An Update on the Long-Term Safety Experience of Ixekizumab: Results from the Psoriasis Clinical Development Program with More than 3 Years of Follow-up from 12 Clinical Trials and More Than 15000 Patient-Years of Exposure to Ixekizumab

April Armstrong,[1] Noah Agada,[2] Wen Xu,[2] Gaia Gallo[2]

[1]Department of Clinical Research, Keck School of Medicine of the University of Southern California, Los Angeles, USA; [2]Eli Lilly and Company, Indianapolis, USA

BACKGROUND

- In moderate-to-severe psoriasis, maintaining adequate control of disease activity generally requires long-term treatment[1-4]
- Ixekizumab is a high-affinity monoclonal antibody that selectively targets interleukin (IL)-17A[5]
  - Has demonstrated significant efficacy in the treatment of moderate-to-severe psoriasis[6-9]
  - Is approved for treating moderate-to-severe plaque psoriasis
  - Safety profile is aligned with IL-17A inhibition and similar to that of etanercept in the short-term (UNCOVER-2 and -3)[8,9]

OBJECTIVE

- To summarize integrated safety data based on more than 15,000 patient-years (PY) of ixekizumab exposure during 12 clinical trials in patients with psoriasis

References

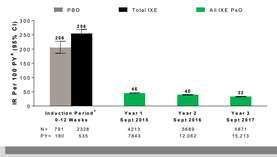
1. Jacobs A, et al. Br J Dermatol. 2015;173:910-921.
2. Mease PJ, et al. Drugs. 2014;74:423-441.
3. Mrowietz U, et al. J Eur Acad Dermatol Venereol. 2012;26(Suppl.2):12-20.
4. Sandoval LF, et al. Am J Clin Dermatol. 2014;15:165-180.
5. Liu L, et al. J Inflamm Res. 2016;9:39-50.
6. Leonardi C, et al. N Eng J Med. 2012;366:1190-1199.
7. Gordon KB, et al. J Am Acad Dermatol. 2014;71:1176-1182.
8. Griffiths CE, et al. Lancet. 2015;386:541-551.
9. Gordon KB, et al. N Eng J Med. 2016;375:345-356.

KEY RESULTS

Duration of Ixekizumab Exposure

n (%)	All PsO IXE (N=5871) PY=15,212.5
≥1 week	5866 (99.9)
≥1 month	5806 (98.9)
≥3 months	5665 (96.5)
≥0.5 years	5455 (92.9)
≥1 year	4640 (79.0)
≥1.5 years	3357 (57.2)
≥2 years	3201 (54.5)
≥3 years	2891 (50.8)
≥4 years	1526 (26.0)
≥5 years	261 (4.4)

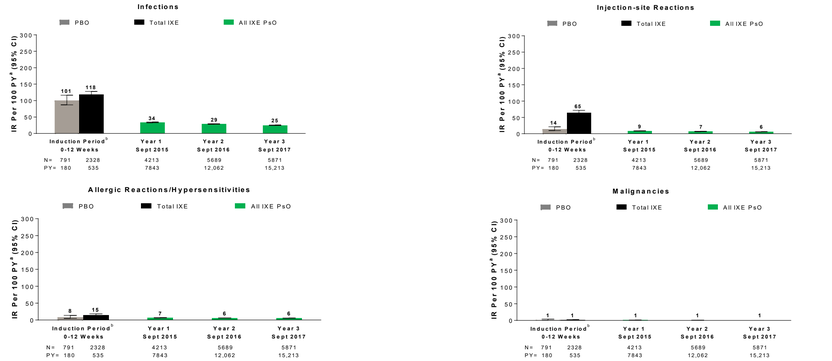
Incidence Rates of Overall TEAEs Decreased or Remained Similar Through Year 3 Database



