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ORIGINAL RESEARCH

Secukinumab in Active Rheumatoid Arthritis after Anti-TNFα Therapy: A Randomized, Double-Blind Placebo-Controlled Phase 3 Study

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ABSTRACT

Introduction: 'REASSURE' (NCT01377012), a phase 3 study, evaluated the efficacy and safety of secukinumab in patients with active rheumatoid arthritis (RA) who had an inadequate response to, or intolerance of, tumor necrosis factor inhibitors (TNF-inhibitors).

Methods: A total of 637 patients were randomized (1:1:1) to receive intravenous secukinumab 10 mg/kg (baseline, weeks 2 and 4) followed by subcutaneous secukinumab 150 mg or 75 mg every 4 weeks (starting from week 8) or placebo at the same dosing schedule. The primary endpoint was the American College of Rheumatology 20% improvement criteria (ACR20) at week 24. Other predefined hierarchical endpoints included Health Assessment Questionnaire-Disability Index, van der Heijde modified total Sharp score (vdH-mTSS) at week 24, and major clinical response (MCR; continuous 6 month period of ACR70 response) at 1 year.

Results: The primary efficacy endpoint was met with both secukinumab dose groups: ACR20 response rate at week 24 was 35.2% for both secukinumab dose groups ($P = 0.0009$) vs 19.6% for placebo. The improvements in secondary endpoints were greater in the secukinumab dose groups vs placebo but did not meet statistical significance. The overall safety profile was similar across all treatment groups.

Conclusion: Secukinumab demonstrated efficacy in reducing disease activity over placebo as measured by ACR20 in patients with active RA who had an inadequate response to TNF-inhibitors. Secukinumab demonstrated a safety profile similar to other biologics currently approved for RA.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic autoimmune disease characterized by symmetric synovitis leading to cartilage damage and joint destruction, which may also be complicated by numerous extra-articular manifestations [1]. Current treatment for RA with traditional disease modifying anti-rheumatic drugs (DMARDs) is often inadequate as these drugs only partially control established disease, and have many adverse effects that limit their use [2]. While tumor necrosis factor inhibitors (TNF-inhibitors) are the first line biologics used in DMARD failure patients, 30–40% of patients with established disease fail to respond to them [2]. Further, many of those who do initially respond do not go on to achieve complete remission or lose response over time [2]. Biologics targeting other disease driving mechanisms, such as co-stimulatory modulators with Cytotoxic T lymphocyte—associated antigen 4 Ig (CTLA-4-immunoglobulin), B cell depletion as well as interleukin (IL)-6 receptor blockers, are approved for use in patients for whom TNF-inhibitor therapy has failed [3–5].

IL-17A, the key pro-inflammatory cytokine in the TH17 pathway, is recognized as a key cytokine in autoimmunity [6]. While its role in the pathogenesis of RA is not yet fully understood, it has been suggested that it plays a pivotal role in both the inflammatory and destructive joint tissue manifestations of RA [7–9]. Secukinumab (AIN457), a fully human monoclonal antibody that neutralizes the activity of IL-17A, [6] has demonstrated efficacy in moderate-to-severe psoriasis, psoriatic arthritis (PsA) and ankylosing spondylitis (AS) [1, 10–14].

While secukinumab displayed some efficacy in RA in several phase II trials, the small size of the trials did not allow for definitive conclusions on the role of IL-17A blockade in RA to be made [15–18]. Subsequently, three phase 3 studies of secukinumab in RA were initiated; two assessed the efficacy and safety of secukinumab in comparison with placebo, and the third compared secukinumab with both placebo and the active comparator abatacept [19]. Here, we report, from the phase 3 REASSURE study, efficacy at week 24 compared with placebo, as well as the longer term safety of secukinumab in patients with RA who had an inadequate response to, or intolerance of, TNF-inhibitors.

METHODS

Study Design

This phase 3 study (ClinicalTrials.gov identifier, NCT01377012) used a double-blind, randomized, parallel-group, placebo-controlled design to assess the efficacy and safety of secukinumab in patients with active RA who had an inadequate response to, or intolerance of, TNF-inhibitors. It included 139 centers in 15 countries. The core study was conducted over 2 years and the extension was planned to be conducted for 3 years, however, due to early termination of the secukinumab RA program, patients remaining in the trial at the time of termination were discontinued.

After a 4-week screening period, patients were randomly assigned (1:1:1) to receive intravenous (i.v.) secukinumab 10 mg/kg (baseline, weeks 2 and 4) followed by subcutaneous (s.c.) secukinumab 150 mg or 75 mg every 4 weeks (starting at week 8) up to week 48, or placebo on the same i.v. and s.c. dosing schedule (Fig. 1).

