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ORIGINAL ARTICLE

A Phase 3 Trial of Upadacitinib for Giant-Cell Arteritis

Daniel Blockmans, M.D., Ph.D.,[1,2] Sara K. Penn, M.D.,[3] Arathi R. Setty, M.D., M.P.H.,[3] Wolfgang A. Schmidt, M.D., M.A.C.R.,[4] Andrea Rubbert-Roth, M.D.,[5] Ellen M. Hauge, M.D., Ph.D.,[6,7] Helen I. Keen, M.B., B.S., Ph.D.,[8] Tomonori Ishii, M.D., Ph.D.,[9] Nader Khalidi, M.D.,[10] Christian Dejaco, M.D., Ph.D.,[11,12] Maria C. Cid, M.D.,[13] Bernhard Hellmich, M.D.,[14] Meng Liu, Ph.D.,[3] Weihan Zhao, Ph.D.,[3] Ivan Lagunes, M.D.,[3] Ana B. Romero, M.D.,[3] Peter K. Wung, M.D., M.H.S.,[3] and Peter A. Merkel, M.D., M.P.H.,[15] for the SELECT-GCA Study Group*

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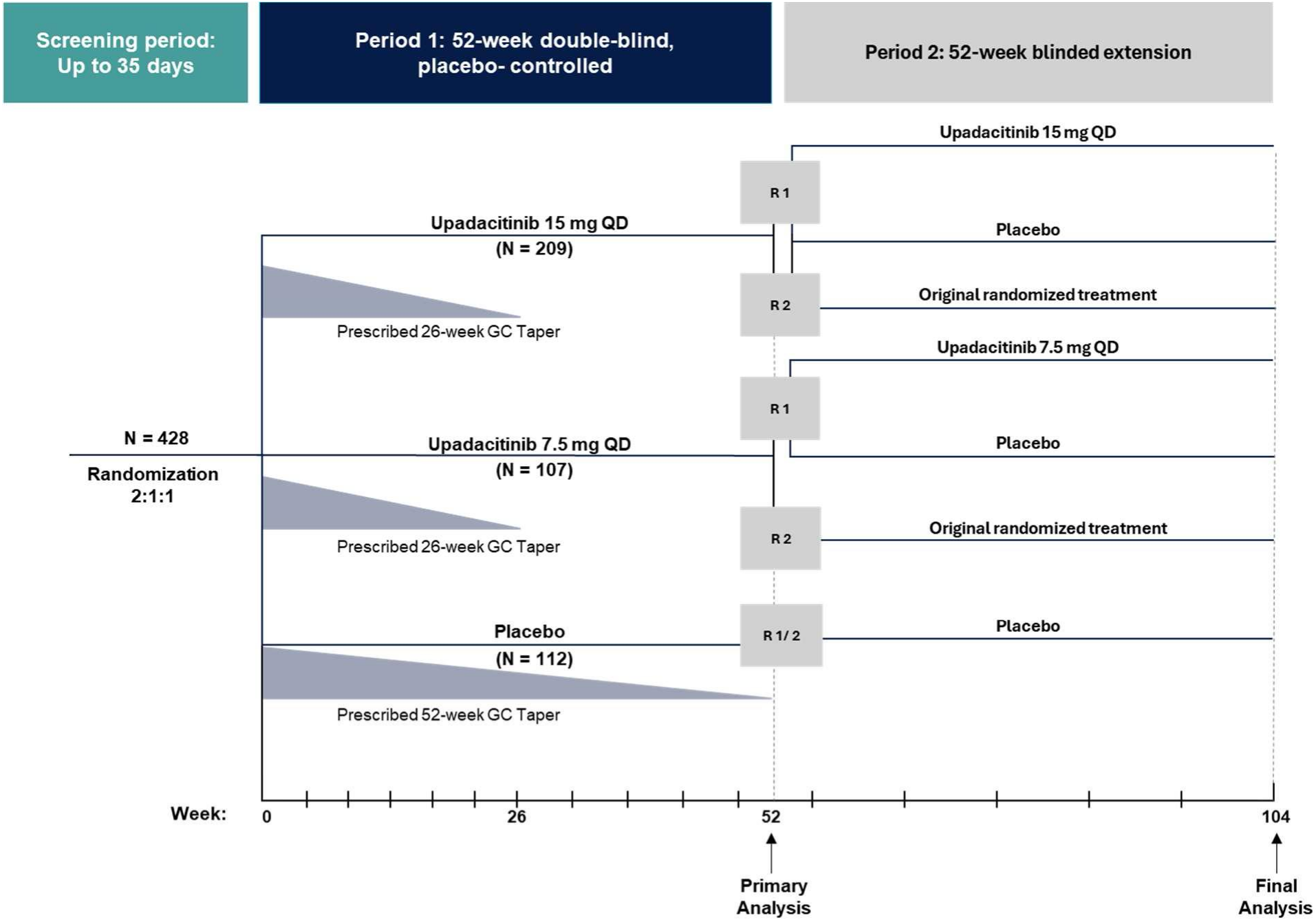
目的

