Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: Results of the randomized phase 3 CADMUS study

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Background: Safe and effective therapies are needed for pediatric patients with psoriasis.

Objective: The purpose of this study was to evaluate ustekinumab in patients age 12 to 17 years who had moderate-to-severe psoriasis.

Methods: Patients (n = 110) were randomly assigned to ustekinumab standard dosing (SD; 0.75 mg/kg [≤60 kg], 45 mg [>60-≤100 kg], and 90 mg [>100 kg]) or half-standard dosing (HSD; 0.375 mg/kg [≤60 kg], 22.5 mg [>60-≤100 kg], and 45 mg [>100 kg]) at weeks 0 and 4 and every 12 weeks or placebo at weeks 0 and 4 with crossover to ustekinumab SD or HSD at week 12. Clinical assessments included the proportion of patients achieving a Physician's Global Assessment of cleared/minimal (PGA 0/1), at least 75% improvement in Psoriasis Area and Severity Index (PASI 75), and at least 90% in PASI (PASI 90). Adverse events (AEs) were monitored through week 60.

Results: At week 12, 67.6% and 69.4% of patients receiving ustekinumab HSD and SD, respectively, achieved PGA 0/1 versus 5.4% for placebo ($P < .001$). Significantly greater proportions receiving

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Conflicts of interest: Dr Landells has served as a consultant to AbbVie, Allergan, Amgen, Astellas, Basilea, Celgene, Dermik, Galderma, GlaxoSmithKline, Graceway, Janssen, L'Oreal, Leo, Merck/Schering-Plough, Roche, Stiefel, Valeant, and Wyeth; has received research grants from AbbVie, Amgen, and Janssen; has served as a trial investigator for AbbVie, Allergan, Amgen, Astellas, Basilea, Galderma, GlaxoSmithKline, Janssen, Leo, Merck/Schering-Plough, Pfizer, Roche, Stiefel, and Wyeth; has received honoraria from AbbVie, Amgen, Astellas, Graceway, Janssen, Merck/Schering-Plough, Steifel, and Wyeth; and has served as a speaker for AbbVie, Allergan, Amgen, Merck/Schering-Plough, Janssen, Roche, Valeant, and Wyeth. Dr Eichenfield has served as a consultant for Janssen and Leo; has served as a trial investigator for Galderma and Leo; and has served on a safety monitoring board for Amgen. Dr Hoeger has served as a consultant for Janssen and as a speaker for Allmirall, Galderma, and Pierre Fabre. Dr Menter has served as a consultant for AbbVie, Allergan, Amgen, Convoy Therapeutics, Eli Lilly, Janssen, Leo, Maruho, Novartis, Pfizer, Syntrix, Wyeth, and XenoPort; has served as a trial investigator for AbbVie, Allergan, Amgen, ApoPharma, Boehringer Ingelheim, Celgene, Convoy Therapeutics, Eli Lilly, Genentech, Janssen, Leo, Maruho, Merck, Novartis, Pfizer, Syntrix, and Wyeth; and has served as a speaker for AbbVie, Amgen, Janssen, Leo, and Wyeth. Dr Paller has served as a consultant for AbbVie, Anacor, and Janssen and as an investigator for Abbvie, Amgen, and Anacor. Dr Taieb has served as a consultant for Janssen. Dr Philipp has served as a consultant Biogen Idec, Eli Lilly, and Pfizer; has received research support from Biogen Idec and Pfizer; has served as an investigator for AbbVie, Almirall, Amgen, Biogen Idec, Boehringer-Ingelheim, Celgene, Dermipsor Biomed LTD, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Leo, Maruho, MSD, Novartis, Pfizer, UCB Pharma, and VBL Therapeutics; has served as a speaker for Almirall, Amgen, Biogen Idec, Leo, Novartis, and Pfizer; and has served on an advisory board for AbbVie and Novartis. Drs Marano, Hsu, Li, Zhu, Szapary, and Randazzo are employees of the study sponsor and own stock in Johnson & Johnson, of which Janssen Research & Development, LLC is a subsidiary.

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ustekinumab achieved PASI 75 (HSD, 78.4%; SD, 80.6%; placebo, 10.8%) or PASI 90 (HSD, 54.1%; SD, 61.1%; placebo, 5.4%) at week 12 ($P < .001$). Through week 12, 56.8% of placebo patients, 51.4% of HSD patients, and 44.4% of SD patients reported at least one AE; through week 60, 81.8% reported AEs.

Limitations: The study was small relative to adult trials.

Conclusions: In this patient population (12−17 years), the standard ustekinumab dose provided response comparable to that in adults with no unexpected AEs through 1 year. (J Am Acad Dermatol 2015;73:594-603.)

Key words: adolescent; biologic; children; pediatric; psoriasis; systemic therapy; ustekinumab.

INTRODUCTION

Psoriasis can present at any age, with approximately one-third of patients having symptoms before age 20 years.[1] Treatment of pediatric patients is complicated by limited approved treatments and the relative paucity of data from randomized, controlled trials available for this population.[2,3] Safe, effective, and convenient therapies are needed for pediatric patients with moderate-to-severe psoriasis.

