ORIGINAL ARTICLE

Adalimumab for nail psoriasis: Efficacy and safety from the first 26 weeks of a phase 3, randomized, placebo-controlled trial

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Background: Previous clinical trials have not evaluated improvement in nail psoriasis as a primary end point.

Objective: This phase 3 trial evaluated the safety and efficacy of adalimumab in patients with moderate-to-severe fingernail psoriasis and moderate-to-severe plaque psoriasis.

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AbbVie funded this study and participated in the study design; study research; collection, analysis and interpretation of data; and writing, review, and approval of this article. All authors had access to the data and participated in the development, review, and approval of this article and in the decision to submit it for publication.

Disclosure: Dr Elewski has received research funding (paid to her institution) from AbbVie, Amgen, Boehinger Ingelheim, Celgene, Incyte, Lilly, Merck, Novan, Novartis, Pfizer, Valeant, and Viament and honoraria for serving as a consultant to Anacor, Celgene, Lilly, Novartis, Pfizer, and Valeant. Dr Okun has received honoraria for serving on an advisory board and/or as a speaker for AbbVie, Crescendo Biosciences, Gilead Science, and UCB, and he is a former AbbVie employee. Dr Papp has received honoraria for serving on an advisory board or panel, serving as a consultant and speaker for and has received grants (as an investigator) from Allergan, Amgen, Celgene, Centocor, Eli Lilly, Galderma, Genentech, Janssen, LEO Pharma, Merck, Merck-Serono, Novartis, Pfizer, Schering Plough, and Wyeth. In addition, Dr Papp has received honoraria (as a consultant) and grants (as an investigator) from Astellas, Apotex, Baxter, Boehringer Ingelheim, Kyowa Kirin, Regeneron, and UCB; received honoraria (for serving on an advisory board and panel) from AbbVie, Apotex, Baxter, Boehringer Ingelheim, and UCB; received honoraria (as a consultant) from AbbVie and Bristol-Myers Squibb; received honoraria (as a speaker) from AbbVie, Astellas, and Janssen-Cilag; and received grants (as an investigator) from Bristol-Myers Squibb anvd GlaxoSmithKline Beecham. Mr Baker has received honoraria (for serving on an advisory board and panel) from Abbvie, Pfizer, Novartis, and Celgene. Dr Crowley has received honoraria (as a consultant and speaker) from AbbVie, Amgen, Celgene, Lilly, and Novartis and has received grants (as an investigator) from AbbVie, Amgen, Astra-Zeneca, Boehringer Ingelheim, Celgene, Janssen, Lilly, Maruho, Merck, Novartis, Pfizer, Regeneron, and Sandoz. Dr Guillet has received grants (as an investigator) from AbbVie. Dr Sudaram is a former AbbVie employee. Dr Poulin has received grants (as an investigator) and honoraria (as a speaker and for serving on advisory boards) from AbbVie, Amgen, and Centocor/Janssen-Ortho and has received grants (as an investigator) from Aquinox, Baxter, Boehringer Ingelheim, Bristol-Myers-Squibb, Celgene, DS Biopharma, Eli Lilly, Galderma, Genentech, GlaxoSmithKline Beecham, LEO Pharma, Medimmune, Merck, Novartis, Pfizer, Regeneron, Schering Plough, Serono, Takeda, and UCB Pharma. Ms Gu, Dr Geng, and Dr Williams are salaried employees of AbbVie and they receive stocks and stock options. Dr Rich has received honoraria (for serving on an advisory board) from AbbVie, Eli Lilly, Novartis, Sandoz, and Valeant; honoraria (as a consultant) from AbbVie, Novartis, Polichem, and Valeant; and grants (as an investigator) from AbbVie, Allergan, Amgen, Anacor, Cassiopea, Dusa, Eli Lilly, Galderma, Janssen, Leo, Meiji, Merck, Neothetics, Novartis, Pfizer, Psolar, Sandoz, Ranbaxy, and Viamet.

Accepted for publication August 13, 2017.

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Published online October 6, 2017.

0190-9622

http://dx.doi.org/10.1016/j.jaad.2017.08.029

Methods: Patients were randomized 1:1 to 40 mg adalimumab every other week or placebo. The primary efficacy end point was at least 75% improvement in total-fingernail modified Nail Psoriasis Severity Index (NAPSI75) response rate at week 26. Ranked secondary end point scores evaluated at week 26 were total-fingernail NAPSI and modified NAPSI, nail pain, Nail Psoriasis Physical Functioning Severity, Brigham Scalp Nail Inverse Palmo-Plantar Psoriasis Index, and Physician's Global Assessment (fingernail psoriasis).

Results: Of the 217 randomized patients (108 received placebo and 109 received adalimumab), 188 (86.6%) completed 26 weeks of treatment (period A) or escaped early to the open-label period. The study met the primary end point (response rate of 3.4% with placebo vs 46.6% with adalimumab [$P < .001$]) and all ranked secondary end points. The serious adverse event rates (placebo vs adalimumab) in period A were 4.6% versus 7.3%; the serious infections rates were 1.9% versus 3.7%.

Limitations: Patients with less than 5% BSA involvement were not eligible for enrollment.

Conclusions: After 26 weeks of adalimumab treatment, significant improvements were seen in the primary and all ranked secondary end points and in signs and symptoms of moderate-to-severe nail psoriasis versus with placebo and no new safety risks were identified. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2017.08.029.)

Key Words: adalimumab; mNAPSI; nail pain; nail psoriasis; NAPSI; NPPFS; phase 3 placebo-control; skin psoriasis.

