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

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Summary

Background Many patients with psoriasis develop psoriatic arthritis, a chronic inflammatory disease that afflicts peripheral synovial, axial, and entheseal structures. The fully human monoclonal antibody ustekinumab is an efficacious treatment for moderate-to-severe plaque psoriasis. We did a randomised, placebo-controlled, phase 3 trial to assess the safety and efficacy of ustekinumab in patients with active psoriatic arthritis.

Methods In this phase 3, multicentre, double-blind, placebo-controlled trial at 104 sites in Europe, North America, and Asia-Pacific, adults with active psoriatic arthritis (≥5 tender and ≥5 swollen joints, C-reactive protein ≥3·0 mg/L) were randomly assigned (1:1:1, by dynamic central randomisation based on an algorithm implemented by an interactive voice–web response system) to 45 mg ustekinumab, 90 mg ustekinumab, or placebo at week 0, week 4, and every 12 weeks thereafter. At week 16, patients with less than 5% improvement in both tender and swollen joint counts entered masked early-escape and were given 45 mg ustekinumab (if in the placebo group) or 90 mg ustekinumab (if in the 45 mg group). At week 24, all remaining patients in the placebo group received ustekinumab 45 mg, which they continued at week 28 and every 12 weeks thereafter. Our primary endpoint was 20% or greater improvement in American College of Rheumatology (ACR20) criteria at week 24. This trial is registered with ClinicalTrials.gov (NCT01009086) and EudraCT (2009-012264-14).

Findings Between Nov 30, 2009, and March 30, 2011, 615 patients were randomly assigned—206 to placebo, 205 to 45 mg ustekinumab, and 204 to 90 mg ustekinumab. More ustekinumab-treated (87 of 205 [42·4%] in the 45 mg group and 101 of 204 [49·5%] in the 90 mg group) than placebo-treated (47 of 206 [22·8%]) patients achieved ACR20 at week 24 (p<0·0001 for both comparisons); responses were maintained at week 52. At week 16, proportions of patients with adverse events were similar in the ustekinumab and placebo groups (171 of 409 [41·8%] *vs* 86 of 205 [42·0%]).

Interpretation Ustekinumab significantly improved active psoriatic arthritis compared with placebo, and might offer an alternative therapeutic mechanism of action to approved biological treatments.

Funding Janssen Research & Development.

Introduction

Psoriatic arthritis is a chronic inflammatory disease that afflicts peripheral synovial, axial, and entheseal structures and is associated with skin psoriasis and nail involvement.[1] Substantial proportions of patients with psoriasis develop psoriatic arthritis,[2,3] which is associated with reduced quality of life, several comorbidities, and increased mortality.[4–9]

Conventional treatment for psoriatic arthritis usually begins with disease-modifying antirheumatic drugs and non-steroidal anti-inflammatory drugs, followed by tumour necrosis factor α (TNFα) inhibitors when necessary. T-helper-17 (Th17) cells are postulated to have a major role in psoriatic inflammation, and thus various biological drugs directed against interleukins 17 and 23 are being investigated.[10–15]

Ustekinumab is a fully human IgG 1κ monoclonal antibody that binds to the common p40 subunit shared by interleukins 12 and 23. Efficacy against plaque psoriasis and an acceptable safety profile have been shown in large phase 3 trials,[12–14] and the drug is approved for use in the treatment of moderate-to-severe psoriasis. In a phase 2 trial[15] of patients with active psoriatic arthritis, ustekinumab significantly improved signs and symptoms of psoriatic arthritis and improved quality of life compared with placebo. Thus, we did the phase 3, placebo-controlled PSUMMIT 1 trial to further assess the safety and efficacy of ustekinumab in patients with active psoriatic arthritis.

Methods

Study design and participants

PSUMMIT 1 was a phase 3, randomised, placebo-controlled trial at 104 sites in 14 countries—specifically, Australia, Austria, Canada, Finland, Germany, Hungary, Latvia, Lithuania, New Zealand, Poland, Russia, Spain, the UK, and the USA. Patients were recruited by individual study sites via clinics, outside referrals, and advertisements. Patients were screened and randomly assigned between Nov 30, 2009, and March 30, 2011.

The week 52 database was locked on July 12, 2012. The trial continues, and the week 108 database lock is planned for July, 2013. Recruitment cohorts were prospectively defined. Adult patients with active psoriatic arthritis for 6 months or longer despite 3 months or more of treatment with disease-modifying antirheumatic drugs or 4 weeks or more of treatment with non-steroidal anti-inflammatory drugs, or both, or with intolerance to these treatments, were eligible. Active psoriatic arthritis was defined as five or more swollen joints (of 66) and five or more tender joints (of 68) at screening and baseline, C-reactive protein (CRP)

