Extension of ustekinumab maintenance dosing interval in moderate-to-severe psoriasis: results of a phase IIIb, randomized, double-blinded, active-controlled, multicentre study (PSTELLAR)

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Summary

Background Phase III studies showed that some patients maintained response for ≥6 months following ustekinumab discontinuation.

Objectives To assess clinical responses with extended ustekinumab maintenance dosing intervals.

Methods Adults with moderate-to-severe plaque psoriasis received ustekinumab at weeks 0, 4 and 16 during open-label treatment. Patients achieving a week-28 Physician’s Global Assessment (PGA) score of cleared/minimal (PGA = 0/1) were randomized 1:4 to group 1 [approved every 12 weeks (q12 wk) maintenance] or group 2 (q12–24 wk; response-based dosing determined by time to loss of PGA = 0/1). Key end points included the number of visits with PGA = 0/1 (primary end point) and ≥75% improvement in Psoriasis Area and Severity Index (PASI 75) between weeks 88 and 112, and PGA/PASI responses between weeks 28 and 112.

Results Overall, 378 patients achieved PGA = 0/1 at week 28 and were randomized to group 1 (n = 76) or group 2 (n = 302). Patients in group 1 had numerically greater mean numbers of visits with PGA = 0/1 than group 2 and also with PASI 75 from week 88 to 112. A higher proportion of patients in group 1 (55%) than group 2 (39%) had PGA = 0/1 at all seven visits from week 88 to 112. Maintenance of response was observed with dose-interval extension beyond q12 wk in a subset of patients. Extending the dosing interval did not affect antibody development or safety.

Conclusions Efficacy was better maintained among week-28 PGA responders randomized to continue q12 wk ustekinumab vs. extending maintenance dosing based on clinical response, although some patients maintained high levels of efficacy with up to q24 wk dosing.
Ustekinumab was approved by the U.S. Food and Drug Administration (FDA) for treating adults with moderate-to-severe psoriasis who are candidates for phototherapy/systemic therapy. The approved dosing, derived from the phase III PHOENIX 1 and PHOENIX 2 studies, is based on weight (45 mg for patients ≤ 100 kg or < 90 mg for patients > 100 kg) and administered at week 0, week 4 and every 12 weeks (q12 wk) thereafter. In PHOENIX 1, week-40 ustekinumab responders who were rerandomized to continue q12 wk maintenance therapy showed superior efficacy vs. responders rerandomized to treatment withdrawal. Maintenance of response through ≥ 24 weeks in a majority of patients following ustekinumab withdrawal raised the possibility that clinical response may be sustained in some patients receiving maintenance doses at intervals > 12 weeks apart.

In general, limited data are available regarding dose-interval extension for biological therapies. Consequently, the FDA requested that the sponsor investigate the impact of extending the approved ustekinumab maintenance dosing interval beyond q12 wk on efficacy, safety and immunogenicity in this Prospective Study to assess Extended Longitudinal dosing with multiple Assessments of Response (PSTELLAR).

Patients and methods

Study design and participants

PSTELLAR (NCT01550744; https://clinicaltrials.gov/ct2/show/NCT01550744?term=ustekinumab%2C+PSTELLAR&rank=1), designed in collaboration with the U.S. FDA, was a phase IIIb, randomized, double-blinded, active treatment-controlled, multicentre study evaluating ustekinumab in adults (18–80 years) with moderate-to-severe plaque psoriasis [≥ 10% body surface area (BSA), Physician’s Global Assessment (PGA) score ≥ 3] for ≥ 6 months before the study began. Patient eligibility criteria were largely consistent with the registrational PHOENIX 1 and 2 trials. Nonplaque or drug-induced psoriasis, confounding inflammatory diseases, or prior anti-interleukin (IL)-12 or IL-23 treatment precluded study participation. Each site’s institutional review board approved the protocol; patients provided written consent to participate.

The study comprised screening, open-label run-in treatment (week 0–28) to identify responders, double-blinded treatment of randomized eligible responders [starting with a dose-interval determination period from week 28 to week 40, followed by visits q4 wks through week 104] and post-treatment follow-up (visits at weeks 108, 112 and 116, and a safety telephone/on-site assessment at week 124) (Fig. 1). During open-label run-in treatment, patients received subcutaneous ustekinumab injections at weeks 0, 4 and 16. Because phase III registrational studies showed steady-state clinical response by week 28,1,2 responders were randomized at this time point. Patients achieving PGA = 0/1 at week 28 were randomized 1 : 4 (stratified by baseline weight ≤ 100 kg or > 100 kg and PGA = 0/1) to group 1 (approved q12 wk maintenance) or group 2 (q12–24 wk response-based dosing determined by time to loss of PGA = 0/1).

