ONLINE SUPPLEMENT

SUPPLEMENTARY METHODS

A copy of the study protocol can be obtained from the study sponsors, Novartis Pharma AG.

Patients

Key exclusion criteria included: total ankylosis of the spine; previous use of any biologic other than an anti-tumor necrosis factor (anti-TNF); active inflammatory diseases other than ankylosing spondylitis (AS); active systemic infection other than the common cold in the two weeks before randomization, or a history of ongoing, chronic, or recurrent infections; history of malignant disease within the past 5 years (except for basal cell carcinoma or actinic keratosis, in-situ cervical cancer, or non-invasive malignant colon polyps).

Patients were enrolled by the study investigators from clinical sites in North America, South America, Europe, and Asia

Randomization procedures

Randomization was performed using a computer-generated automated system that assigned patients to randomization numbers identifying assigned treatments and unique medication numbers for the study treatment packages to be prepared. Randomization was stratified according to prior anti-TNF therapy use, with patients being anti-TNF-naïve or inadequate responders to anti-TNF therapy (anti-TNF-IR). Medication numbers were accessible only to the unblinded pharmacist or other qualified personnel at each site. Doses were prepared from open-label vials by the unblinded pharmacist or other qualified person and provided in identical syringes of reconstituted solution.

Disease activity and efficacy assessments

Disease activity and efficacy assessments were conducted at baseline and throughout the study, with key assessments at weeks 16, 52, and 104: proportion of patients achieving an ASAS20 response (improvement of ≥20% and ≥1 unit in at least three of the four main ASAS domains, and no worsening by ≥20% and ≥1 unit in the remaining domain; primary endpoint at week 16);[1] proportion of patients achieving an ASAS40 response (≥40% improvement and absolute improvement of ≥2 units in at least three of the four main ASAS domains, with no worsening in the remaining domain);[1] median change from baseline in high-sensitivity C-reactive protein (hsCRP); proportion of patients achieving an ASAS5/6 response (≥20% improvement in five out of six ASAS domains);[1] mean change from baseline in total Bath Ankylosing Spondylitis Disease Activity Score (BASDAI) score; summary score for the physical component of the Medical Outcomes Study 36-item Short Form Health Survey version 2 (SF-36 PCS; scores range from 0 [maximum disability] to 100 [no disability] for individual domains, with a normative composite summary score of 50);[2] AS Quality of Life (ASQoL) score (range from 0 [best quality] to 18 [poorest quality]);[3] and proportion of patients meeting ASAS partial remission criteria (a score of ≤2 units in each of the four main ASAS domains).[1]

Radiographic assessments

Radiographs were scored using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) method:[4] all anterior corners (from the lower corner of T12 to the upper corner of S1 and from the lower corner of C2 to the upper corner of T1) were scored for the presence of: erosions, sclerosis, and/or squaring (1 point per site); syndesmophytes[5] (2 points per site); and bridging syndesmophytes (3 points per site). Scores at all individual sites were summed (score range: 0–72). In order to avoid misinterpretation of x-ray findings,

syndesmophytes were considered present and were differentiated for spondylophytes based on a previously published definition (≥2 mSASSS per specific affected vertebral unit).[5]

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. Ware JE, Kosinski M, Dewey JE. How to score Version Two of the SF-36 Health Survey. Lincoln, RI: Quality Metric, 2000.

3. Doward LC, Spoorenberg A, Cook SA, *et al*. Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. *Ann Rheum Dis* 2003;62:20–6.

4. Creemers MC, Franssen MJ, van't Hof MA, *et al*. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. *Ann Rheum Dis* 2005;64:127–9.

5. Baraliakos X, Listing J, Rudwaleit M, *et al*. Progression of radiographic damage in patients with ankylosing spondylitis: defining the central role of syndesmophytes. *Ann Rheum Dis* 2007;66:910–5.