CAPSULE SUMMARY

- Few clinical studies of psoriasis therapies in children are available in the medical literature.
- Every-12-week dosing with ustekinumab was beneficial, with no unexpected adverse events, in treating patients age 12 to 17 years with moderate-to-severe psoriasis.
- Ustekinumab appears to be a viable treatment option for moderate-to-severe plaque psoriasis in the pediatric adolescent population.

Ustekinumab, a human monoclonal antibody targeting the p40 subunit of interleukin-12/23, has proven to be a safe and effective treatment for moderate-to-severe psoriasis in adult patients.[4] In the PHOENIX trials, ustekinumab effectively reduced psoriasis signs and symptoms in adult patients.[5,6] Results of the CADMUS trial of ustekinumab in adolescent patients age 12 to 17 years with active psoriasis are reported here.

METHODS

Eligible patients were age 12 to 17 years, (inclusive), had a diagnosis of moderate-to-severe plaque psoriasis (ie, baseline Psoriasis Area and Severity Index [PASI] ≥12, a Physician's Global Assessment [PGA] ≥3; and ≥10% body surface area involved with psoriasis) for ≥6 months, were candidates for phototherapy or systemic treatment, or had psoriasis that was poorly controlled with topical therapy.

The pharmacokinetics of ustekinumab is affected by body weight. Hence, dosing for adult patients with psoriasis is weight based (45 mg for patients weighing ≤100 kg and 90 mg for patients weighing >100 kg) and administered as subcutaneous injections at weeks 0 and 4 and every 12 weeks subsequently.[4] No clinically meaningful effects of age on the catabolism of immunoglobulins, including ustekinumab,[7] have been reported to date. After accounting for body weight differences, the pharmacokinetics of ustekinumab in pediatric patients in this trial was expected to be similar to that in adults. A standard dose (SD) of 0.75 mg/kg was chosen by adjusting the 45-mg adult dose by a body weight of 60 kg (45/60 = 0.75 mg/kg) leading to the following study dosages: (1) weight-based dose of 0.75 mg/kg (patients weighing ≤60 kg), (2) fixed 45-mg dose (patients weighing >60 to ≤100 kg), and (3) fixed 90-mg dose (patients weighing >100 kg). Additionally, a half-standard dose (HSD) (ie, 0.375 mg/kg for patients weighing ≤60 kg, 22.5 mg for patients weighing >60 to ≤100 kg, and 45 mg for patients weighing >100 kg) was included to identify an optimal dose regimen for pediatric patients.

In this phase 3, multicenter, double-blind, placebo-controlled study, randomization was stratified by investigational site and baseline weight (≤ or >60 kg). Treatment was allocated using a minimization algorithm with a biased-coin assignment[8] via an interactive voice/web response system. Patients were randomly assigned (2:2:1:1) to receive ustekinumab HSD or SD at weeks 0, 4, and 16 and thereafter every 12 weeks through week 40 or placebo at weeks 0 and 4, with crossover to either ustekinumab HSD or SD at weeks 12 and 16 and every 12 weeks through week 40 (Fig 1). At week 8, patients with a PASI increase ≥50% from baseline were eligible to commence treatment with moderate-to-high potency topical steroid preparations through week 12 (early escape).

The protocol was approved by an institutional review board or ethics committee, and all patients or

Abbreviations used:

AE:	adverse event
CDLQI:	Children's Dermatology Life Quality Index
HRQoL:	health-related quality of life
HSD:	half-standard dose
PASI:	Psoriasis Area and Severity Index
PASI 75:	at least 75% improvement in PASI
PASI 90:	at least 90% improvement in PASI
PGA:	Physician's Global Assessment
PGA 0/1:	PGA of cleared (0) or minimal (1)
SAE:	serious adverse event
SD:	standard dose

their legally acceptable representative gave written informed consent/assent before study-related procedures were performed.

Clinical response was evaluated using the PGA and PASI.[9] Health-related quality of life (HRQoL) was assessed using the Children's Dermatology Life Quality Index (CDLQI).[10] The primary endpoint was the proportion of patients with a PGA 0/1 at week 12. Major secondary endpoints were the proportions of patients achieving at least 75% improvement in PASI (PASI 75) and at least 90% improvement in PASI (PASI 90) at week 12 and the change from baseline in CDLQI at week 12. Assessments were performed through week 52.

Adverse events (AEs) were monitored through week 60. Serum samples were collected at selected visits to measure ustekinumab concentrations and evaluate for the presence of antibodies to ustekinumab. Antibody-to-ustekinumab status was determined using a sensitive, drug-tolerant electrochemiluminescent immunoassay on the Meso Scale Discovery platform (Gaithersburg, MD).

Statistical methods

To maintain an overall type I error rate of 0.05, the analyses were conducted sequentially in the order of primary endpoint, then major secondary endpoints based on Holm's procedure,[11] and were contingent on at least 1 ustekinumab dose being significantly different from the placebo group for each endpoint.

