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ORIGINAL ARTICLE

Adalimumab for nail psoriasis: efficacy and safety over 52 weeks from a phase-3, randomized, placebo-controlled trial

B.E. Elewski,[1,*] C.S. Baker,[2] J.J. Crowley,[3] Y. Poulin,[4] M.M. Okun,[5] B. Calimlim,[6] Z. Geng,[6] O. Reyes Servin,[6] P.A. Rich[7]

[1]School of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA
[2]Skin & Cancer Foundation Inc and Probity Medical Research, Carlton, Vic., Australia
[3]Bakersfield Dermatology, Bakersfield, CA, USA
[4]Centre de Recherche Dermatologique du Québec Métropolitain, Québec City, QC, Canada
[5]Fort Healthcare, Fort Atkinson, WI, USA
[6]AbbVie Inc, North Chicago, IL, USA
[7]Oregon Health and Science University Hospital, Portland, OR, USA
*Correspondence: B.E. Elewski. E-mail: beelewski@gmail.com

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Abstract

Background Few clinical trials have evaluated long-term treatment of nail psoriasis with biologics.

Objective Safety and efficacy of adalimumab [ADA; Humira AbbVie Inc, North Chicago, IL, USA)] long-term treatment (52 weeks) was evaluated in a phase-3, randomized trial in patients with moderate-to-severe plaque psoriasis and concomitant moderate-to-severe fingernail psoriasis. Results from the first 26 weeks (Period A) have been reported.

Methods Patients receiving 40 mg ADA every other week or placebo in Period A, continued with or switched to 40 mg ADA every-other-week treatment in the subsequent 26-week open-label extension (OLE) period. Main efficacy evaluations were ≥75% improvement in total-fingernail modified Nail Psoriasis Severity Index (mNAPSI 75) and achievement of Physician's Global Assessment for Fingernail Psoriasis of clear or minimal disease (PGA-F 0/1) with a ≥2-grade improvement from baseline, across the trial for patients who continued ADA from Period A through the OLE (Continuous-ADA Population). Safety was evaluated during the OLE and for patients receiving ADA at any time during the study (All-ADA Population).

Results Of the 217 patients initially randomized in Period A, 188 (86.6%; 94 in each treatment group) entered the OLE after completion of or early escape from Period A. For the Continuous-ADA Population (N = 109), endpoint achievement rates improved from OLE entry (Week 26) to Week 52, including total-fingernail mNAPSI 75 (47.4–54.5%); PGA-F 0/1 (51.1–55.6%) and total-fingernail mNAPSI = 0 (6.6–17.9%). Serious adverse event and serious infection rates for the All-ADA Population (N = 203) were 6.9% and 3.4%, respectively.

Conclusions In this population of psoriasis patients with concomitant, moderate-to-severe nail psoriasis, long-term efficacy and improvement in signs and symptoms of nail disease were demonstrated after every-other-week ADA treatment, including incremental improvements in rate of total clearance of nail disease. No new safety risks were identified for patients receiving at least one ADA dose across 52 weeks.

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Conflicts of interest

B Elewski received grants from AbbVie, Anaptys-Bio, Boehringer Ingelheim, Celgene, Incyte, Leo, Lilly, Merck, Novartis, Pfizer, Regeneron, Sun and Valeant for investigator services, and honoraria from Boehringer Ingelheim, Celgene, Leo, Lilly, Novartis, Pfizer, Sun and Valeant Verrica for consultant services. C Baker received honoraria from AbbVie, Pfizer, Novartis, Lilly and Janssen for participation on ad boards and for investigator and speaker services. J Crowley received honoraria for consultant and speaker services and grants for investigator services from AbbVie, Janssen, Lilly, Novartis, Regeneron, Sanofi-Aventis and UCB; received honoraria and grants for consultant and investigator services, respectively, from Amgen, Celgene and Sun Pharma; and received grants for investigator services from MC2 Therapeutics, Merck, Pfizer, Sandoz and Verrica Pharmaceuticals. Y Poulin received grants for investigator services from AbbVie, Amgen, Baxalta, Celgene, Janssen, Eli Lilly, Glaxo Smith Kline, Incyte, Leo Pharma, Merck, Novartis, Pfizer, Regeneron, Sanofi and UCB Pharma, and received honoraria

for speaker and/or advisory board services from AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Novartis and Leo Pharma. MM Okun received honoraria from AbbVie for advisory board participation and for speaker services, and from AbbVie, Gilead, UCB, GSK, InflaRx, Genentech, Innovaderm and Seattle Genetics for consultant services. PA Rich received grants for investigator services from AbbVie, Allergan, Amgen, Anacor, Cassiopea, Dusa, Eli Lilly, Galderma, Janssen, Leo, Meiji, Merck, Novartis, Pfizer, Psolar, Ranbaxy, Sandoz and Viamet, honoraria for advisory board participation from AbbVie, Eli Lilly, Novartis, Sandoz and Valeant, and honoraria for consultant services from AbbVie, Novartis and Polichem. B Calimlim, Z Geng and O Servin received a salary as AbbVie employees and may have also received stocks and/or stock options.

