Rheumatoid arthritis

Ivarmacitinib, a selective Janus kinase 1 inhibitor, in patients with moderate-to-severe active rheumatoid arthritis and inadequate response to conventional synthetic DMARDs: results from a phase III randomised clinical trial

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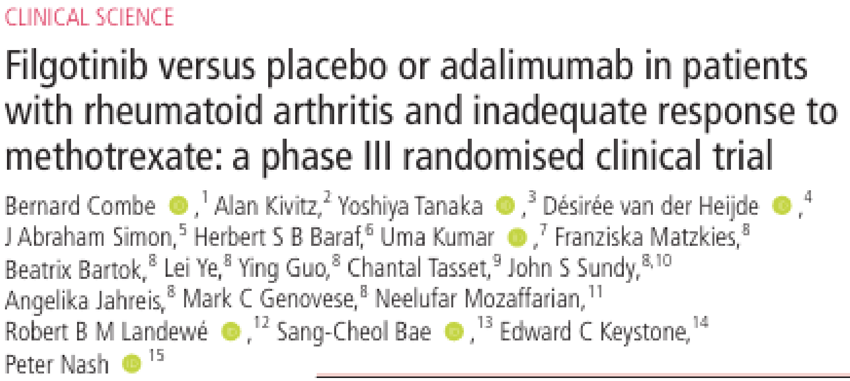
Ann Rheum Dis. 2025 Feb; 84(2): 188-200. PMID 39919893

膠原病 Journal Club 2025/06/10 竹内 遼

FINCH1: Filgotinibのp3 RCT



CLINICAL SCIENCE

Filgotinib versus placebo or adalimumab in patients with rheumatoid arthritis and inadequate response to methotrexate: a phase III randomised clinical trial

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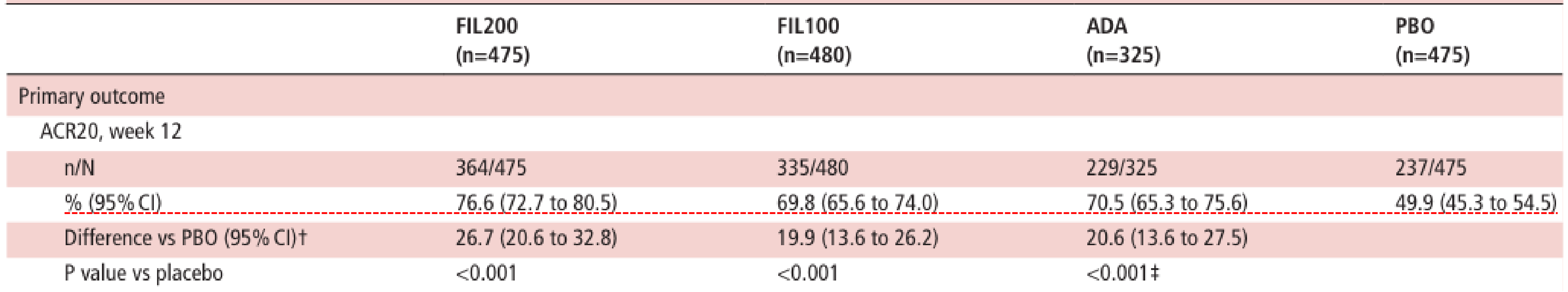
Robert B M Landewé ,[12] Sang-Cheol Bae ,[13] Edward C Keystone,[14]
Peter Nash [15]

MTX効果不十分なRAに対するfilgotinibのp3 RCT (FINCH1)



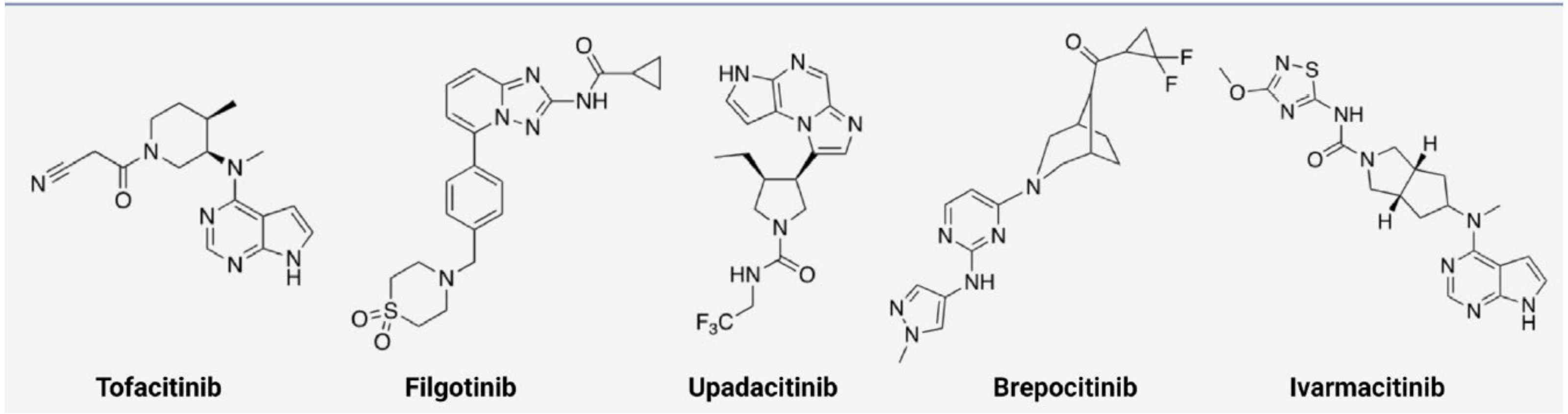
	FIL200 (n=475)	FIL100 (n=480)	ADA (n=325)	PBO (n=475)
Primary outcome				
ACR20, week 12				
n/N	364/475	335/480	229/325	237/475
% (95% CI)	76.6 (72.7 to 80.5)	69.8 (65.6 to 74.0)	70.5 (65.3 to 75.6)	49.9 (45.3 to 54.5)
Difference vs PBO (95% CI)†	26.7 (20.6 to 32.8)	19.9 (13.6 to 26.2)	20.6 (13.6 to 27.5)	
P value vs placebo	<0.001	<0.001	<0.001‡	

