Ustekinumab for the treatment of moderate-to-severe plaque psoriasis in paediatric patients (≥ 6 to < 12 years of age): efficacy, safety, pharmacokinetic and biomarker results from the open-label CADMUS Jr study*

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Summary

Background Limited options are available for treatment of paediatric psoriasis.

Objectives To evaluate the efficacy and safety of ustekinumab in paediatric patients with psoriasis (≥ 6 to < 12 years of age).

Methods CADMUS Jr, a phase III, open-label, single-arm, multicentre study, evaluated ustekinumab in paediatric patients with moderate-to-severe plaque psoriasis. Patients received weight-based dosing of ustekinumab (< 60 kg: 0·75 mg kg^{-1}; ≥ 60 to ≤ 100 kg: 45 mg; > 100 kg: 90 mg) administered by subcutaneous injection at weeks 0 and 4, then every 12 weeks through week 40. Study endpoints (all at week 12) included the proportions of patients achieving a Physician's Global Assessment score of cleared/minimal (PGA 0/1) and ≥ 75%/90% improvement in Psoriasis Area and Severity Index (PASI 75/90), and change in Children's Dermatology Life Quality Index (CDLQI). Serum ustekinumab concentrations, antidrug antibodies and cytokine levels were measured through week 52. Safety was evaluated through week 56.

Results In total, 44 patients (median age 9·5 years) received at least one dose of ustekinumab. Three patients discontinued the study agent through week 40. At week 12, 77% of patients achieved PGA 0/1, 84% achieved PASI 75 and 64% achieved PASI 90 response. The mean change in CDLQI was −6·3. Trough serum ustekinumab concentrations reached steady state at weeks 28–52. The incidence of antidrug antibodies was 10% (n = 4). Mean serum concentrations of interleukin-17A/F and interleukin-22 were significantly reduced at weeks 12 and 52. Overall, 34 patients (77%) had at least one adverse event and three (7%) had a serious adverse event.

Conclusions Ustekinumab effectively treated moderate-to-severe psoriasis in paediatric patients, and no new safety concerns were identified.

> ### What is already known about this topic?
>
> - Ustekinumab is approved for use in adolescents (≥ 12 to < 18 years of age) and adults (≥ 18 years) with moderate-to-severe psoriasis.

What does this study add?

- Ustekinumab effectively treats moderate-to-severe psoriasis in paediatric patients (≥ 6 to < 12 years of age), with no new safety concerns.

Psoriasis is a chronic, immune-mediated, inflammatory skin disease that affects 2–3% of the world's population.[1] Approximately 35% of adults with psoriasis report signs and symptoms before the age of 20 years.[2] Childhood psoriasis represents a significant burden of disease, with a prevalence of 0·2–2·5% reported across studies.[3–5] Beyond the skin manifestations, juvenile psoriasis has been associated with increased rates of hyperlipidaemia, obesity, hypertension, diabetes mellitus, arthritis and Crohn disease.[4]

Relative to adult psoriasis, there is a paucity of clinical data and fewer approved treatment options for psoriasis in children. The biologic agents that are currently available to treat paediatric psoriasis in Europe include two tumour necrosis factor inhibitors (etanercept and adalimumab, in children ≥ 4 years of age) and an interleukin (IL)-12/23 inhibitor (ustekinumab, in children ≥ 12 years of age). All three biologics are administered subcutaneously; however, the frequency of maintenance dosing varies (i.e. weekly for etanercept, every other week for adalimumab, and every 12 weeks for ustekinumab).[6–8]

Ustekinumab has been shown to be effective for the treatment of moderate-to-severe plaque psoriasis, with a favourable safety profile in adults (age ≥ 18 years) and adolescents (age ≥ 12 to < 18 years) based on the PHOENIX and CADMUS trials, respectively,[8–10] and has been approved for the treatment of moderate-to-severe psoriasis in adults and adolescents in multiple countries.[11] Here we report the results of the CADMUS Jr trial, which was the first study to evaluate the efficacy, safety and pharmacokinetic (PK) profiles of ustekinumab, as well as biomarker assessments before and after ustekinumab treatment, in younger paediatric patients (≥ 6 to < 12 years of age) with moderate-to-severe psoriasis.

