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Ixekizumab treatment improves fingernail psoriasis in patients with moderate-to-severe psoriasis: Results from the randomised, controlled and open-label phases of UNCOVER-3

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ABSTRACT

Background: Fingernail psoriasis is difficult to treat.

Objective: The objective was to evaluate the effect of ixekizumab, an anti-IL-17A monoclonal IgG4 antibody, on fingernail psoriasis.

Methods: This Phase 3, double-blind trial (UNCOVER-3) randomised patients to placebo, etanercept (50-mg twice weekly), or 80 mg ixekizumab as one injection every 4 (IXE Q4W) or 2 weeks (IXE Q2W) after a 160-mg starting dose. At Week 12, ixekizumab patients received open-label IXE Q4W through Week 60; placebo patients received a 160-mg starting ixekizumab dose and etanercept patients a 4-week placebo washout before starting IXE Q4W. Efficacy was assessed by mean percent Nail Psoriasis Severity Index (NAPSI) improvement at Weeks 12 and 60.

Results: Of 1346 patients in the UNCOVER-3 trials, this subgroup analysis included only patients with baseline fingernail psoriasis: 116 (60.1%) placebo, 236 (61.8%) etanercept, 228 (59.1%) IXE Q4W, and 229 (59.5%) IXE Q2W. At Week 12, greater mean percent NAPSI improvements were achieved in IXE Q4W (36.7%) and IXE Q2W (35.2%) versus placebo (-34.3%, $p<0.001$ each comparison) and etanercept (20.0%, $p=0.048$ vs. Q4W, $p=0.072$ vs. Q2W). At Week 60, mean

percent NAPSI improvement was >80% regardless of initial treatment. At Week 12 (nonresponder imputation), complete resolution (NAPSI=0) was achieved in 19.7% (IXE Q4W), 17.5% (IXE Q2W), 4.3% (placebo, p<0.001 each comparison), and 10.2% (etanercept, p<0.05 each comparison) of patients. By Week 60, >50% of patients achieved complete resolution. **Conclusions:** At Week 12, significant improvements in fingernail psoriasis were achieved with ixekizumab therapy. With IXE Q4W maintenance dosing, additional improvement was demonstrated through 60 weeks, and >50% of patients achieved complete resolution.

Registered at clinicaltrials.gov: NCT01646177

INTRODUCTION

Psoriasis is a chronic, inflammatory disease affecting the skin, nails, and joints. Up to 82% of patients have nail involvement.[1]

Previous studies have shown that nail involvement may have a greater negative impact on patients' quality of life than skin lesions alone.[2,3] Pain and/or discomfort, restrictions in performing daily activities, an altered sense of touch, reduced manual dexterity, and unsightly appearance are all factors influenced by nail psoriasis that impact patient functioning and well-being.[2,3]

Fingernail psoriasis is also particularly difficult to treat. Not only is it persistent and slow to resolve, but many treatments are ineffective, challenging to administer, or associated with adverse effects that limit patient adherence.[4,5] In recent years, there has been increased interest in the use of biologic therapies for the treatment of nail psoriasis, although few studies have focused exclusively on treatment of nails alone.[1, 6-8]

Ixekizumab is a high-affinity monoclonal antibody that selectively targets interleukin (IL)-17A. Recently, three, Phase 3, randomised, double-blind, placebo-controlled, multicentre trials demonstrated that ixekizumab was efficacious and well tolerated in patients with moderate-to-

severe plaque psoriasis (UNCOVER-1, UNCOVER-2, and UNCOVER-3).[9,10] Unlike UNCOVER-1 and UNCOVER-2 trials, each of which had a randomised withdrawal period, the UNCOVER-3 trial provided the opportunity to evaluate the effect of continuous ixekizumab treatment. Additionally, a major secondary objective of UNCOVER-3 was to evaluate the efficacy of ixekizumab compared to that of placebo or etanercept in patients with baseline fingernail psoriasis. Thus, the present subgroup analysis includes only patients with baseline fingernail psoriasis who were enrolled in the UNCOVER-3 trial.

