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Clinical science

Phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel-group study of ustekinumab in patients with Takayasu arteritis

Hajime Yoshifuji [1], Tomonori Ishii [2], Hiroki Ohashi [3,*], Katsunori Yoshizawa [3], Maki Mihoya [3], Kazuko Nishikawa [3], Yoshikazu Nakaoka [4,5]

[1]Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[2]Division of Hematology and Rheumatology, Tohoku Medical and Pharmaceutical University, Miyagi, Japan
[3]Janssen Pharmaceutical K.K., Tokyo, Japan
[4]Department of Vascular Physiology, National Cerebral and Cardiovascular Center, Osaka, Japan
[5]Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center Hospital, Osaka, Japan

*Correspondence to: Hiroki Ohashi, Janssen Pharmaceutical K.K., 3-5-2, Nishi-Kanda, Chiyoda-ku, Tokyo 101-0065, Japan. E-mail: HOHASHI1@its.jnj.com

Abstract

Objectives: Takayasu arteritis (TAK) is a rare, chronic large vessel vasculitis with unmet treatment needs. This phase 3 study aimed to evaluate efficacy, safety, pharmacokinetics and immunogenicity of ustekinumab (UST) in Japanese patients with TAK.

Methods: Patients with TAK who had relapsed ≤12 weeks prior to study intervention administration and achieved remission thereafter with standard-of-care including corticosteroid intensification were randomized 1:1 to receive UST or matching placebo with protocol-defined oral glucocorticoid taper regimen. The double-blind (DB) phase was up to the patient's relapse/total of 35 relapse events, followed by the open-label extension (OLE) phase. Primary endpoint was the time to relapse of TAK per protocol-defined criteria through the end of the DB phase.

Results: The study was terminated early due to patient recruitment challenge. Of 14 patients randomized, 8 relapsed during the DB phase (UST: 4/6; placebo: 4/8). The median time to relapse (weeks) was 11.14 (95% CI: 4.14, not estimated [NE]) for UST and 12.64 (95% confidence interval [CI]: 12.14, NE) for placebo (hazard ratio [HR] = 1.86 [95% CI: 0.41, 8.47]). In the DB phase, one patient in each group reported serious adverse event (SAE; UST: vascular pseudoaneurysm and brachiocephalic artery stenosis; placebo: cholecystitis); none were related to study intervention. Through the OLE phase, 1/4 (25.0%) patients in the UST-UST group (vascular graft infection considered related to study intervention) and none in the placebo-UST had SAEs. There were no serious infections/deaths throughout the study.

Conclusion: The efficacy of UST in patients with TAK cannot be adequately assessed as the pre-determined sample size was not reached, and the study was prematurely terminated. No new safety signal of UST was identified.

Trial registration: Clinicaltrials.gov, https://clinicaltrials.gov, NCT04882072; jrct.niph.go.jp, https://jrct.niph.go.jp, jRCT2061210007; Clinical Registry, CR108981.

Lay Summary

What does this mean for patients?

Takayasu arteritis (TAK) is an uncommon disease that causes pain and swelling in large blood vessels, leading to serious health problems. Currently, treatment options for TAK are limited; hence, this study tested ustekinumab (UST), a medication that affects the immune system, to assess if it could help manage TAK. This study included Japanese patients with TAK who had recently experienced a flare-up (i.e. worsening of symptoms) while taking steroid treatment and were stabilized/controlled after taking higher doses of steroids. Patients were randomly given UST or placebo (dummy treatment) with gradual reduction in their steroid dose, and the time it took for the symptoms to flare-up was monitored. The study was stopped early due to the patient recruitment challenge. Of the 14 patients who participated, 8 experienced flare-ups during the study (4 each in UST and placebo groups). The average time to flare-up was around 11 weeks for UST and around 13 weeks for placebo. Serious side effects were rare and may not be associated with the treatment. No deaths or severe infections were observed. The early termination of the study prevented adequate assessment of UST's effectiveness for TAK. No new safety concerns with UST were observed.

Keywords: biologics, clinical trial, glucocorticoid, phase 3 study, randomized controlled trial, taper regimen, relapse, TAK, Takayasu arteritis, ustekinumab.

Key messages

- Ustekinumab's efficacy in patients with Takayasu arteritis cannot be adequately assessed due to premature termination.
- No new safety signal of ustekinumab was identified in the current study.
- Relatively short exposure of ustekinumab was generally well-tolerated in a small sample of Takayasu arteritis patients.