Patients who discontinued study treatment because of an unsatisfactory therapeutic effect or an AE of worsening psoriasis or used protocol-prohibited therapies for psoriasis were classified as nonresponders for dichotomous endpoints or as zero change for continuous endpoints thereafter. Patients with missing PGA or PASI at week 12 were classified as nonresponders. Patients who used a moderate-to-high potency topical steroid after entering early escape were considered nonresponders at week 12 for binary endpoints; the last value at or before week 8 was used to impute continuous endpoints.

Dichotomous endpoints were analyzed using a Cochran Mantel Haenszel test, with baseline weight ($\leq$ or $>$60 kg) as a stratification factor. Continuous variables were analyzed using analysis of variance on the van der Waerden normal scores, with baseline weight as a binary covariate.

Primary and major secondary PASI analyses included all randomized patients, and analyses of CDLQI outcomes included randomly assigned patients with evaluable measurements; responses are reported by randomized treatment group. In the placebo groups, only patients who crossed over to ustekinumab at week 12 were included in efficacy summaries after week 12. AEs are reported by actual treatment received for patients who had received $\geq$1 injection of placebo or ustekinumab. All analyses were performed using SAS software Version 9.2 (SAS Institute, Cary, NC).

RESULTS

The study was conducted between March 2010 and January 2014 at 36 sites in Canada and Europe. A total of 110 patients were randomly assigned to receive ustekinumab SD (n = 36), ustekinumab HSD (n = 37), or placebo (n = 37; crossover to SD [n = 18] or HSD [n = 19]) (Fig 2). At week 8, 1 patient each in the HSD and SD groups entered early escape. Through week 40, 9 (8.2%) patients discontinued study agent because of unsatisfactory therapeutic effect (n = 5), AEs (n = 3), or death (n = 1).

Baseline demographics and disease characteristics were well balanced across the treatment groups (Table I). Mean age was 15.2 years, with most patients 15 to 17 years of age (n = 77; 70.0%). Mean body weight was 65.0 kg; 51 (46.4%) patients weighed $\leq$60 kg, 56 (50.9%) weighed greater than 60 to $\leq$100 kg, and 3 (2.7%) weighed greater than 100 kg. Disease activity scores at baseline were consistent with moderate-to-severe disease; mean CDLQI (9.6) indicated a moderate effect of psoriasis on HRQoL.

At week 12, the proportions of patients achieving PGA 0/1 were significantly greater in the HSD (67.6%) and SD (69.4%) groups versus placebo (5.4%; $P < .001$ for both dose groups; Table II). Onset of response was rapid; approximately one-third of patients in each ustekinumab group achieved PGA 0/1 at week 4 (the first postbaseline visit) compared with 1 (2.7%) patient in the placebo group (Fig 3). Additionally, significantly greater proportions of patients in the HSD (32.4%) and SD (47.2%) groups achieved a PGA of 0 at week 12 compared with placebo (2.7%; both

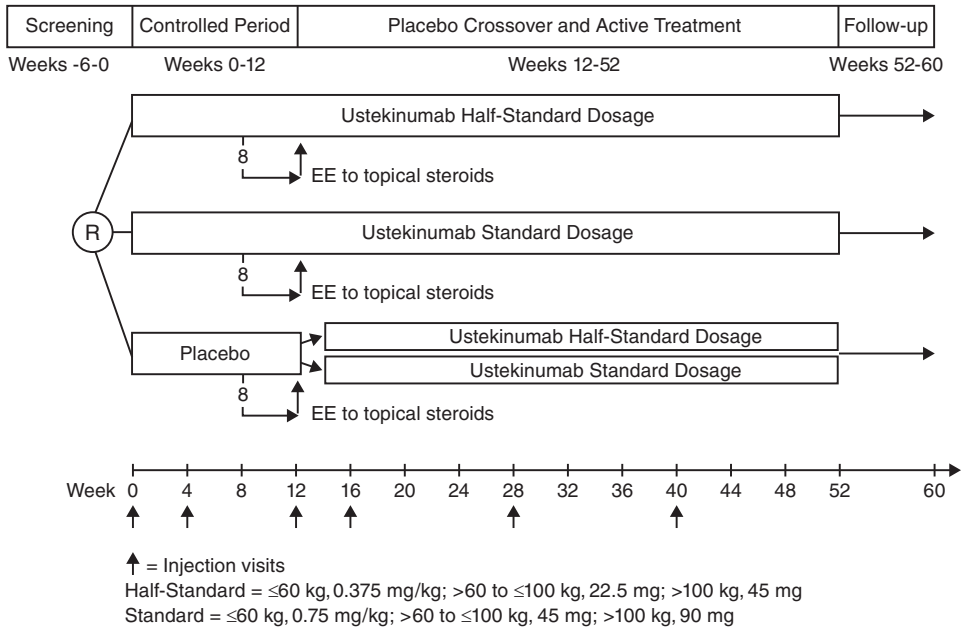

Fig 1. Ustekinumab in adolescent patients with psoriasis. Study schema through week 60. *EE*, Early escape; *R*, randomization.