CAPSULE SUMMARY

- No placebo-controlled clinical trials have evaluated nail psoriasis as a primary end point.
- Adalimumab was studied using clinically validated end points in a large population chosen for extent and severity of fingernail psoriasis.
- Adalimumab demonstrated favorable outcomes over placebo in moderate-to severe fingernail psoriasis and a safety profile similar to that observed in previous clinical trials of other diseases.

Psoriatic involvement of nails is a chronic condition that causes pain and functional impairment, worsens quality of life, and restricts activities of daily living.[1-3] Nail psoriasis can occur concomitantly with skin or scalp psoriasis or with psoriatic arthritis regardless of severity of psoriatic skin and joint disease.[2,4,5] The commonly cited prevalence of nail involvement in psoriasis (50%; lifetime incidence, 80%-90%)[6] may be higher in moderate-to-severe psoriasis and is highest (approximately 80%) in patients with both psoriasis and psoriatic arthritis.[7,8]

Effective treatment of nail psoriasis is challenging on account of limited clinical evidence and guidelines for effective treatments[7,9-11] and the lack of placebo-controlled, clinical trials that have specifically assessed nail outcomes, none of which have included nail outcomes as the primary end point.[12] Treatment with topical agents is minimally effective owing to difficulty penetrating the nail or its matrix.[10,13] Treatment with biologic agents is impeded by health plans that routinely require at least 10% body surface area (BSA) involvement to qualify, without consideration for the level of quality-of-life impairment and pain experienced by patients with moderate-to-severe fingernail psoriasis but less than 10% BSA involvement.

Adalimumab (Humira [AbbVie Inc, North Chicago, IL]), a human monoclonal antibody that targets tumor necrosis factor (TNF)-α, has demonstrated efficacy in nail psoriasis in studies of patients with moderate-to-severe psoriasis and psoriatic arthritis.[14-16] As those studies did not require a minimal degree of nail psoriasis severity, many enrolled patients had relatively mild disease and their improvements may not have been clinically relevant. In this phase 3 trial (ClinicalTrials.gov registration no. NCT02016482), we evaluated the safety and efficacy of the approved adalimumab dose for psoriasis in patients with moderate-to-severe plaque psoriasis and clinically impactful, moderate-to-severe fingernail psoriasis. Unlike most other phase 3 biologic studies of psoriasis, this study permitted enrollment of patients with at least 5% BSA involvement provided they had moderate-to-severe fingernail psoriasis.

METHODS

Study design

This was a phase 3, multicenter, double-blind, randomized, parallel-arm, placebo-controlled trial (Fig 1). In the 26-week double-blind, placebo-controlled period (period A), patients were

Abbreviations used:

B-SNIPI50 (scalp):	50% or more improvement in the scalp portion of the Brigham Scalp Nail Inverse Palmo-Plantar Psoriasis Index
BSA:	body surface area
mNAPSI:	modified Nail Psoriasis Severity Index
mNAPSI75:	75% or more improvement in modified Nail Psoriasis Severity Index
NAPSI:	Nail Psoriasis Severity Index
NPPFS:	Nail Psoriasis Physical Functioning Severity
NRS:	numeric rating scale
PGA-F:	Physician's Global Assessment for Fingernail Psoriasis
TNF:	tumor necrosis factor

randomized 1:1 to receive 40 mg of adalimumab subcutaneously every other week (following an initial dose of 80 mg) or matching placebo. Randomization was determined by an interactive voice/web response system. The investigator, study site, and patients remained blinded to treatment. Starting from week 16, if patients experienced significant worsening of their skin psoriasis (increase in BSA by at least 25% over the baseline measurement), they were required to roll over (escape early) into the 26-week open-label extension period (period B). This allowed the study to remain blinded and allowed patients receiving placebo to avoid undue disease burden. The primary efficacy and safety outcomes for period A are reported here.

The study was conducted in accordance with International Council for Harmonisation guidelines, applicable regulations, and the principles of the Declaration of Helsinki. Patients reviewed and signed an informed consent statement. The study protocol was approved by an independent ethics committee or institutional review board at each site.

Patients

Key enrollment criteria included being an adult with both chronic, moderate-to-severe plaque psoriasis (for at least 6 months) and psoriasis in at least 1 fingernail (any disease duration). Per protocol, patients at baseline had a BSA of at least 10% or BSA of at least 5% with a total modified Nail Psoriasis Severity Index (mNAPSI) score of 20 or higher, target fingernail mNAPSI score of 8 or higher, Physician's Global Assessment for Fingernail Psoriasis (PGA-F[17]) score of at least moderate severity, Physician's Global Assessment for Skin Psoriasis (PGA-S) score of at least moderate severity,

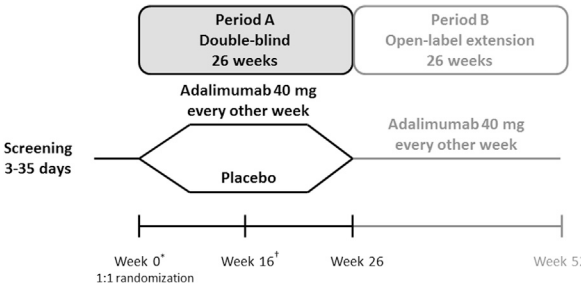

Fig 1. Study design. *Initial dose of adalimumab was 80 mg, followed by 40 mg every other week starting 1 week later. †Starting at week 16, if the psoriasis-affected body surface area increased 25% or more over baseline, patients were rolled over to the open-label extension period.

and Nail Psoriasis Physical Functioning Severity (NPPFS) score higher than 3 or nail psoriasis pain based on a Numeric Rating Scale (NRS) score higher than 3. Patients could not have had previous exposure to adalimumab, nor could they have taken oral or injectable corticosteroids during the study. No concomitant treatment for nail psoriasis was allowed.