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Introduction

Takayasu arteritis (TAK) is a rare, chronic large vessel vasculitis mostly affecting the aorta, its primary branches and coronary and pulmonary arteries [1]. The estimated global prevalence of TAK is 0.4–3.4 million/year, often more prevalent in women [2]. Geographically, TAK is more prevalent in Asia and the Middle-East, highest in Japan with 40 individuals/million versus 9 individuals/million in the United States [2, 3]. In 2019, approximately 4463 patients with moderate-to-severe TAK were registered in a Japan Intractable Disease Information Center (http://www.nanbyou.or.jp) database. The men-to-women ratio is about 1:9, and the age of onset is between the second to third decade of life in women [4, 5].

Glucocorticoids (GC) are the first-line treatment for inducing remission in TAK, but their long-term use poses risks such as cataracts, osteoporosis, infections and adrenal insufficiency [6]. Additionally, higher GC doses increase the risk of complications over time. Therefore, the GC doses should be tapered [6] while maintaining low disease activity. GC-taper is usually combined with immunosuppressants (methotrexate/azathioprine/tacrolimus/cyclosporin A/mycophenolate mofetil) to enhance/spare GC effects and to prevent relapses, but the evidence of their GC-sparing effects in TAK is limited [7].

Tocilizumab, an IL-6 receptor monoclonal antibody, is the only GC-sparing biologic agent approved in Japan for TAK with weekly subcutaneous (SC) administration [8]. However, tocilizumab use in TAK is limited due to inadequate GC-sparing effect and associated adverse effects [9] and interference in interpretation of CRP levels for monitoring disease activity [10, 11]. Thus, significant unmet medical needs exist for new treatments offering a high GC-sparing effect with favourable safety profiles for TAK.

The pathophysiology of TAK involves a combination of genetic/immune-mediated factors (HLA-B52 allele) [12] and inflammatory cytokines (IL-6 and IL-12B loci) [13, 14]. Evidence suggests a pathogenic link between IL-12/23 and TAK clinical manifestations, but it is yet to be confirmed causally [15, 16]. Also, the adaptive immune system, particularly T-lymphocytes including T-helper 1 (Th1) and Th17, is implicated in the pathogenesis of TAK [17]. Th1 has been associated with vascular inflammation and granuloma formation in TAK [17, 18], while increased circulating Th17 from aortic biopsies of TAK patients has been implicated in resistance to corticosteroid [19, 20]. Ustekinumab (UST) is a high-affinity fully-human monoclonal antibody that binds with and prevents the binding of IL-12/23-p40 to the cell surface receptor IL-12Rβ1 and effectively neutralizes the IL-12 Th1- and IL-23 Th17-mediated cellular responses [21]. UST is the approved treatment for several inflammatory diseases including moderate-to-severe ulcerative colitis (UC). Interestingly, it has been suggested that TAK and UC share common pathophysiologic characteristics, including HLA-B52, HLA-DR2 and IL-12B as genetic determinants [22, 23], as well as anti-endothelial protein C receptor autoantibodies [24]. Besides, a literature review had identified that TAK was the most frequent form of vasculitis associated with IBD [25]. UST has been investigated in TAK and showed a potential efficacy signal in a pilot study in three Japanese patients with refractory TAK [26] and in a Caucasian TAK patient who was resistant to GC, immunosuppressant and biologics [27]. Given these preliminary clinical findings as well as the favourable safety and efficacy of UST confirmed in other inflammatory diseases, the current study was planned to evaluate the efficacy, safety, pharmacokinetic (PK) and immunogenicity of i.v. and SC UST in Japanese patients with TAK to provide a safe and effective GC-sparing therapeutic option.

Methods

Study design

This phase 3, randomized, double-blind (DB), placebo-controlled study was conducted from 15 September 2021 to 25 May 2023 (early termination) at 27 centres in Japan.

The planned study duration was ~2 years, consisting of 4 phases: ≤6 weeks of screening phase; the DB phase up to the patient's relapse or a total of 35 relapse events of TAK (the DB phase was to be completed once a total of 35 events of TAK relapse occurs, allowing relatively faster study conclusion while securing sufficient statistical power. Patients who experienced relapse were to be rescued with increased GC dose and were to be rolled over to the escape arm to receive UST. Patients who did not experience relapse at the end of the DB phase [except for patients who reached GC dose of ≤5 mg/day in the placebo group when 35 relapse events occurred] were to be rolled over to the open-label extension [OLE] phase); the OLE phase of 52 weeks or 32 weeks from the first SC administration after the end of the DB phase, whichever was later; and 16 weeks of safety follow-up phase post last SC UST administration (Fig. 1). However, the study was terminated prematurely due to patient recruitment challenges. The limited number of enrolled patients led to the study being underpowered.

This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practices, and applicable regulatory requirements. The study protocol/amendments were approved by the Institutional Review Board (IRB) of Kyoto University Hospital and IRBs of each study centre (Supplementary Table S1, available at *Rheumatology Advances in Practice* online). Safety data were periodically reviewed by an independent data monitoring committee. All participants or their legally acceptable representatives provided written informed consent.

