Long-term Efficacy and Safety Profile Through 5 Years of Treatment With Ixekizumab in Patients With Moderate-to-Severe Psoriasis

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BACKGROUND

- Patients with moderate-to-severe plaque psoriasis typically require long-term treatment to maintain adequate control of disease activity[1-4]
- Ixekizumab, a high-affinity monoclonal antibody that selectively targets interleukin-17A,[5] has been approved for treating moderate-to-severe psoriasis, active psoriatic arthritis, and active ankylosing spondylitis
- UNCOVER-2 (NCT01597245) is a randomized, double-blind, multicenter, Phase 3 clinical trial of ixekizumab for the treatment of moderate-to-severe plaque psoriasis[6]

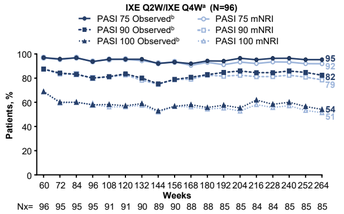
OBJECTIVE

- To evaluate the efficacy and safety findings through 5 years of treatment with the approved ixekizumab dosing regimen[a] in UNCOVER-2

[a] Starting dose of 160 mg, then 80 mg every 2 weeks (IXE Q2W) up to and including Week 12, followed by 80 mg every 4 weeks (IXE Q4W)

KEY RESULTS

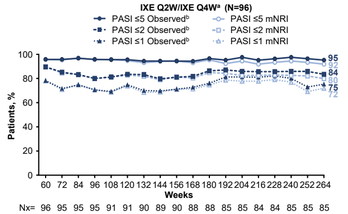
Ixekizumab PASI Response Rates Through 5 Years of Treatment, Long-term Extension Period, mNRI and Observed



- Overall, 20 (20.8%) patients escalated to IXE Q2W dosing during the Long-term Extension Period
  - PASI response rates were consistent regardless of whether visits with escalated dosing were excluded in analyses (Week 264 [observed]: PASI 75=97%; PASI 90=86%; PASI 100=59%. Week 264 [mNRI]: PASI 75=93%; PASI 90=78%; PASI 100=53%)

[a] Approved ixekizumab dosing regimen: starting dose of 160 mg, then IXE Q2W up to and including Week 12, followed by IXE Q4W thereafter
[b] For observed data, response is calculated by n/Nx*100%

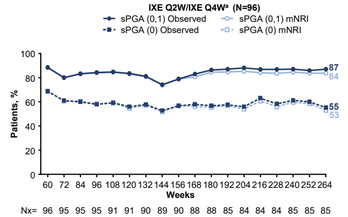
Ixekizumab Absolute PASI Response Rates Through 5 Years of Treatment, Long-term Extension Period, mNRI and Observed



- Absolute PASI response rates were consistent regardless of whether visits with escalated dosing were excluded in analyses (Week 264 [observed]: PASI ≤5=95%; PASI ≤2=88%; PASI ≤1=80%. Week 264 [mNRI]: PASI ≤5=90%; PASI ≤2=80%; PASI ≤1=72%)

[a] Approved ixekizumab dosing regimen: starting dose of 160 mg, then IXE Q2W up to and including Week 12, followed by IXE Q4W thereafter
[b] For observed data, response is calculated by n/Nx*100%

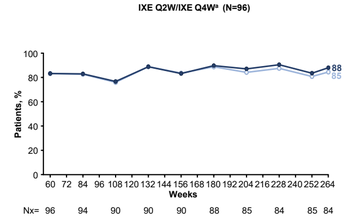
Ixekizumab sPGA (0,1) and sPGA (0) Response Rates Through 5 Years of Treatment, Long-term Extension Period, mNRI and Observed



- sPGA response rates were consistent regardless of whether visits with escalated dosing were excluded in analyses (Week 264 [observed]: sPGA [0,1]=92%; sPGA [0]=59%. Week 264 [mNRI]: sPGA [0,1]=84%; sPGA [0]=48%)

[a] Approved ixekizumab dosing regimen: starting dose of 160 mg, then IXE Q2W up to and including Week 12, followed by IXE Q4W thereafter
[b] For observed data, response is calculated by n/Nx*100%

Ixekizumab DLQI (0,1) Response Rates Through 5 Years of Treatment, Long-term Extension Period, mNRI and Observed