TABLES AND FIGURES

Table S1 Baseline characteristics of the placebo-switcher x-ray completer cohort

Characteristic	Placebo → Secukinumab 150 mg (N=45)	Placebo → Secukinumab 75 mg (N=44)
Age, mean (SD) years	42.6 (12.6)	43.4 (13.3)
Male gender, n (%)	31 (68.9)	33 (75.0)
Weight, mean (SD) kg	78.4 (11.3)	76.8 (17.3)
Time since AS diagnosis, mean (SD) years	8.9 (9.2)	9.7 (10.0)
HLA-B27 positive, n (%)	38 (84.4)	29 (65.9)
Current smoker, n (%)	14 (31.1)	10 (22.7)
Anti-TNF-naïve, n (%)	34 (75.6)	32 (72.7)
Medication use at baseline, n (%)		
Methotrexate	3 (6.7)	8 (18.2)
Sulfasalazine	18 (40.0)	15 (34.1)
Glucocorticoids	6 (13.3)	5 (11.4)
hsCRP, median (min-max), mg/L	6.6 (0.2–146.8)	10.6 (0.2–74.8)
Elevated hsCRP >5 mg/L, n (%)	24 (53.3)	31 (70.5)
Total BASDAI, mean (SD)	6.4 (1.7)	6.5 (1.6)
BASFI, mean (SD)	5.9 (2.0)	5.5 (2.5)
BASMI (linear), mean (SD)	4.0 (1.4)	4.1 (1.8)
mSASSS, mean (SD)	9.6 (16.1)	10.6 (16.3)

Syndesmophyte present, n (%)	20 (44.4)	23 (52.3)
Total back pain, mean (SD)	66.2 (17.0)	65.9 (17.8)
Patient's global assessment of disease activity, mean (SD)	66.4 (19.5)	66.2 (17.7)

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; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; TNF, tumor necrosis factor.

Table S2 mSASSS in the placebo-switcher x-ray completer cohort

Variable	**Placebo → secukinumab 150 mg**	**Placebo → secukinumab 75 mg**	**Placebo → secukinumab pooled**
Overall population			
Patients (n)	45	44	89
Baseline	9.60 (16.10)	10.59 (16·32)	10·09 (16·12)
Change at week 104	0·44 (2·09)	0·64 (2·79)	0.54 (2.45)
Patients with syndesmophytes at baseline			
Patients (n)	20	23	43
Baseline	21.30 (18.45)	20.13 (17.92)	20.67 (17.96)
Change at week 104	0.95 (3.09)	1.22 (3.79)	1.09 (3.44)
Patients without syndesmophytes at baseline			
Patients (n)	25	21	46
Baseline	0.24 (0.54)	0.14 (0.39)	0.20 (0.48)

Change at week 104	0.04 (0.32)	0.00 (0.32)	0.02 (0.32)
Elevated hsCRP			
Patients (n)	24	31	55
Baseline	11.13 (14.23)	13.08 (17.36)	12.23 (15.95)
Change at week 104	0.75 (2.84)	0.81 (3.23)	0.78 (3.04)
Normal hsCRP			
Patients (n)	21	13	34
Baseline	7.86 (18.20)	4.65 (12.13)	6.63 (16.02)
Change at week 104	0.10 (0.38)	0.23 (1.24)	0.15 (0.80)
Male			
Patients (n)	31	33	64
Baseline	13.74 (17.97)	11.76 (17.49)	12.72 (17.61)
Change at week 104	0.65 (2.50)	0.73 (3.13)	0.69 (2.82)
Female			
Patients (n)	14	11	25
Baseline	0.43 (0.55)	7.09 (12.21)	3.36 (8.58)
Change at week 104	0.00 (0.34)	0.36 (1.43)	0.16 (0.98)
Smokers (at baseline)			
Patients (n)	14	10	24
Baseline	13.46 (16.49)	11.85 (19.28)	12.79 (17.32)
Change at week 104	1.32 (2.42)	0.30 (1.49)	0.90 (2.11)
Non-smokers (at baseline)			
Patients (n)	31	34	65
Baseline	7.86 (15.88)	10.22 (15.66)	9.09 (15.68)
Change at week 104	0.05 (1.83)	0.74 (3.08)	0.41 (2.57)

N indicates the total number of patients randomized; n indicates number of patients with evaluable paired x-ray data at both baseline and week 104 (x-ray completers). Data shown as mean (standard deviation). mSASSS scores range from 0 to 72, with higher scores indicating greater radiographic damage. Patients were randomized to receive placebo from baseline, before being switched to receive indicated dose of subcutaneously every 4 weeks from week 16 or 24, depending upon clinical response. hsCRP, high-sensitivity C-reactive protein; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score.