Patients

Japanese men or women aged 15–75 years with TAK as per JCS-2017 Guideline on Management of Vasculitis Syndrome diagnosis criteria [3] who experienced TAK relapse within 12 weeks prior to administration of study intervention were enrolled. As per pre-specified protocol definition (Supplementary Table S2, available at *Rheumatology Advances in Practice* online), relapse must have occurred at a GC dose of at least 7.5 mg/day (prednisolone or equivalent) and must be adequately treated with a GC dose of ≥15 mg/day thereafter. The patients who had achieved remission with an oral GC treatment ≥1 week prior to the first study intervention administration and had maintained remission were deemed eligible. Patients with known ongoing severe/uncontrolled TAK complications, any other active rheumatic disease or GCA were excluded.

Randomization and masking

Patients were randomly assigned 1:1 to UST or matching placebo (Fig. 1) based on a computer-generated randomization

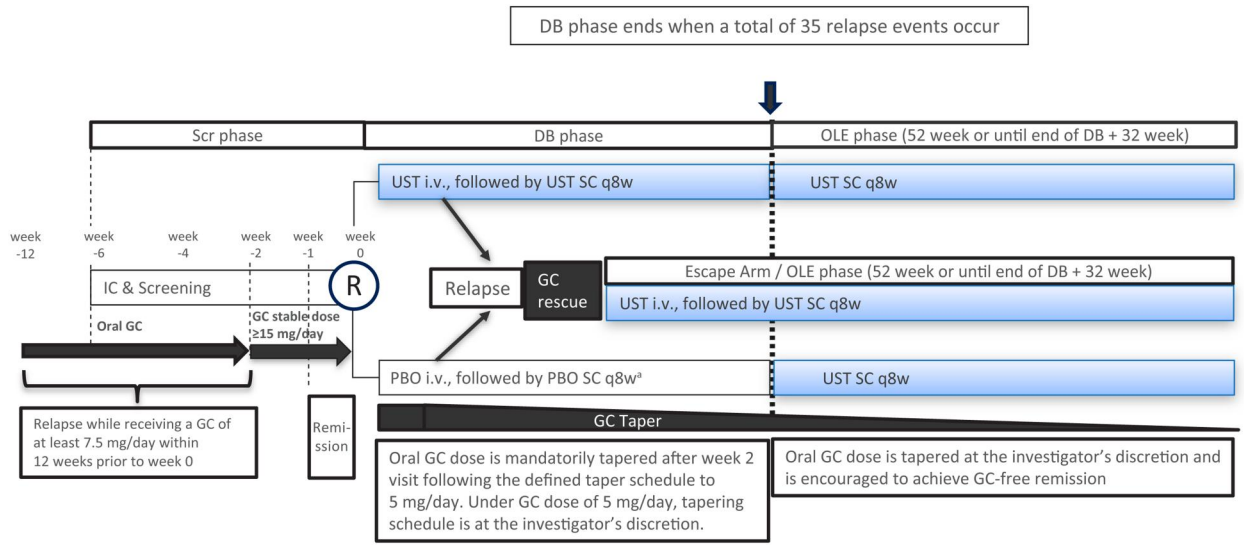

Figure 1. Study design. [a]When a total of 35 relapse events occur, patients who reach the oral GC dose of 5 mg/day (prednisolone or equivalent) or less at the end of the DB phase in the placebo group will terminate the study intervention administration and conduct early-term visit. DB: double-blind; DBL: database lock; Early-Term: early termination; GC: glucocorticoids; IC: informed consent; OLE: open-label extension; PBO: placebo; q8w: every 8 weeks; R: randomization; Scr: screening; UST: ustekinumab

schedule. Randomization was balanced with permuted blocks and was stratified by the GC dose at week 0 (prednisolone or equivalent: <0.5 mg/kg/day or ≥0.5 mg/kg/day) and previous biologic treatments (bio-nonfailure or bio-failure). The interactive web response system (IWRS) dictated the intervention assignment. The patients and investigators were blinded, and the blinding was maintained until the last patient last safety follow-up and the database lock. Integrity of the blind was carefully maintained, and the potential for bias was minimized.

Intervention

In the DB phase, the UST group received body weight-range-based i.v. UST (≤55 kg: 260 mg, >55 kg and ≤85 kg: 390 mg, >85 kg: 520 mg) at week 0 followed by UST, SC 90 mg at week 8 and every 8 weeks (q8w) thereafter. As per the protocol-defined schedule, the oral GC dose was tapered (Supplementary Table S3, available at *Rheumatology Advances in Practice* online) from week 2 onward. During the OLE phase, patients were to receive SC UST 90 mg at OL week 0 and followed by SC UST 90 mg q8w with oral GC-tapering at the investigator's discretion up to OL week 52 or until 32 weeks from the first SC administration after the end of the DB phase, whichever was later.