Funding source and Data sharing

AbbVie Inc. funded this study and participated in the study design; study research; collection, analysis and interpretation of data; and writing, reviewing and approving of this publication. All authors had access to the data and participated in the development, review, and approval and in the decision to submit this publication. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g. protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time, and the data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

Introduction

Nail disease in patients with psoriasis is a chronic, painful condition that can result in impaired function, restrictions in daily life activities, and can aggravate the reduced quality of life, including psychological stress and negative effects on social activities inherent to psoriasis.[1–4] Concomitant skin or scalp psoriasis, or psoriatic arthritis (PsA) can occur with nail psoriasis.[2,5,6] Approximately half of patients with skin psoriasis can have nail involvement,[7] and approximately 80% of patients with both psoriasis and PsA also have nail involvement.[8–10] Longer-term nail disease may precede more severe psoriasis or PsA.[11] Higher rates of nail disease are associated with more severe psoriasis and longer psoriasis duration.[1,6,11] Quality of life for psoriasis patients can be much worse for those with concomitant nail psoriasis.[12]

Treatment of nail psoriasis differs depending on disease severity. Systemic therapy has been recommended for patients with psoriasis that is limited to the nails or who have not responded to topical therapy, as well as for more severe disease and when multiple body areas are involved (skin, nails and joints).[13] Time to treatment response is slow because of the length of time involved in nail growth (5–7 months for complete nail growth[14]). Several clinical trials have evaluated long-term treatment and effectiveness of biologic agents for nail psoriasis. Most have evaluated subpopulations of psoriasis patients who had concomitant moderate-to-severe nail psoriasis [tumour necrosis factor alpha (TNF-α) inhibitors etanercept[15] and infliximab[16,17]; IL 12/23 inhibitor ustekinumab,[18] IL-17A inhibitor ixekizumab[19,20] and JAK inhibitor tofacitinib[21]]; however, none evaluated long-term safety in their respective nail psoriasis populations. Two trials prospectively evaluated patients with moderate-to-severe nail disease: one in patients treated with secukinumab[22,23] and the other in the current phase-3 trial described below.

The anti-TNF-α agent adalimumab [Humira (AbbVie Inc, North Chicago, IL, USA)] has demonstrated efficacy and safety up to 28 weeks for the treatment of nail psoriasis in studies of patients with moderate-to-severe psoriasis and PsA.[24–27] A phase-3, randomized, controlled trial of adalimumab treatment of patients with moderate-to-severe plaque psoriasis and concomitant fingernail psoriasis reported efficacy and safety results from the first 26 weeks.[28] Here, we report long-term efficacy and safety results from the second 26-week, open-label extension (OLE) portion of that trial.

Materials and methods

Study design

This was a phase-3, multicenter, double-blind, randomized, parallel-arm, placebo-controlled trial.[28] In the initial 26-week Period A, patients were randomized in a 1 : 1 ratio to 40-mg adalimumab every other week (starting at Week 1, after an

80 mg dose at Week 0) or to placebo. Patients were required to escape early from Period A into the OLE if starting from Week 16, they experienced significant worsening of their skin psoriasis [increase in body surface area (BSA) involvement by at least 25% over the baseline measurement]. This allowed the study to remain blinded and enabled patients receiving placebo to avoid undue disease burden. Upon completion of Period A, patients entered the 26-week OLE and either continued with or switched to 40-mg adalimumab every other week. Efficacy and safety outcomes throughout the 52 weeks of the study 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.

Enrolment

As previously described,[28] enrolment criteria included BSA ≥10% or ≥5% with a total modified Nail Psoriasis Severity Index (mNAPSI) score ≥20; target fingernail mNAPSI score of ≥8; a score of at least moderate severity for the Physician's Global Assessment for Fingernail Psoriasis (PGA-F[29]) and the Physician's Global Assessment for Skin Psoriasis (PGA-S) scores; and a score of >3 for the Nail Psoriasis Physical Functioning Severity (NPPFS) score or Nail Psoriasis Pain Numeric Rating Scale (NRS) score. Patients were not allowed previous adalimumab treatment or concomitant treatment for nail psoriasis during the study.

Efficacy assessments

The main efficacy analyses across 52 weeks were achievement of 75% or more improvement relative to baseline in total-fingernail mNAPSI[30] (mNAPSI 75), and achievement of PGA-F 0/1 (clear or minimal) with a ≥2-grade improvement from baseline. The mNAPSI endpoint was chosen because nail disease severity and nail involvement are reflected in the scoring. Other efficacy analyses across 52 weeks included per cent improvement from baseline in total-fingernail NAPSI,[31] achievement of total-fingernail mNAPSI score of 0 and achievement of at least 50% improvement in the scalp component of the Brigham Scalp Nail Inverse Palmo-Plantar Psoriasis Index[32] [B-SNIPI50 (scalp)] relative to baseline for patients with baseline scalp psoriasis score of ≥6 (assessed only for patients in US and Puerto Rico). A description of the methods that were used in this study to score nail disease has been published.[28] Patient-reported outcomes across 52 weeks included the following scores: improvement from baseline in Nail Psoriasis Pain numerical rating scale (NRS) using a scale of 0 (no pain) to 10 (severe pain); mean change from baseline in Nail Psoriasis Physical Functioning Severity (NPPFS) score, which measured the impact of fingernail psoriasis on the ability to perform physical tasks, using a scale of 0 (none) to 10 (severe); mean change from baseline in Nail Assessment of Psoriasis and Psoriatic Arthritis Quality of Life (NAPPA QoL) score,[33] which measured the impact of nail psoriasis on hands and/or feet in terms of patient suffering and ability to function, using a scale of 0 (no effect) to 4 (very much of an effect) for each question; and mean change from baseline in Nail Psoriasis Quality of Life (Nail Ps QoL), which measured the impact of nail psoriasis on patient quality of life, using a scale of 0 (none) to 10 (severe).

Post hoc analyses of efficacy during the OLE were performed for a subgroup with a history of PsA. These included achievement at Week 52 of mNAPSI 75, mean change from baseline in Nail Psoriasis Pain NRS and mean change from baseline in Nail Ps QoL.

Statistical analyses

Efficacy of long-term treatment with adalimumab across the trial was determined by evaluating continuous adalimumab treatment from Week 0 to Week 52 for all patients who were randomized to adalimumab at Week 0 (Continuous-ADA Population, $N = 109$; Fig. 1). Missing data for the long-term treatment analysis were handled by multiple imputation for all endpoints. As-observed results are also reported.