GCAに対するUpadacitinibの有効性を評価する

方法

24か国 100施設で実施された
二重盲検化ランダム化比較試験



GC, glucocorticoid; GCA, giant-cell arteritis; R1, sustained remission for 24 consecutive weeks prior to week 52; R2, remission at week 52 but not achieving sustained remission for at least 24 consecutive weeks prior to the week 52 visit; QD, once daily.

Table S1. Glucocorticoid Tapering Schedule for the SELECT-GCA Trial

	Blinded 52-week GC-T (dose in mg)[a]					Blinded 26-week GC-T (dose in mg)[a]					
Baseline	20	30	40	50	60	Baseline	20	30	40	50	60
Week 1	17	25	35	40	50	Week 1	15	25	35	40	50
Week 2	17	20	30	35	40	Week 2	12	20	30	35	40
Week 3	15	17	25	30	35	Week 3	12	15	25	30	35
Week 4	15	17	20	25	30	Week 4	10	12	20	25	30
Week 5	12	15	17	20	25	Week 5	9	12	15	20	25
Week 6	10	15	17	17	20	Week 6	8	10	12	15	20
Week 7	10	12	15	17	17	Week 7	7	9	12	12	15
Week 8	10	10	15	15	17	Week 8	6	8	10	12	12
Week 9	10	10	12	15	15	Week 9	6	7	9	10	12
Week 10	9	10	10	12	15	Week 10	5	6	8	9	10
Week 11	9	10	10	10	12	Week 11	5	6	7	8	9
Week 12	9	9	10	10	10	Week 12	4	5	6	7	8
Week 13	9	9	10	10	10	Week 13	4	5	6	6	7
Week 14	8	9	9	10	10	Week 14	3	4	5	6	6
Week 15	8	9	9	9	10	Week 15	3	4	5	5	6
Week 16	8	8	9	9	9	Week 16	2	3	4	5	5
Week 17	8	8	9	9	9	Week 17	2	3	4	4	5
Week 18	7	8	8	9	9	Week 18	1	2	3	4	4
Week 19	7	8	8	8	9	Week 19	1	2	3	3	4
Week 20	7	7	8	8	8	Week 20	0	1	2	3	3
Week 21	7	7	8	8	8	Week 21	0	1	2	2	3
Week 22	6	7	7	8	8	Week 22	0	0	1	2	2
Week 23	6	7	7	7	8	Week 23	0	0	1	1	2
Week 24	6	6	7	7	7	Week 24	0	0	0	1	1
Week 25	6	6	7	7	7	Week 25	0	0	0	0	1
Week 26	5	6	6	7	7	Week 26	0	0	0	0	0
Week 27	5	6	6	6	7	Week 27	0	0	0	0	0
Week 28	5	5	6	6	6	Week 28	0	0	0	0	0
Week 29	5	5	6	6	6	Week 29	0	0	0	0	0
Week 30	4	5	5	6	6	Week 30	0	0	0	0	0
Week 31	4	5	5	5	6	Week 31	0	0	0	0	0
Week 32	4	4	5	5	5	Week 32	0	0	0	0	0
Week 33	4	4	5	5	5	Week 33	0	0	0	0	0
Week 34	3	4	4	5	5	Week 34	0	0	0	0	0
Week 35	3	4	4	4	5	Week 35	0	0	0	0	0
Week 36	3	3	4	4	4	Week 36	0	0	0	0	0
Week 37	3	3	4	4	4	Week 37	0	0	0	0	0
Week 38	2	3	3	4	4	Week 38	0	0	0	0	0
Week 39	2	3	3	3	4	Week 39	0	0	0	0	0
Week 40	2	2	3	3	3	Week 40	0	0	0	0	0
Week 41	2	2	3	3	3	Week 41	0	0	0	0	0
Week 42	1	2	2	3	3	Week 42	0	0	0	0	0
Week 43	1	2	2	2	3	Week 43	0	0	0	0	0
Week 44	1	1	2	2	2	Week 44	0	0	0	0	0
Week 45	1	1	2	2	2	Week 45	0	0	0	0	0
Week 46	0	1	1	2	2	Week 46	0	0	0	0	0
Week 47	0	1	1	1	2	Week 47	0	0	0	0	0
Week 48	0	0	1	1	1	Week 48	0	0	0	0	0
Week 49	0	0	1	1	1	Week 49	0	0	0	0	0
Week 50	0	0	0	1	1	Week 50	0	0	0	0	0
Week 51	0	0	0	0	1	Week 51	0	0	0	0	0
Week 52	0	0	0	0	0	Week 52	0	0	0	0	0