At week 16, patients on placebo who were non-responders (response was defined as $\geq$ 20% improvement from baseline in both tender and swollen joint counts) were re-randomized (1:1) to receive s.c. secukinumab 150 mg (placebo-secukinumab 150 mg) or 75 mg (placebo-secukinumab 75 mg) every 4 weeks.

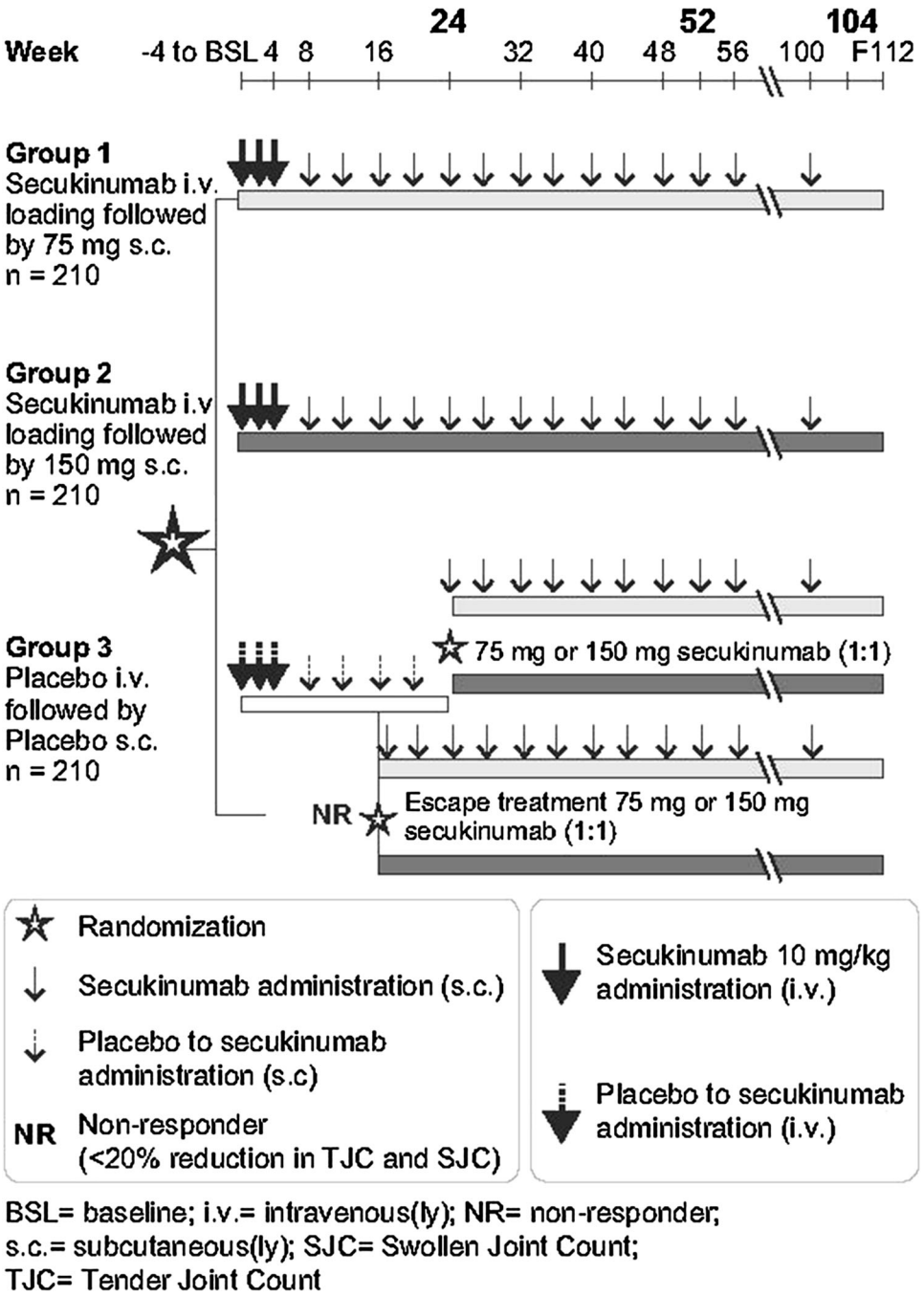

Fig. 1 Study design

Patients who were placebo responders at week 16 continued to receive placebo until week 24, when they were randomized (1:1) to s.c. secukinumab 150 or 75 mg every 4 weeks. Rescue medication was not allowed until week 24. However, patients who were deemed to be not benefiting from the study drug by the investigator, or for any reason on their own accord, were free to discontinue participation in the study at any time. Patients who completed the

2 year core study were eligible to enter the open-label extension study, where all patients received s.c. secukinumab 150 mg every 4 weeks.