Study endpoints and assessments

This study evaluated the efficacy and safety of UST compared with placebo, in combination with an oral GC-taper regimen, in patients with TAK under disease remission. The time to relapse of TAK through the end of the DB phase was the primary endpoint. As per protocol, when ≥2 of 5 categories of symptoms (subjective systemic symptoms, objective systemic symptoms, elevated inflammatory markers, ischaemic symptoms, vascular signs and symptoms) met the criteria for the presence of active TAK disease, patients were judged as relapsed. Apart from this, patients were considered relapsed if emergent hospitalization caused by worsening of TAK and requiring GC treatment or 'vascular signs and symptom' of severe aortic valve incompetence with signs of cardiac failure or 'ischaemic symptoms' of common terminology criteria for adverse events (CTCAE) grade ≥2 or higher (grade ≥3 for myocardial infarction). In the assessment of the disease activities of TAK, the cause of relapse was confirmed by eliminating other causes including infections, unexplained physical symptoms and allergic disorders.

Secondary study endpoints through the end of the DB phase included time to relapse of TAK using Kerr's definition and for each of the above five categories of the relapse criteria: cumulative oral GC dose; change from baseline in oral GC dose; proportion of patients achieving oral GC dose of ≤5 mg/day; change from baseline in imaging evaluation and change from baseline in inflammatory markers (CRP, ESR). Safety, PK and immunogenicity of UST in combination with oral GC-taper regimen were also included. Patient-reported outcomes and relapse of TAK in the OLE phase were the exploratory endpoints.

Statistical analysis

The planned sample size was approximately 50 patients (25 per treatment group) to have a total of 35 TAK relapses expected to occur over 105 weeks after the first patient enrolment. Thirty-five events of relapse should have a power of 80% to detect an HR of 0.371 at a two-sided α level of 0.05 (fixed design with no interim analysis was assumed) assuming a relapse-free rate of 55% in the UST group and 20% in the placebo group at week 24. The assumption of relapse-free rate at week 24 was based on the results of clinical study of tocilizumab showing trend of its GC-sparing effects in patients with moderate-to-severe TAK [8]. Time to relapse of TAK was estimated with Kaplan–Meier method. The efficacy comparison between UST and placebo group was performed based on the HR and its two-sided 95% CI estimated using Cox proportional hazard regression model. Interim efficacy analysis was planned at 15 of 35 TAK relapse events (significance level [α]=0.0012; O'Brien-Fleming alpha spending function); however, it was not performed due to study termination prior to the occurrence of the pre-specified 15 events. Hence, all the analyses presented here are final analyses. GC

(prednisolone) taper dose, change from baseline in inflammatory markers (CRP/ESR) through the end of the DB phase, PK and immunogenicity analysis were summarized descriptively. For exploratory endpoints, the continuous variables were summarized by intervention group and study visit using descriptive statistics. The categorical variables were summarized by intervention group and study visit using frequencies and percentages.

All treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital sign measurements and electrocardiogram data reported during the study were summarized by the analysis phase (DB and OLE). TEAEs were coded by Medical Dictionary for Regulatory Activities, V26.0.

Results

Patient disposition and baseline characteristics

Of 14 patients randomized, 6 received UST and 8 received placebo. In the DB phase, two patients prematurely discontinued (one self-withdrawal, one met protocol-specified withdrawal criterion [received protocol prohibited medication], both in the placebo group). All 14 patients received ≥1 dose of study intervention and were included in the efficacy and safety analysis of the DB phase. Until the study termination, seven patients were rolled over to the OLE phase after experiencing TAK relapse during the DB phase. In the OLE phase, three patients switched their treatment from placebo to UST (the placebo-UST group) and four patients continued to receive UST (the UST-UST group). One patient from the UST-UST group discontinued the study prematurely (self-withdrawal). All seven patients were included in the efficacy and safety analysis of the OLE phase (Fig. 2).

All randomized patients were Asian (Japanese); the majority were women (11, 78.6%). The mean (SD) age of patients in the UST and the placebo groups was 36.5 (12.19) and 49.6 (15.46) years, respectively. The mean (range) weights of the patients in UST and placebo groups were 74.72 (51.1, 100.9) kg and 57.70 (42.4, 84.6) kg, respectively. A total of four (28.6%) patients (UST: 1; placebo: 3) had a history of biological medication use recorded as bio-failure and three (21.4%) of them (UST: 1; placebo: 2) had received tocilizumab. At baseline, mean (SD) GC dose (UST: 0.31 [0.070] mg/kg/day; placebo: 0.37 [0.114] mg/kg/day) and disease duration (UST: 4.24 [3.726] years; placebo: 4.91 [4.404] years) were generally balanced between the treatment groups. The mean CRP (SD) and ESR (SD) levels at baseline in the UST/placebo group were 0.22 (0.171)/0.12 (0.134) mg/dl and 11.33 (8.524)/6.25 (7.479) mm/h, respectively. The daily GC dose was <0.5 mg/kg/day for all patients except one in the placebo group (Table 1).