[a]IR per 100 PY considered exposure time as the entire time on IXE

[b]Data for the Induction Period (0-12 Weeks) are provided for reference and display the IR for 0-12 Weeks for UNCOVER-1, -2, and -3 only; Data for Year 1 and Year 2 are also provided for reference and display IR for the 2 previous database locks (September 2015 including 7 PsO clinical trials and September 2016 including 11 PsO clinical trials)

Incidence Rates of Select TEAEs Decreased or Remained Similar Through Year 3 Database



[a]IR per 100 PY considered exposure time as the entire time on IXE; [b]Data for the Induction Period (0-12 Weeks) are provided for reference and display the IR for 0-12 Weeks for UNCOVER-1, -2, and -3 only; Data for Year 1 and Year 2 are also provided for reference and display IR for the 2 previous database locks (September 2015 including 7 PsO clinical trials and September 2016 including 11 PsO clinical trials)

CONCLUSIONS

- The ixekizumab psoriasis clinical safety database is large with more than 15,000 PY from 12 clinical trials and up to 5 years of study duration
- No new safety signals were identified with longer-term ixekizumab treatment in this population of patients with moderate-to-severe plaque psoriasis
- Ixekizumab exposure of up to greater than 3 years was not associated with an increased rate of any type or category of TEAE

Abbreviations

AC=active comparator; CI=confidence interval; DB=double-blind; EP=optional extension period after Week 24 endpoint where patients received 80 mg IXE Q4W up to Wk 60; ETN=50 mg etanercept twice weekly; FAE=fumaric acid esters 105-mg starting dose followed by 215 mg given orally 1 to 3 times per day; IR=incidence rate; IXE=ixekizumab; IXE Q2W=80 mg ixekizumab every 2 weeks; IXE Q4W=80 mg ixekizumab every 4 weeks; IXE Q12W=80 mg ixekizumab every 12 weeks; LTE=long-term extension; MACE=major adverse cerebro-cardiovascular events; MTX=methotrexate 7.5-mg starting dose up to 30 mg given orally once a week; N=number of patients; n=number of patients who received ixekizumab and included in the September 2017 lock for integrated safety analyses; OL=open-label; PAC=placebo-controlled and active comparator; PBO=placebo; PsO=psoriasis; Pts=patients; PY=patient-years; R=randomized; SAE=serious adverse event; sPGA=static Physician's Global Assessment; TEAE=treatment-emergent adverse event; UST=45 mg ustekinumab given as SC injection for participants ≤100 kg and 90 mg SC injection for participants >100 kg at Wk 0, 4, 16, 28, and 40; Wk=week

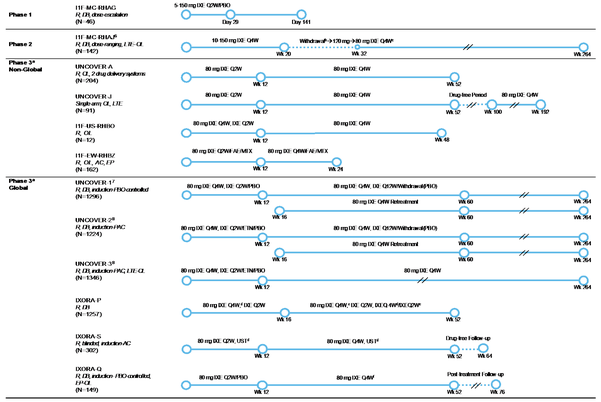
METHODS

Integrated Psoriasis Safety Dataset

Treatment-emergent adverse event (TEAE) data were integrated from 12 controlled and uncontrolled ixekizumab clinical trials in psoriasis, including 3 pivotal Phase 3, randomized, controlled, double-blind clinical trials (UNCOVER-1, -2, and -3)

