Long-term efficacy and safety of ustekinumab, with and without dosing adjustment, in patients with moderate-to-severe psoriasis: results from the PHOENIX 2 study through 5 years of follow-up

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Summary

Background Evaluation of the dosing flexibility and long-term efficacy of biological agents is limited.

Objectives To evaluate the long-term efficacy and safety of ustekinumab with and without dosing adjustment in the 5-year PHOENIX 2 study.

Methods Patients were randomized to placebo or ustekinumab (45 or 90 mg) at weeks 0, 4, then every 12 weeks; patients receiving placebo crossed-over at week 12. Dosing adjustments were permitted at/beyond week 28 for early adjusters (weeks 28 or 40 per response); late adjusters (during long-term extension per investigator judgement); and nonadjusters (maintained randomized treatment throughout the study). Efficacy and safety were evaluated through weeks 244 and 264, respectively.

Results In the overall population, 70% (849 of 1212) of ustekinumab-treated patients completed treatment through week 244, with high proportions of patients responding to the 45-mg and 90-mg doses, respectively: 75% improvement in Psoriasis Area and Severity Index (PASI 75) (76.5% and 78.6%) and PASI 90 (50.0% and 55.5%). Approximately 20% of patients were early adjusters, 30% were late adjusters and 50% were nonadjusters. Approximately half of the late adjusters initiated adjustments after already achieving PASI 75. Improved response was generally observed following dosing adjustments. Through week 264, safety event rates did not increase and event rates were generally comparable between dose groups and between patients with and without dosing adjustment.

Conclusions Treatment with ustekinumab for up to 5 years was safe and effective. Improved response was generally demonstrated following dosing adjustments; further investigations are required to quantify actual incremental benefits. The results also suggest that some patients may desire treatment goals beyond PASI 75.
Many patients with moderate-to-severe psoriasis require long-term treatment with biological agents. The short-term benefits of biologics are well documented; however, the evaluation of long-term maintenance of response is limited. While a substantial proportion of patients respond to currently approved dosing regimens of biologics, some patients achieve only partial response and others may respond initially then subsequently lose response over time. Additionally, patients’ expectations for treatment success may change over time. There may be limited tolerance for any loss of efficacy after achieving response, and some patients may further increase their expectations for even greater improvement. Currently, the efficacy and safety of dosing adjustments tailored to patients’ response or expectations during long-term treatment with biologics have not been thoroughly investigated.

The efficacy and safety of ustekinumab (Stelara®; Janssen Biotech Inc., Horsham, PA, U.S.A.) for the treatment of moderate-to-severe psoriasis were evaluated in the PHOENIX 1 and PHOENIX 2 studies through 5 years, which to date is the longest duration of continuous treatment and follow-up of patients with psoriasis receiving biologics in a clinical trial setting. The impact of dosing adjustments on long-term efficacy was differentially explored in the PHOENIX studies. The PHOENIX 1 study allowed minimal dosing flexibility, and only among initial partial responders at weeks 28 or 40, who were permitted to initiate dose-interval adjustment (every 12 weeks to every 8 weeks). Aside from this, no dose adjustment (45 to 90 mg) was permitted in any patients at any time during the study, and no dosing adjustments were permitted in any patients during the long-term extension. The results through year 5 in PHOENIX 1 indicated that a substantial proportion of patients achieved and maintained response. At week 244 (Year 5), the percentage improvements achieved in the Psoriasis Area and Severity Index (PASI) for patients receiving ustekinumab 45 mg and 90 mg, respectively, were 63.4% and 72.0% (PASI 75), 39.7% and 49.0% (PASI 90) and 21.6% and 26.4% (PASI 100).

The added value of the PHOENIX 2 study was the evaluation of the long-term efficacy of ustekinumab with greater dosing flexibility, including (i) dose-interval adjustment in partial responders early in treatment and (ii) investigator-initiated dosing adjustments (dose and/or dose-interval) based on clinical judgement during the long-term extension. Previously reported results from the randomized dose-interval adjustment period through week 52 demonstrated that improvements were observed among patients adjusted from 90 mg every 12 weeks to 90 mg every 8 weeks, suggesting that increasing exposure may benefit selected subgroups of initial partial responders. To evaluate the longer-term impact of early dose-interval adjustment and the impact of additional dosing flexibility during the long-term extension on the efficacy and safety of ustekinumab, the current report summarizes the observations from PHOENIX 2 through 5 years of follow-up.