At week 28, patients randomized to group 2 entered the dose-interval determination period (week 28–40) and did not receive ustekinumab until the next visit at which the PGA response of 0/1 was not maintained. Patients who failed to maintain PGA = 0/1 at 16, 20 or 24 weeks after their last injected dose during the run-in period at week 16 received ustekinumab at a dosing interval corresponding to the timing of their last visit with a response (q12 wk, q16 wk or q20 wk starting at week 32, week 36 or week 40, respectively), with the final injection at week 104. Patients who did not lose PGA response through week 40 (24 weeks after the week-16 run-in period injection) received q24 wk maintenance dosing starting at week 40. Patients who did not achieve PGA = 0/1 at week 28 discontinued the study agent before week 28, and those who did not receive three study agent injections before week 28 were withdrawn from the...
study with no further study agent injections. Safety was monitored in all patients for ≥20 weeks after their last study agent injection. During the double-blinded treatment period, subcutaneous placebo injections were administered to maintain the blind.

Patient assessments
The static PGA measure documented the investigator’s assessment of the severity of qualitative features (erythema/scale/induration) of psoriasis lesions at a given time point; the Psoriasis Area and Severity Index (PASI) assessed the severity of both the qualitative features and BSA coverage (Table 1).4 PGA and PASI assessments were performed using comparator scoring cards to standardize erythema, scale and induration assessments, in addition to lighting effects.

Blood samples were collected to measure serum ustekinumab concentrations and antibodies to ustekinumab using validated immunoassays. The lowest quantifiable serum ustekinumab concentration was 0.1688 µg mL⁻¹. Safety assessments primarily comprised reporting of adverse events (AEs) and physical examinations. Exploratory analyses based on gene expression and major histocompatibility class 1 Cw6 allele (HLA-Cw6) genotyping, in addition to serum biomarker determinations, are detailed in File S1 (see Supporting Information).

Statistical methods
Sample size estimates
PSTELLAR was sized to provide reasonable response rate estimates among patients undergoing different treatment regimens as part of a postmarketing commitment. A study population of approximately 325 randomized patients was estimated to provide 95% confidence intervals (CIs) of 64.9–85.9% based on a PGA = 0/1 response of 75% for group 1 (n = 65; q12 wk maintenance dosing) and 54.0–66.0% based on a 60% response for group 2 (n = 260; q12–24 wk response-based dosing) during the evaluation period between week 88 and week 112.

Primary, key secondary and additional preplanned efficacy end points
The primary end point was the number of visits at which week-28 randomized patients had PGA = 0/1 between week 88 and week 112. Major secondary end points were (i) proportions of randomized patients with PGA = 0/1 from week 28 to week 112; (ii) numbers of visits at which randomized patients had ≥75% improvement in PASI score (PASI 75) between week 88 and week 112; and (iii) proportions of randomized patients with PASI 75 from week 28 to week 112. No formal statistical comparisons were made between treatment groups; two-sided 95% CIs were provided for selected end points (File S1; see Supporting Information).

Exploratory analyses and profile of extended interval dosing: clinical response
In exploratory analyses, primary and key secondary efficacy end points were assessed among patients achieving PGA = 0 (positive predictor) vs. PGA = 1 (negative predictor) at week 28. Positive predictive values (PPVs) and negative predictive values (NPVs) were calculated to estimate the probability that a patient with a positive or negative predictor would have a particular outcome (File S1; see Supporting Information).5
Further exploratory analyses intended to profile patients who maintained response with extended dosing intervals were also conducted. These analyses were based on clinical features (e.g. demographics, disease activity, duration of disease), gene expression patterns and genetic risk scores, and serum biomarkers (File S1; see Supporting Information).

### Results

#### Patient disposition and demographics

PSTELLAR was conducted at 42 U.S. study sites from March 2012 to July 2015. During the open-label run-in treatment period, 100 of 478 enrolled patients (20.9%) discontinued the study agent, most commonly owing to a failure to achieve PGA = 0/1 at week 28 (12.1% of enrolled patients). The remaining 378 week-28 PGA = 0/1 responders (79.1%) were randomized to group 1 (n = 76) or group 2 (n = 302). From week 28 to week 104, 22% of patients in each randomized group discontinued the study agent, most commonly owing to loss to follow-up (group 1, 8%; group 2, 4%), AEs (group 1, 5%; group 2, 5%) or withdrawal consent (group 1, 3%; group 2, 4%).

