ORIGINAL ARTICLE

Short and long-term safety outcomes with ixekizumab from 7 clinical trials in psoriasis: Etanercept comparisons and integrated data

Bruce Strober, MD, PhD,[a] Craig Leonardi, MD,[b] Kim A. Papp, MD, PhD, FRCPC,[c] Ulrich Mrowietz, MD,[d] Mamitaro Ohtsuki, MD, PhD,[e] Robert Bissonnette, MD, MSc, FRCPC,[f] Laura K. Ferris, MD, PhD,[g] Carle Paul, MD, PhD,[h] Mark Lebwohl, MD, FAAD,[i] Daniel K. Braun, MD, PhD,[j] Lotus Mallbris, MD, PhD,[j] Stefan Wilhelm, MD,[j] Wen Xu, PhD,[j] Anders Ljungberg, MD,[j] Nayan Acharya, MBBS, MRCP, MFPM,[j] and Kristian Reich, MD, PhD[k]

Farmington, Connecticut; St Louis, Missouri; Waterloo, Ontario, and Montreal, Quebec, Canada; Kiel and Hamburg, Germany; Tochigi, Japan; Pittsburgh, Pennsylvania; Toulouse, France; New York, New York; and Indianapolis, Indiana

Background: Safety of biologics is important when treating patients with psoriasis.

Objective: We sought to determine the safety of ixekizumab in psoriasis.

Methods: Integrated safety data are presented from a 12-week induction period, a 12- to 60-week maintenance period, and from all ixekizumab-treated patients from 7 clinical trials. Exposure-adjusted incidence rates (IRs) per 100 patient-years are reported.

Results: Overall, 4209 patients received ixekizumab (total exposure: 6480 patient-years). During the induction period, the IRs of patients experiencing 1 or more treatment-emergent adverse event (AE) were 251 and 236 among ixekizumab- and etanercept-treated patients, respectively, and for serious AEs was 8.3 in both groups. During maintenance, for ixekizumab, the IRs of treatment-emergent AEs and serious AEs were 100.4 and 7.8, respectively. Among all ixekizumab-treated patients from 7 trials, the IR of *Candida* infections was 2.5. The IRs of treatment-emergent AEs of special interest (including serious infections, malignancies, major adverse cardiovascular events) were comparable for ixekizumab and etanercept during the induction period.

Limitations: Additional long-term data are required.

Conclusion: Ixekizumab had an acceptable safety profile with no unexpected safety findings during ixekizumab maintenance in psoriasis. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.09.026.)

Key words: adverse events; etanercept; integrated analysis; interleukin-17A; ixekizumab; psoriasis; safety.

For patients with moderate to severe psoriasis, long-term treatment is usually required for adequate disease control.[1-4] Conventional systemic therapies have been used for decades, but long-term usage is sometimes associated with organ-specific toxicity.[5,6] Current biologic therapies have improved clinical management of psoriasis because of a favorable benefit-risk balance without cumulative organ-specific toxicity.[7-16]

Recently published data from randomized trials involving the anti-interleukin (IL)-17A monoclonal antibodies, secukinumab,[17,18] ixekizumab,[19,20] and brodalumab,[21,22] raised expectations for improved management of psoriasis. However, as with any new

From the Department of Dermatology, University of Connecticut Health Center and Probity Medical Research[a]; Central Dermatology PC, St Louis[b]; K. Papp Clinical Research and Probity Medical Research, Waterloo[c]; Psoriasis-Center, University Medical Center Schleswig-Holstein, Campus Kiel[d]; Jichi Medical University, Shimotsuke, Tochigi[e]; Innovaderm Research, Montreal[f]; Department of Dermatology, University of Pittsburgh Medical Center[g]; Dermatology, Paul Sabatier University, Toulouse[h]; Icahn School of Medicine at Mount Sinai, New York[i]; Eli Lilly and Company, Indianapolis[j]; and Dermatologikum Hamburg and SCIderm, Hamburg.[k]

medication, thorough safety evaluations are needed. We report an integrated safety analysis from 7 psoriasis clinical trials involving ixekizumab.

METHODS

Patients and study design

Main data sources were UNCOVER-1, UNCOVER-2, and UNCOVER-3, randomized, double-blind, placebo-controlled phase III trials of ixekizumab in psoriasis.[19,20] Adult patients (age ≥18 years) with psoriasis (≥10% body surface area involvement, static Physician Global Assessment score of ≥3, Psoriasis Area and Severity Index score ≥12 at baseline) who were candidates for systemic therapy and/or phototherapy were enrolled. UNCOVER-1, -2, and -3 had 12-week randomized placebo-controlled periods. UNCOVER-2 and -3 had an etanercept group to week 12.[19]

There were 4 integrated analysis sets (Table I). The placebo-controlled induction dosing period was

Supported by Eli Lilly and Company.

Disclosure: Dr Strober is a member of the AbbVie speakers bureau and receives honoraria. He is a consultant for and serves on advisory boards of AbbVie, Amgen, AstraZeneca, Celgene, Dermira, Forward Pharma, Janssen, LEO Pharma, Eli Lilly and Company, Maruho, Medac, Novartis, Pfizer, Sun, Stiefel/GlaxoSmithKline, UCB, and Boehringer Ingelheim and receives honoraria for all. He is an investigator for AbbVie, Amgen, Novartis, Eli Lilly and Company, Janssen, Merck, XenoPort, Xoma, and Celgene, and payments from all were made to the University of Connecticut. He is a scientific director for CORRONA Psoriasis Registry and receives consulting fees. Grant support to the University of Connecticut for a fellowship program was received from AbbVie and Janssen (payments to the University of Connecticut). Dr Leonardi is a consultant/advisory board member for AbbVie, Amgen, Boehringer-Ingelheim, Dermira, Eli Lilly and Company, Janssen, LEO Pharma, Pfizer, Sandoz, and VCB and received honoraria paid to him. He is an investigator for Actavis, AbbVie, Amgen, Celgene, Coherus, Dermira, Eli Lilly and Company, Galderma, Janssen, Merck, Pfizer, Sandoz, Stiefel, LEO Pharma, Novartis, and Wyeth and money was paid to his institution. He is a member of the speakers bureau of AbbVie, Celgene, and Novartis and received honoraria paid to him. Dr Papp is speakers bureau member/consultant/investigator/advisory board member of/for Abbott/AbbVie, Amgen, Astellas, Boehringer Ingelheim, Celgene, Eli Lilly and Company, EMDSerono, Galderma, Janssen, Merck, Novartis, and Pfizer. He serves as a consultant and investigator for Celtrion, Kyowa, MedImmune, Regeneron Pharmaceuticals Inc, Sanofi-Aventis, Takeda, and Valeant. He serves as a consultant for Akros, AstraZeneca, Baxter, Bayer, Cipher, Forward Pharma, Genentech, Kirin, Lypanosys, Mitsubishi Pharma, Mylan, Meiji Seika Pharma Co, Ltd, NovImmune, Serono, Stiefel UCB, and Vertex. He is a member of the advisory boards of Actelion, Mylan, Sanofi-Aventis, and UCB. He is an investigator for Allergan, Anacor, Baxalta, Celtic, Dermira, Dow Pharma, GSK, LEO Pharma, Roche, and Xenon. He is a member of the speakers bureau of LEO Pharma. Money was paid to Dr Papp's institution for all of the above. Dr Mrowietz has been an advisor and/or received speakers honoraria and/or received grants and/or participated in clinical trials of the following companies: Abbott/AbbVie, Almirall-Hermal, Amgen, Biogen Idec, Boehringer-Ingelheim, Celgene, Centocor, Eli Lilly and Company, Foamix, Forward Pharma, Janssen, LEO Pharma, Medac, MSD, Miltenyi Biotech, Novartis, Pfizer, VBL, and Xenoport. Dr Ohtsuki has received honoraria as consultant and/or advisory board member and/or acted as paid speaker and/or participated in clinical trials sponsored by AbbVie, Boehringer Ingelheim, Celgene, Eisai, Janssen, Kyowa-Kirin, LEO Pharma, Eli Lilly and Company, Maruho, Novartis, Pfizer, and Tanabe-Mitsubishi. Dr Bissonnette is an advisory board member and has received honoraria from AbbVie, Amgen, Janssen, and Merck. He is a consultant for and receives honoraria from AbbVie, Amgen, Celgene, Eli Lilly and Company, Galderma, Incyte, Janssen, LEO Pharma, Merck, and Novartis. He is a speaker for and receives honoraria from AbbVie, Amgen, Galderma, Janssen, LEO Pharma, and Merck. He is an investigator for and his institution receives grant support from AbbVie, Amgen, Celgene, Eli Lilly and Company, Galderma, Merck, Novartis, Pfizer, Kineta, Incyte, Janssen, and LEO Pharma. Dr Ferris has served as an investigator for AbbVie, Amgen, Janssen, Celgene, Eli Lilly and Company, Medimmune, LEO Pharma, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Pfizer; her institution received payment for these activities. Dr Paul has received honoraria as an advisory board member from AbbVie, Amgen, Celgene, Janssen, LEO Pharma, Eli Lilly and Company, Novartis, Pfizer, and Sandoz; his institution also received payment from Sandoz. He has served as an investigator for Amgen, Boehringer Ingelheim, Celgene, Janssen, LEO Pharma, Eli Lilly and Company, and Novartis and his institution received payments. Dr Lebwohl is an employee of the Mount Sinai Medical Center, which receives research funds from Amgen, Anacor, Boehringer Ingleheim, Celgene, Eli Lilly and Company, Janssen Biotech, Kadmon, LEO Pharmaceuticals, Medimmune, Novartis, Pfizer, Sun Pharmaceuticals, and Valeant. Dr Reich has received honoraria as consultant and/or advisory board member and/or acted as paid speaker and/or participated in clinical trials sponsored by AbbVie, Amgen, Biogen, Boehringer Ingelheim, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Eli Lilly and Company, Medac, Merck Sharp & Dohme, Novartis, Ocean Pharma, Pfizer, Regeneron, Takeda, UCB, and Xenoport. Drs Braun, Mallbris, Wilhelm, Xu, Ljungberg, and Acharya are employed by Eli Lilly and Company and own stock. Writing assistance was provided by Lori Kornberg, PhD, who is a full-time employee of INC Research, Raleigh, NC. Lingling Xie, MS, of Eli Lilly and Company provided statistical assistance.

Presented at the American Academy of Dermatology annual meeting in Washington, DC, March 4-8, 2016.

Supplementary tables and appendix are available at http://www.jaad.org.

Accepted for publication September 23, 2016.

Reprint requests: Bruce Strober, MD, PhD, Department of Dermatology, University of Connecticut Health Center and Probity Medical Research, 21 South Rd, Second Floor, Farmington, CT 06032. E-mail: strober@uchc.edu.

Published online November 23, 2016.

0190-9622

http://dx.doi.org/10.1016/j.jaad.2016.09.026

Abbreviations used:

AE: adverse event
IBD: inflammatory bowel disease
IL: interleukin
IR: exposure-adjusted incidence rate
ISR: injection-site reaction
MACE: major adverse cardiovascular events
NMSC: nonmelanoma skin cancer
PY: patient year
SAE: serious adverse event
TB: tuberculosis
TEAE: treatment-emergent adverse event

included in the Primary Psoriasis Placebo-Controlled Integrated Analysis Set (UNCOVER-1, -2, and -3) and the Psoriasis Placebo- and Active-Controlled Integrated Analysis Set (UNCOVER-2 and -3). For the induction period, Primary Psoriasis Placebo-Controlled Inte-grated Analysis Set data were used to make comparisons between ixekizumab and placebo, and Psoriasis Placebo- and Active-Controlled Integrated Ana-lysis Set data were used to make comparisons between ixekizumab and etanercept. The Psoriasis Maintenance Integrated Analysis Set comprised ixekizumab responders from the UNCOVER-1 and -2 induction periods who were re-randomized at week 12 to either maintenance treatment or treatment withdrawal to week 60. Data in the All Psoriasis Ixekizumab Exposures Analysis Set, which integrates all ixekizumab doses and study periods, were pooled from 7 clinical trials (Supplementary Table I).[19,20,23-26] Data cut-off was April 9, 2015. Protocols received ethical review board approval; patients gave written informed consent.