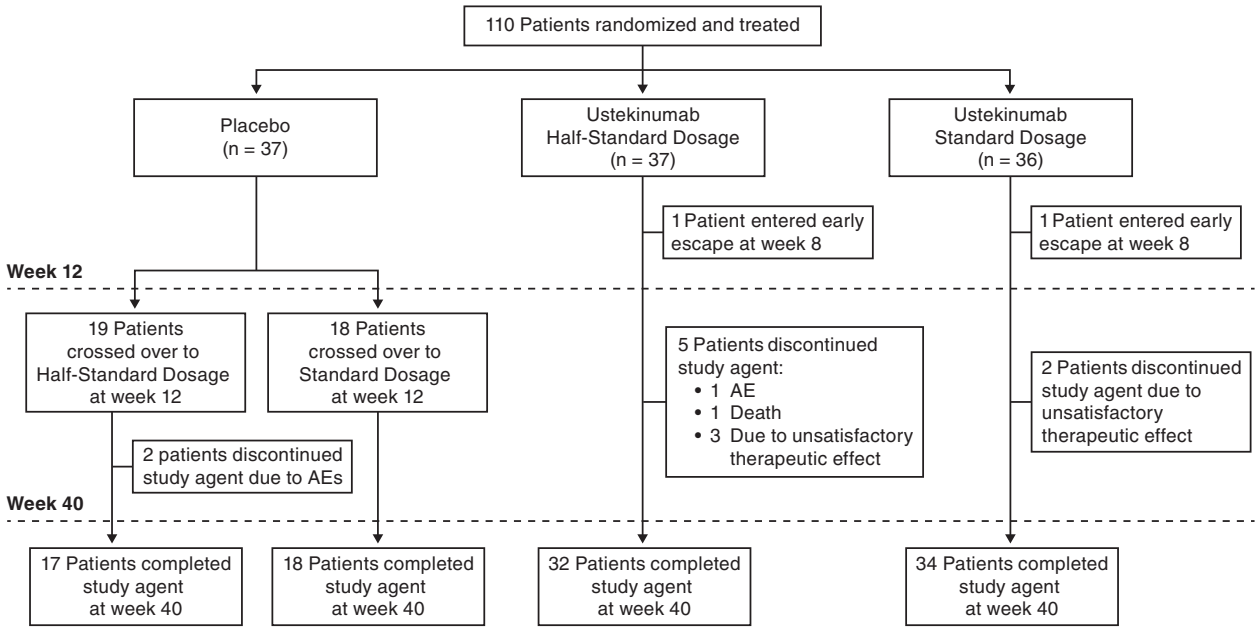

Fig 2. Ustekinumab in adolescent patients with psoriasis. Patient disposition through week 40.

$P < .001$). Likewise, significantly greater proportions of patients receiving ustekinumab achieved PASI 75 (HSD, 78.4%; SD, 80.6%; placebo, 10.8%; $P < .001$) or PASI 90 (HSD, 54.1%; SD, 61.1%; placebo, 5.4%; $P < .001$; Table II). Furthermore, 21.6% of patients in the HSD group and 38.9% in the SD group achieved a PASI score of 0 (cleared) at week 12 compared with 2.7% in the placebo group ($P = .014$ and $P < .001$, respectively). The treatment effect of both the HSD and SD of ustekinumab through week 12 for patients ≤60 kg was consistent with that observed in patients greater than 60 kg to ≤100 kg (data not shown).

In both ustekinumab groups, the proportions of patients who achieved PGA 0/1, PASI 75, or PASI 90

