ONLINE SUPPLEMENT

Supplementary Table 1. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
1. Patients able to understand and communicate with the investigator and comply with the requirements of the study and give a written, signed, and dated informed consent before any study assessment was performed	1. Chest x-ray or Magnetic Resonance Imaging with evidence of ongoing infectious or malignant process obtained within 3 months of screening and evaluated by a qualified physician
2. Male or non-pregnant, non-lactating female patients at least 18 years of age	2. Patients with total ankylosis of the spine
3. Diagnosis of moderate to severe ankylosing spondylitis (AS) with prior documented radiologic evidence (x-ray or radiologist's report) fulfilling the Modified New York criteria for AS	3. Patients taking high potency opioid analgesics (e.g., methadone, hydromorphone, morphine)
4. Active AS assessed by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 (0-10) at baseline	4. Previous exposure to secukinumab or any other biologic drug directly targeting interleukin (IL)-17 or the IL-17 receptor
5. Spinal pain as measured by BASDAI question #2 ≥4 cm (0-10 cm) at baseline	5. Use of any investigational drug and/or devices within 4 weeks of randomization or a period of 5 half-lives of the investigational drug, whichever was longer
6. Patients had to be on NSAIDs at the highest recommended dose for at least 3 months prior to randomization with an inadequate response or failure to respond, or less than 3 months if therapy was withdrawn due to intolerance, toxicity or contraindications	6. History of hypersensitivity to the study drug or its excipients or to drugs of similar chemical classes
7. Patients who were regularly taking NSAIDs (including cyclooxygenase (COX-1 or COX-2) inhibitors)) as part of	7. Any therapy by intra-articular injections (e.g., corticosteroid) within 4 weeks before randomization
	8. Any intramuscular corticosteroid injection within 2 weeks before randomization

their AS therapy were required to be on a stable dose for at least 2 weeks before randomization

8. Patients who had been on a TNFα inhibitor (not more than one) must have had experienced an inadequate response to previous or current treatment given at an approved dose for at least 3 months prior to randomization or had been intolerant to at least one administration of an anti-TNFα agent

9. Patients who had previously been on a TNFα inhibitor were allowed to entry into study after an appropriate wash-out period prior to randomization:

a. Four weeks for Enbrel® or "Yi Sai Pu"® (etanercept) – with a terminal half-life of 102 ± 30 hours (s.c. route)

b. Eight weeks for Remicade® (infliximab) – with a terminal half-life of 8.0-9.5 days (s.c. route)

c. Ten weeks for Humira® (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks) (s.c. route)

d. Ten weeks for Simponi® (golimumab) – with a terminal half-life of 11-14 days

e. Ten weeks for Cimzia® (certolizumab) – with a terminal half-life of 14 days

10. Patients taking MTX (≤25 mg/week) or sulfasalazine (≤3 g/day) were allowed to continue their medication and must have taken it for at least 3 months and have been on a stable dose for at least 4 weeks prior to randomization

9. Patients previously treated with any biological immuno-modulating agents except for those targeting tumor necrosis factor α (TNFα)

10. Previous treatment with any cell-depleting therapies, including but not limited to anti-CD20, investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)

11. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test

12. Women of child-bearing potential, were defined as all women physiologically capable of becoming pregnant, unwilling to use effective contraception during the study and for 16 weeks after stopping treatment.

13. Active ongoing inflammatory diseases other than AS that might confound the evaluation of the benefits of secukinumab therapy, including inflammatory bowel disease or uveitis

14. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromised the subject and/or places the subject at unacceptable risk in case of use of immuno-modulatory therapy

11. Patients on methotrexate (MTX) had to be on stable folic acid supplementation before randomization

12. Patients who were on a disease-modifying anti-rheumatic drug (DMARD) other than MTX or sulfasalazine must have discontinued the DMARD 4 weeks prior to randomization, except for leflunomide, which had to be discontinued for 8 weeks prior to randomization unless a cholestyramine washout had been performed

13. Patients taking systemic glucocorticoids had to be on a stable dose of ≤10 mg/day prednisone or equivalent for at least 2 weeks before randomization

15. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥160/95 mmHg), congestive heart failure (New York Heart

Association status of class III or IV), uncontrolled diabetes or very poor functional status precluding ability to perform self-care

16. History of clinically significant liver disease or liver injury indicated by abnormal liver function tests, such as SGOT (AST), SGPT (ALT), alkaline phosphatase, and serum bilirubin. The investigator was to be guided by the following criteria:

    a. Any single parameter may not exceed 2 x the upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization, to rule out laboratory error

    b. If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into direct and indirect reacting bilirubin