Efficacy end points

All psoriasis-affected fingernails were assessed at weeks 16 and 26 (see description in Supplemental Table I[17-20]; available at http://www.jaad.org). The target fingernail (identified by the study physician as the most severely involved fingernail at baseline) was assessed at all visits. The primary end point was achievement of 75% or more improvement in total-fingernail mNAPSI (mNAPSI75) at week 26 relative to baseline (mNAPSI is a validated score[18]). Ranked secondary end points at week 26 were improvement from baseline in total-fingernail NAPSI,[19] achievement of total-fingernail mNAPSI score of 0, improvement from baseline in nail psoriasis pain NRS, improvement from baseline in NPPFS, achievement of at least 50% improvement in scalp component of the Brigham Scalp Nail Inverse Palmo-Plantar Psoriasis Index[20] (B-SNIPI50 [scalp]) relative to baseline for patients with baseline scalp score of 6 or higher, and achievement of a PGA-F[17] score of 0 (clear) or 1 (minimal) with a 2-grade or more improvement from baseline. B-SNIPI50 (scalp) was assessed only for patients in United States and Puerto Rico. The change from baseline in the Nail Psoriasis Quality of Life measure was also evaluated.

Statistical analyses

The primary efficacy analysis was performed for the period A intent-to-treat population. The primary

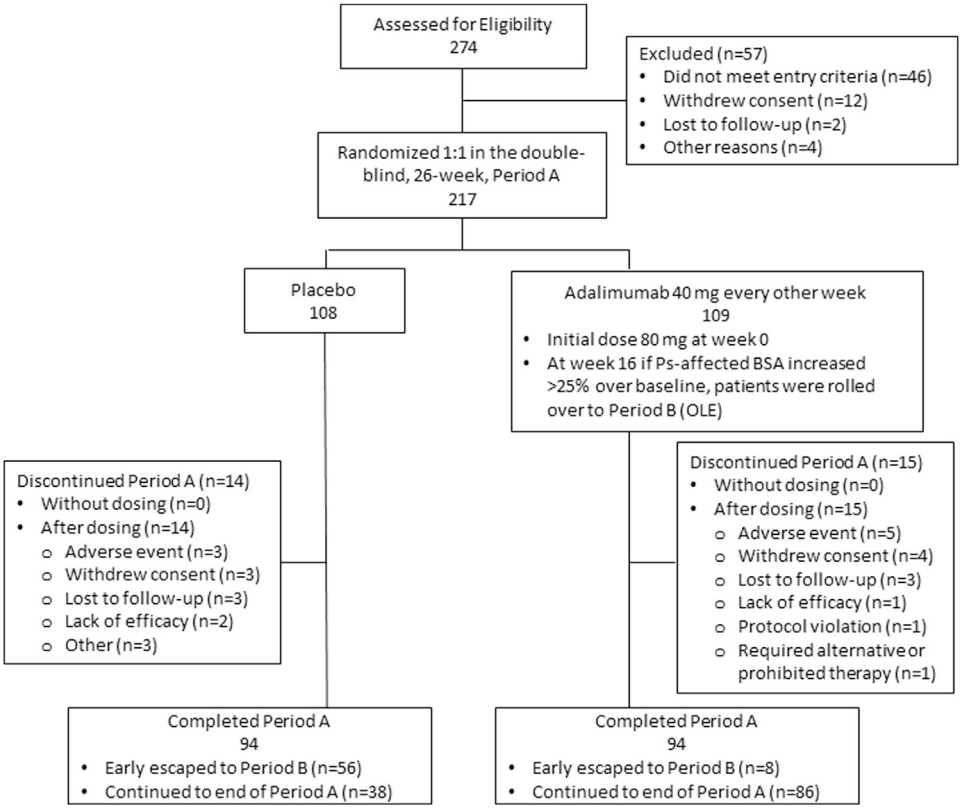

Fig 2. Patient disposition. The 26-week open-label extension period (period B) is not reported. For those patients who discontinued study participation for more than 1 reason, only the primary reason is listed. *BSA*, Body surface area; *OLE*, open-label extension; *Ps*, psoriasis

and ranked secondary end points were tested in ranked order to control multiplicity, and missing data were handled by multiple imputation for all end points. Patients who discontinued the study because of lack of efficacy or who escaped early to period B, were counted as nonresponders for categorical variables, and their last observation was carried forward for continuous variables. The safety analysis included all patients in period A and was determined by the reporting of treatment-emergent adverse events and evaluation of laboratory and vital sign determinations. All statistical tests were 2 tailed with a significance level of .05. The statistical analysis was performed using SAS software (SAS Institute Inc., Cary, NC).

RESULTS

Patients were enrolled at 32 sites in Australia, Belgium, Canada, France, Germany, Greece, Puerto Rico, and the United States. Of the 217 randomized patients, 188 (86.6%) completed period A (reached week 26 or escaped early to period B per protocol) (Fig 2). Key demographics and baseline characteristics were generally comparable between the 2 groups (Table I). The mean patient age was 46.7 years. The majority were male, were white, had a psoriasis-affected BSA of 10% or more, had concomitant scalp psoriasis, and were overweight according to World Health Organization criteria[21] (79.1% had a body mass index higher than 30 kg/m^2). As measured by the PGA-F, nail disease severity was moderate (in 53.5% of patients) or more severe (in 46.5%). Patients had clinically relevant fingernail severity according to the mean mNAPSI and mean NAPSI, clinically relevant fingernail pain, and decreased nail quality of life. The rate of concomitant psoriatic arthritis was 28.6%.