CAPSULE SUMMARY

- Ixekizumab is an anti—interleukin-17A antibody.
- During induction, incidence rates per 100 patient-years of most adverse events of special interest were comparable in the ixekizumab and etanercept groups.
- No unexpected safety signals were observed during ixekizumab maintenance therapy.

Safety evaluations

The safety population consisted of all randomized patients receiving 1 or more doses of study treatment. The Maintenance Dosing Period Primary Population consisted of all re-randomized patients receiving 1 or more doses of study treatment during the maintenance period. Adverse events (AEs) were classified based on the Medical Dictionary for Regulatory Activities versions 17.0 (Primary Psoriasis Placebo-Controlled Integrated Analysis Set and Psoriasis Placebo- and Active-Controlled Integrated Analysis Set) and 17.1 (Psoriasis Maintenance Integrated Analysis Set and All Psoriasis Ixekizumab Exposures Analysis Set). A treatment-emergent AE (TEAE) was an event first occurring or worsening in severity after baseline and on or before the last day within the treatment period. Lowest level terms were used for the TEAE computation and preferred terms are presented. Exposure-adjusted incidence rates (IRs) for TEAEs represent the number of patients with a particular event per 100 patient-years (PY) of exposure. Time during the treatment period was considered entire exposure time. If an event occurred multiple times for a patient, the event was counted once.

Neutropenia was defined as Common Terminology Criteria for AE grade 2 or greater (absolute neutrophil count $<1.5 \times 10^9$/L). Infection events with onset date 14 days or less before or after the grade-2 neutrophil count collection date were considered infections preceded or accompanied by neutropenia.

Data for inflammatory bowel disease (IBD) are presented as reported by the investigator, not as adjudicated. Adjudicated data will be presented in a future publication.

Statistical methods

Treatment comparisons for frequencies were analyzed using the Cochran-Mantel-Haenszel test stratified by study.[27] A Poisson regression model (treatment as explanatory variable) was used to compare exposure-adjusted IRs.[28] In the induction period, statistical comparisons between ixekizumab and placebo were conducted within Primary Psoriasis Placebo-Controlled Integrated Analysis Set, and statistical comparisons between ixekizumab and etanercept were conducted within the Psoriasis Placebo- and Active-Controlled Integrated Analysis Set. Statistical tests with 2-sided *P* values less than .05 were considered statistically significant.

RESULTS

Patients and exposure

Overall, 4209 patients received 1 or more doses of ixekizumab with a total exposure of 6480 patient-years (median 507 days; maximum 1794 days) (Fig 1 and Table I). Supplementary Table II shows patient demographics.

Table I. Databases and exposure

Treatment period	Integrated analysis data set	Treatment	No. of patients*	Median (minimum, maximum) patient-days of exposure	Patient-years
Induction period	Primary Psoriasis Placebo-Controlled Integrated Analysis Set (UNCOVER-1, -2, and -3)	Placebo	791	85.0 (8, 183)	180.0
		IXE 80 mg Q4W	1161	85.0 (1, 197)	265.9
		IXE 80 mg Q2W	1167	85.0 (8, 116)	268.6
		Total IXE 80 mg	2328	85.0 (1, 197)	534.5
	Psoriasis Placebo- and Active-Controlled Integrated Analysis Set (UNCOVER-2 and -3)	Placebo	360	85.0 (11, 146)	83.2
		IXE 80 mg Q4W	729	85.0 (1, 197)	167.6
		IXE 80 mg Q2W	734	85.0 (8, 116)	168.9
		Total IXE 80 mg	1463	85.0 (1, 197)	336.5
		Etanercept	739	85.0 (7, 217)	169.2
Maintenance period	Psoriasis Maintenance (PsM; UNCOVER-1 and -2)†	Placebo	402	152.0 (20, 423)	188.2
		IXE 80 mg Q12W	408	316.0 (1, 361)	282.4
		IXE 80 mg Q4W	416	337.0 (24, 434)	345.2
		Total IXE 80 mg	824	336.0 (1, 434)	627.6
All treatment periods	All Psoriasis IXE Exposures Analysis Set (UNCOVER-1, -2, and -3 plus an additional 4 phase I-III studies)	Total pooled IXE	4209	507.0 (1, 1794)	6479.8

UNCOVER-1, NCT01474512; UNCOVER-2, NCT01597245; and UNCOVER-3, NCT01646177.
IXE, Ixekizumab; *PsM*, Psoriasis Maintenance Integrated Analysis Set; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks; *Q12W*, every 12 weeks.
*The exposure numbers for the induction, maintenance period, and overall categories at any time (ie, all psoriasis) cannot be summed across categories.
†1226 Patients who were responders to treatment during the induction (as measured by static Physician Global Assessment [0,1] at wk 12) and were then re-randomized in the maintenance period were included in PsM (UNCOVER-1 and -2).

Overall safety

Induction period: ixekizumab versus etanercept (Psoriasis Placebo- and Active-Controlled Integrated Analysis Set; UNCOVER-2 and -3). The IRs of TEAEs were similar in the ixekizumab groups and the etanercept group (Supplementary Table III; Supplementary Appendix for Primary Psoriasis Placebo-Controlled Integrated Analysis Set). Most TEAEs were mild or moderate. The overall safety profile of etanercept was comparable with ixekizumab. The most common TEAE type was infection. The IRs of infections were significantly higher in the total ixekizumab group than in the etanercept group, but this was not true for individual infection types. The IRs of injection-site reactions (ISRs) were similar in ixekizumab- and etanercept-treated patients. However, among individual types of ISRs, the IR of injection-site pain was higher in patients treated with ixekizumab every 2 weeks compared with etanercept-treated patients, and the IR of injection-site erythema was lower in patients treated with ixekizumab every 4 weeks compared with etanercept-treated patients.

The IRs of serious AEs (SAEs) and discontinuations because of AEs did not significantly differ between the ixekizumab and the etanercept groups (Supplementary Table III). The IRs of individual SAEs and discontinuations because of AEs were also similar in the ixekizumab and etanercept groups. No deaths occurred during the induction period.

Maintenance period (Psoriasis Maintenance Integrated Analysis Set; ixekizumab only). During maintenance, no significant differences were observed in the IRs of TEAEs between groups taking ixekizumab every 4 weeks and every 12 weeks (Supplementary Table IV). Most TEAEs were mild or moderate (Supplementary Table IV). Nasopharyngitis was the most common TEAE with ixekizumab. SAEs occurring in 2 or more patients in the total ixekizumab group were falls, coronary artery disease, inguinal hernia, osteoarthritis, and intervertebral disc protrusion. In the total ixekizumab group, the IRs of discontinuations because of AE were low; the most common reasons were related to protocol-mandated discontinuation of patients with positive tuberculosis (TB) test results. However, there were no cases of clinically active or reactivated TB. Two deaths occurred in the maintenance period (Supplementary Table V).

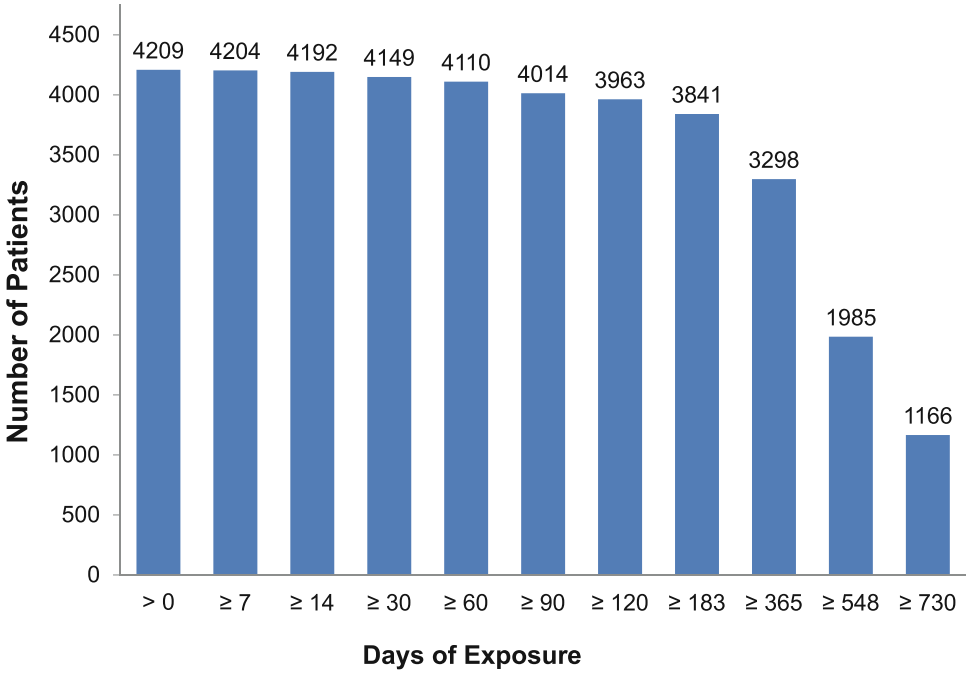

Fig 1. Psoriasis. Drug exposure. The number of patients exposed to ixekizumab. In the Psoriasis Placebo- and Active-Controlled Integrated Analysis Set, the median exposure times were 85.0 days (maximum 197) for ixekizumab every 4 weeks (Q4W) and 85.0 days (maximum 116) for ixekizumab every 2 weeks (Q2W). The median exposure time for patients in the Psoriasis Maintenance Integrated Analysis Set treated with ixekizumab Q2W induction dosing/Q4W maintenance dosing was 337.0 (maximum 370) and with ixekizumab Q4W/Q4W was 337.0 days (maximum 434).

All Psoriasis Ixekizumab Exposures Analysis Set. Supplementary Table VI shows common TEAEs, SAEs, and AEs leading to discontinuation in the All Psoriasis Ixekizumab Exposures Analysis Set. There were 10 fatalities among all entered patients with psoriasis (8 ixekizumab [0.1 per 100 PY]; 1 etanercept; 1 nonrandomized) (Supplementary Table V); the majority of deaths were a result of cardiovascular events.

AEs of special interest

Infections were most often nonserious, mild, or moderate infections of the upper respiratory tract. The IRs of serious infections were similar in the ixekizumab groups and the etanercept group during the induction period (Fig 2, *A*, and Supplementary Table VII); erysipelas (n = 2) was the only serious infection reported by 1 or more ixekizumab-treated patient. No serious infection occurred in more than 1 ixekizumab-treated patient in the Psoriasis Maintenance Integrated Analysis Set. Cellulitis (n = 17; 0.4%) was the most common serious infection in the All Psoriasis Ixekizumab Exposures Analysis Set. The frequencies of infections were not greater for ixekizumab-treated patients compared with placebo-treated patients with preceding or accompanying neutropenia grade 2 or higher.

In the All Psoriasis Ixekizumab Exposures Analysis Set, 36 ixekizumab-treated patients had positive TB test results, and 13 patients were reported to have latent TB during yearly evaluation (Supplementary Table VI). There were no cases of clinically active or reactivated TB in ixekizumab clinical trials.

There were no invasive fungal infections involving candidemia or deep organ infection identified in any treatment period, nor were there discontinuations because of *Candida* infections. Of 165 (2.5 per 100 PY) reported *Candida* cases in the All Psoriasis Ixekizumab Exposures Analysis Set (Fig 2, *B*, and Supplementary Table VII), 5 (0.1% of all patients) were assessed by the investigator as severe. In over 80% of all patients with *Candida*-related events, infection(s) had either resolved or were resolving by database lock per investigator judgement. The most frequently occurring *Candida* infections included vulvovaginal candidiasis (2.4 per 100 PY) and oral candidiasis (1.2 per 100 PY) (Fig 2, *C*).

