Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
eFigure 1. UNCOVER-1 Study Diagram
eFigure 2. UNCOVER-2 Study Diagram
eFigure 3. UNCOVER-3 Study Diagram

Patients consented
N=1783

Patients randomised
N=1346

193 to PBO
10 Discontinued study tx
  3 Lost to follow-up
  3 Subject decision
  2 AE
  1 Investigator decision
  1 Protocol violation

382 to ETN
13 Discontinued study tx
  4 AE
  3 Protocol violation
  2 Subject decision
  2 Investigator decision
  2 Lost to follow-up

386 to IXE Q4W
26 Discontinued study tx
  9 AE
  8 Protocol violation
  4 Subject decision
  2 Lack of efficacy
  2 Lost to follow-up
  1 Investigator decision

385 to IXE Q2W
22 Discontinued study tx
  8 AE
  7 Protocol violation
  4 Subject decision
  2 Investigator decision
  1 Lack of efficacy

183 completed week 12
369 completed week 12
360 completed week 12
363 completed week 12
eFigure 4. Change from Baseline to Week 12 of Absenteeism

Absenteeism

UNCOVER-1  UNCOVER-2  UNCOVER-3
n = 253 250 255 87 199 204 213 120 217 230 218

LS Mean Change From Baseline

-4 -3 -2 -1 0

PBO ETN Q4W Q2W
eFigure 5. Change from Baseline to Week 12 of Presenteeism.

Presenteeism

<table>
<thead>
<tr>
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<th>UNCOVER-2</th>
<th>UNCOVER-3</th>
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<tbody>
<tr>
<td>n</td>
<td>275</td>
<td>273</td>
<td>278</td>
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<tr>
<td>n</td>
<td>94</td>
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<tr>
<td>n</td>
<td>242</td>
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<td></td>
</tr>
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</table>

LS Mean Change From Baseline

- UNCOVER-1: 0.5, a, -18.8, 18.3
- UNCOVER-2: -2.4, a, -12.4, 18.2
- UNCOVER-3: -0.8, a, -16.4, 16.0, 18.1

Legend:
- PBO
- ETN
- Q4W
- Q2W

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eFigure 6. Change from Baseline to Week 12 of Activity Impairment.

Activity Impairment

UNCOVER-1  UNCOVER-2  UNCOVER-3
n = 420 417 427  160 342 332 340  184 376 375 373

LS Mean Change From Baseline

-25 -20 -15 -10 -5 0

PBO  ETN  Q4W  Q2W

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eFigure 7. Change from Baseline to Week 12 of Work Productivity Loss vs PASI Improvement

Work Productivity Loss

UNCOVER-1 | UNCOVER-2 | UNCOVER-3
---|---|---
250 49 96 178 175 | 177 74 122 159 167 | 166 97 157 187 173

PASI Improvement
- <50
- 50 to <75
- 75 to <90
- 90 to <100
- 100

LS Mean Change From Baseline
eFIGURE LEGENDS

eFigure 1. UNCOVER-1 Study Diagram. * One patient was re-randomized and took study drug at week 12; this patient was included in the randomized withdrawal (maintenance) population in this diagram. This patient discontinued from both treatment and study on the same day at week 12 (subject decision) so the discontinuation information is included in the induction period. Abbreviations: AE, adverse event; N, population size; PBO, placebo; IXE Q2W, ixekizumab 80 mg every 2 weeks; IXE Q4W, ixekizumab 80 mg every 4 weeks; IXE Q12W, ixekizumab 80 mg every 12 weeks.

eFigure 2. UNCOVER-2 Study Diagram. Abbreviations: AE, adverse event; ETN, etanercept; N, population size; PBO, placebo; IXE Q2W, ixekizumab 80 mg every 2 weeks; IXE Q4W, ixekizumab 80 mg every 4 weeks; IXE Q12W, ixekizumab 80 mg every 12 weeks; tx, treatment.

eFigure 3. UNCOVER-3 Study Diagram. Abbreviations: AE, adverse event; ETN, etanercept; N, population size; PBO, placebo; IXE Q2W, ixekizumab 80 mg every 2 weeks; IXE Q4W, ixekizumab 80 mg every 4 weeks; tx, treatment.