MATERIALS AND METHODS

UNCOVER-3 is a Phase 3, multicentre, double-blind, placebo- and active-controlled trial that evaluated the efficacy and safety of ixekizumab in patients with moderate-to-severe psoriasis. Patients were randomised 1:2:2:2 by a computer-generated random sequence using an interactive voice response system to receive subcutaneous placebo, etanercept (50 mg twice weekly), or 80 mg ixekizumab as one injection every 4 weeks (IXE Q4W) or 2 weeks (IXE Q2W) after a 160-mg starting ixekizumab dose at Week 0. All patients received the same number of injections to maintain the blind. At Week 12, all ixekizumab-treated patients were assigned to open-label IXE Q4W through Week 60 (IXE Q4W-Q4W and IXE Q2W-Q4W). The placebo group received a 160-mg starting ixekizumab dose at Week 12, then IXE Q4W thereafter (PBO-Q4W). The etanercept group received placebo washout at Week 12, then IXE Q4W at Week 16 and thereafter (ETN-Q4W).

Patients

To be eligible for the study, patients had a confirmed diagnosis of chronic plaque psoriasis for ≥6 months before randomisation; had ≥10% Body Surface Area of psoriasis at screening and randomisation; had a static Physician's Global Assessment score ≥3 (moderate) and a Psoriasis Area and Severity Index (PASI) score ≥12 at screening and at randomisation; were candidates for phototherapy and/or systemic therapy; and agreed to use a reliable birth control method during the study. Main exclusion criteria were primary nonplaque forms of psoriasis; prior use of etanercept or any IL-17 antagonists; recent use of any biologic agent, nonbiologic systemic

psoriasis therapy or phototherapy, or topical psoriasis treatment; excessive exposure to sun or use of a tanning booth; or unstable medical conditions and specific laboratory values related to safety.

For the purposes of this subgroup analysis, only patients enrolled in UNCOVER-3 with baseline fingernail psoriasis were included.

Assessments

The Nail Psoriasis Severity Index (NAPSI) was used to assess fingernail psoriasis at Weeks 0, 1, 2, and 4, and every 4 weeks thereafter through Week 60.[11] In this modified form of the NAPSI, toenail involvement was not assessed. Each fingernail was divided into quadrants and evaluated for the presence (1) or absence (0) of both fingernail bed psoriasis and matrix psoriasis. Values for each fingernail were added for a total NAPSI fingernail score ranging from 0 (no nail psoriasis) to 80 (severe nail psoriasis). PASI was used to assess the clinical response at Weeks 0, 1, 2, and 4, and every 4 weeks thereafter through Week 60.

Statistical Analysis

All randomised patients who had baseline fingernail psoriasis (defined as NAPSI score >0) were analysed according to the treatment to which they were assigned at Week 0 regardless of compliance (intention-to-treat [ITT] population). The NAPSI percent improvement from baseline at each postbaseline visit was analysed using a mixed-effects model of repeated measures. The model included treatment, baseline value, visit, and interaction of treatment-by-visit as fixed factors with unstructured covariance structure. The NAPSI score of 0 was analysed using a Fisher exact test in which patients who do not meet clinical response criteria or who had missing data were imputed using nonresponder imputation. The correlation between NAPSI and PASI scores was assessed at baseline and Week 60 by using Pearson correlation.

RESULTS

Patient Disposition and Baseline Characteristics

In the UNCOVER-3 study, a total of 193 placebo, 382 etanercept, 386 IXE Q4W, and 385 IXE Q2W patients were included in the ITT population (N=1346). Of these patients, 116 (60.1%) placebo, 236 (61.8%) etanercept, 228 (59.1%) IXE Q4W, and 229 (59.5%) IXE Q2W patients had fingernail psoriasis at baseline and were included in this subgroup analysis. Baseline characteristics were generally balanced across treatment groups in the population of patients with fingernail psoriasis (Table 1). On average, patients were 46 years of age with a 19-year history of psoriasis, and the majority (76.0%) were male and white (95.3%). Across all groups, the mean baseline NAPSI score was 26; 22.6% had a history of psoriatic arthritis.

Improvement in Fingernail Psoriasis Over Time

As early as Week 2, the mean percent NAPSI improvement from baseline was significantly greater with IXE Q4W (5.1%) compared with etanercept (-7.9%, p=0.024). By Week 8, both ixekizumab groups had significantly greater mean percent NAPSI improvement from baseline compared with placebo and etanercept (Fig. 1a).

