Long-term effects of interleukin-17A inhibition with secukinumab in active ankylosing spondylitis: 3-year efficacy and safety results from an extension of the Phase 3 MEASURE 1 trial

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Abstract

Objective

Secukinumab, a fully human anti-IL-17A monoclonal antibody, provided rapid and sustained improvements in signs and symptoms of ankylosing spondylitis (AS) over 2 years in the Phase 3 MEASURE 1 trial. Here, we report efficacy and safety after 3 years of treatment.

Methods

AS subjects completing 2 years of treatment every 4 weeks with subcutaneous secukinumab 150 or 75 mg (following intravenous loading or initial placebo treatment to 16/24 weeks) entered a separate 3-year extension study (NCT01863732). Assessments included ASAS20/40, ASAS5/6, BASDAI, BASDAI 50, BASFI, BASMI, SF-36 physical component summary, ASAS partial remission and ASDAS-CRP. Results were also analysed by prior anti-TNF treatment status.

Results

Among 290 subjects completing the core trial, 274 entered the extension study, with 260 subjects (94.9%) completing 156 weeks of treatment. ASAS20/40 response (observed) was 80.2%/61.6% in the IV→150 mg group and 75.5%/50.0% in the IV→75 mg group after 156 weeks. Sustained improvements were also seen in BASDAI, BASFI, BASMI and across all other endpoints regardless of previous exposure to anti-TNF agents. Mean secukinumab exposure was 964.3 days (137.8 weeks). Discontinuation rates were low, and secukinumab had a favourable safety profile, consistent with previous reports. Exposure-adjusted incidence rates for serious infections, Candida infections, Crohn's disease, ulcerative colitis, malignant/unspecified tumours, and adjudicated major adverse cardiac events were 1.1, 0.4, 0.5, 0.1, 0.5 and 0.7 per 100 subject-years, respectively.

Conclusion

Secukinumab provided sustained efficacy in signs, symptoms and physical function in subjects with AS over 3 years. No new safety signals were observed.

Key words

ankylosing spondylitis, secukinumab, safety

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E.M. Delicha, Z. Talloczy and B. Porter are employees of Novartis.
Z. Talloczy and B. Porter own Novartis stock.

Introduction

Ankylosing spondylitis (AS), a chronic inflammatory disease, causes progressive irreversible structural damage to the axial skeleton (1). Patients require long-term treatment to control symptoms and preserve physical function (2). Tumour necrosis factor (TNF) inhibitors improve signs and symptoms of AS (2, 3) but are not efficacious in all patients (4), and loss of efficacy can occur over time (5). Therefore, new treatments with sustained long-term benefits are needed.

Interleukin (IL)-17A is a proinflammatory cytokine with a central role in AS pathogenesis (6-9). In two Phase 3 studies, secukinumab – a fully human anti-IL-17A monoclonal antibody – significantly improved AS signs and symptoms *versus* placebo at 16 weeks (10). Similar efficacy was observed at 52 weeks (10) and 2 years (11, 12) among subjects continuing treatment. Here we present an update on efficacy and safety of secukinumab in the first year of a non-controlled extension study (NCT01863732) to the 2-year core MEASURE 1 trial (*i.e.* total treatment=3 years).

Materials and methods

Study design, eligibility criteria and results of the core 2-year trial have been described (10, 11). Subjects had active AS classified by modified New York Criteria, with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥4 (13) and spinal pain score ≥40 mm (on a 0–100 mm scale) despite prior treatment with non-steroidal anti-inflammatory drugs (NSAIDs). Subjects were anti-TNF-naïve or had received no more than one prior anti-TNF treatment, to which they failed to respond or discontinued because of safety or tolerability issues (anti-TNF-inadequate responders [anti-TNF-IR]).

Secukinumab regimens included intravenous (IV) loading of 10 mg/kg at baseline and Weeks 2 and 4, followed by subcutaneous (SC) injections of 150 mg (IV→150 mg) or 75 mg (IV→75 mg) every 4 weeks. Placebo was administered on a matching IV-to-SC schedule, with subjects switched to secukinumab 75 mg or 150 mg at Week 16/24 as previously described (10).