Efficacy

Adalimumab demonstrated statistically significant efficacy at week 26 in the primary end point and all ranked secondary end points (Figs 3 and 4). The response rates for total-fingernail mNAPSI75 at week 26 were 3.4% (placebo) and 46.6% (adalimumab) ($P < .001$). Response rates for the secondary end points (placebo vs adalimumab) were 11.5% versus 56.2% ($P < .001$) for improvement in total NAPSI; 0% versus 6.6% ($P < .01$) for

Table I. Key demographics and baseline characteristics

Demographics		Placebo n = 108	Adalimumab n = 109	All Patients N = 217
Sex, n (%)	Male	87 (80.6)	96 (88.1)	183 (84.3)
	Female	21 (19.4)	13 (11.9)	34 (15.7)
Race, n (%)	White	103 (95.4)	103 (94.5)	206 (94.9)
	Asian	3 (2.8)	5 (4.6)	1 (0.5)
	Other*	2 (1.8)	1 (0.9)	10 (4.6)
Body surface area of psoriasis, n (%)	5% to <10%	44 (40.7)	43 (39.4)	87 (40.1)
	≥10%	64 (59.3)	66 (60.6)	130 (59.9)
PGA-F, n (%)	Moderate	61 (56.5)	55 (50.5)	116 (53.5)
	>Moderate	47 (43.5)	54 (49.5)	101 (46.5)
PGA-S, n (%)	Moderate	65 (60.2)	68 (62.4)	133 (61.3)
	>Moderate	43 (39.8)	40 (36.7)	83 (38.2)
Scalp psoriasis, n (%)		93 (86.1)	91 (83.5)	184 (84.8)
Psoriatic arthritis, n (%)		32 (29.6)	30 (27.5)	62 (28.6)
Characteristics				
Age, years, mean (SD]		46.2 (12.13)	47.2 (11.86)	46.7 (11.98)
Body mass index, kg/m^2, mean (SD)		(n = 107)	(n = 108)	(n = 215)
		29.1 (6.72)	29.7 (5.72)	29.4 (6.23)
Weight, kg, mean (SD)		88.4 (19.40)	92.03 (19.51)	90.2 (19.50)
Duration of psoriasis, years, mean (SD)		17.7 (13.15)	19.7 (12.28)	18.7 (12.73)
Duration of nail psoriasis, years, mean (SD)		11.3 (10.62)	11.5 (9.35)	11.4 (9.98)
PASI score, mean (SD)		12.8 (9.43)	12.3 (8.59)	12.5 (9.00)
Total-fingernail mNAPSI score (range 0-130), mean (SD)†		58.1 (21.55)	57.6 (20.16)	57.9 (20.82)
Total-fingernail mNAPSI score (range 0-130), median (Q1, Q3)†		55.0 (45.5, 72.5)	57.0 (44.0, 69.0)	56.0 (44.0-70.0)
Onycholysis or oil-drop dyschromia		16.0 (11.0, 23.0)	18.0 (12.0, 22.0)	17.0 (11.0-22.0)
Pitting		13.0 (9.5, 18.0)	14.0 (9.0, 18.0)	14.0 (9.0-18.0)
Nail plate crumbling		8.0 (4.0, 16.0)	9.0 (5.0, 14.0)	8.0 (4.0-15.0)
Leukonychia		6.0 (2.0, 9.0)	5.0 (2.0, 8.0)	5.0 (2.0-9.0)
Splinter hemorrhage		4.0 (1.0, 7.0)	4.0 (2.0, 7.0)	4.0 (2.0-7.0)
Nail bed hyperkeratosis		6.0 (2.0, 10.0)	6.0 (2.0, 9.0)	6.0 (2.0-10.0)
Red spots in lunula		1.0 (0, 2.0)	0 (0, 2.0)	0 (0-2.0)
Total-fingernail NAPSI score (range 0-80), mean (SD)†		46.8 (15.53)	47.9 (16.14)	47.4 (15.82)
Nail psoriasis pain (NRS) score (range 0-10), mean (SD)†		5.7 (2.41)	5.2 (2.38)	5.4 (2.41)
B-SNIPI, scalp component (range 0-20), mean (SD)†		(n = 20)	(n = 27)	(n = 47)
		8.1 (5.69)	9.4 (5.51)	8.8 (5.57)
NPPFS score (range 0-10), mean (SD)†		5.4 (2.18)	5.4 (2.59)	5.4 (2.39)
Nail Ps QoL (range 0-10), mean (SD)‡		(n = 107)		(n = 216)
		5.4 (2.26)	5.1 (2.73)	5.2 (2.50)

B-SNIPI, Brigham Scalp Nail Inverse Palmo-Plantar Psoriasis Index; *mNAPSI*, modified Nail Psoriasis Severity Index; *NAPSI*, Nail Psoriasis Severity Index; *NPPFS*, Nail Psoriasis Physical Functioning Severity; *NRS*, numeric rating scale; *PASI*, Psoriasis Area Severity Index; *PGA-F*, Physician's Global Assessment for Fingernail Psoriasis; *PGA-S*, Physician's Global Assessment for Skin Psoriasis; *Ps*, psoriasis; *Q*, quartile; *QoL*, quality of life; *SD*, standard deviation.

*Other includes Native Hawaiian or other Pacific Islander (n = 1) and multiracial (n = 1) for placebo, and black (n = 1) for adalimumab.

†Higher score indicates higher severity or impairment.