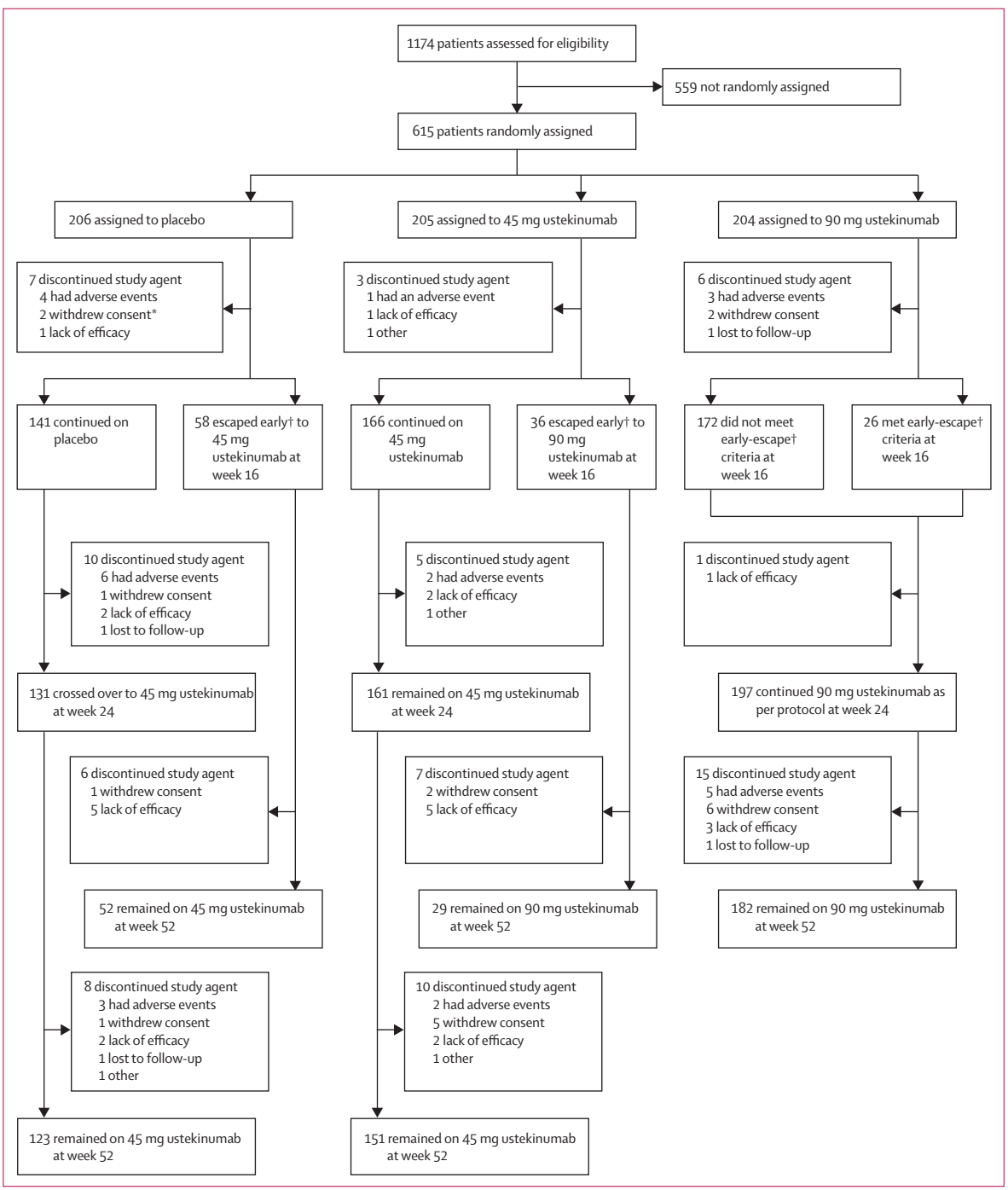

***Figure 1*: Trial profile**
Discontinuation because of an adverse event includes patients who discontinued study agent because of a pre-existing disorder. *Includes one patient who was randomly assigned but not treated. †Patients who had less than 5% improvement from baseline to week 16 in both tender and swollen joint count met criteria for early-escape.

See Online for appendix

concentrations of 3·0 mg/L or more (10 mg/L is the upper limit of normal) at screening, and active or documented history of plaque psoriasis (appendix).

Our study was done according to the Declaration of Helsinki and International Committee on Harmonisation good clinical practices. Our protocol was reviewed and approved by each site's governing institutional review board or ethics committee in line with national requirements for the approval of study conduct. All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1:1) to receive 45 mg subcutaneous ustekinumab, 90 mg subcutaneous ustekinumab, or subcutaneous placebo at baseline, week 4, and every 12 weeks thereafter. At week 16, patients with less than 5% improvement from baseline in both tender and swollen joint counts entered masked early-escape—specifically, patients receiving placebo switched to 45 mg ustekinumab and patients receiving 45 mg ustekinumab were given 90 mg ustekinumab. Patients receiving 90 mg ustekinumab continued their masked dose regimen. Patients taking placebo who did not escape early crossed over to receive 45 mg ustekinumab at week 24, week 28, and every 12 weeks thereafter. Ustekinumab-treated patients received only placebo injections at week 20 and week 24 to maintain the masking. Concomitant drug use had to remain stable until week 52 (appendix).

Dynamic central randomisation based on an algorithm implemented in the interactive voice–web response system used in the study minimised the imbalance in the distribution of patients across treatment groups within the levels of each stratification factor—ie, investigational site, baseline weight (≤100 kg or >100 kg), and baseline methotrexate use (yes or no). On the basis of the algorithm, the interactive system assigned a unique treatment code, which dictated the treatment assignment and matching study drug kit. All study site personnel with roles in the study and patients were masked to treatment assignment; study drug kits were identical irrespective of treatment. To maintain the masking, each administration of study agent comprised two subcutaneous injections (one placebo and one ustekinumab injection or two placebo injections), which were identical in appearance, in two different locations. Within the study, syringe numbers from the kits were recorded on electronic case report forms (eCRFs), and general eCRF pages for efficacy and safety were limited by passcode to only pertinent study site members. At the week 24 database lock, the data were unmasked to the sponsor for analysis while patients were still participating in the study. Study sites and patients will remain masked to treatment assignment until the last enrolled patient completes the assessments at week 108 and the week 108 database is locked.