Efficacy of adalimumab was also analysed in the OLE. The two dose groups included patients who received placebo in Period A (pbo/ADA, $N = 94$) and patients who received adalimumab in Period A (ADA/ADA, $N = 94$; Fig. 1). Efficacy for the subgroup with a history of PsA was evaluated *post hoc* for the two dose groups in the OLE (pbo/ADA and ADA/ADA). Missing data for all OLE efficacy analyses were handled by non-responder imputation (NRI) for categorical variables and by last observation carried forward (LOCF) for continuous variables.

Safety was evaluated by treatment-emergent adverse events for the two OLE treatments and for all patients who received at least one dose of adalimumab during the entire trial (All-ADA Population, $N = 203$; Fig. 1).

Results

Baseline

Of the 217 randomized patients, 188 (86.6%) entered the OLE after reaching Week 26 or escaping early to the OLE (94 in each OLE treatment group) and 168 completed the study (81 pbo/ADA, 87 ADA/ADA; Fig. 1). Demographics and baseline characteristics for the 188 OLE patients showed that the majority were male (84.6%) and White (95.2%) with a mean age of 47.2 years. Mean BMI of 29.4 kg/m^2 indicated that patients were on average, preobese.[34] To evaluate the long-term efficacy of adalimumab treatment, the 109 patients initially randomized to adalimumab were evaluated continuously from baseline to Week 52 (Continuous-ADA Population).

Patients had substantial nail disease and pain at baseline as measured by total-fingernail mNAPSI and NAPSI scores and by

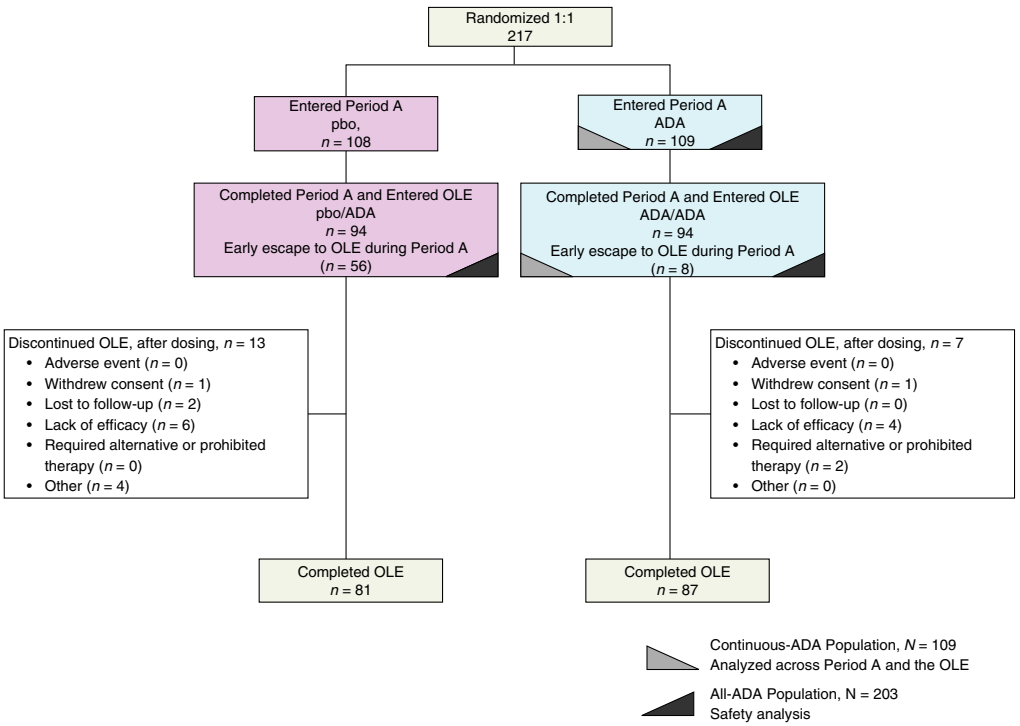

Figure 1 Patient Disposition in the OLE. For those patients who discontinued from study participation for more than one reason, only the primary reason is listed. Abbreviations: ADA, adalimumab; OLE, open-label extension; pbo, placebo.

Nail Psoriasis Pain NRS score. The effect of nail psoriasis at baseline on patient's quality of life was measured by Nail Ps QoL, NAPPA QoL and NPPFS scores (Table 1).

Efficacy

For the Continuous-ADA Population ($N = 109$), the rate of achievement of total-fingernail mNAPSI 75 was 25.9% at Week 16 and increased to 47.4% at Week 26 and to 54.5% at Week 52. Similar results were seen with the rate of achievement of PGA-F 0/1 with ≥2 grades of improvement from baseline (Fig. 2). Improvements in response to adalimumab long-term treatment were also seen from Weeks 16–52 for the other efficacy endpoints in this analysis, including total-fingernail mNAPSI = 0 (Table 2). The observed mean improvement in patient-reported outcomes increased across the trial to Week 52 (Fig. 3). The per cent improvement relative to baseline at Weeks 4 and 52 were 37% and 76% for Nail Psoriasis Pain NRS, 28% and 74% for NPPFS, 28% and 74% for Nail Ps QoL, and 16% and 48% for NAPPA QoL.

Patients who were randomized to placebo in Period A and entered the OLE (pbo/ADA) showed an increase in total-fingernail mNAPSI 75 response starting at the time they switched to ADA at OLE entry (Week 26) (5.3%) and continuing to Week 52 (50.0%) (Fig. 2). Similar rates were seen for the pbo/ADA group in achievement of PGA-F 0/1 with ≥2 grades of improvement from baseline, at OLE entry (5.3%) to Week 52 (53.2%) (Fig. 2). Increased response was also demonstrated across the other efficacy outcomes from OLE entry to Week 52 for the pbo/ADA group (Table 2).