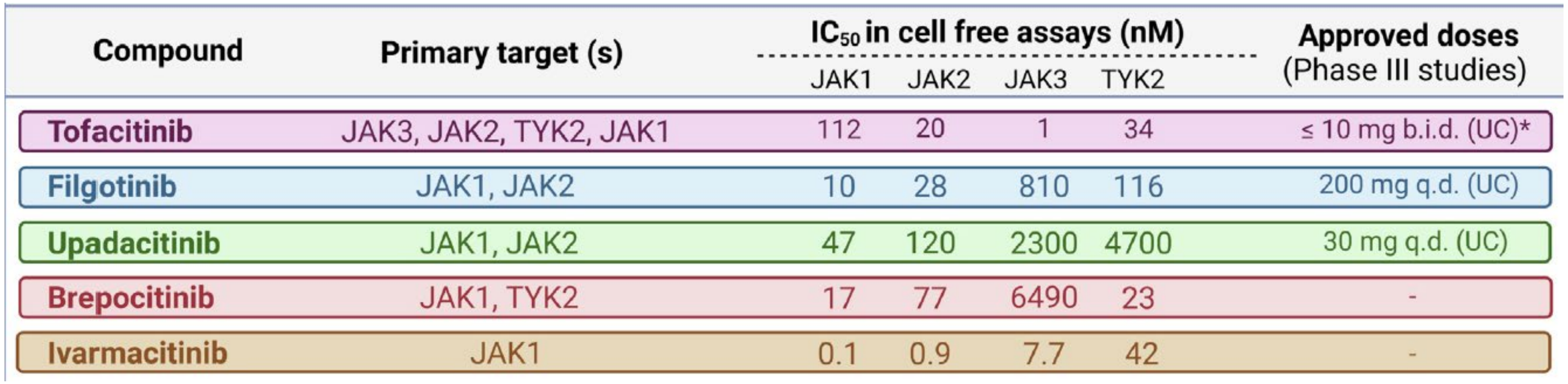
- 12週におけるACR20を達成した患者の割合

Filgotinib 200mg	76.6%
Filgotinib 100mg	69.8%
Adalimumab 40mg 2週おき	70.5%
Placebo群	49.9%

Ann Rheum Dis 2021; 80: 848-858.

Ivarmacitinib: JAK1 selective inhibitor


Tofacitinib
Filgotinib
Upadacitinib
Brepocitinib
Ivarmacitinib



Compound	Primary target (s)	IC_{50} in cell free assays (nM)				Approved doses (Phase III studies)
		JAK1	JAK2	JAK3	TYK2	
Tofacitinib	JAK3, JAK2, TYK2, JAK1	112	20	1	34	≤ 10 mg b.i.d. (UC)*
Filgotinib	JAK1, JAK2	10	28	810	116	200 mg q.d. (UC)
Upadacitinib	JAK1, JAK2	47	120	2300	4700	30 mg q.d. (UC)
Brepocitinib	JAK1, TYK2	17	77	6490	23	-
Ivarmacitinib	JAK1	0.1	0.9	7.7	42	-

- Ivarmacitinib: JAK1 selective inhibitor
- IvarmacitinibはFilgotinibよりもJAK1選択性が高い

IC_{50}
タンパク質の活性阻害するのに必要な濃度
IC_{50}が低いほど強力に阻害

Pharmacol Ther. 2023 May;245:108402.

Methods

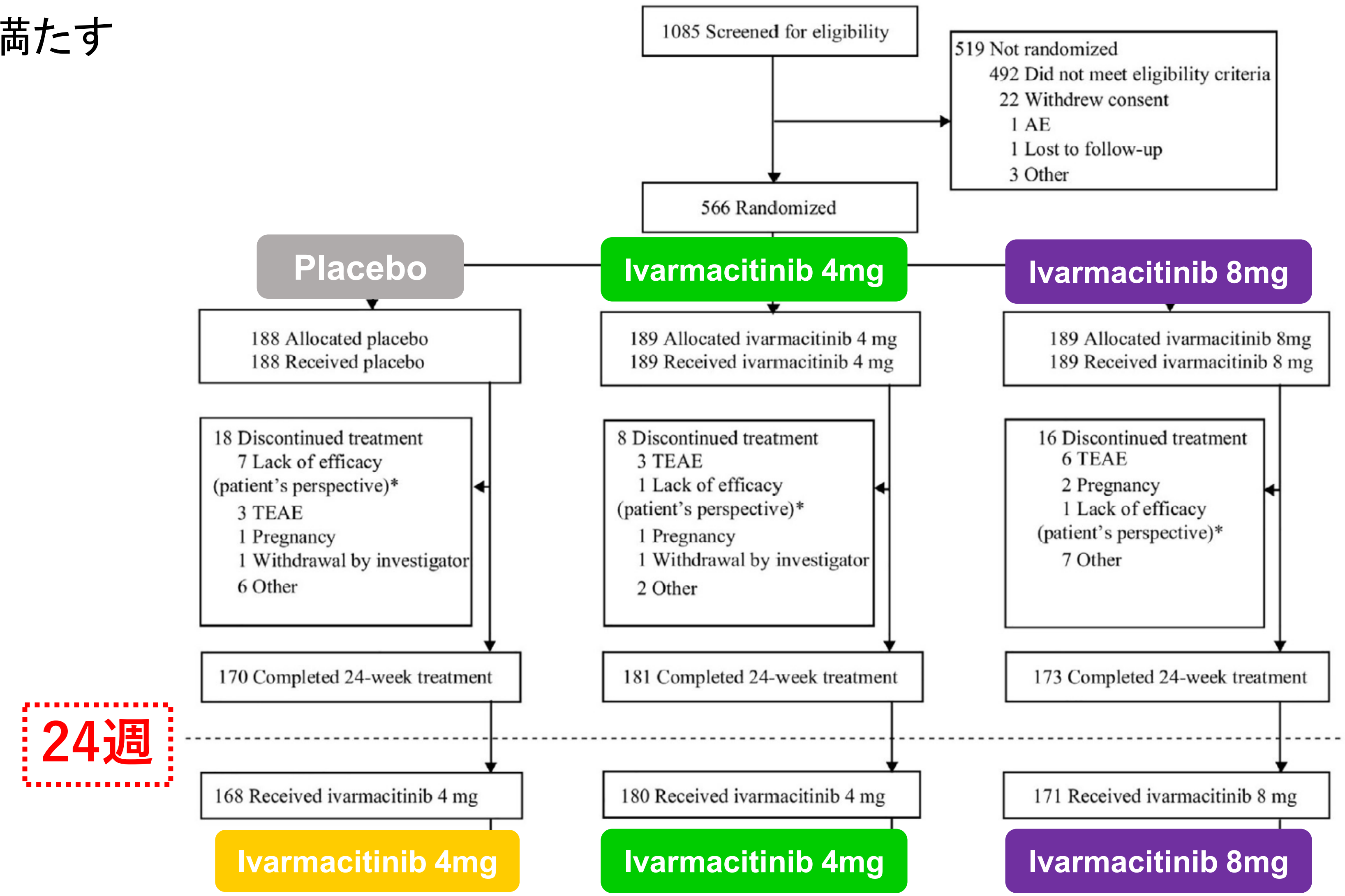
P 2010年ACR/EULAR分類基準を満たす
18歳から75歳のRA患者

I csDMARDs+ Ivarmacitinib

C csDMARDs+ Placebo

O 24週における
ACR20を達成した患者の割合

csDMARDs
メトトレキサート
レフルノミド
ヒドロキシクロロキン
イグラチモド
スルファサラジン
クロロキン



1085 Screened for eligibility

519 Not randomized
- 492 Did not meet eligibility criteria
- 22 Withdrew consent
- 1 AE
- 1 Lost to follow-up
- 3 Other

566 Randomized

Placebo

188 Allocated placebo
188 Received placebo

18 Discontinued treatment
- 7 Lack of efficacy (patient's perspective)*
- 3 TEAE
- 1 Pregnancy
- 1 Withdrawal by investigator
- 6 Other