- Safety analysis population included all randomized patients who received ≥1 dose of study drug
- Data cut-off date was September 22, 2017
- Exposure-adjusted incidence rates (IRs) of TEAEs were summarized
- IR was expressed as the number of unique patients with a given category of TEAE per 100 PY, based on the entire duration of exposure
- Categories included overall TEAEs, infections, injection-site reactions, allergic reactions/hypersensitivities, and malignancies
- Summary data from the Induction Period (12 weeks) of UNCOVER-1, -2, and -3 are provided for reference
- Data for ixekizumab doses were grouped to form the Total IXE group
- Summary data from the 2 previous database locks (September 2015 including 7 psoriasis clinical trials and September 2016 including 11 psoriasis clinical trials) are also included for reference
- Safety topics of special interest included serious infections, oral candida, major adverse cerebro-cardiovascular events (MACE), non-melanoma skin cancer (NMSC), malignancies excluding NMSC, and inflammatory bowel disease (including Crohn's disease and ulcerative colitis)
- MACE were adjudicated by an external adjudication committee

Study Design



[a]For pts receiving IXE the starting dose was 160 mg at Wk 0 prior to receiving 80 mg IXE (Q4W or Q2W); [b]Withdrawal period (Wks 20-32; pts were eligible for treatment with IXE Q4W when improvement in PASI score from baseline was ≤75%); [c]Protocol amendment-mandated dose regimen; [d]PBO administered to maintain study blind; [e]Step-up criteria determined if dosing increased from IXE Q4W to IXE Q2W based on whether a patient achieved sPGA ≥2 at 2 consecutive visits during Wk 12 through Wk 40; [f]Dosing increased from IXE Q4W to IXE Q2W based on investigator opinion between Wk 24 through Wk 40

Overview of Adverse Events

n (IR) [95% CI]	All PsO IXE (N=5871) PY=15,212.5
≥1 TEAE[a]	5072 (33.3) [32.4, 34.3]
Mild	1389 (9.1) [8.7, 9.6]
Moderate	2770 (18.2) [17.5, 18.9]
Severe	912 (6.0) [5.6, 6.4]
≥1 SAE	854 (5.6) [5.2, 6.0]
Deaths	32 (0.2) [0.1, 0.3]
Discontinuations due to adverse event	432 (2.8) [2.6, 3.1]

Patients with multiple occurrences of the same event were categorized by the highest severity

[a]Severity data were missing for 1 patient

- Most common TEAEs (IR [95% confidence interval; CI] per 100 PY) were upper respiratory tract infections (viral: 9.9 [9.4, 10.4]; unspecified: 5.8 [5.5, 6.2]) and injection site-reactions (3.7 [3.5, 4.1]), which were generally mild or moderate in severity
- Most deaths were from cardiovascular events in patients with prior risk factors, and none were due to suicide

Incidence Rates of Safety Topics of Special Interest

n (IR) [95% CI]	All PsO IXE (N=5871) PY=15,212.5
Serious infection	203 (1.3) [1.2, 1.5]
Oral candida	144 (0.9) [0.8, 1.1]
MACE	76 (0.5) [0.4, 0.6]
Non-melanoma skin cancer (NMSC)	47 (0.3) [0.2, 0.4]
Malignancies excluding NMSC	78 (0.5) [0.4, 0.6]
Inflammatory bowel disease (IBD)[a]	23 (0.2) [0.1, 0.2]
Crohn's disease	6 (0.0) [0.0, 0.1]
Ulcerative colitis	16 (0.1) [0.1, 0.2]
IBD preferred term	1 (0.0) [0.0, 0.0]

[a]Inflammatory bowel disease events were defined by narrow terms

Disclosures

- A. Armstrong has served as investigator, advisor, and/or speaker for: AbbVie, Celgene, Eli Lilly and Company, Janssen, Novartis, Regeneron, Sanofi, and Valeant; N. Agada, W. Xu, and G. Gallo are current employees and shareholders of Eli Lilly and Company
- This study was sponsored by Eli Lilly and Company. Medical writing assistance was provided by Cassandra Haley, PhD, CMPP, of ProScribe – part of the Envision Pharma Group, and was funded by Eli Lilly and Company

Study was sponsored by Eli Lilly and Company