Incidence of Inflammatory Bowel Disease Among Ixekizumab-treated Patients With Moderate-to-Severe Plaque Psoriasis and Psoriatic Arthritis: Data From 8 Clinical Trials

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Disclosures

♦ C.E.M. Griffiths has received honoraria and/or research funds from: AbbVie, Actelion, Amgen, Celgene, Janssen, Leo Pharma, Eli Lilly and Company, MSD, Novartis, Pfizer, Regeneron, Roche, Sandoz, Sun Pharma, and UCB Pharma

♦ The studies were sponsored by Eli Lilly and Company. Medical writing services were provided by David Sunter, PhD, of ProScribe – part of the Envision Pharma Group, and were funded by Eli Lilly and Company
Background and Objective

Background

♦ The incidence of inflammatory bowel disease (IBD) is increased in patients with either plaque psoriasis or psoriatic arthritis (PsA) compared to patients without psoriasis or PsA¹

♦ Animal and human studies suggest a potential role for interleukin (IL)-17 in psoriasis, PsA, and IBD²-⁴

♦ Ixekizumab is a high-affinity monoclonal antibody that selectively targets IL-17A⁵
  • Has demonstrated significant efficacy in the treatment of moderate-to-severe psoriasis and PsA⁶-¹⁰

Objective

♦ To report the incidence of IBD (Crohn’s disease and ulcerative colitis) from 8 clinical trials of ixekizumab in patients who have moderate-to-severe psoriasis or moderate-to-severe PsA

Adverse events of suspected IBD were collected from an integrated database of seven randomized, controlled and uncontrolled clinical trials for moderate-to-severe plaque psoriasis and for patients from the double-blind treatment period (Weeks 0-24) of SPIRIT-P1, a randomized, controlled PsA Phase 3 study.

In all studies patients were male or female and ≥18 years old (except UNCOVER-J, ≥20 years old). IBD was not an exclusion criteria.

IXE-treated patients received 160-mg starting dose at Week 0 prior to 80 mg IXE (Q4W or Q2W); withdrawal period (Wk 20-32).

SPIRIT-P1 was an active- (adalimumab) and placebo-controlled 24-week study of ixekizumab followed by a long-term evaluation of efficacy and safety.

Trial included patients with:
- An established diagnosis of active PsA ≥6 months and meeting Classification for Psoriatic Arthritis (CASPAR) criteria
- Active PsA defined as the presence of ≥3 tender and ≥3 swollen joints; ≥1 joint erosion on hand or foot x-rays
- Active plaque psoriasis or a documented history of plaque psoriasis

All psoriasis trials (except Phase 1) included patients with:
- Chronic plaque psoriasis for ≥6 months
- ≥10% body surface area
- Static Physician’s Global Assessment ≥3
- Psoriasis Area Severity Index (PASI) ≥12