170 Completed 24-week treatment

168 Received ivarmacitinib 4 mg

Ivarmacitinib 4mg

Ivarmacitinib 4mg

189 Allocated ivarmacitinib 4 mg
189 Received ivarmacitinib 4 mg

8 Discontinued treatment
- 3 TEAE
- 1 Lack of efficacy (patient's perspective)*
- 1 Pregnancy
- 1 Withdrawal by investigator
- 2 Other

181 Completed 24-week treatment

180 Received ivarmacitinib 4 mg

Ivarmacitinib 4mg

Ivarmacitinib 8mg

189 Allocated ivarmacitinib 8mg
189 Received ivarmacitinib 8 mg

16 Discontinued treatment
- 6 TEAE
- 2 Pregnancy
- 1 Lack of efficacy (patient's perspective)*
- 7 Other

173 Completed 24-week treatment

171 Received ivarmacitinib 8 mg

Ivarmacitinib 8mg

24週

Methods: End Point

Primary End Point:

- 24週におけるACR20を達成した患者の割合

Secondary End Point:

- 24、52週における
  - ACR20/50/70を達成した患者の割合
  - DAS28< 2.6、DAS28-CRP≦ 3.2を達成した患者の割合
  - DAS28-CRP、DAS28-ESR、CDAI、SDAI
  - 朝のこわばりの持続時間、重症度
- QOL End point
  - HAQ-DIのベースラインからの変化
  - SF-36 PCS、MCSのベースラインからの変化 etc…
- 有害事象
  - 感染、悪性腫瘍、血栓イベント、MACE etc…

Methods: Participants

■ Inclusion criteria

- 18-75歳
- 2010年ACR/EULARのRAの分類基準を満たす
- 腫脹、圧痛関節はそれぞれ6関節以上
- 1剤以上のcsDMARDsを3か月以上使用
- ESR> 28mm/h、CRP、hs-CRP> 0.5mg/dL
- 3か月以上csDMARDsの変更なし
- 4週間以上csDMARDsの錠数の変更なし
- csDMARDsの併用は2剤まで
- 内服のグルココルチコイドはPSL 10mg相当まで可

(グルココルチコイドの新規開始、増量は不可)

■ Exclusion criteria

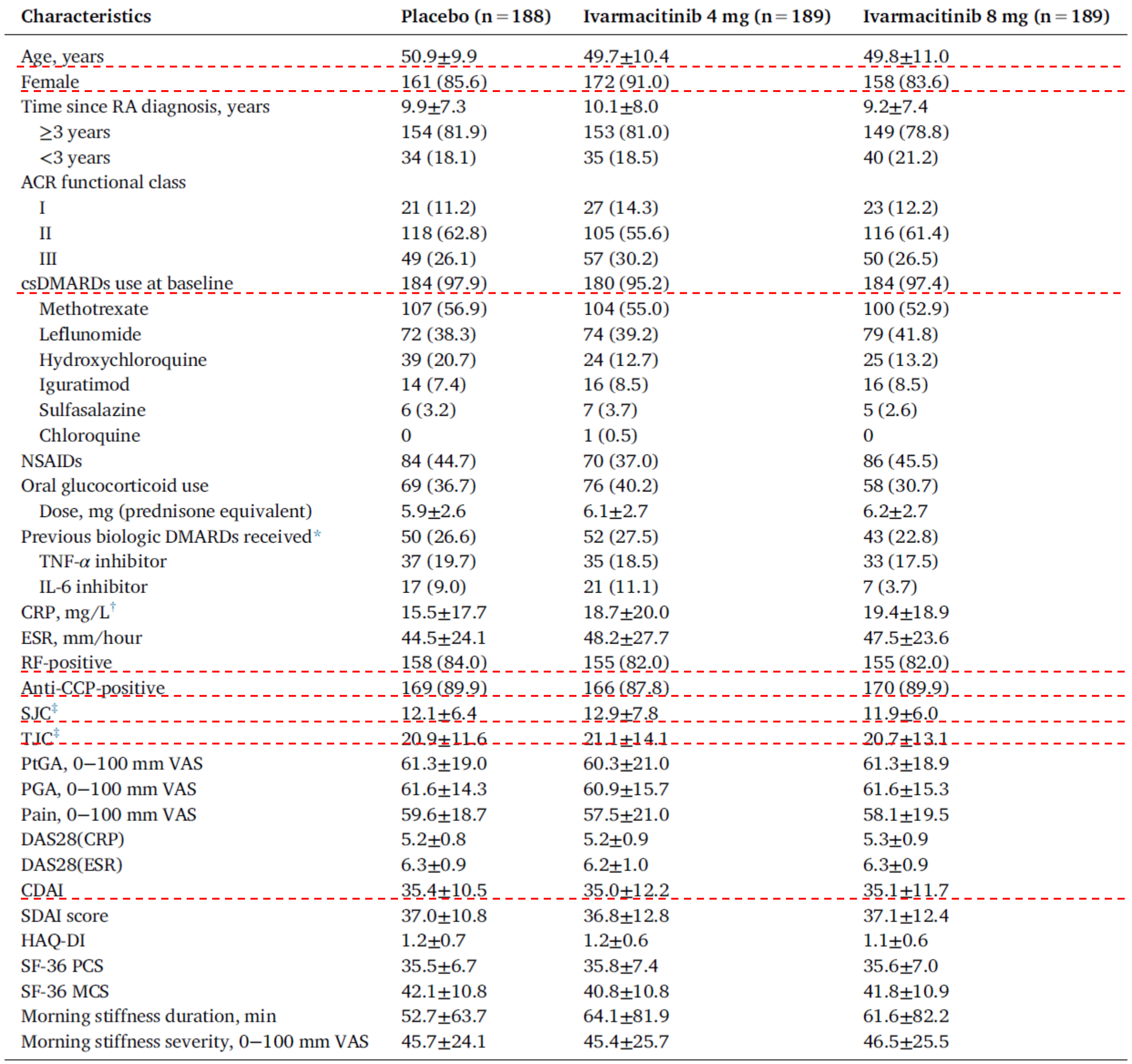
- JAK阻害薬の使用歴
- 血球異常

(WBC< 3,000/μL、Neut< 1,500/μL、Hb< 9.0g/dL、Plt< 100,000/μL)