During the induction period, the IRs of oral candidiasis were 0 per 100 PY in placebo group,

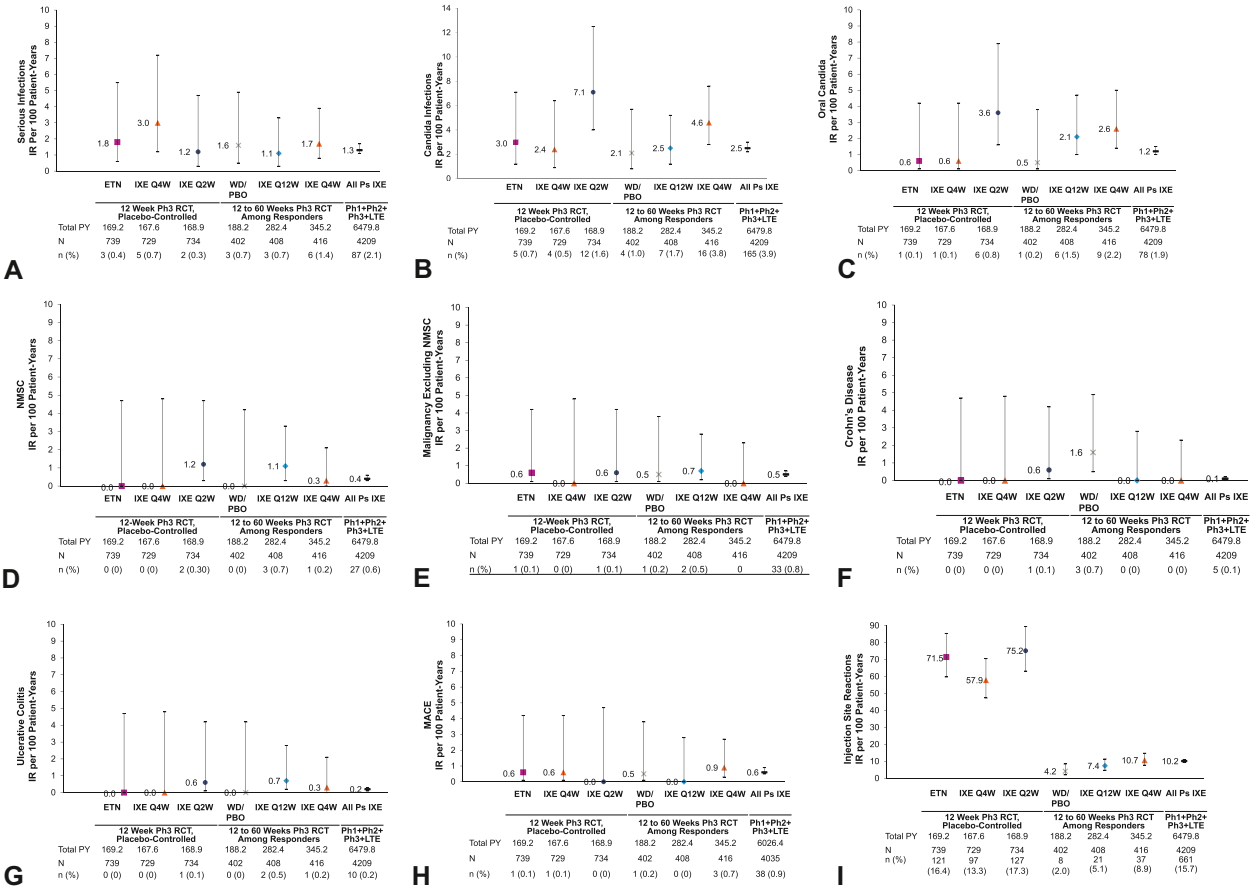

Fig 2. Psoriasis. Adverse events (AEs) of special interest. Exposure-adjusted incidence rates (*IRs*)/100 patient-years (*PY*). The exposure-adjusted IRs for treatment-emergent AEs represent the number of patients with a particular event/100 PY of exposure. Time during the treatment period was considered entire exposure time. The symbol is the exposure-adjusted IR and the bars are 95% confidence intervals. During the induction period, the IRs are from the Psoriasis Placebo (*PBO*)- and Active-Controlled Integrated Analysis Set. **A**, Serious infections. **B**, *Candida* (high-level terms [HLTs] and clinical terms). **C**, Oral *Candida* (HLTs and clinical terms). **D**, Nonmelanoma skin cancers (*NMSC*). **E**, Malignancies excluding NMSC. **F**, Crohn's disease. **G**, Ulcerative colitis. **H**, Major adverse cardiovascular events (*MACE*); total PY is 6026.4 for MACE because adjudication was only performed for the phase (*Ph*) III trials. **I**, Injection-site reactions (composite of injection site reaction–related terms). *ETN*, Etanercept; *IXE*, ixekizumab 80 mg; *LTE*, long-term extension; *Ps*, psoriasis; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks; *Q12W*, every 12 weeks; *RCT*, randomized-controlled trial; *WD*, withdrawal.

0.6 per 100 PY in the etanercept and ixekizumab every 4 weeks groups, and 3.6 per 100 PY in the ixekizumab every 2 weeks group (Fig 2, *C*). In the All Psoriasis Ixekizumab Exposures Analysis Set, the median duration of oral *Candida* infections was 5 weeks; of 78 patients, 3 had a severe event. Among all patients, 8 cases (0.1 per 100 PY) of esophageal candidiasis were reported in patients either receiving or recently administered ixekizumab; of these, 2 were SAEs and 4 were confirmed with esophagogastroduodenoscopy. Most patients with esophageal candidiasis received oral fluconazole alone or with other agents. In all cases, the events resolved, and the patients remained on study.

The IRs of nonmelanoma skin cancers (NMSC) and malignancies excluding NMSC were low (Fig 2, *D* and *E*, and Supplementary Table VII). Of malignancies excluding NMSC, there was no pattern of tumor type (Supplementary Table VIII). In all, 22 patients had malignancies leading to discontinuation; no patient with NMSC discontinued.

Overall, the incidences of reported Crohn's disease (Fig 2, *F*) and ulcerative colitis (Fig 2, *G*) were low. During the induction period, 1 case (0.3 per 100 PY) of newly diagnosed Crohn's disease and 1 case (0.3 per 100 PY) of an exacerbation of ulcerative colitis was reported in ixekizumab-treated patients, whereas no etanercept-treated patient

developed these conditions. In the All Psoriasis Ixekizumab Exposures Analysis Set, 3 and 5 ixekizumab-treated patients discontinued because of Crohn's disease and ulcerative colitis, respectively. There were 4 patients with pre-existing Crohn's disease, none of whom reported an exacerbation during the trials, and 10 patients with pre-existing ulcerative colitis at enrollment, 4 of whom had flares during study participation.

During the induction period, the between-group rates of adjudicated major adverse cardiovascular events (MACE) were similar (Fig 2, *H*). The MACE individual components did not change substantially with longer exposure to ixekizumab. In the All Psoriasis Ixekizumab Exposures Analysis Set, the IR of adjudicated MACE was 0.6 per 100 PY (median time to onset 254.0 days). Of 4035 ixekizumab-treated patients participating in trials with independent MACE adjudication, 7 patients experienced vascular death (Supplementary Tables V and VIII). With the exception of 1 nonfatal stroke, all MACE were SAEs. At baseline, patients subsequently developing treatment-emergent MACE had a higher prevalence of established risk factors for acute atherothrombotic events than patients without MACE. After adjustment for exposure, ixekizumab treatment during the maintenance period was not associated with clinically meaningful changes in blood pressure, body weight, blood glucose, or proatherogenic lipid profile compared with placebo.

There were no completed suicides in the All Psoriasis Ixekizumab Exposures Analysis Set. The rate of suicidal ideation or behavior observed was 1.39 per 1000 patient-years; Supplementary Table VIII lists depression- and self-injury-related TEAEs occurring in 1 or more patients. The IRs of these events were similar between ixekizumab treatment groups. In the All Psoriasis Ixekizumab Exposures Analysis Set, there were 8 reported suicide attempts; 2 additional events were considered by the sponsor to be suicide attempts, 1 of which occurred during patient follow-up 2 months after the last dose of ixekizumab. Only patients with 1 or more risk factors attempted suicide; 2 patients had undisclosed history of suicide attempts, a study exclusion criterion. Depression- and self-injury-related events also occurred in patients treated with placebo (1 suicide attempt in the phase I study, which is not included in the integrated data sets) and etanercept (1 suicidal ideation).

During the induction period, the IRs of ISRs were similar in the total ixekizumab and etanercept groups (Fig 2, *I*). Most ISRs in ixekizumab-treated patients were mild or moderate in severity, and 53.1% of patients experiencing ISRs had only 1 occurrence during induction. In the All Psoriasis Ixekizumab Exposures Analysis Set, the median time to occurrence from the first dose to first occurrence of ISR was 14 days. The median duration of ISRs was 2.03 days. Eight ixekizumab-treated patients discontinued because of ISRs. There were no confirmed cases of ixekizumab-related anaphylaxis events.

DISCUSSION

With 6480 patient-years of exposure in 4209 patients, we evaluated long-term continuous follow-up in one of the largest cohorts of patients with psoriasis treated with an anti—IL-17A monoclonal antibody in a clinical trial setting. Most observed AEs were nonserious and did not lead to treatment discontinuation.

The safety profile reported here is consistent with previous reports for ixekizumab.[19,20] In analyses presented here, IRs are based on numbers of patients with events per 100 patient-years of exposure, with entire time on treatment considered the exposure time. Ixekizumab-treated patients, compared with etanercept- and placebo-treated patients, did not show evidence of an increased risk of suicidal thoughts and behaviors.

In the 2 trials including etanercept (UNCOVER-2 and -3), the 12-week safety profile for ixekizumab was comparable with that of etanercept with some exceptions. A limitation of our data is that direct comparison between ixekizumab and etanercept can be made only for the 12-week induction period. A difference was an increased incidence of oral candidiasis infections with ixekizumab. This is consistent with a proposed role of IL-17 in host defense against extracellular pathogens, including fungi such as the yeast *Candida albicans*.[29-32] The use of ixekizumab was not associated with an overall increased frequency of serious infections (including TB and invasive fungal infections) during induction. Cellulitis was the most frequently reported SAE in the All Psoriasis Ixekizumab Exposures Analysis Set (0.4%). Cellulitis is typically caused by infection with *Streptococcus pyogenes* or *Staphylococcus aureus*.[33] Patients with deficiency with T helper 17 (Th17) cells (hyper-IgE syndrome [HIES]), IL-17RA, or IL-17F have increased risk of cutaneous infection because of *Staphylococcus aureus*.[29,30] It is not unexpected that cellulitis is the most frequent serious infection observed in ixekizumab-treated patients.

Patients whose tuberculin skin test or QuantiFERON (Cellestis, a QIAGEN company, Melbourne, Australia) test results converted to positive during the yearly evaluation were observed. Available evidence suggests that in tested

populations of individuals with a low risk of *Mycobacterium tuberculosis* infection, such as the majority of patients enrolled in these trials, a high proportion of false-positive findings will be observed.[34-36] Importantly, there were no cases of clinically active or reactivated TB in the entire ixekizumab clinical development program.

The rate of malignancies excluding NMSC among ixekizumab-treated patients was comparable with etanercept-treated patients during the induction period. Moreover, the rates of NMSCs and malignancies excluding NMSC in ixekizumab-treated patients were consistent with rates expected in patients with psoriasis.[12,37-40] Conclusions on malignancy risks are, however, limited by the relatively short-term duration of these trials. In addition, ixekizumab use was not associated with an increased risk of MACE.

New onset and exacerbations of Crohn's disease and ulcerative colitis occurred in ixekizumab-treated patients. In the epidemiologic literature, there is an increased prevalence of IBD among patients with psoriasis compared with matched control populations[41,42]; other studies have shown an increased risk of IBD in patients with psoriasis or an increased risk of psoriasis in patients with IBD.[43,44] Because IL-17 inhibitors appear to be ineffective in the treatment of IBD and may worsen the condition,[45,46] additional evaluation is needed to understand the association between IBD and IL-17 inhibitors, including ixekizumab. Practitioners should use caution when considering the use of ixekizumab in patients with pre-existing IBD.