	Placebo (n=206)	Ustekinumab 45 mg (n=205)	Ustekinumab 90 mg (n=204)
Men	108 (52·4%)	106 (51·7%)	116 (56·9%)
Age (years)	48·0 (39·0–57·0)	48·0 (39·0–55·0)	47·0 (38·5–54·0)
Body-mass index (kg/m²)	29·7 (25·4–35·2)	29·4 (25·6–33·9)	30·0 (25·7–34·2)
Duration of disease (years)			
Psoriatic arthritis	3·6 (1·0–9·7)	3·4 (1·2–9·2)	4·9 (1·7–8·3)
Psoriasis	13·1 (5·3–23·5)	12·0 (4·1–22·2)	14·1 (5·4–22·4)
Patients with psoriasis ≥3% of body surface area	146 (70·9%)	145 (70·7%)	149 (73·0%)
PASI score	8·8 (4·4–14·3)	7·1 (3·3–15·3)	8·4 (4·8–14·7)
DLQI score	11·0 (5·0–18·0)	10·0 (5·0–16·0)	9·0 (5·0–16·0)
Swollen joint count	12·0 (8·0–19·0)	10·0 (7·0–15·0)	10·0 (7·0–16·0)
Tender joint count	22·0 (13·0–33·0)	18·0 (12·0–28·0)	20·0 (12·0–32·0)
CRP (mg/L)	9·6 (6·0–18·6)	10·0 (5·9–21·1)	12·3 (6·5–21·7)
HAQ-DI score	1·3 (0·8–1·8)	1·3 (0·8–1·8)	1·3 (0·8–1·6)
DAS28-CRP	5·2 (4·4–6·0)	5·2 (4·6–5·7)	5·2 (4·6–5·8)
Dactylitis in ≥1 digit	96 (46·6%)	101 (49·3%)	99 (48·5%)
Dactylitis score	4·5 (2·0–10·0)	4·0 (2·0–9·0)	4·0 (2·0–11·0)
Enthesitis	145 (70·4%)	142 (69·3%)	154 (75·5%)
Enthesitis score*	4·0 (2·0–8·0)	4·0 (2·0–7·0)	5·0 (2·0–8·0)
SF-36 summary scores			
Mental component	42·5 (37·2–46·2)	42·8 (38·7–48·0)	41·8 (37·7–46·9)
Physical component	35·8 (31·8–40·1)	35·5 (30·6–40·1)	36·5 (30·2–40·1)
Methotrexate	96 (46·6%)	99 (48·3%)	101 (49·5%)
Dose (mg/week)	15·0 (12·5–20·0)	15·0 (10·0–20·0)	15·0 (15·0–20·0)
Mean dose (SD) (mg/week)	15·8 (4·7)	15·9 (4·8)	16·5 (4·8)
Oral corticosteroid	32 (15·5%)	36 (17·6%)	28 (13·7%)
Dose (mg/day)	5·0 (5·0–7·5)	7·5 (5·0–10·0)	5·0 (5·0–10·0)
Mean dose (SD) (mg/day)	5·9 (2·2)	6·9 (2·8)	6·9 (2·6)
Non-steroidal anti-inflammatory drugs	151 (73·3%)	156 (76·1%)	151 (74·0%)

Data are n (%) or median (IQR) unless otherwise specified. PASI scores range from 0 to 72, DLQI scores from 0 to 30, HAQ-DI scores from 0 to 3, dactylitis scores from 1 to 60, enthesitis scores from 1 to 15, and SF-36 summary scores from 0 to 100. The swollen joint count comprises 66 joints and the tender joint count 68. PASI=psoriasis area and severity index. DLQI=dermatology life quality index. CRP=C-reactive protein. HAQ-DI=Health assessment questionnaire disability index. DAS28-CRP=28-joint disease activity score based on CRP. SF-36=36-item short-form health survey.
*Psoriatic-arthritis-modified Maastricht ankylosing spondylitis enthesitis score.

Table 1: **Baseline demographics and disease characteristics**

Procedures

Key study endpoints were assessed by American College of Rheumatology (ACR) response criteria[16] and the 28-joint disease activity score based on CRP (DAS28-CRP), in terms of a European League Against Rheumatism (EULAR) response criteria status of a good or moderate response and a score of <2·6;[17–20] sponsor-trained clinicians used the psoriasis area and severity index[21] to assess skin response in patients in whom 3% or more of body surface area was affected by psoriasis at baseline. We used the health assessment questionnaire disability index (HAQ-DI) to measure physical function.[22]

We assessed dactylitis in the 20 digits of the hands and feet on a scale of 0–3 (0=no dactylitis, 3=severe dactylitis). Entheseal tenderness was scored at 15 body sites (0=absent, 1=present) with the psoriatic-arthritis-modified (to include left and right insertion of the plantar fascia)

Maastricht ankylosing spondylitis enthesitis score.[23] We assessed spondyloarthritis activity via the Bath ankylosing spondylitis disease activity index (BASDAI)—an instrument for assessment of spinal disease in ankylosing spondylitis, which has not yet been validated in psoriatic arthritis.[24] The 36-item short-form health survey was used to measure quality of life,[25] and the dermatology life quality index[26] to assess the effect of skin aspects of disease on daily living (appendix).

Our primary efficacy endpoint was the proportion of patients with at least 20% improvement in ACR response criteria (ACR20) at week 24. The main secondary endpoints were change from baseline in scores on the HAQ-DI at 24 weeks and proportions of patients achieving at least 75% improvement in the psoriasis area severity index, at least 50% improvement in ACR response criteria (ACR50), and at least 70% improvement in ACR response criteria (ACR70) at 24 weeks.

Statistical analysis

The appendix includes details of sample size calculations. To control for multiplicity in analyses of the primary and major secondary endpoints, we did major secondary analyses sequentially, contingent upon the success of the primary statistical analysis. For each endpoint, we did the test between the combined ustekinumab and placebo groups first. If that test was significant at the 0·05 level, then a pairwise comparison between each dose group