Materials and methods

Study design

CADMUS Jr (ClinicalTrials.gov identifier NCT02698475) is a phase III, open-label, single-arm, multicentre study conducted to evaluate ustekinumab (Stelara®; Janssen Biotech, Horsham, PA, USA) in paediatric patients (≥ 6 to < 12 years of age) with moderate-to-severe plaque psoriasis. Patients were required to have Psoriasis Area and Severity Index (PASI) ≥ 12, a Physician's Global Assessment (PGA) score ≥ 3, and a percentage body surface area involved with psoriasis ≥ 10%. They also had to be candidates for phototherapy or systemic treatment for their psoriasis or be considered by the investigator to have psoriasis that was inadequately controlled with

topical therapy, indicating moderate-to-severe disease. A weight-based dose of ustekinumab identical to that recommended for adolescent patients (< 60 kg: 0·75 mg kg^{-1}; ≥ 60 to ≤ 100 kg: 45 mg; > 100 kg: 90 mg) was administered by subcutaneous injection at weeks 0 and 4, followed by dosing every 12 weeks through week 40. Study visits were scheduled every 4 weeks through week 16 then every 12 weeks thereafter through week 52, with a final safety visit at week 56.

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and is consistent with good clinical practices and applicable regulatory requirements. The study protocol was approved by an institutional review board or ethics committee at each investigational site, and patients or their legally acceptable representatives provided written consent for study participation.

Assessments

The PGA and PASI measures were used for assessments at weeks 0, 4, 8, 12, 16, 28, 40 and 52. The severity of the psoriatic lesions at a given point in time was evaluated using the PGA [range 0 (cleared) to 5 (severe)] and PASI [range 0 (no involvement with psoriasis) to 72].[12] The Children's Dermatology Life Quality Index (CDLQI) was used to assess patient-reported health-related quality of life (HRQoL) on a scale of 0–30, with a higher score reflecting a greater degree of impairment.[13] HRQoL evaluations were performed at weeks 0, 4, 12, 28 and 52. Safety was evaluated at all study visits by monitoring adverse events, serious adverse events and adverse events of interest through week 56. Serum samples were collected at selected visits to evaluate the pharmacokinetics and immunogenicity of ustekinumab through week 52. Serum ustekinumab concentrations were measured using a validated electrochemiluminescent immunoassay (ECLIA) method. Antidrug antibodies (ADAs) to ustekinumab were detected using a validated, sensitive and drug-tolerant ECLIA method, in which 50 ng mL^{-1} of ADAs could be detected in the presence of up to 100 μg mL^{-1} of ustekinumab in serum.[14] Serum samples collected at baseline, week 12 and week 52 were used for biomarker studies that assessed a panel of soluble proteins associated with psoriasis and the IL-23/T helper 17 pathways (i.e. IL-17A, IL-17F and IL-22) before and after treatment with ustekinumab.[15]

Statistical analysis

No formal hypothesis testing was conducted, and no P-values are reported. For efficacy assessment, a sample size of 40

would provide a 95% confidence interval (CI) of 50–80% if the observed response rate for the primary endpoint (proportion of patients with PGA 0/1 at week 12) was 65%. In addition, the sample-size calculation considered simulations with a population PK model developed using PK data from the previously completed clinical studies PHOENIX (adult patients > 18 years of age) and CADMUS (adolescent patients ≥ 12 to < 18 years of age).[8–10] It was estimated that at least 40 patients would be needed to provide adequate data to characterize the PK properties of ustekinumab in this younger paediatric population (≥ 6 to < 12 years of age).

Two-sided exact 95% CIs were provided for the primary and major secondary efficacy endpoints. Treatment failures were defined as patients who discontinued study treatment due to lack of efficacy or an adverse event of worsening of psoriasis, or those who started a protocol-prohibited medication or therapy that could affect their psoriasis. Baseline values were used for continuous variables; nonresponder status was assigned for binary variables for all subsequent visits once treatment failure criteria were met. In addition, patients with missing efficacy data for binary variables at week 12 were classified as nonresponders. No imputation was performed for missing data after applying treatment failure rules at other timepoints.