The rate of suicidal ideation or behavior observed among patients with psoriasis who were exposed to ixekizumab was 1.39 per 1000 patient-years, which is within the range reported for patients with psoriasis.[47]

In conclusion, no unexpected safety signals were observed during maintenance with ixekizumab. Long-term extension studies are ongoing.

REFERENCES

1. Jacobs A, Rosumeck S, Nast A. Systematic review on the maintenance of response during systemic antipsoriatic therapy. *Br J Dermatol*. 2015;173:910-921.
2. Mease PJ, Armstrong AW. Managing patients with psoriatic disease: the diagnosis and pharmacologic treatment of psoriatic arthritis in patients with psoriasis. *Drugs*. 2014;74:423-441.
3. Mrowietz U. Implementing treatment goals for successful long-term management of psoriasis. *J Eur Acad Dermatol Venereol*. 2012;26 Suppl 2:12-20.
4. Sandoval LF, Pierce A, Feldman SR. Systemic therapies for psoriasis: an evidence-based update. *Am J Clin Dermatol*. 2014;15:165-180.
5. Archier E, Devaux S, Castela E, et al. Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. *J Eur Acad Dermatol Venereol*. 2012;26 Suppl 3:22-31.
6. Pathirana D, Ormerod AD, Saiag P, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. *J Eur Acad Dermatol Venereol*. 2009;23 Suppl 2:1-70.
7. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet*. 2008;371:1665-1674.
8. Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med*. 2003;349:2014-2022.
9. Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. *J Am Acad Dermatol*. 2008;58:106-115.
10. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet*. 2008;371:1675-1684.
11. Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicenter, double-blind trial. *Lancet*. 2005;366:1367-1374.
12. Kimball AB, Pariser D, Yamauchi PS, et al. OBSERVE-5 interim analysis: an observational postmarketing safety registry of etanercept for the treatment of psoriasis. *J Am Acad Dermatol*. 2013;68:756-764.
13. Menter A, Thaci D, Papp KA, et al. Five-year analysis from the ESPRIT 10-year postmarketing surveillance registry of adalimumab treatment for moderate to severe psoriasis. *J Am Acad Dermatol*. 2015;73:410-419.e6.
14. Papp K, Gottlieb AB, Naldi L, et al. Safety surveillance for ustekinumab and other psoriasis treatments from the psoriasis longitudinal assessment and registry (PSOLAR). *J Drugs Dermatol*. 2015;14:706-714.
15. Papp KA, Griffiths CE, Gordon K, et al. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. *Br J Dermatol*. 2013;168:844-854.
16. Shear NH, Hartmann M, Toledo-Bahena M, et al. Long-term efficacy and safety of infliximab maintenance therapy in patients with plaque-type psoriasis in real-world practice. *Br J Dermatol*. 2014;171:631-641.
17. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis—results of two phase 3 trials. *N Engl J Med*. 2014;371:326-338.
18. Thaci D, Blauvelt A, Reich K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. *J Am Acad Dermatol*. 2015;73:400-409.
19. Griffiths CE, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomized trials. *Lancet*. 2015;386:541-551.
20. Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *New England Journal of Medicine*. 2016;375:345-356.
21. Lebwohl M, Strober B, Menter A, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *N Engl J Med*. 2015;373:1318-1328.

22. Papp K, Leonardi C, Menter A, et al. Safety and efficacy of brodalumab for psoriasis after 120 weeks of treatment. *J Am Acad Dermatol*. 2014;71:1183-1190.e3.
23. Gordon KB, Leonardi CL, Lebwohl M, et al. A 52-week, open-label study of the efficacy and safety of ixekizumab, an anti-interleukin-17A monoclonal antibody, in patients with chronic plaque psoriasis. *J Am Acad Dermatol*. 2014;71:1176-1182.
24. Krueger JG, Fretzin S, Suarez-Farinas M, et al. IL-17A is essential for cell activation and inflammatory gene circuits in subjects with psoriasis. *J Allergy Clin Immunol*. 2012;130:145-154.e9.
25. Leonardi C, Matheson R, Zachariae C, et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N Engl J Med*. 2012;366:1190-1199.
26. Saeki H, Nakagawa H, Ishii T, et al. Efficacy and safety of open-label ixekizumab treatment in Japanese patients with moderate-to-severe plaque psoriasis, erythrodermic psoriasis and generalized pustular psoriasis. *J Eur Acad Dermatol Venereol*. 2015;29:1148-1155.
27. Mantel N. Chi-square tests with one degree of freedom; extensions of the Mantel-Haenszel procedure. *J Am Stat Assoc*. 1963;58:690-700.
28. Long JS. In: *Regression models for categorical and limited dependent variables. Advanced quantitative techniques in the social sciences*. 1st ed. Number 7. Thousand Oaks, CA: Sage Publications; 1997.
29. Puel A, Cypowyj S, Bustamante J, et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. *Science*. 2011;332:65-68.
30. Cypowyj S, Picard C, Marodi L, et al. Immunity to infection in IL-17-deficient mice and humans. *Eur J Immunol*. 2012;42:2246-2254.
31. Gaffen SL, Hernandez-Santos N, Peterson AC. IL-17 signaling in host defense against *Candida albicans*. *Immunol Res*. 2011;50:181-187.
32. Peck A, Mellins ED. Precarious balance: Th17 cells in host defense. *Infect Immun*. 2010;78:32-38.
33. Stevens DL, Bryant AE. Impetigo, erysipelas and cellulitis. In: Ferretti JJ, Stevens DL, Fischetti VA, eds. *Streptococcus pyogenes: basic biology to clinical manifestations*. Oklahoma City (OK): University of Oklahoma Health Sciences Center; 2016:1-15.
34. Centers for Disease Control and Prevention. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection — United States, 2010. *MMWR Recomm Rep*. 2010;59(RR-5):1-28.
35. *Canadian tuberculosis standards*. 7th ed. Public Health Agency of Canada. 2014;469:1-468.
36. Tsiouri G, Gaitanis G, Kiorpelidou D, et al. Tuberculin skin test overestimates tuberculosis hypersensitivity in adult patients with psoriasis. *Dermatology*. 2009;219:119-125.
37. Fiorentino D, Langley R, Fakharzadeh S, et al. Malignancy events in the psoriasis longitudinal assessment and registry (PSOLAR) study: current status of observations. *J Am Acad Dermatol*. 2014:AB175. Abstract P8155.
38. Kimball AB, Schenfeld J, Accortt NA, et al. Incidence rates of malignancies and hospitalized infectious events in patients with psoriasis with or without treatment and a general population in the U.S.A.: 2005-09. *Br J Dermatol*. 2014;170:366-373.
39. Margolis D, Bilker W, Hennessy S, et al. The risk of malignancy associated with psoriasis. *Arch Dermatol*. 2001;137:778-783.
40. Haynes K, Beukelman T, Curtis JR, et al. Tumor necrosis factor alpha inhibitor therapy and cancer risk in chronic immune-mediated diseases. *Arthritis Rheum*. 2013;65:48-58.
41. Makredes M, Robinson D Jr, Bala M, Kimball AB. The burden of autoimmune disease: a comparison of prevalence ratios in patients with psoriatic arthritis and psoriasis. *J Am Acad Dermatol*. 2009;61:405-410.
42. Wu JJ, Nguyen TU, Poon KY, Herrinton LJ. The association of psoriasis with autoimmune diseases. *J Am Acad Dermatol*. 2012;67:924-930.
43. Li WQ, Han JL, Chan AT, Qureshi AA. Psoriasis, psoriatic arthritis and increased risk of incident Crohn's disease in US women. *Ann Rheum Dis*. 2013;72:1200-1205.
44. Egeberg A, Mallbris L, Warren RB, et al. Association between psoriasis and inflammatory bowel disease - a Danish nationwide cohort study. *Br J Dermatol*. 2016;175:487-492.
45. Hueber W, Sands BE, Lewitzky S, et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomized, double-blind placebo-controlled trial. *Gut*. 2012;61:1693-1700.
46. Mozaffari S, Nikfar S, Abdollahi M. Inflammatory bowel disease therapies discontinued between 2009 and 2014. *Expert Opin Investig Drugs*. 2015;24:949-956.
47. Kurd SK, Troxel AB, Crits-Christoph P, et al. The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study. *Arch Dermatol*. 2010;146:891-895.

SUPPLEMENTARY APPENDIX

Induction period: ixekizumab versus placebo (Primary Psoriasis Placebo-Controlled Integrated Analysis Set; UNCOVER-1,−2, and -3).

During the 12-week induction period, the incidence rates of patients experiencing 1 or more treatment-emergent adverse event (AE) were higher in the ixekizumab every 2 week and every 4 week groups compared with the placebo group.[20] Most treatment-emergent AEs were mild or moderate. Among individual treatment-emergent AEs occurring in 1% or more of patients in the total ixekizumab group, there were higher incidences of injection-site reactions, nausea, and oropharyngeal pain in the total ixekizumab group compared with the placebo group.

The incidence rates for patients with 1 or more serious AEs and discontinuations because of AEs did not significantly differ between the ixekizumab and placebo groups.[20] The most common AE leading to discontinuation were injection-site reactions in ixekizumab groups and worsening psoriasis in the placebo group.

Supplementary Table I. Details of studies comprising integrated data sets

Study type	Indication	Study identification	Design	Randomized patients	Population	Treatment period	Treatment(s)
Plaque psoriasis—pivotal phase III placebo- and/or active-comparator-controlled clinical studies							
Placebo- and active-controlled clinical studies	Psoriasis	RHAZ NCT01474512	Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study	1296 Total patients (433 ixekizumab 80 mg Q2W; 432 ixekizumab 80 mg Q4W; 431 placebo)	Patients with moderate to severe psoriasis (≥10% BSA involvement, sPGA score of ≥3, PASI score ≥12 at baseline) who were candidates for systemic therapy and/or phototherapy	12-wk Induction dosing period, 48-wk maintenance dosing period (wk 12-60), and 204-wk LTE period (wk 60-264)	Induction dosing period: at wk 0, ixekizumab 160 mg or placebo SC injection; thereafter, ixekizumab 80 mg Q2W or 80 mg Q4W vs placebo Maintenance dosing period: ixekizumab 80 mg Q4W or Q12W vs placebo SC injection LTE period: ixekizumab 80 mg Q4W, ixekizumab 80 mg Q12W SC injection, or placebo

Continued

Supplementary Table I. Cont'd

Study type	Indication	Study identification	Design	Randomized patients	Population	Treatment period	Treatment(s)
Placebo- and active-controlled clinical studies	Psoriasis	RHBA NCT01597245	Phase III, multicenter, randomized, double-blind, placebo-controlled, active-comparator, parallel-group study	1224 Total patients (351 ixekizumab 80 mg Q2W; 347 ixekizumab 80 mg Q4W; 358 etanercept; 168 placebo)	Patients with moderate to severe psoriasis (≥10% BSA involvement, sPGA score of ≥3, PASI score ≥12 at baseline) who were candidates for systemic therapy and/or phototherapy	12-wk Induction dosing period, 48-wk maintenance dosing period (wk 12-60), and 204-wk LTE dosing period (wk 60-264)	Induction dosing period: at wk 0, ixekizumab 160 mg or placebo or etanercept 50 mg SC injection; thereafter, ixekizumab 80 mg Q2W or 80 mg Q4W vs placebo and vs etanercept 50 mg (twice weekly) SC injection Maintenance dosing period: ixekizumab 80 mg Q4W or 80 mg Q12W vs placebo SC injection LTE period: ixekizumab 80 mg Q4W or 80 mg Q12W vs placebo SC injection
		RHBC NCT01646177	Phase III, multicenter, randomized, double-blind, placebo-controlled, active-comparator, parallel-group study	1346 Total patients (193 placebo; 382 etanercept 50 mg Q2W; 386 ixekizumab 80 mg Q4W; 385 ixekizumab 80 mg Q2W)	Patients with moderate to severe psoriasis (≥10% BSA involvement, sPGA score of ≥3, PASI score ≥12 at baseline) who were candidates for systemic therapy and/or phototherapy	12-wk Induction dosing period and 252-wk LTE period (wk 12-264)	Induction dosing period: at wk 0, ixekizumab 160 mg or placebo or etanercept 50 mg SC injection; thereafter, ixekizumab 80 mg Q2W or 80 mg Q4W vs placebo and vs etanercept 50 mg (twice weekly) SC injection LTE period: ixekizumab 80 mg Q4W SC injection