Patients and methods

Patients and study design

PHOENIX 2 was a phase 3, multicentre, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of ustekinumab 45 mg and 90 mg through 5 years of follow-up. This trial was initiated on 3 March 2006 and completed on 10 October 2011. The study included four distinct periods: (i) placebo-control (weeks 0–12); (ii) placebo-cross-over and active treatment (weeks 12–28); (iii) randomized dose-interval adjustment (weeks 28–52) and (iv) long-term extension (weeks 52–264), during which investigator-initiated adjustments of dose and/or dose-interval were permitted. The baseline randomization was stratified by investigational site, weight (≤ 90 kg or > 90 kg) and whether or not the patient had an inadequate response, intolerance, or contraindication to fewer than, or more than, three conventional systemic therapies. The second randomization, at week 28, was stratified by investigational site and baseline weight.
A previous report summarized the data through week 52, focusing on the overall population and the randomized dose-interval adjustment population. The current report summarizes data through year 5 for the following four patient populations: (i) overall, (ii) early adjusters, (iii) late adjusters and (iv) nonadjusters. The overall population includes all patients treated with at least one dose of ustekinumab regardless of dosing adjustment status. The early adjusters include all patients who were partial responders (PASI 50 to < PASI 75) at weeks 28 or 40 who were adjusted per protocol (both randomized and nonrandomized) from every 12-week dosing to every 8-week dosing at their originally randomized dose of 45 or 90 mg. The late adjusters include all patients who continued their randomized dose and dose interval through week 52, and initiated dosing adjustments for the first time in the long-term extension, during which investigators were permitted to initiate the following dosing adjustments at their discretion: (i) patients who were receiving 45 mg every 12 weeks were eligible for up to two adjustments (i.e. from 45 mg every 12 weeks to 45 mg every 8 weeks, then from 45 mg every 8 weeks to 90 mg every 8 weeks); (ii) patients who were receiving 45 mg every 8 weeks were eligible for a single dose-interval adjustment to 90 mg every 8 weeks; and (iii) patients who were receiving 90 mg every 12 weeks were eligible for a single dose-interval adjustment to 90 mg every 8 weeks. Finally, the nonadjusters include all patients who received their original randomized ustekinumab dose every 12 weeks throughout the 5-year study, without adjusting the dose or the dosing interval at any time.
Efficacy and safety evaluations

Through week 244 (the last year-5 dose), disease severity and treatment response were evaluated at each study visit prior to dosing using PASI and Physician’s Global Assessment (PGA). Safety end points were evaluated through week 264 (the final year-5 visit). Serum samples were collected prior to ustekinumab dosing and assessed using a bridging immunoassay to determine the presence of antibodies to ustekinumab.

Statistical analyses

To evaluate clinical response over time (weeks 0–244) in the overall population, the proportion of patients achieving PASI 75/90/100 (i.e. at least 75%, 90% and 100% improvement from baseline), the proportion achieving PGA (0, clear; 1, minimal) responses, and the proportion achieving PASI scores (≤ 5, ≤ 3, ≤ 1) were reported. To evaluate the incidence of dosing adjustments, the proportions of patients with dosing adjustments were summarized by dose group and by time of first adjustment (i.e. before or during the long-term extension). To evaluate the level of disease severity that may have triggered investigator-initiated adjustments among late adjusters, PASI response at the time of initiating adjustment was summarized.

The impact of dosing adjustment on clinical response over time was evaluated separately for patients who did and did not have dosing adjustments. The proportion of early adjusters achieving PASI 75 from week 28 through 244 was summarized. For late adjusters, the proportion of patients achieving various PASI response targets for up to 144 weeks after initiating adjustment was summarized by PASI responder status at the time of initial dosing adjustment. The 144-week time point was chosen because it was the longest duration of follow-up with a sample size sufficient for meaningful comparisons. Finally, PASI 75 and 90 responses from baseline through week 244 were summarized for nonadjusters.

All analyses were performed based on randomized dose group assignment at baseline, regardless of dose adjustment status (i.e. patients originally receiving 45 mg who were adjusted to 90 mg were included in the 45-mg group for analysis). Patients who discontinued treatment due to unsatisfactory therapeutic effect or an adverse event (AE) of worsening psoriasis, and those who used a protocol-prohibited medication/therapy were included in all subsequent time points as nonresponders, regardless of observed data. Week 28-nonresponders (< PASI 50) who discontinued treatment per protocol had their week-28 data carried forward through week 244. Patients with missing week-12 data were considered nonresponders at week 12. Other missing data (e.g. discontinuation for reasons unrelated to efficacy such as safety or loss to follow-up) were not imputed. To assess the impact of missing data, a sensitivity analysis was performed in the overall population using a last-observation-carried-forward (LOCF) procedure to impute additional missing data (e.g. discontinuations for any reason unrelated to efficacy).