### Table 1 Baseline demography and disease characteristics, among all patients randomized at week 28

|                      | Group 1 | Overall | q12 wk | q16 wk | q20 wk | q24 wk | Groups 1 and 2 |
|----------------------|---------|---------|--------|--------|--------|--------|----------------|
| Treated patients randomized at week 28, n | 76      | 302     | 84     | 61     | 51     | 84     | 378            |
| Age (years)          | 44-3 (15-34) | 45-3 (13-82) | 45-8 (14-18) | 45-3 (12-89) | 42-7 (13-84) | 46-2 (14-13) | 45-1 (14-12) |
| Male, n (%)          | 44 (57.9) | 192 (63-6) | 45 (53-6) | 39 (65-9) | 39 (76-5) | 54 (64-3) | 236 (62-4)    |
| Weight (kg)          | 90-5 (27-72) | 93-4 (23-47) | 95-4 (24-00) | 93-9 (22-61) | 90-5 (21-94) | 92-6 (25-39) | 92-8 (24-38) |
| BMI (kg m⁻²), n (%)  | Normal (< 25) | 19 (25-0) | 58 (19-2) | 12 (14-3) | 10 (16-4) | 11 (21-6) | 20 (23-8) | 77 (20-4) |
|                  | Overweight (≥ 25 to < 30) | 19 (25-0) | 92 (30-5) | 21 (25-0) | 19 (31-1) | 21 (41-2) | 24 (28-6) | 111 (29-4) |
|                  | Obese (≥ 30) | 38 (50-0) | 152 (50-3) | 51 (60-7) | 32 (52-5) | 19 (37-3) | 40 (47-6) | 190 (50-3) |
| Psoriasis disease duration (years) | 19-0 (12-05) | 15-2 (12-20) | 15-1 (11-85) | 15-9 (11-37) | 14-8 (11-13) | 13-6 (12-81) | 15-9 (12-25) |
| Age at diagnosis (years) | 25-9 (14-42) | 30-7 (15-18) | 31-2 (15-70) | 29-9 (13-26) | 28-4 (14-36) | 33-1 (15-58) | 29-7 (15-13) |
| BSA (%)              | 27-3 (17-89) | 23-2 (15-49) | 25-3 (17-99) | 24-4 (15-69) | 23-5 (15-35) | 20-8 (13-26) | 24-0 (16-06) |
| Historical peak BSA³, N | 37       | 149      | 42      | 27      | 23      | 45      | 186           |
| ≥ 20%, n (%)         | 25 (67-6) | 69 (46-3) | 20 (47-6) | 12 (44-4) | 13 (56-5) | 18 (40-0) | 94 (50-5)    |
| < 20%, n (%)         | 12 (32-4) | 80 (53-7) | 22 (52-4) | 15 (55-6) | 10 (43-5) | 27 (60-0) | 92 (49-5)    |
| PASI score (0–72)⁴   | 19-0 (8-90) | 17-9 (8-62) | 19-2 (10-18) | 19-5 (8-98) | 17-3 (9-27) | 16-3 (6-22) | 18-11 (8-68) |
| PGA score, n (%)     | Moderate (3) | 50 (65-8) | 198 (65-6) | 47 (56-0) | 41 (67-2) | 36 (70-6) | 56 (66-7) | 248 (65-6) |
|                  | Marked (4) | 25 (32-9) | 84 (27-8) | 31 (36-9) | 16 (26-2) | 10 (19-6) | 23 (27-4) | 109 (28-8) |
|                  | Severe (5) | 1 (1-3) | 20 (6-6) | 6 (7-1) | 4 (6-6) | 5 (9-8) | 5 (6-0) | 21 (5-6) |
| Historical peak PGA score, n ⁵ | 37       | 149      | 42      | 27      | 23      | 45      | 186           |
| Marked or severe (≥ 4), n (%) | 14 (37-8) | 65 (43-6) | 24 (57-1) | 9 (33-3) | 8 (34-8) | 19 (42-2) | 79 (42-5)   |
| Systemic psoriasis therapy, n (%) | Prior conventional therapy | 30 (39-5) | 94 (31-1) | 27 (32-1) | 20 (32-8) | 14 (27-5) | 28 (33-3) | 124 (32-8) |
|                  | Prior biological therapy | 27 (35-5) | 77 (25-5) | 28 (33-3) | 12 (19-7) | 16 (31-4) | 18 (21-4) | 104 (27-5) |