Continued

Supplementary Table I. Cont'd

Study type	Indication	Study identification	Design	Randomized patients	Population	Treatment period	Treatment(s)
Additional clinical studies							
Placebo-controlled, supporting clinical safety studies	Psoriasis	RHAJ NCT01107457	Phase II, multicenter, randomized, placebo-controlled study in 2 parts: part A: 16-wk, double-blind, parallel-group, dose-ranging design (20 wk; A → B transition) and part B: 240-wk, optional open-label extension	142 Randomized: (115 ixekizumab, 27 placebo)	Patients with moderate to severe psoriasis (≥10% BSA involvement, sPGA score of ≥3, and PASI total score ≥12 at baseline) who were candidates for systemic therapy	Part A: 16-wk, double-blind, parallel-group, dose-ranging design (20 wk; A → B transition) and part B: 240-wk, optional open-label extension	Part A: ixekizumab 10, 25, 75, and 150 mg SC injection at 0, 2, 4, 8, 12, and 16 wk; placebo SC injection at 0, 2, 4, 8, 12, and 16 wk Part B: ixekizumab 120 mg Q4W until the implementation of amendment (c), and thereafter, ixekizumab 80 mg Q4W for up to 5 y (240 wk)
		RHAG	Phase I, multicenter, randomized, double-blind, placebo-controlled, dose-escalation, 20-wk study	46 Randomized (37 ixekizumab, 9 placebo)	Patients with severe psoriasis (≥15% BSA involvement and PASI total score ≥13 at baseline) who were candidates for biological therapy	6 wk	Ixekizumab or placebo Q2W × 3 doses: 5, 15, 50, and 150 mg SC injection; 15 mg IV

Continued

Supplementary Table I. Cont'd

Study type	Indication	Study identification	Design	Randomized patients	Population	Treatment period	Treatment(s)
Open-label supporting safety study	Psoriasis	RHAT NCT01624233	Phase III, multicenter, single-arm, open-label, long-term study	91 Randomized	Japanese patients with psoriasis	12-wk Induction dosing period, 40-wk Maintenance dosing period (wk 12-52), and retreatment dosing period up to 192 wk after starting study retreatment	Induction dosing period doses: at wk 0, ixekizumab 160 mg SC injection; thereafter, ixekizumab 80 mg Q2W SC injection Maintenance and retreatment periods dose: ixekizumab 80 mg Q4W SC injection
		RHBL NCT01777191	Phase III, multicenter, randomized, open-label, parallel-group study examining the effect of the drug delivery device (prefilled syringe or autoinjector), the site of injection (arm, thigh, or abdomen), and body weight on the pharmacokinetics after SC administration of ixekizumab	204 Randomized	Patients with moderate to severe plaque psoriasis	12-wk Study, with optional 40-wk safety extension: (wk 12-52)	Randomized study period: ixekizumab 160 mg loading dose by SC injection; thereafter, ixekizumab 80 mg Q2W by prefilled syringe or autoinjector Safety extension period: ixekizumab 80 mg Q4W by prefilled syringe

BSA, Body surface area; *IV*, intravenous; *LTE*, long-term extension; *PASI*, Psoriasis Area Severity Index; *Q2W*, every 2 wk; *Q4W*, every 4 wk; *Q12W*, every 12 wk; *SC*, subcutaneous; *sPGA*, static Physician Global Assessment.

Supplementary Table II. Baseline characteristics

	PBO- and active-controlled database (UNCOVER-2 and -3)					Maintenance phase (UNCOVER-1 and -2 maintenance dosing primary population)				All psoriasis IXE (7 trials)
Characteristic	PBO	ETN	IXE 80 mg Q2W	IXE 80 mg Q4W	IXE total	Withdrawal/ PBO	IXE 80 mg Q4W	IXE 80 mg Q12W	IXE total	All psoriasis IXE
No. of patients	360	739	734	729	1463	402	416	408	824	4209
Age mean, y	45.9 ± 12.1	45.5 ± 13.3	45.1 ± 13.2	45.3 ± 13.1	45.2 ± 13.2	44.2 ± 12.9	43.8 ± 13.0	45.4 ± 13.0	44.6 ± 13.0	45.5 ± 13.0
Male, %	71.1	68.2	64.7	68.3	66.5	65.7	69.0	66.2	67.6	67.7
Race, %										
Asian	3.6	2.6	3.1	3.0	3.1	4.2	4.1	2.7	3.4	5.5
Black	5.0	3.1	1.4	2.8	2.1	2.5	1.2	2.5	1.8	2.8
White	90.0	92.7	94.1	92.6	93.3	92.3	94.2	93.1	93.7	90.5
Other or multiple	1.4	1.6	1.4	1.7	1.5	1.0	0.5	1.7	1.1	1.2
Geographic region, %										
Asia	0	0	0	0	0	1.5	1.2	1.2	1.2	2.9
North America	50.0	51.8	50.4	51.7	51.1	49.5	51.9	50.7	51.3	53.4
Europe	44.2	42.4	43.5	42.2	42.9	44.8	43.8	44.9	44.3	39.2
Central/South America	3.9	4.1	4.0	4.0	4.0	0	0	0	0	2.4
Australia	1.9	1.8	2.2	2.1	2.1	4.2	3.1	3.2	3.2	2.1
BMI mean, kg/m^2	30.5 ± 6.7	31.0 ± 7.4	30.1 ± 7.1	30.6 ± 7.0	30.4 ± 7.0	30.1 ± 6.4	30.1 ± 6.7	29.8 ± 6.0	30.0 ± 6.4	30.6 ± 7.2
Prior systemic therapy, %										
Never	41.9	39.6	40.1	37.6	38.8	35.6	31.5	25.0	28.3	35.9
Nonbiologic only	36.9	42.1	40.6	42.8	41.7	37.1	35.6	42.6	39.1	36.3
Biologic only	9.7	8.0	7.4	7.0	7.2	9.7	9.9	12.0	10.9	10.6
Biologic and nonbiologic	11.4	10.3	12.0	12.6	12.3	17.7	23.1	20.3	21.7	17.2
Prior biologic therapy, %										
Never	78.9	81.7	80.7	80.4	80.5	72.6	67.1	67.6	67.4	72.2
1	15.6	13.7	12.8	13.6	13.2	18.4	22.6	17.6	20.1	17.3
2	4.4	3.0	4.4	4.0	4.2	5.7	4.3	10.0	7.2	6.0
≥3	1.1	1.6	2.2	2.1	2.1	3.2	6.0	4.7	5.3	4.4
Duration of psoriasis symptoms mean, y	18.7 ± 12.6	18.5 ± 12.1	18.1 ± 12.1	18.5 ± 12.6	18.3 ± 12.4	19.1 ± 11.5	19.3 ± 12.6	20.1 ± 12.6	19.7 ± 12.6	18.8 ± 12.2
Tobacco use, %	41.6	37.1	38.1	37.6	37.9	39.3	34.9	36.1	35.5	37.5

BMI, Body mass index; *ETN*, etanercept; *IXE*, ixekizumab; *PBO*, placebo; *Q2W*, every 2 wk; *Q4W*, every 4 wk; *Q12W*, every 12 wk.

Supplementary Table III. Summary of safety in placebo- and active-controlled database (UNCOVER-2 and -3): weeks 1-12

	Summary of TEAE				
	PBO	ETN	IXE 80 mg Q2W	IXE 80 mg Q4W	IXE total
No. of patients	360	739	734	729	1463
Patients with ≥1 TEAE, n (%)	160 (44.4)	399 (54.0)*	424 (57.8)*	419 (57.5)*	843 (57.6)*
Mild	96 (26.7)	226 (30.6)	225 (30.7)	227 (31.1)	452 (30.9)
Moderate	54 (15.0)	136 (18.4)	177 (24.1)	168 (23.0)	345 (23.6)
Severe	10 (2.8)	36 (4.9)	22 (3.0)	24 (3.3)	46 (3.1)†
Missing	0	1 (0.1)	0	0	0
PY	83.2	169.2	168.9	167.6	336.5
Patients with ≥1 TEAE, [IR/100 PY]	160 [192.3]	399 [235.8]*	424 [251.1]*	419 [250.0]*	843 [250.5]*
Common TEAEs with incidence ≥5/100 PY (system organ class and preferred term)‡					
Infections and infestations	74 [89.0]	159 [93.9]	190 [112.5]	191 [113.9]	381 [113.2]†
Nasopharyngitis	28 [337]	55 [32.5]	61 [36.1]	58 [34.6]	119 [35.4]
Upper respiratory tract infection	12 [14.4]	34 [20.1]	27 [16.0]	24 [14.3]	51 [15.2]
Urinary tract infection	2 [2.4]	5 [3.0]	10 [5.9]	13 [7.8]	23 [6.8]
General disorders and administration site conditions	30 [36.1]	151 [89.2]*	146 [86.5]*	117 [69.8]*†	263 [78.2]*
Injection-site reaction	4 [4.8]	80 [47.3]*	76 [45.0]*	62 [37.0]*	138 [41.0]*
Injection-site erythema	2 [2.4]	29 [17.1]*	24 [14.2]*	14 [8.4]†	38 [11.3]*
Injection-site pain	5 [6.0]	9 [5.3]	21 [12.4]†	10 [6.0]	31 [9.2]
Fatigue	5 [6.0]	11 [6.5]	13 [7.7]	13 [7.8]	26 [7.7]
Skin and subcutaneous tissue disorders	27 [32.5]	48 [28.4]	72 [42.6]†	71 [41.4]†	143 [42.5]†
Pruritus	5 [6.0]	8 [4.7]	14 [8.3]	16 [9.5]	30 [8.9]
Psoriasis	8 [9.6]	7 [4.1]	9 [5.3]	11 [6.6]	20 [5.9]
Gastrointestinal disorders	17 [20.4]	46 [27.2]	66 [39.1]*	58 [34.6]	124 [36.8]*
Diarrhea	3 [3.6]	8 [4.7]	17 [10.1]	8 [4.8]	25 [7.4]
Nausea	2 [2.4]	3 [1.8]	15 [8.9]†	9 [5.4]	24 [7.1]†
Musculoskeletal and connective tissue disorders	25 [30.1]	44 [26.0]	63 [37.3]	61 [36.4]	124 [36.8]†
Arthralgia	8 [9.6]	17 [10.0]	20 [11.8]	18 [10.7]	38 [11.3]
Back pain	5 [6.0]	7 [4.1]	10 [5.9]	10 [6.0]	20 [5.9]
Nervous system disorders	13 [15.6]	49 [29.0]*	44 [26.1]	53 [31.6]*	97 [28.8]*
Headache	8 [9.6]	31 [18.3]	33 [19.5]	34 [20.3]	67 [19.9]
Injury, poisoning, and procedural complications	21 [25.2]	27 [16.0]	27 [16.0]	42 [25.1]	69 [20.5]
Respiratory, thoracic, and mediastinal disorders	14 [16.8]	29 [17.1]	33 [19.5]	34 [20.3]	67 [19.9]
Oropharyngeal pain	3 [3.6]	7 [4.1]	9 [5.3]	12 [7.2]	21 [6.2]
Cough	1 [1.2]	11 [6.5]	9 [5.3]	10 [6.0]	19 [5.6]
Investigations	12 [14.4]	29 [17.1]	30 [17.8]	22 [13.1]	52 [15.5]
Blood creatine phosphokinase increased	5 [6.0]	7 [4.1]	11 [6.5]	9 [5.4]	20 [5.9]
Metabolism and nutrition disorders	5 [6.0]	23 [13.6]	13 [7.7]	21 [12.5]	34 [10.1]
Vascular disorders	5 [6.0]	20 [11.8]	8 [4.7]†	14 [8.4]	22 [6.5]
Psychiatric disorders	9 [10.8]	11 [6.5]	7 [4.1]	11 [6.6]	18 [5.3]
Blood and lymphatic system disorders	2 [2.4]	11 [6.5]	8 [4.7]	9 [5.4]	17 [5.1]
Patients with ≥1 SAE, [IR/100 PY]	7 [8.4]	14 [8.3]	14 [8.3]	14 [8.4]	28 [8.3]
SAEs occurring in ≥2 patients (system organ class and preferred term), n [IR]§					
Infections and infestations	2 [2.4]	3 [1.8]	2 [1.2]	5 [3.0]	7 [2.1]
Erysipelas	0	0	0	2 [1.2]	2 [0.6]
Gastrointestinal disorders	1 [1.2]	0	2 [1.2]	2 [1.2]	4 [1.2]
Skin and subcutaneous tissue disorders	2 [2.4]	0	2 [1.2]	1 [0.6]	3 [0.9]
Psychiatric disorders	1 [1.2]	0	2 [1.2]	1 [0.6]	3 [0.9]
Depression	0	0	2 [1.2]	0	2 [0.6]
Suicide attempt	0	0	1 [0.6]	1 [0.6]	2 [0.6]
Metabolism and nutrition disorders	0	0	2 [1.2]	1 [0.6]	3 [0.9]
Hepatobiliary disorders	0	0	2 [1.2]	0	2 [0.6]
Renal and urinary disorders	0	3 [1.8]	1 [0.6]	1 [0.6]	2 [0.6]
Injury, poisoning, and procedural complications	1 [1.2]	1 [0.6]	1 [0.6]	1 [0.6]	2 [0.6]