Through week 264, the incidence of safety events [i.e. overall AEs; AEs leading to discontinuation; serious AEs (SAEs) and AEs of interest, including infections, nonmelanoma skin cancers (NMSCs), other malignancies and major adverse cardiovascular events (MACEs), defined as cardiovascular death, myocardial infarction or stroke] were reported per 100 patient-years of follow-up. Safety outcomes were summarized for the overall population by dose received, to evaluate the potential effect of dose (45 mg vs. 90 mg) on safety, and by dosing adjustment status (nonadjusters vs. adjusters) to evaluate the potential impact of dosing adjustment. Patients who adjusted from 45 to 90 mg were included in the 45-mg or 90-mg group based on the dose received when the event was reported. Safety events reported for patients in the adjusters group included events occurring both before and after adjustments.

Results

Patients

This report is based on 1212 of 1230 randomized patients who received at least one dose of ustekinumab (Fig. 1b). Overall, 849 patients (70.0%) completed treatment through week 244 (year 5), with comparable retention rates between dose groups and between patients with and without dosing adjustment. Treatment discontinuation rates and related reasons were 7.8% (efficacy), 9.8% (safety) and 4.4% (loss to follow-up). Discontinuations for other reasons were reported in 7.9% of patients; the most common reason was withdrawal of consent (4.1%).

Baseline demographic and clinical characteristics were similar between patients randomized to ustekinumab 45 mg and 90 mg in the overall population. Patients with dosing adjustments were heavier (mean weight 94.6 vs. 85.7 kg, \( P < 0.001 \)), had a higher percentage of body surface area (mean 29.0% vs. 22.9%, \( P < 0.001 \)), had higher a PASI score (mean 20.5 vs. 18.4, \( P < 0.001 \)), were more likely to have comorbidities (hyperlipidaemia 24.6% vs. 16.4%, \( P < 0.001 \); hypertension 29.6% vs. 24.3%, \( P = 0.046 \); or psoriatic arthritis 28.7% vs. 21.9%, \( P = 0.009 \)) and had received more systemic therapies (63.2% vs. 47.8%, \( P < 0.001 \)) and biologies (44.4% vs. 30.3%, \( P < 0.001 \); Table 1).

Efficacy

Overall population

High levels of clinical response were achieved and maintained through year 5 in the overall population, which included patients with and without dosing adjustment. At week 244, 76.5% and 78.6% of patients initially randomized to 45 and 90 mg, respectively, achieved PASI 75 (Fig. 2a), while 50.0% and 55.5% achieved PASI 90 (Fig. 2b). Results were similar for the LOCF analyses (Fig. 2a,b), indicating that inclusion/exclusion of patients who discontinued from the study for reasons unrelated to efficacy did not alter the results. The
Table 1 Baseline demographic and clinical characteristics of all patients treated with at least one dose of ustekinumab by randomized dose group and of patients treated at or beyond week 28 by dosing adjustment status

| Relevant medical history | Patients treated with ustekinumab by randomized dose groups | Patients treated with ustekinumab by dosing adjustment status |
|--------------------------|-------------------------------------------------------------|---------------------------------------------------------------|
|                         | 45 mg<sup>b</sup> | 90 mg<sup>b</sup> | Combined | Nonadjusters | Adjusters | Combined |
| Patients treated, n     | 606              | 606              | 1212     | 544          | 568       | 1112     |
| Age (years)             | 45.7 ± 12.5      | 46.7 ± 11.9      | 46.2 ± 12.2 | 45.9 ± 12.8 | 46.5 ± 11.3 | 46.2 ± 12.1 |
| Weight (kg)             | 90.7 ± 21.4      | 91.2 ± 21.0      | 91.0 ± 21.2 | 85.7 ± 18.9 | 94.6 ± 21.1 | 90.3 ± 20.5 |
| Psoriasis duration (years) | 19.4 ± 11.8    | 20.8 ± 12.4      | 20.1 ± 12.1 | 19.2 ± 12.5 | 21.2 ± 11.6 | 20.2 ± 12.1 |
| Involved BSA (%)        | 26.0 ± 16.3      | 26.6 ± 17.0      | 26.3 ± 16.7 | 22.9 ± 14.5 | 29.0 ± 17.9 | 26.0 ± 16.6 |
| PGA, marked or severe   | 2.4 (1-8)        | 2.3 (1-8)        | 2.4 (1-8) | 2.0 (1-8) | 2.4 (1-8) | 2.4 (1-8) |
| PASI score (0–72)       | 19.3 ± 7.1       | 19.8 ± 7.4       | 19.6 ± 7.2 | 18.4 ± 6.7 | 20.5 ± 7.5 | 19.5 ± 7.2 |
| DLQI score (0–30)       | 12.2 ± 7.0       | 12.4 ± 7.1       | 12.3 ± 7.1 | 11.8 ± 6.8 | 12.7 ± 7.2 | 12.3 ± 7.0 |