Table I. Baseline demographics and disease characteristics

		Ustekinumab			
	Placebo	Half-standard dosage*	Standard dosage†	Combined	Total
Patients randomized, n	37	37	36	73	110
Males, n (%)	20 (54.1)	18 (48.6)	16 (44.4)	34 (46.6)	54 (49.1)
Age, y					
Mean (SD)	15.6 (1.5)	15.1 (1.7)	14.8 (1.7)	14.9 (1.7)	15.2 (1.7)
Body weight, kg					
Mean (SD)	64.7 (14.7)	68.2 (24.5)	62.0 (17.1)	65.1 (21.2)	65.0 (19.2)
Race, n (%)					
White	34 (91.9)	30 (81.1)	34 (94.4)	64 (87.7)	98 (89.1)
Psoriasis disease duration, y					
Mean (SD)	6.2 (5.0)	5.9 (4.0)	5.6 (3.8)	5.7 (3.9)	5.9 (4.3)
Age at diagnosis, y					
Mean (SD)	9.5 (5.0)	9.2 (4.5)	9.3 (4.3)	9.2 (4.4)	9.3 (4.6)
BSA, %					
Mean (SD)	27.4 (16.4)	33.6 (21.4)	31.9 (23.2)	32.7 (22.1)	30.9 (20.5)
PASI score (0-72)					
Mean (SD)	20.8 (8.0)	21.0 (8.5)	21.7 (10.4)	21.3 (9.4)	21.1 (8.9)
PGA score, n (%)					
Marked or severe (≥4)	15 (40.5)	15 (40.5)	12 (33.3)	27 (37.0)	42 (38.2)
CDLQI (0-30), n	33	36	32	68	101
Mean (SD)	9.1 (6.4)	9.4 (6.5)	10.3 (6.6)	9.8 (6.5)	9.6 (6.5)
Prior medications for psoriasis, n (%)					
Topical agents	34 (91.9)	31 (83.8)	33 (91.7)	64 (87.7)	98 (89.1)
Conventional systemic therapies	16 (43.2)	14 (37.8)	17 (47.2)	31 (42.5)	47 (42.7)
UVB	11 (29.7)	15 (40.5)	13 (36.1)	28 (38.4)	39 (35.5)
Methotrexate	8 (21.6)	8 (21.6)	6 (16.7)	14 (19.2)	22 (20.0)
Biologics	5 (13.5)	4 (10.8)	3 (8.3)	7 (9.6)	12 (10.9)
PUVA	0	3 (8.1)	4 (11.1)	7 (9.6)	7 (6.4)

BSA, Body surface area; *PUVA*, psoralen with ultraviolet light A; *SD*, standard deviation; *UVB*, ultraviolet B.
*Ustekinumab half-standard dosage: 0.375 mg/kg for patients weighing ≤60 kg, 22.5 mg for patients weighing >60 kg to ≤100 kg, and 45 mg for patients weighing >100 kg.
†Ustekinumab standard dosage: 0.75 mg/kg for patients weighing ≤60 kg, 45 mg for patients weighing >60 kg to ≤100 kg, and 90 mg for patients weighing >100 kg.

Table II. Primary and select secondary endpoints at week 12

		Ustekinumab	
	Placebo	Half-standard dosage*	Standard dosage†
Patients randomized, n	37	37	36
PGA 0/1, n (%)	2 (5.4)	25 (67.6)‡	25 (69.4)‡
PGA 0	1 (2.7)	12 (32.4)‡	17 (47.2)‡
PASI 75, n (%)	4 (10.8)	29 (78.4)‡	29 (80.6)‡
PASI 90, n (%)	2 (5.4)	20 (54.1)‡	22 (61.1)‡
Change from baseline in CDLQI, n	32	35	32
Mean (SD)	−1.5 (3.2)	−5.6 (6.4)§	−6.7 (5.6)‡
Patients with CDLQI score 0/1, n (%)	4/30 (13.3)	12/31 (38.7)¶	17/30 (56.7)‡

SD, Standard deviation.
*Ustekinumab half-standard dosage: 0.375 mg/kg for patients weighing ≤60 kg, 22.5 mg for patients weighing >60 kg to ≤100 kg, and 45 mg for patients weighing >100 kg.
†Ustekinumab standard dosage: 0.75 mg/kg for patients weighing ≤60 kg, 45 mg for patients weighing >60 kg to ≤100 kg, and 90 mg for patients weighing >100 kg.
‡$P < .001$ vs placebo.
§$P < .01$ vs placebo.
¶$P < .05$ vs placebo.

