mgを皮下投与した.

オープンラベル延長試験に参加しなかった患者，あるいは早期に治療を中止した患者はビメキズマブ最終投与から20週間後に安全性追跡調査を実施した.

今回は，初回投与から24週目までのデータを報告する.
（スクリーニング期間を除いたプラセボ比較期間16週間＋積極的治療盲検期間8週間）

Method: Patients

対象は18歳以上で，スクリーニングの少なくとも6ヶ月前から乾癬性関節炎の分類基準(CASPAR分類基準)を満たす成人発症の患者
患者は圧痛関節数（TJC）が3以上（68関節中），腫脹関節数（SJC）が3以上（66関節中），1つ以上の活動性乾癬病変・乾癬の病歴（どちらかまたは両方）がある活動性の乾癬性関節炎を有していた.

非ステロイド性抗炎症薬，経口コルチコステロイド，または安定した用量のcsDMARDs併用は，対象・除外基準の制限のもとで許可された.
現在または過去に乾癬性関節炎または乾癬の治療で，生物学的製剤使用のある患者は除外した.

Table 6. The CASPAR criteria*

To meet the CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from the following 5 categories:

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis.
   Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.†
   A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider.
   A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report.
2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination.
3. A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range.
4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist.
5. Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.

* The CASPAR criteria have specificity of 98.7% and sensitivity of 91.4%.
† Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.

Supplement

表 1　CASPAR 分類基準（文献 33 をもとに作成）

炎症性筋骨格系疾患（関節，脊椎，または付着部）があり，下記 5 項目で 3 点以上であれば，PsA と診断する（感度 91.4%，特異度 98.7%）

1．乾癬の証拠（a，b，c のうちの 1 つ）	a．現存する乾癬	（2 点）	皮膚科医あるいはリウマチ医によって診断された乾癬性の皮疹や頭皮症状が認められる
	b．乾癬の既往歴	（1 点）	患者の申告，かかりつけ医，皮膚科医，リウマチ医あるいは他の医療従事者により乾癬の既往が確認されている
	c．乾癬の家族歴	（1 点）	第一親等，第二親等の家族に乾癬の既往歴がある
2．爪乾癬		（1 点）	爪甲剝離，点状陥凹，爪甲下角質増殖などの典型的な乾癬性爪病変が認められる
3．リウマトイド因子（RF）陰性		（1 点）	リウマトイド因子陰性（基準値以下） 測定はラテックス法以外の ELISA 法または比濁法が好ましい
4．指趾炎（a か b のどちらか）	a．現存する指趾炎	（1 点）	指全体の腫脹が認められる
	b．指趾炎の既往歴	（1 点）	リウマチ医によって診断・記録された既往歴がある
5．関節近傍部の骨新生の画像所見		（1 点）	手足の単純 X 線画像所見で関節辺縁近くに境界不明瞭な骨形成（骨棘形成は除く）が認められる

日本皮膚科学会乾癬性関節炎診療ガイドライン作成委員会:
乾癬性関節炎診療ガイドライン 2019

Taylor W, et al. Arthritis Rheum. 2006 ;54 :2665.

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the patient.

2. Patient is considered reliable and capable of adhering to the protocol (e.g. able to understand and complete diaries), visit schedule, or medication intake according to the judgment of the Investigator.

3. Patient is male or female at least 18 years of age.

4. Female patients must be:

    - Postmenopausal (menopause is defined as 12 consecutive months of amenorrhoea, for which there is no other obvious pathological or physiological cause),

    - Permanently sterilised (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy),

    - Or, if of childbearing potential (and engaged in sexual activity that could result in procreation), must be willing to use a highly effective method of contraception throughout the duration of the study until 20 weeks after last administration of investigational medicinal product (IMP), and have a negative pregnancy test at screening and immediately prior to the first dose. The following methods are considered highly effective when used consistently and correctly:

        - Combined (oestrogen and progestogen) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)

        - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)

        - Intrauterine device

        - Intrauterine hormone-releasing system

        - Vasectomised partner

        - Abstinence as a form of birth control is generally not allowed in the study unless abstinence is in accordance with a patient's preferred and common lifestyle.

    Study personnel must confirm the continued use of abstinence is still in accordance with the patient's lifestyle at regular intervals during the study.

5. Patient has a documented diagnosis of adult-onset PsA classified and meets the Classification Criteria for Psoriatic Arthritis (CASPAR) for at least 6 months prior to screening with active PsA and must have at Baseline TJC ≥3 out of 68 and SJC ≥3 out of 66 (dactylitis of a digit counts as one joint each).

6. Patient must be negative for rheumatoid factor and anti-cyclic citrullinated peptide (CCP) antibodies.

7. Patient must have at least one active psoriatic lesion(s) and/or a documented history of psoriasis.

8. Patient must be considered, in the opinion of the investigator, to be a suitable candidate for treatment with adalimumab per regional labelling and has no contraindications to receive adalimumab as per the local label.

9. Patients who are regularly taking NSAIDs/cyclooxygenase (COX)-2 inhibitors or analgaesics (including mild opioids) as part of their PsA therapy are required to be on a stable dose/dose regimen for at least 14 days before Baseline and should remain on a stable dose until week 16.

10. Patients taking oral corticosteroids must be on an average daily dose of ≤10 mg/day prednisone or equivalent for at least 14 days before baseline and should remain on a stable dose until week 16.

11. Patient taking methotrexate (MTX) (≤25 mg/week) are allowed to continue their medication if started at least 12 weeks prior to baseline, with a stable dose for at least 8 weeks before randomisation. Dose, dosing schedule and route of administration (oral or subcutaneous) should remain stable until week 16. It is strongly recommended that patients taking MTX are also taking folic acid supplementation.

12. Patients taking leflunomide (LEF) (≤20 mg/day or an average of 20 mg/day if not dosed daily) are allowed to continue their medication if started at least 12 weeks prior to baseline, with a stable dose for at least 8 weeks before randomisation. Dose and dosing schedule should remain stable until week 16.

13. Patient taking sulfasalazine (SSZ) (up to 3 g/day, for arthritis or 4 g/day if in accordance with local standard of care, hydroxychloroquine (HCQ) (up to 400 mg/day), or apremilast (up to 60 mg/day and dosed as per local label) are allowed to continue their medication if started 8 weeks prior to baseline, with a stable dose for at least 4 weeks before randomisation. Dose and dosing schedule should remain stable until week 16.

Supplement
-Inclusion Criteria-

NSAIDs/COX-2阻害剤服用患者はベースラインの14日前から安定した用量で16週目まで安定した用量を維持していること.

経口コルチコステロイド服用患者はベースライン前の14日間から平均10mg/day以下のプレドニゾンで16週目まで安定した用量を維持していること

メトトレキサート(≦25mg/週)服用患者はベースラインの12週間前に投与を開始し，無作為化8週間前から安定した投与量であること.

Supplement
-Exclusion Criteria-

1. Female patients who are breastfeeding, pregnant, or plan to become pregnant during the study or within 20 weeks following last dose of IMP.

2. Patients with current or prior exposure to any biologics for the treatment of PsA or psoriasis, including participation in a bimekizumab clinical study who received at least one dose of IMP (including placebo).

3. Patient previously participated in another study of a medication (systemic) under investigation. Patient must be washed out of the medication for 12 weeks or at least five half-lives prior to the baseline visit, whichever is greater, or is currently participating in another study of a medication (systemic) under investigation, with the exception of patients who were screen failures in BE COMPLETE.

4. Patient previously participated in another study of a medical device under investigation within the 4 weeks prior to the screening visit or is currently participating in another study of a medical device under investigation.

5. Patient has a known hypersensitivity to any excipients of bimekizumab or adalimumab.

6. Patient is taking or has taken prohibited PsA or psoriasis medications without meeting the mandatory wash-out period relative to the baseline visit.

7. Patient has an active infection or history of infections as follows:

    - Any active infection (except common cold) within 14 days prior to Baseline.
    - A serious infection, defined as requiring hospitalisation or intravenous anti-infectives within 2 months prior to baseline.
    - A history of opportunistic, recurrent or chronic infections that, in the opinion of the investigator, might cause this study to be detrimental to the patient. Opportunistic infections are infections caused by uncommon pathogens (e.g. pneumocystis jirovecii, cryptococcosis) or unusually severe infections caused by common pathogens (e.g. cytomegalovirus, herpes zoster).

8. Patient has concurrent acute or chronic viral hepatitis B or C or human immunodeficiency virus (HIV) infection. Patients who have evidence of or tested positive for hepatitis B or hepatitis C are excluded.

    - A positive test for the hepatitis B virus is defined as:
        - Positive for hepatitis B surface antigen; or,
        - positive for anti-hepatitis B core antibody
    - A positive test for the hepatitis C virus (HCV) is defined as:
        - positive for hepatitis C antibody (anti-HCV antibody), and
        - positive via a confirmatory test for HCV (for example, HCV polymerase chain reaction)

9. Patient has received any live (includes attenuated) vaccination within the 8 weeks prior to the baseline (e.g. inactivated influenza and pneumococcal vaccines are allowed, but nasal influenza vaccination is not permitted).

10. Patient has received Bacillus Calmette-Guérin (BCG) vaccinations within 1 year prior to the baseline visit.

11. Patient has known tuberculosis (TB) infection, is at high risk of acquiring TB infection, or has current or history of nontuberculous mycobacterium (NTMB) infection. A patient with latent tuberculosis (LTB) (a positive interferon gamma release assay [IGRA] and diagnosis confirmed by TB specialist) may be rescreened once and enrolled after receiving at least 4 weeks of appropriate LTB infection (LTBI) therapy and if no evidence of therapy-related hepatotoxicity has occurred prior to the first injection (alanine aminotransferase [ALT]/aspartate aminotransferase [AST] remain ≤3 times upper limit of normal [ULN]). Patient has a past history of active TB involving any organ system unless adequately treated according to World Health Organization/Center for Disease Control and Prevention therapeutic guidance and proven to be fully recovered upon consult with a TB specialist.

12. Patient has a history of a lymphoproliferative disorder including lymphoma and/or current signs and symptoms suggestive of lymphoproliferative disease.

13. Patient has a diagnosis of inflammatory conditions other than psoriasis or PsA including, but not limited to rheumatoid arthritis (RA), sarcoidosis, systemic lupus erythematosus, and reactive arthritis. Patients with a diagnosis of Crohn's disease, ulcerative colitis, or other inflammatory bowel disease (IBD) are allowed as long as they have no active symptomatic disease at screening or baseline.

14. Patient had acute anterior uveitis within 6 weeks of baseline.

15. Patients with fibromyalgia or osteoarthritis symptoms that in the Investigator's opinion would have potential to interfere with efficacy assessments.

16. Patient has any active malignancy or history of malignancy within 5 years prior to the Screening Visit EXCEPT treated and considered cured cutaneous squamous or basal cell carcinoma, or in situ cervical cancer.

17. Patient has a form of psoriasis other than chronic plaque-type (eg, pustular, erythrodermic and guttate psoriasis, or drug-induced psoriasis).

18. Patient has had major surgery (including joint surgery) within the 3 months prior to Baseline, or planned surgery within 6 months after entering the study.