Relevant medical history

- Psoriatic arthritis
- Diabetes
- Hypertension
- Hyperlipidaemia
- Previous treatment
  - Topical agent
  - Phototherapy (UVB or PUVA)
  - Conventional systemic agents<sup>c</sup>
  - Biological agents<sup>d</sup>
  - Patients with latent TB<sup>e</sup>

Values are presented as number of patients (%) or mean ± SD. BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PGA, Physician’s Global Assessment; PUVA, psoralen + ultraviolet A; TB, tuberculosis; UV, ultraviolet. *Includes patients treated at or beyond week 28, the first opportunity for dosing adjustment per study design. **Placebo crossover patients are included after cross-over to ustekinumab. Conventional systemic agents included PUVA, methotrexate, acitretin and ciclosporin. Biological agents included adalimumab, efalizumab, etanercept and infliximab. "Latent TB infection was defined as a positive Mantoux tuberculin skin test result in a patient with no signs or symptoms suggestive of active TB by medical history, physical examination and chest radiograph."
narrowing dose response over time between the 45-mg and 90-mg groups may be attributable to the effects of dosing adjustments in a subgroup of patients in the 45-mg group who could have received up to two adjustments (45 mg every 12 weeks to 45 mg every 8 weeks to 90 mg every 8 weeks) during the study.

Among patients originally randomized to 45 and 90 mg, respectively, 28% and 31% of patients achieved PASI 100, and 54% and 58% achieved PGA 0 or 1 at week 244. The proportions of patients achieving PASI scores ≤ 5, ≤ 3 and ≤ 1, respectively, were 76.7%, 64.2% and 39.3% (45 mg; Fig. 3a) and 78.1%, 67.0% and 41.4% (90 mg; Fig. 3b) at week 244.

Incidence of dosing adjustments

Among patients treated at or beyond week 28, 20% (223 of 1112) were early adjusters, 31% (345/1112) were late adjusters and 49% (544/1112) were nonadjusters (Table 2). Overall, the incidence of dosing adjustments in the 45-mg group was greater than that in the 90-mg group. When examined by baseline body weight (≤ 100 kg, > 100 kg), a greater proportion of patients weighing > 100 kg had dosing adjustments (73% for 45 mg, 58% for 90 mg), compared with patients weighing ≤ 100 kg (52% for 45 mg, 39% for 90 mg). The greatest incidence of dosing adjustments occurred among patients weighing > 100 kg originally randomized to 45 mg.

Early adjusters

Early adjusters were partial responders who initiated dose-interval adjustment per protocol at weeks 28 or 40. At the end of the randomized dose-interval adjustment period (weeks 28–52), the rate of PASI 75 response was not different between patients
who were re-randomized at week 28 to every-8-week dosing and those continuing every-12-week dosing in the 45-mg group (34.9% vs. 31.3%, \( P = 0.0718 \)). However, improvements were observed in the 90-mg group (68.8% vs. 33.3%, \( P = 0.004 \)), suggesting that dosing adjustment to 90 mg every 8 weeks may benefit some initial partial responders.\(^5\)

The current analysis included all early adjusters followed for up to 5 years, including patients who had randomized and those who had nonrandomized dose-interval adjustment. Approximately 50–60% of early adjusters achieved PASI 75 responses at about 6 months following dose-interval adjustment (Fig. 4). The proportion of early adjusters achieving PASI 75 in the 45-mg group continued to increase during the long-term extension and approached that of the 90-mg group, while the response rate in the 90-mg group remained relatively stable (week 244 PASI 75: 64.2% for 45 mg and 67.9% for 90 mg; Fig. 4). This narrowing dose response observed during the long-term extension may be attributable to the effects of additional investigator-initiated dose adjustments (to 90 mg every 8 weeks) in a subgroup of patients originally receiving 45 mg.