The rate of achievement of total-fingernail mNAPSI 75 and of PGA-F 0/1 increased substantially from OLE entry to Week 52 for the pbo/ADA group, regardless of PsA history, and for the ADA/ADA group with a history of PsA (Fig. 4). The rate of achievement of total-fingernail mNAPSI 75 and PGA-F 0/1 for the ADA/ADA group with no history of PsA was stable from OLE entry up to Week 52. Mean improvement in patient-reported outcomes of nail pain NRS, NPPFS, Nail Ps QoL score and NAPPA QoL score also increased from OLE entry to Week 52 for both treatment groups, regardless of PsA history (Fig. 4).

Safety

For the 203 patients in the All-ADA population, the majority of adverse events were mild (46, 22.7%) or moderate (64, 31.5%) in severity. The most common events were nasopharyngitis (12.3%) and upper respiratory tract infection (8.4%). The rates of serious adverse events and of serious infections were 6.9% and 3.4%, respectively (Table 3).

Table 1 Key demographics and baseline characteristics for patients in the OLE

Demographics		**By dose received in period A and the OLE**	
		pbo/ADA ***N*** **= 94** ***n*** **(%)**	**ADA/ADA** ***N*** **= 94** ***n*** **(%)**
Sex	Male	76 (80.9)	83 (88.3)
	Female	18 (19.1)	11 (11.7)
Race	White	90 (95.7)	89 (94.7)
	Asian	3 (3.2)	4 (4.3)
	Other†	1 (1.1)	1 (1.1)
BSA of Ps	5% to < 10%	34 (36.2)	37 (39.4)
	≥10%	60 (63.8)	57 (60.6)
PGA-F	Moderate	53 (56.4)	44 (46.8)
	>Moderate	41 (43.6)	50 (53.2)
PGA-S	Moderate	55 (58.5)	56 (59.6)
	>Moderate	39 (41.5)	37 (39.4)
Scalp psoriasis		80 (85.1)	80 (85.1)
Psoriatic arthritis		26 (27.7)	28 (29.8)
Characteristics		**Mean [SD]‡**	**Mean [SD]‡**
Age, years		47.1 [11.44]	47.3 [11.82]
Body mass index, kg/m^2		(*N* = 93) 29.2 [6.88]	(*N* = 93) 29.6 [5.09]
Weight, kg		88.6 [20.07]	91.7 [17.27]
Duration of psoriasis, years		18.7 [13.73]	20.7 [12.34]
Duration of nail psoriasis, years		12.0 [11.12]	12.4 [9.65]
PASI score		13.3 [9.87]	12.8 [9.00]
Total-fingernail mNAPSI score (range 0–130)‡		58.6 [20.78]	57.0 [18.34]
Total-fingernail mNAPSI score (range 0–130)‡, median [Q1, Q3]		57.0 [46, 73]	57.0 [44, 68]
Onycholysis or oil-drop dyschromia		16.5 [12, 23]	17.5 [12, 22]
Pitting		13.0 [10, 18]	14.0 [9, 18]
Nail plate crumbling		8.0 [4, 16]	9.0 [5, 14]
Leukonychia		6.0 [2, 9]	5.0 [2, 8]
Splinter haemorrhage		4.0 [2, 7]	5.0 [3, 7]
Nail bed hyperkeratosis		6.5 [2, 10]	6.0 [2, 9]
Red spots in lunula		0 [0, 2]	0 [0, 2]
Total-fingernail NAPSI score (range 0–80)§		46.6 [15.40]	48.0 [15.67]
Nail psoriasis pain (NRS) score (range 0–10)§		5.7 [2.25]	5.0 [2.48]
B-SNIPI, scalp component (range 0–20)§		(*N* = 16) 7.9 [5.82]	(*N* = 23) 9.7 [5.32]
NPPFS score (range 0–10)§		5.2 [2.15]	5.23 [2.63]
Nail Ps QoL (range 0–10)¶		5.2 [2.28]	4.9 [2.79]
NAPPA QoL (range 0–4)§		3.1 [0.83]	3.1 [0.87]

†Other includes multirace (*n* = 1 for pbo/ADA) and black (*n* = 1 for ADA/ADA). ‡All are mean [SD] unless otherwise indicated. §Higher score indicates higher severity or impairment. ¶0 indicates no impact on quality of life; 10 indicates severe impact.

ADA, adalimumab; B-SNIPI, Brigham Scalp Nail Inverse Palmo-Plantar Psoriasis Index; DLQI, Dermatology Life Quality Index; NAPPA, Nail Assessment of Psoriasis and Psoriatic Arthritis; NAPSI, Nail Psoriasis Severity Index (m, modified); NPPFS, Nail Psoriasis Physical Functioning Severity; NRS, Numeric Rating Scale; OLE, open-label extension; PASI, Psoriasis Area Severity Index; pbo, placebo; PGA, Physician's Global Assessment of psoriasis (-F, fingernail; -S, skin); Ps, psoriasis; Q, quartile; QoL, quality of life, SD, standard deviation.

Rates of adverse events for the 188 patients in the OLE (Table 3) were similar to those for the All-ADA population. For these patients, most of the events were mild (40, 21.3%) or moderate (45, 23.9%) in severity. The most common were nasopharyngitis (9.6% pbo/ADA vs. 12.8% ADA/ADA) and upper respiratory tract infection (6.4% pbo/ADA; 4.3% ADA/ADA). The rates of serious adverse events and of serious infections were similar between the two OLE treatment groups (3.2% and 2.1% pbo/ADA vs. 3.2% and 1.1% ADA/ADA).