‡A value of 0 indicates no impact on quality of life, and a value of 10 indicates severe impact.

achievement of a total-fingernail mNAPSI score of 0; 1.1 versus 3.7 ($P < .001$) for improvement in nail psoriasis pain (according to the NRS); 0.8 versus 3.7 ($P < .001$) for improvement in NPPFS, 0.4% versus 58.3% ($P < .01$) for achievement of B-SNIPI50 (scalp), and 6.9% versus 48.9% ($P < .001$) for achievement of PGA-F score of 0 or 1 with 2 or more grades of improvement from baseline. Differences between treatment groups were also seen at week 16 for the primary and all of the ranked secondary end points ($P < .001$), except for the percentage of patients achieving a total-fingernail mNAPSI of 0 (Fig 4).

Treatment response was also seen in the patients' target nail, which was identified at baseline. Outcomes were measured at all study visits in period A (Fig 5). The target-nail mNAPSI75 response rate was greater for adalimumab versus placebo starting

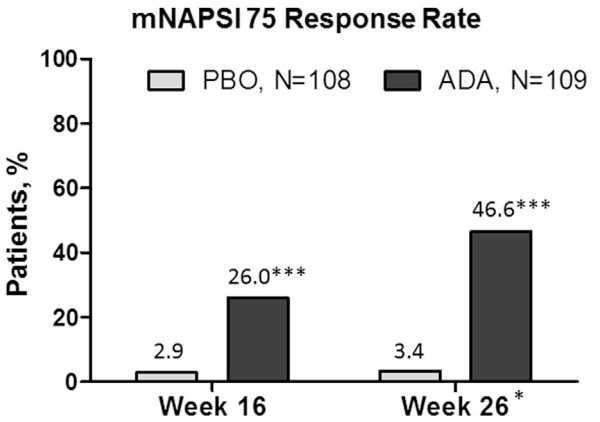

Fig 3. Primary efficacy end point. Multiple imputation. Statistically significant at ***$P < .001$. *ADA*, Adalimumab; *mNAPSI*, modified Nail Psoriasis Severity Index; *PBO*, placebo. *Primary end point was at week 26.

at week 12 (16.5% vs 2.8%), with continued increase to week 26 (42.4% vs 7.3%) ($P < .001$ at weeks 12, 16, 21, and 26). At week 8, the mean percent improvement in NAPSI was greater for adalimumab (18.8% vs placebo 3.5%), with continued rate increase to week 26 (54.6% vs 14.4%) ($P < .001$ at weeks 8, 12, 16, 21, and 26).

Adalimumab also demonstrated greater improvement from baseline in the Nail Psoriasis Quality of Life measure compared with placebo (3.1 vs 0.4 at week 16 and 3.3 vs 0.6 at week 26 [adalimumab, n = 109; placebo, n = 107]) ($P < .001$]).

Safety

Treatment-emergent adverse events were reported by 56.5% of patients who received placebo and 58.7% who received adalimumab (Table II). Most events were mild or moderate in severity. The most common were nasopharyngitis (9.3% of those who received placebo vs 5.5% of those who received adalimumab) and upper respiratory tract infection (8.3% of patients in each treatment group). The rates of serious adverse events and serious infections were higher for adalimumab (7.3% and 3.7%) than for placebo (4.6% and 1.9%). Serious noninfectious adverse events in the placebo group were atrial fibrillation, carotid artery stenosis, bronchospasm, and psoriasis (each reported by 1 patient). In the adalimumab group, serious noninfectious adverse events were congestive cardiac failure, diverticular perforation, and hypertensive crisis (each reported by 1 patient); anaphylactic reaction and arthropod sting (reported by 1 patient); and major depression and suicidal ideation (reported by 1 patient). Serious infections in the placebo group included pneumonia (reported by 2 patients), and in the adalimumab group, they were endocarditis, prostatitis, erysipelas, diverticulitis, and bronchitis (each reported by 1 patient). No occurrences of tuberculosis, malignancy, opportunistic infections excluding oral candidiasis, demyelinating disorders, or death were reported.

DISCUSSION

Adalimumab therapy for 26 weeks at the dose approved for treatment of moderate-to-severe psoriasis was effective for treatment of moderate-to-severe nail psoriasis and its associated pain, as well as for scalp psoriasis. The majority of patients experienced improvement in their nail psoriasis signs and symptoms. Few patients achieved completely normal nails (6.6% at 26 weeks); however, full regrowth may not have completely occurred by 26 weeks. This study, which was specifically designed to evaluate fingernail psoriasis, addresses the previous lack of approved biologic agents to treat nail psoriasis and the previously limited clinical trial data supporting the effectiveness of biologics for nail psoriasis. These results also support recently published nail psoriasis guidelines identifying adalimumab as a recommended biologic treatment for patients with significant nail disease and with concomitant, significant skin and/or joint disease.[13,22]

Many patients with psoriasis suffer considerable morbidity from their nail psoriasis disease that is manifested as nail pain and/or impairment in nail function, and yet they are considered inappropriate candidates for systemic therapy if they lack at least 10% BSA involvement. The baseline level of nail psoriasis pain in this study, averaging 5.7 on a scale of 0 to 10, was substantial. Treatment with adalimumab not only improved the objective findings of nail psoriasis when multiple validated end points were used but also improved subjective symptoms of pain, functionality, scalp involvement, and nail-specific quality of life. These outcomes substantiate that patients with moderate-to-severe fingernail psoriasis with substantial psoriatic skin disease are likely the most appropriate candidates for systemic therapy and that following adalimumab treatment, improvement in quality of life for both skin[23] and nail psoriasis can be expected. Although this study also enrolled patients with at least 5% psoriasis-involved BSA, the associated considerable overall burden of nail disease represented that of moderate-to-severe psoriasis. This supports existing guidelines stating that systemic treatment, including biologics, is often recommended for patients with skin, nail, or scalp psoriasis.[13,24]