	Placebo (n=206)	Ustekinumab 45 mg (n=205)	% difference 45 mg *vs* placebo (95% CI)	p (45 mg *vs* placebo)	Ustekinumab 90 mg (n=204)	% difference 90 mg *vs* placebo (95% CI)	p (90 mg *vs* placebo)	Combined ustekinumab (n=409)	p (combined *vs* placebo)
ACR20 response	47 (22·8%)	87 (42·4%)	19·6 (10·8 to 28·5)	<0·0001	101 (49·5%)	26·7 (17·8 to 35·6)	<0·0001	188 (46·0%)	<0·0001
ACR20 by methotrexate use									
Yes	25/96 (26·0%)	43/99 (43·4%)	..	..	46/101 (45·5%)	..	..	89/200 (44·5%)	..
No	22/110 (20·0%)	44/106 (41·5%)	..	..	55/103 (53·4%)	..	..	99/209 (47·4%)	..
ACR50 response	18 (8·7%)	51 (24·9%)	16·1 (9·1 to 23·2)	<0·0001	57 (27·9%)	19·2 (11·9 to 26·5)	<0·0001	108 (26·4%)	<0·0001
ACR70 response	5 (2·4%)	25 (12·2%)	9·8 (4·8 to 14·7)	0·0001	29 (14·2%)	11·8 (6·6 to 17·0)	<0·0001	54 (13·2%)	<0·0001
DAS28-CRP/EULAR*	71 (34·5%)	135 (65·9%)	..	<0·0001	138 (67·6%)	..	<0·0001	273 (66·7%)	<0·0001
DAS28-CRP <2·6	17 (8·3%)	42 (20·5%)	..	0·0004	40 (19·6%)	..	0·0009	82 (20·0%)	0·0002
Patients with dactylitis†	70/92 (76·1%)	56/99 (56·6%)	..	0·0050	53/95 (55·8%)	..	0·0038	109/194 (56·2%)	0·0013
Patients with enthesitis‡	111/137 (81·0%)	96/140 (68·6%)	..	0·0179	90/148 (60·8%)	..	0·0002	186/288 (64·6%)	0·0006
PASI75 response§	16/146 (11·0%)	83/145 (57·2%)	46·3 (36·8 to 55·8)	<0·0001	93/149 (62·4%)	51·5 (42·2 to 60·7)	<0·0001	176/294 (59·9%)	<0·0001
PASI75 by methotrexate use									
Yes	10/66 (15·2%)	32/66 (48·5%)	..	..	38/69 (55·1%)	..	..	70/135 (51·9%)	..
No	6/80 (7·5%)	51/79 (64·6%)	..	..	55/80 (68·8%)	..	..	106/159 (66·7%)	..
BASDAI¶									
BASDAI20	16/61 (26·2%)	25/51 (49·0%)	..	0·0131	35/60 (58·3%)	..	0·0005	60/111 (54·1%)	0·0005
BASDAI50	8/61 (13·1%)	12/51 (23·5%)	..	0·1328	19/60 (31·7%)	..	0·0137	31/111 (27·9%)	0·0232
BASADI70	0/61 (0·0%)	7/51 (13·7%)	..	0·0030	9/60 (15·0%)	..	0·0021	16/111 (14·4%)	0·0021
HAQ-DI									
Improvement ≥0·3 units	58 (28·2%)	98 (47·8%)	..	<0·0001	97 (47·5%)		<0·0001	195 (47·7%)	<0·0001
Change from baseline	0·00 (–0·38 to 0·13)	–0·25 (–0·63 to 0·00)	–0·25 (–0·25 to –0·13)	<0·0001	–0·25 (–0·75 to 0·00)	–0·25 (–0·38 to –0·13)	<0·0001	–0·25 (–0·63 to 0·00)	<0·0001
Change from baseline in SF-36									
Mental component	0·3 (–3·3 to 7·2)	2·7 (–2·7 to 9·5)	..	0·0654	4·4 (–1·4 to 11·0)	..	0·0010	3·5 (–2·3 to 10·6)	0·0033
Physical component	1·2 (–2·3 to 5·2)	3·9 (–1·3 to 10·7)	..	<0·0001	5·8 (0·6 to 10·9)	..	<0·0001	4·7 (–0·1 to 10·8)	<0·0001
DLQI§									
Change from baseline	–1·0 (-5·0 to 2·0)	–6·0 (–11·0 to –2·0)	..	<0·0001	–6·0 (–12·0 to 3·0)	..	<0·0001	–6·0 (–11·0 to –2·0)	<0·0001
Score of 0 or 1§ ||	11/132 (8·3%)	48/129 (37·2%)	..	<0·0001	71/134 (53·0%)	..	<0·0001	119/263 (45·2%)	<0·0001

Data are n (%), n/N (%), or median (IQR). ACR20=at least 20% improvement in the American College of Rheumatology response criteria. ACR50=at least 50% improvement in the American College of Rheumatology response criteria. ACR70=at least 70% improvement in the American College of Rheumatology response criteria. DAS28-CRP=28-joint disease activity score based on C-reactive protein. EULAR=European League Against Rheumatism. PASI=psoriasis area and severity index. BASDAI=Bath ankylosing spondylitis disease activity index. HAQ-DI=health assessment questionnaire disability index. SF-36=36-item short-form health survey. DLQI=Dermatology life quality index. *A good or moderate EULAR DAS28-CRP response. †In patients with dactylitis in one digit or more at baseline. ‡In patients with psoriatic-arthritis-modified Maastricht ankylosing spondylitis enthesitis score ≥1 at baseline. §In patients with ≥3% body-surface area affected by psoriasis at baseline. ¶Assessed in patients with spondylitis and peripheral joint involvement at baseline. ||In patients with DLQI >1 at baseline.

***Table 2*: Efficacy of ustekinumab versus placebo at week 24 in randomly assigned patients**

and the placebo group was done. The test for the combined group and at least one pairwise comparison had to be significant to proceed to the next endpoint. The primary and major secondary analyses were done on an intention-to-treat basis.

Treatment was deemed unsuccessful in patients who used drugs not allowed by our protocol or discontinued study drugs because of poor efficacy or adverse events of worsening of disease. We judged patients meeting criteria for unsuccessful treatment to be non-responders for binary endpoints, and thus we carried baseline values forward for continuous endpoints. Both of these rules were applied until week 52. Data at week 16 were carried forward to week 24 for patients who escaped early at week 16. After week 24, available recorded data were used for patients who escaped early.

We used a last-observation-carried-forward procedure to impute missing ACR component data when patients had data for at least one component. Patients who discontinued the study drug before week 24 or had missing data at week 24 were deemed non-responders for most of the week 24 binary endpoints. For the change in scores on the HAQ-DI at week 24, we used last-observation-carried-forward procedures to impute missing data after application of unsuccessful-treatment rules. After application of all rules, missing data were not imputed.

To assess treatment differences at week 24, we used the Cochran-Mantel-Haenszel tests for binary variables and did analyses of variance on the van der Waerden normal scores—ie, rank-transformed scores based on normal distribution[27]—for continuous variables. Both tests were adjusted for baseline methotrexate use. We did not do statistical hypothesis testing for data at week 52 because of the absence of a control group after week 24. We did subgroup analyses to assess the consistency of efficacy in the primary endpoint across demographic data, baseline disease characteristics, and drug history for psoriatic arthritis.

We summarised safety data for all patients who received a study drug at least once. Major adverse cardiovascular events were predefined to include cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (appendix). This trial is registered with ClinicalTrials.gov (NCT01009086) and EudraCT (2009-012264-14).

Role of the funding source

CB, SL, YW, AMM, and MKD were employed by the funding source during the study and preparation of the Article for publication. All authors participated in the decision to publish the paper. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

Results

1174 patients were screened, 615 of whom were randomly assigned (figure 1). Most of the patients who were not randomly assigned did not meet the inclusion criteria of five or more swollen and tender joints at screening and baseline and CRP concentrations of 3·0 mg/L or more at screening. 397 patients were randomly assigned at European sites, 175 at North American sites, and 43 at Asia-Pacific sites. 78 (12·7%) patients discontinued study agent by week 52 (figure 1).