- Dermatology Life Quality Index (DLQI) response rates were consistent regardless of whether visits with escalated dose were excluded in analyses (Week 264 [observed]: DLQI [0,1]=91%; Week 264 [mNRI]: DLQI [0,1]=85%)

[a] Approved ixekizumab dosing regimen: starting dose of 160 mg, then IXE Q2W up to and including Week 12, followed by IXE Q4W thereafter
[b] For observed data, response is calculated by n/Nx*100%

Treatment-Emergent Adverse Events Through Week 60 to Week 264 of Ixekizumab Treatment[a]

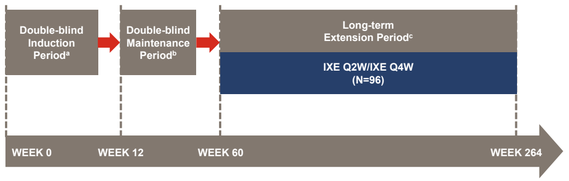
	IXE Q2W/IXE Q4W (N=96)					
Incidence Rate per 100 PY (95% CI)	Total PY=284.8	Year 0-1 PY=95.7	Year 1-2 PY= 90.4	Year 2-3 PY=78.8	Year 3-4 PY=64.3	Year 4-5 PY=58.3
Patients with ≥1 TEAE	31.9 (26.0, 39.2)	88.8 (71.8, 109.9)	74.1 (58.3, 94.1)	81.2 (63.5, 103.7)	90.2 (69.8, 116.7)	80.6 (60.6, 107.3)
Mild	8.1 (5.4, 12.2)	31.4 (21.9, 44.8)	33.2 (23.2, 47.4)	36.8 (25.6, 52.9)	37.3 (25.0, 55.7)	30.9 (19.5, 49.0)
Moderate	18.3 (13.9, 24.0)	48.1 (36.0, 64.2)	34.3 (24.1, 48.7)	38.0 (26.6, 54.4)	48.2 (33.9, 68.6)	39.5 (26.2, 59.4)
Severe	5.6 (3.4, 9.2)	9.4 (4.9, 18.1)	6.6 (3.0, 14.8)	6.3 (2.6, 15.2)	4.7 (1.5, 14.5)	10.3 (4.6, 22.9)
Serious AEs	6.0 (3.7, 9.6)	3.1 (1.0, 9.7)	8.8 (4.4, 17.7)	3.8 (1.2, 11.8)	9.3 (4.2, 20.8)	6.9 (2.6, 18.3)
Discontinuation owing to AEs	1.1 (0.3, 3.3)	0.0 (0.0, 8.4)	0.0 (0.0, 8.8)	1.3 (0.2, 9.0)	3.1 (0.8, 12.4)	0.0 (0.1, 13.7)
Death	0.0 (0.0, 2.8)	0.0 (0.0, 8.4)	0.0 (0.0, 8.8)	0.0 (0.0, 10.1)	0.0 (0.0, 12.4)	0.0 (0.1, 13.7)

[a] All IXE Q2W responders at Week 12 who received IXE Q4W and completed Week 60 in the Maintenance Period and continued in the Long-term Extension Period (includes those patients that escalated to IXE Q2W during the Long-term Extension Period)

CONCLUSIONS

- Results from UNCOVER-2 demonstrate that high-efficacy response with the approved ixekizumab dosing regimen was sustained through 5 years of continuous treatment in patients with moderate-to-severe plaque psoriasis
- The safety profile remained consistent with prior findings, with no new or unexpected safety concerns

Study Design, UNCOVER-2 Long-term Extension



[a] Week 0: patients randomized to IXE Q2W, IXE Q4W, ETN, or PBO
[b] Week 12: ixekizumab responders (sPGA [0,1]) randomized to IXE Q4W, IXE Q12W, or PBO
[c] From Weeks 60-264, any patient treated for minimum of 12 weeks with IXE Q4W could escalate to IXE Q2W, through the end of the study to achieve or maintain efficacy, if determined by the patient and the investigator

Assessments

Efficacy

- PASI 75/90/100
- Absolute PASI ≤5/2/1
- sPGA (0,1) or (0)
- DLQI (0,1)