After the 2-year core trial, subjects were invited to enter the extension for up to 3 additional years, continuing on the same treatment. Both studies were conducted in accordance with Good Clinical Practice and the principles of the Declaration of Helsinki; all subjects provided written informed consent. Assessments of disease activity (1, 13) and quality of life (14) were conducted throughout the study, including Assessment of Spondyloarthritis International Society (ASAS) 20/40 response, ASAS5/6, BASDAI, BASDAI 50, Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Functional Index (BASFI), SF-36 physical component summary, ASAS partial remission and Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDAS-CRP). Routine safety monitoring was performed; adverse events (AEs) and serious AEs are reported.

Statistical analysis

Efficacy analyses are presented in subjects randomised to secukinumab at baseline and in those randomised to placebo who switched to secukinumab. Subjects attending the Week 156 visit included Week 156 completers and those who discontinued after Week 104, returning for an end-of-treatment visit. Analyses for binary efficacy variables are reported "as observed" and using multiple imputation to account for missing data; continuous variables were analysed as observed and as mixed-model for repeated measures (MMRM) with treatment, visit, and anti-TNF status as factors, weight and baseline score as covariates, and visits by treatment as well as visit by baseline score as interaction terms. Pre-specified analyses in anti-TNF-naïve and anti-TNF-IR subjects are reported as observed. Safety analyses included all subjects who received ≥1 dose of secukinumab at any time throughout the core trial or extension.

Results

Subjects

Of the 371 subjects randomised at baseline, 290 completed the 2-year core trial; 274 (94.5%) of these subjects consented to enrol in the separate 3-year extension study. Of the 274 patients

Table I. Baseline characteristics (at first randomisation in MEASURE 1) of subjects who entered the long-term extension trial (N=274).

Characteristic	Secukinumab IV→150 mg (n=87)	Secukinumab IV→75 mg (n=100)	Placebo→ secukinumab 150 mg (n=41)	Placebo→ secukinumab 75 mg (n=46)
Age, mean (SD) years	38.2 (11.6)	42.5 (13.4)	42.5 (12.1)	43.0 (13.0)
Male gender, n (%)	58 (66.7)	75 (75.0)	29 (70.7)	36 (78.3)
Weight, mean (SD) kg	72.5 (15.3)	77.6 (19.3)	78.5 (12.0)	75.0 (14.0)
Time since AS diagnosis, mean (SD) years	5.64 (6.42)	7.01 (7.71)	8.33 (8.74)	9.70 (9.93)
HLA-B27 positive, n (%)	61 (70.1)	81 (81.0)	34 (82.9)	33 (71.7)
Current smoker, n (%)	18 (20.7)	20 (20.0)	12 (29.3)	11 (23.9)
Anti-TNF-naïve, n (%)	70 (80.5)	76 (76.0)	33 (80.5)	36 (78.3)
Medication use at randomisation, n (%)				
Methotrexate	15 (17.2)	18 (18.0)	3 (7.3)	8 (17.4)
Sulfasalazine	31 (35.6)	34 (34.0)	18 (43.9)	16 (34.8)
Glucocorticoids	13 (14.9)	13 (13.0)	4 (9.8)	5 (10.9)
hsCRP, median (min–max), mg/L	8.20 (0.2–147.7)	9.40 (0.4–139.7)	7.80 (0.6–146.8)	8.35 (0.2–74.8)
Total BASDAI, mean (SD)	6.10 (1.54)	6.04 (1.48)	6.22 (1.70)	6.38 (1.55)
BASFI, mean (SD)	5.40 (2.24)	5.39 (2.22)	5.79 (1.94)	5.43 (2.34)
BASMI (linear), mean (SD)	3.75 (1.68)	4.27 (1.80)	4.25 (1.39)	4.11 (1.71)
Total back pain (0–100 mm), mean (SD)	62.8 (17.0)	61.1 (19.0)	65.1 (16.1)	63.7 (16.6)
Patient's global assessment of disease activity (0–100 mm), mean (SD)	64.2 (18.2)	60.3 (18.8)	65.0 (18.7)	63.2 (17.6)

Data are n (%), mean (standard deviation) or median (minimum–maximum). AS: ankylosing spondylitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; HLA: Human Leukocyte Antigen; hsCRP: high-sensitivity C-reactive protein; IV: intravenously; SD: standard deviation; TNF: tumour necrosis factor.