Table S3 New syndesmophyte formation through week 104 in x-ray completer cohort

Treatment group	Baseline	With new syndesmophytes at week 104 n/N (%)	Without new syndesmophytes at week 104 n/N (%)
Secukinumab IV-150 mg	With syndesmophyte	14/51 (27.5)	37/51 (72.5)
	Without syndesmophytes	1/35 (2.9)	34/35 (97.1)
Secukinumab IV-75 mg	With syndesmophyte	17/53 (32.1)	36/53 (67.9)
	Without syndesmophytes	2/29 (6.9)	27/29 (93.1)
Placebo → secukinumab 150 mg	With syndesmophyte	6/20 (30.0)	14/20 (70.0)
	Without syndesmophytes	1/25 (4.0)	24/25 (96.0)
Placebo → secukinumab 75 mg	With syndesmophyte	14/43 (32.6)	29/43 (67.4)
	Without syndesmophytes	2/46 (4.3)	44/46 (95.7)

Syndesmophytes were considered present if mSASSS was ≥2 per specific affected vertebral unit. Patients randomized to secukinumab received a 10 mg/kg intravenous loading dose at baseline and weeks 2 and 4, before receiving indicated dose of secukinumab subcutaneously every 4

weeks from week 8. Patients randomized to placebo were switched to receive indicated dose of subcutaneously every 4 weeks from week 16 or 24, depending upon clinical response.

Table S4 Serious adverse events through entire treatment period*

Primary system organ class	**Any secukinumab 150 mg (N=181)**	**Any secukinumab 75 mg (N=179)**	**Any secukinumab pooled (N=360)**	**Placebo up to week 24 (N=122)**
Any serious adverse event	24 (13.4)	22 (12.2)	46 (12.8)	5 (4.1)
Injury, poisoning and procedural complications	6 (3.4)	5 (2.8)	11 (3.1)	0 (0.0)
Gastrointestinal disorders	3 (1.7)	4 (2.2)	7 (1.9)	0 (0.0)
Cardiac disorders	4 (2.2)	2 (1.1)	6 (1.7)	0 (0.0)
Infections and infestations	3 (1.7)	3 (1.7)	6 (1.7)	0 (0.0)
Nervous system disorders	3 (1.7)	3 (1.7)	6 (1.7)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	5 (2.8)	1 (0.6)	6 (1.7)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (0.6)	4 (2.2)	5 (1.4)	0 (0.0)
Hepatobiliary disorders	3 (1.7)	1 (0.6)	4 (1.1)	0 (0.0)

Eye disorders	1 (0.6)	2 (1.1)	3 (0.8)	0 (0.0)
General disorders and administration site conditions	3 (1.7)	0 (0.0)	3 (0.8)	1 (0.8)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.6)	2 (1.1)	3 (0.8)	1 (0.8)
Vascular disorders	1 (0.6)	1 (0.6)	2 (0.6)	0 (0.0)
Blood and lymphatic disorders	1 (0.6)	0 (0.0)	1 (0.3)	1 (0.8)
Ear and labyrinth disorders	1 (0.6)	0 (0.0)	1 (0.3)	1 (0.8)
Endocrine disorders	1 (0.6)	0 (0.0)	1 (0.3)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)
Renal and urinary disorders	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)

[*]The safety data reporting period was defined as the period from baseline through week 104 visit of the last patient (mean [SD] exposure in days: any secukinumab 150 mg, 621.3 [187.5]; any secukinumab 75 mg, 642.0 [180.9]; placebo, 125.8 [35.2]). The placebo group includes all patients who received placebo during the study. The secukinumab groups in this period include any patients who received the stated dose of secukinumab and include those patients randomized to placebo at baseline who were re-randomized to receive active treatment from week 16/24 onwards.