The study population comprised 330 (53·7%) men and 285 (46·3%) women; the age range was 18–81 years (median 48 years). Overall median HAQ-DI score was 1·3 (IQR 0·8–1·8) and serum CRP concentration 10·3 mg/L (6·0–20·7). Baseline demographic and disease characteristics were well balanced between groups (table 1). Baseline ACR core set measurements were consistent between patients irrespective of concomitant methotrexate treatment (data not shown). Although 319 (51·9%) patients were not receiving concomitant methotrexate (table 1), most (roughly 75%) had received methotrexate previously (data not shown).

A significantly higher proportion of patients in the ustekinumab groups than in the placebo group achieved an ACR20 response at week 24 (table 2; p<0·0001). ACR20 responses in the ustekinumab groups differed significantly

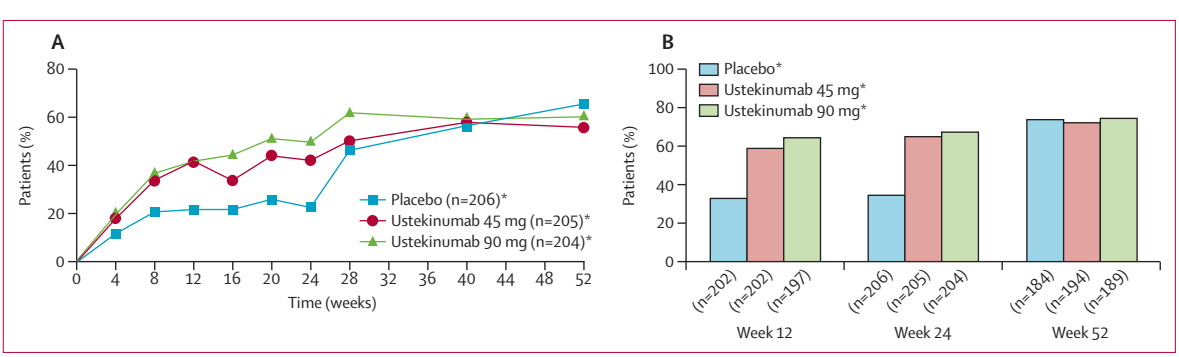

Figure 2: **Proportions of patients achieving ACR20 responses (A), and EULAR response at weeks 12, 24 and 52 (B)**
EULAR response is defined as a good or moderate DAS28-CRP response. p<0·0001 versus placebo for both ustekinumab doses at weeks 12 and 24 for both (A) and (B). ACR20=at least 20% improvement in the American College of Rheumatology response criteria. EULAR=European League Against Rheumatism. DAS28-CRP=28-joint disease activity score based on C-reactive protein. *For patients who escaped early, data at or before week 16 were carried forward to week 24. After week 24, observed data were used.

from those in the placebo group by week 8 (p<0·0001) and generally increased with time (although trough responses in the 45 mg group were noted at week 16; figure 2A). The highest ACR20 response rates were at week 28; response rates were maintained at week 52 (figure 2A). We also noted significant differences at week 24 for ACR50 (108 of 409 [26·4%] patients in the combined ustekinumab group, 51 of 205 [24·9%] in the 45 mg group, and 57 of 204 [27·9%] in the 90 mg group *vs* 18 of 206 [8·7%] in the placebo group achieved an ACR50 response; p<0·0001 for all placebo comparisons) and ACR70 (54 of 409 [13·2%], 25 of 205 [12·2%], and 29 of 204 [14·2%] *vs* five of 206 [2·4%]; p<0·0001, p=0·0001, and p<0·0001, respectively). The proportion of patients achieving ACR50 (70 of 184 [38·0%] patients in the placebo→45 mg group, 131 of 383 [34·2%] in the combined ustekinumab group) and ACR70 (30 of 184 [16·3%] in the placebo→45 mg group, 75 of 383 [19·6%] in the combined ustekinumab group) further improved from week 24 to week 52. ACR20 treatment effects at week 24 were numerically lower for patients receiving concomitant methotrexate than for those who were not, but tests of significance were not done (table 2; appendix). Ustekinumab provided significant clinical benefit versus placebo in many subgroups of patients defined by baseline demographic and disease characteristics and drug use (appendix).

At weeks 12 and 24, a significantly higher proportion of patients in the ustekinumab groups than in the placebo group achieved DAS28-CRP (EULAR) responses (figure 2B; p<0·0001). DAS28-CRP scores improved with time in all groups (appendix). Compared with placebo, treatment with ustekinumab (both doses) resulted in a significantly higher proportion of patients with DAS28-CRP scores less than 2·6 at week 24 (p=0·0002; table 2). By week 52, 118 of 383 (30·8%) combined ustekinumab patients and 54 of 184 (29·3%) of patients in the placebo→45 mg group had a DAS28-CRP score of less than 2·6.

Of the patients with dactylitis at baseline, significantly lower proportions in the ustekinumab groups (109 of 194 [56·2%] patients in the combined group, 56 of 99 [56·6%] in the 45 mg group, and 53 of 95 [55·8%] in the 90 mg group) than in the placebo groups (70 of 92 [76·1%]) had digits with dactylitis at week 24 (p=0·0013, 0·0050, and 0·0038, respectively). Patients in the ustekinumab groups had significantly greater improvements in the dactylitis (p=0·0003; figure 3A) and enthesitis (45 mg group p=0·0019, 90 mg p<0·0001; figure 3B) scores at week 24 when compared with placebo. Of patients with spondylitis and peripheral joint involvement at baseline, a significantly higher proportion in the ustekinumab groups achieved responses on the BASDAI than in the placebo group (table 2).

In patients with 3% or more of body surface area affected by psoriasis at baseline, significantly greater proportions of patients in the ustekinumab groups than in the placebo group achieved at least a 75% improvement in the psoriasis area and severity index (figure 3C, table 2; p<0·0001 for all comparisons) or at least a 90% improvement in baseline scores on the index (125 of 294 [42·5%] patients in the ustekinumab groups *vs* 4 of 146 [2·7%] in the placebo group; p<0·0001) at week 24. At week 52, 190 of 275 (69·1%) ustekinumab-treated patients achieved at least a 75% improvement in the psoriasis area and severity index (figure 3C; appendix) and 136 of 275 (49·5%) achieved at least a 90% improvement (data not shown).