**Late adjusters**

Late adjusters were patients who continued their randomized treatment until at least week 52, and first initiated dosing adjustments during the long-term extension, based on investigators’ clinical judgement. At the time of dosing adjustment, half of the late adjusters in the 45-mg and 90-mg groups were already PASI 75 responders (including 12% PASI 90 responders), 40% were partial responders (PASI 50 to <75) and 10% were nonresponders (<PASI 50; Fig. 5), suggesting that many patients may desire treatment response targets greater than PASI 75.

Among patients originally receiving 45 mg, a substantial proportion experienced improvements following dosing adjustment. At 144 weeks of follow-up, 57.1% of nonresponders and 88.6% of partial responders achieved PASI 75 (Fig. 6a,c); 56.4% of PASI 75 to <90 responders achieved PASI 90 (Fig. 6e) and 31.6% of PASI 90 to <100 responders achieved PASI 100 (data not shown). Among patients originally receiving 90 mg, improvements were also observed, but response rates were slightly lower: 44.4% of nonresponders and 77.8% of partial responders achieved PASI 75 (Fig. 6a,c); 52.9% of PASI 75 to <90 responders achieved PASI 90 (Fig. 6e) and 18.2% of PASI 90 to <100 responders achieved PASI 100 (data not shown) at 144 weeks of follow-up. The slightly higher response rates observed among late adjusters originally receiving 45 mg may be attributable to an additional adjustment for which they were eligible (60% of patients adjusted from 45 mg every 12 weeks to 45 mg every 8 weeks to 90 mg every 8 weeks), which would have resulted in a substantially greater increase in ustekinumab exposure compared...
with patients making a single-step adjustment from 90 mg every 12 weeks to every 8 weeks. Consistent with the increased PASI response rates, improvements in absolute PASI scores were also observed. At the time of dosing adjustment, the median PASI scores in the ustekinumab 45-mg and 90-mg groups, respectively, were 12 (nonresponders, Fig. 6b), 12 (partial responders, Fig. 6d), 3 (PASI 75 to <90 responders, Fig. 6f) and 1 (PASI 90 to <100 responders, data not shown). At 144 weeks of follow-up, the corresponding median PASI scores were 3 (Fig. 6b), 2 (Fig. 6d), 0 and 0 (data not shown), respectively, demonstrating an overall improvement in efficacy.

### Nonadjusters
Nonadjusters were patients who continued their randomized treatment from baseline throughout the 5-year study.

**Table 2. Summary of dosing adjustments; patients treated with at least one dose of ustekinumab at or beyond week 28**

| Patients treated, n | Ustekinumab 45 mg | Ustekinumab 90 mg | Combined |
|---------------------|-------------------|-------------------|----------|
|                      | 549               |                   | 1112     |
| Total adjusters     |                   |                   |          |
| Early adjustersb    | 114 (20-8)        | 203 (37-0)        | 317 (57-7) |
| Late adjustersd     | 39 (7-1)          | 89 (16-2)c        | 128 (23-3) |
| Nonadjusters        | 75 (13-7)         | 114 (20-8)        | 232 (42-3) |

Data are presented as number of patients (%). q12wk, every 12 weeks; q8wk, every 8 weeks. bIncludes patients treated (by actual treatment received) at or beyond week 28, which was the first opportunity for dosing adjustment per study design. Note that placebo-crossover patients are included after crossover to ustekinumab at week 12. cBefore the long-term extension, patients could adjust their dose interval at weeks 28 and 40 based on protocol-defined Psoriasis Area and Severity Index response criteria as described in Figure 1a. dIncludes patients who made the first-step adjustment per protocol before the long-term extension and made the second-step adjustment based on investigator judgement during the long-term extension. eDuring the long-term extension, investigators could initiate dose-interval and/or dose adjustment based on clinical judgement. fIncludes patients who made both the first- and second-step adjustments based on investigator judgement during the long-term extension.

**Fig 4.** Proportion of patients achieving at least a 75% improvement in Psoriasis Area and Severity Index (PASI 75) response from week 28 through week 244 (5 years) in patients randomized to ustekinumab 45 mg and 90 mg. Early adjusters by assigned treatment. q12wk, every 12 weeks; q8wk, every 8 weeks.
out any dosing adjustments. Most nonadjusters (95-0%) had already achieved PASI 75 at week 28, and continued to maintain PASI 75 response through week 244 (PASI 75, 91-3%; PASI 90, 74-2%). At week 244, the median PASI scores for the 45-mg and 90-mg groups were 0-10 and 0-00, respectively. These patients likely represent a sub-population that is very responsive to ustekinumab.