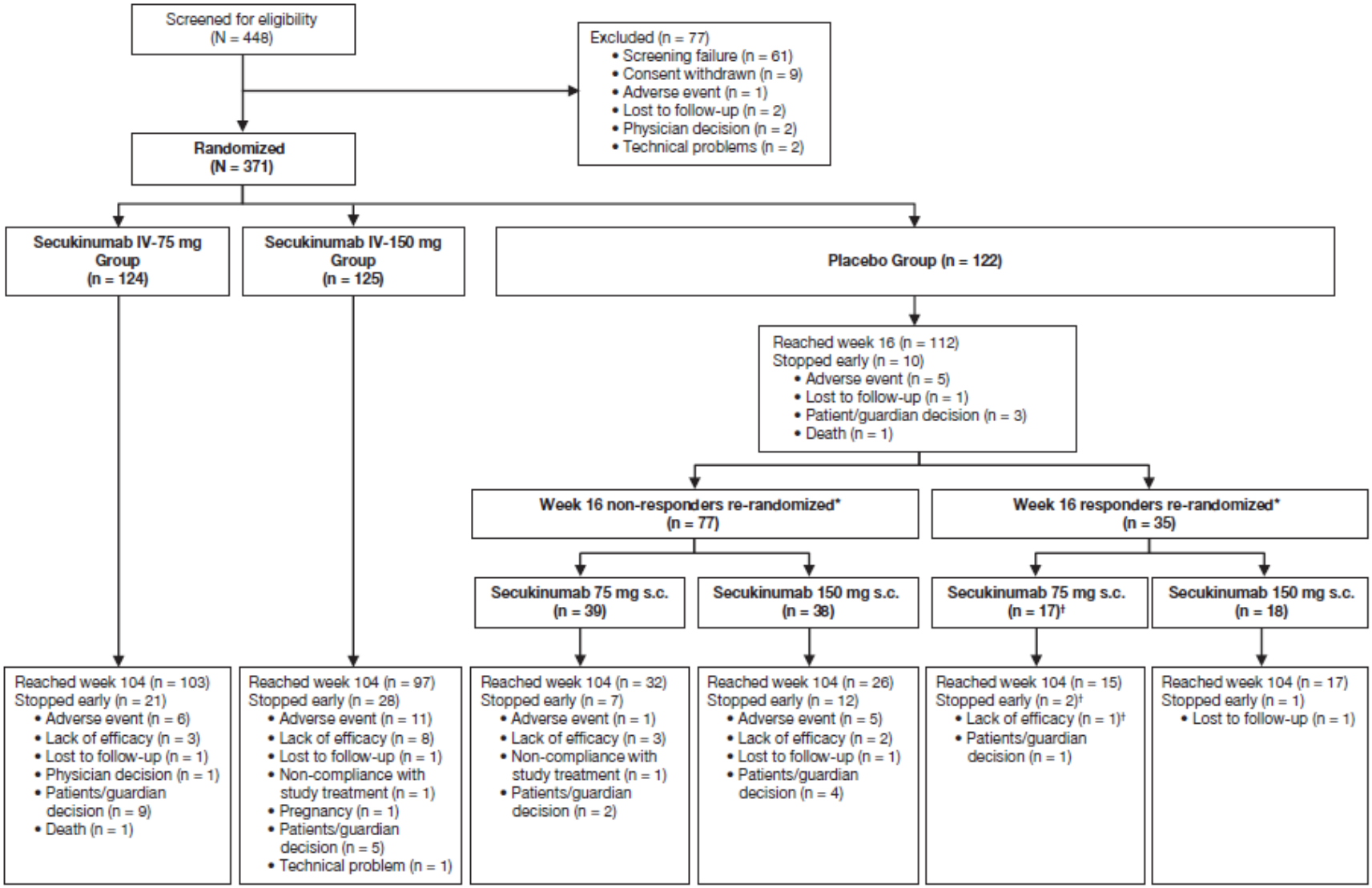
Table S5 Details of major adverse cardiovascular events (MACE) reported through entire treatment period[*]

Treatment group	Reported AE (preferred term)	Time to onset (days)	Serious AE?	Discontinued?	Adjudicated[†] as MACE? / Event type	Considered related to study treatment? (Investigator opinion)	Patient history
IV-75 mg	MI	463	Yes	No	Yes / Type 1 spontaneous MI	No	54-year-old male; history of hypertension, diabetes, dyslipidemia, transient ischemic attack, hemorrhagic stroke, and ischemic stroke
IV-75 mg	MI	707	Yes	No	Yes / Type 1 spontaneous MI	No	41-year-old male; smoker but no reported cardiovascular history
IV-150 mg	MI	470	Yes	No	No / MI criteria not met; classified as angina pectoris	No	61-year-old male; history of smoking, hyperlipidemia, hypercholesterolemia and arterial hypertension
IV-150 mg	MI	538	Yes	No	Yes / Type 1 spontaneous MI	No	42-year-old female; history of uncomplicated diabetes and obesity
Placebo responder – 150 mg	Cerebro-vascular accident	310	Yes	No (temporarily interrupted)	Yes / ischemic stroke	No	40-year-old male with arterial hypertension

[*]The safety data reporting period was defined as the period from baseline through week 104 visit of the last patient (mean [SD] exposure in days: any secukinumab 150 mg, 621.3 [187.5]; any secukinumab 75 mg, 642.0 [180.9]; placebo, 125.8 [35.2]); [†]An Adjudication Committee reviewed

and adjudicated potential major adverse cardiovascular events (MACE) in a blinded manner. AE, adverse event; IV, intravenously; MI, myocardial infarction.