- 肝機能異常
- eGFR< 60mL/分/1.73m^2

Methods: 患者背景

Placebo　Ivarmacitinib 4mg　Ivarmacitinib 8mg



Characteristics	Placebo (n = 188)	Ivarmacitinib 4 mg (n = 189)	Ivarmacitinib 8 mg (n = 189)
Age, years	50.9±9.9	49.7±10.4	49.8±11.0
Female	161 (85.6)	172 (91.0)	158 (83.6)
Time since RA diagnosis, years	9.9±7.3	10.1±8.0	9.2±7.4
≥3 years	154 (81.9)	153 (81.0)	149 (78.8)
<3 years	34 (18.1)	35 (18.5)	40 (21.2)
ACR functional class			
I	21 (11.2)	27 (14.3)	23 (12.2)
II	118 (62.8)	105 (55.6)	116 (61.4)
III	49 (26.1)	57 (30.2)	50 (26.5)
csDMARDs use at baseline	184 (97.9)	180 (95.2)	184 (97.4)
Methothrexate	107 (56.9)	104 (55.0)	100 (52.9)
Leflunomide	72 (38.3)	74 (39.2)	79 (41.8)
Hydroxychloroquine	39 (20.7)	24 (12.7)	25 (13.2)
Iguratimod	14 (7.4)	16 (8.5)	16 (8.5)
Sulfasalazine	6 (3.2)	7 (3.7)	5 (2.6)
Chloroquine	0	1 (0.5)	0
NSAIDs	84 (44.7)	70 (37.0)	86 (45.5)
Oral glucocorticoid use	69 (36.7)	76 (40.2)	58 (30.7)
Dose, mg (prednisone equivalent)	5.9±2.6	6.1±2.7	6.2±2.7
Previous biologic DMARDs received*	50 (26.6)	52 (27.5)	43 (22.8)
TNF-*α* inhibitor	37 (19.7)	35 (18.5)	33 (17.5)
IL-6 inhibitor	17 (9.0)	21 (11.1)	7 (3.7)
CRP, mg/L†	15.5±17.7	18.7±20.0	19.4±18.9
ESR, mm/hour	44.5±24.1	48.2±27.7	47.5±23.6
RF-positive	158 (84.0)	155 (82.0)	155 (82.0)
Anti-CCP-positive	169 (89.9)	166 (87.8)	170 (89.9)
SJC‡	12.1±6.4	12.9±7.8	11.9±6.0
TJC‡	20.9±11.6	21.1±14.1	20.7±13.1
PtGA, 0–100 mm VAS	61.3±19.0	60.3±21.0	61.3±18.9
PGA, 0–100 mm VAS	61.6±14.3	60.9±15.7	61.6±15.3
Pain, 0–100 mm VAS	59.6±18.7	57.5±21.0	58.1±19.5
DAS28(CRP)	5.2±0.8	5.2±0.9	5.3±0.9
DAS28(ESR)	6.3±0.9	6.2±1.0	6.3±0.9
CDAI	35.4±10.5	35.0±12.2	35.1±11.7
SDAI score	37.0±10.8	36.8±12.8	37.1±12.4
HAQ-DI	1.2±0.7	1.2±0.6	1.1±0.6
SF-36 PCS	35.5±6.7	35.8±7.4	35.6±7.0
SF-36 MCS	42.1±10.8	40.8±10.8	41.8±10.9
Morning stiffness duration, min	52.7±63.7	64.1±81.9	61.6±82.2
Morning stiffness severity, 0–100 mm VAS	45.7±24.1	45.4±25.7	46.5±25.5

年齢は50歳程度、女性が8～9割

csDMARDsは95%程度が内服、MTXは5割程度

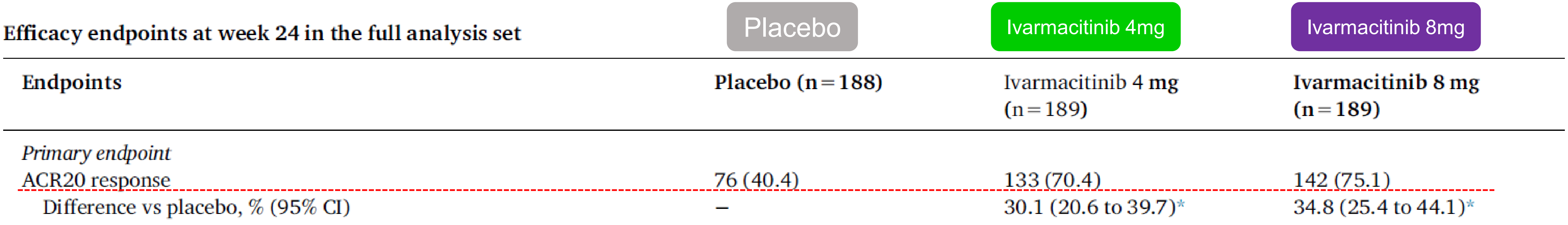
RF陽性は8割程度、ACPA陽性は9割程度

腫脹関節数は12程度、圧痛関節数は20程度

CDAIは35程度で高疾患活動性

Results: Primary End Point

Placebo　Ivarmacitinib 4mg　Ivarmacitinib 8mg



Efficacy endpoints at week 24 in the full analysis set

Endpoints	**Placebo (n = 188)**	Ivarmacitinib 4 **mg** (n = 189)	**Ivarmacitinib 8 mg (n = 189)**
Primary endpoint			
ACR20 response	76 (40.4)	133 (70.4)	142 (75.1)
Difference vs placebo, % (95% CI)	–	30.1 (20.6 to 39.7)*	34.8 (25.4 to 44.1)*

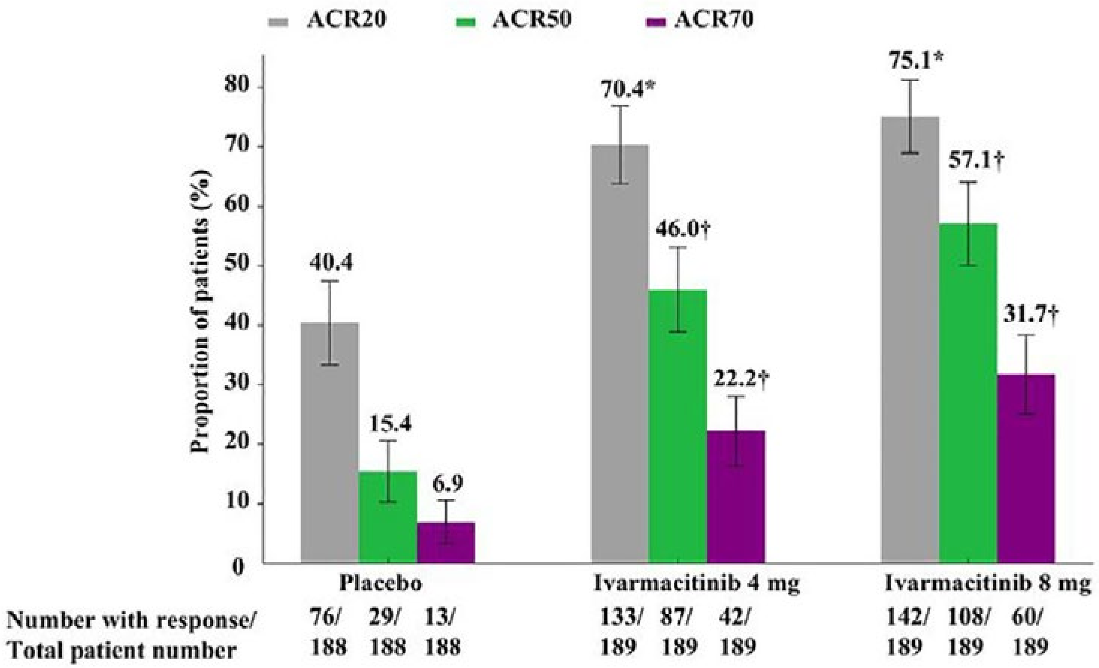
24週においてACR20を達成した患者の割合

Placebo	40.4%
Ivarmacitinib 4mg	70.4%
Ivarmacitinib 8mg	75.1%

- Ivarmacitinib 4mg、8mgはPlacebo群と比較して有意差が示された ($P< 0.0001$)