Table II. Summary of efficacy data at Week 156 among subjects randomised to secukinumab at baseline who entered the long-term extension trial.

	Observed		Missing data considered*	
	Secukinumab IV→150 mg (n=86)	Secukinumab IV→75 mg (n=98)	Secukinumab IV→150 mg (N=87)	Secukinumab IV→75 mg (N=100)
ASAS20, % response	80.2	75.5	79.5	75.0
ASAS40, % response	61.6	50.0	60.9	50.0
ASAS5/6, % response	64.0	57.1	63.4	59.0
ASAS partial remission, % response	26.7	14.3	26.6	14.0
BASDAI				
Baseline, mean ± SD	6.13 ± 1.53	6.03 ± 1.46	6.10 ± 1.54	6.04 ± 1.48
Change from baseline¥, mean ± SD	–3.32 ± 2.36	–2.99 ± 1.72	–3.12 ± 0.20	–2.91 ± 0.19
BASDAI 50 response rate, %	59.3	52.0	58.8	52.1
BASFI				
Baseline, mean ± SD	5.45 ± 2.20	5.39 ± 2.23	–	–
Change from baseline, mean ± SD	–2.81 ± 2.24	–2.23 ± 2.06	–	–
BASMI				
Baseline, mean ± SD	3.78 ± 1.65¶	4.27 ± 1.80¶	–	–
Change from baseline, mean ± SD	–0.68 ± 0.99¶	–0.44 ± 0.94¶	–	–
ASDAS-CRP				
Major improvement, %	38.8**	29.5**	39.1	30.4
Clinically important change, %	67.1**	70.5**	66.8	70.1
Inactive disease, %	23.5**	21.1**	24.4	20.0
SF36-PCS				
Baseline	37.74 ± 6.87	37.57 ± 6.65	–	–
Change from baseline, mean ± SD	7.86 ± 8.45	7.48 ± 6.51	–	–

*Multiple imputation applied to handle missing data for binary variables; for continuous variables mixed-model repeat measures estimates are shown with treatment, visit, and anti-TNF status as factors, weight and baseline score as covariates, and visits by treatment and visit by baseline score as interaction terms; ¥Least square mean ± SE values are presented for MMRM estimates and mean ± SD values for observed data; ¶Evaluable data available in n=81 and n=93 subjects in the secukinumab IV→150 mg and IV→75 mg groups, respectively, at Week 156; **Evaluable data available in n=85 and n=95 subjects in the secukinumab IV→150 mg and IV→75 mg groups, respectively, at Week 156.

Legend to Table II (continued)
ASAS20: response indicates improvement of at least 20% and absolute improvement of at least 1 unit (on a 10-unit scale) in at least three of the four main ASAS domains, with no worsening by 20% or more in the remaining domain; ASAS40: response indicates improvement of at least 40% and absolute improvement of at least 2 units (on a 10-unit scale) in at least three of the four main ASAS domains, with no worsening in the remaining domain; ASAS5/6: response indicates 20% or more improvement in five of the six ASAS response criteria; ASAS partial remission: a score of 2 units or less (on a scale from 0 to 10) in each of the four core ASAS domains; ASDAS-CRP: (calculated using the following formula: 0.121 x total back pain + 0.110 x patient global assessment of disease activity + 0.073 x peripheral pain/swelling + 0.058 x duration of morning stiffness + 0.579 x ln[C-reactive protein +1]); ASDAS-CRP clinically important change: ASDAS-CRP ≥1.1; ASDAS-CRP inactive disease: ASDAS-CRP <1.3; ASDAS-CRP major improvement: ASDAS-CRP ≥2.0; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASDAI 50: 50% improvement in BASDAI from baseline; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; IV: intravenously; MMRM: mixed-model for repeated measures; N: number of subjects randomised who entered the extension trial; n: number of subjects with evaluable data at Week 156; SD: standard deviation; SE: standard error of the mean; SF-36 PCS: Short Form-36 physical component summary (scores range from 0 [maximum disability] to 100 [no disability]); TNF: tumour necrosis factor; ASAS: Assessment of Spondyloarthritis International Society; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score using C-reactive protein.