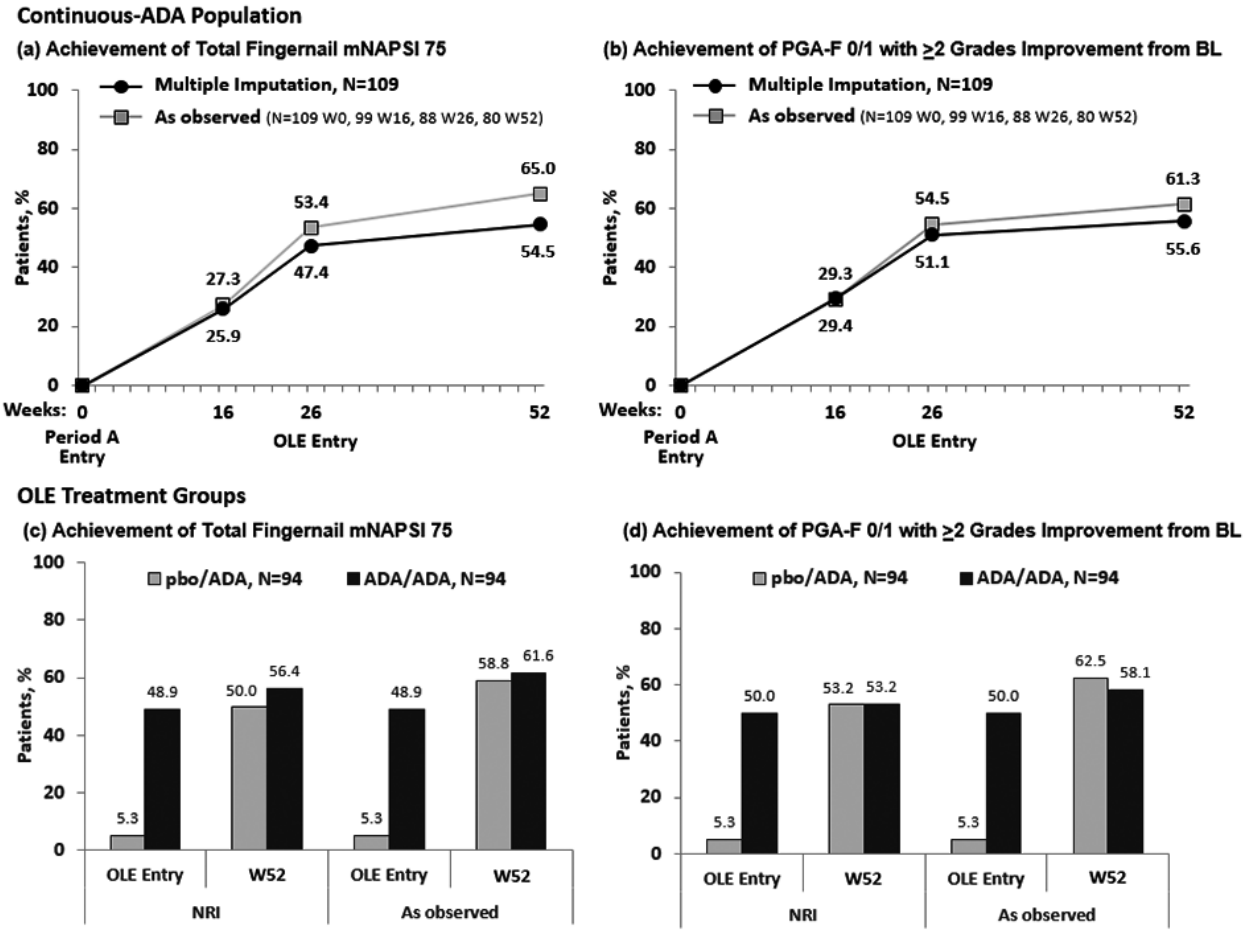

Figure 2 Main Efficacy outcomes over 52 weeks. (a) Achievement of Total-Fingernail mNAPSI 75 (Continuous-ADA Population). (b) Achievement of PGA-F 0/1 with ≥2 Grades Improvement from BL (Continuous-ADA Population). (c) Achievement of Total-Fingernail mNAPSI 75 (OLE). (d) Achievement of PGA-F 0/1 with ≥2 Grades Improvement from BL (OLE). Missing data were handled by multiple imputation. Abbreviations: ADA, adalimumab; BL, baseline; mNAPSI, modified Nail Psoriasis Severity Index; NRI, non-responder imputation; OLE, open-label extension; pbo, placebo; PGA-F, Physician's Global Assessment of Fingernail Psoriasis; W, week.

Table 2 Other efficacy results

	Continuous-ADA population, *N* = 109			OLE treatment groups			
				pbo/ADA, *N* = 94		ADA/ADA, *N* = 94	
	W16	W26	W52	W26 (entry)	W52	W26 (entry)	W52
Total-fingernail NAPSI; mean % improvement [SE]	44.8 [2.84]	57.0 [3.86]	65.5 [3.52]	(*N* = 94) 8.8 [3.28]	(*N* = 88) 67.4 [3.28]	(*N* = 94) 57.3 [3.25]	(*N* = 90) 68.3 [3.22]
Total-fingernail mNAPSI = 0; achievement; % for Continuous-ADA; *n* (%) for OLE	2.8	6.6	17.9	0	11 (11.7)	7 (7.4)	19 (20.2)
B-SNIPI 50 (scalp) achievement; % for Continuous-ADA; *n* (%) for OLE	(*N* = 18) 66.4	(*N* = 18) 57.8	(*N* = 18) 65.8	(*N* = 9) 0	(*N* = 9) 4 (44.4)	(*N* = 16) 10 (62.5)	(*N* = 16) 11 (68.8)

Mean improvement is based on mean change in relation to baseline. Missing data were handled by multiple imputation for long-term analysis and for the OLE analysis by non-responder imputation for categorical variables and last observation carried forward for continuous variables.
ADA, adalimumab; B-SNIPI, Brigham Scalp Nail Inverse Palmo-Plantar Psoriasis Index; NAPSI, Nail Psoriasis Severity Index (m, modified); OLE, open-label extension; pbo, placebo; W, week.