Efficacy

The HR for time to relapse of TAK through the end of the DB phase (primary endpoint) in the UST group compared with the placebo group was 1.86 (95% CI: 0.41, 8.47). In the DB phase, relapse occurred in four patients in each treatment group (Table 2). The median time to relapse was 11.14 (95% CI: 4.14, NE) weeks in the UST and 12.64 (95% CI: 12.14, NE) weeks in the placebo group.

Results for the secondary endpoint, the time to relapse of TAK according to Kerr's definition through the end of the DB phase, were similar to the primary endpoint (Supplementary Table S4, available at *Rheumatology Advances in Practice* online). A total of five and four relapses occurred in the UST and the placebo group, respectively.

Patients started the protocol-defined oral GC-taper regimen from week 2. Mean (SD) baseline GC dose was 23.3 (8.16) mg/day and 0.37 (0.114) mg/kg/day in the UST group and 20.9 (7.55) mg/day and 0.31 (0.070) mg/kg/day in the placebo group. The mean (SD) GC dose at relapse was 11.5 (6.10) mg/day and 0.16 (0.058) mg/kg/day in the UST group and 5.0 (0.07) mg/day and 0.09 (0.019) mg/kg/day in the placebo group. The proportion of patients who achieved a GC dose of 5 mg/day in the DB phase in the UST and placebo groups were 1/6 (16.7%) and 3/8 (37.5%) patients, respectively (Supplementary Table S5, available at *Rheumatology Advances in Practice* online). Of all relapsed patients, 2/4 (50%) patients in UST and 4/4 (100%) patients in the placebo group achieved a GC dose that was less than the dose at the time of relapse before the randomization.

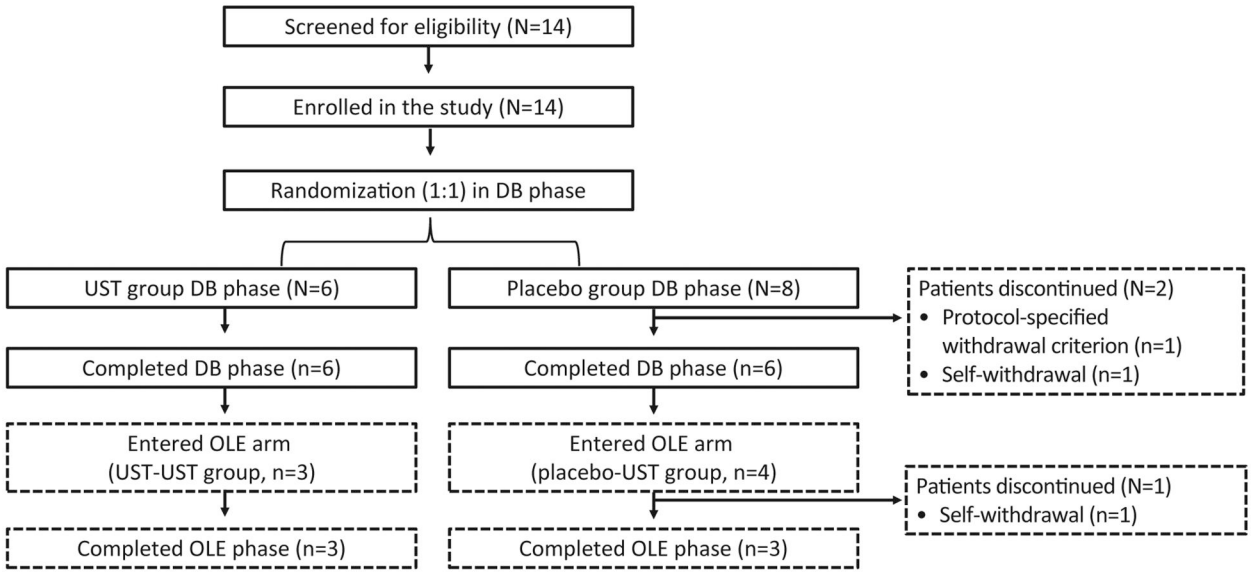

Figure 2. Patient disposition. DB: double-blind; OLE: open-label extension; UST: ustekinumab

Table 1. Baseline demographic and clinical characteristics in full analysis set in the DB phase