19. Patient has any systemic disease (i.e. cardiovascular, neurological, renal, liver, metabolic, GI, haematological, immunological, etc.) considered by the Investigator to be uncontrolled, unstable or likely to progress to a clinically significant degree during the course of the study.

20. Patient has had myocardial infarction or stroke within the 6 months prior to the screening visit.

21. Patient has laboratory abnormalities at screening, including any of the following:

    - ≥3x ULN of any of the following: ALT, AST, alkaline phosphatase (ALP); or >ULN total bilirubin (≥1·5xULN total bilirubin if known Gilbert's syndrome)
    - White blood cell count <3·0x10^3/μL
    - Absolute neutrophil count <1·5x10^3/μL
    - Lymphocyte count <500 cells/μL
    - Haemoglobin <8·5 g/dL
    - Creatinine >2 mg/dL
    - Any other laboratory abnormality, which, in the opinion of the investigator, will prevent the patient from completing the study or will interfere with the interpretation of the study results.

Individual screening tests for which the results are in error, borderline, or indeterminate for inclusion in the study, can be repeated once for confirmation during the screening period. Upon retesting, patients whose results remain outside this threshold should not be randomised.

22. Patient has any other condition including medical or psychiatric which, in the investigator's judgment, would make the patient unsuitable for inclusion in the study.

23. Presence of active suicidal ideation, or positive suicide behavior using the "Screening" version of the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) with either of the following criteria:

    - Patient has a history of a suicide attempt within the 5 years prior to the Screening Visit.
    - Patients with a history of a suicide attempt more than 5 years ago should be evaluated by a mental healthcare professional (e.g. locally licensed psychiatrist, psychologist, or master's level therapist) before enrolling into the study.
    - Patient has suicidal ideation in the past month prior to the screening visit as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Screening" version of the eC-SSRS

24. Patient has presence of moderately severe major depression, or severe major depression, indicated by a Score ≥15 using the screening PHQ-9. Medication used to treat depression should be stable for 8 weeks prior to Baseline.

25. Patients taking PsA medications other than MTX, SSZ, apremilast, HCQ, LEF, NSAIDs/COX-2 inhibitors, and oral corticosteroids as outlined in the Inclusion criteria. Stable doses/regimens of analgaesics are also permitted.

26. Patient has a history of chronic alcohol or drug abuse within 6 months prior to screening evaluated by the investigator based on medical history, site interview, and results of the specified urine drug screen.

27. Patient is a member of investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

28. Patient is a UCB employee or is an employee of third-party organisations involved in the study.

Method: Randomisation and masking

患者は3:2:1(地域[北米, 西ヨーロッパ, 東ヨーロッパ, アジア]とベースライン時の骨びらん数[0 or 1以上]で層別化)に4週間毎にビメキズマブ160mg皮下投与(ビメキズマブ群), 2週間毎にプラセボ皮下投与(プラセボ群), 2週間ごとにアダリムマブ40mg皮下投与(アダリムマブ群)にランダムに割り付けた.

プラセボ群は16週目以降に, ビメキズマブ160mgの4週毎の皮下投与(52週目まで)に変更した.
ビメキズマブ群またはアダリムマブ群は52週目まで投与が継続した.
患者の登録は治験責任医師または治験分担医師が行った.

Method: Randomisation and masking

対話型音声システムまたはウェブ回答システムにより，患者は無作為化スケジュールに基づいて，治療レジメンに割り付けられた.

ビメキズマブ群はアダリムマブ群スケジュールに合わせて，プラセボが投与され，治療の盲検化がなされた.

試験期間中は患者，治験責任医師，スポンサーは治療割り付けについて盲検化された.

Method: Procedures

ベースライン時にビメキズマブ, プラセボ(0.9%塩化ナトリウム水溶液), アダリムマブを投与した.

盲検化を維持するため, ビメキズマブを4週間ごとに投与し, プラセボはその間に投与した.
プラセボとアダリムマブは2週間ごとに投与した.

試験薬は腹部外側壁と大腿部上外側に皮下注射で投与した.

Method: Procedures

有効性はベースライン時および2, 4, 8, 12, 16, 20, 24週目に評価した.

安全性はベースラインと各訪問時に評価した. 手, 手首, 足の構造的損傷の進行はvan der Heijde modified Total Sharp Score（vdHmTSS）を用い, 骨びらんと関節裂隙の程度を定量化し, 単純X線写真で評価した.ベースラインと16週目に手と足のX線写真を撮影した.
画像は治療内容や撮影期間を盲検化された経験豊富な2人の読影医が独立して読影し, そのスコアを平均した. 大幅に意見が異なる場合は3人目の読影医が判定を行った.

16週目以降, 治験責任医師による評価で治療に乏しいと判断された患者は, 事前に指定された治療薬による救助療法を受けることができた.
救助療法が必要な患者は指定された治療を継続した.

Method: Outcomes

主要評価項目は投与16週目に米国リウマチ学会基準（ACR；ACR50）で50％以上の奏効を達成した患者の割合

16週目の副次評価項目は以下の項目が事前に計画された.

- 健康評価質問票（HAQ-DI）合計スコアのベースラインからの変化
- 体表面積（BSA）の3％以上の乾癬患者での乾癬面積・重症度指数（PASI 90）のベースラインから90％以上の改善
- Short Form 36-item Health Survey Physical Component Summary (SF-36 PCS)のベースラインからの変化
- MDA（minimal disease activity）反応を達成した患者の割合

:（TJC ≦ 1, SJC ≦ 1, PASI ≦ 1, BSA ≦ 3%, pVAS[0-100] ≦15, PGA[0-100] ≦20, HAQ-DI ≦0.5, Leeds Enthesitis Index [LEI]による圧痛点が≦1）

- 高感度CRP濃度 6mg/L以上または骨びらんを少なくとも1つ有する患者のvdHmTSSのベースラインからの変化
- LEIを用いて評価した腱鞘炎の改善
- Leeds Dactylitis Index（LDI）を用いて評価した指炎の改善
- X線写真でのvdHmTSSのベースラインからの変化

Method: Outcomes

16週目の追加有効性評価項目は以下の項目が事前に計画された.

- 20%以上の奏効（ACR20）
- 70%以上の奏効（ACR70）
- BSA3%以上の乾癬患者のPASIの75%以上の改善（PASI75）
- BSA3%以上の乾癬患者のPASIの100%改善（PASI100）
- ベースライン時にBSA3%以上の乾癬病変を有していた, ACR50とPASI100を同時に満たす患者割合
- 非常に低い疾患活動性を有する患者割合（VLDA, 7つのMDA基準の全てを満たす）患者の割合
- ベースライン時に乾癬性皮膚病変を有する患者で治験医師グローバル評価（IGA）スコアが0または1で,

ベースラインから少なくとも2grade低下した患者の割合

- ベースライン時のHAQ-DIが0.35以上の患者での臨床的に重要な最小差（MCID）を有する患者の割合
- PsAID-12（Psoriatic Arthritis Impact of Disease）総スコアのベースラインからの変化
- PtAAP（Patient's Assessment of Arthritis Pain）スコアのベースラインからの変化
- FACIT-Fatigue（Functional Assessment of Chronic Illness Therapy- Fatigue）スコアのベースラインからの変化

Supplement

ACR Core set

Disease activity measure	Method of assessment
1. Tender joint count†	ACR tender joint count (see ref. 47), an assessment of 68 joints. The joint count should be done by scoring several different aspects of tenderness, as assessed by pressure and joint manipulation on physical examination. The information on various types of tenderness should then be collapsed into a single tender-versus-nontender dichotomy.
2. Swollen joint count‡	ACR swollen joint count (see ref. 47), an assessment of 66 joints. Joints are classified as either swollen or not swollen.
3. Patient's assessment of pain	A horizontal visual analog scale (usually 10 cm) or Likert scale assessment of the patient's current level of pain.
4. Patient's global assessment of disease activity	The patient's overall assessment of how the arthritis is doing. One acceptable method for determining this is the question from the AIMS instrument: "Considering all the ways your arthritis affects you, mark 'X' on the scale for how well you are doing." An anchored, horizontal, visual analog scale (usually 10 cm) should be provided. A Likert scale response is also acceptable.
5. Physician's global assessment of disease activity	A horizontal visual analog scale (usually 10 cm) or Likert scale measure of the physician's assessment of the patient's current disease activity.
6. Patient's assessment of physical function	Any patient self-assessment instrument which has been validated, has reliability, has been proven in RA trials to be sensitive to change, and which measures physical function in RA patients is acceptable. Instruments which have been demonstrated to be sensitive in RA trials include the AIMS, the HAQ, the Quality (or Index) of Well Being, the MHIQ, and the MACTAR.
7. Acute-phase reactant value	A Westergren erythrocyte sedimentation rate or a C-reactive protein level.

David T, et al. Arthritis and Rheum. 1993 ;36 :6.

Feldman SR, et al. Ann Rheum Dis. 2005 ;64 :65.

PASI score

Table 1 Elements of the Psoriasis Area and Severity Index (PASI)*

		Head	Upper extremities	Trunk	Lower extremities
1	Redness†				
2	Thickness†				
3	Scale†				
4	Sum of rows 1, 2, and 3				
5	Area score‡				
6	Score of row 4×row 5×the area multiplier	row 4×row 5×0.1	row 4×row 5×0.2	row 4×row 5×0.3	row 4×row 5×0.4
7	**Sum row 6 for each column for PASI score**				

**Steps in generating PASI score*
(*a*) Divide body into four areas: head, arms, trunk to groin, and legs to top of buttocks.
(*b*) Generate an average score for the erythema, thickness, and scale for each of the 4 areas (0 = clear; 1–4 = increasing severity)†.
(*c*) Sum scores of erythema, thickness, and scale for each area.
(*d*) Generate a percentage for skin covered with psoriasis for each area and convert that to a 0–6 scale (0 = 0%; 1 = <10%; 2 = 10–<30%; 3 = 30–<50%; 4 = 50–<70%; 5 = 70–<90%; 6 = 90–100%).
(*e*) Multiply score of item (*c*) above times item (*d*) above for each area and multiply that by 0.1, 0.2, 0.3, and 0.4 for head, arms, trunk, and legs, respectively.
(*f*) Add these scores to get the PASI score.
†Erythema, induration and scale are measured on a 0–4 scale (none, slight, mild, moderate, severe)
‡*Area scoring criteria* (score: % involvement)
0: 0 (clear)
1: <10%
2: 10–<30%
3: 30–<50%
4: 50–<70%
5: 70–<90%
6: 90–<100%

MDA

A core set definition therefore places patients with PsA in MDA when they meet 5/7 of the following criteria:

- Tender joint count $\leqslant 1$
- Swollen joint count $\leqslant 1$
- PASI $\leqslant 1$ or BSA $\leqslant 3$
- Patient pain VAS $\leqslant 15$
- Patient global activity VAS $\leqslant 20$
- HAQ $\leqslant 0.5$
- Tender entheseal points $\leqslant 1$

Coates LC, et al. Ann Rheum Dis. 2010 ;69:48.

Table 5
Components included in disease activity measure.