Results: 24週のACR20/50/70を達成した患者の割合

(A) ACR20/50/70 responses at Week 24



24週においてACR50を達成した患者の割合

Placebo	15.4%
Ivarmacitinib 4mg	46.0%
Ivarmacitinib 8mg	75.1%

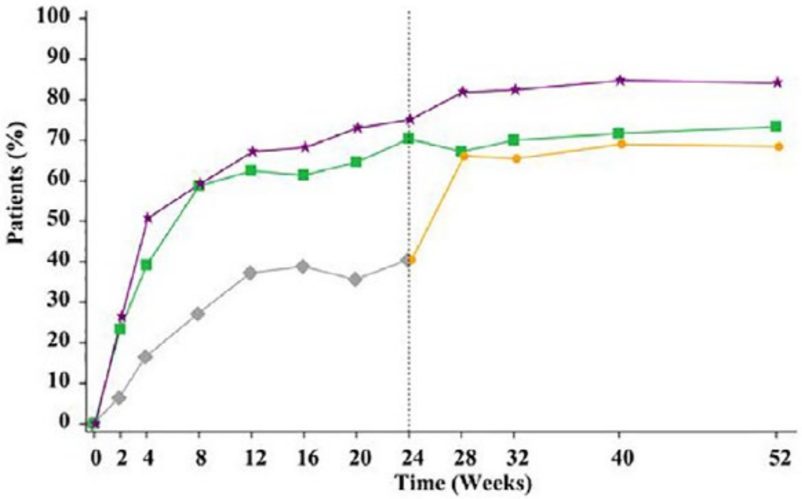
24週においてACR70を達成した患者の割合

Placebo	6.9%
Ivarmacitinib 4mg	22.2%
Ivarmacitinib 8mg	31.7%

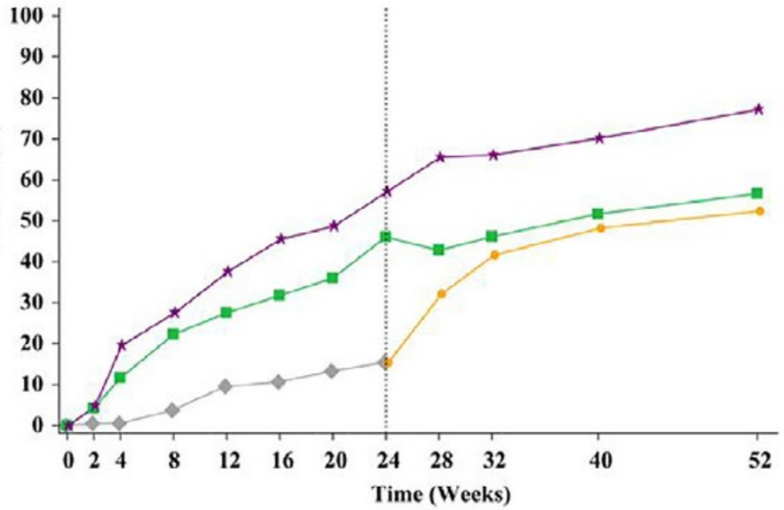
24週におけるACR50、70を達成した患者の割合は、Ivarmacitinib 4mg、8mgともにPlacebo群と比較して有意差が示された(P< 0.0001、多重調整なし)