eFigure 4. Change from Baseline to Week 12 of Absenteeism in UNCOVER-1, UNCOVER-2, and UNCOVER-3. WPAI scores were expressed as percent absenteeism due to psoriasis. Treatment group comparisons of LS mean score change from baseline (LOCF) are presented here. Baseline is defined as the last nonmissing assessment recorded on or prior to the date of first study drug injection at week 0. The values in the Figure are the mean changes. The values above the graphs are the number of patients (LOCF) in the change from baseline to week 12 calculation. UNCOVER-1: N = 431, 432, 433 for PBO, Q4W, and Q2W, respectively; UNCOVER-2: N = 168, 358, 347, 351 for PBO, ETN, Q4W, and Q2W, respectively; UNCOVER-3: N = 193, 382, 386, 385 for PBO, ETN, Q4W, and Q2W, respectively.

- $P < .001$ for each treatment versus placebo comparison at each visit and using an ANCOVA model including treatment, geographic region, previous nonbiologic systemic therapy, baseline weight category, and baseline WPAI value in the model for UNCOVER-1.
- $P < .001$ for ixekizumab versus etanercept comparison at each visit using the model described in superscript “a”.
- $P < .001$ for each treatment versus placebo comparison at each visit and using an ANCOVA model including treatment, geographic region, previous nonbiologic systemic therapy, baseline weight category, and baseline WPAI value in the model for UNCOVER-1.

* One patient was re-randomized and took study drug at week 12; this patient was included in the randomized withdrawal (maintenance) population in this diagram. This patient discontinued from both treatment and study on the same day at week 12 (subject decision) so the discontinuation information is included in the induction period. Abbreviations: AE, adverse event; N, population size; PBO, placebo; IXE Q2W, ixekizumab 80 mg every 2 weeks; IXE Q4W, ixekizumab 80 mg every 4 weeks; IXE Q12W, ixekizumab 80 mg every 12 weeks.

a $P < .001$ for each treatment versus placebo comparison at each visit and using an ANCOVA model including treatment, geographic region, previous nonbiologic systemic therapy, baseline weight category, and baseline WPAI value in the model for UNCOVER-1.

b $P < .001$ for treatment versus placebo comparison at each visit and using the models described in superscript “a”.

c $P < .05$ for treatment versus placebo comparison at each visit using the models described in superscript “a”.

Abbreviations: ANCOVA, analysis of covariance; ETN, etanercept; n, number in group; LOCF, last observation carried forward; LS, least squares; PBO, placebo; Q2W, ixekizumab 80 mg every 2 weeks; Q4W, ixekizumab 80 mg every 4 weeks; WPAI, Work Productivity Activity Impairment.

eFigure 5. Change from Baseline to Week 12 of Presenteeism in UNCOVER-1, UNCOVER-2, and UNCOVER-3. WPAI scores were expressed as percent presenteeism due to psoriasis. Treatment group comparisons of LS mean score change from baseline (LOCF) are presented here. Baseline is defined as the last nonmissing assessment recorded on or prior to the date of first study drug injection at week 0. The values in the Figure are the mean changes. The values above the graphs are the number of patients (LOCF) in the change from baseline to week 12 calculation. UNCOVER-1: N = 431, 432, 433 for PBO, Q4W, and Q2W, respectively; UNCOVER-2: N = 168, 358, 347, 351 for PBO, ETN, Q4W, and Q2W, respectively; UNCOVER-3: N = 193, 382, 386, 385 for PBO, ETN, Q4W, and Q2W, respectively.

- $P < .001$ for each treatment versus placebo comparison at each visit and using an ANCOVA model including treatment, geographic region, previous nonbiologic systemic therapy, baseline weight category, and baseline WPAI value in the model for UNCOVER-1.
- $P < .001$ for ixekizumab versus etanercept comparison at each visit using the model described in superscript “a”.