The primary endpoint was the proportion of patients with a PGA score of cleared (0) or minimal (1) at week 12. Major secondary endpoints of ≥ 75% improvement in PASI (PASI 75) and ≥ 90% improvement in PASI (PASI 90) responses at week 12 were summarized for all patients who received at least one injection of ustekinumab during the study, and change from baseline in CDLQI at week 12 was based on efficacy-evaluable patients. Other secondary endpoints included the proportions of patients achieving PGA 0 and PASI 100 response over time. For patients with CDLQI > 1 at baseline, the proportions achieving a CDLQI = 0 or 1 score at weeks 12, 28 and 52 were reported.

Adverse events were reported for patients who received at least one injection of ustekinumab. The incidences and titres of ADAs to ustekinumab were summarized among patients who had received at least one treatment administration and had appropriate samples for antibody detection. Serum ustekinumab concentrations over time were summarized through week 52 for treated patients who had at least one serum concentration measurement. Potential association between serum ustekinumab levels and clinical response was evaluated at week 40.

For biomarker studies, serum concentrations of each cytokine (IL-17A, IL-17F and IL-22) are reported in pg mL^{-1}. Data are presented as geometric means with CIs at baseline, week 12 and week 52, as well as geometric means of ratios between baseline and both week 12 and week 52. The pharmacodynamic effect of ustekinumab (change from baseline) was evaluated using a mixed-effects model for repeated measures, where the time (week 12 or 52) was a fixed effect and the patient was a random effect. Missing data points (e.g. samples not collected or with insufficient volume) were not

imputed, and patients with missing baseline values were not included in pharmacodynamic analyses. P-values were not adjusted for multiple comparisons (three cytokines). The possible association between clinical improvement and cytokine levels was assessed by comparing patients who maintained PASI < 2 and PASI < 3 with those who did not reach these clinical thresholds at baseline, week 12 and week 52. Significant differences between groups were analysed using Welch's t-test.

Results

This study was conducted from 7 June 2016 to 25 October 2018 at 19 sites in Europe, Canada and the USA. Through week 40, three of the 44 patients discontinued the study agent: one for lack of efficacy and two for protocol violations. The baseline demographics and disease characteristics were typical of a paediatric population with moderate-to-severe psoriasis (Table 1). The median age was 9·5 years [interquartile range (IQR) 7·5–10·0, range 6–11] and all ages were represented in the study population. The mean weight was 33·3 kg (IQR 29·3–45·8, range 19–99), with the majority of patients (91%) weighing < 60 kg. Only four patients had a bodyweight of ≥ 60 to ≤ 100 kg and no patient weighed > 100 kg. The median involved body surface area was 18·0%

Table 1 Demographics and disease characteristics at baseline

Number of enrolled patients	44
Age (years), median (IQR)	9·5 (7·5–10·0)
Sex male	17 (39)
Race white	40 (91)
Bodyweight (kg), median (IQR)	33·3 (29·3–45·8)
Duration of psoriasis (years), mean ± SD	3·5 ± 2·49
Family history of psoriasis	27 (61)
Body mass index (kg m^{-2}), mean ± SD	19·5 ± 4·62
Body surface area (%), median (IQR)	18·0 (13·5–29·5)
PASI, median (IQR)	16·1 (13·7–19·8)
PGA score	
Moderate (3)	29 (66)
Marked (4)	14 (32)
Severe (5)	1 (2)
CDLQI, mean ± SD	8·1 ± 5·69
Prior treatment for psoriasis	
Topical agents	43 (98)
Phototherapy (PUVA or UVB)	15 (34)
Conventional systemic agents[a]	8 (18)
Biologic agents[b]	2 (5)

The data are presented as the number of patients (%), unless otherwise indicated. CLDQI, Children's Dermatology Life Quality Index; IQR, interquartile range; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; PUVA, psoralen plus ultraviolet A; UVB, ultraviolet B. [a]Conventional systemic treatment included PUVA, methotrexate, ciclosporin, acitretin, apremilast or tofacitinib. [b]Biologic agents included adalimumab, alefacept, briakinumab, brodalumab, efalizumab, etanercept, infliximab, ixekizumab or secukinumab.

(IQR 13·5–29·5%, range 11–73%), and the median PASI was 16·1 (IQR 13·7–19·8, range 4–53). All patients had PGA scores indicative of moderate (66%), marked (32%) or severe (2%) psoriasis. Prior treatment for psoriasis included topical agents for 98%, phototherapy for 34%, conventional systemic treatment for 18% and biologic agents for 5% of patients.