Results: 52週までのACR20/50/70を達成した患者の割合

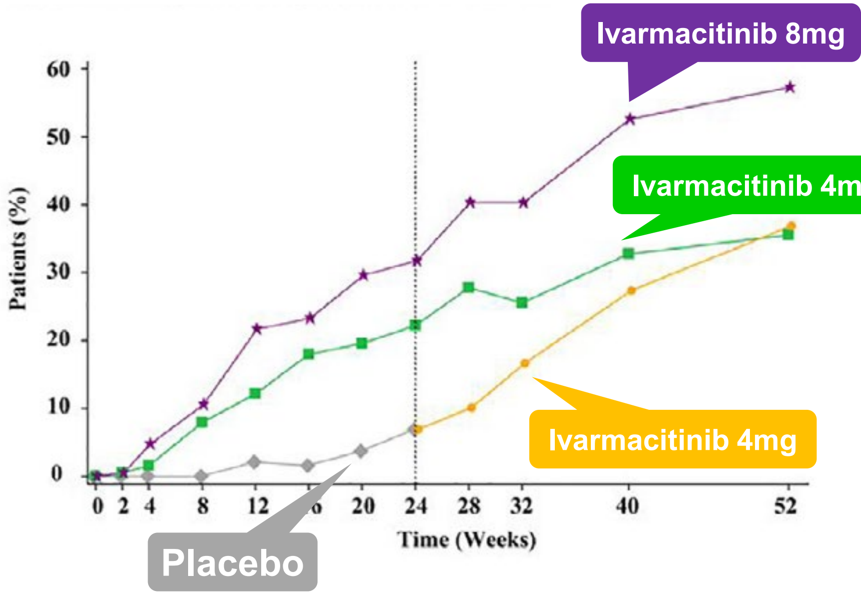
ACR20



ACR50

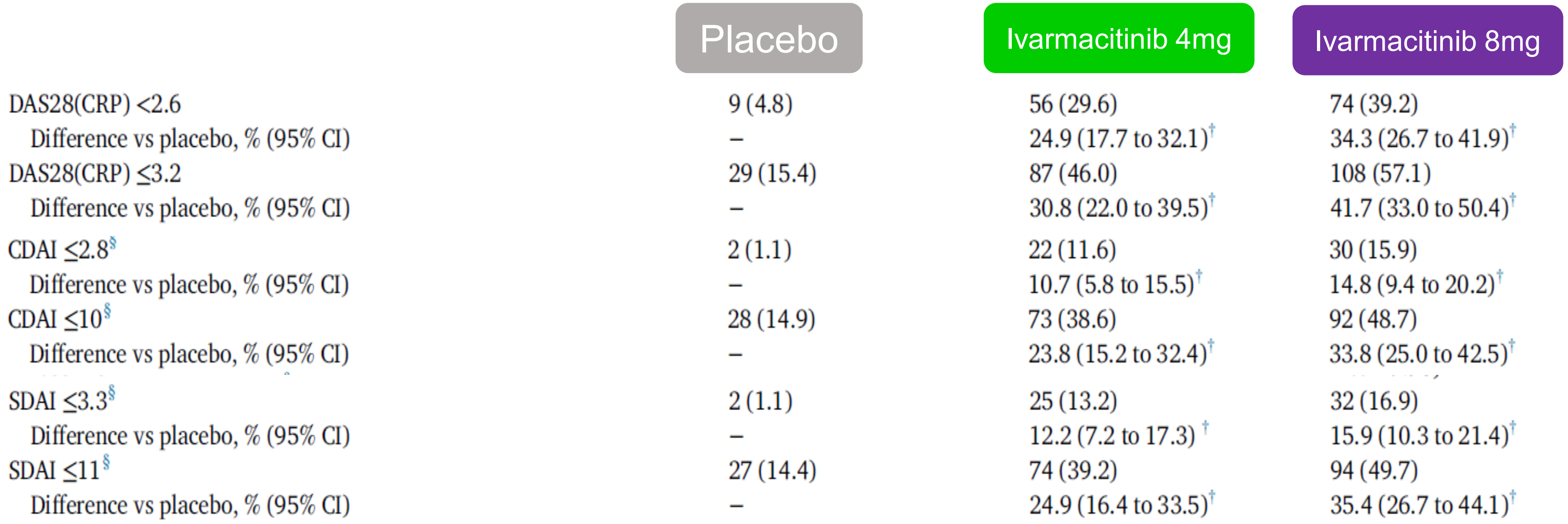


ACR70



2、4、8週目の時点でIvarmacitinib 4mg、8mg群の方がPlacebo群よりもACR 20/50/70を達成した患者した患者は多かった

Results: DAS28-CRP、CDAI、SDAIにおける寛解、低疾患活動性



	Placebo	Ivarmacitinib 4mg	Ivarmacitinib 8mg
DAS28(CRP) <2.6	9 (4.8)	56 (29.6)	74 (39.2)
Difference vs placebo, % (95% CI)	–	24.9 (17.7 to 32.1)[†]	34.3 (26.7 to 41.9)[†]
DAS28(CRP) ≤3.2	29 (15.4)	87 (46.0)	108 (57.1)
Difference vs placebo, % (95% CI)	–	30.8 (22.0 to 39.5)[†]	41.7 (33.0 to 50.4)[†]
CDAI ≤2.8[§]	2 (1.1)	22 (11.6)	30 (15.9)
Difference vs placebo, % (95% CI)	–	10.7 (5.8 to 15.5)[†]	14.8 (9.4 to 20.2)[†]
CDAI ≤10[§]	28 (14.9)	73 (38.6)	92 (48.7)
Difference vs placebo, % (95% CI)	–	23.8 (15.2 to 32.4)[†]	33.8 (25.0 to 42.5)[†]
SDAI ≤3.3[§]	2 (1.1)	25 (13.2)	32 (16.9)
Difference vs placebo, % (95% CI)	–	12.2 (7.2 to 17.3) [†]	15.9 (10.3 to 21.4)[†]
SDAI ≤11[§]	27 (14.4)	74 (39.2)	94 (49.7)
Difference vs placebo, % (95% CI)	–	24.9 (16.4 to 33.5)[†]	35.4 (26.7 to 44.1)[†]

24週における

DAS28-CRP<2.6、DAS28-CRP≦3.2

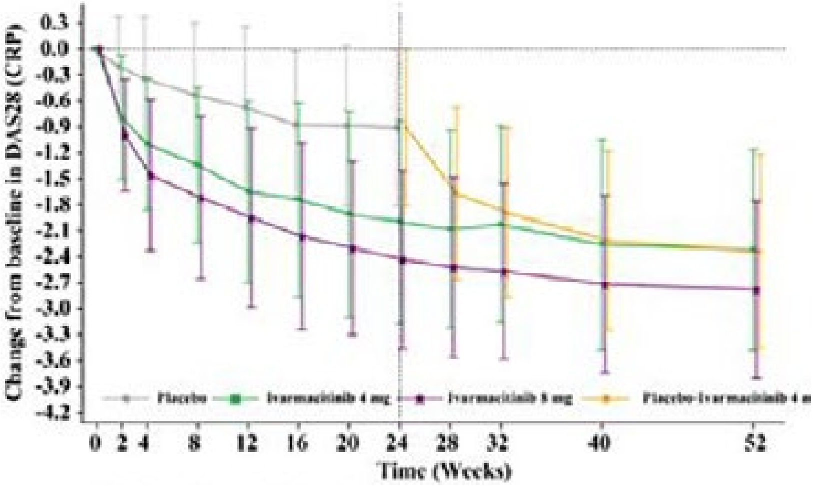
CDAI≦ 2.8、CDAI≦ 10

SDAI≦ 3.3、SDAI≦ 11を達成した患者の割合

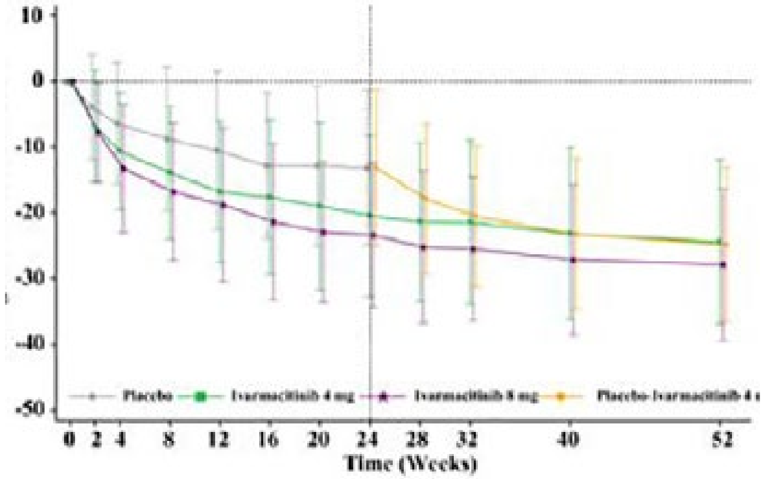
Ivarmacitinib 4mg、8mgともPlacebo群と比較して有意差が示された(P< 0.001、多重調整なし)