Safety

- TEAEs

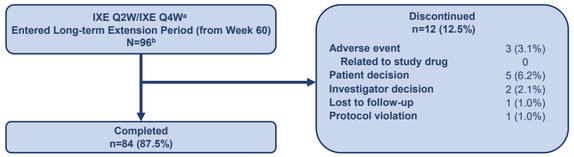
Key Eligibility Criteria

- Key Inclusion Criteria
  - ≥18 years old with moderate-to-severe plaque psoriasis
  - Psoriasis Area and Severity Index (PASI) ≥12 at the Screening and Baseline visits
  - ≥10% body surface area affected at the Screening and Baseline visits
  - Static Physician's Global Assessment (sPGA) score ≥3 at the Screening and Baseline visits
- Key Exclusion Criteria
  - Prior etanercept use
  - Other forms of psoriasis or history of drug-induced psoriasis

Statistical Analysis

- Analysis population: Patients randomized to 80 mg ixekizumab (IXE) every 2 weeks (Q2W) during the first 12 weeks, who were sPGA (0,1) responders at Week 12, and who then received IXE every 4 weeks (Q4W) in the Maintenance Period and Long-term Extension Period
- Efficacy was summarized using modified non-responder imputation (mNRI) and by observed case
  - Data from visits with escalated IXE Q2W dosing in the Long-term Extension Period were included in the analyses
- Safety was summarized by incidence rate per 100 patient-years
  - Data from visits with escalated IXE Q2W dosing in the Long-term Extension Period were included in the analyses

Patient Disposition: Long-term Extension Period



[a] Approved ixekizumab dosing regimen: starting dose of 160 mg, then IXE Q2W up to and including Week 12, followed by IXE Q4W thereafter
[b] Overall, 20 (20.8%) patients escalated to IXE Q2W dosing during the Long-term Extension Period

DISCLOSURES

- **C. Leonardi** has been a consultant and/or investigator and/or has received honoraria/other financial benefit from: AbbVie, Amgen, Boehringer Ingelheim, Celgene, Corrona, Dermira, Eli Lilly and Company, Galderma Laboratories, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Sandoz, Sienna Tribute, UCB Pharma, and Vitae Pharmaceuticals; **K. Reich** has served as an advisor and/or paid speaker for and/or participated in clinical trials sponsored by: AbbVie, Affibody, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene, Covagen, Eli Lilly and Company, Forward Pharma, Fresenius Medical Care, Galapagos NV, GlaxoSmithKline, Janssen Cilag, Kyowa Kirin, LEO Pharma, Medac, Merck Sharp & Dohme, Mitteroy Biotec, Novartis, Ocean Pharma, Pfizer, Samsung Bioepis, Sanofi, Takeda, UCB Pharma, Valeant Pharmaceuticals, XBiotech, and XenoPort; **L. Guenther** is on the speakers bureau of, a consultant for, and has received grant/research support from: AbbVie, Amgen, Celgene, Eli Lilly and Company, Galderma Laboratories, Janssen, LEO Pharma, and Novartis and has received grant/research support from: Boehringer Ingelheim, Merck-Froast, Sun Pharma, and UCB Pharma; **M. Gooderham** has received honoraria, grants, and/or research funding as a speaker, investigatory, advisory board member, data safety monitoring board member, and/or consultant for: AbbVie, Amgen, Boehringer Ingelheim, Celgene, Dermira, Eli Lilly and Company, Galderma Laboratories, GlaxoSmithKline, Janssen, Kyowa Kirin, LEO Pharma, Medimmune, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Sun Pharma, UCB Pharma, and Valeant Pharmaceuticals; **L. K. Ferris** has been a consultant and/or investigator for: AbbVie, Amgen, Arcutis, Boehringer Ingelheim, Celgene, Corrona, Dermavant, Eli Lilly and Company, Galderma Laboratories, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Regeneron, and UCB Pharma; **A. Leung** is an employee of Syneos Health; **H. Elmaraghy**, **H. Crane**, and **D. Shrom** are employees and shareholders of Eli Lilly and Company; **C. E. M. Griffiths** has received honoraria and/or research funds from: AbbVie, Almirall, Amgen, Celgene, Eli Lilly and Company, Janssen, LEO Pharma, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, Roche, Sandoz, Sun Pharma, and UCB Pharma
- This study was sponsored by Eli Lilly and Company. Medical writing assistance was provided by John Bilbruck, PhD, of ProScribe – Envision Pharma Group, and was funded by Eli Lilly and Company