Abbreviations: ANCOVA, analysis of covariance; ETN, etanercept; n, number in group; LOCF, last observation carried forward; LS, least squares; PBO, placebo; Q2W, ixekizumab 80 mg every 2 weeks; Q4W, ixekizumab 80 mg every 4 weeks; WPAI, Work Productivity Activity Impairment.

eFigure 6. Change from Baseline to Week 12 of Activity Impairment in UNCOVER-1, UNCOVER-2, and UNCOVER-3. WPAI scores were expressed as percent Activity Impairment due to psoriasis. Treatment group comparisons of LS mean score change from baseline (LOCF) are presented here. Baseline is defined as the last nonmissing assessment recorded on or prior to the date of first study drug injection at week 0. The values in the Figure are the mean changes. The values above the graphs are the number of patients (LOCF) in the change from baseline to week 12 calculation. UNCOVER-1: N = 431, 432, 433 for PBO, Q4W, and Q2W, respectively; UNCOVER-2: N = 168, 358, 347, 351 for PBO, ETN, Q4W, and Q2W, respectively; UNCOVER-3: N = 193, 382, 386, 385 for PBO, ETN, Q4W, and Q2W, respectively.

- $P < .001$ for each treatment versus placebo comparison at each visit and using an ANCOVA model including treatment, geographic region, previous nonbiologic systemic therapy, baseline weight category, and baseline WPAI value in the model for UNCOVER-1.
- $P < .001$ for each treatment versus placebo comparison at each visit and using an ANCOVA model including treatment, geographic region, previous nonbiologic systemic therapy, baseline weight category, and baseline WPAI value in the model for UNCOVER-1.

Abbreviations: ANCOVA, analysis of covariance; ETN, etanercept; n, number in group; LOCF, last observation carried forward; LS, least squares; PBO, placebo; Q2W, ixekizumab 80 mg every 2 weeks; Q4W, ixekizumab 80 mg every 4 weeks; WPAI, Work Productivity Activity Impairment.
eFigure 7. Change from Baseline to Week 12 of Work Productivity Loss vs PASI Improvement. Work Productivity Loss associated with increasing levels of PASI improvement at Week 12 in UNCOVER-1, UNCOVER-2, and UNCOVER-3, irrespective of treatment group. PASI improvement from baseline to Week 12 was subdivided into 5 groups: less than 50% improvement (<50), 50% to less than 75% improvement (50 to <75), 75% to less than 90% improvement (75 to <90), 90% to less than 100% improvement (90 to <100), and 100% clearance of psoriasis (100). N-values for each subgroup are shown. The WPAI score of Work Productivity Loss Week 12 change from baseline (LS mean, LOCF) is shown for each PASI improvement group.

a $P < .001$ with respect to PASI<50. UNCOVER-1 used an ANCOVA model including PASI groups, baseline health outcome score and stratification factor(s). UNCOVER-2 and UNCOVER-3 used an ANCOVA model including PASI groups, pooled center and the baseline health outcome score.

b $P < 0.05$ with respect to 50$\leq$PASI$<75$ using the model described in superscript “a”.

c $P < 0.05$ with respect to 75$\leq$PASI$<90$ using the model described in superscript “a”.

Abbreviations: ANCOVA, analysis of covariance; n, number in group; LOCF, last observation carried forward; LS, least squares; PASI, Psoriasis Area and Severity Index.
### eTable 1. sPGA and PASI-75 Responses in UNCOVER-1, UNCOVER-2, and UNCOVER-3

#### WEEK 12

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<td>IXE Q4W</td>
<td>IXE Q2W</td>
<td>PBO</td>
<td>ETN</td>
<td>IXE Q4W</td>
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<td><strong>sPGA 0 or 1, n (%)</strong></td>
<td>N=431</td>
<td>N=432</td>
<td>N=433</td>
<td>N=168</td>
<td>N=358</td>
<td>N=347</td>
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<tr>
<td></td>
<td>14 (3.2)</td>
<td>330 (76.4)</td>
<td>354 (81.8)</td>
<td>4 (2.4)</td>
<td>129 (36.0)</td>
<td>253 (72.9)</td>
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<td><em>P</em> value treatment vs PBO&lt;sup&gt;a&lt;/sup&gt;</td>
<td>--</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
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<tr>
<td><strong>PASI-75, n (%)</strong></td>
<td>17 (3.9)</td>
<td>357 (82.6)</td>
<td>386 (89.1)</td>
<td>4 (2.4)</td>
<td>149 (41.6)</td>
<td>269 (77.5)</td>
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#### WEEK 60

