BJD
British Journal of Dermatology

Transition to ustekinumab in patients with moderate-to-severe psoriasis and inadequate response to methotrexate: a randomized clinical trial (TRANSIT)

C. Paul,[1] L. Puig,[2] K. Kragballe,[3] T. Luger,[4] J. Lambert,[5] S. Chimenti,[6] G. Girolomoni,[7] J.-F. Nicolas,[8] E. Rizova,[9] F. Lavie,[9] S. Mistry,[10] P. Bergmans,[11] J. Barker[12] and K. Reich,[13,14] on behalf of the TRANSIT Investigators*

[1]Hôpital Larrey, Service de Dermatologie, Toulouse cedex 9, 31059, France
[2]Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, 08025 Barcelona, Spain
[3]Department of Dermatology, Århus University Hospital, Århus Sygehus, 8000 Århus, Denmark
[4]Department of Dermatology, University of Münster, D-48149 Münster, Germany
[5]Department of Dermatology, Ghent University, 9000 Ghent, Belgium
[6]Policlinico Universitario Tor Vergata, Clinica Dermatologica, 00133 Rome, Italy
[7]Clinica Dermatologica, University of Verona, 37126 Verona, Italy
[8]Hospital Lyon-Sud, Lyon University, 69495 Lyon, France
[9]Janssen-Cilag 1, rue Camille Desmoulins, TSA 91003, 92787 Issy les Moulineaux, Cedex 9, France
[10]Janssen, 50-100 Holmers Farm Way, High Wycombe, Bucks HP12 4EG, U.K.
[11]Janssen-Cilag B.V., Postbus 90240, 5000 LT Tilburg, the Netherlands
[12]St John's Institute of Dermatology, King's College, London SE1 9RT, U.K.
[13]Dermatologikum Hamburg, Stephansplatz 5, 20354 Hamburg, Germany
[14]Georg-August-University, Göttingen, Germany

Summary

Background Limited data exist on transitioning patients with psoriasis from conventional systemic agents to biologics.
Objectives The TRANSIT study aimed to assess the efficacy and safety of two methotrexate-to-ustekinumab transition strategies.
Methods Patients with moderate-to-severe psoriasis and inadequate methotrexate response were randomized 1 : 1 to receive ustekinumab with immediate (arm 1) or 4-week gradual (arm 2) methotrexate withdrawal. Patients weighing ≤ 100 kg or > 100 kg received ustekinumab 45 mg or 90 mg, respectively. The primary endpoint was the frequency of adverse events (AEs) at week 12. Secondary endpoints included additional safety, efficacy and patient-reported outcomes. We report the 12-week efficacy and safety results.
Results Overall, 244 patients in arm 1 and 245 in arm 2 were randomized and received ustekinumab. Four patients per arm discontinued the trial by week 12. At week 12 in arms 1 and 2, respectively, 61% and 65% of patients experienced an AE, 2·9% and 2·4% had a serious AE, and 1·2% and 0·4% had an AE leading to ustekinumab discontinuation. In arms 1 and 2, respectively, median Psoriasis Area and Severity Index (PASI) score decreased from 15·2 and 15·4 at baseline to 2·9 and 2·8 at week 12; 58% and 62% of patients achieved a 75% reduction from baseline in PASI score (PASI 75) at week 12; median baseline Dermatology Life Quality Index fell from 8 and 9 at baseline to 1 (both arms) at week 16.
Conclusions Ustekinumab was well tolerated and effective in patients who had an inadequate response to methotrexate. Both transition strategies resulted in similar week 12 safety and efficacy outcomes.

Correspondence
Carle Paul.
E-mail: paul.c@chu-toulouse.fr

Accepted for publication
19 September 2013

*The members are TRANSIT Investigators presented in Appendix 1.

Funding sources
This clinical trial was sponsored by Janssen Pharmaceutica NV. Funding for medical writing support and assistance in collating author contributions was provided by Janssen.

Conflicts of interest
See Appendix 2 for details.

Clinicaltrials.gov identifier: NCT01059773.

DOI 10.1111/bjd.12646

What's already known about this topic?

- In patients with moderate-to-severe psoriasis, biologics are recommended for use after conventional systemic agents have failed, or in patients for whom they are not suitable.
- There are limited data on how to transition patients from conventional systemic treatment to biologics.

What does this study add?

- In patients with an inadequate response to methotrexate, similar efficacy and safety/tolerability outcomes were observed at week 12 after initiating ustekinumab, irrespective of whether methotrexate was immediately or gradually withdrawn. Therefore, immediate transitioning from methotrexate to ustekinumab can be recommended and a washout period is not needed.
- No adverse safety or efficacy effects were noted after overlapping ustekinumab and methotrexate treatment for up to 1 month.

In Europe, biological agents are recommended for use in patients with moderate-to-severe psoriasis after conventional systemic agents have failed, or in patients with contraindication to, or intolerance of, conventional therapy.[1] Therefore, in clinical practice, many patients who are started on a biologic will be receiving a conventional systemic agent, and, theoretically, there are several approaches that the dermatologist could use to achieve the transition from one agent to the other.

A 'washout' strategy is usually used in phase III clinical trials of biological agents, where it is important to distinguish the effect of the investigational agent from previously administered therapy. In the phase III clinical trials PHOENIX 1[2] and 2,[3] patients could not receive systemic therapy within 4 weeks of ustekinumab initiation. A shorter, 4–17-day washout has been explored in a small study where patients transitioned from etanercept, methotrexate or phototherapy to adalimumab.[4] However, the use of a washout period may not be practical in clinical practice, as symptoms could worsen during the 'no treatment' phase. Unfortunately, there are few evidence-based clinical data to support other transition strategies.