Improvements in HAQ-DI scores at week 24 were significantly greater in patients given ustekinumab

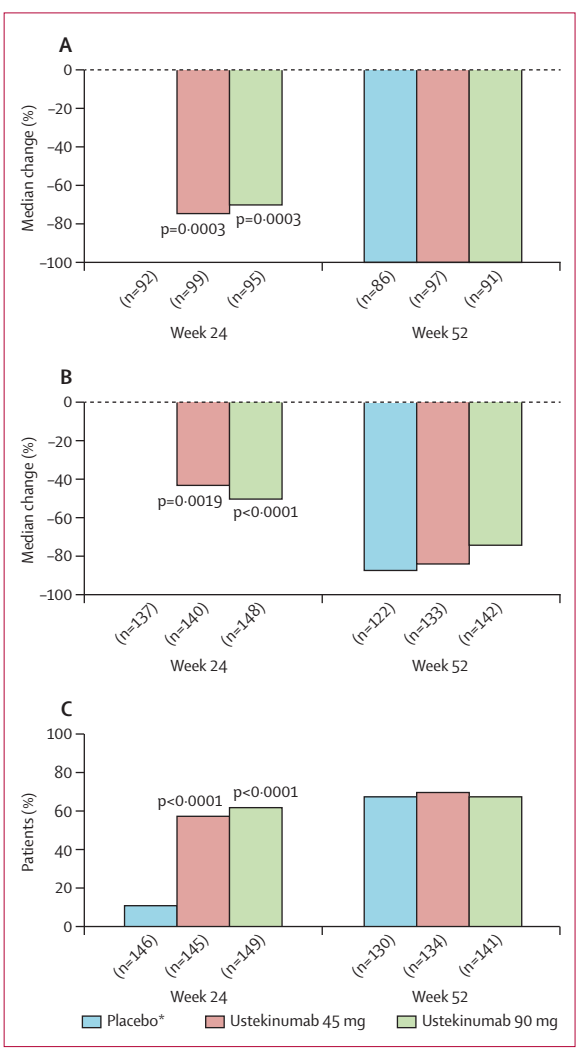

Figure 3: **Median change from baseline in dactylitis (A) and psoriatic-arthritis-modified MASES enthesitis (B) scores and proportions of patients achieving PASI75 responses (C) at weeks 24 and 52**

Dactylitis scores are measured in patients who had dactylitis at baseline, psoriatic-arthritis-modified MASES scores in those who had enthesitis at baseline, and PASI75 in those with 3% or more of body surface area affected by psoriasis at baseline. MASES=Maastricht ankylosing spondylitis enthesitis score. PASI75=at least 75% improvement in the psoriasis area and severity index. *For patients who escaped early, data at or before week 16 were carried forward to week 24. After week 24, observed data were used.

(median change –0·25) than in those given placebo (0·00; p<0·0001 for all comparisons). Significantly greater proportions of ustekinumab-treated patients achieved a clinically meaningful improvement[28] of 0·3 or more in HAQ-DI scores (195 of 409 [47·7%] patients) than did patients in the placebo group (58 of 206 [28·2%]; p<0·0001; table 2). Improvements in physical function were maintained at week 52 (appendix). We noted significant improvements in summary scores on the 36-item short-form health survey (both physical and mental components) and scores on the dermatology life quality index at week 24 in the ustekinumab group compared with placebo (table 2). However, improvements in the mental component of the short-form health survey were not significant at the 45 mg dose (table 2). Improvements were maintained at week 52 (appendix).

Table 3 and the appendix list safety findings and the main adverse events in each group in patients who received at least one dose of study agent. At week 16, proportions of patients with adverse events were similar in the ustekinumab and placebo groups (171 of 409 [41·8%] *vs* 86 of 205 [42·0%]); similar rates of investigator-reported infections and serious adverse events were also noted (table 3). The most common adverse events in ustekinumab-treated patients were nasopharyngitis (19 [4·6%] patients), upper-respiratory-tract infection (14 [3·4%]), and headache (14 [3·4%]). The proportions of patients reporting adverse events and the types of adverse events did not seem to differ relative to concomitant methotrexate treatment (data not shown). Adverse event patterns by week 24 were closely similar to those by week 16 (table 3), and increases in the frequency of adverse events at week 52 were consistent with the additional ustekinumab exposure accrued after week 24; no obvious dose-related trend was noted (appendix).

No opportunistic infections (including tuberculosis), death, or malignancies were reported by week 52. No serious infections were reported by week 24; after week 24, cholecystitis was noted in two patients (one in the placebo group who escaped early to 45 mg ustekinumab, and one in the 45 mg group), salpingitis in one patient in the 45 mg group, erysipelas in one patient in the 90 mg group, and an pharyngolaryngeal abscess in one patient in the 90 mg group.

No major adverse cardiovascular events were noted in any treatment group by week 16. One serious cardiac adverse event (angina pectoris) was reported during the placebo-controlled period in a patient given placebo (data not shown). Between week 16 and week 24, a non-fatal stroke was reported in a 53-year-old former smoker with pre-existing hypertension and hyperlipidaemia who had had a previous cerebrovascular event necessitating internal carotid-artery stenting. This patient was initially assigned to 45 mg ustekinumab and did not escape early. Between week 24 and week 52, two additional patients (who were both originally given