	Joints	Entheses	Dactylitis	Spine	PtGA	PtP	EGA	Physical function	Skin	CRP
Multi-dimensional scores										
CPDAI	+	+	+	+	−	−	−	+	+	−
GRACE/AMDF[73;77]	+	−	−	−	+	+	−	+	+	−
MDA	+	+	−	−	+	+	−	+	+	−
PASDAS	+	+	+	−	+	−	+	+		+
Unidimensional Arthritis score										
DAPSA	+	−	−	−	+	+	−	−	−	+

CPDAI, composite psoriatic disease activity index; DAPSA, disease activity index for psoriatic arthritis; GRACE, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) composite exercise; AMDF, Arithmetic Mean of Desirability Function; MDA, minimal disease activity; PASDAS, Psoriatic arthritis disease activity score; CRP, C-reactive protein; EGA, evaluator (physician) global assessment; PtGA, patient global assessment; PtP, Patient Pain assessment.

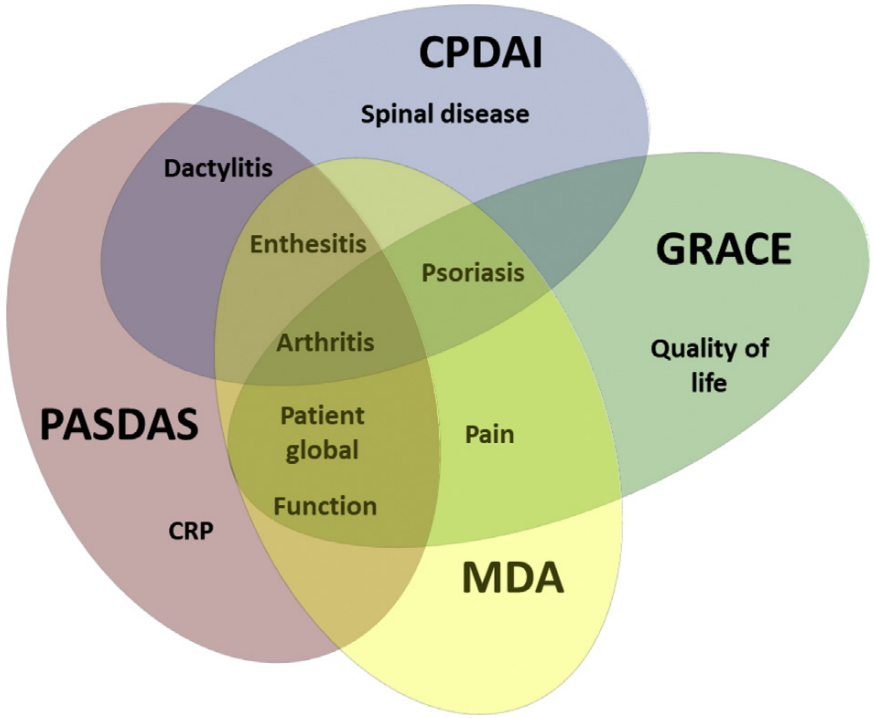


Fig. 1. Venn diagram of multi-dimensional composite disease activity measures for PsA and their assessed domains.

Supplement

MDAは寛解～低疾患活動性の指標で，PsAにおけるT2Tの指標としても用いられる．

多くのドメインを比較的容易に評価できる点が利点である．
特に，骨病変の進行と関連がある．

Kerschbaumer A et al.
Best Pract Res Clin Rheumatol. 2018 ;32 :401.

Method: Outcomes

安全性は，治療上緊急に発生した有害事象（TEAE），治療上緊急に発生した重篤な有害事象（SAE），試験中止に至ったTEAEの発生とした.

TEAEは，すべての試験群で0週から16週までのビメキズマブ群およびアダリムマブ群では0週から24週までで報告した.

プラセボからビメキズマブ投与に変更した患者は16週目から24週目までのビメキズマブ群として事象を報告した.

Method: Outcomes

事前に規定した安全性の項目は，感染症（重症，日和見感染，真菌症，結核），好中球減少，過敏症，自殺念慮および行動，主要な心血管有害事象，肝酵素上昇，悪性腫瘍，炎症性腸疾患とした

自殺企図，主要な心血管系有害事象，炎症性腸疾患の事象は，外部の判定委員会が判定を行った.

Method: Statistical analysis

主要評価項目のビメキズマブ群とプラセボ群の比較での統計的検出力は第2相BE ACTIVE試験データおよび他の介入試験データに基づき，16週目のACR50奏功率はビメキズマブ群が43.8%，プラセボ群が16.0%と仮定した.

これらの仮定のもとで，ビメキズマブ群420例，プラセボ群280例のサンプルサイズは主要評価項目のプラセボ群と比較しビメキズマブ群が統計学的優越性を示す99%以上の検出力があった.
また，副次評価項目でも十分な検出力を確保できると判断した.

Method: Statistical analysis

すべてのサンプルサイズの計算はnQuery Advisor（バージョン7.0）を使用し，両側検定で0.05の有意水準で行った.

なお，アダリムマブ群とビメキズマブ群またはプラセボ群を比較するための検出力は算出していない.

アダリムマブ群とビメキズマブ群またはプラセボ群との統計的な比較は行わなかった.

Method: Statistical analysis

本試験の24週目の有効性及び安全性解析は事前に計画した.
24週目を終了後, または24週目以前に試験中断後に全ての患者（intention-to-treat集団）で解析が行われた.

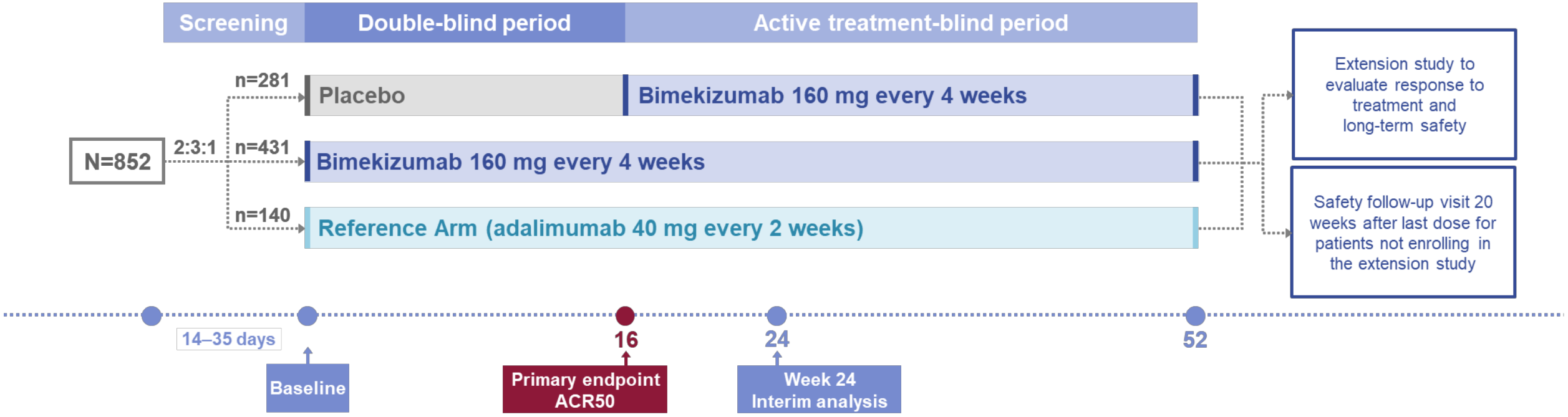
安全性は24週目までのビメキズマブ群, プラセボ群, アダリムマブ群で, 試験薬を1回以上投与された, 全ての患者を対象にして解析した.

ベースライン時の腱鞘炎/指炎(どちらかまたは両方) を有する患者数が予想より少なかった.
十分な検出力を確保するため, これらの治癒に関する評価項目はBE COMPLETEのデータと統合するよう事前に指定した.

Method: Statistical analysis

各評価項目の統計的有意性はαレベル0.05を用いた両側検定で評価した.
主要評価/副次評価項目の欠損値は非応答者代入法を用いた.
治療, 地域, ベースライン時の骨びらん(0または1以上)で調整ロジスティック回帰を用いて,
評価項目のオッズ比(OR), 信頼区間(CI), およびp値を算出した.
連続的な評価項目の欠損データは多重代入法を用いた.
参照ベースの多重代入法を用いて, 副次的評価項目の階層的検定を行った.
治療, 地域, ベースライン時の骨びらん, ベースライン値を共変量に調整したANCOVAを用いて,
評価項目の最小二乗平均, SE, 最小二乗平均の差, CI, およびp値を算出した.
統計解析での骨びらん層別化はベースライン時の実際の骨びらんに基づいた.
すべての解析はSASを用いた.

Method: Study design



Bimekizumab in patients with psoriatic arthritis, naive to biologic treatment: a randomised, double-blind, placebo-controlled, phase 3 trial (BE OPTIMAL)