Continued

Supplementary Table III. Cont'd

	Summary of TEAE				
	PBO	ETN	IXE 80 mg Q2W	IXE 80 mg Q4W	IXE total
Nervous system disorders	0	1 [0.6]	0	2 [1.2]	2 [0.6]
Deaths, n [IR]	0	0	0	0	0
Patients with ≥1 discontinuation because of AEs (system organ class and preferred term), n [IR]‖	3 [3.6]	9 [5.3]	15 [8.9]	14 [8.4]	29 [8.6]
Gastrointestinal disorders	0	0	5 [3.0]	2 [1.2]	7 [2.1]
Diarrhea	0	0	1 [0.6]	1 [0.6]	2 [0.6]
General disorders and administration site conditions	1 [1.2]	3 [1.8]	3 [1.8]	1 [0.6]	4 [1.2]
Skin and subcutaneous tissue disorders	1 [1.2]	1 [0.6]	2 [1.2]	2 [1.2]	4 [1.2]
Psoriasis	1 [1.2]	0	1 [0.6]	1 [0.6]	2 [0.6]
Infections and infestations	0	0	2 [1.2]	2 [1.2]	4 [1.2]
Injury, poisoning, and procedural complications	0	0	1 [0.6]	1 [0.6]	2 [0.6]
Psychiatric disorders	0	0	1 [0.6]	1 [0.6]	2 [0.6]
Nervous System disorders	0	1 [0.6]	0	2 [1.2]	2 [0.6]

Exposure-adjusted IR for TEAEs represent the number of patients with a particular event/100 PY of exposure. Time during the treatment period was considered entire exposure time.
Medical Dictionary for Regulatory Activities preferred terms are presented under system organ classification.
AE, Adverse event; *ETN*, etanercept; *IR*, incidence rate/100 PY; *IXE*, ixekizumab; *PBO*, placebo; *PY*, patient-years; *Q2W*, every 2 wk; *Q4W*, every 4 wk; *SAE*, serious adverse event; *TEAE*, treatment-emergent adverse event.
*Statistically significant compared with placebo.
†Statistically significant compared with etanercept.
‡TEAEs listed are those that appeared at ≥5/100 PY in the total IXE treatment group in both studies combined.
§SAEs listed are those that appeared in ≥2 patients in the total IXE treatment group in both studies combined.
‖AEs listed are those that appeared in ≥2 patients in the total IXE treatment group in both studies combined; includes death.

Supplementary Table IV. Summary of safety: maintenance phase (UNCOVER-1 and -2 maintenance dosing period primary population: weeks 12-60)

	Withdrawal/ PBO, n [IR]	IXE 80 mg Q4W, n [IR]	IXE 80 mg Q12W, n [IR]	IXE total, n [IR]
No. of patients	402	416	408	824
Total PY	188.2	345.2	282.4	627.6
Patients with ≥1 TEAE	233 [123.8]	330 [95.6]*	300 [106.2]	630 [100.4]*
Mild	107 [56.8]	138 [40.0]	122 [43.2]	260 [41.4]
Moderate	106 [56.3]	160 [46.4]	152 [53.8]	312 [49.7]
Severe	20 [10.6]	32 [9.3]	26 [9.2]	58 [9.2]
Deaths	0	2 [0.6]	0	2 [0.3]
Common TEAEs with incidence ≥2/100 PY (system organ class and preferred term)†				
Infections and infestations	143 [76.0]	240 [69.5]	206 [72.9]	446 [71.1]
Nasopharyngitis	46 [24.4]	81 [23.5]	65 [23.0]	146 [23.3]
Upper respiratory tract infection	31 [16.5]	43 [12.5]	41 [14.5]	84 [13.4]
Sinusitis	10 [5.3]	18 [5.2]	17 [6.0]	35 [5.6]
Bronchitis	4 [2.1]	13 [3.8]	16 [5.7]	29 [4.6]
Influenza	6 [3.2]	13 [3.8]	14 [5.0]	27 [4.3]
Urinary tract infection	7 [3.7]	15 [4.3]	9 [3.2]	24 [3.8]
Pharyngitis	6 [3.2]	12 [3.5]	11 [3.9]	23 [3.7]
Gastroenteritis	9 [4.8]	8 [2.3]	8 [2.8]	16 [2.5]
Rhinitis	2 [1.1]	5 [1.4]	10 [3.5]	15 [2.4]
Tinea pedis	1 [0.5]	9 [2.6]	5 [1.8]	14 [2.2]
Folliculitis	2 [1.1]	8 [2.3]	5 [1.8]	13 [2.1]
Oral candidiasis	1 [0.5]	7 [2.0]	6 [2.1]	13 [2.1]
Musculoskeletal and connective tissue disorders	41 [21.8]	71 [20.6]	78 [27.6]	149 [23.7]
Arthralgia	13 [6.9]	21 [6.1]	24 [8.5]	45 [7.2]
Back pain	8 [4.2]	15 [4.3]	19 [6.7]	34 [5.4]
Myalgia	1 [0.5]	7 [2.0]	7 [2.5]	14 [2.2]
Skin and subcutaneous tissue disorders	47 [25.0]	71 [20.6]	56 [19.8]	127 [20.2]
Pruritus	3 [1.6]	9 [2.6]	7 [2.5]	16 [2.5]
Psoriasis	9 [4.8]	5 [1.4]*	11 [3.9]	16 [2.5]
Gastrointestinal disorders	35 [18.6]	63 [18.3]	51 [18.1]	114 [18.2]
Diarrhea	12 [6.4]	12 [3.5]	10 [3.5]	22 [3.5]
General disorders and administration site conditions	21 [11.2]	54 [15.6]	46 [16.3]	100 [15.9]
Injection-site reaction	2 [1.1]	27 [7.8]*	11 [3.9]	38 [6.1]*
Injection-site erythema	2 [1.1]	8 [2.3]	7 [2.5]	15 [2.4]
Pyrexia	2 [1.1]	8 [2.3]	5 [1.8]	13 [2.1]
Injury, poisoning, and procedural complications	22 [11.7]	52 [15.1]	32 [11.3]	84 [13.4]
Nervous system disorders	32 [17.0]	35 [10.1]*	45 [15.9]	80 [12.7]
Headache	12 [6.4]	21 [6.1]	25 [8.9]	46 [7.3]
Respiratory, thoracic, and mediastinal disorders	20 [10.6]	40 [11.6]	33 [11.7]	73 [11.6]
Oropharyngeal pain	5 [2.7]	12 [3.5]	9 [3.2]	21 [3.3]
Cough	3 [1.6]	7 [2.0]	7 [2.5]	14 [2.2]
Investigations	15 [8.0]	40 [11.6]	28 [9.9]	68 [10.8]
Blood creatine phosphokinase increased	5 [2.7]	8 [2.3]	8 [2.8]	16 [2.5]
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	5 [2.7]	14 [4.1]	14 [5.0]	28 [4.5]
Vascular disorders	6 [3.2]	11 [3.2]	12 [4.2]	23 [3.7]
Hypertension	6 [3.2]	8 [2.3]	10 [3.5]	18 [2.9]
Immune system disorders	2 [1.1]	10 [2.9]	10 [3.5]	20 [3.2]
Seasonal allergy	1 [0.5]	8 [2.3]	5 [1.8]	13 [2.1]
Psychiatric disorders	7 [3.7]	8 [2.3]	11 [3.9]	19 [3.0]
Patients with ≥1 SAE	15 [8.0]	26 [7.5]	23 [8.1]	49 [7.8]
SAEs occurring in ≥2 patients (system organ class and preferred term)‡				
Infections and infestations	3 [1.6]	6 [1.7]	3 [1.1]	9 [1.4]

Continued

Supplementary Table IV. Cont'd

	Withdrawal/ PBO, n [IR]	IXE 80 mg Q4W, n [IR]	IXE 80 mg Q12W, n [IR]	IXE total, n [IR]
Musculoskeletal and connective tissue disorders	1 [0.5]	5 [1.4]	3 [1.1]	8 [1.3]
Osteoarthritis	0	2 [0.6]	1 [0.4]	3 [0.5]
Intervertebral disc protrusion	0	0	2 [0.7]	2 [0.3]
Cardiac disorders	1 [0.5]	3 [0.9]	4 [1.4]	7 [1.1]
Coronary artery disease	0	1 [0.3]	1 [0.4]	2 [0.3]
Gastrointestinal disorders	3 [1.6]	3 [0.9]	2 [0.7]	5 [0.8]
Inguinal hernia	0	1 [0.3]	1 [0.4]	2 [0.3]
Injury, poisoning, and procedural complications	2 [1.1]	4 [1.2]	0	4 [0.6]
Fall	2 [1.1]	2 [0.6]	0	2 [0.3]
Respiratory, thoracic, and mediastinal disorders	2 [1.1]	2 [0.6]	2 [0.7]	4 [0.6]
Hepatobiliary disorders	1 [0.5]	2 [0.6]	1 [0.4]	3 [0.5]
Nervous system disorders	3 [1.6]	1 [0.3]	2 [0.7]	3 [0.5]
Neoplasms benign, malignant, and unspecified	2 [1.1]	1 [0.3]	2 [0.7]	3 [0.5]
General disorders and administration site conditions	0	2 [0.6]	0	2 [0.3]
Vascular disorders	0	0	2 [0.7]	2 [0.3]
Patients with ≥1 discontinuation from study drug because of AEs	8 [4.2]	15 [4.3]	9 [3.2]	24 [3.8]
Discontinuations from study drug because of AEs occurring in ≥2 patients (system organ class and preferred term)[§]				
Investigations	2 [1.1]	5 [1.4]	2 [0.7]	7 [1.1]
Mycobacterium tuberculosis complex test positive	0	3 [0.9]	2 [0.7]	5 [0.8]
Tuberculin test positive[‖]	0	2 [0.6]	0	2 [0.3]
Infections and infestations	1 [0.5]	3 [0.9]	1 [0.4]	4 [0.6]
Latent tuberculosis	0	2 [0.6]	0	2 [0.3]
Cardiac disorders	0	2 [0.6]	0	2 [0.3]
General disorders and administration site conditions	0	2 [0.6]	0	2 [0.3]
Nervous system disorders	0	0	2 [0.7]	2 [0.3]

Exposure-adjusted IR for TEAEs represent the number of patients with a particular event/100 PY of exposure. Time during the treatment period was considered entire exposure time.