At Week 12, the mean percent NAPSI improvement was significantly greater with IXE Q4W (36.7%) and IXE Q2W (35.2%) versus placebo (-34.3%, p<0.001 each comparison) and versus etanercept (20.0%, p=0.048 vs. IXE Q4W only) (Table 2, Fig. 1a). With continuous ixekizumab treatment, the mean percent NAPSI improvement was 81.8% for IXE Q4W-Q4W and 83.6% for IXE Q2W-Q4W groups at Week 60. Patients assigned to placebo or etanercept before starting IXE Q4W demonstrated comparable improvements at Week 60 (PBO-Q4W: 80.8%; ETN-Q4W: 82.7%).

Resolution of Fingernail Psoriasis

At Week 12, complete resolution of fingernail psoriasis (NAPSI score=0) was observed in a significantly higher percentage of patients in the IXE Q4W (19.7%) and IXE Q2W (17.5%) groups than placebo (4.3%, p<0.001 each comparison) or etanercept (10.2%, p<0.05 each comparison)

(Table 2, Fig. 1b). With IXE Q4W dosing through Week 60, a high percentage of patients in each group achieved NAPSI 0 at Week 60 (IXE Q4W-Q4W: 54.4%, IXE Q2W-Q4W: 62.4%, PBO-Q4W: 59.5%, ETN-Q4W: 53.4%). These improvements were comparable for patients regardless of treatment group assignment during the 12-week, induction dosing period.

NAPSI and PASI Correlation

There was an overall correlation between the baseline NAPSI and PASI scores at baseline (Pearson correlation: 0.105, p=0.003, 95% CI: 0.036, 0.172). Statistical significance of the overall baseline correlation was primarily driven by the IXE Q4W group at baseline (0.214, p=0.001, 95% CI: 0.086, 0.334); there was no correlation at baseline for the IXE Q2W, PBO, and ETN groups. With IXE Q4W through Week 60, a correlation in percent improvement from baseline NAPSI and percent improvement from baseline PASI scores was observed (Pearson correlation: 0.118, p=0.002, 95% CI: 0.045, 0.190).

DISCUSSION

Overall, this trial demonstrated the efficacy of ixekizumab compared to placebo or etanercept twice weekly in the treatment of fingernail psoriasis among patients with moderate-to-severe plaque psoriasis. Ixekizumab provided significant improvement in fingernail psoriasis as early as Week 2, with both IXE Q4W and IXE Q2W dosing regimens demonstrating significantly greater NAPSI improvement than placebo or etanercept at Week 12. This effect was continued through 60 weeks of treatment. Patients receiving placebo or etanercept who began treatment with ixekizumab at Week 12 or 16, respectively, had improvements similar to patients who received continuous ixekizumab treatment.

Complete resolution (NAPSI score=0) of fingernail psoriasis was achieved in a significantly higher percentage of patients receiving ixekizumab than placebo or etanercept at Week 12. Regardless of initial treatment group assignment, greater than 50% of patients achieved complete resolution by Week 60 with IXE Q4W treatment. The percentage of patients demonstrating complete clearance with ixekizumab treatment in this study is markedly higher

(approximately 20% more patients) when compared with reports of clearance rates with many other biologics.[12-14] Notably, these and other populations studied have had considerably higher baseline fingernail psoriasis severity (approximately 5-20 points higher on the NAPSI) than in the present study.[1, 12-15] Differences in baseline severity could be attributed, in part, to the design of the present study (UNCOVER-3), which did not require fingernail psoriasis for enrolment. For this subgroup analysis, only patients with any degree of fingernail psoriasis (NAPSI >0) were included.

Overall, the percent change in NAPSI and complete resolution of fingernail psoriasis observed in this study are in line with the findings within the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) report, which notes that biologic agents are the most rigorously studied and are highly efficacious in treating nail psoriasis.[16]

The relationship between PASI improvement and NAPSI improvement was also examined in this study. Similar to a nail psoriasis infliximab study,[1] this subgroup analysis found no notable correlation between PASI and NAPSI scores at baseline, whereas changes in PASI and NAPSI scores did correlate at Week 60.