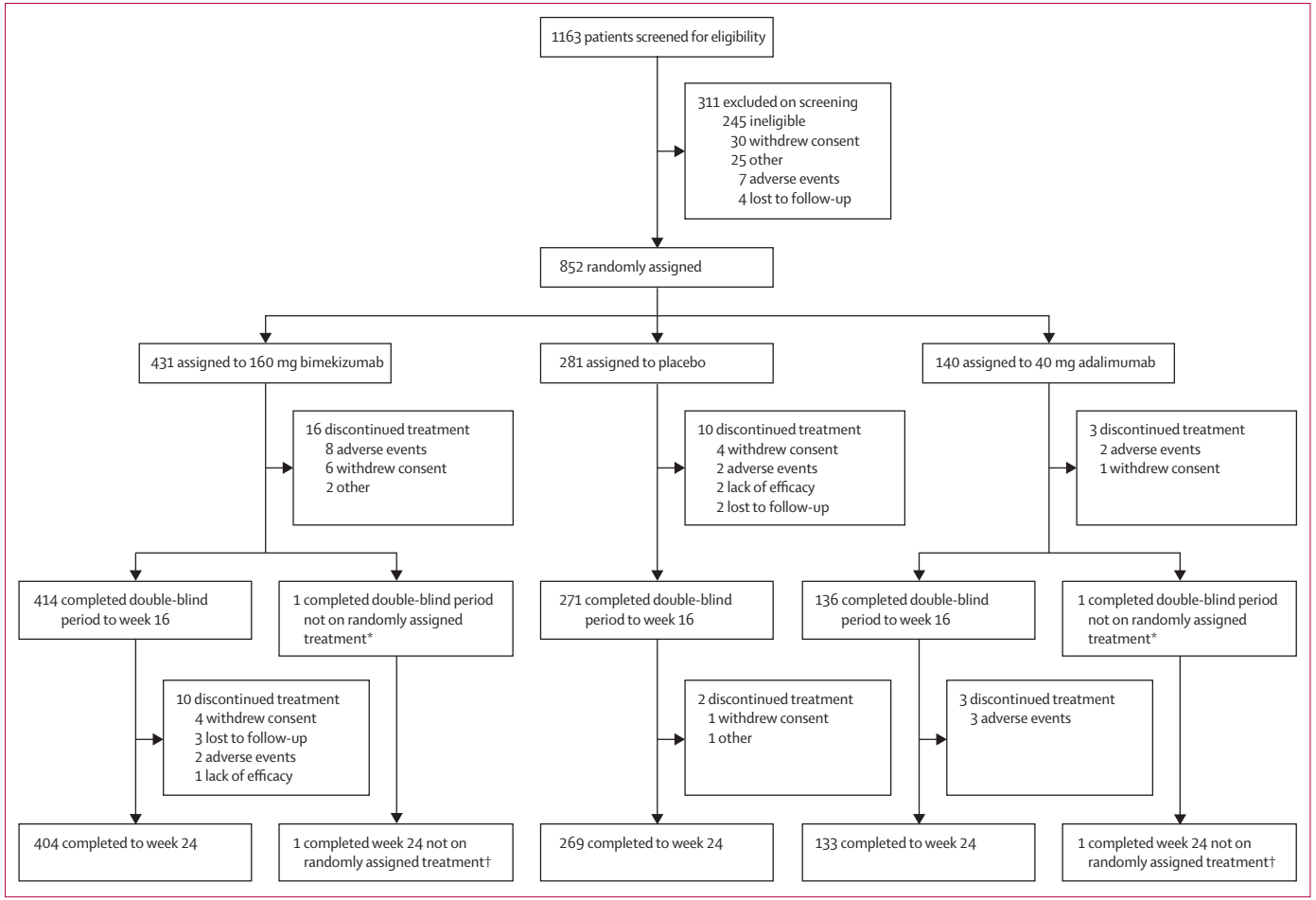
Introduction

Method

Result

Discussion

Result



	Placebo (n=281)	Bimekizumab 160 mg (n=431)	Reference group (adalimumab 40 mg) (n=140)	All patients (n=852)
Any important protocol deviation	38 (13·5%)	48 (11·1%)	18 (12·9%)	104 (12·2%)
Inclusion criteria deviation	3 (1·1%)	3 (0·7%)	1 (0·7%)	7 (0·8%)
Exclusion criteria deviation	0	0	0	0
Withdrawal criteria deviation	1 (0·4%)	0	0	1 (0·1%)
Prohibited concomitant medication use	14 (5·0%)	14 (3·2%)	7 (5·0%)	35 (4·1%)
Incorrect treatment or dose	2 (0·7%)	4 (0·9%)	0	6 (0·7%)
Treatment non-compliance	0	0	0	0
Procedural non-compliance	17 (6·0%)	22 (5·1%)	6 (4·3%)	45 (5·3%)
COVID-19 visit deviation	3 (1·1%)	7 (1·6%)	5 (3·6%)	15 (1·8%)
COVID-19 treatment deviation	0	1 (0·2%)	0	1 (0·1%)
COVID-19 termination	0	0	0	0
COVID-19 other important protocol deviation	0	0	0	0

2019年4月3日から2021年10月25日の間に1163例が登録され，852例が無作為に割り当てられた.

852例中821例（96%）が16週目の治療を完了し，806例（95%）が24週目の治療を完了した.

	Placebo (n=281)	Bimekizumab 160 mg every 4 weeks (n=431)	Reference group (adalimumab 40 mg every 2 weeks; n=140)*	All patients (n=852)
Age, years	48·7 (11·7)	48·5 (12·6)	49·0 (12·8)	48·7 (12·3)
Gender				
Male	127 (45%)	201 (47%)	71 (51%)	399 (47%)
Female	154 (55%)	230 (53%)	69 (49%)	453 (53%)
BMI, kg/m²	29·6 (6·1)	29·2 (6·8)	28·4 (5·9)	29·2 (6·4)
Race, White†	270 (96%)	410 (95%)	133 (95%)	813 (95%)
Time since first psoriatic arthritis diagnosis, years‡	5·6 (6·5)	6·0 (7·3)	6·1 (6·8)	5·9 (7·0)
Any conventional synthetic DMARD at baseline	192 (68%)	301 (70%)	99 (71%)	592 (69%)
Methotrexate at baseline	162 (58%)	252 (58%)	82 (59%)	496 (58%)
TJC of 68 joints	17·1 (12·5)	16·8 (11·8)	17·5 (13·1)	17·0 (12·2)
SJC of 66 joints	9·5 (7·3)	9·0 (6·2)	9·6 (7·1)	9·2 (6·7)
High-sensitivity CRP ≥6 mg/L	121 (43%)	158 (37%)	44 (31%)	323 (38%)
Affected BSA ≥3%	140 (50%)	217 (50%)	68 (49%)	425 (50%)
PASI score§	7·9 (5·6)	8·2 (6·8)	8·5 (7·6)	8·1 (6·6)
Bone erosion ≥1 or high-sensitivity CRP ≥6 mg/L or both	236 (84%)	365 (85%)	116 (83%)	717 (84%)
Bone erosion ≥1	210 (75%)	341 (79%)	105 (75%)	656 (77%)
HAQ-DI score¶	0·89 (0·61)	0·82 (0·59)	0·86 (0·54)	0·85 (0·59)
PtAAP score¶	56·8 (23·2)	53·6 (24·3)	56·7 (23·9)	55·2 (23·9)
PhGA score||	57·2 (15·1)	57·2 (16·3)	57·3 (17·5)	57·2 (16·1)
PGA score¶	58·6 (23·5)	54·4 (23·4)	57·1 (21·8)	56·2 (23·2)
SF-36 PCS score¶	36·9 (9·7)	38·1 (9·4)	37·6 (8·8)	37·6 (9·4)
Presence of enthesitis**††	70 (25%)	143 (33%)	36 (26%)	249 (29%)
LEI score	2·9 (1·5)	2·5 (1·5)	2·3 (1·6)	2·6 (1·5)
Presence of dactylitis‡‡§§	33 (12%)	56 (13%)	11 (8%)	100 (12%)
Dactylitic sites	1·5 (0·6)	1·4 (0·8)	1·4 (0·7)	1·4 (0·8)
LDI score	47·3 (41·1)	46·7 (54·3)	49·7 (31·9)	47·3 (47·8)

Data are mean (SD) or n (%). BSA, body surface area; CRP, C-reactive protein; DMARD, disease-modifying

	Placebo (n=281)	Bimekizumab 160 mg every 4 weeks (n=431)	Reference group (adalimumab 40 mg every 2 weeks) (n=140)	All patients (n=852)
Geographic region				
Asia	28 (10·0%)	45 (10·4%)	15 (10·7%)	88 (10·3%)
Eastern Europe	179 (63·7%)	266 (61·7%)	89 (63·6%)	534 (62·7%)
North America	33 (11·7%)	54 (12·5%)	16 (11·4%)	103 (12·1%)
Western Europe	41 (14·6%)	66 (15·3%)	20 (14·3%)	127 (14·9%)
Racial group[a]				
American Indian/Alaskan native	0	1 (0·2%)	0	1 (0·1%)
Asian	7 (2·5%)	17 (3·9%)	4 (2·9%)	28 (3·3%)
Black	0	1 (0·2%)	1 (0·7%)	2 (0·2%)
Native Hawaiian or other Pacific Islander	0	0	0	0
White	270 (96·1%)	410 (95·1%)	133 (95·0%)	813 (95·4%)
Other/mixed	4 (1·4%)	1 (0·2%)	0	5 (0·6%)
Missing	0	1 (0·2%)	2 (1·4%)	3 (0·4%)
PsA subtype				
Polyarticular (symmetric arthritis)	181 (64·4%)	271 (62·9%)	72 (51·4%)	524 (61·5%)
Oligoarticular (asymmetric arthritis)	76 (27·0%)	118 (27·4%)	53 (37·9%)	247 (29·0%)

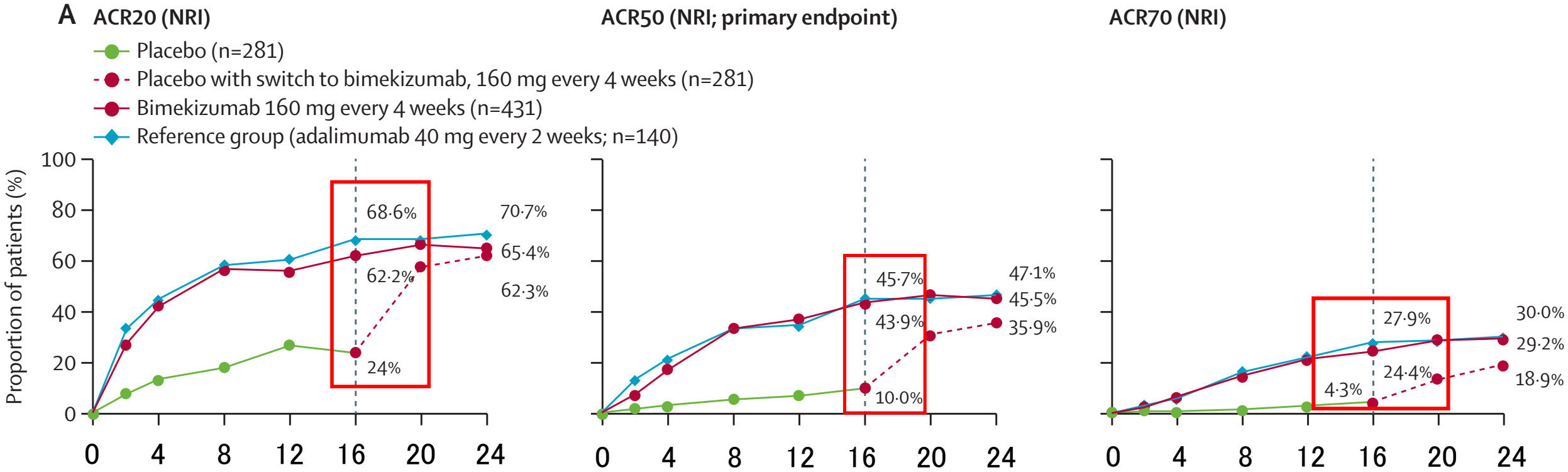
ベースライン時の852例中496例（58%）がメトトレキサート投与治療を受けており，425例（50%）がBSA3%以上の乾癬を有していた．

Result: Primary Outcome

	Week 16				Week 24		
	Placebo (n=281)	Bimekizumab 160 mg every 4 weeks (n=431)	Bimekizumab vs placebo, OR or least squares mean difference (95% CI)	Reference group (adalimumab 40 mg every 2 weeks; n=140)*	Placebo to bimekizumab 160 mg every 4 weeks (n=281)†	Bimekizumab 160 mg every 4 weeks (n=431)	Reference group (adalimumab 40 mg every 2 weeks; n=140)*
Primary efficacy endpoint							
ACR50 response	28 (10%)	189 (44%)	OR 7·1 (4·6 to 10·9); p<0·0001	64 (46%)	101 (36%)	196 (45%)	66 (47%)