	UST ($n=6$)	Placebo ($n=8$)	Total ($n=14$)
Age, years			
Mean (S.D.)	36.5 (12.19)	49.6 (15.46)	44.0 (15.21)
Median (range)	37.5 (19; 49)	46.5 (31; 73)	44.0 (19; 73)
Female, *n* (%)	4 (66.7)	7 (87.5)	11 (78.6)
Weight, kg			
Mean (S.D.)	74.72 (19.51)	57.70 (13.79)	64.99 (18.04)
Median (range)	76.0 (51.1; 100.9)	52.0 (42.4; 84.6)	60.1 (42.4; 100.9)
<50 kg, *n* (%)	0	3 (37.5)	3 (21.4)
≥50 kg, *n* (%)	6 (100.0)	5 (62.5)	11 (78.6)
Height, cm			
Mean (S.D.)	165.73 (6.49)	162.34 (6.41)	163.79 (6.44)
Median (range)	165.2 (155.8; 175.3)	162.6 (154.7; 171.0)	163.7 (154.7; 175.3)
Body mass index, kg/m^2			
Mean (S.D.)	27.2 (7.19)	21.7 (3.89)	24.1 (6.00)
Median (range)	25.7 (19.7; 37.7)	21.4 (16.0; 28.9)	22.9 (16.0; 37.7)
Underweight <18.5, *n* (%)	0	2 (25.0)	2 (14.3)
Normal 18.5– <25, *n* (%)	3 (50.0)	5 (62.5)	8 (57.1)
Overweight 25– <30, *n* (%)	1 (16.7)	1 (12.5)	2 (14.3)
C-reactive protein, mg/dl			
Mean (S.D.)	0.22 (0.171)	0.12 (0.134)	0.16 (0.155)
Erythrocyte sedimentation rate, mm/h			
Mean (S.D.)	11.33 (8.52)	6.25 (7.48)	8.43 (8.05)
Status of previous biologic medication			
Bio-nonfailure	5 (83.3)	5 (62.5)	10 (71.4)
Biofailure[a]	1 (16.7)	3 (37.5)	4 (28.6)
Tocilizumab	1 (16.7)	2 (25.0)	3 (21.4)
TNF	0	1 (12.5)	1 (7.1)
Other	0	1 (12.5)	1 (7.1)
Takayasu arteritis disease duration, years[b]			
Mean (S.D.)	4.2 (3.73)	4.9 (4.40)	4.6 (3.95)
<5 years, *n* (%)	4 (66.7)	4 (57.1)	8 (61.5)
≥5 years	2 (33.3)	3 (42.9)	5 (38.5)
Glucocorticoid at baseline, mg/kg/day			
Mean (S.D.)	0.3 (0.07)	0.4 (0.11)	0.3 (0.10)
<0.5 mg/kg/day	6 (100.0)	7 (87.5)	13 (92.9)
≥0.5 mg/kg/day	0	1 (12.5)	1 (7.1)

[a] Patients appear in more than one category when meeting multiple categories.
[b] $n=7$ for placebo group and $n=13$ to total patients.
DB: double-blind; UST: ustekinumab.

Table 2. Summary of time to relapse of TAK according to protocol-defined criteria during DB phase

Efficacy analysis set **Per protocol definition**	**UST ($n=6$)**		**Placebo ($n=8$)**
Patients with relapse, *n* (%)	4 (66.7)		4 (50.0)
Censored patients, *n* (%)	2 (33.3)		4 (50.0)
Time to event, weeks, median (95% CI)	11.14 (4.14, NE)		12.64 (12.14, NE)
Hazard ratio[a] (95% CI)		1.86 (0.41, 8.47)	

Patients who died or discontinued study interventions before relapse during the DB phase were censored at the date of last disease assessment on or prior to death or treatment discontinuation through the end of the DB phase; otherwise, patients were censored at the date of last disease assessment before the end of the DB phase if no relapse was observed.
[a] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment group as the sole explanatory variable and stratified with oral GC dose at week 0 and the status of previous biologic medication at randomization.
DB: double-blind; GC: glucocorticoids; NE: not estimable; TAK: Takayasu arteritis; UST: ustekinumab.

During the DB phase, among the five categories of the protocol-defined relapse criteria, the most reported category was vascular signs and symptoms (UST: 6/6 [100%]; placebo: 4/8 [50%]). Elevated inflammation markers were reported in 3/6 (50%) in UST and 4/8 (50%) patients in placebo group. None of the patients reported ischaemic symptoms (Supplementary Table S6, available at *Rheumatology Advances in Practice* online).