Efficacy and health-related quality of life

At week 12, 34 patients (77%, 95% CI 62·2–88·5%) achieved the primary endpoint of PGA 0/1 response (Figure 1d). The major secondary endpoints of PASI 75 and PASI 90 were achieved by 37 patients (84%, 95% CI 69·9–93·4%) and 28
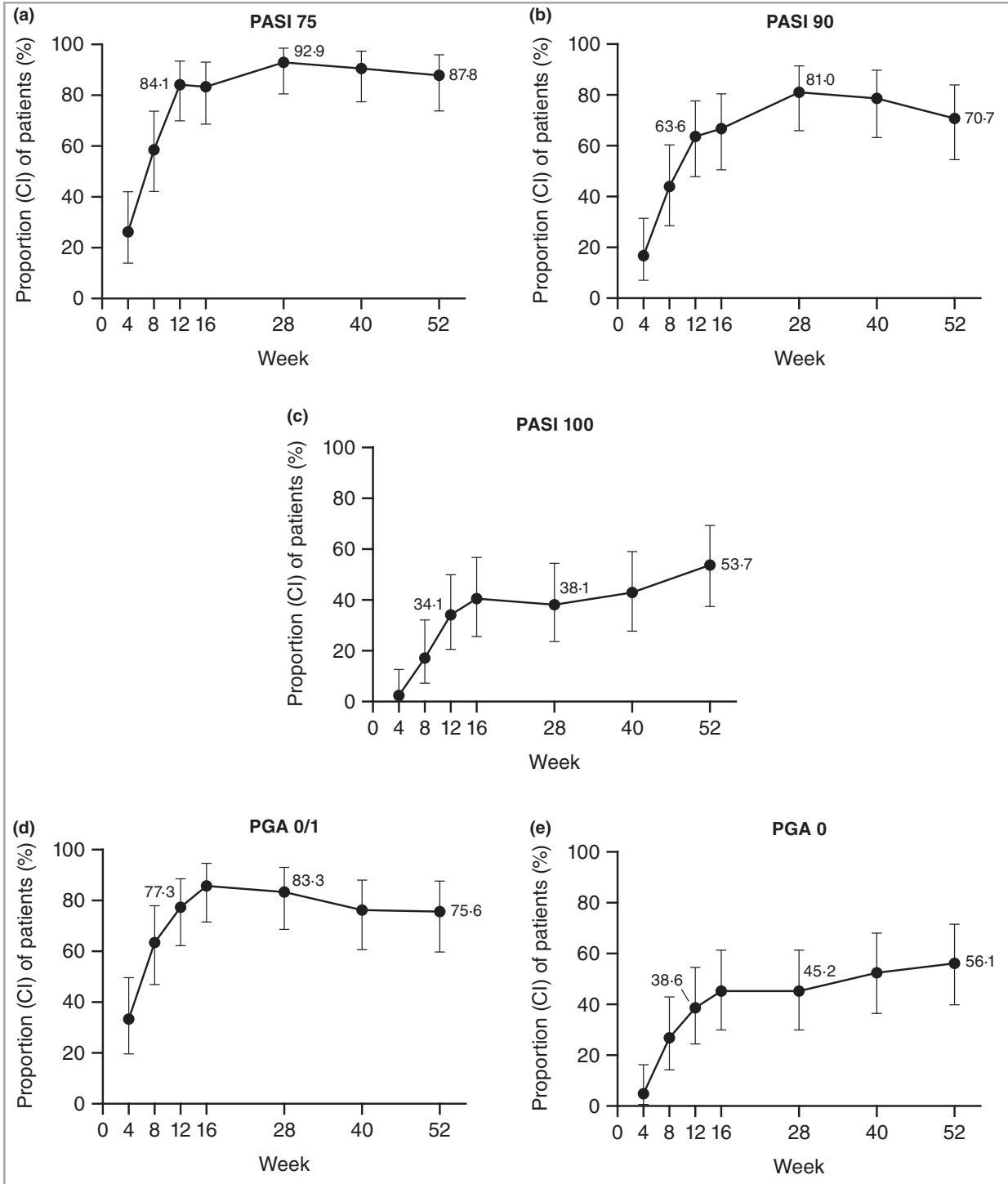
Figure 1 Proportions of patients (95% confidence interval, CI) achieving ≥ 75% improvement in (a) Psoriasis Area and Severity Index (PASI 75), (b) PASI 90, (c) PASI 100, (d) Physician's Global Assessment (PGA) 0 (cleared) or 1 (minimal), and (e) PGA 0 over time through week 52.

patients (64%, 95% CI 47·8–77·6%), respectively, at week 12 (Figure 1a, b). In addition, PASI 100 response was achieved by 15 patients (34%, 95% CI 20·5–49·9%) at week 12 (Figure 1c) and PGA 0 was achieved by 17 patients (39%, 95% CI 24·4–54·5%) (Figure 1e) at week 12. Clinical responses continued to increase or remained stable through week 52.