Figure S1 Patient disposition through week 104



[*]All patients were re-randomized at week 16: placebo non-responders received active treatment at week 16 while placebo responders received active treatment at week 24; [†]One placebo patient attended the week 16 visit, and was re-randomized as a placebo responder; however, this patient discontinued at week 20 and did not receive active treatment. IV, intravenously; SC, subcutaneous.

Figure S2 Summary of ASAS20 and ASAS40 response with secukinumab by prior exposure to anti-TNF therapy

Missing data were imputed as non-responses up to week 16. Data presented at week 104 are as observed.

*p<0.0001; †p< 0.001; §p<0.01; ‡p<0.05 versus placebo. ASAS, Assessment of SpondyloArthritis international Society response criteria; anti-TNF-IR, inadequate response or intolerance to prior anti-TNF therapy; IV, intravenously; TNF, tumor necrosis factor.

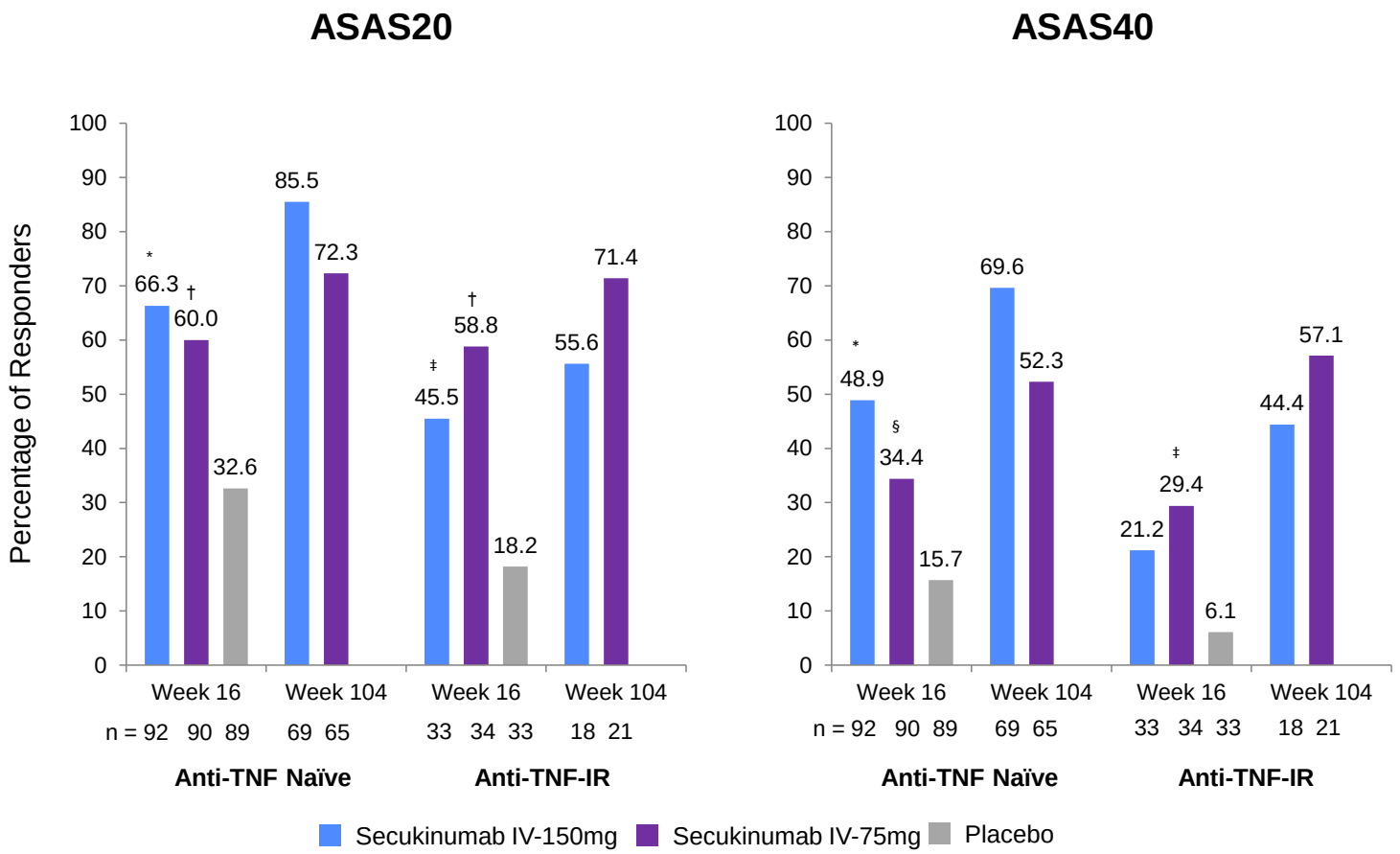

ASAS20
ASAS40
Percentage of Responders