17. History of renal trauma, glomerulonephritis, or patients with one kidney only, or a serum creatinine level exceeding 1.5 mg/dl (132.6 µmol/L)

18. Screening total WBC count <3,000/µl, or platelets <100,000/µl or neutrophils <1,500/µl or hemoglobin <8.5 g/dl (85 g/L)

	19. Active systemic infections during the last 2 weeks (exception: common cold) prior to randomization
	20. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive purified protein derivative (PPD) skin test (the size of induration was measured after 48-72 hours, and a positive result was defined as an induration of ≥5 mm or according to local practice/guidelines) or a positive QuantiFERON TB-Gold test. Patients with a positive test were allowed to participate in the study if further work up (according to local practice/guidelines) established conclusively that the patient had no evidence of active tuberculosis. If presence of latent tuberculosis was established, then treatment according to local country guidelines had to be initiated
	21. Known infection with HIV, hepatitis B, or hepatitis C at screening or randomization
	22. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratosis that had been treated with no evidence of recurrence in the past 3 months, in situ carcinoma of the cervix or non-invasive malignant colon polyps that had been removed)
	23. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator rendered the subject unsuitable for the trial

	24. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins) 25. Any medical or psychiatric condition which, in the investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol 26. Blood donation or loss of 400 mL or more blood within 8 weeks before dosing 27. History or evidence of ongoing alcohol or drug abuse within the last 6 months before randomization 28. Plans for administration of live vaccines during the study period or 6 weeks prior to randomization

Supplementary Table 2. List of Institutional Review Boards (IRB) or Ethics Committees (IEC) by study center.

Study	Investigator	Center name	Center number	IRB/IEC name	IRB/IEC approval number
NCT01358175	A. Deodhar	Rheumatology Clinics, Oregon Health & Science University, Portland, US	5301	Institutional Review Board, Research Integrity Office, Oregon Health & Science University, Portland, US	# 28594
NCT01649375	J. Sieper	Charité University Medicine Berlin, Berlin, Germany	7011	Landesamt für Gesundheit und Soziales, Geschäftsstelle der Ethik-Komission des Landes Berlin, Fehrbelliner Platz 1, 10707 Berlin	12/0415 - ZS EK 12
NCT02008916	K. Pavelka	Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic.	1000	Ethics Committee on Clinical Trial on Human Medicinal Products, IKEM a Thomayerova nemocnice	5637/2013
NCT02159053	A.J. Kivitz	Altoona Center for Clinical Research, 175 Meadowbrook Lane, Duncansville, PA 16635	1357	Chesapeake Institutional Review Board, 6940 Columbia Gateway Drive, Suite 110 Columbia, MD 21046	SSU00027089

Supplementary Table 3. Baseline characteristics of patients without enthesitis.

Variable	Secukinumab		Placebo N = 109
	300 mg N = 18	150 mg N = 149	
Female, n (%)	3 (16.7)	25 (16.8)	21 (19.3)
Age in years, mean (SD)	43.9 (13.6)	40.1 (10.2)	43.7 (11.6)
Age in years, n (%) **<65** **≥65** **≥75**	16 (88.9) 2 (11.1) 0	147 (98.7) 2 (1.3) 0	104 (95.4) 5 (4.6) 1 (0.9)
Time since AS diagnosis, years, mean (SD)	7.5 (9.2)	7.2 (7.6)	8.6 (9.7)
Total BASDAI score, mean (SD)	6.9 (1.4)	6.4 (1.5)	6.4 (1.4)
HLA-B27, n (%)	14 (77.8)	123 (82.6)	89 (81.7)
hsCRP, median (min, max) mg/L	11.2 (1, 48)	8.4 (0, 216)	7.3 (0, 147)
Total BASMI (linear) score, mean (SD)	3.8 (2.0)	3.6 (1.8)	3.9 (1.6)
Total BASFI score, mean (SD)	6.7 (1.8)	5.7 (2.0)	5.7 (2.1)
Total ASDAS-CRP score, mean (SD)	3.9 (0.8)	3.7 (0.9)	3.7 (0.9)
Total ASDAS-ESR score, mean (SD)	3.9 (0.6)	3.7 (0.8)	3.7 (0.8)
Anti–TNF-naive, n (%)	5 (27.8)	33 (22.1)	31 (28.4)

N = total number of patients without enthesitis at baseline
AS, Ankylosing Spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; ESR, erythrocyte sedimentation rate; hsCRP, high sensitivity C-reactive protein; HLA,

human leukocyte antigen; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; max, maximum; min, minimum; SD, standard deviation; TNF, tumor necrosis factor