	Week 16*				Week 24*				
	Placebo (n=205)	Ustekinumab 45 mg (n=205)	Ustekinumab 90 mg (n=204)	Combined ustekinumab (n=409)	Placebo (n=205)	Placebo→ ustekinumab 45 mg (n=58)	Ustekinumab 45 mg (n=205)	Ustekinumab 90 mg (n=204)	Combined ustekinumab (n=467)
Mean follow-up (weeks)	16·2 (1·4)	16·2 (0·8)	16·0 (1·9)	16·1 (1·5)	21·5 (4·4)	8·2 (0·8)	24·2 (1·6)	23·9 (3·2)	22·1 (5·7)
Any adverse event	86 (42·0%)	82 (40·0%)	89 (43·6%)	171 (41·8%)	102 (49·8%)	14 (24·1%)	111 (54·1%)	106 (52·0%)	231 (49·5%)
Common (>2%) adverse events									
Nasopharyngitis	8 (3·9%)	8 (3·9%)	11 (5·4%)	19 (4·6%)	9 (4·4%)	0 (0·0%)	13 (6·3%)	15 (7·4%)	28 (6·0%)
Upper-respiratory-tract infection	10 (4·9%)	5 (2·4%)	9 (4·4%)	14 (3·4%)	11 (5·4%)	2 (3·4%)	9 (4·4%)	12 (5·9%)	23 (4·9%)
Headache	2 (1·0%)	10 (4·9%)	4 (2·0%)	14 (3·4%)	2 (1·0%)	0 (0·0%)	11 (5·4%)	5 (2·5%)	16 (3·4%)
Arthralgia	3 (1·5%)	4 (2·0%)	6 (2·9%)	10 (2·4%)	3 (1·5%)	0 (0·0%)	7 (3·4%)	8 (3·9%)	15 (3·2%)
Nausea	0 (0·0%)	4 (2·0%)	6 (2·9%)	10 (2·4%)	0 (0·0%)	0 (0·0%)	6 (2·9%)	6 (2·9%)	12 (2·6%)
Diarrhoea	0 (0·0%)	5 (2·4%)	4 (2·0%)	9 (2·2%)	0 (0·0%)	0 (0·0%)	11 (5·4%)	4 (2·0%)	15 (3·2%)
Discontinued study agent because of adverse event	3 (1·5%)	1 (0·5%)	2 (1·0%)	3 (0·7%)	7 (3·4%)	0 (0·0%)	3 (1·5%)	3 (1·5%)	6 (1·3%)
Serious adverse event	4 (2·0%)†	4 (2·0%)†	3 (1·5%)†	7 (1·7%)	5 (2·4%)†	1 (1·7%)†	6 (2·9%)†	3 (1·5%)†	10 (2·1%)
Investigator-reported infection	43 (21·0%)	34 (16·6%)	40 (19·6%)	74 (18·1%)	47 (22·9%)	4 (6·9%)	55 (26·8%)	55 (27·0%)	114 (24·4%)

Data are mean (SD) or n (%). Adverse events leading to discontinuation of study agent refers only to those that occurred after the first dose of study agent (appendix). *At week 16, patients with less than 5% improvement from baseline in both tender and swollen joint counts entered masked early-escape—ie, patients receiving 45 mg ustekinumab switched to 90 mg ustekinumab and those receiving placebo switched to 45 mg ustekinumab; patients receiving 90 mg ustekinumab from baseline continued with their regimen. Adverse events at week 24 are cumulative and include those at week 16. †For placebo, serious adverse events at week 16 were joint dislocation (one patient), radius fracture (one), angina pectoris (one), and foot deformity (one). Additional serious adverse events at week 24 were erythrodermic psoriasis in one patient taking placebo, suicidal ideation and depression in the patient with angina pectoris, and benign prostatic hyperplasia in a patient roughly 2 weeks after early-escape to 45 mg ustekinumab. For 45 mg ustekinumab, serious adverse events at week 16 were duodenitis (one patient), spinal compression fracture (one), acute renal failure (one), and cervical polyps (one). Two additional patients had serious adverse events at week 24 (device [pin] breakage and cerebrovascular accident). In the 90 mg group, serious adverse events at week 16 included gastroduodenitis, chronic pancreatitis, and cholecystitis (one); anxiety and depression (one); and erythrodermic psoriasis (lack of efficacy; one).

***Table 3*: Summary of adverse events at week 16 and week 24**

placebo and escaped early to 45 mg ustekinumab) had myocardial infarctions (data not shown).

Six patients who had at least one dose of study agent discontinued their assigned treatment because of adverse events by week 16—three patients in the ustekinumab groups (acute renal failure, 45 mg; pregnancy, 90 mg [as a precaution]; erythrodermic psoriasis, 90 mg) and three in the placebo group (all because of increased psoriatic arthropathy activity). Between week 16 and week 52, 12 further ustekinumab-treated patients discontinued the study agent because of an adverse event by week 52 (appendix).

By week 52, four (1·0%) patients receiving 45 mg ustekinumab and five (2·1%) receiving 90 mg ustekinumab had had an injection-site reaction, compared with ten (1·6%) patients in the placebo group. All injection-site reactions were mild, and none resulted in discontinuation of study drug. By week 52, no anaphylactic or serum sickness-like reactions associated were noted.

Discussion

In this multicentre, phase 3, double-blind, placebo-controlled trial, subcutaneous ustekinumab was effective and well tolerated in patients with active psoriatic arthritis at week 52 (panel). ACR20 responses were significantly higher in ustekinumab-treated than in placebo-treated patients at week 24, and thus we met our primary study endpoint. We noted differences in efficacy by weeks 4–8. Data about the effects of ustekinumab on radiographic progression are forthcoming.

The highest ACR20 response rates were recorded at week 28 with 90 mg ustekinumab and week 40 with 45 mg ustekinumab, and response was maintained at week 52. However, interpretation of these data is limited because early-escape rules were not applied after week 24. Bearing in mind the limitations of cross-study comparisons,[29] time to maximum effect seemed longer with ustekinumab than with anti-TNFα biological agents, but response rates were similar to those achieved with TNFα antagonists at week 52. Although assessments after week 24 were not placebo-controlled and could have been biased, maximum improvement in several objective measurements of disease activity was also noted after week 24.