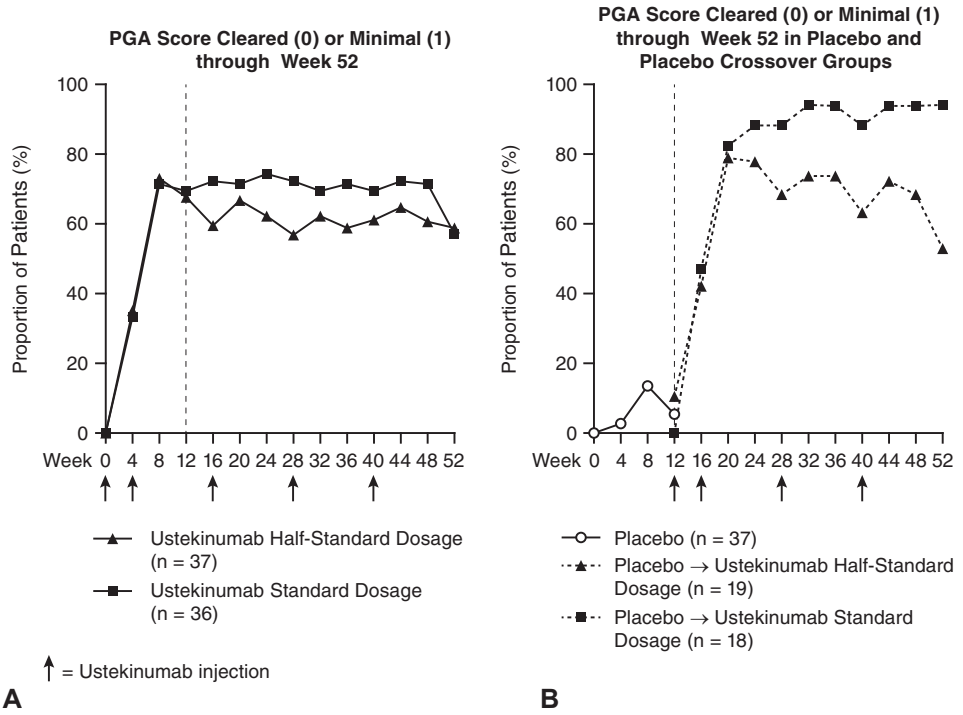

Fig 3. Ustekinumab in adolescent patients with psoriasis. Proportions of patients with a PGA 0/1 in the ustekinumab half-standard and standard dose groups (**A**) and the placebo group (**B**) through week 52.

were maintained from week 12 through 52 (Figs 3 and 4). Among placebo patients who crossed over to ustekinumab at week 12, PASI 75 response rates increased by week 16 and were maintained through week 52. The proportions of patients achieving PGA 0/1, PASI 75, or PASI 90 after crossover were generally similar to those observed in patients who started ustekinumab at baseline (Figs 3 and 4). Through week 52, the proportions of patients with PGA 0/1, PASI 75, or PASI 90 were numerically greater in the SD group compared with the HSD group; however, no formal statistical comparisons were performed (Figs 3 and 4).

HRQoL also improved among ustekinumab-treated patients through week 12. Mean changes in CDLQI from baseline were significantly greater in the HSD (−5.6) and SD (−6.7) groups compared with placebo (−1.5; $P = .003$ and $P < .001$, respectively) (Table II). Among patients with CDLQI greater than 1 at baseline, significantly greater proportions of ustekinumab-treated patients achieved a CDLQI 0/1 (indicative of no effect of psoriasis on HRQoL) compared with placebo (Table II). Mean improvements in CDLQI were maintained through week 52 in both the HSD (−4.9) and SD (−7.6) groups. At week 52, CDLQI 0/1 was achieved by 50.0% and 58.6% of patients in the HSD and SD groups, respectively.

Through week 12, 51.4% of patients in the HSD group, 44.4% in the SD group, and 56.8% in the placebo group reported ≥1 AE (Table III); most AEs were mild or moderate. In general, AE rates were similar across treatment groups, and no dose effect was observed. AEs in the Infections and Infestations category were the most common (HSD, 32.4%; SD, 25.0%; placebo, 40.5%); none was considered serious. Through week 12, the most common AEs were nasopharyngitis (HSD, 13.5%; SD, 2.8%; placebo, 27.0%) and headache (HSD, 10.8%; SD, 8.3%; placebo, 5.4%). One serious AE (SAE; worsening of psoriasis) was reported in the HSD group.

Through week 40, all 110 patients received ≥1 injection of ustekinumab; among these, 81.8% reported an AE through week 60 (Table III). Infections and Infestations was the most common category of AEs, with nasopharyngitis (34.5%), upper respiratory tract infection (12.7%), and pharyngitis (8.2%) occurring most often. After week 12, 5 additional singular SAEs were reported (total, 6; HSD, 5; SD, 1) through week 60. An SAE of leukopenia, described by the investigator as