Ustekinumab improved HRQoL as measured by the CDLQI. The mean ± SD change in CDLQI was −6·3 ± 6·43 at week 12, and this level of improvement was maintained over time through week 52 (−6·4 ± 6·10). Among patients with CDLQI > 1 at baseline, 62% (24 of 39) achieved a CDLQI 0/1 response at week 12 and 58% (21 of 36) did so at week 52 (Figure 2).

Pharmacokinetics

Median trough serum ustekinumab concentrations were maintained at steady-state levels from week 28 (0·34 µg mL^{-1}, IQR 0·18–0·49) to week 52 (0·38 µg mL^{-1}, IQR 0·21–0·50),

with no evidence of accumulation or attenuation in serum ustekinumab concentrations over time (Figure 3). Similar concentration levels were observed for patients weighing < 60 kg treated with the dose of 0·75 mg kg^{-1} and those weighing ≥ 60 to ≤ 100 kg treated with the 45-mg dose. Efficacy endpoints (PGA 0/1, PGA 0, PASI 75 and PASI 90) appeared to be associated with quantifiable steady-state trough serum ustekinumab levels at week 40 (data not shown).

Immunogenicity

Of the 44 treated patients, 42 had at least one post-treatment serum sample evaluable for ADAs. Through week 52, the incidence of ADAs was 10% (n = 4). Two of the four patients who were positive for ADAs had antibodies that were able to neutralize the bioactivity of ustekinumab *in vitro*. Two of the four ADA-positive patients achieved PGA 0/1 and PASI 75 responses at week 52, and none reported injection-site reactions (ISRs) after developing ADAs. The titres of antibodies to
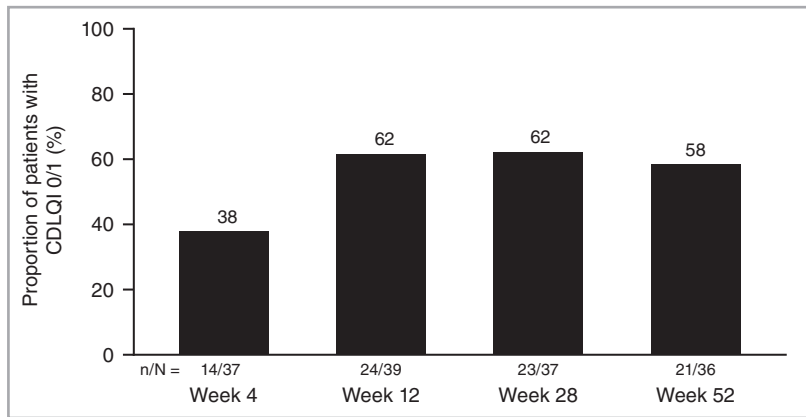

Figure 2 Proportions of patients achieving Children's Dermatology Life Quality Index (CDLQI) 0 or 1 (no effect on health-related quality of life) by study visit through week 52.
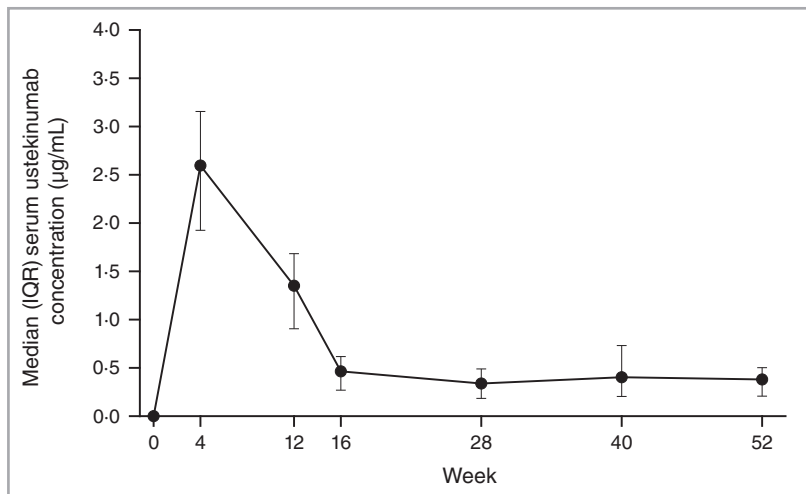