Unlike the current study, which specifically chose participants with clinically substantial nail disease at baseline, the majority of other trials of biologic and

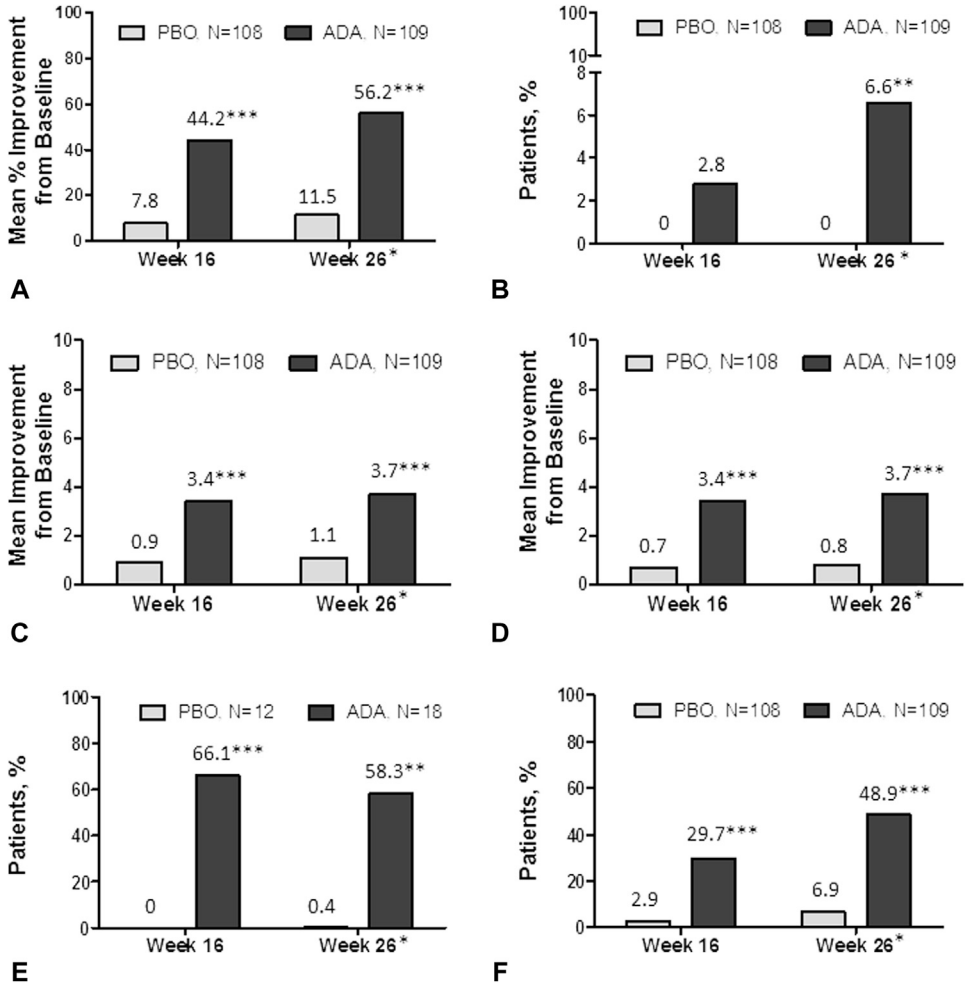

Fig 4. Ranked secondary end points. **A**, Mean percent improvement in total Nail Psoriasis Severity Index (NAPSI). **B**, Achievement of total fingernail modified Nail Psoriasis Severity Index (mNAPSI) of 0. **C**, Mean improvement in nail (psoriasis) Ps pain Numeric Rating Scale (NRS). **D**, Mean improvement in Nail Psoriasis Physical Functioning Severity (NPPFS). **E**, Achievement of at least 50% improvement in the scalp component of the Brigham Scalp Nail Inverse Palmo-Plantar Psoriasis Index among patients with baseline scalp score of 6 or higher (B-SNIPI50). **F**, Achievement of Physician's Global Assessment of Fingernail Psoriasis (PGA-F) score of 0 or 1 with 2 or more grades of improvement from baseline. *Ranked secondary end points were at week 26; total nail end points were collected only at weeks 16 and 26. Multiple imputation. Statistically significant at $^{***}P < .001$ and $^{**}P < .01$. *ADA*, Adalimumab; *PBO*, placebo.

systemic therapies that showed concomitant improvements in nail response (according to the NAPSI), assessed nail psoriasis in subsets of patients with psoriasis who also had nail disease of varying severity.[13,25] These include the following: a trial of adalimumab, 40 mg every other week, for treatment of psoriasis of the hands and feet (mean percent improvement in target-nail NAPSI at week 28, 54.6%)[14]; a retrospective analysis of nail psoriasis in psoriasis patients receiving 5 mg/kg every 8 weeks of the TNF-inhibitor infliximab (mean percent improvement in NAPSI at week 27, 57.2%)[26]; a trial of the TNF-inhibitor etanercept, 50 mg twice weekly for 12 weeks and then either weekly or twice weekly for 12 weeks for the treatment of nail psoriasis (mean percent improvement in NAPSI at week 24, 22.6% for both regimens)[27]; subanalyses of patients with psoriasis treated with the interleukin 12/23 inhibitor ustekinumab, 45 mg at weeks 0, 4, 16 and 28 (mean percent improvement in NAPSI at week 24, 46.5%),[28] and with the interleukin 17 inhibitors ixekizumab, 75 mg at weeks 0, 2, 4, 8, 12 and 16 (mean percent improvement in NAPSI at week 12, 57.1%),[27,29] and secukinumab, 300 mg weekly for 4 weeks and then