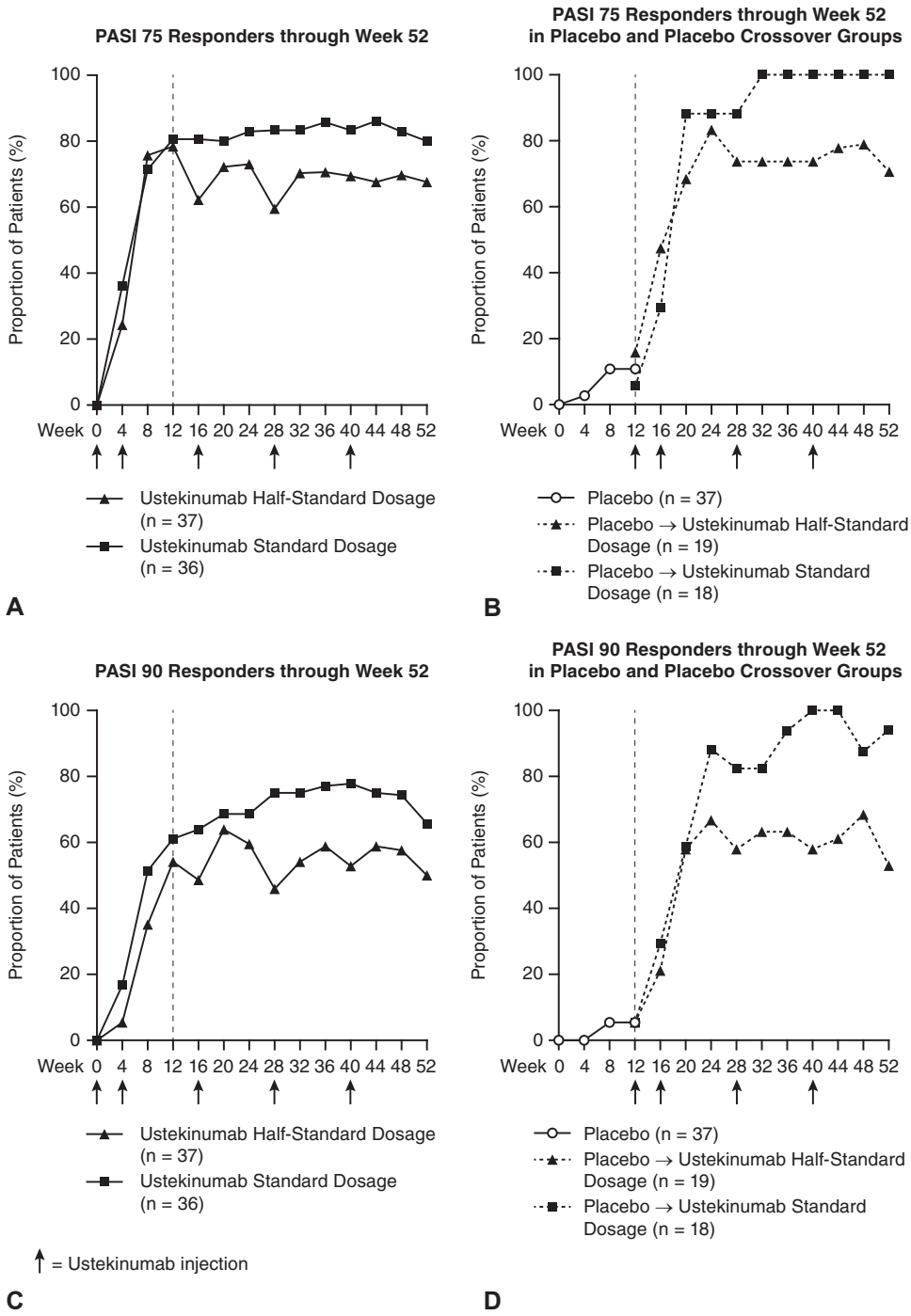

Fig 4. Ustekinumab in adolescent patients with psoriasis. Proportions of patients with a PASI 75 (**A**, **B**) or PASI 90 (**C**, **D**) response through week 52.

transient and coincident with recurrent herpes simplex infection, occurred in one patient (HSD group). Two serious infections were reported (pyelonephritis [HSD]; ear infection [SD]). One patient in the HSD group experienced acute contact allergic dermatitis caused by hair dye, and another died in an automobile accident. Of the 508 ustekinumab injections, only one was associated with an injection site reaction; this mild reaction occurred at baseline in the SD group. There were no malignancies, active tuberculosis cases, opportunistic infections, anaphylactic reactions, or serum sickness–like reactions through week 60.

Table III. Adverse events

Adverse events through week 12 (placebo-controlled period)				
		Ustekinumab		
	Placebo	Half-standard dosage	Standard dosage	Combined
Patients, n	37	37	36	73
Mean duration of follow-up, wk	12.2	12.2	12.4	12.3
Mean exposure, wk	4.2	4.2	4.1	4.1
Patients with ≥1 AE	21 (56.8)	19 (51.4)	16 (44.4)	35 (47.9)
Patients who discontinued due to AE	0	0	0	0
Infections	14 (37.8)	12 (32.4)	8 (22.2)	20 (27.4)
Patients with ≥1 SAE	0	1 (2.7)	0	1 (1.4)
Serious infections	0	0	0	0
Malignancies	0	0	0	0

Adverse events through week 60					
	Ustekinumab				
	Placebo → Half-standard dosage	Placebo → Standard dosage	Half-standard dosage	Standard dosage	Combined
Patients, n	19	18	37	36	110
Mean duration of follow-up, wk	45.9	46.9	55.2	58.0	53.2
Mean exposure, wk	27.3	28.1	38.0	39.0	34.9
Patients with ≥1 AE	15 (78.9)	13 (72.2)	33 (89.2)	29 (80.6)	90 (81.8)
Patients who discontinued due to AE	2 (10.5)	0	2 (5.4)	0	4 (3.6)
Infections	13 (68.4)	11 (61.1)	26 (70.3)	24 (66.7)	74 (67.3)
Patients with ≥ 1 SAE	0	0	5 (13.5)	1 (2.8)	6 (5.5)
Serious infections	0	0	1 (2.7)	1 (2.8)	2 (1.8)
Malignancies	0	0	0	0	0

Data presented as n (%) unless otherwise noted.

All 110 patients had at least one serum sample available after ustekinumab treatment for evaluating antibodies to ustekinumab. Through week 60, 9 (8.2%) patients tested positive for antibodies to ustekinumab: 6 and 3 in the HSD and SD groups, respectively. Among these patients, 6 achieved a PGA 0/1 simultaneously to the detection of antibodies to ustekinumab; therefore, the presence of antibodies to ustekinumab did not appear to preclude a clinical response. One of the patients who tested positive for antibodies to ustekinumab experienced the single mild injection site reaction at baseline.