Figure 3 Median (interquartile range, IQR) of serum ustekinumab concentrations through week 52.

ustekinumab ranged from 1 : 200 to 1 : 12 800. Two of the four antibody-positive patients had titre levels ≤ 1 : 400.

Safety

Treatment-emergent adverse events are summarized in Table 2 for all 44 enrolled patients who received at least one dose of ustekinumab. Overall, 34 of the 44 patients (77%) reported at least one adverse event, with the most commonly reported being nasopharyngitis, pharyngitis and upper respiratory tract infection. Infections occurred in 29 patients (66%), of whom 12 (27%) received antimicrobial treatment. Through week 56, 16 of 210 injections (7·6%) were associated with an ISR, in six patients (14%). All ISRs were mild in intensity and resolved within 1 day, and the vast majority of ISRs were reported at a single study site. Three serious adverse events (infectious mononucleosis, eyelid injury, and attention deficit/hyperactivity disorder) occurred through week 56. None of these events was considered by the investigator to be related to the study treatment. No deaths, malignancies or major adverse cardiovascular events were reported through week 56. No cases of tuberculosis, opportunistic infection or anaphylactic or serum-sickness-like reactions were reported through week 56.

Biomarkers

Cytokine levels were measured in serum samples collected from 41, 39 and 40 patients with measurements for at least one of the three analytes at baseline, week 12 and week 52, respectively. Serum levels of IL-17A, IL-17F and IL-22 were

Table 2 Treatment-emergent adverse events through week 56

Number of enrolled patients	44
Average duration of follow-up (weeks)	53·15
Adverse events[a]	34 (77)
Nasopharyngitis	11 (25)
Pharyngitis	6 (14)
Upper respiratory tract infection	6 (14)
Injection-site erythema	6 (14)
Tonsillitis	4 (9)
Gastroenteritis	3 (7)
Otitis media	3 (7)
Abdominal pain	3 (7)
Serious adverse events[b]	3 (7)
Overall infections	29 (66)
Infections requiring treatment	12 (27)
Serious infections	1 (2)
Malignancy	0
MACE[c]	0

The data are presented as the number of patients (%), unless otherwise indicated. [a]Includes adverse events occurring in ≥ 5% of patients. [b]Included mononucleosis, eyelid injury and attention deficit/hyperactivity disorder. [c]MACE, investigator-reported cardiovascular death, myocardial infarction or nonfatal stroke.

reduced significantly from baseline after treatment with ustekinumab at both week 12 and week 52. Specifically, the geometric means (95% CI) at baseline, week 12 and week 52, respectively, were 0·50 (0·39–0·63), 0·28 (0·22–0·34) and 0·25 (0·20–0·31) pg mL^{-1} for IL-17A; 1·52 (1·06–2·17), 0·57 (0·40–0·80) and 0·56 (0·45–0·71) pg mL^{-1} for IL-17F; and 7·89 (5·80–10·75), 4·36 (2·89–6·58) and 4·05 (3·04–5·39) pg mL^{-1} for IL-22. The geometric means of the ratios between baseline and both timepoints showed a similar pattern, with all P-values ≤ 0·001 (Figure 4). The extent of reduction in the serum concentration of each cytokine was slightly greater at week 52 than at week 12.

A subset of patients who maintained PASI < 2 from week 28 to week 52 (31 of 42, 74%) had lower levels of IL-17F at baseline, week 12 and week 52 than those who did not maintain PASI < 2 at these timepoints. Differences in IL-17F levels between these groups were significant at baseline (P = 0·048) and week 52 (P = 0·014); a trend towards significance was observed at week 12 (P = 0·06). Similar differences (although not statistically significant) were observed using a PASI < 3 cutoff at all timepoints.