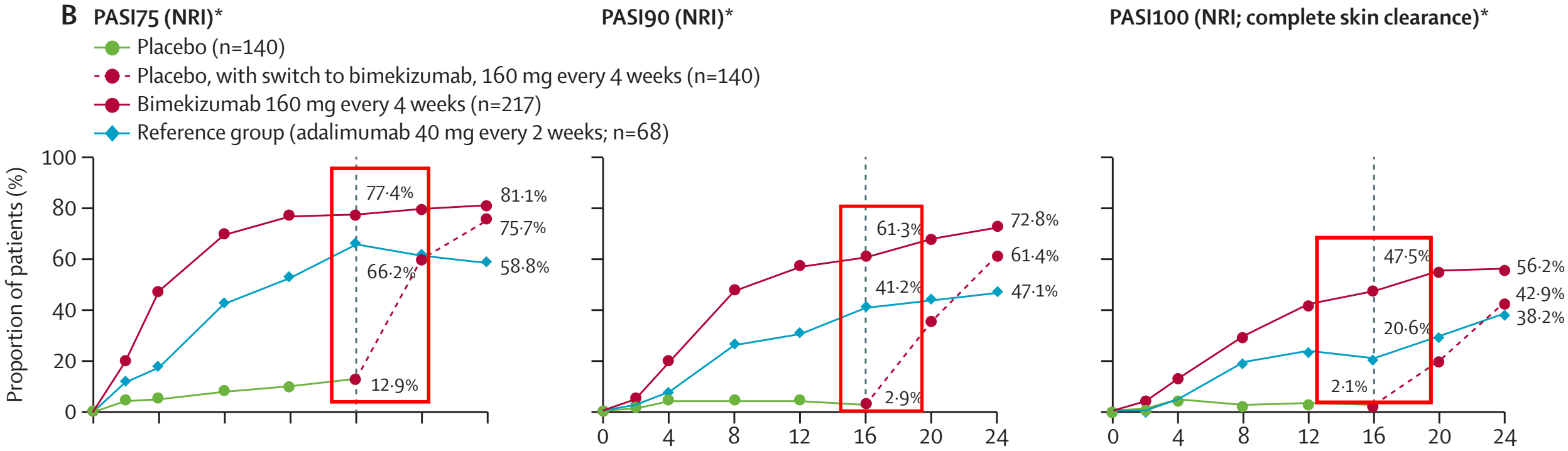
ビメキズマブ群は，プラセボ群に比べ16週目に主要評価項目のACR50に達成した患者の割合が高かった.

事前に指定された，すべての補助的解析は主要解析と一致した.

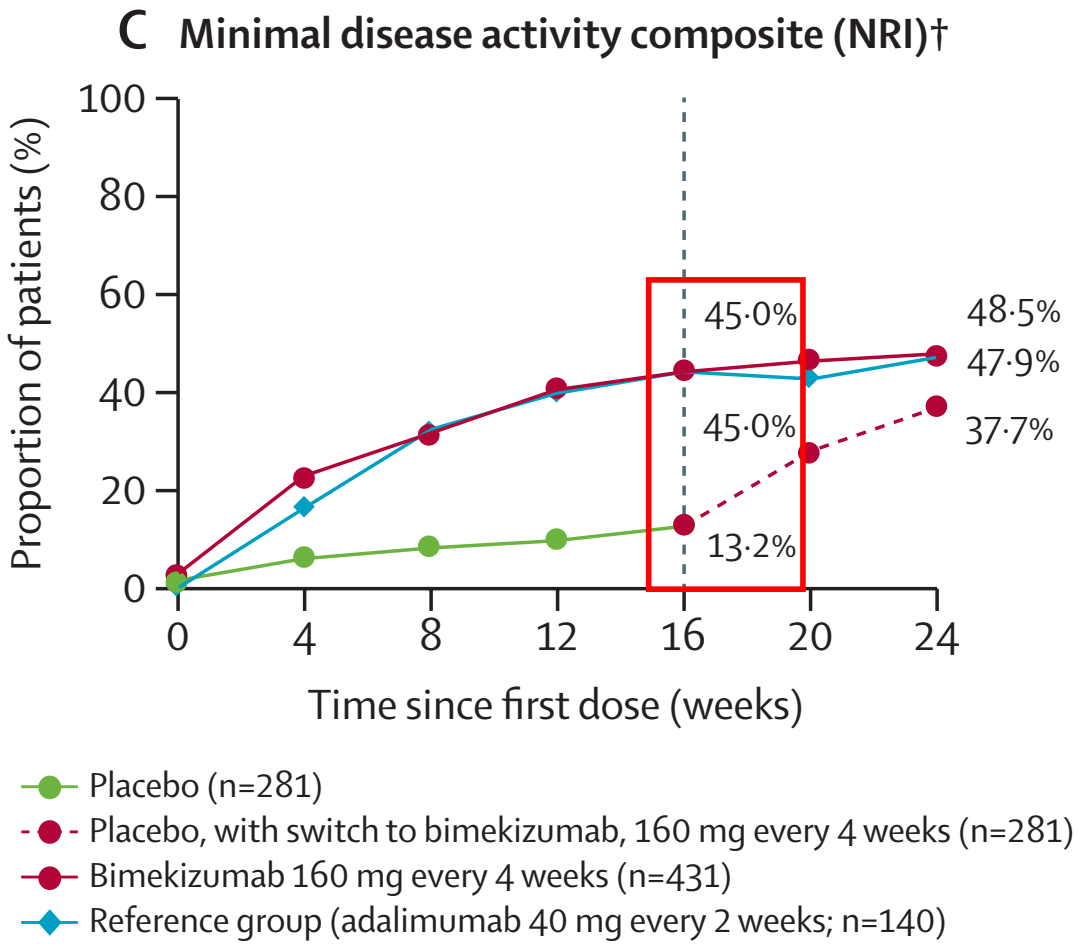


ビメキズマブ群はプラセボ群に比べ，投与16週目にACR20およびACR70に達成した患者割合が高かった.

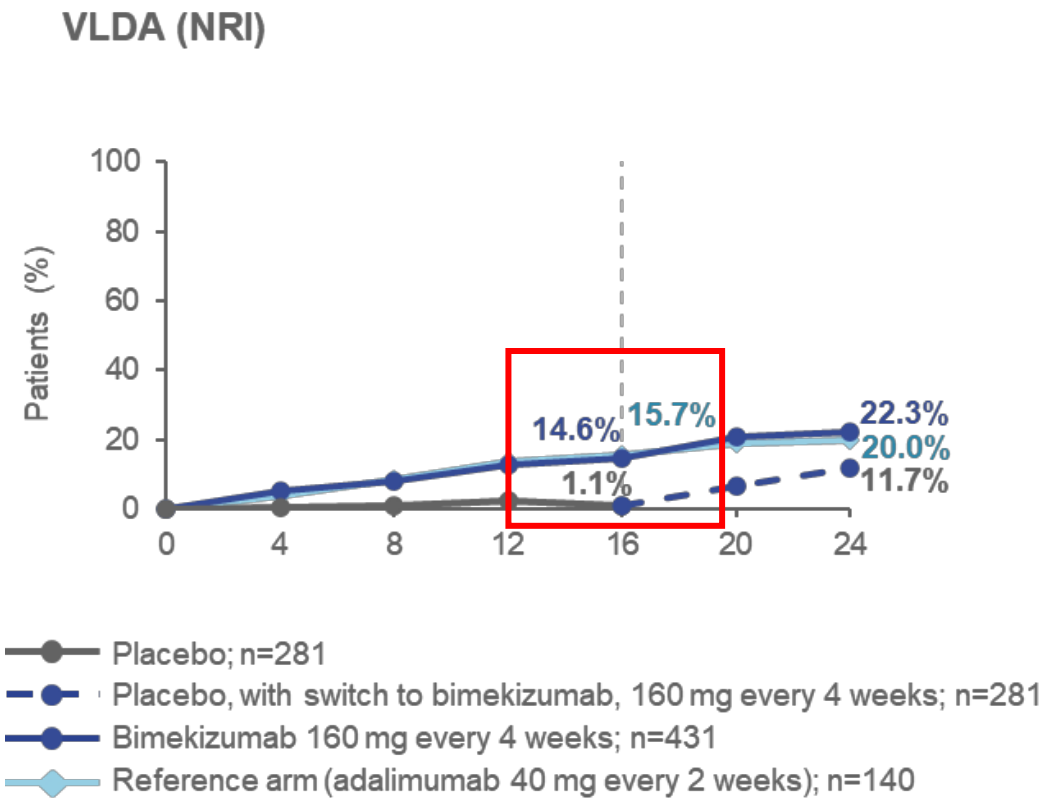
24週目でビメキズマブ群は431例中282例（65%）がACR20，196例（45%）がACR50，126例（29%）がACR70を達成した.



ベースラインでBSAが3%以上の乾癬を有するビメキズマブ群のほぼ半数が16週目にPASI 100を達成した.
24週目にビメキズマブ群217例中176例（81%）がPASI75を，158例（73%）がPASI90を，122例（56%）がPASI100を達成した.



Supplementary Figure S5. Proportion of patients achieving VLDA to week 24



16週目にビメキズマブ群の方がプラセボ群より，有意に高い割合でMDAを達成し，
さらに多くの患者がVLDAも達成した.

	Week 16				Week 24		
	Placebo (n=281)	Bimekizumab 160 mg every 4 weeks (n=431)	Bimekizumab vs placebo, OR or least squares mean difference (95% CI)	Reference group (adalimumab 40 mg every 2 weeks; n=140)*	Placebo to bimekizumab 160 mg every 4 weeks (n=281)†	Bimekizumab 160 mg every 4 weeks (n=431)	Reference group (adalimumab 40 mg every 2 weeks; n=140)*
Ranked secondary endpoints							
HAQ-DI score change from baseline	−0·09 (0·03)	−0·26 (0·02)	Least squares mean difference −0·19 (−0·26 to −0·13); p<0·0001	−0·33 (0·04)	−0·28 (0·03)	−0·30 (0·02)	−0·34 (0·05)
PASI90 response‡	4 (3%) of 140	133 (61%) of 217	OR 63·0 (22·2 to 178·9); p<0·0001	28 (41%) of 68	86 (61%) of 140	158 (73%) of 217	32 (47%) of 68
SF-36 PCS change from baseline	2·3 (0·5)	6·3 (0·4)	Least squares mean difference 4·3 (3·2 to 5·4); p<0·0001	6·8 (0·8)	6·2 (0·5)	7·3 (0·4)	7·3 (0·8)
MDA response	37 (13%)	194 (45%)	OR 5·4 (3·7 to 8·1); p<0·0001	63 (45%)	106 (38%)	209 (48%)	67 (48%)
vdHmTSS change from baseline (subgroup); number of patients, n	0·36 (0·10); 227	0·01 (0·04); 361	Least squares mean difference −0·33 (−0·52 to −0·13); p=0·0012	−0·06 (0·08); 112	..	..	..
Complete resolution of enthesitis (pooled)§	37 (35%) of 106	124 (50%) of 249	OR 1·9 (1·2 to 3·1); p=0·0083	18 (50%) of 36	..	..	..
Complete resolution of dactylitis (pooled)§	24 (51%) of 47	68 (76%) of 90	OR 3·4 (1·6 to 7·6); p=0·0022	9 (82%) of 11	..	..	..
vdHmTSS change from baseline (overall); number of patients, n	0·31 (0·09); 269	0·01 (0·04); 420	Least squares mean difference −0·28 (−0·45 to −0·11); p=0·0012	−0·03 (0·07); 135	..	..	..

ビメキズマブ群はプラセボ群に比べ16週目の構造的進行が有意に少なかった.