BMI, body mass index; BSA, body surface area; PASI, Psoriasis Area and Severity Index; PGA, Physician’s Global Assessment; q12/16/20/24w, every 12/16/20/24 weeks. ¹Ustekinumab q12 wk maintenance dosing. ²Ustekinumab q12–24 wk response-based dosing. Includes 22 patients who were randomized but not assigned to extended dosing, because they discontinued study agent or were withdrawn from the study before first loss of PGA response. ³Historical peak BSA/PGA information was collected after the week 28 visit for some patients. ⁴The PASI employs a 5-point scale (0–4) to assess erythema, scale and induration in each of four body regions scored for percentage of BSA involved. ⁵Overall lesions were graded for induration (0 = no evidence of plaque elevation, 5 = severe plaque elevation ≥ 1.25 mm), erythema (0 = no evidence of erythema, hyperpigmentation may be present, 5 = dusky to deep red coloration) and scaling (0 = no evidence of scaling, 5 = severe; very thick tenacious scale predominates). The overall PGA score is the average of the three subscale scores, with scores of 0, 1, 2, 3, 4 and 5 denoting cleared (except for residual discoloration), minimal, mild, moderate, marked and severe lesions, respectively. Data presented are mean (SD) unless otherwise specified.
between randomized groups, although some numerical differences were noted (Table 1).

**Primary, key secondary and additional preplanned efficacy analyses**

In descriptive assessments of the primary end point, group 2 exhibited a numerically lower mean number of visits with PGA = 0/1 than group 1 between week 88 and week 112 [4.1 vs. 4.5, respectively; mean difference = -0.46 (95% CI = -1.20–0.29)]. Additionally, 39% of patients in group 2 and 55% of patients in group 1 had PGA = 0/1 at all seven assessment period visits (Table S1 and Fig. S2; see Supporting Information).

Similarly, group 2 had a numerically lower mean number of visits at which patients had a PASI 75 response than group 1 between week 88 and week 112 [5.4 vs. 5.8; mean difference = -0.32 (95% CI = -0.66–0.33)]. Similar proportions of patients in group 2 and group 1 (67% and 70%) had a PASI 75 response at all seven assessment period visits (Table S1 and Fig. S2; see Supporting Information).

Response rates over time showed that the proportion of patients maintaining PGA = 0/1 from week 28 to week 112 was somewhat lower for group 2 than for group 1. Response rates decreased during the dose-interval determination period (week 28–40) for both randomized groups. However, the decrease in response rate was greater for group 2 as would be expected, given that dosing interval was defined by loss of response for most subgroups of group 2. After week 40, PGA response rates remained generally stable through week 112, with some modest variability at time points between doses for both groups (Fig. 2a). PASI 75 response patterns from week 28 to week 112 paralleled those for PGA = 0/1, although PASI 75 rates were generally better maintained during the dose-interval determination period between week 28 and week 40 (Fig. 2b).

The proportion of patients with PGA = 0 was consistently higher for group 1 vs. group 2 at each time point between the first postrandomization visit (week 32) and week 112 (Fig. 2a). Higher proportions of patients in group 1 also had ≥ 90% improvement (PASI 90) and 100% improvement (PASI 100) in PASI score over time. Separation between the PASI 90 response curves for group 1 and group 2 was observed starting at the first postrandomization visit (week 32) and maintained through week 108; similar patterns were observed for PASI 100 responses (Fig. 2b).

**Profile of extended interval dosing**

Clinical responses for the q24-week subgroup of group 2

Higher PGA = 0/1 and PGA = 0 response rates were observed for the q24 wk subgroup than for the other subgroups of

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**Fig 2.** Percentage of patients with (a) Physician’s Global Assessment (PGA) = 0/1 and PGA = 0 and (b) ≥ 75%, 90% and 100% improvement of Psoriasis Area and Severity Index (PASI) responses (PASI 75, PASI 90 and PASI 100) from week 28 to week 112 by visit, among all patients randomized at week 28. q12/24 wk, every 12/24 weeks.
group 2 over time from week 40 to week 112 (Fig. 3a). The mean number of visits at which patients had PGA = 0/1 between week 88 and week 112 was higher for the q24 wk subgroup of group 2 (5/5) than for the q12 wk (3/2), q16 wk (2/8) and q20 wk (4/1) subgroups. In addition, a higher proportion of patients in the q24 wk dosing subgroup had PGA = 0/1 for at least five of seven assessment period visits between week 88 and week 112 vs. other subgroups of group 2 (Table S1 and Fig. S2; see Supporting Information).