Because nail growth is slow, short-term trials may be insufficient to observe the full effect of treatment on nail psoriasis.[17] For ixekizumab, improvements were observed as early as Week 2, but complete clearance of fingernail psoriasis took longer to occur. This may be due to the time required for healthy nail growth. For patients receiving placebo or etanercept during the 12-week induction dosing period, improvement was less than for patients receiving ixekizumab during the induction dosing period, but at 60 weeks these groups were comparable to those patients who were treated with continuous ixekizumab therapy. Based on these findings, treatment with ixekizumab demonstrates significant nail improvement compared with etanercept at early time points.

Nail improvements seen in this report are consistent with results publicly disclosed by other IL-17 agents such as secukinumab.[18] A head-to-head comparison of ixekizumab to other IL-17 agents has not been conducted.

The following limitations should be considered. The UNCOVER-3 study was designed to examine a patient population with moderate-to-severe plaque psoriasis, not fingernail psoriasis specifically. This subgroup analysis examined all patients with a NAPSI score greater than 0, regardless of baseline severity of nail disease. Despite these limitations, >50% patients receiving ixekizumab treatment demonstrated clearance of fingernail psoriasis. This study also restricted assessment of nail psoriasis to the fingernails and did not include toenail assessments, which may limit generalisability of results. It should also be considered that the etanercept group was only studied for 12 weeks, which is not a long enough period to observe full fingernail growth. This analysis did not examine safety in this subpopulation. The safety profile for ixekizumab has been reported elsewhere for UNCOVER-3.[9]

Conclusion

In this subgroup analysis of patients with baseline fingernail psoriasis, ixekizumab provided significant improvement in fingernail psoriasis in the first 12 weeks of treatment. These improvements were continued through Week 60. The improvements observed with ixekizumab were significantly greater than with placebo or etanercept at Week 12. Patients who switched from placebo or etanercept to ixekizumab during the longer-term, open-label phase had improvements similar to patients on continuous ixekizumab treatment for 60 weeks. At the end of the 60-week study, greater than 50% of ixekizumab-treated patients had complete resolution of fingernail psoriasis.

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Table 1 Baseline characteristics of patients with baseline fingernail psoriasis

	PBO N=116	ETN N=236	IXE Q4W N=228	IXE Q2W N=229
Age, years	47.5±11.3	46.3±13.5	45.9±11.6	45.5±12.5
Age, range	20-75	18-88	20-76	19-73
Sex, n (%)				
Male	92 (79%)	183 (78%)	177 (78%)	163 (71%)
Female	24 (21%)	53 (23%)	51 (22%)	66 (29%)
Race, n (%)				
Indigenous American[a]	1 (0.9%)	2 (0.8%)	2 (0.9%)	0
Asian	1 (0.9%)	5 (2.1%)	3 (1.3%)	5 (2.2%)
Black/African American	0	5 (2.1%)	3 (1.3%)	4 (1.7%)
Native Hawaiian or Pacific Islander	0	0	0	1 (0.4%)
White	113 (97.4%)	222 (94.1%)	219 (96.1%)	217 (94.8%)
Multiple races	1 (0.9%)	2 (0.8%)	1 (0.4%)	2 (0.9%)
Hispanic/Latino origin, n (%)	12 (10.3%)	28 (11.9%)	27 (11.8%)	26 (11.4%)
Duration of psoriasis, years	20.7±12.3	19.5±12.0	19.2±12.2	18.8±11.9
PASI score	21.9±9.3	21.8±8.9	22.0±8.3	21.7±8.8
NAPSI score	25.5±19.6	25.1±20.0	26.2±20.2	26.1±20.1
Psoriatic arthritis, n (%)	26 (22.4%)	53 (22.5%)	53 (23.2%)	51 (22.3%)

Data are mean±SD unless noted otherwise.

Abbreviations: ETN, etanercept; IXE Q4W, ixekizumab dosing every 4 weeks; IXE Q2W, ixekizumab dosing every 2 weeks; NAPSI, Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index; PBO, placebo;

[a]American Indian from North, Central, and South America and Alaska Native.