	Week 16				Week 24		
	Placebo (n=281)	Bimekizumab 160 mg every 4 weeks (n=431)	Bimekizumab vs placebo, OR or least squares mean difference (95% CI)	Reference group (adalimumab 40 mg every 2 weeks; n=140)*	Placebo to bimekizumab 160 mg every 4 weeks (n=281)†	Bimekizumab 160 mg every 4 weeks (n=431)	Reference group (adalimumab 40 mg every 2 weeks; n=140)*
Additional efficacy outcomes							
ACR20 response	67 (24%)	268 (62%)	..	96 (69%)	175 (62%)	282 (65%)	99 (71%)
ACR70 response	12 (4%)	105 (24%)	..	39 (28%)	53 (19%)	126 (29%)	42 (30%)
PASI75 response‡	18 (13%) of 140	168 (77%) of 217	..	45 (66%) of 68	106 (76%) of 140	176 (81%) of 217	40 (59%) of 68
PASI100 response‡	3 (2%) of 140	103 (47%) of 217	..	14 (21%) of 68	60 (43%) of 140	122 (56%) of 217	26 (38%) of 68
VLDA	3 (1%)	63 (15%)	..	22 (16%)	33 (12%)	96 (22%)	28 (20%)
IGA 0 or 1 response¶	5 (4%) of 129	103 (50%) of 204	..	21 (34%) of 62	62 (48%) of 129	120 (59%) of 204	27 (44%) of 62
HAQ-DI MCID‖	71 (32%) of 221	161 (51%) of 318	..	63 (55%) of 115	106 (48%) of 221	170 (53%) of 318	64 (56%) of 115
PsAID-12 change from baseline	−0·5 (0·1)	−1·8 (0·1)	..	−2·1 (0·2)	−1·8 (0·1)	−2·0 (0·1)	−2·2 (0·2)
PtAAP change from baseline	−6·2 (1·5)	−23·6 (1·3)	..	−25·7 (2·5)	−22·7 (1·6)	−27·0 (1·4)	−27·2 (2·7)
FACIT-Fatigue change from baseline	1·5 (0·5)	3·9 (0·4)	..	5·0 (0·7)	4·5 (0·5)	4·5 (0·4)	5·2 (0·8)

16週目の患者報告式の身体機能および症状は改善認めた.

	Week 0–16			Week 0–24		
	Placebo (n=281)	Bimekizumab 160 mg every 4 weeks (n=431)	Reference group (adalimumab 40 mg every 2 weeks; n=140)	Placebo to bimekizumab 160 mg every 4 weeks (week 16–24; n=271)*	Bimekizumab 160 mg every 4 weeks (n=431)	Reference group (adalimumab 40 mg every 2 weeks; n=140)
Any TEAE	139 (49%)	258 (60%)	83 (59%)	95 (35%)	300 (70%)	96 (69%)
Serious TEAE	3 (1%)	7 (2%)	2 (1%)	3 (1%)	17 (4%)	5 (4%)
Discontinuation due to TEAE	3 (1%)	8 (2%)	3 (2%)	0	12 (3%)	7 (5%)
Drug-related TEAE	35 (12%)	101 (23%)	34 (24%)	27 (10%)	122 (28%)	43 (31%)
Severe TEAE	0	4 (1%)	3 (2%)	1 (<1%)	9 (2%)	3 (2%)
Deaths	0	0	0	0	0	0
Most frequent TEAEs†						
Nasopharyngitis	13 (5%)	40 (9%)	7 (5%)	8 (3%)	50 (12%)	12 (9%)
Upper respiratory tract infection	18 (6%)	21 (5%)	3 (2%)	5 (2%)	26 (6%)	5 (4%)
Headache	7 (2%)	20 (5%)	2 (1%)	6 (2%)	20 (5%)	3 (2%)
Diarrhoea	7 (2%)	16 (4%)	5 (4%)	1 (<1%)	20 (5%)	5 (4%)
Oral candidiasis	0	9 (2%)	0	1 (<1%)	15 (3%)	0
Pharyngitis	4 (1%)	11 (3%)	2 (1%)	3 (1%)	15 (3%)	2 (1%)
Hypertension	11 (4%)	12 (3%)	4 (3%)	5 (2%)	14 (3%)	4 (3%)
Urinary tract infection	4 (1%)	9 (2%)	3 (2%)	4 (1%)	14 (3%)	3 (2%)
Oral herpes	3 (1%)	5 (1%)	3 (2%)	0	7 (2%)	6 (4%)
Increased alanine aminotransferase	2 (1%)	3 (1%)	7 (5%)	1 (<1%)	4 (1%)	8 (6%)
Injection site erythema	0	1 (<1%)	4 (3%)	0	2 (<1%)	5 (4%)
Infections	56 (20%)	131 (30%)	35 (25%)	41 (15%)	170 (39%)	41 (29%)
Serious	0	1 (<1%)	1 (1%)	0	3 (1%)	2 (1%)
Opportunistic	0	0	1 (1%)	3 (1%)	1 (<1%)	1 (1%)
Active tuberculosis	0	0	0	0	0	0
SARS-CoV-2 infections	0	0	0	1 (<1%)	1 (<1%)	0

第16週までにビメキズマブ群431名中258例（60%），プラセボ群281例中139例（49%），アダリムマブ群140例中83例（59%）が少なくとも1つのTEAEが報告された．

有害事象による治療中止は少なかった．
（ビメキズマブ群：8例［2%］，
プラセボ群：3例［1%］，
アダリムマブ群：3例［2%］）．

	Week 0–16			Week 0–24		
	Placebo (n=281)	Bimekizumab 160 mg every 4 weeks (n=431)	Reference group (adalimumab 40 mg every 2 weeks; n=140)	Placebo to bimekizumab 160 mg every 4 weeks (week 16–24; n=271)*	Bimekizumab 160 mg every 4 weeks (n=431)	Reference group (adalimumab 40 mg every 2 weeks; n=140)
Fungal infections	4 (1%)	20 (5%)	1 (1%)	7 (3%)	33 (8%)	1 (1%)
Candida infections	2 (1%)	11 (3%)	0	4 (1%)	18 (4%)	0
Oral candidiasis	0	9 (2%)	0	1 (<1%)	15 (3%)	0
Vulvovaginal candidiasis	2 (1%)	1 (<1%)	0	2 (1%)	1 (<1%)	0
Oesophageal candidiasis	0	0	0	1 (<1%)	1 (<1%)	0
Skin candida	0	1 (<1%)	0	0	2 (<1%)	0
Fungal infections not elsewhere classified	2 (1%)	9 (2%)	0	2 (1%)	15 (3%)	0
Fungal skin infection	0	3 (1%)	0	0	5 (1%)	0
Tongue fungal infection	0	3 (1%)	0	0	3 (1%)	0
Oral fungal infection	0	2 (<1%)	0	0	4 (1%)	0
Onychomycosis	0	1 (<1%)	0	0	1 (<1%)	0
Fungal oesophagitis	0	0	0	1 (<1%)	0	0
Laryngitis fungal	0	0	0	1 (<1%)	0	0
Vulvovaginal mycotic infection	2 (1%)	0	0	0	3 (1%)	0
Tinea infections	0	0	1 (1%)	1 (<1%)	1 (<1%)	1 (1%)
Tinea pedis	0	0	0	0	1 (<1%)	0
Tinea versicolour	0	0	1 (1%)	1 (<1%)	0	1 (1%)
Serious *Candida* infections	0	0	0	0	0	0
Systemic fungal infections	0	0	0	0	0	0
Candida infections leading to study discontinuation	0	1 (<1%)	0	0	1 (<1%)	0

16週目までにビメキズマブ群の20例（5%）が真菌感染症を発症し，11例（3%）がカンジダ感染症であった．

また，そのうち，中等度の口腔カンジダ症が1例報告され，試験中止となった．

	Week 0–16			Week 0–24		
	Placebo (n=281)	Bimekizumab 160 mg every 4 weeks (n=431)	Reference group (adalimumab 40 mg every 2 weeks; n=140)	Placebo to bimekizumab 160 mg every 4 weeks (week 16–24; n=271)*	Bimekizumab 160 mg every 4 weeks (n=431)	Reference group (adalimumab 40 mg every 2 weeks; n=140)
Neutropenia	1 (<1%)	5 (1%)	1 (1%)	1 (<1%)	5 (1%)	2 (1%)
Serious hypersensitivity	0	0	0	0	0	0
Injection site reactions	3 (1%)	5 (1%)	7 (5%)	1 (<1%)	6 (1%)	11 (8%)
Adjudicated suicidal ideation and behaviour	0	0	0	0	0	0
Adjudicated major adverse cardiovascular event	0	0	0	0	1 (<1%)	0
Liver function test changes or enzyme concentration increases‡						
Alanine aminotransferase more than three times upper limit of normal	0	5 (1%)	2 (1%)	0	6 (1%)	5 (4%)
Aspartate aminotransferase or alanine aminotransferase more than three times upper limit of normal	0	5 (1%)	3 (2%)	0	7 (2%)	6 (4%)
Adjudicated inflammatory bowel disease	0	0	0	0§	1 (<1%)¶	0
Malignancies	1 (<1%)	1 (<1%)	0	1 (<1%)	2 (<1%)	0
Breast cancer stage I	1 (<1%)	0	0	0	0	0
Non-melanoma skin cancers	0	1 (<1%)	0	1 (<1%)	2 (<1%)	0

16週目までに悪性腫瘍が2例発生し，ビメキズマブ群で1例（1%未満/基底細胞癌），プラセボ群で1例（1%未満/乳癌ステージI/試験中止）であった.

Bimekizumab in patients with psoriatic arthritis, naive to biologic treatment: a randomised, double-blind, placebo-controlled, phase 3 trial (BE OPTIMAL)

Introduction

Method

Result

Discussion

Discussion

ビメキズマブによるIL-17AとIL-17Fの二重による阻害はbDMARDs未治療患者で，症状や関節炎，構造的損傷の進行抑制について，プラセボ群と比較し優れた有効性を示した.

ビメキズマブはいくつかの主要な関節炎評価項目で改善した. 奏効は24週間を通じて持続し，評価項目でも16週目から24週目まで改善または維持した.

ACRおよびPASIでの関節および皮膚の評価項目は，プラセボ群に対して有意に改善した.

Discussion

乾癬性関節炎と乾癬を併発している患者の70%以上が24週目までにPASI 90に到達し，50%以上がPASI 100を達成した.

また乾癬性関節炎の疾患領域を総合的に評価するMDA複合指標でも，プラセボ群に対し優れた効果が認められた.

プールデータでもビメキズマブ投与により，腱鞘炎および指炎を有する患者で高い割合で，これらの症状が消失した.

またvdHmTSSで評価した病態進行の抑制はビメキズマブ投与群で16週目という早い段階で確認され，プラセボ群よりも優れていた.

Discussion

このbDMARD未使用集団でのビメキズマブ投与による16週目までの有効性指標の改善はTNFα阻害剤で効果不十分または忍容性の低い乾癬性関節炎患者を対象としたBE COMPLETE試験の報告と同程度であった.

この結果はビメキズマブが乾癬性関節炎の病勢重症度を軽減し，構造的損傷の防止にも有効であることを証明した.

身体機能の改善，疼痛と疲労の軽減は，臨床症状の改善に伴い疾患による負担が軽減したと推測された.

アダリムマブ群とビメキズマブ群の統計的比較は行わなかったが，乾癬性関節炎の標準治療のアダリムマブ群の結果はビメキズマブ治療群での有益性とリスクプロファイルを示唆した.