Primary and secondary efficacy data are presented for the core study (placebo-controlled up to week 24) up to week 52. Additionally, longer-term (104-week) efficacy data are presented. Safety data are presented for the initial 16-week period, as well as for the entire study including the extension, up to last patient last visit (LPLV).

Patients

Patients aged at least 18 years who had been diagnosed with RA at least 3 months before screening, and classified using the ACR 2010 classification criteria were eligible for the study. Patients were required to have active disease at baseline, defined by $\geq$ 6/68 tender joints and $\geq$ 6/66 swollen joints, and be positive for either rheumatoid factor or anti-cyclic citrullinated peptides (CCP) antibodies, in combination with high-sensitivity C-reactive protein (hsCRP) $\geq$ 10 mg/L or erythrocyte sedimentation rate (ESR) $\geq$ 28 mm/h.

Patients had to have been on at least one TNF-inhibitor for at least 3 months before randomization and have experienced an inadequate response or intolerance. Patients should also have received methotrexate for at least 3 months, and be on a stable dose for at least 4 weeks, before randomization. Patients taking systemic corticosteroids or NSAIDs had to be on a stable dose for at least 4 weeks before randomization. Patients who had been taking DMARDs other than methotrexate (MTX), or were on a TNF-inhibitor, underwent an appropriate wash-out period prior to randomization.

The major exclusion criteria included RA patients having functional status class IV according to the ACR 1991 revised criteria, ongoing rheumatic or inflammatory joint diseases other than RA, evidence of malignancy or infection seen on chest X-ray, active tuberculosis infection, previous use of biologic immunomodulating agents except TNF-inhibitors, or previous exposure to secukinumab or other biologic drugs targeting IL-17.

The study was conducted in accordance with the Declaration of Helsinki, and was approved by the institutional review boards or independent ethics committees. Written informed consent was provided by all enrolled patients.

Outcomes

The primary objective was to demonstrate that the efficacy of secukinumab 150 or 75 mg at week 24 was superior to placebo, based on the proportion of patients achieving the American College of Rheumatology 20% improvement criteria (ACR20 response).

Secondary objectives included in the pre-defined hierarchical testing strategy were to demonstrate superiority of secukinumab 150 mg or 75 mg over placebo in terms of change from baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI), van der Heijde modified total Sharp score (vdH-mTSS) at week 24 (pooled for both secukinumab dose regimens), and achieving a continuous six-month period of ACR70 response (major clinical response; MCR) at week 52.

Additional secondary efficacy endpoints included change from baseline in joint/bone damage (radiographic score), erosion and joint space narrowing, ACR20/50/70 and EULAR responses, as well as Disease Activity Score 28 (DAS28), DAS28 remission (DAS28 $<$ 2.6) and low disease activity (DAS28 $\leq$ 3.2, using hsCRP), vs placebo, over time up to week 104.

Safety was assessed throughout the core and extension periods. All treatment emergent adverse events (TEAEs), serious AEs (SAEs), laboratory evaluations, immunogenicity (anti-secukinumab antibodies) were evaluated.

Statistical Analysis

Sample size calculations were performed using Fisher's exact test; as two secukinumab regimens were tested against placebo with respect to the primary endpoint (ACR20 response at week 24), the type-I-error was split to 2.5% two-sided for each comparison.

With 210 patients randomized to each treatment group, this trial had

approximately > 99% power to detect between-group differences in the primary endpoint, and was also sufficiently powered to detect between-group differences in the secondary endpoints, such as changes from baseline to week 24 in HAQ-DI (> 99% power) and van der Heijde modified total Sharp score (68%), and MCR at week 52 (88%).

In terms of minimum sample sizes, for 90% power, and assuming a response rate of 20% in the placebo regimen, at least 70 patients per regimen were needed to show a response rate of 50% in the secukinumab regimens.

Analyses of efficacy variables were performed on all patients who were randomized and to whom study treatment had been assigned (full analysis set, FAS). The primary endpoint of ACR20 at week 24 was analyzed via logistic regression with treatment as a factor and baseline body weight as a covariate. Odds ratios and 95% CIs were presented comparing each secukinumab regimen to placebo. Continuous variables (e.g. ACR components, HAQ-DI, etc.) were analyzed using a mixed-effects repeated measures model (MMRM). As such, single-point imputation of missing data was not performed. A predefined hierarchical test was used to protect the family-wise type I error rate at 5% across the primary and the ranked secondary endpoints.