entering the extension, 260 (94.9%) completed 156 weeks of total treatment (*i.e.* through Year 1 of the extension study): 83 of 87 (95.4%) subjects in the IV→150 mg group, 95 of 100 (95.0%) in the IV→75 mg group, and 82 of 87 (94.3%) in the placebo→secukinumab group. Reasons for discontinuation during the extension were AEs (0.7%), lack of efficacy (1.1%) and subject/guardian decision (3.3%). Demographic and baseline characteristics were similar to the core trial population (Table I) (10). Use of concomitant medications was consistent with earlier reports (10) and included sulfasalazine (35.6%), methotrexate (16.1%), systemic glucocorticoids (23.3%) and NSAIDs (93.9%). Mean secukinumab exposure was 964.3 days (137.8 weeks); total exposure was 950.4 subject-years.

Clinical efficacy

At Week 156, ASAS20/40 response rates with secukinumab 150 mg were 80.2%/61.6% as observed and 79.5%/60.9% with multiple imputa-

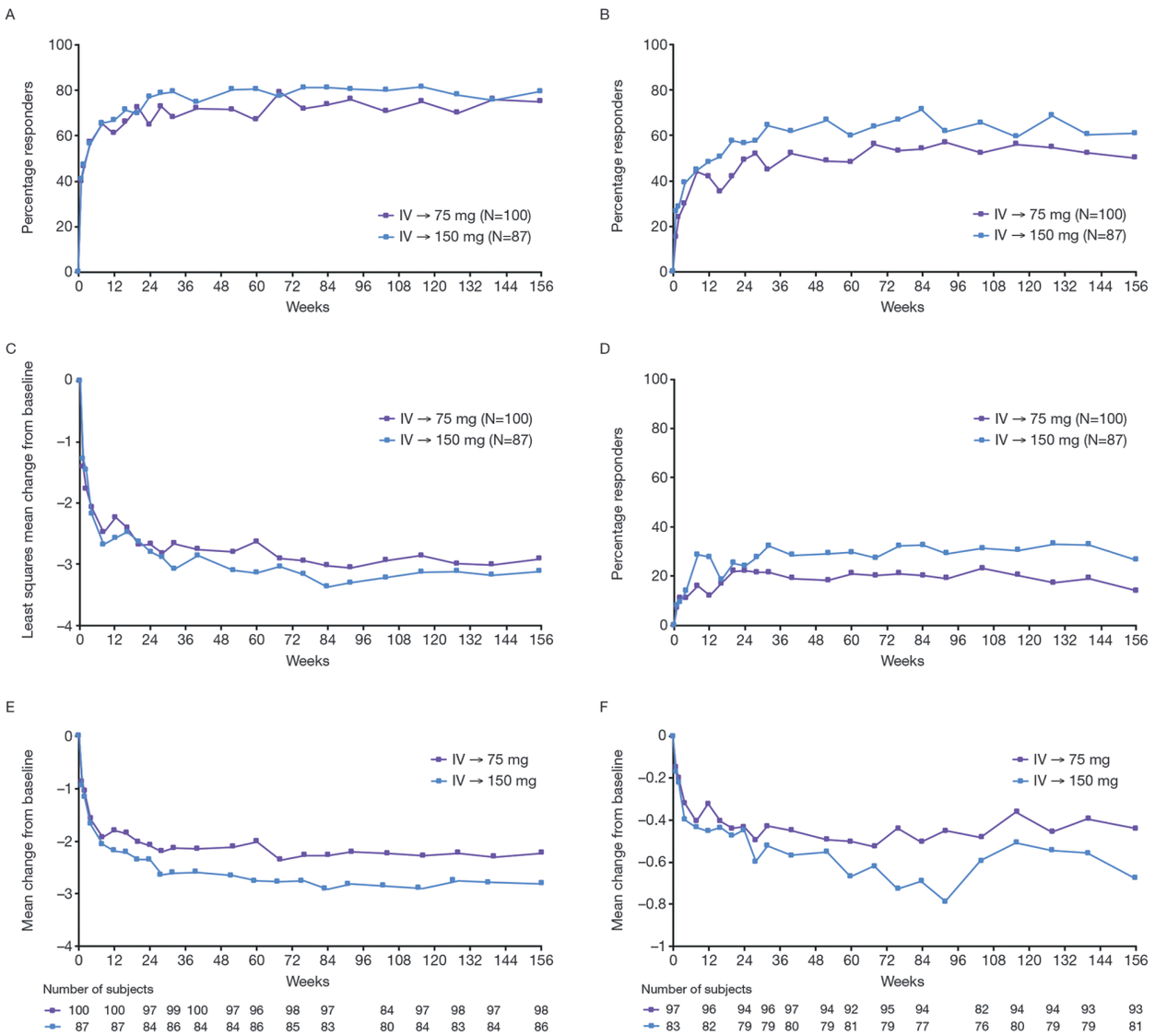

Fig. 1. Summary of key clinical efficacy endpoints through Week 156 for patients randomised to secukinumab at baseline who entered the long-term extension trial: (**A**) ASAS20 response rate; (**B**) ASAS40 response rate; (**C**) least square mean change from baseline in total BASDAI score; (**D**) ASAS partial remission; (**E**) mean change from baseline in BASFI; (**F**) mean change from baseline in BASMI. Multiple imputation applied to handle missing data for ASAS20, ASAS40 and ASAS partial remission; mixed-model for repeated measures used for BASDAI. Observed data presented for BASFI and BASMI (exploratory analysis). ASAS20: response indicates improvement of at least 20% and absolute improvement of at least 1 unit (on a 10-unit scale) in at least three of the four main ASAS domains, with no worsening by 20% or more in the remaining domain; ASAS40: response indicates improvement of at least 40% and absolute improvement of at least 2 units (on a 10-unit scale) in at least three of the four main ASAS domains, with no worsening in the remaining domain; ASAS partial remission: a score of 2 units or less (on a scale from 0 to 10) in each of the four core ASAS domains; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; ASAS: Assessment of Spondyloarthritis International Society.