Similarly, PASI 75 and PASI 90 (Fig. 3b) response rates were higher from week 28 to week 112 for the q24 wk subgroup vs. other subgroups of group 2. The mean number of visits with a PASI 75 response between week 88 and week 112 was highest for the q24 wk subgroup (6/3) and progressively lower for the q20 wk (5/6), q16 wk (5/2) and q12 wk (4/7) subgroups (Table S1 and Fig. S2; see Supporting Information).

Further exploratory analyses

Results concerning the value of potential genetic determinants, serum biomarkers and achievement of three consecutive PGA = 0 responses at different time points for predicting ustekinumab response are provided in File S1 (see Supporting Information).

Pharmacokinetics

For patients in group 1 receiving continuous q12 wk dosing, steady-state serum ustekinumab concentrations were achieved by week 28 and consistent median trough serum ustekinumab concentrations were generally maintained at steady state through week 112. Median trough serum ustekinumab concentrations at week 28 were progressively higher for each subgroup of group 2 that eventually received ustekinumab at less frequent intervals (q12 wk 0.44 μg mL⁻¹; q16 wk 0.55 μg mL⁻¹; q20 wk 0.67 μg mL⁻¹; q24 wk 0.79 μg mL⁻¹). However, interquartile ranges surrounding the median
concentrations for the subgroups overlapped substantially, limiting their predictive value for individual patients. Significantly higher trough serum ustekinumab concentrations were observed for the q24 wk subgroup of group 2 vs. the q12 wk subgroup at week 4, week 16 and week 28 (all P < 0.001; Fig. 4).

**Safety**

Assessments during the open-label run-in period through week 28 raised no new safety concerns (Table S2; see Supporting Information). From week 28 to week 124 (core safety analysis), similar proportions of patients in group 1 (72%) and group 2 (73%) had at least one AE (Table S3; see Supporting Information). Seven patients in group 1 (9%) and 21 patients in group 2 (7%) experienced serious AEs. With the exception of rib fracture in two patients (0-7%) (both in the q24 wk subgroup of group 2), no other serious AE was reported for more than one patient. Three serious infections were reported in group 2: bacterial infection (q20 wk), cystitis (q12 wk) and urinary tract infection (q12 wk). Two deaths occurred during the double-blinded treatment period (week 28–124). One patient (group 1) died of natural causes (possible cardiovascular AE) approximately 10 weeks after the last dose of ustekinumab 90 mg given at week 28. One patient (q12 wk subgroup of group 2) was diagnosed with acute myeloid leukemia approximately 1 month after the last dose of ustekinumab 90 mg administered at week 80 and died approximately 5 months later. AEs led to discontinuation of the study agent in 7% of patients in group 1 and 6% of patients in group 2.

Malignancies (excluding nonmelanoma skin cancer) were reported in two patients through week 28 (colon cancer, prostate cancer) and in four patients during the double-blinded treatment period (group 1: transitional cell bladder carcinoma; group 2: pancreatic carcinoma, acute myeloid leukemia, chronic myeloid leukemia). One major cardiac AE occurred during the run-in period (myocardial infarction), and two occurred during the double-blinded treatment period (myocardial infarction, cerebrovascular accident). All three patients had at least two cardiovascular risk factors at study entry. No possible anaphylactic reactions or possible serum-sickness-like reactions associated with the study agent were reported through week 124. None of the 63 patients positive for antibodies to ustekinumab had an injection site reaction during the study.

**Immunogenicity**

Overall, 63 of 455 patients (13.8%) treated with ustekinumab who had evaluable samples tested positive for antibodies to ustekinumab through week 124. The incidence of antibody development was similar among patients receiving ustekinumab 45 mg (n = 41, 13.9%) and 90 mg (n = 22, 13.7%), and for patients in group 1 (n = 7, 9%) and patients in group 2 (n = 32, 11%). Most patients who were positive...
**Discussion**

This study was conducted to address an FDA postmarketing request to assess the impact of extending ustekinumab dosing beyond the approved q12 wk interval on efficacy, safety and immunogenicity in patients with moderate-to-severe psoriasis. Overall, 378 patients (79%) demonstrated a PGA = 0/1 response at week 28 and were randomized to continue with q12 wk maintenance dosing (group 1) or attempt a response-based dose-interval extension up to q24 wks (group 2).