初期GC量は、医療者の裁量によって決定された

主な組み入れ基準

1) 50歳以上
2) 新規発症あるいは再発例
3) 側頭動脈生検あるいは画像検査 (US, PET, CT, MRI, 血管造影)で確定
4) ベースライン前8週間は活動性がある
5) いずれかの時点でPSL 40 mg相当を使用したことがあり、
   ベースライン時点でPSL 20-60 mgを使用している。

*活動性: 明らかなcranial symptomsあるいはPMR症状がある
+ ESR>30 mm/h or CRP≧1 mg/dL

*再発: 少なくとも1度のGC減量による疾患コントロールの失敗

主な除外基準

1) JAK阻害薬の使用歴がある
2) IL-6阻害薬使用中に再燃歴がある

アウトカム

- **主要評価項目**

- 52週時点での寛解維持 (sustained remission)

12週から52週にかけて、GCAの症状や徴候がない
かつ
GC減量プロトコルを遵守した

アウトカム

- **副次評価項目**

- 完全寛解維持 (sustained complete remission)
  - 12-52週を通じて寛解維持+ESRとCRP正常化
- 疾患再発
- GC累積量
- GC関連有害事象
- PRO

結果

Table 1. Baseline Demographics and Disease Characteristics of the Patients.*

Characteristic	Placebo + 52-week GC-T (N=112)	Upadacitinib 7.5 mg + 26-week GC-T (N=107)	Upadacitinib 15 mg + 26-week GC-T (N=209)
Female sex — no. (%)	77 (68.8)	80 (74.8)	156 (74.6)
Age — yr	71.6±7.3	71.1±7.6	70.8±7.3
Age group — no. (%)			
<65 yr	17 (15.2)	19 (17.8)	42 (20.1)
≥65 to <75 yr	59 (52.7)	49 (45.8)	102 (48.8)
≥75 yr	36 (32.1)	39 (36.4)	65 (31.1)
Body-mass index†	25.8±4.3	25.2±5.1	25.3±4.6
Race or ethnic group — no. (%)‡			
Asian	6 (5.4)	6 (5.6)	10 (4.8)
Black or African American	2 (1.8)	1 (0.9)	0
Native Hawaiian or other Pacific Islander	0	1 (0.9)	0
White	103 (92.0)	99 (92.5)	199 (95.2)
Multiple races or ethnic groups	1 (0.9)	0	0
Disease status — no. (%)			
New-onset giant-cell arteritis	76 (67.9)	75 (70.1)	148 (70.8)
Relapsing giant-cell arteritis	36 (32.1)	32 (29.9)	61 (29.2)
Duration of new-onset giant-cell arteritis — days			
Mean	38.2±14.8	35.7±11.1	39.5±28.1
Median	37.0	35.0	36.0
Duration of relapsing giant-cell arteritis — days			
Mean	665.7±816.3	999.2±1179.0	664.9±687.5
Median	277.0	539.5	343.0