Abbreviations

AE=adverse event; CI=confidence interval; DLQI=Dermatology Life Quality Index; ETN=etanercept; IXE=80 mg ixekizumab; mNRI=modified non-responder imputation; Nx=number of patients with non-missing data; PASI 75/90/100=Psoriasis Area and Severity Index ≥75%/≥90%/100% response; PBO=placebo; PY=patient-years; Q2W=every 2 weeks; Q4W=every 4 weeks; Q12W=every 12 weeks; sPGA=static Physician's Global Assessment; TEAE=treatment-emergent adverse event

Adverse Events of Special Interest Through Week 60 to Week 264 of Ixekizumab Treatment[a]

	IXE Q2W/IXE Q4W (N=96)					
Incidence Rate per 100 PY (95% CI)	Total PY=284.8	Year 0-1 PY=95.7	Year 1-2 PY=90.4	Year 2-3 PY=78.8	Year 3-4 PY=64.3	Year 4-5 PY=58.3
AEs of special interest						
Cytopenias	1.4 (0.5, 3.7)	1.0 (0.1, 7.4)	2.2 (0.6, 8.8)	3.8 (1.2, 11.8)	0.0 (0.0, 12.4)	1.7 (0.2, 12.2)
Hepatic	1.8 (0.7, 4.2)	5.2 (2.2, 12.6)	1.1 (0.2, 7.8)	1.3 (0.2, 9.0)	6.2 (2.3, 16.6)	1.7 (0.2, 12.2)
Infection	23.5 (18.5, 29.9)	70.0 (55.1, 89.0)	48.6 (36.2, 65.4)	43.1 (30.8, 60.4)	42.0 (28.8, 61.3)	44.6 (30.4, 65.5)
Allergic reactions/hypersensitivities	3.5 (1.9, 6.5)	6.3 (2.8, 14.0)	3.3 (1.1, 10.3)	2.5 (0.6, 10.1)	4.7 (1.5, 14.5)	5.1 (1.7, 16.0)
Potential anaphylaxis	0.0 (0.0, 2.8)	0.0 (0.0, 8.4)	0.0 (0.0, 8.8)	0.0 (0.0, 10.1)	0.0 (0.0, 12.4)	0.0 (0.1, 13.7)
Non-anaphylaxis	3.5 (1.9, 6.5)	6.3 (2.8, 14.0)	3.3 (1.1, 10.3)	2.5 (0.6, 10.1)	4.7 (1.5, 14.5)	5.1 (1.7, 16.0)
Injection-site reactions	2.8 (1.4, 5.6)	31.4 (21.9, 44.8)	8.8 (4.4, 17.7)	2.5 (0.6, 10.1)	4.7 (1.5, 14.5)	1.7 (0.2, 12.2)
Cerebro-cardiovascular events	1.1 (0.3, 3.3)	0.0 (0.0, 8.4)	1.1 (0.2, 7.8)	2.5 (0.6, 10.1)	0.0 (0.0, 12.4)	0.0 (0.1, 13.7)
Depression	2.1 (0.9, 4.7)	0.0 (0.0, 8.4)	2.2 (0.6, 8.8)	2.5 (0.6, 10.1)	3.1 (0.8, 12.4)	1.7 (0.2, 12.2)
Malignancy	0.7 (0.2, 2.8)	1.0 (0.1, 7.4)	0.0 (0.0, 8.8)	0.0 (0.0, 10.1)	3.1 (0.8, 12.4)	0.0 (0.1, 13.7)
Interstitial lung disease	0.0 (0.0, 2.8)	0.0 (0.0, 8.4)	0.0 (0.0, 8.8)	0.0 (0.0, 10.1)	0.0 (0.0, 12.4)	0.0 (0.1, 13.7)
Crohn's Disease	0.0 (0.0, 2.8)	0.0 (0.0, 8.4)	1.1 (0.2, 7.8)	0.0 (0.0, 10.1)	0.0 (0.0, 12.4)	0.0 (0.1, 13.7)
Ulcerative colitis	0.0 (0.0, 2.8)	0.0 (0.0, 8.4)	0.0 (0.0, 8.8)	0.0 (0.0, 10.1)	0.0 (0.0, 12.4)	0.0 (0.1, 13.7)

[a] All IXE Q2W responders at Week 12 who received IXE Q4W and completed Week 60 in the Maintenance Period and continued in the Long-term Extension Period (includes those patients that escalated to IXE Q2W during the Long-term Extension Period)

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Study was sponsored by Eli Lilly and Company