Safety

Through week 264, the cumulative rates of AEs, SAEs and AEs of interest were generally comparable between the 45-mg and 90-mg groups in the overall population (Table 3), and between the nonadjusters and adjusters (Table 4). Through week 264, rates of SAEs, AEs leading to discontinuations, serious infections, NMSC, other malignancies and MACE demonstrated year-to-year variability, but no trend of an increase over time was observed (Fig. 7).

No cases of active tuberculosis or other infections of interest (e.g. atypical mycobacteria, systemic fungus or salmonella) were reported through week 264, and the most common types of serious infections were diverticulitis (n = 7), cellulitis (n = 5) and cholecystitis (n = 3). No cases of anaphylaxis or serum-sickness-like reactions associated with ustekinumab were observed. As reported previously, 5-4% of patients (65 of 1202) with evaluable samples had developed antibodies to ustekinumab by week 52;10 no additional patients developed antibodies to ustekinumab through week 264. Development of antibodies was not associated with injection-site reactions.

Discussion

This final report from PHOENIX 2 evaluated the long-term efficacy and safety of ustekinumab in more than 1200 patients with moderate-to-severe psoriasis treated continuously for up to 5 years. Together with the results from PHOENIX 1,6 the collective clinical experience from approximately 2000 patients across the PHOENIX trials confirms that ustekinumab maintains efficacy over time and is well tolerated for long-term treatment.

Efficacy analyses of the overall population included all patients regardless of dosing adjustment status. A notable rate of patient retention (70% through year 5) allows authoritative assessments of the long-term efficacy data. High levels of clinical response were achieved and maintained over time in a substantial proportion of patients, with PASI 75/90/100 response rates of approximately 75%/50%/30%, respectively, in the 45-mg and 90-mg groups at week 244. The highly consistent results between the primary and LOCF analyses confirm the robustness of the data and analytical methods. While PASI 75 has been regarded as the gold standard in assessing treatment success in psoriasis trials, recent consensus guidelines propose the use of PGA ≤ 1 (almost clear) or PASI ≤ 5 (minimal localized residual disease) as alternative efficacy measures that may be more clinically relevant.11–13 More than half of the overall population achieved PGA ≤ 1 and more than three-quarters achieved PASI ≤ 5 at week 244. In summary, our results indicate that ustekinumab effectively improved psoriasis in the majority of patients who received continuous maintenance treatment with 45 mg or 90 mg for up to 5 years.

The data presented here also suggest potential benefits of dosing adjustments. Among early adjusters, benefit was apparent within 6 months of adjustment and was maintained through week 244 (~60% achieved PASI 75). The narrowing difference in PASI 75 response rates between the 45-mg and 90-mg groups during the long-term extension may be attributable to the benefits of additional dose adjustments (from 45 mg to 90 mg every 8 weeks) in a subgroup of patients originally receiving 45 mg every 12 weeks. Among late adjusters, approximately 50-90% of the patients achieved and maintained PASI response targets (nonresponders and partial
responders achieving PASI 75, and PASI 75 < 90 responders achieving PASI 90, respectively) through up to 3 years of follow-up after dosing adjustment. These improvements were accompanied by corresponding reductions in median PASI scores to ≤2 in all but one subgroup, indicating significant improvements in many late adjusters.

The extent of dosing flexibility desired by patients or investigators to maintain satisfactory symptom control over the course of long-term treatment has not been extensively studied. The pragmatic design of the PHOENIX 2 long-term extension offers an opportunity to explore patients’ and investigators’ potential desires for dosing flexibility, as well as the identification of patient characteristics that may be associated with a greater need for dosing flexibility.

Generally, patients who had dosing adjustments were heavier, had more severe psoriasis, were more treatment experienced and were more likely to have comorbidities. When examined by baseline body weight and baseline randomized dose assignment, the overall incidence of dosing adjustments was greater in the 45-mg group than in the 90-mg group, and the highest incidence of dosing adjustments was observed among patients weighing > 100 kg who were originally randomized to 45 mg. These findings suggest that heavier patients may render greater benefit from the 90-mg dose.