Medical Dictionary for Regulatory Activities preferred terms are presented under system organ classification.

AE, Adverse event; *IR*, incidence rate/100 PY; *IXE*, ixekizumab; *n*, number of patients with at least 1 event in the specified category; *PBO*, placebo; *PY*, patient-years; *Q4W*, every 4 wk; *Q12W*, every 12 wk; *SAE*, serious adverse event; *TEAE*, treatment-emergent adverse event.

*Statistically significant compared with withdrawal/placebo.

[†]TEAEs listed are those that appeared at ≥2/100 PY in the total IXE treatment group.

[‡]SAEs listed are those that occurred in ≥2 patients in total IXE treatment group.

[§]AEs listed are those that occurred in ≥2 patients in the total IXE treatment group; includes death.

[‖]Positive results from tuberculin skin test or interferon gamma release assay in 1 patient each.

Supplementary Table V. Deaths among patients with psoriasis (all treatment periods)

Patient	Age, y	Gender	Treatment period at time of death	Study drug dose*	Duration of IXE exposure	Cause of death	Other relevant medical conditions
1	52	Male	Maintenance dosing	IXE 80 mg Q4W/IXE 80 mg Q4W	134	Unknown	Hypertension; smoking
2	70	Female	Maintenance dosing	IXE 80 mg Q2W/IXE 80 mg Q4W	246	Myocardial infarction	Hypertension; coronary artery disease; prior myocardial infarction; type 1 diabetes mellitus
3	39	Male	Long-term extension	IXE 80 mg Q4W/IXE 80 mg Q12W	454	Sudden cardiac arrest	Dyslipidemia; alcohol abuse
4	66	Female	Long-term extension	IXE 80 mg Q2W/IXE 80 mg Q4W	219	Hemorrhagic cerebral infarction	Prior cerebrovascular accident; gastric ulcer; gastroesophageal reflux disease; hypertension; hyperlipidemia; deep vein thrombosis; tobacco use
5	55	Male	Optional safety extension	IXE 80 mg Q2W/IXE 80 mg Q4W	128	Cardiorespiratory arrest	Coronary artery disease, hypertension; type 2 diabetes mellitus; dyslipidemia; obesity
6	63	Female	Long-term extension	PBO/IXE 80 mg Q4W	900	Sudden cardiovascular death	Obesity; hypertension
7	47	Male	Long-term extension	IXE 80 mg Q4W/IXE 80 mg Q4W	462	Accidental death	Relevant history not available
8	52	Male	Long-term extension	PBO/IXE 80 mg Q4W	432	Possible myocardial infarction	Obesity
9	60	Male	Follow-up	ETN	—	Upper gastrointestinal hemorrhage caused by hepatic cirrhosis associated with chronic alcohol misuse	Chronic alcohol misuse; hepatic enzymes increased
10	60	Male	Not randomized	Died before randomization	—	Accidental head trauma	—

ETN, Etanercept; *IXE*, ixekizumab; *PBO*, placebo; *Q2W*, every 2 wk; *Q4W*, every 4 wk; *Q12W*, every 12 wk.
*Study dose at induction and time of death.

Supplementary Table VI. Summary of safety in all ixekizumab data set

TEAEs	
	All psoriasis IXE (7 trials) N = 4209 n [IR]
Total PY	6479.8
Patients with ≥1 TEAE	3523 [54.4]
TEAEs with adjusted incidence ≥1.3 in all IXE psoriasis data set (preferred term)	
Nasopharyngitis	911 [14.1]
Upper respiratory tract infection	512 [7.9]
Injection-site reaction	441 [6.8]
Headache	313 [4.8]
Arthralgia	270 [4.2]
Sinusitis	225 [3.5]
Back pain	209 [3.2]
Bronchitis	202 [3.1]
Diarrhea	189 [2.9]
Hypertension	172 [2.7]
Urinary tract infection	179 [2.8]
Influenza	161 [2.5]
Pharyngitis	160 [2.5]
Oropharyngeal pain	147 [2.3]
Cough	145 [2.2]
Pruritus	143 [2.2]
Injection-site erythema	139 [2.1]
Psoriasis	135 [2.1]
Blood creatine phosphokinase increased	124 [1.9]
Gastroenteritis	114 [1.8]
Nausea	113 [1.7]
Fatigue	94 [1.5]
Eczema	92 [1.4]
Laceration	91 [1.4]
Vulvovaginal candidiasis*	30 [1.5]
Folliculitis	90 [1.4]
Myalgia	84 [1.3]
Rhinitis	84 [1.3]
Tinea pedis	83 [1.3]

SAE	
	All psoriasis IXE (7 trials) N = 4209 n [IR]
Total PY	6479.8
Patients with ≥1 SAE	411 [6.3]
SAEs occurring at a frequency of exposure adjusted rate of ≥0.1 in all IXE psoriasis data set (preferred term)	
Cellulitis	17 [0.3]
Fall	13 [0.2]
Myocardial infarction	11 [0.2]
Osteoarthritis	11 [0.2]
Acute myocardial infarction	9 [0.1]
Chronic obstructive pulmonary disease	8 [0.1]
Nephrolithiasis	8 [0.1]
Suicide attempt	8 [0.1]
Coronary artery disease	7 [0.1]
Depression	6 [0.1]
Inguinal hernia	6 [0.1]
Intervertebral disc protrusion	6 [0.1]
Pneumonia	6 [0.1]
Angina pectoris	5 [0.1]
Angina unstable	5 [0.1]
Appendicitis	5 [0.1]

Continued

Supplementary Table VI. Cont'd

SAE	
	All psoriasis IXE (7 trials) N = 4209 n [IR]
Cholelithiasis	5 [0.1]
Cholecystitis	5 [0.1]
Diverticulitis	5 [0.1]
Prostate cancer†	5 [0.1]
Pulmonary embolism	5 [0.1]
Urinary tract infection	5 [0.1]
Type 2 diabetes mellitus	5 [0.1]
Deep vein thrombosis	4 [0.1]
Dyspnea	4 [0.1]
Hand fracture	4 [0.1]
Road traffic accident	4 [0.1]
Sleep apnea syndrome	4 [0.1]
AEs leading to discontinuation	
	All psoriasis IXE (7 trials) N = 4209 n [IR]
Total PY	6479.8
Patients with ≥1 AE leading to discontinuation	252 [3.9]
AEs leading to discontinuation occurring in ≥2 patients (preferred term)	
Mycobacterium tuberculosis complex test positive‡	19 [0.3]
Tuberculin test positive§	16 [0.2]
Latent tuberculosis	13 [0.2]
Pregnancy*	4 [0.2]
Maternal exposure during pregnancy*	3 [0.1]
Injection-site reaction	6 [0.1]
Psoriasis	6 [0.1]
Prostate cancer†	4 [0.1]
Ulcerative colitis	5 [0.1]
Arthralgia	4 [0.1]
Drug hypersensitivity	4 [0.1]
Pustular psoriasis	4 [0.1]
Suicide attempt	4 [0.1]
Acute myocardial infarction	3 [0.0]
Cellulitis	3 [0.0]
Crohn's disease	3 [0.0]
Depression	3 [0.0]
Exposure during pregnancy	3 [0.0]
Hepatic enzyme increased	3 [0.0]
Hypersensitivity	3 [0.0]
Myocardial infarction	3 [0.0]
Edema peripheral	3 [0.0]
Psoriatic arthropathy	3 [0.0]
Urticaria	3 [0.0]
Alanine aminotransferase increased	2 [0.0]
Anaphylactic reaction‖	2 [0.0]
Appendicitis	2 [0.0]
Aspartate aminotransferase increased	2 [0.0]
Bronchopneumonia	2 [0.0]
Colon cancer	2 [0.0]
Diarrhea	2 [0.0]
Ear infection	2 [0.0]
Headache	2 [0.0]
Hypertension	2 [0.0]
Invasive ductal breast carcinoma	2 [0.0]
Liver function test abnormal	2 [0.0]

Continued

Supplementary Table VI. Cont'd

AEs leading to discontinuation	
	All psoriasis IXE (7 trials) N = 4209 n [IR]
Neutropenia	2 [0.0]
Rash generalized	2 [0.0]
Sciatica	2 [0.0]
Staphylococcal infection	2 [0.0]
Weight decreased	2 [0.0]

Exposure-adjusted IR for TEAEs represent the number of patients with a particular event/100 PY of exposure. Time during the treatment period was considered entire exposure time.
Medical Dictionary for Regulatory Activities preferred terms are presented.
AE, Adverse event; *IR*, incidence rate/100 PY; *IXE*, ixekizumab; *N*, number of patients in the analysis population; *n*, number of patients with at least 1 common AE/TEAE/SAE in the specified category; *PY*, patient-years; *SAE*, serious adverse event; *TEAE*, treatment-emergent adverse event.
*Denominator adjusted because of gender-specific event for females.
†Denominator adjusted because of gender-specific event for males.
‡One additional patient was discontinued because of investigator decision with a comment "positive QuantiFERON (Cellestis) tuberculosis."
§Approximately 60% of these patients had positive results from interferon gamma release assays.
‖These cases were reported as anaphylaxis, but not confirmed as such after external review. These events occurred approximately 10-14 days after the only IXE dose, which is beyond the expected time frame for anaphylaxis.

Supplementary Table VII. Summary of selected treatment-emergent adverse events of special interest

	PBO- and active-controlled database (UNCOVER-2 and -3)					Maintenance phase (UNCOVER-1 and -2 maintenance dosing primary population)				All psoriasis IXE (7 trials)
	PBO	ETN	IXE 80 mg Q2W	IXE 80 mg Q4W	IXE total	Withdrawal/ PBO n [IR]	IXE 80 mg Q4W n [IR]	IXE 80 mg Q12W n [IR]	IXE total n [IR]	All IXE n [IR]
No. of patients	360	739	734	729	1463	402	416	408	824	4209
Total PY	83.2	169.2	168.9	167.6	336.5	188.2	345.2	282.4	627.6	6479.8
Selected adverse events of special interest										
Infections and infestations SOC	74 [89.0]	159 [93.9]	190 [112.5]	191 [113.9]	381 [113.2]	143 [76.0]	240 [69.5]	206 [72.9]	446 [71.1]	2537 [39.2]
Candida (HLTs and clinical terms)	2 [2.4]	5 [3.0]	12 [7.1]	4 [2.4]	16 [4.8]	4 [2.1]	16 [4.6]	7 [2.5]	23 [3.7]	165 [2.5]
Oral	0	1 [0.6]	6 [3.6]	1 [0.6]	7 [2.1]	1 [0.5]	9 [2.6]	6 [2.1]	15 [2.4]	78 [1.2]
Vulvovaginal*	1 [4.2]	2 [3.7]	2 [3.3]	3 [5.6]	5 [4.4]	1 [1.6]	3 [2.8]	1 [1.1]	4 [2.0]	50 [2.4]
Skin	1 [1.2]	0	3 [1.8]	0	3 [0.9]	1 [0.5]	4 [1.2]	1 [0.4]	5 [0.8]	25 [0.4]
Esophageal	0	0	1 [0.6]	0	1 [0.3]	1 [0.5]	1 [0.3]	0	1 [0.2]	7† [0.1]
Nail	0	0	0	0	0	0	0	0	0	1 [0]
Unspecified	0	0	0	0	0	0	0	0	0	18 [0.3]
MACE‡	1 [1.2]	1 [0.6]	0	1 [0.6]	1 [0.3]	1 [0.5]	3 [0.9]	0	3 [0.5]	38 [0.6]§
Crohn's disease	0	0	1 [0.6]	0	1 [0.3]	3 [1.6]	0	0	0	5 [0.1]
Ulcerative colitis	0	0	1 [0.6]	0	1 [0.3]	0	1 [0.3]	2 [0.7]	3 [0.5]	10 [0.2]
Malignancy, excluding NMSC	0	1 [0.6]	1 [0.6]	0	1 [0.3]	1 [0.5]	0	2 [0.7]	2 [0.3]	33 [0.5]
Malignancy, NMSC	0	0	2 [1.2]	0	2 [0.6]	0	1 [0.3]	3 [1.1]	4 [0.6]	27 [0.4]
Selected serious adverse events of special interest										
Infections and infestations SOC	2 [2.4]	3 [1.8]	2 [1.2]	5 [3.0]	7 [2.1]	3 [1.6]	6 [1.7]	3 [1.1]	9 [1.4]	87 [1.3]
Candida (HLTs and clinical terms)	0	0	0	0	0	0	0	0	0	2 [0]
MACE‡	1 [1.2]	1 [0.6]	0	1 [0.6]	1 [0.3]	1 [0.5]	3 [0.9]	0	3 [0.5]	37 [0.6]§
Crohn's disease	0	0	1 [0.6]	0	1 [0.3]	2 [1.1]	0	0	0	3 [0]
Ulcerative colitis	0	0	0	0	0	0	0	1 [0.4]	1 [0.2]	3 [0]
Malignancy, excluding NMSC	0	1 [0.6]	0	0	0	1 [0.5]	0	2 [0.7]	2 [0.3]	24 [0.3]
Malignancy, NMSC	0	0	0	0	0	0	0	0	0	4 [0.1]

Exposure-adjusted IR for treatment-emergent adverse events represent the number of patients with a particular event/100 PY of exposure. Time during the treatment period was considered entire exposure time.