Ustekinumab was efficacious irrespective of methotrexate use, although differences in ACR20 and PASI75 response rates between active and placebo groups seemed higher in patients not taking methotrexate than in those taking methotrexate. The trial, however, was not designed to assess such differences, and no tests of significance were done (table 2). Methotrexate was used by roughly 50% of patients, which is consistent with frequency of use in studies of golimumab[30] and infliximab.[31]

Psoriatic arthritis encompasses a range of target tissue pathological changes. Ustekinumab was significantly better than placebo in terms of DAS28-CRP and BASDAI scores, and improvements in skin disease, dactylitis, and enthesitis. Notably, the BASDAI data are novel and provide exploratory information about the spondylo-arthritic component of psoriatic arthritis. The proportion of patients with at least 75% improvement in the psoriasis area and severity index at week 24 was somewhat lower than those noted in trials of ustekinumab in psoriasis.[12,13] Lower baseline scores on the psoriasis area and severity index in psoriatic arthritis than in psoriasis might have established a floor effect and yielded less sensitivity to change. We noted a significant treatment difference in the rates of at least 90% improvement on the index at week 24—a response level representing clear or nearly clear skin disease that is increasingly thought of as a treatment goal in psoriasis.[32]

The benefits of ustekinumab in psoriatic arthritis might be related to the dual effects of inhibiting interleukin 23, with downstream effects on Th17 cells, and interleukin 12, with downstream effects on T-helper-1 cells, or could be because of inhibition of the interleukin 23–Th17 axis alone. Interleukins 12 and 23 are expressed in the synovia of patients with arthritis,[33,34] and are highly expressed in lesional psoriatic skin;[35] single nucleotide polymorphisms in these genetic pathways are related to genetic susceptibility to psoriatic arthritis.[36,37] Assessment of the functional roles of interleukins 12 and 23 in rodent models of arthritis has shown divergent effects.[38,39] Interleukin 23 in particular has been shown to drive entheseal inflammation in a rodent model.[40] Detailed clinical mechanism-of-action studies, including whole-blood gene expression and

Panel: Research in context

Systematic review

We searched PubMed on Feb 20, 2013, with the search terms "ustekinumab" and "psoriatic arthritis" for reports published in English (with no date restriction) to identify any additional clinical trials that have examined ustekinumab in the treatment of psoriatic arthritis. Efficacy and an acceptable safety profile have been shown in several large phase 3 trials of ustekinumab in patients with moderate-to-severe psoriasis,[12-14] and ustekinumab is approved for this indication. Efficacy and safety were assessed previously in a phase 2 trial of ustekinumab in psoriatic arthritis.[15] In this trial, ustekinumab significantly reduced signs and symptoms of psoriatic arthritis and diminished skin lesions compared with placebo. We did not identify any other studies of ustekinumab in psoriatic arthritis. However, the dose administration strategy used in the phase 2 trial varied from the approved dosage for ustekinumab in psoriasis. In this trial, ustekinumab significantly reduced signs and symptoms of psoriatic arthritis and diminished skin lesions as compared with placebo.

Interpretation

An unmet clinical need exists for new treatments in psoriatic arthritis. PSUMMIT 1 is the first large phase 3 trial of ustekinumab for psoriatic arthritis in patients with an inadequate response to disease-modifying antirheumatic drugs or non-steroidal anti-inflammatory drugs, or both. The 52 week results of our study showed that ustekinumab significantly improves signs and symptoms of psoriatic arthritis compared with placebo (including skin and soft tissue manifestations of the disease), a safety profile similar to that noted with the use of ustekinumab in psoriasis alone, and additional safety data about concomitant methotrexate. Taken together, our findings suggest that ustekinumab provides a good alternative biological treatment for patients with moderate-to-severe psoriatic arthritis across the subpopulations of patients assessed.

serum biomarker determinations, are underway to assess the relative contribution of inhibition of interleukin 23 versus 12 in the context of p40 neutralisation in psoriatic arthritis.

The safety of long-term ustekinumab therapy has been assessed through several years in psoriasis,[41] and our findings to week 52 in psoriatic arthritis accord with these data. The types and numbers of patients with adverse events (including serious adverse events) were similar across treatment groups. No deaths, opportunistic infections, cases of tuberculosis, or malignancies were reported by week 52. Three patients had major adverse cardiovascular events, including myocardial infarction at 8 weeks, myocardial infarction at 22 weeks, and stroke at 29 weeks after starting ustekinumab. We noted no serious infections by week 24, and those occurring from week 24 to week 52 were infrequent—ie, two cases of cholecystitis and one each of salpingitis, erysipelas, and pharyngolaryngeal abscess. Injection-site reactions were uncommon, and all were mild in intensity.

As with other biological agents, the safety of ustekinumab merits close long-term follow up in the context of registries, especially to fully assess cardiovascular risks. Furthermore, the generalisability of our efficacy and safety findings to a more diverse patient population needs continued assessment. As noted, interpretation of our data is also restricted because rules for handling of early-escape data were not applied after week 24, and because of the shortness of the placebo-controlled period. Furthermore, radiographic data have been gathered but are not reported. These data were prespecified to be analysed in combination with radiographic data from a second phase 3 trial in psoriatic arthritis (PSUMMIT 2) and will be reported in a forthcoming paper. Findings related to ustekinumab-treated patients with psoriatic arthritis who were anti-TNFα-experienced will also be reported in a forthcoming paper, which will be specific to the efficacy and safety findings of the PSUMMIT 2 trial.

For the **trial details** see http://clinicaltrials.gov/show/NCT01077362

Contributors

All authors participated in trial design; data collection, analysis, or interpretation; or manuscript preparation (or combinations thereof).

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Conflicts of interest

IBM has received grant funding and honoraria from Abbott, BMS, Janssen, Pfizer, Roche, Merck/Schering-Plough, and UCB. AK has received funding for clinical research sponsored by Abbott, Amgen, Janssen, and UCB. ABG currently has consulting or advisory board agreements in place with Abbott (AbbVie), Actelion, Amgen, Astellas, Beiersdorf, Bristol-Myers Squibb, Canfite, Celgene, Coronado, Dermipsor, Incyte, Janssen, Karyopharm, Lilly, Novo Nordisk, Novartis, Pfizer, Teva, UCB, and Vertex, and has received research or educational grants (paid to Tufts Medical Center) from Amgen, Abbott, Celgene, Janssen, Lilly, Novartis, and Pfizer. LP has received funding for clinical research or honoraria, or both, from Abbott, Amgen, Celgene, Janssen, Merck/Schering-Plough, and Pfizer. PR has received research grant funding and honoraria from Abbott, Amgen, Janssen, Merck/Schering-Plough, and Wyeth. CR has received research grant support from Amgen, Janssen, and UCB, and has received consultancy fees from Abbott, Amgen, Janssen, Regeneron, Roche, and UCB. CB, SL, YW, and AMM are employees of Janssen Research & Development. MKD was an employee of Janssen at the time this paper was drafted, and is now an employee of Alexion Pharmaceuticals.

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