Steady state was achieved at week 28 in both the HSD and SD groups with no systemic drug accumulation evident over time. Approximate dose proportionality in serum ustekinumab concentration was observed, such that mean concentrations in the SD group were 1.4-fold to 3.2-fold higher than those in the HSD group. In each dose group, similar serum ustekinumab concentrations were observed between patients weighing ≤60 kg receiving a weight-adjusted ustekinumab dose (0.375 mg/kg or 0.75 mg/kg) and those greater than 60 to ≤100 kg receiving a fixed ustekinumab dose (22.5 mg or 45 mg). Only 3 patients weighed more than 100 kg at baseline, making comparisons with this weight group difficult.

DISCUSSION

CADMUS is the first phase 3, randomized, placebo-controlled trial of ustekinumab in adolescent patients age 12 to 17 years (inclusive) with moderate-to-severe plaque psoriasis. Patients in both the HSD and SD ustekinumab groups experienced robust and clinically meaningful improvements in disease activity. Of note, more than half of ustekinumab-treated patients (HSD, 54.1%; SD, 61.1%) achieved PASI 90 at week 12. The therapeutic effect of ustekinumab was observed in a number of patients as early as week 4. Improvements in HRQoL were also significantly greater in the ustekinumab groups compared with the placebo group. Although PGA 0/1 and PASI 75 results were generally comparable between the HSD and SD groups through week 12, differences in responses favored the SD for higher level responses such as PGA 0, PASI 90, and CDLQI 0/1. Beyond week 12, clinical response in the SD group was generally higher and better sustained than in the HSD group, in which a modest loss of response was more frequently observed toward the

end of each 12-week dosing interval. Differences in clinical response between the 2 dose groups were less pronounced through week 12, likely as a result of the additional loading dose administered at week 4 in both dose groups. Maximum responses based on PGA and PASI were achieved by week 12 and maintained through week 52.

Comparisons of clinical response at week 28, when steady state was achieved, from the CADMUS trial and the PHOENIX adult ustekinumab studies[5,6] showed that the response observed with the HSD in the CADMUS trial was generally lower than that seen in adults, whereas response with the SD was similar to (or higher than) that in adults. Comparable ustekinumab exposures were achieved in patients weighing ≤60 kg with the milligram to kilogram weight-adjusted dose and in patients weighing greater than 60 to ≤100 kg who received the fixed dose. This suggests that the 0.75-mg/kg dose adjustment implemented in CADMUS is appropriate for adolescents with a body weight ≤60 kg. Moreover, comparing serum ustekinumab concentrations from this trial and the previous adult trials suggests that systemic exposure to ustekinumab in adolescent patients (age ≥12 years) receiving the body weight–adjusted SD was comparable to that of adults receiving the approved psoriasis dosage (data not shown).

Our results also provide information that is more broadly applicable to adolescent psoriasis treatment, particularly for therapeutic monoclonal antibodies. The observation that weight-adjusted dosing in the pediatric population in CADMUS resulted in ustekinumab exposure comparable to that in adults provides additional evidence that the metabolism of therapeutic monoclonal antibodies in adolescent patients aged 12 to 17 years is similar to that in adult patients. The AEs in this trial were consistent with those previously observed in adult patients receiving ustekinumab. The challenges to effective disease management that pediatric psoriasis patients currently face is highlighted by the substantial proportion of CADMUS patients who had not previously received either systemic treatment or phototherapy, even though they had relatively severe psoriasis, a major HRQoL issue in this young population.[12]

Among the biologic agents approved worldwide for adult patients with psoriasis, only etanercept and adalimumab are currently indicated for use in children and only in Europe. Paller et al[13] reported that 53% of 106 patients (age 4 to 17 years) receiving weekly etanercept (0.8 mg/kg) achieved PGA 0/1, 57% achieved PASI 75, and 27% achieved PASI 90 at week 12.

Limitations of our study include the relatively small number of patients, the predominantly white study population, and the 1-year treatment duration. That only 3 patients weighed >100 kg at baseline limits the generalizability of these findings to heavier children. However, it is clear the weight-based SD provided exposure comparable to that in adults with comparable clinical response and that the lower HSD provided suboptimal long-term response in this CADMUS population. The similar ustekinumab exposure observed in adult patients and patients 12 to 17 years is reassuring, given the well-characterized safety profile from the extensive experience in adult patients.[14,15]

Our findings suggest a positive benefit-to-risk profile for ustekinumab treatment of adolescents with moderate-to-severe psoriasis. A weight-based dosing strategy achieving exposure similar to that observed with the current adult dosage resulted in robust improvements in disease activity and HRQoL with no unexpected AEs noted. Ustekinumab appears to provide a beneficial and convenient treatment option for moderate-to-severe psoriasis in the pediatric population age 12 years and older.

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