100
90
80
70
60
50
40
30
20
10
0
*
66.3
†
60.0
32.6
85.5
72.3
‡
45.5
†
58.8
18.2
55.6
71.4
*
48.9
§
34.4
15.7
69.6
52.3
‡
21.2
29.4
6.1
44.4
57.1
Week 16
Week 104
Week 16
Week 104
n = 92 90 89
69 65
33 34 33
18 21
Anti-TNF Naïve
Anti-TNF-IR
Secukinumab IV-150mg
Secukinumab IV-75mg
Placebo

Figure S3 Probability plot of progression in the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) at week 104 in placebo-switcher x-ray completer cohort (observed data)

Cumulative probability plot for change from baseline in mSASSS at week 104 in x-ray completers randomized to placebo at baseline who switched to secukinumab at weeks 16 or 24. X-ray completers are those patients with x-rays at both baseline and at week 104.

mSASSS, modified Stoke Ankylosing Spondylitis Spine Score.

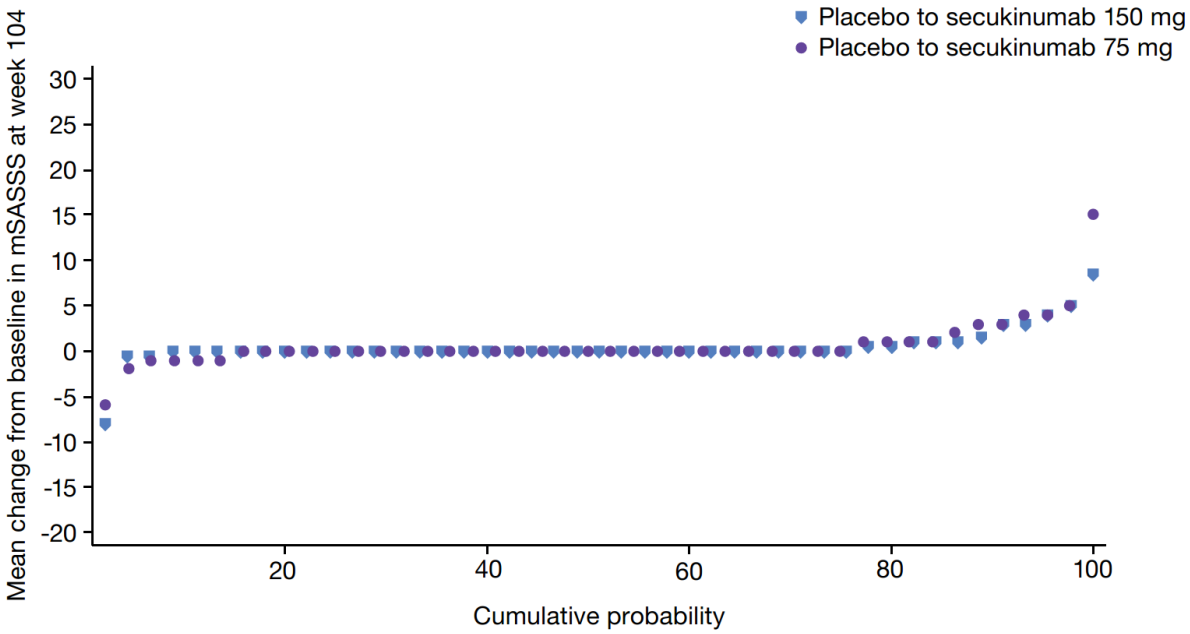


Figure S4 Bland-Altman plot showing the level of agreement between readers for change in modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) at week 104.