Results: DAS28-CRP、CDAI、SDAIの変化

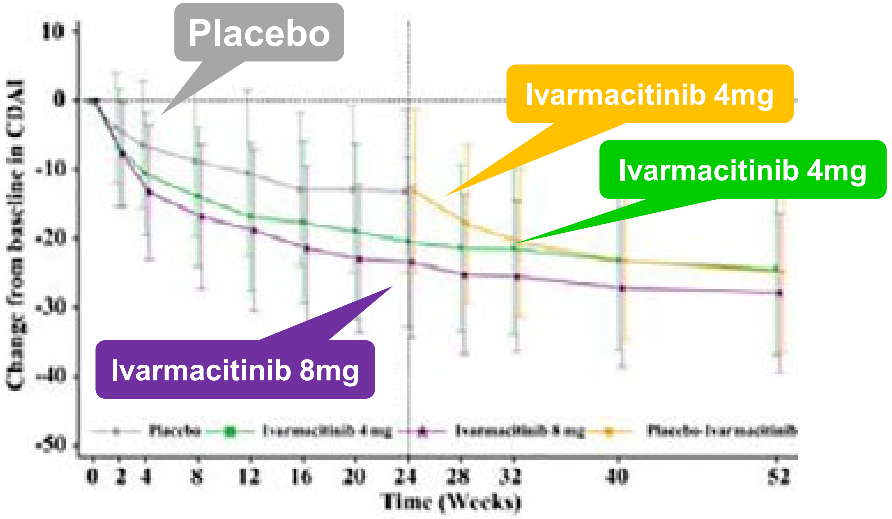
DAS28−CRP



CDAI

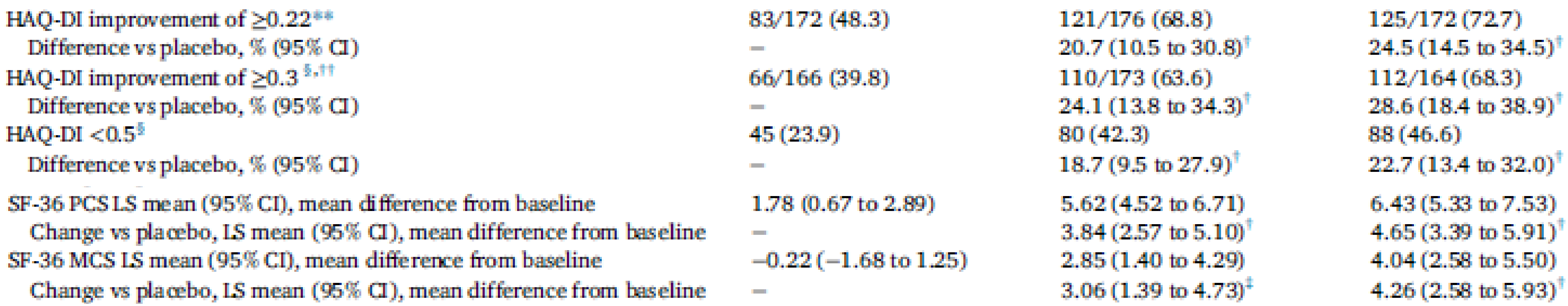


SDAI



- 治療開始早期から24週までIvarmacitinib 4mg、8mg群の方がPlacebo群よりもDAS28-CRP、CDAI、SDAIともに改善していた
- Placebo群は24週からIvarmacitinib 4mgを開始することで、Ivarmacitinib 4mg群と同程度のDAS28-CRP、CDAI、SDAIに改善した

Results: Patient-reported outcomes(PRO)



	Placebo	Ivarmacitinib 4mg	Ivarmacitinib 8mg
HAQ-DI improvement of ≥0.22[**]	83/172 (48.3)	121/176 (68.8)	125/172 (72.7)
Difference vs placebo, % (95% CI)	–	20.7 (10.5 to 30.8)[†]	24.5 (14.5 to 34.5)[†]
HAQ-DI improvement of ≥0.3[§,††]	66/166 (39.8)	110/173 (63.6)	112/164 (68.3)
Difference vs placebo, % (95% CI)	–	24.1 (13.8 to 34.3)[†]	28.6 (18.4 to 38.9)[†]
HAQ-DI <0.5[§]	45 (23.9)	80 (42.3)	88 (46.6)
Difference vs placebo, % (95% CI)	–	18.7 (9.5 to 27.9)[†]	22.7 (13.4 to 32.0)[†]
SF-36 PCS LS mean (95% CI), mean difference from baseline	1.78 (0.67 to 2.89)	5.62 (4.52 to 6.71)	6.43 (5.33 to 7.53)
Change vs placebo, LS mean (95% CI), mean difference from baseline	–	3.84 (2.57 to 5.10)[†]	4.65 (3.39 to 5.91)[†]
SF-36 MCS LS mean (95% CI), mean difference from baseline	−0.22 (−1.68 to 1.25)	2.85 (1.40 to 4.29)	4.04 (2.58 to 5.50)
Change vs placebo, LS mean (95% CI), mean difference from baseline	–	3.06 (1.39 to 4.73)[‡]	4.26 (2.58 to 5.93)[†]

24週における

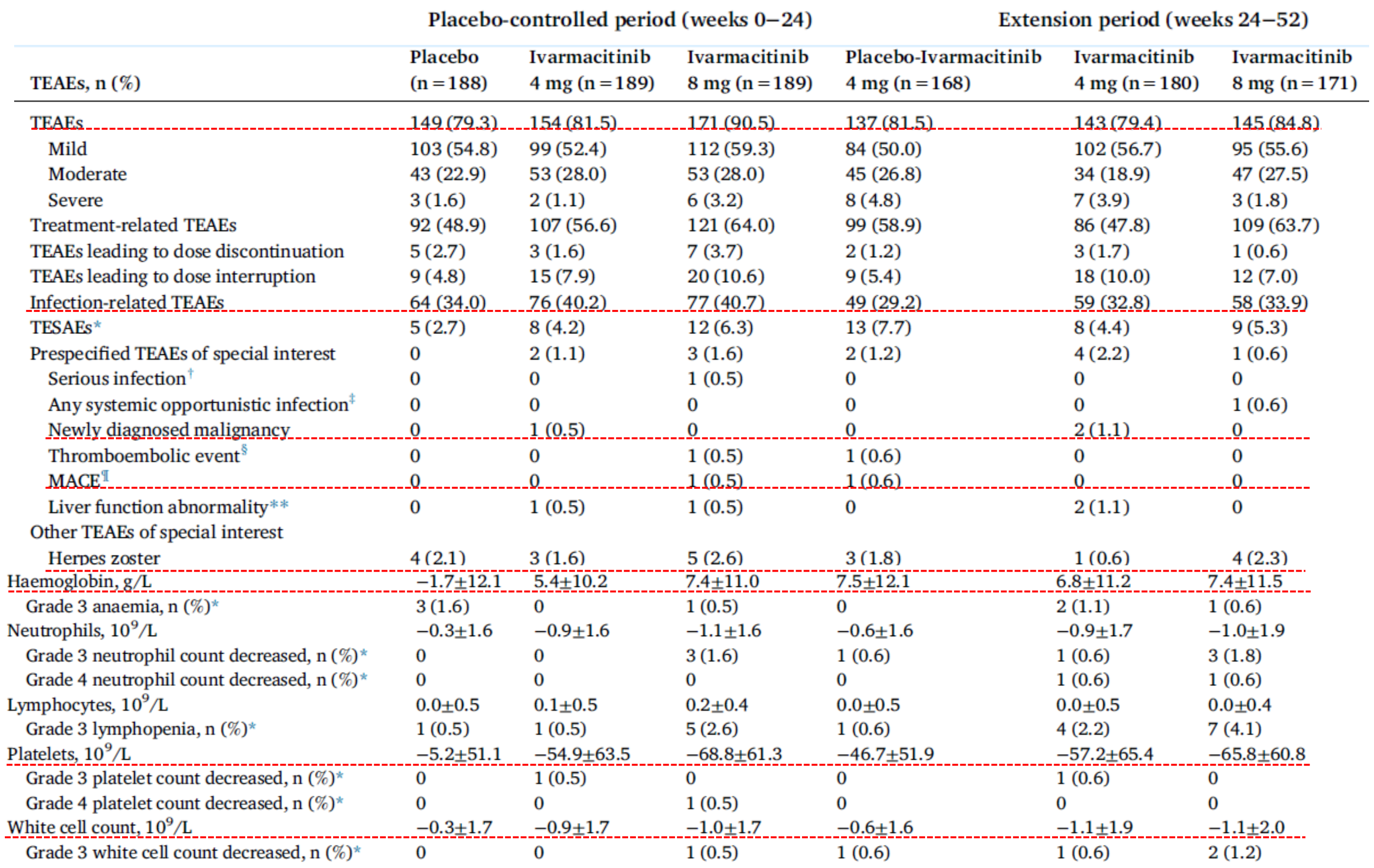
HAQ-DIが0.22以上、0.3以上改善した患者の割合、HAQ-DI<0.5を満たす患者の割合