tion (Fig. 1; Table II). Improvements in other major efficacy endpoints were sustained through Week 156 (Fig. 1; Table II). Subjects who switched from placebo to secukinumab also showed sustained ASAS20/40 responses and reductions in BASDAI through Week 156 (Supplemental Table I).

At Week 156, ASAS20/40 response rates with secukinumab 150 mg were 80.0%/61.4% in anti-TNF-naïve subjects and 81.3%/62.5% in anti-TNF-IR subjects (Table III). Results for most other endpoints were similar across subgroups, except for ASAS partial remission and BASDAI 50, where response rates were numerically lower in anti-TNF-IR subjects in the IV→75 mg group (Table III).

Safety

Across the core trial and extension study, the incidence and severity of AEs were consistent with previous reports (10, 11) (Table IV). The incidence of serious AEs was low and not dose-related; discontinuations due to AEs were infrequent.

Of the two deaths in secukinumab-treated subjects through 156 weeks, one was reported previously (11) and one was due to stroke in a subject with history of hypertension, chronic obstructive pulmonary disease and smoking.

Among AEs of special interest, exposure-adjusted incidence rates (EAIRs) for serious infections, Crohn's disease, ulcerative colitis, malignant/unspecified tumours and adjudicated major adverse

Table III. Analysis of key efficacy data by anti-TNF status (observed data) at Week 156 among subjects randomised to secukinumab at baseline who entered the long-term extension trial.

	Anti-TNF-naïve		Anti-TNF-IR	
	Secukinumab IV→150 mg (n=70)	Secukinumab IV→75 mg (n=75)	Secukinumab IV→150 mg (n=16)	Secukinumab IV→75 mg (n=23)
ASAS20, % response	80.0	76.0	81.3	73.9
ASAS40, % response	61.4	48.0	62.5	56.5
ASAS5/6, % response	61.4	56.0	75.0	60.9
ASAS partial remission, % response	25.7	17.3	31.3	4.3
BASDAI				
Baseline, mean ± SD	6.16 ± 1.55	5.90 ± 1.49	5.98 ± 1.50	6.44 ± 1.30
Change from baseline, mean ± SD	–3.26 ± 2.51	–3.09 ± 1.76	–3.54 ± 1.59	–2.66 ± 1.57
BASDAI 50, % response	60.0	60.0	56.3	26.1
SF-36 PCS score				
Baseline, mean ± SD	37.89 ± 7.13	38.36 ± 6.28	37.09 ± 5.78	34.98 ± 7.29
Change from baseline, mean ± SD	7.72 ± 8.62	7.47 ± 6.30	8.44 ± 7.90	7.52 ± 7.31