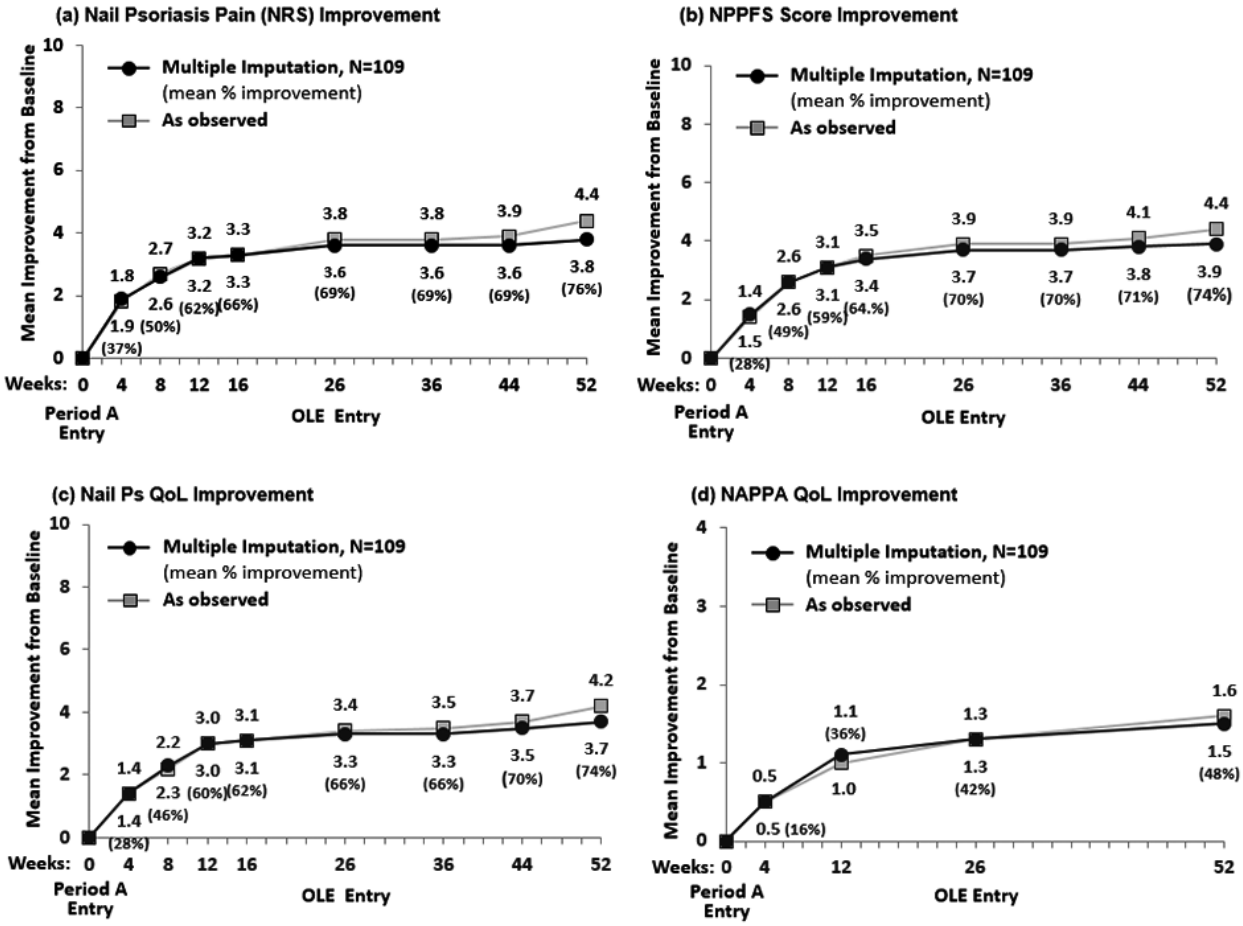

Figure 3 Patient-reported outcomes over 52 weeks. (a) Nail Psoriasis Pain (NRS) Improvement. (b) NPPFS Score Improvement. (c) Nail Ps QoL Improvement. (d) NAPPA QoL Improvement. Results are reported as mean improvement from baseline. Missing data were handled by multiple imputation. NAPPA, Nail Assessment of Psoriasis and Psoriatic Arthritis; NPPFS, Nail Psoriasis Physical Functioning Severity; NRS, Numeric Rating Scale; OLE, open-label extension; Ps, psoriasis; QoL, quality of life.

Serious non-infectious adverse events for the All-ADA Population were cardiac failure, myocardial infarction, diverticular perforation, anaphylactic reaction, arthropod sting, tenosynovitis, seizure, major depression, suicidal ideation, bladder sphincter atony, stress urinary incontinence, prostatitis and hypertensive crisis (n = 1 for each event). Serious non-infectious adverse events in the OLE were myocardial infarction (pbo/ADA, n = 1) and tenosynovitis, seizure and stress incontinence (ADA/ADA, n = 1 for each).

There were no events of tuberculosis, opportunistic infections, demyelinating disorders or deaths. There was 1 event of benign breast neoplasm in the ADA/ADA group.

Discussion

In this trial, adalimumab at the dose approved for treatment of moderate-to-severe plaque psoriasis also treated patients with moderate-to-severe nail psoriasis across 52 weeks of treatment. The treatment response appeared sustainable, and incremental improvements were observed in the rate of achievement of total clearance of nail disease across 52 weeks. The OLE results corroborate and extend the results reported from the placebo-controlled portion of the study and suggest that adalimumab efficacy after 52 weeks of continuous therapy may be higher than after 26 weeks.