In general, for binary endpoints, data missing due to patients meeting the criteria for early escape at week 16 was handled as non-responders. This was done for all treatment regimens in order to minimize bias. For continuous endpoints, data collected after the patient switched to secukinumab was treated as missing for placebo patients and was analyzed using a mixed-effects repeated measures model (MMRM), which is valid under the missing at random (MAR) assumption. For secukinumab patients, the actual values were used in the analysis.

Analyses of safety endpoints were performed on all patients who received at least one dose of the study drug during the treatment period (safety set). Patients were evaluated according to treatment received. As appropriate, the incidence of AEs was presented per 100 patient years of exposure.

RESULTS

Patients

In total, 637 patients were randomized to secukinumab 150 mg ($n = 213$), secukinumab 75 mg ($n = 210$) or placebo ($n = 214$). This study and its extension were discontinued early, due to initial results from the direct comparison with abatacept [19] suggesting no additional benefit to RA patients with inadequate response to TNF-inhibitors. Overall, 237 (37.2%) patients completed 104 weeks of treatment: 81 (38.0% of those randomized) in the secukinumab 150 mg group, 76 (36.2% of those randomized) in the secukinumab 75 mg group, and 80 (37.4% of those randomized) in the placebo group (supplementary Fig. S1). Of these, 196 (82.7%) entered the extension study and were treated with s.c. secukinumab 150 mg (only dose studied in extension). The main reason for discontinuation other than study termination was lack of efficacy (106 patients), followed by subject decision (56 patients). The maximum exposure time for any secukinumab dose in the study, including the extension study, was 184 weeks, with a mean exposure of 604 (SD ± 341.23) days, and a median exposure of 588 days.

Of the 214 patients randomized to placebo, 190 remained on the study at week 16. Of these, 110 were non-responders at week 16, and 109 of these were randomized to secukinumab 150 mg ($n = 53$) or secukinumab 75 mg ($n = 56$). Of the 80 placebo responders at week 16, 72 were randomized at week 24 to secukinumab 150 mg ($n = 34$) or secukinumab 75 mg ($n = 38$).

Patient demographics and baseline characteristics were comparable across the treatment groups (Table 1). Most patients (≥ 80% in each treatment group) were < 65 years of age, with median age ranging from 53.0 (placebo group) to 54.0 years (both secukinumab treatment groups). The majority of patients were female (range 85.0–88.6% in all treatment groups), were of Caucasian (range 38.6–41.8%) or Asian (range 31.0–36.7%) origin and weighed < 90 kg (range 85.5–86.7%). The mean BMI was approximately 27 kg/m^2 across all treatment groups.

Table 1 Demographics and baseline characteristics

Characteristic	Secukinumab 150 mg ($n = 213$)	Secukinumab 75 mg ($n = 210$)	Placebo ($n = 214$)
Age (years), mean (SD)	53.2 (11.6)	53.3 (12.3)	52.2 (11.6)
Female, *n* (%)	188 (88.3)	186 (88.6)	182 (85.0)
Weight (kg), mean (SD)	67.6 (20.0)	67.5 (18.9)	69.1 (19.8)
Race, *n* (%)			
Caucasian	89 (41.8)	81 (38.6)	84 (39.3)
Black	12 (5.6)	10 (4.8)	7 (3.3)
Asian	66 (31.0)	77 (36.7)	74 (34.6)
Native American	34 (16.0)	30 (14.3)	40 (18.7)
Other	12 (5.6)	11 (5.2)	9 (4.2)
Unknown	0 (0.0)	1 (0.5)	0 (0.0)
Tender 68-joint count, mean (SD)	26.6 (16.2)	26.6 (15.6)	24.7 (15.8)
Swollen 66-joint count, mean (SD)	17.1 (11.0)	17.2 (10.9)	16.4 (11.3)
Duration of RA (years), mean (SD)	9.0 (8.0)	8.4 (8.0)	7.8 (8.0)
HAQ-DI, mean (SD)	1.7 (0.7)	1.7 (0.6)	1.7 (0.6)
Total vdH-mTSS score, mean (SD)	48.1 (51.8)	55.0 (55.3)	57.7 (66.8)
DAS28-CRP	4.9 (0.9)	4.9 (0.9)	4.8 (0.8)
DAS-28-ESR	5.7 (0.9)	5.7 (0.8)	5.6 (0.8)
Positive for RF[a], *n* (%)	200 (93.9)	191 (91.0)	200 (93.5)
Positive for anti-CCP antibodies, *n* (%)	194 (91.1)	189 (90.0)	194 (90.7)
TNF-naïve patients, *n* (%)	1 (0.5)	9 (4.3)	5 (2.3)
Prior use of other biologic DMARD, *n* (%)[b]	1 (0.5)	0 (0.0)	1 (0.5)
Use of oral DMARDs at randomization, *n* (%)			
Methotrexate	208 (97.7)	208 (99.0)	210 (98.1)
Leflunomide	1 (0.5)	0 (0)	1 (0.5)
Other[c]	6 (2.8)	9 (4.3)	15 (7.0)
Systemic glucocorticoids use, *n* (%)	124 (58.2)	130 (61.9)	126 (58.9)