ASAS20: response indicates improvement of at least 20% and absolute improvement of at least 1 unit (on a 10-unit scale) in at least three of the four main ASAS domains, with no worsening by 20% or more in the remaining domain; ASAS40: response indicates improvement of at least 40% and absolute improvement of at least 2 units (on a 10-unit scale) in at least three of the four main ASAS domains, with no worsening in the remaining domain; ASAS5/6: response indicates 20% or more improvement in five of the six ASAS response criteria; ASAS partial remission: a score of 2 units or less (on a scale from 0 to 10) in each of the four core ASAS domains; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASAS: Assessment of Spondyloarthritis International Society; IR: inadequate responders; IV: intravenously; n: number of subjects with evaluable data at Week 156; SD: standard deviation; SF-36 PCS: Short Form-36 physical component summary (scores range from 0 [maximum disability] to 100 [no disability]); TNF: tumour necrosis factor.

cardiac events (MACE) were 1.1, 0.5, 0.1, 0.5 and 0.7 per 100 subject-years, respectively, similar to previous reports (11).

In addition to six previous serious infections (11), six new serious infections were reported through Week 156 (appendicitis [n=3], cellulitis, pulmonary tuberculosis [*de novo* event] and urinary tract infection [all n=1]). The overall EAIR was 1.1 per 100 subject-years. No new *Candida* infections were reported.

More specific analysis of neutropenia (MedDRA 18.1) than in previous reports indicated that eight secukinumab-treated subjects experienced at least one AE of neutropenia through 156 weeks. Analysis of laboratory parameters, regardless of AE reporting status, indicated that 32 secukinumab-treated subjects had low neutrophil counts during this period (10 Common Terminology Criteria for Adverse Events Grade 1, 14 Grade 2, 5 Grade 3 and 3 Grade 4; any subject with multiple events was counted once under the worst grade).

Five cases of Crohn's disease, all reported as non-serious AEs, were previously described with secukinumab in MEASURE 1 (11). During the first year of the extension, one new case of mild ulcerative colitis (that did not lead to study discontinuation) was reported in a patient with no prior history of inflammatory bowel disease.

One new case of malignant/unspecified tumour was reported (gastrointestinal stromal tumour); treatment was not interrupted or discontinued and the tumour resolved.

Seven secukinumab-treated subjects had adjudicated MACE through Week 156; four were described previously (11). New events included one myocardial infarction and two strokes; one stroke led to cardiovascular death.

Prior history of uveitis was reported in 17% of all subjects randomised in MEASURE 1 (11). AEs of uveitis were reported in 17 subjects on secukinumab through Week 156 (10 with prior history of uveitis and 7 *de novo* cases in subjects with no prior history); 12 of these events have been reported previously (11) and two were serious AEs.

Five secukinumab-treated subjects experienced psoriasis AEs through Week 156; all cases have been reported previously (11). Secukinumab injection site reactions occurred in 1.1% of subjects. Non-neutralising treatment-emergent anti-secukinumab antibodies were detected in two subjects through Week 156; these were not associated with loss of efficacy and have been previously reported (11).

Discussion

Significant clinical efficacy was demonstrated with secukinumab *versus* placebo during Weeks 0–16 of MEASURE 1, with benefits sustained through Week 104 (10, 11). In the present analysis, clinical improvements were sustained through Week 156 across all endpoints measured. At Week 156, ASAS20/40 response rates were 80.2%/61.6% with secukinumab IV→150 mg and 75.5%/50.0% with secukinumab IV→75 mg. As reported previously (10), both the IV→150 mg and IV→75 mg regimens had similar efficacy responses at Week 16 and Week 52, due to the large IV loading regimen. However, by Week 156, the increased exposure due to IV loading in the first month of treatment was no longer apparent, and decreased efficacy was noted with the 75 mg dose as compared with 150 mg (the licensed dose in AS). For higher-hurdle endpoints, such as ASAS partial remission, numerically greater improvements were seen with secukinumab IV→150 mg (26.7%) *versus* IV→75 mg (14.3%) (Fig. 1). Similar sustained improvements were observed in anti-TNF-naïve and anti-TNF-IR groups, and in patients who switched from placebo to secukinumab. In contrast to earlier time points (10, 11), ASAS20/40 responses were generally similar in anti-TNF-IR and anti-TNF-naïve subjects at Week 156. EAIRs for AEs of special interest were similar to previous reports; no new safety risks were identified with extended secukinumab treatment.