During the long-term extension, approximately 50% of the late adjusters were already PASI 75 responders (including 12% PASI 90 responders) at the time of initiating adjustment. As the reasons for initiating dosing adjustments were not collected,
we leveraged the study completion rates between the two PHOENIX studies as a surrogate for patient/investigator satisfaction with treatment outcome, considering that discontinuations for reasons unrelated to efficacy were not substantially different between the studies. Despite the greater dosing flexibility offered in PHOENIX 2 compared with PHOENIX 1, a similar proportion (~70%) of patients completed the two 5-year studies, suggesting that patients are generally satisfied with their treatment outcomes. The findings from the

### Table 3
Summary of safety events per 100 patient-years of follow-up through week 264 (year 5) by dose received; overall population treated with at least one dose of ustekinumab

|                  | Ustekinumab 45 mg | Ustekinumab 90 mg | Combined |
|------------------|-------------------|-------------------|----------|
| Patients treated, n | 606               | 809               | 1212     |
| Average duration of follow-up (weeks) | 167               | 198               | 216      |
| Patient-years of follow-up | 1952              | 3085              | 5037     |
| Adverse events, n | 222               | 195               | 206      |
| % of patients with: |                   |                   |          |
| Adverse events leading to discontinuation, % | 7.99              | 6.87              | 7.31     |
| Serious adverse events, % | 85.6              | 75.9              | 79.7     |
| Infections requiring treatment | 26.0              | 23.6              | 24.5     |
| Serious infections | 1.08              | 0.88              | 0.95     |
| Overall malignancies, % | 1.08              | 1.07              | 1.08     |
| NMSC | 0.57              | 0.32              | 0.42     |
| Other malignancies (excludes NMSC) | 0.51              | 0.75              | 0.66     |
| MACE, % | 0.56              | 0.42              | 0.48     |

MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer. a Patients who adjusted their dose from 45 to 90 mg were included in the 45-mg or 90-mg group based on the dose received at the time the event was reported.

### Table 4
Summary of safety events per 100 patient-years of follow-up through year 5 by dosing adjustment status; population eligible for dose adjustment treated at or beyond week 28

|                  | Nonadjusters a | Adjusters b,c | Combined |
|------------------|----------------|--------------|----------|
| Patients treated, n | 544            | 568          | 1112     |
| Average duration of follow-up (weeks) | 227            | 239          | 233      |
| Patient-years of follow-up | 2373      | 2612         | 4986     |
| AEs | 187             | 216          | 202      |
| AEs leading to discontinuation | 2.51            | 1.66          | 2.06     |
| Serious AEs | 6.57            | 7.43          | 7.02     |
| Overall infections | 73.9           | 83.4         | 78.9     |
| Infections requiring treatment | 22.5          | 25.9         | 24.3     |
| Serious infections | 0.84            | 0.96         | 0.90     |
| Overall malignancies, % | 1.27          | 0.65         | 0.95     |
| NMSC | 0.38              | 0.19          | 0.28     |
| Other malignancies (excluding NMSC) | 0.89            | 0.46          | 0.66     |
| MACE | 0.38              | 0.54          | 0.46     |

AE, adverse event; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer. a Nonadjusters include all patients treated with ustekinumab beyond week 28 who had no dose-interval or dose adjustment during study participation. b Adjusters include patients who adjusted their dose interval from every 12 weeks to every 8 weeks at week 28 or 40, per study design, and patients who had investigator-initiated dosing adjustment (dose interval: every 12 weeks to every 8 weeks; or dose: 45–90 mg) during the long-term extension (weeks 52–244). c Events reported in the adjusters group included all events reported by this group throughout the study, i.e. events occurring both prior to and after dosing adjustments.
PHOENIX 2 long-term extension suggest that in the event that
dosing flexibility is offered and access to therapy is not an
issue, some patients and investigators may desire treatment
goals beyond the traditional PASI 75 goal after experiencing
initial success and therefore, may desire greater dosing flexibil-
ity.

Interpretation of the efficacy results presented here merits
further discussion to acknowledge notable limitations and to
textualize these observations with those previously
reported. In PHOENIX 2, patients did not receive weight-
based dosing consistent with the approved label (i.e. 45 mg
in ≤ 100 kg, 90 mg in > 100 kg), and the availability of dos-
ing flexibility in the real world varies by region [e.g. prescrib-
ing information in Japan, Canada and Australia (but not in the
U.S.A. or Europe) allows for adjustment to every-8-week dos-
ing]; therefore, the results reported here should not be extrap-
olated broadly. A parallel, randomized control group with no
dosing adjustment was not included in the long-term exten-
sion, making it difficult to quantify and distinguish the ben-
efits that may be attributable to dosing adjustment from clinical
improvements that may be due to the naturally remitting and
relapsing nature of psoriasis. As described previously,5 the
major secondary end point of the randomized dose-interval
adjustment period was not met.