DAS28 Disease Activity Score in 28 joints, *DMARD* disease-modifying anti-rheumatic drug, *ESR* erythrocyte sedimentation rate, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *IV* intravenous, *SD* standard deviation, *vdH-mTSS* van der Heijde modified total Sharp score, *RA* rheumatoid arthritis, *RF* rheumatoid factor, *TNF* tumor necrosis factor

[a] Negative was defined as RF < 14 U/mL

[b] Other than TNF-alpha inhibitors

[c] Other than MTX and Leflunomide

Table 2 Summary of primary and secondary endpoints at weeks 24, 52 and 104

Endpoint, *n* (%) unless stated	Week	Secukinumab 150 mg (*n* = 213)	Secukinumab 75 mg (*n* = 210)	Placebo (*n* = 214)
ACR20[a]	24	75 (35.2)*	74 (35.2)*	42 (19.6)
	52	88 (61.5)	75 (57.7)	N/A
	104	50 (69.4)	50 (74.6)	N/A
ACR50[a]	24	34 (16.0)*	37 (17.6)*	14 (6.5)
	52	36 (27.7)	34 (23.8)	N/A
	104	28 (38.9)	25 (37.3)	N/A
ACR70[a]	24	8 (3.8)	17 (8.1)*	5 (2.3)
	52	14 (9.8)	13 (10.0)	N/A
	104	12 (16.7)	9 (13.4)	N/A
HAQ-DI[b]	24	− 0.4 (0.0)	− 0.4 (0.0)	− 0.2 (0.1)
	52	− 0.4 (0.6)	− 0.4 (0.6)	N/A
	104	− 0.5 (0.7)	− 0.5 (0.7)	N/A

ACR American College of Rheumatology, *CRP* C-reactive protein, *DAS28* disease activity score in 28 joints, *ESR* erythrocyte sedimentation rate, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *N/A* not assessed, *SD* standard deviation, *SE* standard error

[a] Non-responder imputation data at week 24 and observed data at week 52, *n* (%)

[b] Mixed-effect model repeated measures (MMRM) ± SE data at week 24 and observed data ± SD at week 52

* $P < 0.05$ for secukinumab vs placebo

Efficacy

Primary Efficacy Endpoint

The primary endpoint was met by both the secukinumab groups; 35.2% of patients in the 150 mg group and 35.2% of patients in the 75 mg group achieved ACR20, compared with 19.6% in the placebo group ($P = 0.0009$; Table 2 and Fig. 2). In both treatment groups, secukinumab groups had a rapid onset of action, and both groups demonstrated numerically higher ACR20 response rates than placebo at all time points up to week 24, with a more pronounced difference over placebo after week 8 (Fig. 2).

Secondary Efficacy Endpoints Included in the Pre-defined Hierarchical Testing Strategy

The first secondary endpoint, HAQ-DI at week 24, was not met by either secukinumab group, and consequently neither were the remaining secondary endpoints in the hierarchal analysis. For HAQ-DI score, LS mean changes from baseline at week 24 were − 0.35 for both secukinumab groups, compared with − 0.24 the placebo group (supplementary Fig. S2). Secukinumab (pooled 150 mg and 75 mg) reduced numerically the progression of structural damage over 24 weeks; vdH-mTSS was numerically lower in the pooled secukinumab group compared with the placebo group (treatment comparison estimate 0.82; $P = 0.0673$, unadjusted). This did not achieve statistical significance in the testing hierarchy ($P = 0.2009$, adjusted; Table 2). Mean changes in vdH-mTSS from baseline to week 24 were 0.56 and 1.10 in the secukinumab 150 mg and 75 mg groups, respectively, and 1.35 in the placebo group.