Two other transition strategies can be used when moving from conventional systemic to biological therapy. Overlapping treatment with both agents followed by gradual withdrawal of conventional therapy may be an appealing option as it provides continuous coverage with active treatment. Alternatively, patients could switch immediately from conventional therapy to the biologic. The TRANSIT (TRrial to Assess Naturalistic Safety and efficacy outcomes In patients Transitioned to ustekinumab from previous methotrexate therapy) trial is a 52-week study that aimed to investigate these two approaches in patients with moderate-to-severe psoriasis. Methotrexate was selected as the conventional systemic agent as it is widely used in Europe.[1] Patients were transitioned to ustekinumab, a human monoclonal antibody targeting interleukin (IL)-12 and IL-23. In patients who were randomized to an overlapping phase of methotrexate and ustekinumab, a 4-week methotrexate-tapering phase was considered adequate given the rapid onset of efficacy reported with ustekinumab.[5]

We describe the primary analysis of the TRANSIT trial; the primary endpoint was safety at week 12 in patients who transitioned to ustekinumab using these two strategies. In addition, efficacy outcomes at week 12 and patient-reported outcomes at week 16 are reported. The 52-week outcomes of the study, including the effect of dose adjustment on efficacy, are presented in a separate article.[6]

Materials and methods

Patients and study design

TRANSIT was a 52-week, phase IV, open-label, parallel-group, randomized clinical trial conducted at 86 centres in Europe and Israel. The study investigators enrolled adult patients with moderate-to-severe plaque psoriasis (concurrent psoriatic arthritis was allowed), defined as a Psoriasis Area and Severity Index (PASI) score ≥ 10 at screening and at the time of first administration of ustekinumab, and a diagnosis of plaque psoriasis for ≥ 6 months. Patients had to have an inadequate response (PASI ≥ 10) to a methotrexate regimen of 10–25 mg weekly for eight or more consecutive weeks and, in the judgement of the treating physician and patient, required a treatment change. Patients were ineligible if they had an active/chronic/recurrent infection or recent serious infection, a history or symptoms of active or latent tuberculosis, a history of malignancy (except *in situ* basal or squamous cell skin carcinoma; treated *in situ* cervical carcinoma with no evidence of recurrence; or treated squamous cell skin carcinoma with no evidence of recurrence within 5 years), or had received treatment with any agent that specifically targeted IL-12 and IL-23, any biological therapy within 12 weeks, any B/T cell-inhibitory agents (or had evidence of persistent lymphocyte depletion), topical psoriasis treatments (except low-potency topical

corticosteroids), systemic psoriasis treatments other than methotrexate, or phototherapy within 2 weeks.

Patients were randomized 1 : 1 to receive ustekinumab (Stelara®; Janssen-Cilag International NV, Beerse, Belgium) either with immediate withdrawal of methotrexate (arm 1) or with 4 weeks' overlap with a tapering methotrexate regimen (arm 2). Randomization was according to a computer-generated central schedule prepared by the study sponsor and based on a minimization with biased-coin assignment method. Patients were assigned via an interactive voice-response system and randomization was stratified by site and patient weight (≤ 100 kg or > 100 kg). Ustekinumab was initiated according to the European Summary of Product Characteristics,[7] with weight-based doses given subcutaneously at weeks 0, 4, 16, 28 and 40. Patients weighing > 100 kg received ustekinumab 90 mg at each time point; patients weighing ≤ 100 kg received 45 mg initially. In arm 1, the last methotrexate dose was received during the week before the first ustekinumab injection. In arm 2, the predefined methotrexate dose-reduction schedule depended on the dose at screening. For example, patients receiving methotrexate 25 mg weekly at screening were to decrease the dose to 20 mg at day 0 and then by 5 mg each week, whereas those receiving 10 mg weekly at screening were to reduce this to 5 mg at day 0 and then by 2·5 mg every 2 weeks. All patients had to stop methotrexate within 7 days before the second ustekinumab injection (scheduled for week 4) irrespective of the final methotrexate dose. Low-potency topical corticosteroids being taken at stable doses for ≥ 4 weeks prior to screening could be continued.

In a protocol amendment, an exploratory dose-adjustment schedule was investigated at weeks 28 and 40, with findings described elsewhere;[6] planned enrolment was also increased from 500 to 576 to account for premature discontinuations. The clinical trial protocol was approved by the appropriate institutional review boards in each participating country, and the trial was performed in accordance with Good Clinical Practice. All patients provided written informed consent. The clinical trial was registered with clinicaltrials.gov (NCT01059773).

Assessments

Study visits were planned at weeks 0, 2, 4, 12, 16, 28, 40 and 52. Patients underwent physical examination and routine laboratory testing, including testing for tuberculosis, at screening. Efficacy evaluations included PASI score (0–72) and the Physician's Global Assessment (PGA; 0–5), which were performed at every study visit. In addition to absolute scores, PASI responses were defined as 50%, 75%, 90% or 100% reductions from baseline (PASI 50, 75, 90, 100, respectively); additionally, absolute PASI scores were categorized by PASI score ≤ 1, ≤ 3 or ≤ 5. Quality-of-life assessments were carried out at weeks 0, 4, 16, 28 and 52 and included the Dermatology Life Quality Index (DLQI),[8] EuroQol-5D visual analogue scale (EQ-5D VAS)[9] and Hospital Anxiety and Depression Scale (HADS).[10] Routine safety evaluations included the assessment of vital signs, treatment-emergent adverse events (AEs), and standard laboratory investigations. AEs spontaneously reported by the patient were recorded throughout the trial. Any clinically significant AEs present at the end of the study were followed up until clinically stable or resolved. Haematology, serum chemistry and pregnancy testing were performed by a central laboratory (Covance, Geneva, Switzerland).

Statistical analyses

The primary endpoint was the proportion of patients experiencing one or more AE(s) by week 12 in each treatment arm. Secondary outcome measures included additional safety, efficacy and patient-reported outcomes at weeks 12 or 16, over the 52-week trial period, and following exploratory dose adjustment (reported elsewhere[6]). No interim analyses were conducted.

A sample size of 576 patients (288 patients per arm) was calculated to give ~80% power to detect a significant difference between treatment arms if there was a 1·21-fold difference in AEs, a 2·0-fold difference in treated infections, and a 4·1-fold difference in serious AEs (SAEs). The calculation was based on a two-sided Fisher's exact test with a type I error rate of 0·05, and on safety data from the ustekinumab clinical development programme. However, the planned sample size of 576 patients was not reached (489 patients were enrolled, randomized and received at least one dose of study drug). Nevertheless, the slight decrease of power associated with this reduction in the number of patients was considered to be within acceptable limits because of the low number of dropouts observed to week 12.

All assessments were summarized using descriptive statistics. Efficacy analyses included patients with a valid measurement (observation) at the relevant time point and excluded patients who did not have a baseline and at least one postbaseline observation. Confirmatory last-observation-carried-forward (LOCF) imputed analyses were performed for some efficacy endpoints. Formal statistical hypotheses were not prespecified and statistical comparisons between treatment arms were not performed.