Preferred terms and groupings are presented.

ETN, Etanercept; *HLT*, high-level term; *IR*, incidence rate/100 PY; *IXE*, ixekizumab; *MACE*, major adverse cardiovascular events; *NMSC*, nonmelanoma skin cancer; *PBO*, placebo; *PY*, patient-years; *Q2W*, every 2 wk; *Q4W*, every 4 wk; *Q12W*, every 12 wk; *SOC*, system organ class.

*Denominator adjusted because of gender-specific event for females.

†There was an additional patient with esophageal candidiasis who had been recently re-randomized from IXE to placebo.

‡Only events confirmed after adjudication; only phase III studies were adjudicated.

§Total PY for adjudicated trials = 6026.4.

Supplementary Table VIII. Additional adverse events of special interest

	PBO- and active-controlled database (UNCOVER-2 and -3)					Maintenance phase (UNCOVER-1 and -2 maintenance dosing primary population)				All Psoriasis IXE (7 trials)
	PBO n [IR]	ETN n [IR]	IXE 80 mg Q2W n [IR]	IXE 80 mg Q4W n [IR]	IXE total n [IR]	Withdrawal/ PBO n [IR]	IXE 80 mg Q4W n [IR]	IXE 80 mg Q12W n [IR]	IXE total n [IR]	All psoriasis IXE n [IR]
No. of patients	360	739	734	729	1463	402	416	408	824	4209
Total PY	83.2	169.2	168.9	167.6	336.5	188.2	345.2	282.4	627.6	6479.8
Depression and suicide/self-injury occurring in ≥1 patient, n [IR]	2 [2.4]	6 [3.5]	3 [1.8]	3 [1.8]	6 [1.8]	2 [1.1]	5 [1.4]	5 [1.8]	10 [1.6]	86 [1.3]*
Depression	1 [1.2]	3 [1.8]	3 [1.8]	2 [1.2]	5 [1.5]	2 [1.1]	3 [0.9]	4 [1.4]	7 [1.1]	62 [1.0]
Suicide attempt	0†	0	1 [0.6]	1 [0.6]	2 [0.6]	0	0	1 [0.4]	1 [0.2]	8 [0.1]
Mood swings	0	0	0	1 [0.6]	1 [0.3]	0	0	0	0	3 [0.0]
Depressed mood	1 [1.2]	1 [0.6]	0	0	0	0	0	0	0	3 [0.0]
Apathy	0	1 [0.6]	0	0	0	0	0	0	0	0
Hypersomnia	0	1 [0.6]	0	0	0	0	0	0	0	0
Suicidal ideation	0	1 [0.6]	0	0	0	0	0	0	0	1 [0.0]
Alcohol abuse	0	0	0	0	0	0	1 [0.3]	0	1 [0.2]	2 [0.0]
Alcohol poisoning	0	0	0	0	0	0	1 [0.3]	0	1 [0.2]	4 [0.1]
Initial insomnia	0	0	0	0	0	0	0	0	0	2 [0.0]
Completed suicide	0	0	0	0	0	0	0	0	0	0
Malignancy occurring in ≥1 patient, n [IR]	0	1 [0.6]	3 [1.8]	0	3 [0.9]	1 [0.5]	1 [0.3]	5 [1.8]	6 [1.0]	60 [0.9]‡
NMSC	0	0	2 [1.2]	0	2 [0.6]	0	1 [0.3]	3 [1.1]	4 [0.6]	27 [0.4]
Basal cell carcinoma	0	0	2 [1.2]	0	2 [0.6]	0	0	2 [0.7]	2 [0.3]	20 [0.3]
Squamous cell carcinoma	0	0	0	0	0	0	1 [0.3]	1 [0.4]	2 [0.3]	8 [0.1]§
Malignancies excluding NMSC	0	1 [0.6]	1 [0.6]	0	1 [0.3]	1 [0.5]	0	2 [0.7]	2 [0.3]	33 [0.5]
Thyroid neoplasm	0	0	1 [0.6]	0	1 [0.3]	0	0	0	0	5 [0.1]
Malignant melanoma	0	1 [0.6]	0	0	0	0	0	0	0	0
Invasive ductal breast carcinoma	0	0	0	0	0	0	0	0	0	2 [0.0]
Thyroid cancer	0	0	0	0	0	0	0	0	0	1 [0.0]
Prostate cancer‖	0	0	0	0	0	0	0	1 [0.5]	1 [0.2]	5 [0.1]
Small intestine adenocarcinoma	0	0	0	0	0	0	0	1 [0.4]	1 [0.2]	1 [0.0]
Papillary thyroid cancer	0	0	0	0	0	1 [0.5]	0	0	0	0
B-cell lymphoma	0	0	0	0	0	0	0	0	0	2 [0.0]
Colon cancer	0	0	0	0	0	0	0	0	0	2 [0.0]
MACE occurring in ≥1 patient,¶ n [IR]	1 [1.2]	1 [0.6]	0	1 [0.6]	1 [0.3]	1 [0.5]	3 [0.9]	0	3 [0.5]	38 [0.6]
No. of patients	360	739	734	729	1463	402	416	408	824	4035#
Total PY	83.2	169.2	168.9	167.6	336.5	188.2	345.2	282.4	627.6	6026.4#
Vascular death**	0	0	0	0	0	0	2 [0.6]	0	2 [0.3]	7 [0.1]
Death	0	0	0	0	0	0	1 [0.3]	0	1 [0.2]	1 [0.0]
MI	0	0	0	0	0	0	1 [0.3]	0	1 [0.2]	2 [0.0]
Cardiac arrest	0	0	0	0	0	0	0	0	0	1 [0.0]

Continued

Supplementary Table VIII. Cont'd

	PBO- and active-controlled database (UNCOVER-2 and -3)					Maintenance phase (UNCOVER-1 and -2 maintenance dosing primary population)				All Psoriasis IXE (7 trials)
	PBO n [IR]	ETN n [IR]	IXE 80 mg Q2W n [IR]	IXE 80 mg Q4W n [IR]	IXE total n [IR]	Withdrawal/ PBO n [IR]	IXE 80 mg Q4W n [IR]	IXE 80 mg Q12W n [IR]	IXE total n [IR]	All psoriasis IXE n [IR]
Cardiorespiratory arrest	0	0	0	0	0	0	0	0	0	1 [0.0]
Coronary artery disease	0	0	0	0	0	0	0	0	0	1 [0.0]
Hemorrhagic cerebral infarction	0	0	0	0	0	0	0	0	0	1 [0.0]
Nonfatal MI[††]	1 [1.2]	1 [0.6]	0	0	0	0	1 [0.3]	0	1 [0.2]	25 [0.4]
Acute MI	1 [1.2]	0	0	0	0	0	1 [0.3]	0	1 [0.2]	9 [0.1]
MI	0	1 [0.6]	0	0	0	0	0	0	0	9 [0.1]
Angina pectoris	0	0	0	0	0	0	0	0	0	2 [0.0]
Angina unstable	0	0	0	0	0	0	0	0	0	2 [0.0]
Acute coronary syndrome	0	0	0	0	0	0	0	0	0	1 [0.0]
Arteriospasm coronary	0	0	0	0	0	0	0	0	0	1 [0.0]
Stress cardiomyopathy	0	0	0	0	0	0	0	0	0	1 [0.0]
Nonfatal stroke[‡‡]	0	0	0	1 [0.6]	1 [0.3]	1 [0.5]	0	0	0	6 [0.1]
Ischemic stroke	0	0	0	1 [0.6]	1 [0.3]	1 [0.5]	0	0	0	6 [0.1]
Ischemic stroke	0	0	0	0	0	1 [0.5]	0	0	0	1 [0.0]
Cerebral artery embolism	0	0	0	1 [0.6]	1 [0.3]	0	0	0	0	1 [0.0]
Cerebrovascular accident	0	0	0	0	0	0	0	0	0	1 [0.0]
Hemiparesis	0	0	0	0	0	0	0	0	0	1 [0.0]
Lacunar infarction	0	0	0	0	0	0	0	0	0	1 [0.0]
Optic ischemic neuropathy	0	0	0	0	0	0	0	0	0	1 [0.0]

Exposure-adjusted IR for treatment-emergent adverse events represent the number of patients with a particular event/100 PY of exposure. Time during the treatment period was considered entire exposure time.

Medical Dictionary for Regulatory Activities preferred terms under groupings are presented.

ETN, Etanercept; *IR*, incidence rate; *IXE*, ixekizumab; *MACE*, major adverse cardiovascular events; *MI*, myocardial infarction; *N*, number of patients in the analysis population; *n*, number of patients with at least 1 event in the specified category; *NMSC*, nonmelanoma skin cancer; *PBO*, placebo; *PY*, patient-years; *Q2W*, every 2 wk; *Q4W*, every 4 wk; *Q12W*, every 12 wk.

*In addition to the listed treatment-emergent adverse events, the following additional treatment-emergent adverse events occurred in 1 patient each in the all psoriasis data set: alcoholism, drug dependence, dysphoria, dyssomnia, emotional distress, intentional overdose, major depression, memory impairment, poor quality sleep, and substance abuse.

[†]There was 1 suicide attempt in the phase I study, which was not counted in the Psoriasis Placebo- and Active-Controlled Integrated Analysis Set database.

[‡]In addition to the listed treatment-emergent adverse events, the following additional treatment-emergent adverse events occurred in 1 patient each in the all psoriasis data set: vulval cancer, metastatic prostate cancer, breast cancer, lip squamous cell carcinoma, malignant lung neoplasm, metastases to liver, metastases to lung, malignant neoplasm, metastatic nonsmall cell lung cancer, rectal adenocarcinoma, rectal cancer, renal cancer stage II, renal cell carcinoma, renal neoplasm, squamous cell carcinoma, squamous cell carcinoma of lung, synovial sarcoma, tonsillar neoplasm, and transitional cell carcinoma.

[§]Includes 1 case of Bowen disease.

[‖]Denominator adjusted because of gender-specific event for males.

[¶]Adjudicated Antithrombotic Trialists' Collaboration Events.

[#]Adjudication was performed only for the following studies: RHAT, UNCOVER-1, UNCOVER-2, UNCOVER-3, and RHBL.

**Includes cardiovascular and cerebrovascular causes excluding hemorrhagic deaths outside of the central nervous system.

[††]These reported events were adjudicated as nonfatal MIs.

[‡‡]Nonfatal stroke includes ischemic, hemorrhagic, and unknown stroke type.