At week 24, 71.6% and 66.7% of patients in the secukinumab 150 mg and 75 mg groups, respectively, had no radiographic disease progression

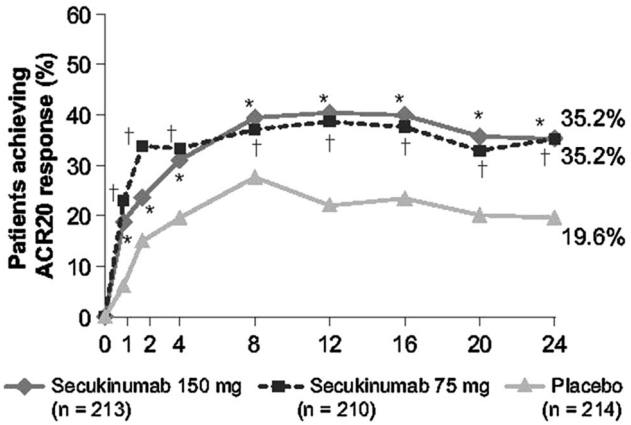

Fig. 2 ACR20 response using non-responder imputation over 24 weeks. Symbols indicate $P \leq 0.05$. $^{*}P < 0.05$ for secukinumab 150 mg vs placebo; $^{\dagger}P < 0.05$ for secukinumab 75 mg vs placebo. *P* values are adjusted for multiplicity of testing for secukinumab 150 mg and secukinumab 75 mg vs placebo at week 24. *ACR* American College of Rheumatology, *ACR20* improvement of ≥ 20% in ACR disease activity, *IV* intravenous, *n* number of subjects randomized

(change ≤ 0 from baseline in vdH-mTSS), both of which were numerically higher than the placebo group (59.0%), as calculated by logistic regression with evaluable cases in the full analysis set.

MCR rate over the first 52 weeks was 0.9% [odds ratio (OR) 1.00; $P = 1.000$, unadjusted] and 2.4% (OR 2.57; $P = 0.2821$, unadjusted) for the secukinumab 150 mg and 75 mg groups, respectively, compared with 0.9% for the placebo group (Table 2).

Other Secondary Efficacy Endpoints

Observed ACR20 response rates for both secukinumab groups were stable from week 8 through week 104. Following a rapid onset of action, with a numerically higher proportion of patients in both secukinumab groups achieving the ACR20 response at week 1 compared with the placebo group. After the placebo controlled period the observed response rates for secukinumab were sustained.

Observed ACR50 responses at week 24 were numerically greater for both secukinumab groups [secukinumab 150 mg, 17.6% (OR 2.69; $P = 0.0031$, unadjusted) and secukinumab 75 mg, 16.0% (OR 3.03; $P = 0.0008$, unadjusted)], compared with placebo (6.5%; Table 2).

Progression in vdH-mTSS over time was lower in patients treated with secukinumab 150 mg than those treated with the 75 mg dose. From baseline to week 52, mean changes in vdH-mTSS were 1.66 and 2.21 for the secukinumab 150 mg and 75 mg groups, respectively. From baseline to week 104, mean changes in vdH-mTSS were 3.83 and 5.58 for the secukinumab 150 mg and 75 mg groups, respectively.

Safety

Short Term Placebo-Controlled Period (to Week 16)

During the first 16 weeks, AEs were reported at a similar frequency across all treatment groups, with 54.5% and 58.1% of patients in the secukinumab 150 mg and 75 mg groups experiencing an AE, respectively, compared with 57.0% of patients in the placebo group (Table 3).

The most frequently reported treatment-emergent AEs (TEAEs) by system organ class were infections and infestations (23.5% and 28.6% in the secukinumab 150 mg and 75 mg groups, respectively, compared with 25.2% in the placebo group), gastrointestinal disorders (10.3% and 11.4% compared with 16.8%), and musculoskeletal and connective tissue disorders (9.4% and 8.6% compared with 15.0%) (Table 3). Nasopharyngitis, pharyngitis, bronchitis, upper respiratory tract infection and headache were the most frequently reported TEAEs in the any secukinumab group up to

Table 3 Treatment-emergent adverse events over 16-weeks and entire treatment period