Discussion

The results of the open-label CADMUS Jr study provide evidence of the efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis in paediatric patients ≥ 6 to < 12 years of age. Substantial efficacy was achieved and maintained through 1 year. The majority of patients reported no effect of psoriasis on HRQoL (CDLQI 0 or 1) following treatment. The safety data reported here indicate that ustekinumab is well tolerated, while the PK and immunogenicity results confirm that the weight-based standard dose is appropriate for use in this paediatric population. Furthermore, the results of the biomarker analyses were consistent with findings observed in older patient populations regarding the mechanism of action of ustekinumab.

The clinical responses in paediatric patients (≥ 6 to < 12 years of age) were similar to those observed in the phase III CADMUS study of adolescent patients (≥ 12 to < 18 years of age) receiving the standard dose of ustekinumab.[8] Ustekinumab provides an alternative mode of action to the currently approved biologics for the treatment of psoriasis in children. Two anti-tumour necrosis factor agents (etanercept and adalimumab, approved in children aged ≥ 4 years in Europe) are currently available for the treatment of moderate-to-severe psoriasis.[6,7] While we acknowledge the limitations of comparing results across studies due to differences in study design, baseline characteristics and clinical measures, the response rates with the standard dose of ustekinumab (an IL-12/23 blocker) reported here for the CADMUS Jr study in children (77% achieved PGA 0/1, 84% achieved PASI 75 and 64% achieved PASI 90 at week 12) and in the previously reported CADMUS study in adolescents (69·4%, 80·6% and 61·1%, respectively, at week 12)[8] compare favourably with both etanercept and adalimumab in similar populations. In addition,
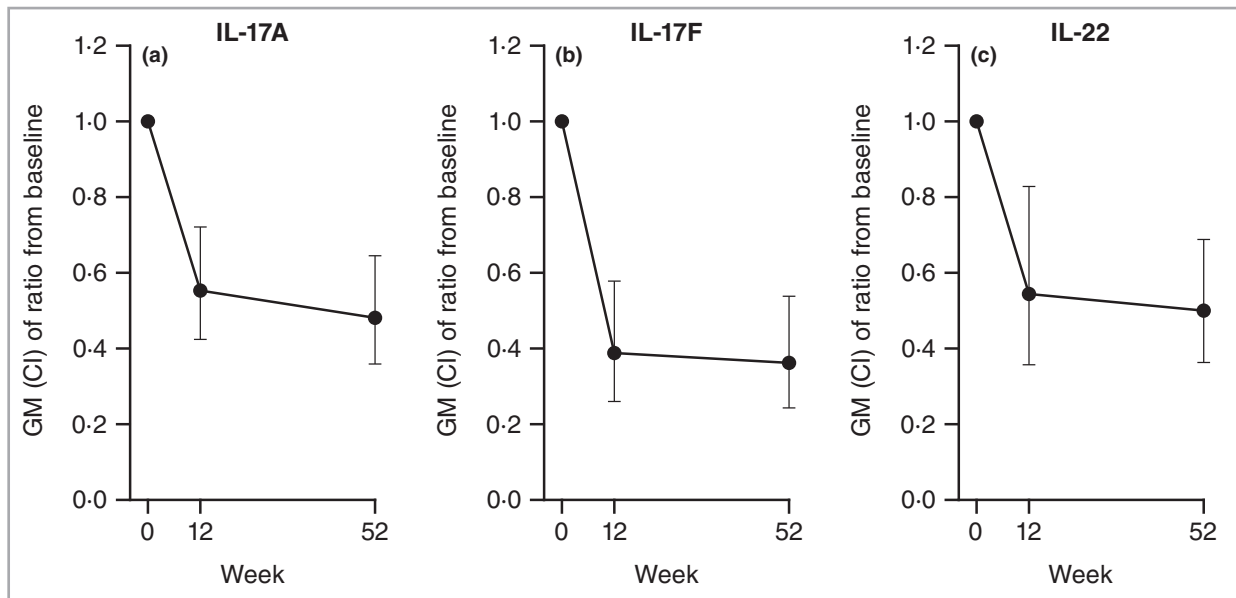
Figure 4 Geometric means (GMs) of ratios of serum cytokine levels at weeks 12 and 52 vs. baseline: (a) interleukin (IL)-17A, (b) IL-17F and (c) IL-22. The error bars represent the 95% confidence interval (CI).

ustekinumab offers dosing every 12 weeks in contrast to weekly and every other week with etanercept and adalimumab, respectively.