- 女性が70%前後
- 年齢　約70歳
- 白人が90%以上
- 新規発症が約70%
  再発が約30%

Table 1. Baseline Demographics and Disease Characteristics of the Patients.*

Characteristic	Placebo + 52-week GC-T (N=112)	Upadacitinib 7.5 mg + 26-week GC-T (N=107)	Upadacitinib 15 mg + 26-week GC-T (N=209)
Glucocorticoid dose — mg	34.6±11.9	34.5±12.5	34.6±12.7
ESR — mm/hr	21.7±25.5	19.9±21.1	19.5±17.5
Median CRP level (range) — mg/dl	0.23 (0.02–5.83)	0.27 (0.02–5.82)	0.24 (0.02–10.10)
Previous use of interleukin-6 inhibitor — no. (%)§	7 (6.2)	7 (6.5)	9 (4.3)
Ischemia-related vision loss — no. (%)¶	22 (19.6)	14 (13.1)	20 (9.6)
History of PMR — no. (%)	69 (61.6)	54 (50.5)	109 (52.2)
History of unequivocal symptoms of PMR without cranial symptoms of giant-cell arteritis — no. (%)	18 (16.1)	7 (6.5)	15 (7.2)
Basis for diagnosis — no. (%)			
History of positive temporal-artery biopsy	44 (39.3)	48 (44.9)	86 (41.1)
Evidence of large-vessel vasculitis on imaging‖	81 (73.0)	83 (77.6)	159 (76.1)
FACIT-Fatigue score**	37.5±11.7	35.6±11.3	36.0±11.2
SF-36 PCS score††	45.0±10.0	44.3±10.2	44.3±9.3

診断

- TAB*陽性　40%前後
- 画像でのLVV 75%前後

*全患者でTABは施行された

治療

- GC使用量　PSL 35mg相当
- IL-6阻害薬使用歴　4-6%

治験薬中断が多い

Upa 15 mg群	25.8%
Upa 7.5 mg群	31.8%
PBO群	36.6%

主要評価項目

Table 2. Primary and Secondary End Points through Week 52.*

End Points	Placebo + 52-week GC-T (N = 112)	Upadacitinib 7.5 mg + 26-week GC-T (N = 107)	Upadacitinib 15 mg + 26-week GC-T (N = 209)	Treatment Effect, Upadacitinib 7.5 mg (95% CI)	Treatment Effect, Upadacitinib 15 mg (95% CI)	P Value for Treatment Effect, Upadacitinib 15 mg
Primary end point						
Sustained remission at week 52 — no. (% [95% CI])	33 (29.0 [20.6 to 37.5])	44 (41.1 [31.8 to 50.4])	97 (46.4 [39.6 to 53.2])	12.1 (–0.4 to 24.6)	17.1 (6.3 to 27.8)	0.002

52週時点での寛解維持

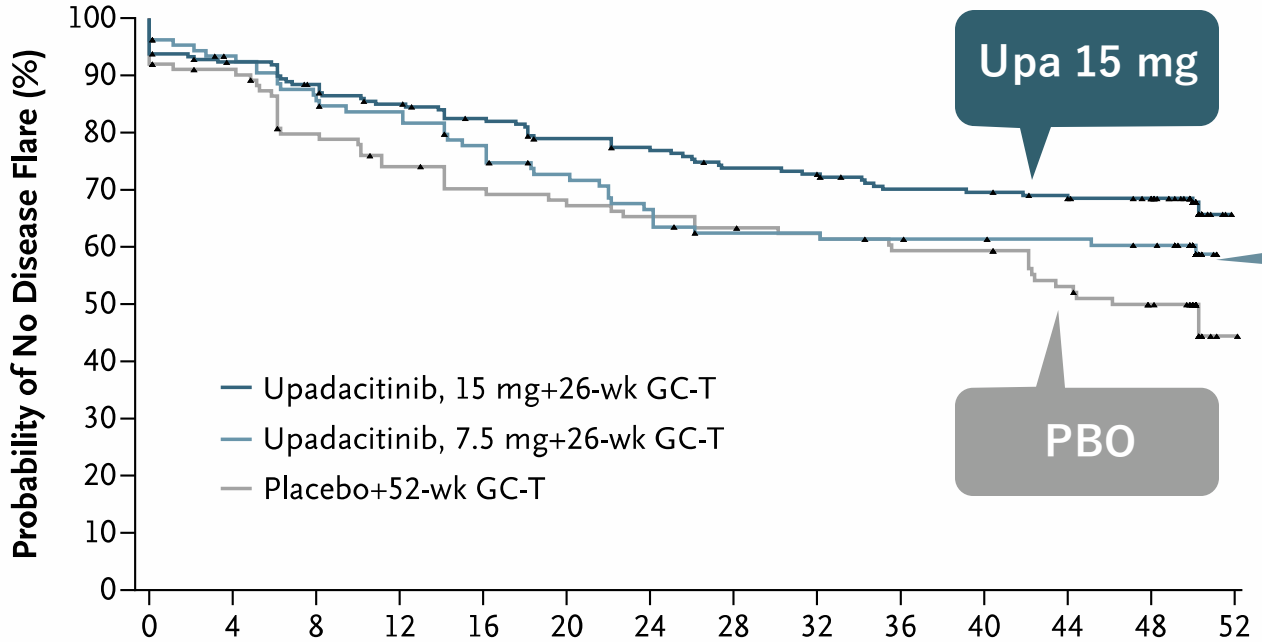
- Upa 15 mg群はPBOよりも有意に優れていた
- Upa 7.5 mg群はPBOと有意差はなかった