Results

Patient disposition and baseline characteristics

From 19 October 2009 to 23 August 2010, 649 patients with moderate-to-severe plaque psoriasis were screened, 490 were enrolled and randomized, and 489 received at least one dose of study drug [intent-to-treat population (Fig. S1, Support Information)]. Planned study enrolment was not reached due to delays in recruitment that could have put the execution of the study at risk. Overall, 391 patients (195 in arm 1; 196 in arm 2) weighed ≤ 100 kg and received ustekinumab 45 mg, while 98 patients (49 in each arm) weighed > 100 kg and received the 90-mg dose. Few patients (8; 1·6%) discontinued therapy by week 12.

Patients' baseline characteristics were well balanced between treatment arms (Table 1). At baseline, patients had a median PASI score of 15 (interquartile range 12–20), 25% had a PGA of 4 or 5 (marked or severe), and 26% had a diagnosis of psoriatic arthritis. Median DLQI was 8 at baseline, indicating that the condition had a moderate effect on the patients' quality of life.[11] Median EQ-5D VAS was 70, slightly lower than population norms for European countries (72–83),[12] and approximately one-quarter of patients had clinically relevant anxiety and/or depression according to HADS (HADS ≥ 8).[13] Mean methotrexate dose at screening was 14·5 mg weekly; 59% of patients had previously used methotrexate for < 1 year, 28% for 1 to < 3 years, and 13% for ≥ 3 years. Among the 29% of patients who had previously used a biologic, the most common reason for having discontinued it was lack of efficacy (82 patients; 59%).

Table 1 Baseline patient characteristics according to treatment arm

Baseline characteristic[a]	Arm 1: ustekinumab with immediate methotrexate withdrawal (n = 244)	Arm 2: ustekinumab with gradual methotrexate withdrawal (n = 245)
Age (years), mean (SD)	45 (12)	47 (13)
Male, n (%)	170 (70)	162 (66)
Weight (kg), mean (SD)	86 (20)	85 (19)
BMI (kg m^{-2}), mean (SD)	28 (5·5)	28 (5·5)
Diagnosis of psoriatic arthritis, n (%)	55 (23)	71 (29)
Duration of prior methotrexate use (years) (n = 243, 245), n (%)		
< 1	147 (61)	139 (57)
≥ 1 and < 3	62 (26)	75 (31)
≥ 3	34 (14)	31 (13)
Methotrexate dose at screening (mg weekly) (n = 243, 244), mean (SD)	14·6 (3·8)	14·4 (4·1)
Received ≥ 1 previous biologic (n = 244, 245),[b] n (%)	73 (30)	67 (27)
PASI (n = 244, 243), median (Q1, Q3)	15·2 (12, 20)	15·4 (12, 19)
PGA 0 or 1 (cleared or minimal) (n = 242, 242),[c] n (%)	1 (0·4)	1 (0·4)
PGA 4 or 5 (marked or severe) (n = 242, 242), n (%)	64 (26)	58 (24)
DLQI (n = 242, 241), median (Q1, Q3)	8 (4, 14)	9 (4, 14)
EQ-5D VAS (n = 190, 197), median (Q1, Q3)	70 (50, 80)	70 (50, 85)
HADS-A (n = 235, 238), median (Q1, Q3)	5 (3, 8)	5 (3, 9)
HADS-D (n = 233, 238), median (Q1, Q3)	3 (1, 6)	4 (1, 7)

BMI, body mass index; DLQI, Dermatology Life Quality Index; EQ-5D VAS, EuroQol-5D visual analogue scale; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; Q1, lower quartile; Q3, upper quartile. [a]Where data are not available for all patients, numbers of patients are given in parentheses for arms 1 and 2, respectively; [b]including infliximab (83 patients), etanercept (64 patients), adalimumab (51 patients), efalizumab (39 patients) and alefacept (1 patient); [c]one patient in arm 1 had a PGA score of 1 and a PASI score of 11, one patient in arm 2 had a PGA score of 1 and a PASI score of 13.

Efficacy

Psoriasis Area and Severity Index scores decreased rapidly and substantially from baseline and were similar at week 12 irrespective of the transition strategy used (Fig. 1). A similar proportion of patients in the two treatment arms achieved an absolute PASI score of ≤ 1, ≤ 3 or ≤ 5 (Fig. 2a) and PASI 50, 75, 90 or 100 responses (Fig. 2b) at week 12. A PGA of 0 or 1 was achieved by most patients [156 of 239 (65%) patients in arm 1 and 164 of 236 (69%) patients in arm 2] at week 12 irrespective of the transition strategy used. PASI and PGA scores were similar in confirmatory LOCF analyses (Table 2).

Safety

The safety and tolerability profile of ustekinumab at week 12 was similar irrespective of the transition strategy used (Table 3). At least one AE was reported for 149 (61%) and 158 (65%) patients in arms 1 and 2, respectively. The number of patients with an SAE [seven (2·9%) and six (2·4%) patients, respectively] or an AE leading to discontinuation of ustekinumab [three (1·2%) and one (0·4%) patients, respectively] was low.

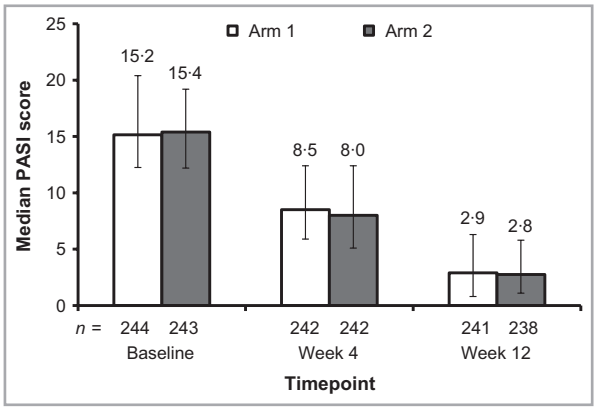

Fig 1. Median Psoriasis Area and Severity Index (PASI) score at baseline, week 4 and week 12 after starting ustekinumab in arm 1 (immediate withdrawal of methotrexate) or arm 2 (gradual methotrexate withdrawal). Values for each data point are shown above the error bars, and error bars represent interquartile ranges.