As postulated in Elewski *et al.*,[28] patients who had a partial treatment response at 26 weeks may have experienced additional response to longer-term treatment, given the slower growth dynamics of the nail apparatus than of skin plaques, and therefore, the time to achieve ultimate improvement in nail disease could be beyond 26 weeks We observed that the response rate to adalimumab treatment increased from OLE entry to Week 52.

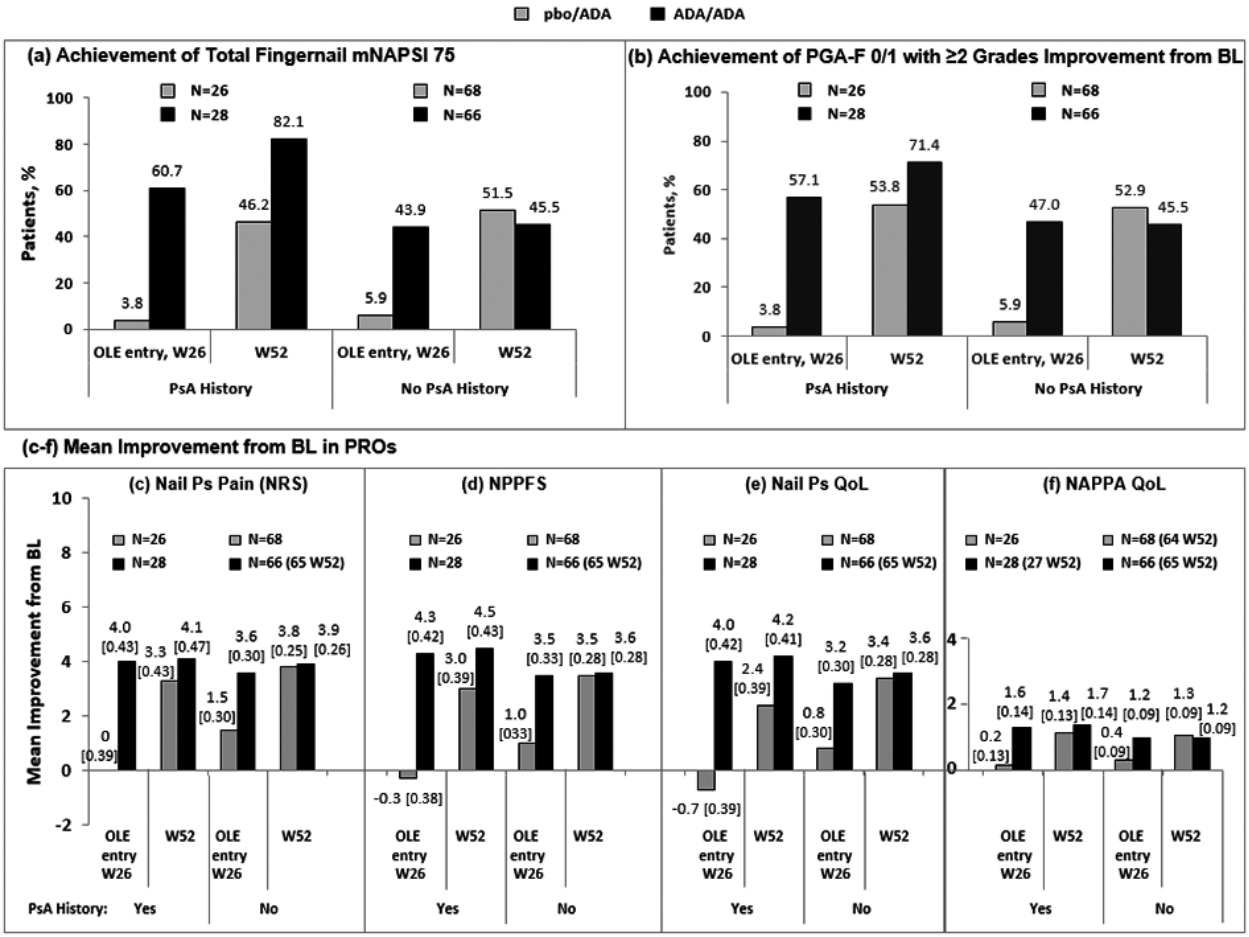

Figure 4 Efficacy and patient-reported outcomes by history of psoriatic arthritis, OLE. (a) Achievement of Total-Fingernail mNAPSI 75. (b) Achievement of PGA-F 0/1 with ≥2 Grades Improvement from BL. (c) Mean Improvement from BL in Nail Ps Pain (NRS). (d) Mean Improvement from BL in NPPFS score. (e) Mean Improvement from BL in Nail Ps QoL. (f) Mean Improvement from BL in NAPPA QoL. Missing data were handled by NRI for mNAPSI 75 and PGA-F 0/1 and by LOCF for Nail Psoriasis Pain NRS, NPPFS, Nail Ps QoL and NAPPA QoL; LOCF data include standard error. Range of scores for Nail Ps Pain NRS, NPPFS and Nail Ps QoL scores are 0–10, and for NAPPA QoL, 0–4. ADA, adalimumab; DLQI, Dermatology Life Quality Index; LOCF, last observation carried forward; mNAPSI, modified Nail Psoriasis Severity Index; NAPPA, Nail Assessment of Psoriasis and Psoriatic Arthritis; NPPFS, Nail Psoriasis Physical Functioning Severity; NRI, non-responder imputation; NRS, Numeric Rating Scale; OLE, open-label extension; pbo, placebo; PGA-F, Physician's Global Assessment of Psoriasis of the Fingernail; Ps, psoriasis; PsA, psoriatic arthritis; QoL, quality of life; W, week.

Patients who had been randomized to placebo in Period A were able to achieve similar results by the end of the OLE after being switched to adalimumab in the OLE. Week-52 efficacy for patients randomized to placebo in Period A and receiving adalimumab starting at Week 26 (i.e. efficacy for these patients after 26 weeks of continuous adalimumab) was numerically similar to the efficacy observed at Week 26 for patients who had been randomized to adalimumab in Period A, indicating that the results across the study are internally consistent.