SF-36 PCS(身体要素の得点)、MCS(精神要素の得点)の最小二乗

Ivarmacitinib 4mg、8mgともPlacebo群と比較して有意差が示された

(P< 0.0001、多重調整なし)

Results: 有害事象



	Placebo-controlled period (weeks 0–24)			Extension period (weeks 24–52)		
TEAEs, n (%)	Placebo (n = 188)	Ivarmacitinib 4 mg (n = 189)	Ivarmacitinib 8 mg (n = 189)	Placebo-Ivarmacitinib 4 mg (n = 168)	Ivarmacitinib 4 mg (n = 180)	Ivarmacitinib 8 mg (n = 171)
TEAEs	149 (79.3)	154 (81.5)	171 (90.5)	137 (81.5)	143 (79.4)	145 (84.8)
Mild	103 (54.8)	99 (52.4)	112 (59.3)	84 (50.0)	102 (56.7)	95 (55.6)
Moderate	43 (22.9)	53 (28.0)	53 (28.0)	45 (26.8)	34 (18.9)	47 (27.5)
Severe	3 (1.6)	2 (1.1)	6 (3.2)	8 (4.8)	7 (3.9)	3 (1.8)
Treatment-related TEAEs	92 (48.9)	107 (56.6)	121 (64.0)	99 (58.9)	86 (47.8)	109 (63.7)
TEAEs leading to dose discontinuation	5 (2.7)	3 (1.6)	7 (3.7)	2 (1.2)	3 (1.7)	1 (0.6)
TEAEs leading to dose interruption	9 (4.8)	15 (7.9)	20 (10.6)	9 (5.4)	18 (10.0)	12 (7.0)
Infection-related TEAEs	64 (34.0)	76 (40.2)	77 (40.7)	49 (29.2)	59 (32.8)	58 (33.9)
TESAEs[*]	5 (2.7)	8 (4.2)	12 (6.3)	13 (7.7)	8 (4.4)	9 (5.3)
Prespecified TEAEs of special interest	0	2 (1.1)	3 (1.6)	2 (1.2)	4 (2.2)	1 (0.6)
Serious infection[†]	0	0	1 (0.5)	0	0	0
Any systemic opportunistic infection[‡]	0	0	0	0	0	1 (0.6)
Newly diagnosed malignancy	0	1 (0.5)	0	0	2 (1.1)	0
Thromboembolic event[§]	0	0	1 (0.5)	1 (0.6)	0	0
MACE[¶]	0	0	1 (0.5)	1 (0.6)	0	0
Liver function abnormality[**]	0	1 (0.5)	1 (0.5)	0	2 (1.1)	0
Other TEAEs of special interest						
Herpes zoster	4 (2.1)	3 (1.6)	5 (2.6)	3 (1.8)	1 (0.6)	4 (2.3)
Haemoglobin, g/L	−1.7±12.1	5.4±10.2	7.4±11.0	7.5±12.1	6.8±11.2	7.4±11.5
Grade 3 anaemia, n (%)[*]	3 (1.6)	0	1 (0.5)	0	2 (1.1)	1 (0.6)
Neutrophils, 10^9/L	−0.3±1.6	−0.9±1.6	−1.1±1.6	−0.6±1.6	−0.9±1.7	−1.0±1.9
Grade 3 neutrophil count decreased, n (%)[*]	0	0	3 (1.6)	1 (0.6)	1 (0.6)	3 (1.8)
Grade 4 neutrophil count decreased, n (%)[*]	0	0	0	0	1 (0.6)	1 (0.6)
Lymphocytes, 10^9/L	0.0±0.5	0.1±0.5	0.2±0.4	0.0±0.5	0.0±0.5	0.0±0.4
Grade 3 lymphopenia, n (%)[*]	1 (0.5)	1 (0.5)	5 (2.6)	1 (0.6)	4 (2.2)	7 (4.1)
Platelets, 10^9/L	−5.2±51.1	−54.9±63.5	−68.8±61.3	−46.7±51.9	−57.2±65.4	−65.8±60.8
Grade 3 platelet count decreased, n (%)[*]	0	1 (0.5)	0	0	1 (0.6)	0
Grade 4 platelet count decreased, n (%)[*]	0	0	1 (0.5)	0	0	0
White cell count, 10^9/L	−0.3±1.7	−0.9±1.7	−1.0±1.7	−0.6±1.6	−1.1±1.9	−1.1±2.0
Grade 3 white cell count decreased, n (%)[*]	0	0	1 (0.5)	1 (0.6)	1 (0.6)	2 (1.2)

- Ivarmacitinib 8mgでAEは増加

- 感染症は増加
- 帯状疱疹は増加しない

- 悪性腫瘍はIvarmacitinib群で3例のみ

- MACEはIvarmacitinib群で1例のみ

- Hbは増加、WBC、Pltは減少

Discussion

- RAに対する他のJAK阻害薬におけるp3のRCTと12、24週におけるACR20達成率がほぼ同じ
- Ivarmacitinib 8mgは4mgの場合やplacebo群に比べて有害事象が多い
- JAK阻害薬に特徴的な悪性腫瘍、血栓イベント、MACE、帯状疱疹は増加しない

Limitation

- 対象が中国人のみである
- IvarmacitinibとcsDMARDsを24週しか比較できていない