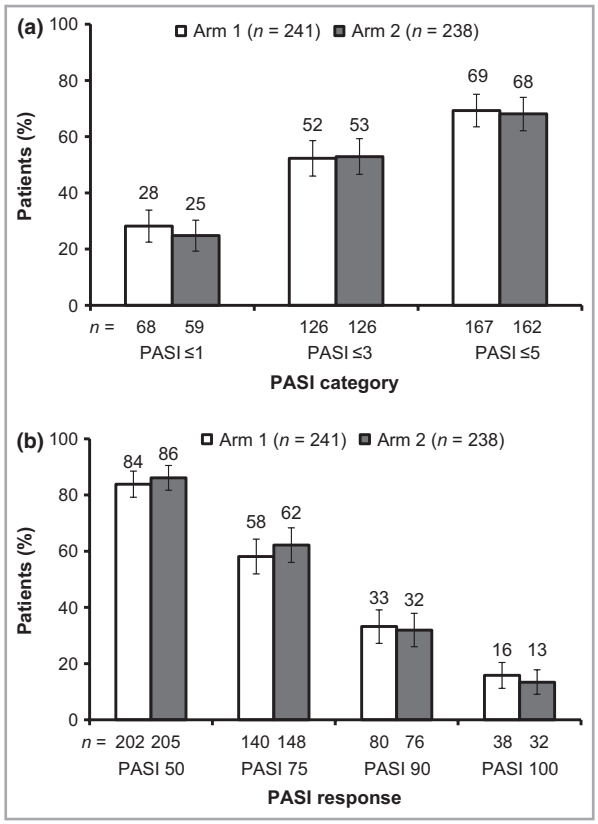

Fig 2. Proportion of patients achieving (a) Psoriasis Area and Severity Index (PASI) score ≤ 1, ≤ 3 or ≤ 5 or (b) a reduction from baseline of 50% (PASI 50), 75% (PASI 75), 90% (PASI 90) or 100% (PASI 100) at 12 weeks after starting ustekinumab in arm 1 (immediate withdrawal of methotrexate) or arm 2 (gradual methotrexate withdrawal). Values for each data point are shown above the error bars, and error bars represent 95% confidence intervals.

Some investigators reported psoriasis as an AE, based on their clinical judgement (Table 3), and this was reported more often for patients in the gradual withdrawal arm than with immediate withdrawal. Five patients in the gradual withdrawal arm and two patients in the immediate withdrawal arm had PASI ≥ 25% higher at week 2 and/or week 4 than at baseline. One patient in the immediate withdrawal arm experienced psoriasis as an SAE, but this occurred > 2 months after starting ustekinumab. The most commonly reported AEs were headache, nasopharyngitis, arthralgia, hypertension and pruritus. By week 12, no deaths occurred and the only SAE reported in more than one patient was abdominal pain, occurring in two patients.

One patient had acute hepatitis B that was classified as an AE of special interest and a serious infection. After appropriate treatment, the hepatologist considered the condition under control and liver biochemistry was normal; a case study is presented elsewhere.[14] No other AEs of special interest, such as nonmelanoma skin cancer, malignancies or major adverse cardiovascular events (MACE), were reported by week 12 (Table 3). The incidence of infections was similar irrespective of the transition strategy used; the majority of these were minor and did not require treatment with antibiotics (Table 3). There was no obvious difference between the two treatment arms in changes in the liver enzymes, alanine aminotransferase (ALT) or aspartate aminotransferase (AST). However, in both arms, a general decrease in ALT was seen. At baseline, median ALT levels were 28 U L^{-1} in both treatment arms, decreasing at week 4 (to 25 and 26 U L^{-1} in the immediate and gradual withdrawal arms, respectively), but then remaining constant in both arms up to week 12 (25 U L^{-1}). Consistent with median change, in both arms there was a decrease in the proportion of patients with elevated ALT or AST, along with an increase in the proportion of patients with low ALT or AST (≤ 1 × the upper limit of normal) (Fig. 3).

Patient-reported outcomes

Median DLQI was substantially reduced between baseline and week 16, and a high proportion of patients achieved a ≥ 5-

Table 2 Observed and last-observation-carried-forward (LOCF) imputed data for Psoriasis Area and Severity Index (PASI) score and Physician's Global Assessment (PGA) at week 12

	Arm 1: ustekinumab with immediate methotrexate withdrawal		Arm 2: ustekinumab with gradual methotrexate withdrawal	
	Observed data	LOCF imputed data	Observed data	LOCF imputed data
PASI				
n	241	244	238	243
Mean (SD)	4·4 (5·0)	4·6 (5·3)	4·2 (4·3)	4·4 (4·4)
95% confidence interval	3·8–5·1	3·9–5·2	3·7–4·8	3·8–4·9
Median (Q1, Q3)	2·9 (0·8, 6·3)	2·9 (0·9, 6·5)	2·8 (1·1, 5·8)	2·8 (1·2, 6·0)
Range (min.–max.)	0·0–33	0·0–33	0·0–20	0·0–20
PGA				
n	239	242	236	242
Mean (SD)	1·2 (0·9)	1·4 (0·9)	1·2 (0·8)	1·2 (0·9)
95% confidence interval	1·1–1·4	1·1–1·4	1·1–1·3	1·1–1·3
Median (Q1, Q3)	1·0 (1·0, 2·0)	1·0 (1·0, 2·0)	1·0 (1·0, 2·0)	1·0 (1·0, 2·0)
Range (min.–max.)	0·0–4·0	0·0–4·0	0·0–4·0	0·0–4·0

Table 3 Overall safety profile, most common treatment-emergent adverse events (AEs) and serious AEs (SAEs) at 12 weeks after initiation of ustekinumab, according to treatment arm