Safety

The average duration of the follow-up phase in the DB phase was 24.0 weeks and 17.0 weeks for UST and placebo groups, respectively. Through the end of the DB phase, ≥1 TEAEs were reported in 5/6 (83.3%) UST-treated and 6/8 (75.0%) placebo-treated patients. The most frequently reported TEAEs by system organ class (SOC) in both groups through the end of the DB phase were 'infections and infestations',

and 'vascular disorders' (UST: 3/6 [50%]; placebo: 1/8 [12.5%] for each SOC). TEAEs reported in at least two patients in either treatment group by preferred term (PT) were pyrexia, vaccination site pain (UST: 2/6 [33.3%] for each PT, none in placebo) and TAK (UST: 2/6 [33.3%]; placebo: 1/8 [12.5%]).

Through the end of the DB phase, 1/8 (12.5%) patients in the placebo (PT: cholecystitis) and 1/6 (16.7%) patients in the UST group (PT: vascular pseudoaneurysm and brachiocephalic artery stenosis) reported serious adverse events (SAEs); none of these events were considered related to study intervention. During the DB phase, one (12.5%) patient in the placebo group had TEAEs leading to discontinuation of treatment (PT: aspergillus infection), while no TEAE led to treatment discontinuation in the UST group. Infections were reported in 3/6 (50.0%) and 1/6 (12.5%) patients in UST and placebo groups, respectively. All infections in both groups during the DB phase were mild-to-moderate in severity (Table 3).

During the OLE phase, the average duration of the follow-up was 27.9 weeks and 46.8 weeks for the UST-UST and the placebo-UST groups, respectively; ≥1 TEAEs were reported in 2/4 (50.0%) patients in the UST-UST and 1/3 (33.3%) patients in the placebo-UST group. Through the OLE phase, 1/4 (25.0%) patients in the UST-UST (PT: vascular graft infection, relationship to study intervention not excluded; the event was resolved) and none in the placebo-UST had SAEs. No TEAEs led to treatment discontinuation in the OLE phase in both treatment groups. Infections were reported in 2/4 (50.0%) and 1/3 (33.3%) patients in UST-UST and placebo-UST groups, respectively. Apart from vascular graft infection, there was no serious infection in the UST-UST group or placebo-UST group (Table 3).

Throughout the study, no infusion or injection-site reactions were reported. There was no death throughout the study including DB and OLE phases.

Discussion

In Japan, tocilizumab SC is available to treat large vessel vasculitis including TAK as an advanced biologic therapy. However, TAK has not been adequately managed as evidenced by case reports of disease relapse despite the treatment with tocilizumab [28, 29]. The current study indeed had three patients with insufficient response/intolerance to tocilizumab. Thus, there is a significant unmet need for new treatment options in TAK, but given the limited number of study participants suitable for controlled clinical trials, designing such clinical trials that demonstrate compelling results for regulatory approval is extremely challenging.

The current study was designed to evaluate the efficacy, safety, PK and immunogenicity of UST in patients with TAK generally following the study design employed in the TAKT study of tocilizumab in patients with TAK (8) but was terminated prematurely due to patient recruitment challenges despite continued efforts. In this study, the target patient population was smaller than expected despite more relaxed inclusion criteria, the generally lower GC dose required for the pre-study relapse (7.5 mg/day or more) compared with that of the TAKT study (at least 0.2 mg/kg/day). In total, 10

Table 3. Safety summary

	DB phase		OLE phase	
Safety summary	**UST (*n* = 6)**	**Placebo (*n* = 8)**	**UST-UST (*n* = 4)**	**Placebo-UST (*n* = 3)**
Mean duration of follow-up (weeks)	24.0	17.0	27.9	46.8
Mean exposure (number of study intervention administrations)	2.7	1.6	2.5	5.0
Patients with ≥1 TEAE, *n* (%)	5 (83.3)	6 (75.0)	2 (50.0)	1 (33.3)
TEAEs[a] related to study intervention, *n* (%)	1 (16.7)	1 (12.5)	1 (25.0)	0
TEAEs leading to death[a], *n* (%)	0	0	0	0
Serious AEs, *n* (%)	1 (16.7)	1 (12.5)	1 (25.0)	0
SAEs[b] related to study intervention, *n* (%)	0	0	1 (25.0)	0
TEAEs leading to discontinuation of study intervention, *n* (%)	0	1 (12.5)	0	0
Most frequent TEAEs by SOC and PT[c], *n* (%)				
Infections[d]	3 (50.0)	1 (12.5)	2 (50.0)	1 (33.3)
Vascular disorders	3 (50.0)	1 (12.5)	1 (25.0)	0
General disorders and administration site conditions	3 (50.0)	0	1 (25.0)	0
Gastrointestinal disorders	0	3 (37.5)	1 (25.0)	1 (33.3)
Eye disorders	1(16.7)	2 (25.0)		
Nervous system disorders	2 (33.3)	0	1 (25.0)	1 (33.3)
Ear and labyrinth disorders	1 (16.7)	0		
Injury/poisoning/procedural complications	1 (16.7)	1 (12.5)	1 (25.0)	1 (33.3)
Investigations	1 (16.7)	0	1 (25.0)	0
Diabetes mellitus	1 (16.7)	0		
Musculoskeletal and connective tissue disorders	1 (16.7)	1 (12.5)		
Hepatobiliary disorders	0	1 (12.5)		
Skin and SC tissue disorders	0	2 (25.0)		
Respiratory/thoracic/mediastinal disorders	0	0	1 (25.0)	0