Discussion

臨床効果は迅速で, ビメキズマブ単回投与後のACR20では2週目, PASI 75, PASI 90, PASI 100で4週目にビメキズマブ群とプラセボ群の間で解離を認めた.

また, 16週目にプラセボからビメキズマブにスイッチした患者も、ビメキズマブ初回投与から4週間後の20週目には臨床転帰の改善が認められ反応の速さが証明された.

24週目までのビメキズマブの忍容性は良好で, 全体的な安全性プロファイルはこの適応症に関する過去の試験と一致していた.

16週目のSAEおよび投与中止の発生率は低く, プラセボと同様で, 忍容性についてさらなる裏付けとなった.

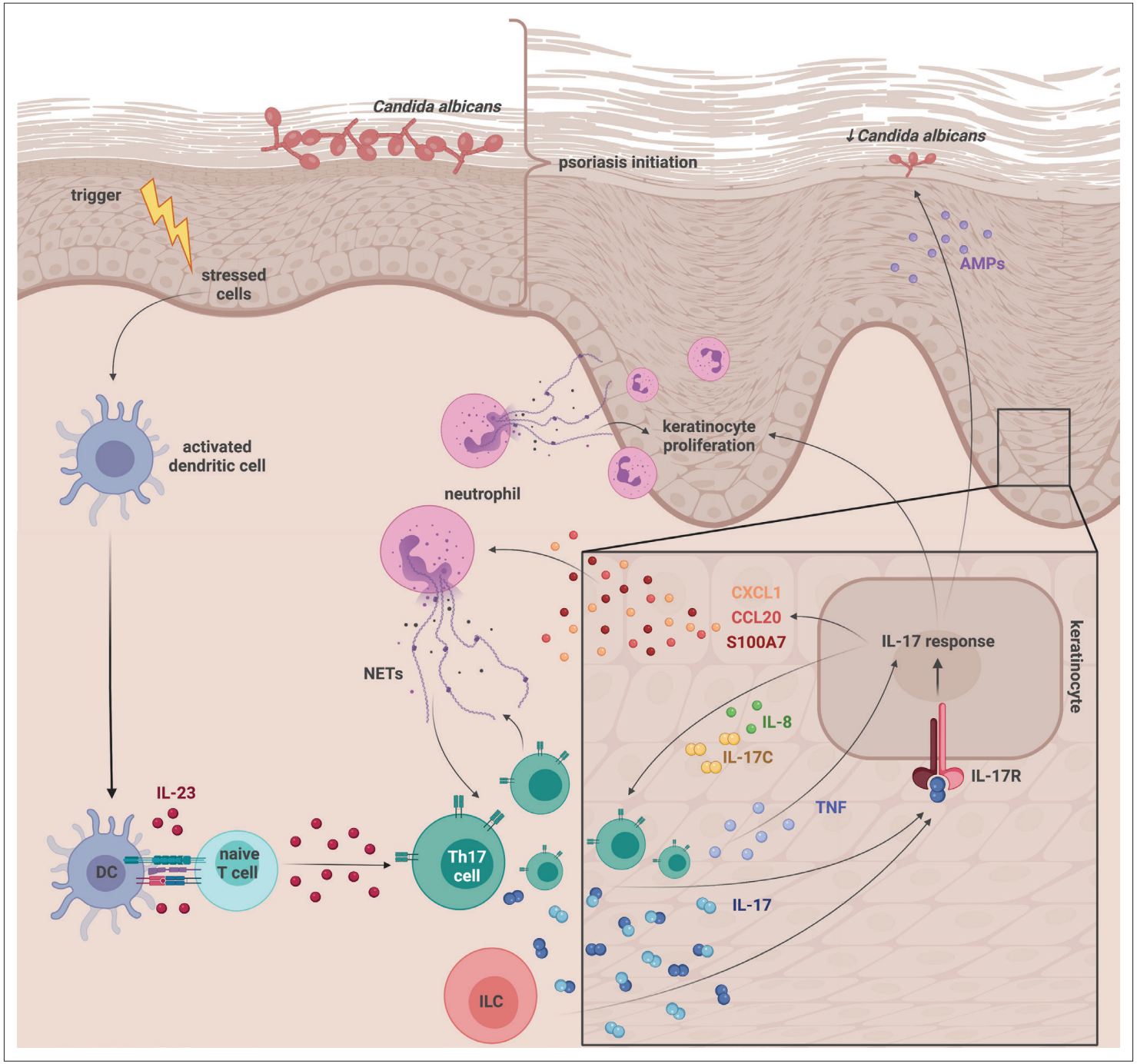
Discussion

これまでの試験と同様に，真菌への粘膜免疫におけるIL−17AおよびIL−17Fの役割と一致し，カンジダ感染症がビメキズマブ群でよく報告された.

適切な診断検査なしにカンジダと分類することに躊躇する状況もあり，一部の症例はカンジダと特定されず，これらの事象は分類されない真菌事象として報告された可能性がある.

真菌感染症はプラセボ群よりビメキズマブ群で多く発生したが，報告された症例は全て軽度，または中等度で全身性のものはなく，ほとんどが適切な抗真菌治療により治癒した.

ビメキズマブ投与中の患者1名が中等度の口腔カンジダ症を発症し，投与を中止した.



Supplement

IL−17シグナルは粘膜表面の感染，特にCandida albicans による感染を防ぐために抗菌ペプチドの発現を誘導する.

IL−17生物学的製剤間でも作用機序や結合親和性の違いがCandida症発症率の差につながる可能性がある.

Yeung J et al. J Cutan Med Surg. 2022 ;26 :3S.

Discussion

この研究の制限は，実臨床診療で観察されるよりも多関節型乾癬性関節炎の患者の割合が高かったこと，および研究集団から重度の併存疾患を持つ患者を除外している.

そのため人口統計や特性は研究集団と臨床現場での患者集団間に差異がある.

参照群を含めることで，ビメキズマブと標準治療との数値的な比較が可能であった.
一方で治療群間の統計学的比較が行われていないため，直接比較することはできない.
そのため今後，乾癬性関節炎治療について正確に比較するにはhead to head試験が計画されるべきである.

Discussion

以上より, 本試験でbDMARD未使用の活動性乾癬性関節症患者では, ビメキズマブ投与により関節, 皮膚, 画像所見, 患者報告アウトカムで臨床的に有意かつ一貫した改善が得られることが示された.

今後は52週目までの長期データとオープンラベル延長試験を実施し, 乾癬性関節炎へのビメキズマブの安全性と有効性を評価する予定である.

Bimekizumab in patients with active psoriatic arthritis and previous inadequate response or intolerance to tumour necrosis factor-α inhibitors : a randomised, double-blind, placebo-controlled, phase 3 trial (BE COMPLETE)

多国籍 多施設共同 盲検 無作為化試験

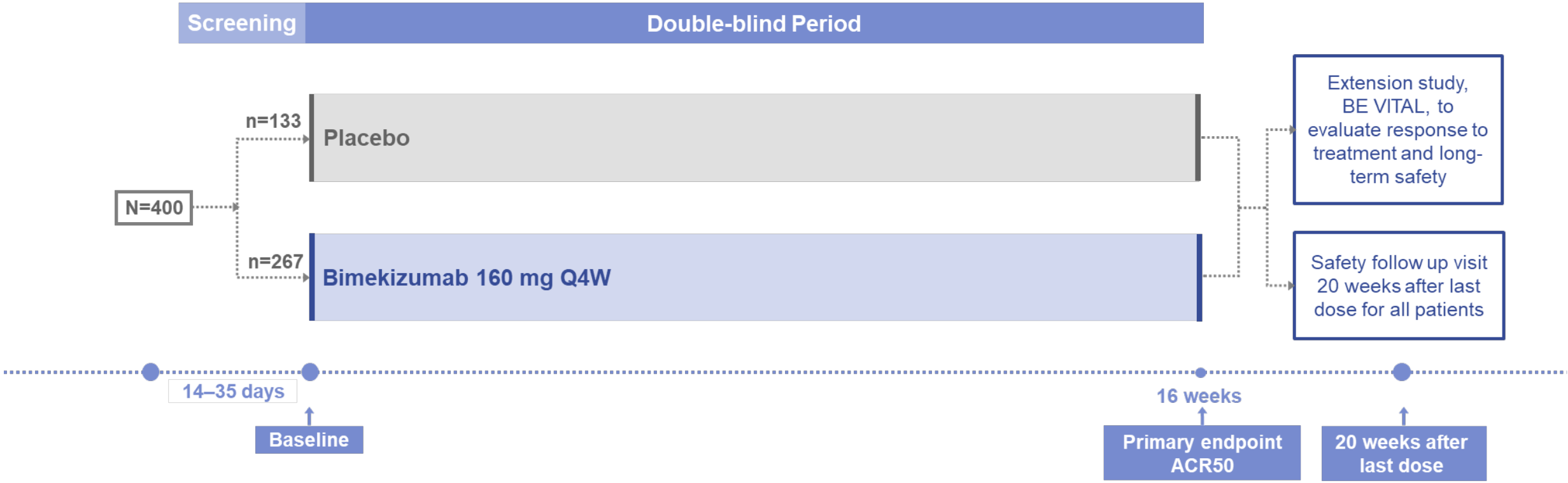
- Patients: 1剤または2剤のTNFα阻害薬抵抗性の乾癬性関節炎患者

(CASPER分類基準を満たす18歳以上の患者)

- Exposure: ビメキズマブ群 (ビメキズマブ 160mg 4週間毎 皮下注射)
- Comparison: プラセボ群
- Outcome: 16週目でのACR50を満たす患者の割合

Merola JF, et al . Lancet. 2023 ;401 :38.

Supplementary Figure S1. Study design



Merola JF, et al . Lancet. 2023 ;401 :38.