	Arm 1: ustekinumab with immediate methotrexate withdrawal (n = 244)	Arm 2: ustekinumab with gradual methotrexate withdrawal (n = 245)
Overall safety profile		
Any AE	149 (61)	158 (65)
Any SAE	7 (2·9)	6 (2·4)
Discontinuation of ustekinumab due to AEs[a]	3 (1·2)	1 (0·4)
Death	0	0
Psoriasis worsening reported as an AE		
Psoriasis as an AE	4 (1·6)	8 (3·3)
Psoriasis as an SAE (psoriasis exacerbation)	1 (0·4)	0
Most common[b] AEs by system organ class		
Nervous system disorders		
Headache	26 (10·7)	24 (9·8)
Respiratory, thoracic and mediastinal disorders		
Nasopharyngitis	27 (11)	19 (7·8)
Cough	4 (1·6)	6 (2·4)
Rhinitis	4 (1·6)	6 (2·4)
Oropharyngeal pain	3 (1·2)	5 (2·0)
Musculoskeletal and connective tissue disorders		
Arthralgia	15 (6·1)	14 (5·7)
Myalgia	4 (1·6)	6 (2·4)
Skin and subcutaneous tissue disorders		
Pruritus	6 (2·5)	12 (4·9)
Generalized pruritus	4 (1·6)	2 (0·8)
Gastrointestinal disorders		
Diarrhoea	6 (2·5)	7 (2·9)
Gastroenteritis	6 (2·5)	2 (0·8)
General disorders and administration-site conditions		
Pyrexia	1 (0·4)	7 (2·9)
Infections and infestations		
Oral herpes	2 (0·8)	5 (2·0)
Upper respiratory tract infection	2 (0·8)	5 (2·0)
Vascular disorders		
Hypertension	11 (45)	12 (49)
Laboratory investigations		
Blood creatine phosphokinase increased	4 (1·6)	5 (2·0)
Alanine aminotransferase increased	1 (0·4)	5 (2·0)
SAEs[c]		
Abdominal pain	0	2 (0·8)
Alcoholism	1 (0·4)	0
Ankle fracture	1 (0·4)	0
Deep vein thrombosis	0	1 (0·4)
Drug hypersensitivity[d]	0	1 (0·4)
Foot fracture	1 (0·4)	0
Headache	1 (0·4)	0
Hepatitis B	1 (0·4)	0
Hypertension	0	1 (0·4)
Joint dislocation	1 (0·4)	0
Uterine polyp	0	1 (0·4)
AEs of special interest		
Serious infections[e]	1 (0·4)	0
Nonmelanoma skin cancer	0	0
Malignancies	0	0
MACEs[f]	0	0
Infections and infections requiring antibiotics[g]		
Infections	49 (20)	53 (22)
Infections requiring antibiotics	18 (7·4)	14 (5·7)

Data are presented as n (%). MACE, major adverse cardiovascular event. [a]Discontinuation (n = 4) due to: AE temporally associated with study (n = 1 in each arm); severe injection-site reaction or infection classified as a serious AE (n = 1 in arm 1), and investigator or sponsor decision (n = 1 in arm 1). [b]Most common AEs (by MedDRA preferred term) occurring in ≥ 5 patients in any treatment group from baseline to week 12 and excluding psoriasis. [c]SAEs from baseline to week 12 and excluding psoriasis. [d]The patient was hospitalized with suspected laryngeal dyspnoea and cutaneous eruptions, reported by the investigator as induced by amoxicillin. [e]One case of acute hepatitis B, with elevated liver enzymes detected at study week 2; the patient was negative for hepatitis B surface antigen antibodies at screening but was not tested for hepatitis B core antigen antibodies. [f]MACEs comprise myocardial infarction, cerebrovascular accident and any-cause cardiovascular death. [g]Infections and infections requiring antibiotics irrespective of whether these were serious enough to be reported as AEs.

point reduction in DLQI or a DLQI of 0 or 1 at week 16, irrespective of the transition strategy used (Table 4). EQ-5D VAS and HADS showed a small improvement by week 16 (Table 4).

Discussion

The TRANSIT study is the first evidence-based assessment of strategies for transitioning patients with moderate-to-severe psoriasis from a conventional systemic agent to a biological agent without a 'no treatment' washout period. In patients with an inadequate response to methotrexate, we showed similar efficacy after initiating ustekinumab irrespective of whether methotrexate was immediately or gradually withdrawn. Similarly, both an immediate switch from methotrexate to ustekinumab and an overlapping 4-week methotrexate-tapering strategy were well tolerated, with low discontinuation rates. Therefore, either immediate or gradual transition is a feasible approach in patients switching from methotrexate to ustekinumab. This has important implications for the day-to-day clinical management of patients, confirming that a

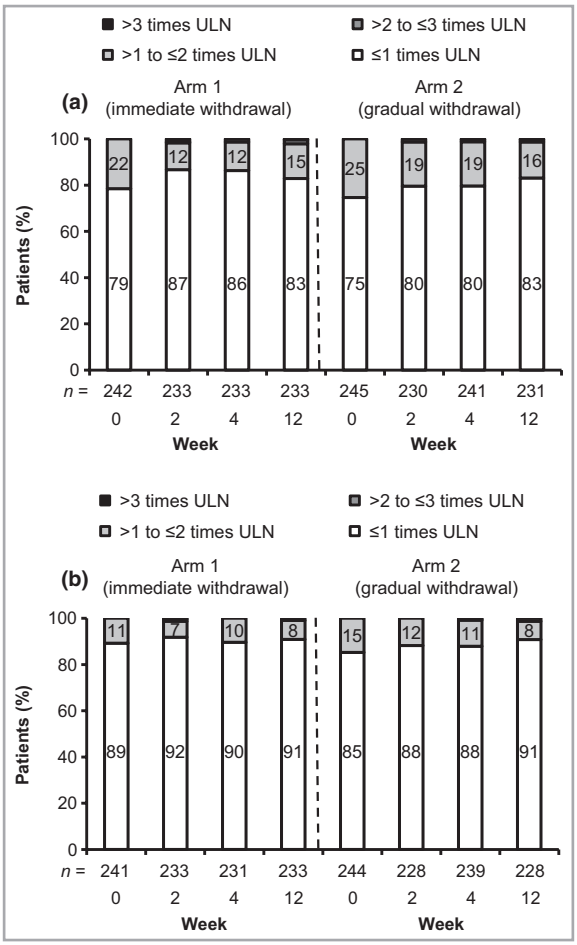

Fig 3. The proportion of patients with (a) alanine aminotransferase or (b) aspartate aminotransferase levels according to categories above the upper limit of normal (ULN) over time from baseline to 12 weeks after starting ustekinumab in arm 1 (immediate withdrawal of methotrexate) or arm 2 (gradual methotrexate withdrawal). The proportion of patients within each of the two lower level categories is shown within each bar.