副次評価項目

Table 2. Primary and Secondary End Points through Week 52.*

End Points	Placebo + 52-week GC-T (N=112)	Upadacitinib 7.5 mg + 26-week GC-T (N=107)	Upadacitinib 15 mg + 26-week GC-T (N=209)	Treatment Effect, Upadacitinib 7.5 mg (95% CI)	Treatment Effect, Upadacitinib 15 mg (95% CI)	P Value for Treatment Effect, Upadacitinib 15 mg
Secondary end points						
Sustained complete remission at week 52 — no. (% [95% CI])	18 (16.1 [9.3 to 22.9])	28 (26.2 [17.8 to 34.5])	78 (37.1 [30.5 to 43.7])	9.9 (–0.8 to 20.6)	20.7 (11.3 to 30.2)	<0.001
Median cumulative glucocorticoid exposure through week 52 (95% CI) — mg†	2882 (2762 to 3253)	1905 (1615 to 2265)	1615 (1615 to 1635)	–1206 (–1452 to –802)	–1267 (–1587 to –1133)	<0.001
Median time to first disease flare through week 52 (95% CI) — days‡	323 (249 to >365)	>365 (316 to >365)	>365	0.75 (0.50 to 1.14)	0.57 (0.40 to 0.83)	0.003
≥1 disease flare through week 52 (95% CI) — %§	55.6 (42.9 to 69.2)	41.3 (32.2 to 51.7)	34.3 (27.4 to 42.4)	0.60 (0.35 to 1.03)	0.47 (0.29 to 0.74)	0.001
Complete remission at week 52 — no. (% [95% CI])	22 (19.6 [12.3 to 27.0])	46 (43.0 [33.6 to 52.4])	105 (50.2 [43.4 to 57.1])	23.5 (11.7 to 35.3)	30.3 (20.4 to 40.2)	<0.001
Complete remission at week 24 — no. (% [95% CI])	40 (36.1 [27.2 to 45.1])	42 (39.3 [30.0 to 48.5])	120 (57.2 [50.5 to 64.0])	3.2 (–9.6 to 16.0)	20.8 (9.7 to 31.9)	<0.001
LS mean change from baseline in SF-36 PCS score at week 52 (95% CI)¶	–1.3 (–3.3 to 0.7)	1.3 (–0.7 to 3.3)	2.5 (1.2 to 3.8)	2.6 (–0.2 to 5.4)	3.8 (1.4 to 6.1)	0.002
Mean no. of disease flares through week 52 per patient-year (95% CI)‖	0.7 (0.5 to 0.9)	0.6 (0.4 to 0.7)	0.4 (0.3 to 0.5)	0.8 (0.6 to 1.2)	0.6 (0.4 to 0.8)	0.001
LS mean change from baseline in FACIT-Fatigue score at week 52 (95% CI)**	–2.4 (–4.7 to –0.1)	1.1 (–1.2 to 3.4)	1.7 (0.2 to 3.1)	3.5 (0.3 to 6.7)	4.0 (1.3 to 6.8)	0.004
LS mean TSQM score at week 52 (95% CI)††	68.8 (63.8 to 73.9)	74.3 (69.4 to 79.1)	71.6 (68.3 to 74.8)	5.4 (–1.4 to 12.3)	2.7 (–3.1 to 8.6)	
Mean no. of glucocorticoid-related adverse events through week 52 per patient-year (95% CI)	1.7 (1.3 to 2.3)	1.7 (1.2 to 2.2)	2.0 (1.7 to 2.4)	0.9 (0.6 to 1.4)	1.1 (0.8 to 1.6)‖	