Findings indicate that efficacy was better maintained in group 1 vs. group 2 (primary assessment), as evidenced by the numerically higher mean number of visits with a PGA = 0/1 response during the week 88 to week 112 assessment period. Additionally, higher PGA = 0/1, PASI 75 and PASI 90 response rates, along with higher PGA = 0 and PASI 100 response rates indicating complete clearance, were consistently observed for group 1 vs. group 2 from week 32 to week 112. Therefore, standard q12 wk maintenance ustekinumab dosing provided better clinical outcomes than dose-interval extension.

Some patients, however, maintained high levels of PGA = 0/1 and other responses with dosing intervals extended to q16 wk, q20 wk and q24 wk, suggesting that a subset of patients may be able to maintain response with maintenance dosing at intervals longer than 12 weeks. Post hoc exploratory analyses were conducted to gain a better understanding of potential clinical parameters and biomarkers that correlate with the ability to extend dosing interval and maintain response. Defining predictive factors that would provide a high level of confidence for maintaining response with an extended dosing interval could further establish guidelines and set expectations for practitioners and patients who might be considering administering ustekinumab on a less frequent basis.

In assessing clinical parameters, higher PGA, BSA and PASI responses were observed at week 28 for patients who ultimately extended to q24 wk dosing compared with patients who were unable to extend the dosing interval beyond 12 weeks. In particular, achieving a PGA = 0 response at week 28 provided informative PPVs for identifying patients who were potentially capable of extending the dosing interval. In contrast, neither baseline patient/disease characteristics nor biomarker/gene expression profiling analyses identified specific parameters that could predict ability to extend the dosing interval and maintain response. Although the mean trough serum ustekinumab concentration at week 28 for the q24 wk subgroup was significantly higher than that for the q12 wk subgroup of group 2, the wide range and overlap of values among individual patients in different dosing subgroups precluded the predictive utility of this parameter. Thus, based on the parameters examined, the ability of some patients to extend the dosing interval and maintain response seems to correlate best with early high-level response (i.e. week 28 PGA = 0). Nonetheless, further studies are needed to determine whether alternative factors may provide better predictive value.

A potential concern of response-based dosing is the risk of developing antidrug antibodies, especially if drug levels become undetectable at points between injections. In the PHOENIX 1 psoriasis trial, one cycle of ustekinumab withdrawal and retreatment did not predispose patients to antidrug antibody development.\(^1\) In testing dosing intervals that allowed ustekinumab concentrations to decline to below quantifiable levels between injections (resembling multiple withdrawal/retreatment cycles), no increased susceptibility to antidrug antibody development was noted. These findings suggest that there is no increased risk of immunogenicity when extending the maintenance dosing interval for ustekinumab up to 24 weeks.

No new safety signals were observed. Safety findings were similar between group 1 and group 2. The overall ustekinumab safety profile observed in this study was consistent with the larger body of data from the phase III ustekinumab clinical trial programme through up to 5 years of follow-up.\(^3\) Thus, our findings suggest no safety advantage or disadvantage for extending maintenance dosing intervals beyond q12 wks through up to q24 wks based on a desire to minimize ustekinumab exposure.

Several limitations should be noted. As the opportunity for patients to advance to the randomized treatment period depended on a PGA = 0/1 response at week 28, investigators may have been biased to overscore patients with borderline responses. However, the sponsor had education plans in place for investigators to minimize this potential bias. Additionally, patients were assigned to one of four group-2 dosing interval subgroups based on PGA response rather than being randomized, which limited the

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ability to perform direct comparisons between subgroups. Also, mean numbers of visits and clinical response rates for each subgroup do not necessarily translate into individual responses in clinical practice. The PGA tool itself can be a potential source of rater bias, as it does not include a BSA assessment, unlike the PASI. Thus, the study included PASI as a secondary end point. Reassuringly, the proportion of patients with a PASI 75 response at week 28 [371 of 478 (77-6%)] was similar to the proportion randomized based on PGA = 0/1 response [378 of 478, (79-1%)], suggesting that potential biases related to the PGA measure had minimal impact on randomization. Also, PGA and PASI scoring systems have been shown to change in concert and be sensitive to detect reductions in psoriasis severity with both placebo and active therapy in clinical trials. Additionally, alternative approaches for dose-interval extension (e.g. retreatment upon loss of response) could be practised and may be considered for future studies. Lastly, more extended dosing intervals that could potentially allow for maintenance of response were not studied.