Table 4 Patient-reported outcomes at 16 weeks after initiation of ustekinumab, according to treatment arm

Patient-reported outcome	Arm 1: ustekinumab with immediate methotrexate withdrawal	Arm 2: ustekinumab with gradual methotrexate withdrawal
DLQI, median (Q1, Q3)		
n	234	238
Baseline	8 (4, 14)	9 (4, 14)
Week 16	1 (0, 4)	1 (0, 4)
DLQI decrease, n (%)		
n	234	238
Reduction of ≥ 5 points by week 16[a]	134 (57)	142 (60)
DLQI 0 or 1, n (%)		
n	234	238
Baseline	19 (8)	17 (7)
Week 16	131 (56)	137 (58)
EQ-5D VAS, median (Q1, Q3)		
n	189	194
Baseline	70 (50, 80)	70 (50, 85)
Week 16	80 (65, 90)	80 (70, 90)
HADS-Anxiety, median (Q1, Q3)		
n	232	237
Baseline	5 (3, 8)	5 (3, 9)
Week 16	4 (2, 8)	4 (2, 7)
HADS-Depression, median (Q1, Q3)		
n	231	237
Baseline	3 (1, 6)	4 (1, 7)
Week 16	2 (1, 5)	2 (1, 4)

DLQI, Dermatology Life Quality Index; EQ-5D VAS, EuroQol-5D visual analogue scale; HADS, Hospital Anxiety and Depression Scale; Q1, lower quartile; Q3, upper quartile. [a]At baseline, 140 patients [70 per arm (each 29%)] had a DLQI score of <5 and, therefore, could not achieve a DLQI reduction of ≥5.

washout period or methotrexate-tapering strategy are not necessary when switching from methotrexate to ustekinumab in patients with an inadequate response to methotrexate. The pragmatic approach tested in this study is closer to real-life clinical situations than the regimens usually tested in clinical trials and our data support the simplification of transition strategies for these patients.

Timing of drug administration in our study should be noted. After stopping methotrexate, the time to relapse has been reported as 4–5 weeks[15] and the effect of ustekinumab is rapid.[5] This suggests that patients would receive sufficient exposure to active therapy throughout both the early and later weeks of ustekinumab treatment, which was supported by this study. Similarly, in this analysis, the rate of AEs was not higher among patients who received overlapping treatment than in patients who stopped methotrexate immediately. This might be partly because the methotrexate dose was rapidly reduced in the gradual withdrawal arm. However, our results do not indicate a need for longer overlap periods.

Overall, the safety and tolerability profile was consistent with previous ustekinumab studies.[2,3,7,16] Very few patients discontinued treatment before week 12. Methotrexate is known to be hepatotoxic,[17] therefore it is not surprising that liver enzyme levels tended to decrease during and after withdrawal of methotrexate. This may also explain why an increase in ALT tended to be more frequently reported as an AE in the gradual vs. immediate methotrexate withdrawal arm. Ustekinumab showed substantial efficacy at week 12, with 69%, 53% and 27% of patients, overall, achieving an absolute PASI score ≤ 5, ≤ 3 and ≤ 1, respectively, in this population of patients with inadequate response to methotrexate at baseline and of which a notable proportion had received prior biological treatment (29%) or a diagnosis of psoriatic arthritis (26%). A slightly lower proportion (60%) of patients achieved PASI 75 at week 12 in this study than in the phase III ustekinumab clinical trials (64–76% in PHOENIX 1 and 2).[2,3]

This can primarily be explained by differences in baseline PASI scores due to differences in study design (use of a washout period in the PHOENIX trials) and inclusion criteria (PASI threshold ≥ 10 in TRANSIT vs. ≥ 12 in the PHOENIX trials). As a washout was not used in TRANSIT, baseline PASI may represent partially treated psoriasis. In addition, all patients in TRANSIT had previously shown an inadequate response to methotrexate, and could therefore be considered more treatment refractory than the patients enrolled in the PHOENIX trials. It should also be noted that PASI is not linear[18,19] and, therefore, comparisons of percentage reductions between trials may have limited validity. Indeed, a similar or higher proportion of patients achieved PGA 0 or 1 at week 12 in this study (67%) compared with PHOENIX 1 (60–62%) or 2 (68–73%).[2,3] Additionally, it is encouraging to note that during this 12-week study period there was no increased incidence of MACE, not inconsistent with the available clinical data,[20,21] suggesting neither a detrimental nor a beneficial effect of ustekinumab on serious cardiovascular events.

Psoriasis has a negative effect on a patient's quality of life.[22] In TRANSIT, patient-reported outcomes were assessed at week 16 (rather than at week 12) as this is when the third dose is given, and when the decision to continue treatment is often made in clinical practice.[23] In addition, national healthcare organizations, such as the U.K. National Institute for Health and Care Excellence, define stopping rules for ustekinumab at week 16 on the basis of PASI and DLQI outcomes.[24] This is in contrast to the European Summary of Product Characteristics,[7] which states that consideration should be given to discontinuing treatment in the case of nonresponse at week 28. In TRANSIT, more than half of patients achieved a clinically meaningful[25] ≥ 5-point reduction in DLQI, or a DLQI score of 0 or 1 indicating no effect of the disease at all on the patients' quality of life[26] at week 16, irrespective of the transition strategy used. EQ-5D VAS and HADS both showed a small improvement from baseline to week 16, but baseline scores were within or close to the 'normal' range for both scales; population norms for EQ-5D VAS are around 72–83 for European countries,[12] and a HADS of ≥ 8 on either scale can be considered clinically relevant anxiety/depression.[13] By this definition, approximately one-quarter of patients in TRANSIT had clinically relevant anxiety and/or depression at baseline, a similar proportion to that reported in PHOENIX 2.[27]

Although our findings are useful in the clinical setting, this study has some limitations: a nonustekinumab comparator arm was not included; psoriatic arthritis was not assessed during the trial; there was no dose-adjustment possibility for patients weighing > 100 kg in this study; the planned sample size of 576 patients was not reached and, therefore, statistical power to detect a difference between treatment arms would be limited; we cannot exclude the possibility that different transition strategies and inclusion or exclusion criteria would yield different results; and we collected only categorical data on the duration of prior methotrexate use (< 1 year, 1 to < 3 years and ≥ 3 years). In addition, as there was no washout, it is possible that the baseline PASI score (absolute) could have been influenced by prior treatment with methotrexate. Finally, albeit not addressed in this study, adding ustekinumab to methotrexate may be a potential option for patients, and examining this combination in the long-term could be merited.