いずれの副次評価項目においても、
Upa 15 mg群はPBOよりも有意に優れていた



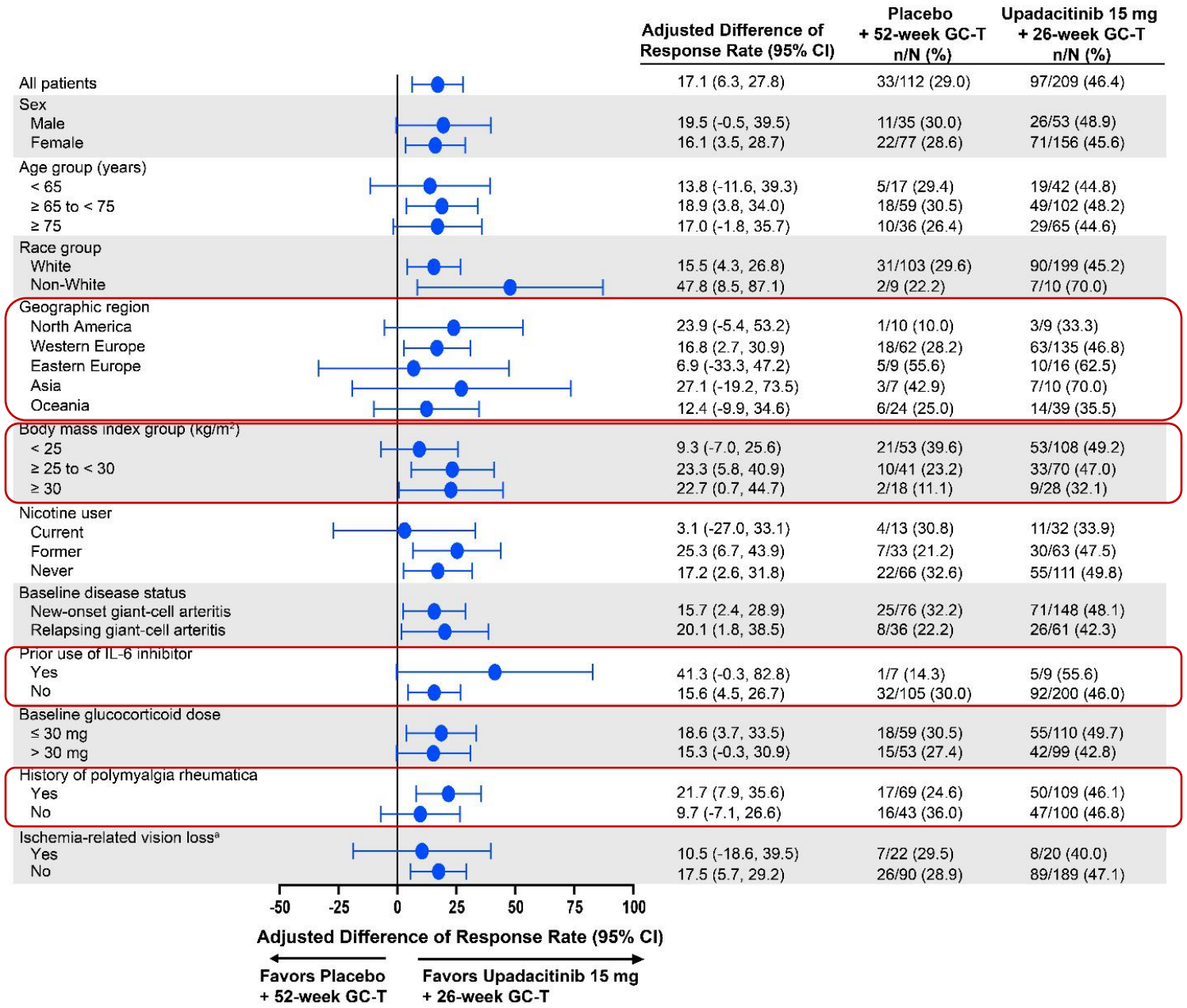
No. at Risk														Median Time to Disease Flare (95% CI) *wk*	Hazard Ratio for Disease Flare (95% CI)	P Value
Upadacitinib, 15 mg +26-wk GC-T	209	190	180	171	163	154	150	142	140	132	131	128	123	NE (NE–NE)	0.57 (0.40–0.83)	0.003
Upadacitinib, 7.5 mg +26-wk GC-T	107	96	89	85	78	71	65	59	59	58	57	56	54	NE (45.1–NE)	0.75 (0.50–1.14)	
Placebo+52-wk GC-T	112	98	84	77	72	70	67	65	63	59	59	51	45	46.1 (35.6–NE)	Reference	