Table 2 Summary of efficacy in patients with baseline fingernail psoriasis

Double-Blind Phase **Week 12**	PBO N=116	ETN N=236	IXE Q4W N=228	IXE Q2W N=229
Percent NAPSI improvement, LSM (SE)	-34.31 (8.4)	20.0 (5.9)	36.7 (6.0)	35.2 (6.0)

p-value vs. PBO		<0.001	<0.001	<0.001
p-value vs. ETN			0.048	0.072
Achieved NAPSI 0 (NRI), n (%)	5 (4.3%)	24 (10.2%)	45 (19.7%)	40 (17.5%)
p-value vs. PBO		0.065	<0.001	<0.001
p-value vs. ETN			0.004	0.031
Open-label Phase	PBO-Q4W	ETN-Q4W	IXE Q4W-Q4W	IXE Q2W-Q4W
Week 60	N=116	N=236	N=228	N=229
Percent NAPSI improvement, LSM (SE)	80.8 (4.3)	82.7 (3.0)	81.8 (3.1)	83.6 (3.0)
Achieved NAPSI 0 (NRI), n (%)	69 (59.5%)	126 (53.4%)	124 (54.4%)	143 (62.4%)

Abbreviations: ETN, etanercept; ETN-Q4W, etanercept up to week 12 followed by IXE Q4W treatment; IXE Q4W, ixekizumab dosing every 4 weeks; IXE Q2W, ixekizumab dosing every 2 weeks; IXE Q4W-Q4W, ixekizumab dosing every 4 weeks through week 60; IXE Q2W-Q4W, ixekizumab dosing every 2 weeks up to week 12 followed by IXE Q4W; LSM, least squares mean; NAPSI, Nail Psoriasis Severity Index; NRI, nonresponder imputation; PBO, placebo; PBO-Q4W, placebo up to week 12 followed by IXE Q4W treatment; SE, standard error.

FIGURE LEGEND

Fig 1. Mean percent NAPSI change from baseline (panel a). Percentage of patients achieving NAPSI score of 0 (panel b). The first 12-weeks were randomised and controlled; open-label treatment was administered thereafter. [a]p≤0.05 vs. PBO; [b]p≤0.05 vs. ETN.

Abbreviations: ETN = etanercept, IXE Q4W = 80 mg ixekizumab every 4 weeks, IXE Q2W = 80 mg ixekizumab every 2 weeks, N = number of patients in the intent-to-treat population with baseline nail psoriasis involvement, N* = patients with nonmissing values at Week 1, NAPSI = Nail Psoriasis Severity Index, PBO = placebo.