Taken together, our data demonstrate that either an immediate or a gradual transition from methotrexate to ustekinumab is a feasible approach in patients with an inadequate response to methotrexate; a washout period or methotrexate-tapering strategy is not necessary. Ustekinumab showed favourable efficacy and tolerability, irrespective of whether methotrexate was immediately or gradually withdrawn. Both of these transition scenarios are highly relevant in day-to-day clinical practice.

Acknowledgments

The authors thank the study coordinators, nurses and patients involved in the trial. We also thank Tamara Borie (Parexel International) who performed the statistical analyses, and Pavel Smirnov and Lynne Douglas (both at Janssen Pharmaceutica NV), who were responsible for the day-to-day management of the trial. We acknowledge Joanne Williams and David Evans (Gardiner-Caldwell Communications) for medical writing support and assistance in collating author contributions.

References

1 Pathirana D, Ormerod AD, Saiag P *et al.* European S3-guidelines on the systemic treatment of psoriasis vulgaris. *J Eur Acad Dermatol Venereol* 2009; **23**(Suppl. 2):1–70.

2 Leonardi CL, Kimball AB, Papp KA *et al.* Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008; **371**:1665–74.

3 Papp KA, Langley RG, Lebwohl M *et al.* Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008; **371**:1675–84.

4 Strober BE, Poulin Y, Kerdel FA *et al.* Switching to adalimumab for psoriasis patients with a suboptimal response to etanercept, methotrexate, or phototherapy: efficacy and safety results from an open-label study. *J Am Acad Dermatol* 2011; **64**:671–81.

5 Krueger GG, Langley RG, Leonardi C *et al.* A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. *N Engl J Med* 2007; **356**:580–92.

6 Reich K, Puig L, Paul C *et al.* One-year safety and efficacy of ustekinumab and results of dose adjustment after switching from inadequate methotrexate treatment: the TRANSIT randomized trial in moderate-to-severe plaque psoriasis. *Br J Dermatol* 2014; **170**: 435–444.

7 European Medicines Agency. Ustekinumab. Summary of Product Characteristics, updated September 2013. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000958/human_med_001065.jsp&mid=WC0b01ac058001d125&murl=menus/medicines/medicines.jsp (last accessed 13 November 2013).

8 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19**:210–16.
9 EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16**:199–208.
10 Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983; **67**:361–70.
11 Cardiff University. Dermatology Life Quality Index (DLQI). Frequently Asked Questions (FAQs), 2012. Available at: http://www.dermatology.org.uk/quality/dlqi/quality-dlqi-faqs.html (last accessed 13 November 2013).
12 EuroQol Group. Measuring self-reported population health: an international perspective based on EQ-5D, 2004. Available at: http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Books/Measuring_Self-Reported_Population_Health_-_An_International_Perspective_based_on_EQ-5D.pdf (last accessed 13 November 2013).
13 Bjelland I, Dahl AA, Haug TT *et al.* The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002; **52**:69–77.
14 Opel D, Economidi A, Chan D *et al.* Two cases of hepatitis B in patients with moderate-to-severe psoriasis with ustekinumab. *J Drugs Dermatol* 2012; **11**:1498–501.
15 de Jong EM, Mørk NJ, Seijger MM *et al.* The combination of calcipotriol and methotrexate compared with methotrexate and vehicle in psoriasis: results of a multicentre placebo-controlled randomized trial. *Br J Dermatol* 2003; **148**:318–25.
16 Griffiths CE, Strober BE, van de Kerkhof P *et al.* Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med* 2010; **362**:118–28.
17 European Medicines Agency. Methotrexate. Summary of Product Characteristics, updated July 2012. Available at: http://www.medicines.org.uk/emc/medicine/12034/SPC/ (last accessed 13 November 2013).
18 Berth-Jones J, Thompson J, Papp K; Copenhagen Psoriasis Working Group. A study examining inter-rater and intrarater reliability of a novel instrument for assessment of psoriasis: the Copenhagen Psoriasis Severity Index. *Br J Dermatol* 2008; **159**:407–12.
19 Gourraud PA, Le Gall C, Puzenat E *et al.* Why statistics matter: limited inter-rater agreement prevents using the Psoriasis Area and Severity Index as a unique determinant of therapeutic decision in psoriasis. *J Invest Dermatol* 2012; **132**:2171–5.
20 McInnes IB, Kavanaugh A, Gottlieb AB *et al.* Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet* 2013; **382**:780–9.
21 Reich K, Langley RG, Lebwohl M *et al.* Cardiovascular safety of ustekinumab in patients with moderate-to-severe psoriasis: results of integrated analyses of data from phase II and III clinical studies. *Br J Dermatol* 2011; **164**:862–72.
22 Heller MM, Wong JW, Nguyen TV *et al.* Quality-of-life instruments: evaluation of the impact of psoriasis on patients. *Dermatol Clin* 2012; **30**:281–91.
23 Mrowietz U, Kragballe K, Reich K *et al.* Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res* 2011; **303**:1–10.
24 National Institute for Health and Care Excellence. Ustekinumab for the treatment of adults with moderate to severe psoriasis, August 2009. Available at: http://www.nice.org.uk/nicemedia/live/12038/45160/45160.pdf (last accessed 13 November 2013).
25 Khilji FA, Gonzalez M, Finlay AY. Clinical meaning of change in Dermatology Life Quality Index scores. *Br J Dermatol* 2002; **147** (Suppl. 62):50.
26 Hongbo Y, Thomas CL, Harrison MA *et al.* Translating the science of quality of life into practice: what do Dermatology Life Quality Index scores mean? *J Invest Dermatol* 2005; **125**:659–64.
27 Langley RG, Feldman SR, Han C *et al.* Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-severe psoriasis: results from a randomized, double-blind, placebo-controlled phase III trial. *J Am Acad Dermatol* 2010; **63**:457–65.