Variables	Up to week 16				During entire period		
	Secukinumab 150 mg (*N* = 213)	Secukinumab 75 mg (*N* = 210)	Any secukinumab (*N* = 423)	Placebo (*N* = 214)	Any secukinumab 150 mg (*N* = 392)	Any secukinumab 75 mg (*N* = 301)	Any secukinumab (*N* = 601)
Any AE, *N* (%)	116 (54.5)	122 (58.1)	238 (56.3)	122 (57.0)	237 (78.7)	298 (76.0)	488 (81.2)
SAEs, *N* (%)	6 (2.8)	13 (6.2)	19 (4.5)	7 (3.3)	48 (12.2)	33 (11.0)	79 (13.1)
Discontinued study treatment due AE(s), *n* (%)	6 (2.8)	6 (2.9)	12 (2.8)	10 (4.7)	22 (5.6)	13 (4.3)	35 (5.8)
Deaths, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	2 (0.5)	3 (1.0)	5 (0.8)
Common adverse events, *n* (%)							
Rheumatoid arthritis	2 (0.9)	3 (1.4)	5 (1.2)	12 (5.6)	20 (5.1)	22 (7.3)	41 (6.8)
Nasopharyngitis	10 (4.7)	8 (3.8)	18 (4.3)	11 (5.1)	63 (16.1)	49 (16.3)	102 (17.0)
Pharyngitis	1 (0.5)	15 (7.1)	16 (3.8)	4 (1.9)	18 (4.6)	23 (7.6)	40 (6.7)
Bronchitis	10 (4.7)	4 (1.9)	14 (3.3)	1 (0.5)	31 (7.9)	16 (5.3)	45 (7.5)
Upper respiratory tract infection	10 (4.7)	4 (1.9)	14 (3.3)	10 (4.7)	39 (9.9)	25 (8.3)	63 (10.5)
Headache	4 (1.9)	8 (3.8)	12 (2.8)	8 (3.7)	18 (4.6)	15 (5.0)	33 (5.5)
Hypertension	2 (0.9)	8 (3.8)	10 (2.4)	5 (2.3)	13 (3.3)	18 (6.0)	30 (5.0)
Diarrhea	3 (1.4)	6 (2.9)	9 (2.1)	5 (2.3)	22 (5.6)	14 (4.7)	35 (5.8)
Urinary tract infection	3 (1.4)	6 (2.9)	9 (2.1)	7 (3.3)	33 (8.4)	28 (9.3)	58 (9.7)
	***n* (%)**				***n* (EAIR)**		
AEs of special interest							
MACE	0 (0.0)	1 (0.5)	1 (0.2)	2 (0.9)	2 (0.3)	3 (0.7)	5 (0.5)
Neutropenia	3 (1.4)	3 (1.4)	6 (1.4)	1 (0.5)	6 (1.0)	7 (1.8)	13 (1.3)
Fungal infections	5 (2.3)	2 (1.0)	7 (1.7)	0	21 (3.8)	12 (3.1)	33 (3.5)
Esophageal candidiasis	1 (0.5)	2 (1.0)	3 (0.7)	2 (0.9)	8 (1.4)	6 (1.5)	14 (1.4)

Cases of esophageal candidiasis as reported without requirement for culture or endoscopy confirmation

EAIR exposure adjusted incidence rate, *MACE* major adverse cardiovascular event (myocardial infarction, stroke, cardiovascular death)

week 16. The majority of AEs reported up to week 16 in the any secukinumab dose group were mild (31.4%) or moderate (19.6%) in severity.

SAEs were reported for a higher percentage of patients in the any secukinumab group (4.5%) compared with the placebo group (3.7%). Infections and infestations qualifying as SAEs were reported by 5 (1.9%) patients in the any secukinumab group compared with three patients (0.5%) in the placebo group. Gastrointestinal disorders were reported as SAEs by three patients (1.4%) in the secukinumab 75 group only. There were no reports of IBD. There were no clinically meaningful differences in the incidence of SAEs between the two secukinumab groups.

Lower proportions of patients in the any secukinumab dose group (2.8%) had TEAEs leading to discontinuation from study treatment compared with the placebo group (4.7%), which was mainly driven by the higher incidence of patients discontinuing treatment due to RA in the placebo group (1.4% and 0.2%, respectively).

In the placebo-controlled period up to week 16, one death was reported; a patient in the placebo group who suffered cardiopulmonary failure, with pneumonia as a contributing factor.

Entire Treatment Period

The incidence of AEs during the entire treatment period was comparable within the two secukinumab groups (76.0% and 78.7% in the any secukinumab 150 mg and 75 mg groups, respectively). The most common reason for the discontinuation was study discontinuation by sponsor (25.4% and 22.4% in the any secukinumab 150 mg and 75 mg groups, respectively) followed by lack of efficacy (13.1% and 19.5%, respectively; supplementary Fig. S1).

Similar to the first 16 weeks of the study, AEs over the entire treatment period in the any secukinumab group were reported most frequently in the SOCs infections and infestations (55.6%), musculoskeletal and connective tissue disorders (27.3%), and gastrointestinal disorders (26.5%). No dose dependency in AEs in any SOC was observed for secukinumab. Of TEAEs by preferred term in the any secukinumab group, nasopharyngitis, upper respiratory tract infection, urinary tract infection, bronchitis and RA were the most frequently reported (Table 3). There were no clinically meaningful differences in the incidence of AEs between the two secukinumab regimens. The majority of AEs reported in the any secukinumab dose group during the entire treatment period were mild (35.8%) or moderate (33.9%) in severity.