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<td><strong>sPGA 0 or 1, n (%)</strong></td>
<td>N=226</td>
<td>N=229</td>
<td>N=176</td>
<td>N=187</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td></td>
<td>17 (7.5)</td>
<td>167 (72.9)</td>
<td>11 (6.3)</td>
<td>140 (74.9)&lt;sup&gt;b&lt;/sup&gt;</td>
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<td><em>P</em> value vs IXE/PBO&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td><strong>PASI-75 n (%)</strong></td>
<td>20 (8.8)</td>
<td>178 (77.7)</td>
<td>14 (8.0)</td>
<td>151 (80.7)</td>
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<td><em>P</em> value vs IXE/PBO&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>&lt;.001</td>
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<sup>a</sup> UNCOVER-1 uses a logistic regression analysis with treatment, geographic region, previous non-biologic systemic therapy, and baseline weight category as factors. UNCOVER-2 and UNCOVER-3 use a Cochran-Mantel-Haenszel (CMH) test stratified by pooled center.<br>

<sup>b</sup> UNCOVER-1 uses a logistic regression analysis with treatment and baseline weight category as factors. UNCOVER-2 uses the Fisher exact test.<br>

<sup>c</sup> UNCOVER-3 does not contain a randomized withdrawal (maintenance phase).

Abbreviations: ETN, etanercept; IXE, ixekizumab; IXE Q4W, ixekizumab 80 mg every 4 weeks; IXE Q2W, ixekizumab 80 mg every 2 weeks; LS, least squares; na, not applicable; PBO, placebo; PASI-75, 75% reduction in Psoriasis Area and Severity Index; SE, standard error; sPGA, static Physician's Global Assessment.
### Table 2. WPAI-PSO Mean Change from Baseline at Week 12 and Week 60 in UNCOVER-1, UNCOVER-2, and UNCOVER-3

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<th>UNCOVER-2</th>
<th>UNCOVER-3</th>
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<td>PBO N=431</td>
<td>IXE Q4W N=432</td>
<td>IXE Q2W N=433</td>
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<tr>
<td>Absenteeism, LS mean change (SE)</td>
<td>0.2 (0.88)</td>
<td>–3.5 (0.87)</td>
<td>–2.6 (0.84)</td>
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<td>P value treatment vs PBO(^a)</td>
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<td>.003</td>
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<tr>
<td>P value ETN vs IXE(^a)</td>
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<td>Presenteeism, LS mean change (SE)</td>
<td>0.5 (1.30)</td>
<td>–18.8 (1.28)</td>
<td>–18.3 (1.24)</td>
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<td>&lt;.001</td>
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<td>P value ETN vs IXE(^a)</td>
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<td>Work Productivity Loss, LS mean change (SE)</td>
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<td>P value treatment vs PBO(^a)</td>
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<td>P value ETN vs IXE(^a)</td>
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<td>Activity Impairment, LS mean change (SE)</td>
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<td>–24.5 (1.18)</td>
<td>–25.2 (1.15)</td>
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<td>Absenteeism, LS</td>
<td>N=226</td>
<td>N=229</td>
<td>N=176</td>
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<td>mean change (SE)</td>
<td>–1.9 (1.10)</td>
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<td>N=176</td>
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<td>Activity Impairment, LS</td>
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<td>N=229</td>
<td>N=176</td>
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<td>mean change (SE)</td>
<td>–21.5 (1.09)</td>
<td>–29.2 (1.03)</td>
<td>–18.5 (1.19)</td>
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<td>--</td>
<td>&lt;.001</td>
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</tbody>
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<sup>a</sup> UNCOVER-1 uses ANCOVA with treatment, geographic region, previous non-biologic systemic therapy, baseline weight category, and baseline WPAI value in the model. UNCOVER-2 and UNCOVER-3 use ANCOVA with treatment, pooled center and baseline WPAI value in the model.

<sup>b</sup> UNCOVER-1 uses ANCOVA with baseline as a covariate, treatment group and baseline weight category as factors in the model. UNCOVER-2 uses ANCOVA with baseline as a covariate, treatment group as factors in the model.

<sup>c</sup> UNCOVER-3 does not contain a randomized withdrawal (maintenance phase).

Abbreviations: ETN, etanercept; IXE, ixekizumab; IXE Q4W, ixekizumab 80 mg every 4 weeks; IXE Q2W, ixekizumab 80 mg every 2 weeks; LS, least squares; na, not applicable; PBO, placebo.