In summary, study results indicate that efficacy was generally better maintained over time among week-28 PGA responders randomized to continue regular q12 wk maintenance dosing vs. extended response-based maintenance dosing regimens. Nonetheless, 28% of patients randomized to group 2 (84 of 302) were able to extend their maintenance dosing interval to q24 wks and maintain high levels of response. Previous studies have shown that most patients maintain response with q12 wk ustekinumab maintenance dosing and that in some cases additional clinical benefit may be achieved with dose escalation or interval reduction. However, results of the PSTELLAR study suggest that, within the confines of the study design and population, some patients are able to maintain clinical responses with maintenance dosing intervals longer than 12 weeks and up to 24 weeks. No adverse effects of extending the dosing interval on safety outcomes or antibody development were observed among study participants, suggesting neither a safety advantage with extended dosing nor an immunogenic penalty for administering the drug following extended drug-free intervals. Only a week-28 PGA = 0 response may have utility for predicting the ability to extend the dosing interval and maintain response among the parameters assessed. Overall, these findings further our understanding of the clinical response to ustekinumab in moderate-to-severe psoriasis.

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Appendix

Conflicts of interest

A.B. has received research support from Amgen, Boehringer Ingelheim, Celgene, Dermira, Genentech, GlaxoSmithKline, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Sanofi Genzyme, Sandoz, Sun Pharma, UCB and Valeant (> U.S. $10 000), as well as consultancy fees from Amgen, AbbVie, Boehringer Ingelheim, Celgene, Dermira, Eli Lilly, Genentech, Janssen, Eli Lilly, Merck, Novartis, Pfizer, Regeneron, Sandoz, Sanofi Genzyme, Sun Pharma, UCB and Valeant (> U.S. $10 000) and speaking fees from Eli Lilly, Janssen, Regeneron and Sanofi Genzyme (> U.S. $10 000). L.K.F. has received research support (paid to institution) from AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, GlaxoSmithKline, Janssen, Leo Pharma Inc., Medimmune, Novartis Pharmaceuticals, Pfizer, Regeneron and Sandoz, as well as consultancy fees (< U.S. $10 000) from Eli Lilly, Janssen, Nuvo Pharma and Pfizer. K.C.D. has received research support (paid to institution) from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Novartis Pharmaceuticals, Pfizer Regeneron, and Stiefel, as well as consultancy fees from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Novartis Pharmaceuticals and Pfizer (< U.S. $10 000). A.Q. has received research support (paid to institution) from Amgen, as well as...
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Supporting Information

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

File S1 Supplementary methods and results.

Fig S1. PSTELLAR patient disposition.

Fig S2. Number of visits patients had a Physician’s Global Assessment (PGA) = 0/1 or ≥ 75% improvement in Psoriasis Area and Severity Index (PASI 75) response between week 88 and week 112, all patients randomized at week 28 to ustekinumab maintenance dosing group 1 (approved q12 wk) or group 2 (q12–24 wk response-based dosing).

Fig S3. Boxplot of serum interleukin (IL)-17A levels in log2 (pg mL\(^{-1}\)) scale at multiple time points for each of the group-2 every 24 week (q24 wk) and q12 wk response-based dosing subgroups. Medians and 25/75% quartiles are marked by box lines, ‘+’ symbol represents the mean, and whiskers represent the maximal and minimal values of all samples in the group. Control samples are from a different cohort of normal healthy donors obtained from commercial vendors (BioreclamationIVT, Westbury, NY, U.S.A. and Biological Specialty Corporation, Colmar, PA, U.S.A.).

Table S1 Number of visits at which patients had a Physician’s Global Assessment (PGA) = 0/1 or ≥ 75% improvement in Psoriasis Area and Severity Index (PASI 75) response between week 88 and week 112 among patients randomized at week 28.

Table S2 Summary of adverse events from baseline through week 28 among all enrolled patients.

Table S3 Summary of adverse events from week 28 to week 124 among treated patients randomized at week 28.