Efficacy outcomes in this trial as measured by mean per cent improvement from baseline in NAPSI (Table 2) were reported in other randomized, controlled trials of long-term biologic treatment of nail psoriasis. These include a trial (REACH) of adalimumab 40 mg every-other-week treatment for psoriasis of the hands and feet (Week 28, 54.6%),[24] and a trial (TRANSFIGURE) of the IL-17A inhibitor, secukinumab 150 and 300 mg once weekly for 5 weeks then every 4 weeks (Week 32, 52.6% for 150 mg and 63.2% for 300 mg).[35] Published results from other long-term trials may help to further contextualize the results from our trial (Table 4), although psoriasis was the primary analysis in those trials, and nail psoriasis was a secondary or *post hoc* analysis in subsets of the psoriasis patients.

Table 3 Treatment-emergent adverse events

Adverse events, *n* (%)	During OLE by dose group, *n* (%)		During the trial
	pbo/ADA, *N* = 94	ADA/ADA, *N* = 94	All-ADA,† *N* = 203
Any adverse event	44 (46.8)	47 (50.0)	121 (59.6)
Events leading to study drug discontinuation	0	0	6 (3.0)
Serious	3 (3.2)	3 (3.2)	14 (6.9)
Infections	25 (26.6)	30 (31.9)	77 (37.9)
Serious infection	2 (2.1)	1 (1.1)	7 (3.4)
Diverticulitis	1 (1.1)	0	2 (1.0)
Bronchitis	0	0	1 (0.5)
Endocarditis	0	0	1 (0.5)
Erysipelas	0	0	1 (0.5)
Influenza	0	1 (1.1)	1 (0.5)
Lung infection	1 (1.1)	0	1 (0.5)
Pneumonia	0	1 (1.1)	1 (0.5)
Special interest‡			
Worsening/new onset of psoriasis	4 (4.3)	1 (1.1)	7 (3.4)
Injection site reaction	2 (2.1)	2 (2.1)	8 (3.9)
Allergic reaction including angio-oedema/anaphylaxis	1 (1.1)	0	2 (1.0)
Any haematologic disorders including pancytopenia	1 (1.1)	0	2 (1.0)

†Patients who received at least one dose of ADA during Period A plus any patient who received ADA in the OLE. ‡For ≥2 patients in any treatment group.
ADA, adalimumab; OLE, open-label extension; pbo, placebo.

Table 4 Summary of clinical trials with primary analysis in psoriasis and additional analyses in subsets with nail psoriasis

Study drug	Study analysis	Dose	Mean % improvement in NAPSI
Infliximab, TNF-α inhibitor[16]	Phase 3, RCT Retrospective	5 mg Q8W	W50, 67.8%
Etanercept, TNF-α inhibitor[15]	Randomized, open-label *Post hoc*	25 mg biw	W54, 51.0%
Ustekinumab, IL-2/23 inhibitor[18]	Phase 2/3, RCT Secondary endpoint	45 mg and 90 mg Q12W	W64, 56.6% (45 mg) W64, 67.8% (90 mg)
Ixekizumab, IL-17A inhibitor[19]	Phase 2, RCT *Post hoc*	120 mg Q4W	W48, 75.4%
Ixekizumab, IL-17A inhibitor[20]	Phase 3, RCT Subgroup	80 mg Q4W	W60, 81.8%
Tofacitinib, JAK inhibitor[21]	Phase 3, RCT *Post hoc*	5 mg and 10 mg bid	W52, 65.6% (5 mg) W52, 75.5% (10 mg)

bid, twice daily; biw, twice weekly; eow, every other week; NAPSI, Nail Psoriasis Severity Index; Ps, psoriasis; RCT, randomized controlled trial; Q*n*W, every *n* week(s); W, week.

Improvements in treatment response were generally also observed regardless of whether patients had a prior history of PsA or not. Improved treatment response to adalimumab regardless of baseline PsA status was also seen in a *post hoc* analysis of psoriasis patients from another phase-3 trial of adalimumab; mean NAPSI scores improved after 16 weeks of adalimumab treatment.[27]

Like nail psoriasis, scalp psoriasis is associated with the development of PsA,[36] is frequently a manifestation of skin psoriasis, is difficult to treat and can have a negative impact on patient quality of life.[37,38] In the current trial, the incidence of concomitant scalp psoriasis was similar to the published rate in patients with chronic plaque psoriasis.[39,40] Improvement in scalp psoriasis was achieved by over 60% of patients during the OLE, including patients who were switched from placebo to adalimumab upon entry to the OLE and patients receiving long-term adalimumab treatment.

The safety results from this study are consistent with the known adalimumab safety profile, although the serious infection rate for adalimumab was higher than in other adalimumab trials evaluating patients with moderate-to-severe psoriasis[41–43]and with moderate-to-severe psoriasis of the hands and feet.[24] Safety results over 52 weeks were comparable to those after 26 weeks of adalimumab treatment.[28] No unexpected safety risk was

identified.[24,44] Adverse event rates are not comparable to the other trials of long-term, biologics treatment for nail psoriasis mentioned earlier, as they did not report safety results for the nail psoriasis populations in their trials.

This study was limited by the requirement of at least 5% affected BSA involvement and the small sample size of patients with scalp psoriasis.

In conclusion, 52 weeks of every-other-week treatment with 40-mg adalimumab improved patient response to the study endpoints, signs and symptoms of moderate-to-severe nail psoriasis and patient-reported quality of life. The achievement rates of mNAPSI and total clearance of nail disease (mNAPSI = 0) improved across 52 weeks. No new safety risks were identified with adalimumab treatment in this population.

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