	Placebo (n=133)	Bimekizumab 160 mg every 4 weeks (n=267)	All patients (n=400)
Age, years	51·3 (12·9)	50·1 (12·4)	50·5 (12·5)
Gender			
Male	60 (45%)	130 (49%)	190 (48%)
Female	73 (55%)	137 (51%)	210 (53%)
BMI, kg/m²	29·0 (5·4)	30·1 (6·5)	29·8 (6·2)
Race, White*	128 (96%)	256 (96%)	384 (96%)
Time since psoriatic arthritis diagnosis, years†	9·2 (8·1)	9·6 (9·9)	9·5 (9·3)
Previous TNFα inhibitors			
Inadequate response to one TNFα inhibitor	103 (77%)	204 (76%)	307 (77%)
Inadequate response to two TNFα inhibitors	15 (11%)	29 (11%)	44 (11%)
Intolerance to TNFα inhibitors	15 (11%)	34 (13%)	49 (12%)
Any conventional synthetic DMARD at baseline	63 (47%)	139 (52%)	202 (51%)
Methotrexate at baseline	51 (38%)	119 (45%)	170 (43%)
TJC of 68 joints	19·3 (14·2)	18·4 (13·5)	18·7 (13·8)
SJC of 66 joints	10·3 (8·2)	9·7 (7·5)	9·9 (7·7)
High-sensitivity CRP ≥6 mg/L	59 (44%)	118 (44%)	177 (44%)
Affected BSA ≥3%	88 (66%)	176 (66%)	264 (66%)
PASI score‡	8·5 (6·6)	10·1 (9·1)	9·6 (8·4)
Nail psoriasis§	83 (62%)	159 (60%)	242 (61%)
mNAPSI score¶	4·5 (2·8)	4·3 (2·8)	4·4 (2·8)
HAQ-DI score	1·04 (0·69)	0·97 (0·59)	0·99 (0·62)
PtAAP score	61·7 (24·6)	58·3 (24·2)	59·5 (24·3)
PhGA score	57·7 (18·8)	59·3 (17·2)	58·7 (17·7)
PGA score	63·0 (22·0)	60·5 (22·5)	61·4 (22·3)
SF-36 PCS score	35·9 (10·2)	36·4 (9·0)	36·3 (9·4)
Presence of enthesitis (LEI >0)§	36 (27%)	106 (40%)	142 (36%)
LEI score‖	2·9 (1·6)	2·6 (1·5)	2·7 (1·5)
Presence of dactylitis (LDI >0)§	14 (11%)	34 (13%)	48 (12%)
Dactylitic sites**	1·9 (2·4)	2·0 (1·8)	1·9 (2·0)
LDI score**	66·4 (127·6)	72·7 (114·4)	70·9 (117·0)

	Placebo (n=133)	Bimekizumab 160 mg every 4 weeks (n=267)	All patients (N=400)
Geographic region			
Asia	4 (3·0%)	9 (3·4%)	13 (3·3%)
Eastern Europe	84 (63·2%)	166 (62·2%)	250 (62·5%)
North America	36 (27·1%)	73 (27·3%)	109 (27·3%)
Western Europe	9 (6·8%)	19 (7·1%)	28 (7·0%)
Racial group			
American Indian/Alaskan native	0	0	0
Asian	4 (3·0%)	9 (3·4%)	13 (3·3%)
Black	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
White	128 (96·2%)	256 (95·9%)	384 (96·0%)
Other/mixed	1 (0·8%)	2 (0·7%)	3 (0·8%)
PsA subtype			
Polyarticular (symmetric)	86 (64·7%)	168 (62·9%)	254 (63·5%)
Oligoarticular (asymmetric)	32 (24·1%)	62 (23·2%)	94 (23·5%)
Distal interphalangeal joint predominant	7 (5·3%)	13 (4·9%)	20 (5·0%)
Spondylitis predominant	7 (5·3%)	15 (5·6%)	22 (5·5%)
Arthritis mutilans	0	8 (3·0%)	8 (2·0%)
Missing	1 (0·8%)	1 (0·4%)	2 (0·5%)

Merola JF, et al . Lancet. 2023 ;401 :38.

	Placebo (n=133)	Bimekizumab 160 mg every 4 weeks (n=267)
Primary efficacy endpoint		
ACR50 response	9 (7%)	116 (43%)
OR *vs* placebo (95% CI); p value	..	11·1 (5·4 to 23·0); p<0·0001
Ranked secondary endpoints		
HAQ-DI score change from baseline, mean (SE)	−0·07 (0·04)	−0·38 (0·03)
Least squares mean difference *vs* placebo (95% CI); p value	..	−0·33 (−0·42 to −0·23); p<0·0001
PASI90 response*	6 (7%) of 88	121 (69%) of 176
OR *vs* placebo (95% CI); p value	..	30·2 (12·4 to 73·9); p<0·0001
SF-36 PCS score change from baseline, mean (SE)	1·4 (0·7)	7·3 (0·5)
Least squares mean difference *vs* placebo (95% CI); p value	..	6·0 (4·4 to 7·7); p<0·0001
MDA response	8 (6%)	118 (44%)
OR *vs* placebo (95% CI); p value	..	13·1 (6·1 to 28·0); p<0·0001
Additional efficacy outcomes		
ACR20†	21 (16%)	179 (67%)
ACR70†	1 (1%)	71 (27%)
PASI75*	9 (10%) of 88	145 (82%) of 176
PASI100*	4 (5%) of 88	103 (59%) of 176
ACR50+PASI100*	1 (1%) of 88	59 (34%) of 176
VLDA	3 (2%)	36 (13%)
IGA 0 or 1†‡§	3 (4%) of 82	99 (61%) of 163
mNAPSI 0¶	12 (14%) of 83	73 (46%) of 159
HAQ-DI MCID‖	24 (22%) of 110	130 (56%) of 231
PsAID-12 score change from baseline†, mean (SE)	−0·3 (0·2)	−2·2 (0·1)
PtAAP score change from baseline†, mean (SE)	−4·5 (2·1)	−27·7 (1·7)
FACIT-Fatigue score change from baseline, mean (SE)	0·1 (0·7)	5·5 (0·6)

	Placebo (n=132)*	Bimekizumab 160 mg every 4 weeks (n=267)
Any TEAE	44 (33%)	108 (40%)
Serious TEAEs†	0	5 (2%)
Discontinuation due to TEAEs‡	0	2 (1%)
Drug-related TEAEs	4 (3%)	35 (13%)
Severe TEAEs§	0	5 (2%)
Deaths	0	0
Most frequent TEAEs in the bimekizumab group¶		
Nasopharyngitis	1 (1%)	10 (4%)
Oral candidiasis	0	7 (3%)
Upper respiratory tract infection	2 (2%)	6 (2%)
Infections‖		
Serious**	0	2 (1%)
Opportunistic	0	0
Active tuberculosis	0	0
SARS-CoV-2 infections	6 (5%)	5 (2%)
Fungal infections	0	12 (4%)
Candida infections††	0	7 (3%)
Oral candidiasis††	0	7 (3%)
Fungal infections not elsewhere classified	0	4 (1%)
Fungal skin infection	0	1 (<1%)
Tongue fungal infection	0	1 (<1%)
Vulvovaginal mycotic infection	0	2 (1%)
Tinea infections	0	1 (<1%)
Tinea pedis	0	1 (<1%)
Serious fungal infections	0	0
Systemic fungal infections	0	0
Fungal infections leading to discontinuation	0	1 (<1%)
Candida infections leading to discontination	0	1 (<1%)
Neutropenia‡‡	0	4 (1%)
Serious hypersensitivity	0	0
Injection site reactions	0	3 (1%)
Adjudicated suicidal ideation and behaviour	0	0
Adjudicated major adverse cardiovascular event	0	0
Liver function test changes or increases in enzyme concentrations		
Alanine aminotransferase more than three times upper limit of normal	0	2 (1%)
Aspartate aminotransferase or alanine aminotransferase more than three times upper limit of normal	0	4 (1%)
Adjudicated inflammatory bowel disease	0	0
Malignancies	1 (1%)	0
Basal cell carcinoma	1 (1%)	0

Merola JF, et al . Lancet. 2023 ;401 :38.

Secukinumab, a human anti-interleukin-17A monoclonal antibody, in psoriatic arthritis: a randomized, double-blind, placebo-controlled, phase 3 trial (FUTURE 2)

多国籍 多施設共同 盲検 無作為化試験

- Patients: CASPER分類基準を満たす18歳以上の乾癬性関節炎患
- Exposure:

75mg セクキヌマブ群 (セクキヌマブ75mg 4週間毎 皮下注射)

150mg セクキヌマブ群 (セクキヌマブ150mg 4週間毎 皮下注射)

300mg セクキヌマブ群 (セクキヌマブ 300mg 4週間毎 皮下注射)

- Comparison: プラセボ群
- Outcome: 24週目でのACR20を満たす患者の割合

McInnes IB, et al. Lancet. 2015 ;386 :1137.

Table 3: **Efficacy of secukinumab at week 24 in anti–TNF-naïve and anti–TNF-IR patients**

	Secukinumab 300 mg			Secukinumab 150 mg			Secukinumab 150 mg			
Efficacy endpoint[a]	**Value[a]**	**Effect size vs. placebo (95% CI)**	**p-value vs. placebo**	**Value[a]**	**Effect size vs. placebo (95% CI)**	**p-value vs. placebo**	**Value[a]**	**Effect size vs. placebo (95% CI)**	**p-value vs. placebo**	**Placebo**
Anti–TNF-naïve patients										
ACR20 response	39/67 (58·2)	OR 7·77 (3·36–17·98)	0·0040	40/63 (63·5)	OR 9·99 (4·22–23·66)	<0·0001	24/65 (36·9)	OR 3·17 (1·36–7.40)	0·0075	10/63 (15·9)
ACR50 response	26/67 (38·8)	OR 9·72 (3·14–30·09)	<0·0001	28/63 (44·4)	OR 12·54 (4·03–39·05)	<0·0001	16/65 (24·6)	OR 4·90 (1·53–15·64)	0·0074	4/63 (6·3)
ACR70 response	15/67 (22·4)	OR 9·72 (3·14–30·09)	0·0003	17/63 (27·0)		<0·0001	4/65 (6·2)		0·3654	1/63 (1·6)
PASI75 response[b]	19/30 (63·3)	OR 7·96 (2·42–	0·0006	20/36 (55·6)	OR 6·33 (1·99–20·15)	0·0018	10/33 (30·3)	OR 1·94 (0·59–6·34)	0·2729	6/31 (19·4)
PASI90 response[b]	16/30 (53·3)	OR 13·11 (3·09–55·59)	0·0005	14/36 (38·9)	OR 8·09 (1·92–34·09)	0·0044	4/33 (12·1)	OR 1·40 (0·28–7·02)	0·6825	3/31 (9·7)
Anti–TNF-IR patients										
ACR20 response	15/33 (45·5)	OR 4·97 (1.05–18·26)	0·0077	11/37 (29·7)	OR 2·55 (0.78–8·32)	0·1216	5/34 (14·7)	OR 1·03 (0.27–3·95)	0·9639	5/35 (14·3)
ACR50 response	9/33 (27·3)	OR 4·37 (3·14–30·09)	0·0431	7/37 (18·9)	OR 2·39 (0.56–10·15)	0·2374	2/34 (5·9)	OR 0·69 (0.11–4·42)	0·6941	3/35 (8·6)
ACR70 response	5/33 (15·2)		0·0228	4/37 (10·8)		0·1151	2/34 (5·9)		0·2391	0/35 (0·0)
PASI75 response[b]	7/11 (63·6)	OR 19·29 (1·77–210·18)	0·0152	8/22 (36·4)	OR 6·17 (0·66–57·30)	0·1094	4/17 (23·5)	OR 3·46 (0·33–36·06)	0·2986	1/12 (8·3)
PASI90 response[b]	4/11 (36·4)	OR 6·43 (0·58–70·74)	0·1282	5/22 (22·7)	OR 3·50 (0·35–34·91)	0·2859	2/17 (11·8)	OR 1·37 (0·11–17·30)	0·8098	1/12 (8·3)

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この論文を通して

明らかに皮膚症状を伴う乾癬性関節炎には効果が大きく，効果発現までの時間が早いため，非常に良い選択肢である．

他のIL17阻害薬の副作用と同様に真菌感染症には注意する必要がある．

この論文ではTNFα阻害薬とIL17阻害薬と比較し，どちらがいいかは判断できない．また，皮下注製剤の用量について疑問が残る．

研究集団は，日本の臨床集団と比較しアジア人は少なく，肥満が多いこと，多関節炎型乾癬性関節炎が多い