Appendix 1

TRANSIT Principal Investigators

Z. Adamski (Poznań, Poland); G. Altomare (Milano, Italy); M. Aricò (Palermo, Italy); N. Aste (Cagliari, Italy); F. Aubin (Besançon, France); M. Augustin (Hamburg, Germany); F. Ayala (Napoli, Italy); H. Bachelez (Paris, France); E. Baran (Wrocław, Poland); J. Barker (London, England); I. Belinchón (Alicante, Spain); P. Berbis (Marseille, France); M.G. Bernengo (Torino, Italy); D. Bessis (Montpellier, France); M. Beylot-Barry (Pessac, France); F.J. Bordas Orpinell (Barcelona, Spain); D. Burden (Glasgow, Scotland); M. Bylaite (Vilnius, Lithuania); F. Cambazard (St Priest-En-Jarez, France); S. Carazo (Valencia, Spain); J.M. Carrascosa (Barcelona, Spain); G. Carretero (Las Palmas De Gran Canaria, Spain); R. Cerio (London, England); S. Chimenti (Rome, Italy); M. David (Petah-Tikva, Israel); A.B. Duval-Modeste (Rouen, France); D. Eedy (Portadown, Northern Ireland); L. Estebaranz (Madrid, Spain); P. Filipe (Lisbon, Portugal); I. Flytström (Göteborg, Sweden); E. Fonseca (A Coruña, Spain); R. Gamanya (Cardiff, Wales); P.-D. Ghislain (Woluwe-Saint-Lambert, Belgium); A. Giannetti (Modena, Italy); G. Girolomoni (Verona, Italy); D. Gospodinov (Pleven, Bulgaria); C. Griffiths (Manchester, England); J.-J. Grob (Marseille, France); G. Guillet (Poitiers, France); J.M. Hernanz Hermosa (Madrid, Spain); M. Hoffmann (Witten, Germany); D. Ioannidis (Thessaloniki, Greece); A. Jacobi (Marburg, Germany); G. Jemec (Roskilde, Denmark); M. Kadurina (Sofia, Bulgaria); K. Kaszuba (Łódź, Poland); A. Katsambas (Athens, Greece); L. Kemeny (Szeged, Hungary); P. Kerkhof (Nijmegen, the Netherlands); K. Kragballe (Århus, Denmark); N. Kuzmina (Stockholm, Sweden); K. Lambert (Ghent, Belgium); P. Lázaro (Madrid, Spain); T. Lotti (Firenze, Italy); T. Luger (Münster, Germany); H. Matz (Tel Aviv, Israel); P. Modiano (Lille, France); R. Moessner (Göttingen, Germany); D. Moreno (Sevilla, Spain); J.C. Moreno Jímenez (Córdoba, Spain); N.J. Mørk (Oslo, Norway); U. Mrowietz (Kiel, Germany); R. Murphy (Nottingham, England); J.-F. Nicolas (Lyon, France); A. Nikkels (Liège, Belgium); H. Oliveira (Coimbra, Portugal); A. Ormerod (Aberdeen, Scotland); J.-P. Ortonne (Nice, France); A. Parodi (Genova, Italy); R. Pasternack (Tampere, Finland); C. Paul (Toulouse, France); J. Pec (Martin, Slovakia); A. Peserico (Padova, Italy); S. Philipp (Berlin, Germany); L. Piquet (Tours, France); P. Plantin (Quimper, France); L. Puig (Barcelona, Spain); K. Reich (Hamburg, Germany); E. Reményik (Debrecen, Hungary); E. Riedl (Wien, Austria); M. Röcken (Tübingen, Germany); M. Rustin (Lon-

don, England); S. Saari (Turku, Finland); P. Saiag (Boulogne-Billancourt, France); W. Salmhofer (Graz, Austria); D. Schadendorf (Essen, Germany); M. Sebastian (Mahlow, Germany); M. Simaljakova (Bratislava, Slovakia); J.C. Simon (Leipzig, Germany); A. Spirén (Malmö, Sweden); J.-F. Stalder (Nantes, France); N. Stavrianeas (Chaidari, Greece); M. Sticherling (Erlangen, Germany); T. Ternowitz (Stavanger, Norway); D. Thaci (Frankfurt, Germany); B. Thio (Rotterdam, the Netherlands); D. Uhlig (Landau, Germany); S. Valiukeviciene (Kaunas, Lithuania); F.J. Vanaclocha Sebastián (Madrid, Spain); G. Wozel (Dresden, Germany).

Appendix 2

Conflicts of interest

C.P. has been an investigator or consultant for Abbott, Amgen, Celgene, Janssen, LEO Pharma, Pierre Fabre and Pfizer. L.P. has received advisory/speaker honoraria and/or research funding from Abbott, Almirall, Celgene, Janssen, LEO Pharma, MSD, Novartis and Pfizer. K.K. has been an investigator, speaker and advisor for Abbott, Almirall, Celgene, Janssen, LEO Pharma, MSD and Pfizer. T.L. has been an investigator and consultant for Abbott, Almirall, Basilea, Bayer, Biogen Idec, Boehringer Ingelheim, CERIES, Clinuvel, Delenex, Galderma, Janssen, La Roche Posay, LEO Pharma, Lilly, Maruho, Meda, Merck-Serono, MSD, Novartis, Spirig, Symrise and Wolff. J.L. has been a consultant or investigator for Abbott, Janssen, Pfizer, LEO Pharma and Galderma. S.C. has received advisory/speaker honoraria and/or research funding from Abbott, Janssen, LEO Pharma, MSD, Novartis and Pfizer. G.G. has received advisory/speaker honoraria and/or research funding from Abbott, Almirall, Boehringer Ingelheim, Celgene, Dompè, Galderma, GSK, Janssen, LEO Pharma, Merck-Serono, Maruho, MSD, Novartis and Pfizer. J.-F.N. has been an investigator and consultant for Janssen. J.B. has served as consultant and/or paid speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for or being developed for the treatment of psoriasis including Abbott, Celgene, Centocor, Creabilis, Eli-Lilly, Janssen, Merck, MSD, Novartis and Pfizer. K.R. has served as consultant and/or paid speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis including Abbott, Biogen-Idec, Celgene, Centocor, Janssen, LEO Pharma, Medac, Merck, MSD (formerly Essex, Schering-Plough), Novartis and Pfizer (formerly Wyeth). E.R., F.L., S.M. and P.B. are employees of Janssen-Cilag.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Fig S1. Patient flow through the trial to week 12 (primary endpoint).