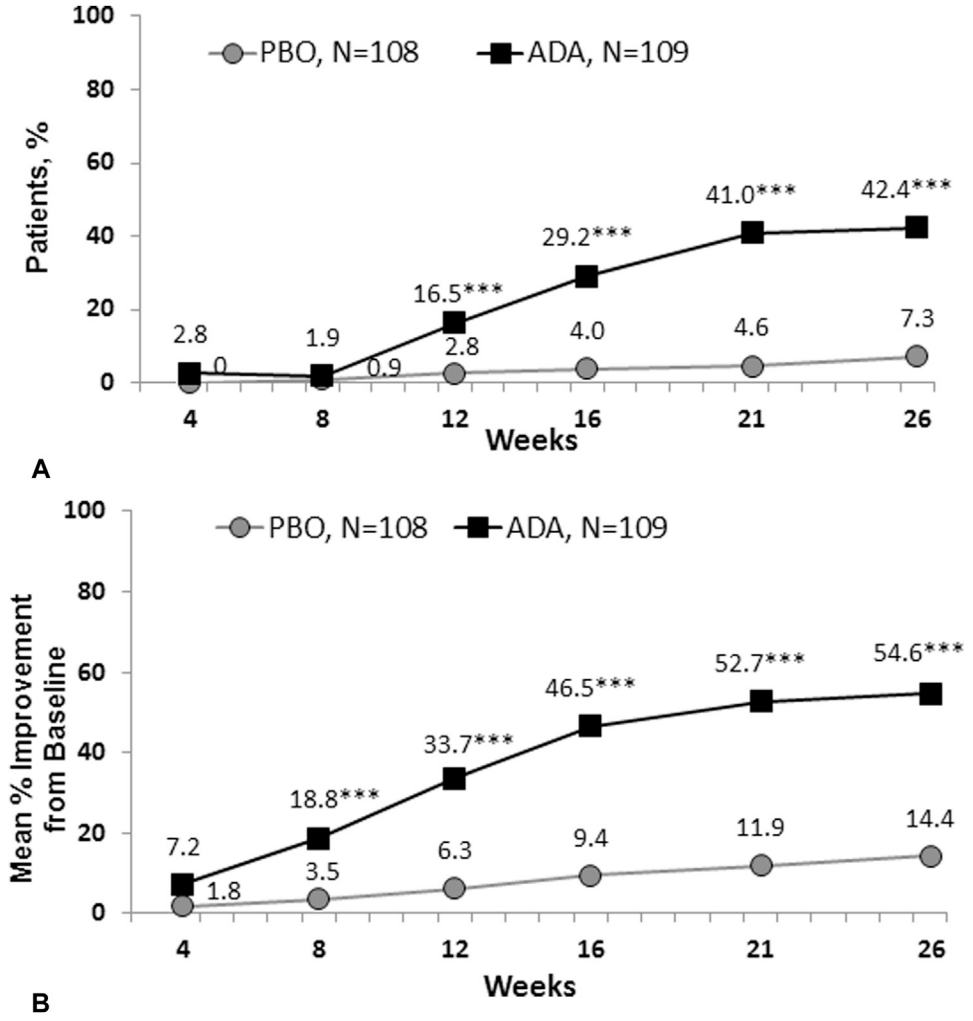

Fig 5. Improvement over time in target fingernail. **A**, modified Nail Psoriasis Severity Index (mNAPSI75) response rate of at least 75% relative to baseline in target fingernail. **B**, Mean percent improvement in target fingernail Nail Psoriasis Severity Index (NAPSI). Multiple imputation. Statistically significant at ***$P < .001$. *ADA*, Adalimumab; *PBO*, placebo.

every 4 weeks (mean percent improvement in composite fingernail score at week 12, 10.6%)[30]; and a trial of nail psoriasis treatment with the traditional systemic agents cyclosporine, 5 mg/kg daily for 12 weeks and 2.5 to 3.5 mg/kg daily for 12 weeks (mean percent improvement in NAPSI at week 24, 37.2%), and methotrexate, 15 mg weekly for 12 weeks and 10 mg weekly for 12 weeks (mean percent improvement in NAPSI at week 24, 43.3%).[31] Although these different agents were not compared directly in head-to-head studies, based on the similar levels of efficacy among the biologic agents and their higher reported efficacy than methotrexate or cyclosporine, biologic therapy may be the more appropriate choice for psoriasis patients with clinically significant nail disease.

Like nail psoriasis, scalp psoriasis is associated with the development of psoriatic arthritis,[32] is frequently a manifestation of skin psoriasis, is difficult to treat, and can have a negative impact on patient quality of life.[33,34] Significant scalp involvement can qualify the severity level of psoriasis as moderate to severe.[35] In the current trial, the incidence of concomitant scalp psoriasis was similar to the published rate in patients with chronic plaque psoriasis,[36,37] and more than half of the patients achieved a clinically relevant, statistically significant improvement compared with placebo following 16 and 26 weeks of adalimumab treatment.

Although this study was restricted to fingernail psoriasis, psoriasis can also affect toenails and negatively affect quality of life and pose treatment challenges. The period A results of this study indicate

Table II. Treatment-emergent adverse events (safety population in period A)

Adverse events, n (%)	Placebo, n = 108 n (%)	Adalimumab, n = 109 n (%)
Any adverse event	61 (56.5)	64 (58.7)
Serious	5 (4.6)	8 (7.3)
Infections	30 (27.8)	32 (29.4)
Serious infection	2 (1.9)	4 (3.7)
Tuberculosis	0	0
Malignancy	0	0
Leading to study drug discontinuation	3 (2.8)	6 (5.5)
Opportunistic infection, excluding oral candidiasis	0	0
Demyelinating disorder	0	0
Death	0	0
Special interest*		
Allergic reaction including angioedema and anaphylaxis	2 (1.9)	1 (0.9)
Worsening/new onset of psoriasis	7 (6.5)	2 (1.8)
Injection site reaction	3 (2.8)	4 (3.7)

*Adverse events of special interest in fewer than 2 patients in a treatment group were oral candidiasis, congestive heart failure, intestinal perforation, and anemia (adalimumab n = 1 [0.9%, for each]). There were no significant differences between treatment groups ($P > .100$).

that anti-TNF treatment may be helpful for toenail psoriasis, but further studies are needed to evaluate this.