Although significant improvements were observed in the
subgroup re-randomized to adjust from 90 mg every 12 weeks
to every 8 weeks, a substantial proportion of the control group
continuing either 45 mg or 90 mg every 12 weeks also
reported improvements without having any adjustments. This
suggests that the actual incremental benefits of early dose-interval
adjustment described in this report, based on all patients who
have received early dose-interval adjustment (i.e. both ran-
domized and nonrandomized), may be more modest in reality.
In addition, the overall improvements in efficacy as a result of
the dose-interval and/or dose adjustments described in this
report represent an overall increase of approximately 10%
(45 mg) and 5% (90 mg) in all PASI response thresholds in the
PHOENIX 2 overall population, compared with PHOENIX 1,
suggesting that the overall incremental benefit of dosing adjust-
ment may be more modest at a population level. One final limi-
tation of the study design is that only patients achieving at least
a PASI 50 response at week 28 were eligible to continue receiv-
ing the study drug beyond week 28, and be eligible for dosing
adjustments during the long-term extension. Therefore, the effi-
cacy of dosing adjustment among initial nonresponders was not
evaluated and remains to be determined.

Safety observations after 5 years of follow-up are consist-
tent with previously reported results from an integrated
analysis of phase 2 and 3 trials of ustekinumab in psoriasis
(including PHOENIX 2)14 and an earlier report based on the
same PHOENIX 2 population after 1 year of follow-up.5
No dose response was observed between 45 mg and 90 mg
in overall AEs, AEs leading to treatment discontinuation and
AEs of interest at year 5. In addition, safety outcomes were
generally comparable between patients with and without
dosing adjustment, even though the patients whose dose
was adjusted tended to be heavier and have more comor-
bidities.

In conclusion, the results from the 5-year follow-up of
PHOENIX 2 are generally consistent with those reported for
PHOENIX 1,6 confirming that a substantial proportion of
patients respond to ustekinumab and that continuous treat-
ment effectively maintains long-term control of psoriasis. The
significant disease improvements made possible by biological
therapies in recent years may have increased expectations for
treatment success to levels beyond the traditional goal of PASI
75. The PHOENIX 2 long-term extension, which provided
investigators with the flexibility to customize treatment based
on clinical judgement, supports this hypothesis. While addi-
tional clinical benefits may be achieved with dosing adjust-
ment in certain patients, further evaluations are needed to
quantify the benefits and to understand the association
between particular patient characteristics and the effectiveness
doing adjustments.

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Appendix

Conflicts of interest statements

R.G.L. has served as an advisor, investigator and speaker for Abbott, Amgen, Biogen, Celgene, Janssen, LEO Pharma, Merck, Novartis and Pfizer. M.L. has received honoraria and/or grant funding as a consultant and/or investigator and/or speaker from AbbVie, Amgen, Anacor Pharmaceuticals Inc., BioLineRX Ltd, Celgene, Dermipsor, Eli Lilly, Galderma, GlaxoSmithKline–Stiefel, Janssen, LEO Pharma, Maruho, Nov-
artis, Pfizer, Ranbaxy and Valeant. G.G.K. has served as a consultant for AbbVie, Amgen and Janssen; had grants or has pending grants from AbbVie and Amgen; and has received payment for lectures and travel-related expenses from AbbVie, Amgen and Janssen. Y.P. has served as an advisor and/or consultant and/or investigator and/or speaker and/or has received grants and/or honoraria from Abbott, Amgen, Cel-
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tis and Pfizer. N.K. has served as a consultant for Abbott, Astellas, Centocor and Genentech, and as a speaker for Abbott, Amgen, Centocor/Janssen and Genentech. J.C.P. has served as a consultant, investigator, speaker or advisory board member for Biogen-Idec (formerly Biogen), Novartis, Wyeth, Pfizer, Merck-Serono (formerly Serono), Essex Pharma, MSD, Galderma, Centocor/Janssen, Abbott and Jans-
sen-Cilag/Janssen-Ortho, and has received an unrestricted research grant from Biogen-Idec and Wyeth. K.R. has served as a consultant and/or paid speaker for and/or participated in clinical trials for Abbott, Biogen-Idec, Celgene, Centocor/ Janssen, Janssen-Cilag, LEO Pharma, Medac, Merck, MSD (formerly Essex, Schering-Plough), Novartis and Pfizer (for-
merly Wyeth). P.O.S., Y.W., D.C., M.C.H. and Y.Y. are employees of Janssen Research & Development, LLC and own stock in Johnson & Johnson, of which Janssen is a wholly owned subsidiary.

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