SAEs were reported for similar percentages of patients in the any secukinumab 150 mg group (12.2%) and the any secukinumab 75 mg group (11.0%). The two most common SAEs in the any secukinumab group during the entire treatment period were infections and infestations [$n = 30$, incidence rate (IR) 3.1 per 100 patient years] and musculoskeletal and connective tissue disorders ($n = 15$, IR 1.5 per 100 patient years). There were no clinically meaningful differences in the incidence of SAEs between the two secukinumab groups.

Similar proportions of patients in the any secukinumab 150 mg and 75 mg groups (5.6% and 4.3%, respectively) discontinued treatment due to TEAEs (Table 3). There were no clinically meaningful differences in the proportions of patients with potential compound- and class-related risks based on AEs in both secukinumab groups.

The exposure-adjusted incidence rate (EAIR) of adjudicated major adverse cardiovascular events (MACE) in the any secukinumab group was 0.5 per 100 patient years. The EAIR for neutropenia in the any secukinumab group was 1.3 per 100 patient years. The EAIR for fungal infections in the any secukinumab group was 3.5 per 100 patient years.

Treatment emergent anti-drug antibodies (ADAs; developing on secukinumab treatment in patients negative at baseline) were detected for 38 patients. Neutralizing antibodies were not detected in any patients. Of the 38 patients with treatment emergent ADAs, 28 had detectable ADAs at single time points, while ADAs were detectable at more than one time point in only 10 patients.

Five deaths occurred after week 16; two in the any secukinumab 150 mg group (due to sepsis and myocardial infarction), and three in

the any secukinumab 75 mg group (one due to acute myocardial infarction, one due to interstitial lung disease, and one of unknown cause). Over the entire treatment period, a total of 6 deaths were reported: 2 in the secukinumab 150 mg group, 3 in the any secukinumab 75 mg group, and 1 in the placebo group.

DISCUSSION

The treatment of RA continues to evolve and the potential role of IL-17 inhibition in the management of this disease remains an important issue. This phase 3 trial presents the only formal study of the effect of IL-17A inhibition on structural progression in patients with RA. Based on pre-defined hierarchical testing the primary endpoint was met by both the 150 mg and 75 mg secukinumab dose groups, indicating a statistically superior treatment effect over placebo. However, the main secondary objective (HAQ-DI at week 24) was not met for either secukinumab dose. A numerical reduction in radiographic progression was observed for the pooled secukinumab doses vs placebo in the placebo-controlled period of 24 weeks, but fell short of meeting statistical significance as pre-defined in the hierarchical testing. The protocol mandated escape of placebo patients to secukinumab after week 16, and more than half the placebo patients switched to secukinumab at that time. This means that there was only a very short period during which radiographic progression on placebo could be captured given this placebo-controlled trial design.

Results from the phase 3 NURTURE trial, that directly compared secukinumab with abatacept in RA [19], as well as indirect comparisons of the efficacy from this trial with the efficacy of biologics approved for use in patients for whom TNF-inhibitors have failed, suggest that IL-17A inhibition offers no additional benefit to RA patients with inadequate response to TNF-inhibitors over currently approved therapies [20, 21]. These findings led to a decision to discontinue the present trial, which bore influence on discontinuation rates in the core part of this trial (up to week 104), meaning that no patient completed the long-term extension. Of the 637 patients randomized, only 237 (37.2%) completed 104 weeks of treatment. The most frequent reasons for study discontinuation were termination by sponsor (23.1%) and lack of efficacy (16.6%). Therefore, any conclusions, in particular on the longer-term efficacy outcomes, are very limited.

Safety data from this trial confirmed the safety profile of secukinumab as seen in the phase 3 trials in psoriasis [10], PsA [12] and AS [13]. The overall safety profiles of the secukinumab 150 mg and secukinumab 75 mg dose groups in this study were similar, with nasopharyngitis, upper respiratory tract infection, urinary tract infection, bronchitis and RA being most frequently reported TEAEs with secukinumab during entire treatment period. EAIRs for MACE [22] and deaths [23] are comparable to those observed for other biologics in patients with RA.

CONCLUSIONS

In summary this phase 3 trial is the only study of IL-17A inhibition on structural progression in RA. While there may have been a numerical trend for inhibition of structural progression the trial was hampered by high discontinuation rates and a very short placebo period. In contrast to the good efficacy of IL-17A inhibition seen in psoriasis, PsA and AS, secukinumab is of lesser benefit in RA patients for whom TNF-inhibitor therapy has failed. Given that multiple biologics with good efficacy are already available to these patients, further development of secukinumab for RA patients was not pursued.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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