	PBO *N* = 116	ETN *N* = 236	IXE Q4W *N* = 228	IXE Q2W *N* = 229
Age, years	47.5 ± 11.3	46.3 ± 13.5	45.9 ± 11.6	45.5 ± 12.5
Age, range	20-75	18-88	20-76	19-73
Sex, n (%)				
Male	92 (79%)	183 (78%)	177 (78%)	163 (71%)
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White	113 (97.4%)	222 (94.1%)	219 (96.1%)	217 (94.8%)
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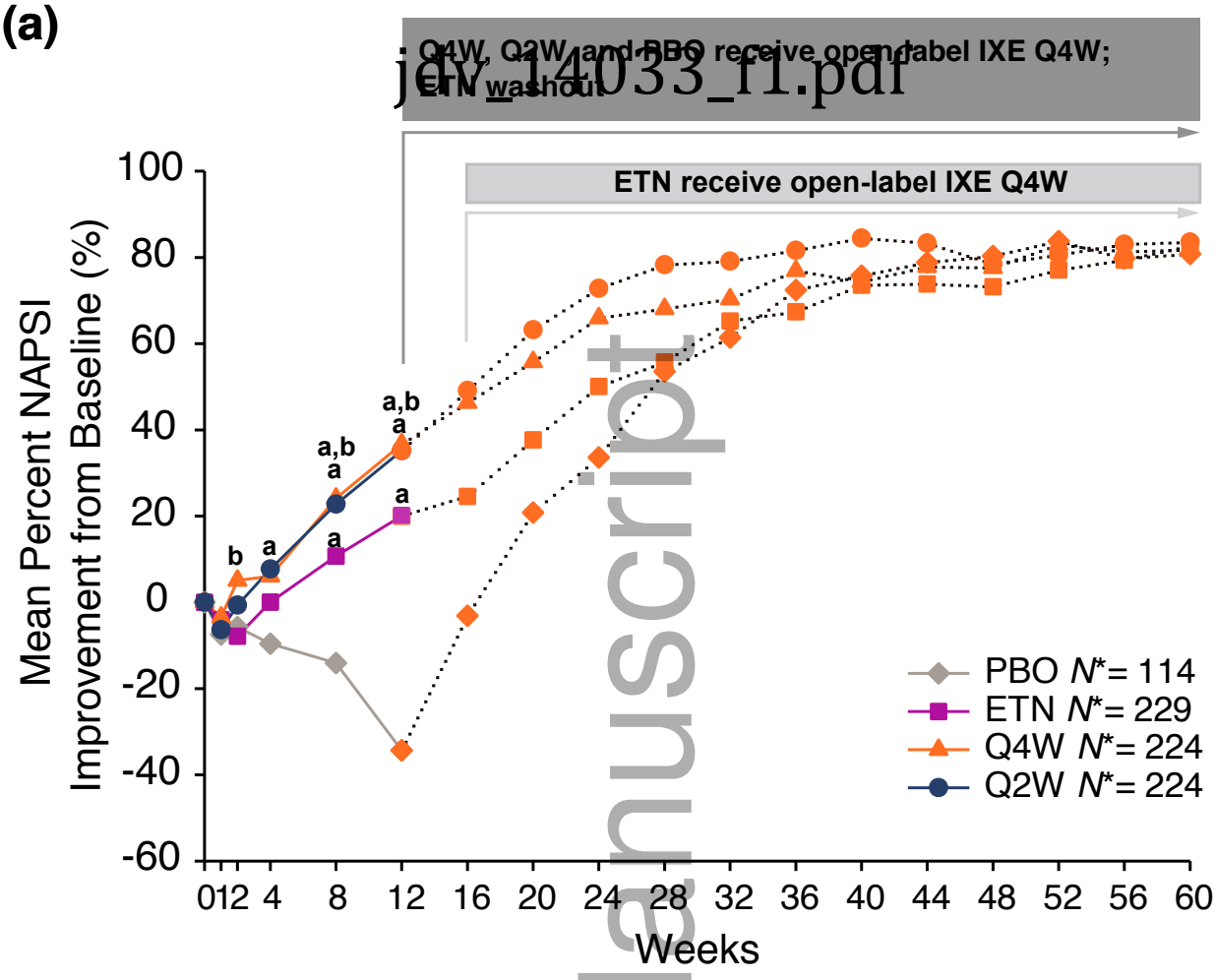
Duration of psoriasis, years	20.7 ± 12.3	19.5 ± 12.0	19.2 ± 12.2	18.8 ± 11.9
PASI score	21.9 ± 9.3	21.8 ± 8.9	22.0 ± 8.3	21.7 ± 8.8
NAPSI score	25.5 ± 19.6	25.1 ± 20.0	26.2 ± 20.2	26.1 ± 20.1
Psoriatic arthritis, n (%)	26 (22.4%)	53 (22.5%)	53 (23.2%)	51 (22.3%)

Double-Blind Phase Week 12	PBO N = 116	ETN N = 236	IXE Q4W N = 228	IXE Q2W N = 229
Percent NAPSI improvement, LSM (SE)	-34.31 (8.4)	20.0 (5.9)	36.7 (6.0)	35.2 (6.0)
P-value vs. PBO		<0.001	<0.001	<0.001
P-value vs. ETN			0.048	0.072
Achieved NAPSI 0 (NRI), n (%)	5 (4.3%)	24 (10.2%)	45 (19.7%)	40 (17.5%)
P-value vs. PBO		0.065	<0.001	<0.001
P-value vs. ETN			0.004	0.031
Open-label Phase **Week 60**	**PBO-Q4W** **N = 116**	**ETN-Q8W** **N = 236**	**IXE Q4W-Q4W** **N = 228**	**IXE Q2W-Q4W** **N = 229**
Percent NAPSI improvement, LSM (SE)	80.8 (4.3)	82.7 (3.0)	81.8 (3.1)	83.6 (3.0)
Achieved NAPSI 0 (NRI), n (%)	69 (59.5%)	126 (53.4%)	124 (54.4%)	143 (62.4%)

(a)



(b)