The negative effect of juvenile psoriasis on HRQoL has been demonstrated, and it is particularly important to consider both clinical and HRQoL outcomes when evaluating the effect of treatment on psoriasis in children.[16] In our study, patients treated with ustekinumab reported improvements in HRQoL as measured by the CDLQI, with a mean change of -6.3 ± 6.43 at week 12, which was sustained through week 52 (-6.4 ± 6.10). Furthermore, the majority of patients treated with ustekinumab achieved a CDLQI of 0 or 1, indicating no effect of psoriasis on HRQoL, at week 12 (62%) and week 52 (58%). These improvements in CDLQI for paediatric patients are similar to those reported for adolescents treated with the standard dose of ustekinumab in the CADMUS study.[8]

Based on the data presented here through 1 year, no new safety signals were reported for ustekinumab in CADMUS Jr. Furthermore, the safety profile and PK exposure observed for paediatric patients in this study are similar to findings observed for both adolescent patients in the CADMUS trial and adult patients in the PHOENIX 1 and PHOENIX 2 studies.[8–10] Together, these data represent assessment of approximately 2100 patients with psoriasis, the majority of whom have been evaluated through 5 years. Furthermore, cumulative safety data continue to support a favourable benefit–risk profile for ustekinumab for currently approved indications based on an estimated exposure of 11 349 patients (including healthy controls) in clinical trials across indications in both adult and paediatric patients. The estimated cumulative worldwide post-marketing exposure to ustekinumab from launch to 31 December 2018 is 1 375 007 person-years (data on file; Periodic Benefit Risk Evaluation Report, December 2018).[17]

Biomarker analyses in this study were conducted to characterize pharmacodynamic markers associated with ustekinumab treatment in children with psoriasis. Ustekinumab reduced systemic levels of serum cytokines associated with the pathogenesis of psoriasis and the IL-23 pathway (IL-17A, IL-17F and IL-22), with the pharmacodynamic effect of ustekinumab treatment on each cytokine apparent at week 12 and sustained at week 52. These results are consistent with similar mechanistic data on the impact of ustekinumab treatment on these cytokines in adult patients in the PSTELLAR study.[17] These observations suggest that, by blocking IL-23, a key cytokine involved in the maintenance and pathogenic phenotype of inflammatory T cells in psoriatic skin, ustekinumab reduces the ability of these cells to produce effector cytokines implicated in the immunopathogenesis of psoriasis in both adult and paediatric patients.

This study is possibly limited by the relatively small number of patients enrolled, although other paediatric studies have assessed treatment groups of similar sizes.[6,7] Also, our study did not include a placebo arm. However, the open-label design addressed potential ethical concerns of withholding active treatment, and allowed these paediatric patients the potential to experience improvements in their psoriasis. Although bias with regard to efficacy assessment is possible due to the open-label design, clinical studies of both adult and adolescent patients have demonstrated consistently low response rates to placebo, suggesting that the efficacy of ustekinumab could be accurately assessed even in the absence of a placebo control group.

The weight-based standard dose of ustekinumab used in this study, which is identical to the dose approved for use in adolescent patients (≥ 12 to < 18 years of age), resulted in improvements in clinical measures of psoriasis accompanied

by improvements in HRQoL in our patients aged ≥ 6 to < 12 years. In addition, no new safety issues were identified in this paediatric population studied through 1 year of continuous ustekinumab treatment, which further supports this as the appropriate dosing regimen in paediatric patients. The PK (i.e. systemic exposure) and immunogenicity profiles of ustekinumab described in this younger paediatric population are similar to those observed in adolescent and adult patients. Furthermore, treatment with ustekinumab reduced systemic levels of specific inflammatory cytokines, supporting the pathogenic role of IL-17A, IL-17F and IL-22 in psoriasis and the mechanism of action of ustekinumab across the broad scope of patients with psoriasis.

Overall, these data expand the already sizeable dataset available from randomized clinical trials and observational studies of ustekinumab in psoriasis,[8–10,17–19] and demonstrate a favourable benefit–risk profile of ustekinumab for the treatment of younger paediatric patients with moderate-to-severe psoriasis.

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Appendix

Supporting Information

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

Powerpoint S1 Journal Club Slide Set.