Limitations of this long-term extension include lack of a control group beyond Week 16 and potential selection bias of subjects who elected to remain on treatment and enter the extension study, although this encompassed 94.5% of patients who completed the core study. Nevertheless, retention rates were high with minimal withdrawals due to lack of efficacy (1.1%).

Building on earlier findings, these results

Table IV. Incidence of treatment-emergent AEs during the entire treatment period through Week 156.

	Any secukinumab 150 mg (n=181)*	Any secukinumab 75 mg (n=179)*	Any secukinumab pooled (n=360)*
Mean exposure to study treatment, days (SD)	879.2 (357.54)	1050.4 (367.55)	964.3 (372.05)
Number of subjects with event (%)			
Any AE	161 (89.0)	151 (84.4)	312 (86.7)
Serious AE¥	26 (14.4)	34 (19.0)	60 (16.7)
Any AE leading to discontinuation	18 (9.9)	11 (6.1)	29 (8.1)
Infection or infestation	113 (62.4)	110 (61.5)	223 (61.9)
Common AEs (seen in more than 5% of subjects on secukinumab), n (%)			
Nasopharyngitis	49 (27.1)	40 (22.3)	89 (24.7)
Diarrhoea	27 (14.9)	24 (13.4)	51 (14.2)
Headache	25 (13.8)	26 (14.5)	51 (14.2)
Upper respiratory tract infection	19 (10.5)	28 (15.6)	47 (13.1)
Influenza	22 (12.2)	18 (10.1)	40 (11.1)
Pharyngitis	22 (12.2)	13 (7.3)	35 (9.7)
Oropharyngeal pain	17 (9.4)	14 (7.8)	31 (8.6)
Dyslipidaemia	14 (7.7)	17 (9.5)	31 (8.6)
Arthralgia	15 (8.3)	14 (7.8)	29 (8.1)
Back pain	15 (8.3)	10 (5.6)	25 (6.9)
Cough	13 (7.2)	12 (6.7)	25 (6.9)
Bronchitis	13 (7.2)	9 (5.0)	22 (6.1)
Nausea	11 (6.1)	11 (6.1)	22 (6.1)
Leukopenia	8 (4.4)	14 (7.8)	22 (6.1)
Urinary tract infection	11 (6.1)	10 (5.6)	21 (5.8)
Ankylosing spondylitis	12 (6.6)	8 (4.5)	20 (5.6)
Hypertension	8 (4.4)	12 (6.7)	20 (5.6)
AEs of special interest, n (exposure-adjusted incidence rate per 100 subject-years)			
Candida infections	2 (0.4)	2 (0.4)	4 (0.4)
Serious infections	3 (0.6)	8 (1.5)	11 (1.1)
Crohn's disease	1 (0.2)	4 (0.8)	5 (0.5)
Ulcerative colitis	0	1 (0.2)	1 (0.1)
Major adverse cardiac events (adjudicated)	2 (0.4)	5 (1.0)	7 (0.7)
Malignancy	3 (0.6)	2 (0.4)	5 (0.5)
Neutropenia	3 (0.6)	5 (1.0)	8 (0.8)

*Includes subjects randomised to secukinumab at baseline and subjects who were randomised to placebo who switched to secukinumab at Weeks 16 or 24; ¥Serious AEs also include deaths; AE: adverse event; SD: standard deviation.

Supplementary Table I. Summary of efficacy at Week 156 (observed data) in patients originally randomised to placebo who switched to secukinumab and entered the long-term extension trial.