Figure 1. Time to First Flare of Giant-Cell Arteritis through Week 52.

Upa 15 mg群はPBOよりも有意に再燃が少なかった

*再発：GCAの症状/徴候の再出現 or ESR>30 mm/h(GCAによる) and GC増量が必要

サブグループ解析



- アジア人では差がない
  (ただしnが少ない)
- BMI<25では差がない
- IL-6i使用歴がある場合は差がない
  (ただしnが少ない)
- PMR合併がない場合は差がない

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

Adverse Events	Placebo + 52-week GC-T (N=112)	Upadacitinib 7.5 mg + 26-week GC-T (N=107)	Upadacitinib 15 mg + 26-week GC-T (N=209)
		number (percent)	
Any adverse event†	105 (93.8)	101 (94.4)	200 (95.7)
Serious adverse events†	24 (21.4)	13 (12.1)	47 (22.5)
Adverse events leading to discontinuation of upadacitinib or placebo†	22 (19.6)	17 (15.9)	31 (14.8)
Death‡	2 (1.8)	0	2 (1.0)
Adverse events of special interest			
Serious infection	12 (10.7)	6 (5.6)	12 (5.7)
Opportunistic infection, excluding herpes zoster	1 (0.9)	0	4 (1.9)
Herpes zoster	3 (2.7)	3 (2.8)	11 (5.3)
Cancer, excluding nonmelanoma skin cancer	2 (1.8)	0	4 (1.9)
Nonmelanoma skin cancer	2 (1.8)	1 (0.9)	5 (2.4)
Major adverse cardiovascular events§	2 (1.8)	0	0
Venous thromboembolism¶	4 (3.6)	4 (3.7)	7 (3.3)
Renal dysfunction	3 (2.7)	0	4 (1.9)
Hepatic disorder	5 (4.5)	2 (1.9)	11 (5.3)
Anemia	3 (2.7)	3 (2.8)	14 (6.7)
Neutropenia	1 (0.9)	0	0
Lymphopenia	0	1 (0.9)	3 (1.4)
Creatine kinase elevation	0	0	6 (2.9)
Retinal detachment	6 (5.4)	6 (5.6)	13 (6.2)
Bone fracture	3 (2.7)	1 (0.9)	3 (1.4)

安全性

- **重篤な感染症**：
  - PBO群で多い
- **Herpes zoster**：
  - Upa 15 mg群で多い
- **MACE**：
  - PBO群の2例のみ
- **VTE**：
  - 発生率は群間で同等
- **悪性腫瘍**：
  - Upa 15 mgとPBOで同等の発生率

Discussion

- 本研究で、Upa 15 mg + GC 26週減量は、PBO + GC 52週減量と比べてGC free寛解率が優れており疾患再燃が少なかった。

- 平均年齢71.1歳の高齢者集団であったが、新たな臨床的に重要な安全性リスクは確認されなかった。悪性腫瘍やVTEを含む特別な関心のある有害事象の発生率はUpa群とPBO群で概ね同等だった。しかし、心血管リスクへの相対的な影響を評価するには、より長期的なフォローアップが必要である。

- CRP/ESRに依存しない寛解維持 (sustained remission) を主要評価項目に選択したことで、UpaによるCRP/ESR低下の影響を排除できた。

Limitation

1. 予想以上に治験薬中断が発生した
   - 試験実施時期がCOVID-19パンデミック中だった
   - GCAに対するTCZの承認の影響
2. IL-6阻害薬が無効だった患者での有効性は評価されなかった
3. GC関連有害事象は、GCとの関連性が治験担当医師により判断されたため、注意して解釈する必要がある
4. 試験期間が短い
   - 2年間のextension studyが報告予定