Avg exposure (number of study intervention administrations) = (number of i.v. and SC study intervention administrations)/(number of patients).
[a] TEAEs leading to death are based on AE outcome of fatal.
[b] A TEAE is categorized as related if assessed by the investigator as related to study intervention.
[c] TEAEs reported in at least one patient in either treatment group.
[d] Infections as assessed by the investigator.
AE: adverse event; DB: double-blind; OLE: open-label extension; PT: preferred term; SAE: serious adverse event; SOC: system organ class; TEAE: treatment-emergent AE; UST: ustekinumab.

of 14 randomized patients in this study experienced the pre-study TAK relapse at GC dose below 0.2 mg/kg/day, indicating that it was indeed possible to include patients who could not be enrolled in the TAKT study. Although this study was significantly impacted by the SARS-CoV-2 pandemic, patient enrolment was not improved even after the stringent restrictions and measures were lifted. The premature termination with an extremely small sample size greatly impeded the interpretation of the study results. Thus, to overcome the recruitment challenge, study regions might be expanded and to multi-national clinical trials. There were additional potential reasons for the recruitment challenges. The current study design included a narrow enrolment window where patients must have experienced a relapse within 12 weeks before the start of the study intervention, which might potentially pose recruitment issues. Additionally, the mandatory GC-tapering regimen also complicates patient enrolment. These potential issues need to be addressed when designing clinical trials for TAK under a similar randomized withdrawal design. Alternatively, another potential study design would be to assess whether an intervention decreases TAK disease activity in patients with active TAK despite existing treatments.

In addition to the small sample size, demographics and baseline characteristics in this study were not evenly balanced between the treatment groups. This variability in the patients' backgrounds could further complicate the interpretation of the study results.

With the confirmed efficacy profile of UST in IBD along with the proposed association between TAK and IBD [22–24], it would have been interesting to assess the response of TAK patients with comorbid UC to UST treatment. However, no subject in the current study had UC as a comorbidity.

Association between HLA-B52 and the single nucleotide polymorphism of IL-12B (rs6871626) was reported in the Japanese patients with TAK [13]. In the current study, there were four patients who had HLA-B52 and at least one risk genotype of IL-12B (placebo: 2; UST: 2). Of these, one patient in the UST group relapsed in the DB phase. Despite thorough assessments of these cases, there was no clinically meaningful interpretation extracted from the analyses due to the small sample size.

Samson and Bonnotte [30] commented on an open-label trial [31] investigating the efficacy of UST in another large vessel vasculitis, GCA, and pointed out that the effects of UST might require a longer time to manifest. They discussed that, unlike tocilizumab, which rapidly decreases inflammation by directly targeting inflammatory cytokines, UST modulates T cell homeostasis by targeting both the IL-12 and IL-23 pathways resulting in an onset of action 8–12 weeks later [30]. Also, a case series of 20 patients with GCA has shown that long-term UST treatment over 52 weeks [32] resulted in successful GC-tapering while controlling disease activity. Overall, more discretional and slower GC-tapering might be required to observe the benefits of UST when treating TAK. Nevertheless, the clinical significance of such treatments requiring slower GC-tapering is unclear considering the significant toxicities associated with long-term use of GC.

There was no significant difference between treatment groups in the primary endpoint (time to TAK relapse) at the time of early study termination. The insufficient sample size together with observed variabilities in patient background between treatment groups precludes any interpretable results from the inter-group analyses for the primary and secondary endpoints including changes in GC dose, inflammatory markers and imaging.

Despite the early termination, the relatively short exposure to UST was generally well-tolerated in this small group of TAK patients with no new safety signal. Except for events associated with the underlying disease such as vascular disorders, the safety findings were consistent with those identified in other indications [33, 34].

The limitations of the study were the small sample size due to premature termination and variability in patient characteristics between treatment groups, which made any meaningful inter-group analyses difficult.

In conclusion, although we aimed to establish the efficacy of UST combined with the specified GC-taper regimen following a similar study design approach used for the TAKT study, the desired patient recruitment was not achieved. Future clinical trial design should be carefully assessed based on the significant recruitment challenge in the current study.

Supplementary material

Supplementary material is available at *Rheumatology Advances in Practice* online.

Data availability

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson are available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access [YODA] Project site at http://yoda.yale.edu.

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