	Placebo→secukinumab 150 mg (n=40)	Placebo→secukinumab 75 mg (n=46)
ASAS20, % response*	67.5	76.1
ASAS40, % response*	55.0	54.3
BASDAI*		
Baseline, mean ± SD	6.22 ± 1.72	6.38 ± 1.55
Change from baseline, mean ± SD	–2.85 ± 2.15	–3.02 ± 2.09

*Data presented as observed. ASAS20: response indicates improvement of at least 20% and absolute improvement of at least 1 unit (on a 10-unit scale) in at least three of the four mainA SAS domains, with no worsening by 20% or more in the remaining domain; ASAS40: response indicates improvement of at least 40% and absolute improvement of at least 2 units (on a 10-unit scale) in at least three of the four main ASAS domains, with no worsening in the remaining domain; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASAS: Assessment of Spondyloarthritis International Society; n: number of subjects with evaluable data at Week 156; SD: standard deviation.

show sustained improvement through 3 years in signs, symptoms and physical function in AS subjects who remained on secukinumab 150 mg. Discontinuation rates were low and secukinumab was well tolerated with a favourable safety profile, consistent with previous reports. This ongoing study will provide valuable longer-term data over a further 2 years.

References

1. SIEPER J, RUDWALEIT M, BARALIAKOS X *et al*.: The assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009; 68 (Suppl. 2): ii1-44.
2. VAN DER HEIJDE D, RAMIRO S, LANDEWÉ R *et al*.: 2016 update of the ASAS/EULAR management recommendations for ankylosing spondylitis. *Ann Rheum Dis* 2017 Jan 13 (doi: 10.1136/annrheumdis-2016-210770) [Epub].
3. WARD MM, DEODHAR A, AKL EA *et al*.: American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol* 2016; 68: 282-98.
4. BRAUN J, KILTZ U, HELDMANN F *et al*.: Emerging drugs for the treatment of axial and peripheral spondyloarthritis. *Expert Opin Emerg Drugs* 2015; 20: 1-14.
5. BARALIAKOS X, LISTING J, FRITZ C *et al*.: Persistent clinical efficacy and safety of infliximab in ankylosing spondylitis after 8 years - early clinical response predicts long-term outcome. *Rheumatology* (Oxford) 2011; 50: 1690-9.
6. KENNA TJ, DAVIDSON SI, DUAN R *et al*.: Enrichment of circulating interleukin-17-secreting interleukin-23 receptor-positive γ/δ T cells in patients with active ankylosing spondylitis. *Arthritis Rheum* 2012; 64: 1420-9.
7. NOORDENBOS T, YEREMENKO N, GOFITA I *et al*.: Interleukin-17-positive mast cells contribute to synovial inflammation in spondyloarthritis. *Arthritis Rheum* 2012; 64: 99-109.
8. SHEN H, GOODALL JC, HILL GASTON JS: Frequency and phenotype of peripheral blood Th17 cells in ankylosing spondylitis and rheumatoid arthritis. *Arthritis Rheum* 2009; 60: 1647-56.
9. VAN TOK M, VAN DUIVENVOORDE L, KRAMER I *et al*.: Anti-IL-17A treatment blocks inflammation, destruction and new bone formation in experimental spondyloarthritis in HLA-B27 transgenic rats. *Arthritis Rheumatol* 2015; 67 (Suppl. 10): Abstract 981.
10. BAETEN D, SIEPER J, BRAUN J *et al*.: Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. *N Engl J Med* 2015; 373: 2534-48.
11. BRAUN J, BARALIAKOS X, DEODHAR A *et al*.: Effect of secukinumab on clinical and radiographic outcomes in ankylosing spondylitis: 2-year results from the randomised phase III MEASURE 1 study. *Ann Rheum Dis* 2017; 76: 1070-77
12. MARZO-ORTEGA H, LEGERTON CW, SIEPER J *et al*.: Secukinumab provides sustained improvements in the signs and symptoms of active ankylosing spondylitis: 2-year results from a phase 3 trial with subcutaneous loading and maintenance dosing (MEASURE 2). *Ann Rheum Dis* 2016; 75 (Suppl. 2): 812-3.
13. GARRET S, JENKINSON T, KENNEDY LG *et al*.: A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994; 21: 2286-91.
14. WARE JE, KOSINSKI M, DEWEY JE: How to score Version Two of the SF-36 Health Survey. Lincoln, RI: Quality Metric, 2000.