The 26 weeks in period A may have been sufficient to observe treatment response; however, patients with partial response at 26 weeks may experience additional response to longer-term treatment given the slower growth dynamics of the nail apparatus than of skin plaques. These improvements may be observed in the 26-week open-label treatment period (period B).

The safety results from this study are consistent with the known adalimumab safety profile for dermatologic and other disease states, although the serious infection rate for adalimumab was higher than in other adalimumab trials evaluating patients with moderate-to-severe psoriasis[38-40] and moderate-to-severe psoriasis of the hands and feet.[14] No unexpected safety risk was identified.[14,41]

This study was limited by the requirement of at least 5% affected BSA involvement, the small sample size of patients with scalp psoriasis, and a lack of power to robustly compare the safety of adalimumab versus placebo. Also, the definition of *clinically meaningful* has not been validated in nail psoriasis.

The results of this study using clinically validated end points have recently been added to the product label.[42,43] As this study enrolled a larger number of patients with this specific constellation of psoriatic disease than had been accomplished in earlier studies of biologic treatment, the results demonstrated robust efficacy over placebo.

In conclusion, after 26 weeks of treatment, adalimumab improved signs and symptoms of moderate-to-severe nail psoriasis compared with placebo; significant improvements were seen in primary and all ranked secondary end points, including the scalp, although the sample size with scalp involvement was small. No new safety risks were identified with adalimumab treatment in this population. Adalimumab should be considered for treatment of patients with moderate-to-severe psoriasis who have as little as 5% BSA involvement and moderate-to-severe fingernail psoriasis.

AbbVie and the authors thank the patients who participated in this clinical trial, and all of the study investigators for their contributions. The authors would also like to acknowledge Jody Bennett, employed by AbbVie, for medical writing support in the production of this publication.

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Supplemental Table I. Scoring for nail, skin, and scalp psoriasis evaluations

Score	Measurement/Evaluation	Scoring*
mNAPSI[18]	Nail pitting	0 (none), 1 (1%-10%), 2 (11%-49%), 3 (>50%)
	Nail onycholysis or oil-drop dyschromia	0 (none), 1 (10%), 2 (11%-30%), 3 (>30%)
	Nail crumbling	0 (none), 1 (1%-25%), 2 (26%-50%), 3 (>50%)
	Nail leukonychia, splinter hemorrhages, hyperkeratosis, red spots in the lunula	0 (absent) or 1 (present) for each item
		Total score range 0-130 (or 13 for each nail)
PGA-F[17]	Nail bed plus nail matrix signs of disease	0 (clear), 1 (minimal), 2 (mild), 3 (moderate), 4 (severe) Total score = the worse of nail bed or matrix scores (range 0-4)
NAPSI[19]	Nail matrix: pitting, leukonychia, red spots in the lunula, crumbling	0 (none), 1-4 (present in 1/4, 1/2, 3/4, 4/4 of nail, respectively)
	Nail bed: onycholysis, splinter hemorrhages, oil drop discoloration, hyperkeratosis	0 (none), 1-4 (present in 1/4, 1/2, 3/4, 4/4 of nail, respectively)
		Total score range 0-80 (nail bed + matrix scores)
Nail psoriasis pain	Pain due to nail psoriasis	NRS: 0 (no pain) to 10 (severe pain)
NPPFS	Impact of fingernail psoriasis on ability to perform physical tasks	NRS: 0 (none) to 10 (severe)
B-SNIPI[20] (scalp component)	Severity	0 (clear) 1 (erythema, no raised plaques, no scale) 2 (erythema, mildly thick plaques, mild scale) 3 (erythema, moderately thick plaques, mild scale) 4 (prominent erythema, moderately thick plaques, moderate scale) 5 (prominent erythema, thick plaques, hypertrophic scale with/without excoriations, irrespective of area involved)
	Involved area	0 (clear), 1 (<10%), 2 (11%-20%), 3 (21%-30%), 4 (31%-40%), 5 (41%-50%)
	Patient-reported outcomes (PROs):	VAS
	Scalp itch	0 (none) to 10 (worst imaginable)
	Scalp pain	0 (none) to 10 (worst imaginable)
		Total score range 0-20: Severity + area: range 0-10 PROs: range 0-10; higher of the 2 scores
PGA-S	Skin: scaling, erythema, induration	0 (clear), 1 (minimal), 2 (mild), 3 (moderate), 4 (moderate), 5 (severe)

B-SNIPI, Brigham Scalp Nail Inverse Palmo-Plantar Psoriasis Index; *mNAPSI*, Modified Nail Psoriasis Severity Index; *NAPSI*, Nail Psoriasis Severity Index; *NPPFS*, Nail Psoriasis Physical Functioning Severity; *NRS*, numeric rating scale; *PGA-F*, Physician's Global Assessment for Fingernail Psoriasis; *PGA-S*, Physician's Global Assessment for Skin Psoriasis; *PRO*, patient-reported outcome; *VAS*, visual analog scale.
*Higher score indicates greater severity or impairment.