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3 Non-Global</th>
<th>Phase 3 Global</th>
</tr>
</thead>
<tbody>
<tr>
<td>I1F-MC-RHAG (N=46)</td>
<td>I1F-MC-RHAJ (N=142)</td>
<td>UNCOVER-A (N=204)</td>
<td>UNCOVER-1 (N=1296)</td>
</tr>
<tr>
<td>5-150 mg IXEQ2W, PBO</td>
<td>10-150 mg IXEQ4W to Wk 20&lt;sup&gt;a&lt;/sup&gt;</td>
<td>80 mg IXEQ4W to Wk 12</td>
<td>80 mg IXEQ4W, IXEQ2W, PBO to Wk 12</td>
</tr>
<tr>
<td>R, DB, dose-escalation</td>
<td>80 mg IXEQ4W to Wk 12</td>
<td>80 mg IXEQ4W, IXEQ12W, PBO to Wk 264</td>
<td></td>
</tr>
<tr>
<td>80 mg IXEQ4W to Wk 12-52</td>
<td>R, OL, 2 drug delivery systems</td>
<td>R, DB, induction, PBO-controlled</td>
<td></td>
</tr>
<tr>
<td>UNCOVER-J (N=91)</td>
<td>UNCOVER-J (N=91)</td>
<td>UNCOVER-2 (N=1224)</td>
<td>UNCOVER-3 (N=1346)</td>
</tr>
<tr>
<td>80 mg IXEQ2W to Wk 12</td>
<td>80 mg IXEQ2W to Wk 12</td>
<td>80 mg IXEQ4W, IXEQ2W, ETN, PBO to Wk 12</td>
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<tr>
<td>80 mg IXEQ4W to Wk 12</td>
<td>80 mg IXEQ4W, IXEQ12W, PBO to Wk 264</td>
<td>80 mg IXEQ4W, IXEQ2W, PBO to Wk 12</td>
<td></td>
</tr>
<tr>
<td>80 mg IXEQ4W to Wk 12-52</td>
<td>R, DB, induction, PBO-controlled and active comparator</td>
<td>80 mg IXEQ4W, IXEQ4W to Wk 284</td>
<td></td>
</tr>
<tr>
<td>80 mg IXEQ4W to Wk 100-192</td>
<td>Single-arm, OL, LTE</td>
<td>R, DB, induction, PBO-controlled and active comparator, LTE, OL</td>
<td></td>
</tr>
</tbody>
</table>

SIPRIT-P1 (N=417) 80 mg IXEQ4W, ADA, IXEQ2W, PBO to Wk 24 R, DB, induction, PBO-controlled
Adjudication Procedure

- Retrospective review of adverse events from the Phase 1 and 2, Phase 3 UNCOVER and SPIRIT-P1 trials

- Suspected cases of IBD were identified by broad and narrow search terms and individually adjudicated by independent external experts using internationally recognized (EPIMAD) classification criteria\(^\text{11}\):  
  - Definite; Probable; Possible

- Additional categories:
  - Not enough information
  - Not consistent with IBD

- Of 209 patients exposed to ixekizumab in the double-blind treatment period of SPIRIT-P1 (90 patient-years [mean exposure=157 days, standard deviation=31]), no cases of suspected IBD were reported; thus there was no adjudication

History of IBD was not solicited from patients and only recorded if volunteered

The patient with Crohn’s disease and a past history of IBD also had baseline self-reported PsA; 4 ulcerative colitis cases (3 definitive, 1 probable) had baseline self-reported PsA (1 case with baseline self-reported PsA had a past history of IBD)

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*IBD=inflammatory bowel diseases; MedDRA=Medical Dictionary for Regulatory Activities*
Incidence of Crohn’s Disease and Ulcerative Colitis
All Ixekizumab-treated Patients

Psoriasis Trials and SPIRIT-P1 Trial

<table>
<thead>
<tr>
<th></th>
<th>Psoriasis Trials (N=4209)</th>
<th>SPIRIT-P1 (N=209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total exposure, patient-years</td>
<td>6480</td>
<td>90</td>
</tr>
<tr>
<td>Crohn’s disease: Incidence rate per 1000 patient-years</td>
<td>1.08</td>
<td>0</td>
</tr>
<tr>
<td>Ulcerative Colitis: Incidence rate per 1000 patient-years</td>
<td>1.85</td>
<td>0</td>
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</table>

♦ No suspected cases of IBD were reported for the PsA trial (SPIRIT-P1)
♦ Suspected IBD cases classified as possible are not included when determining incidence rate. Incidence rate was calculated as the total of definite and probable cases/N multiplied by 1000
<table>
<thead>
<tr>
<th>Probable</th>
<th>Definite</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=5</strong></td>
<td><strong>N=2</strong></td>
</tr>
</tbody>
</table>
| Discontinued  
N=4  
2 IXE Q4W; 2 IXE Q2W | Discontinued  
N=1  
IXE Q2W |
| Continued  
N=1  
IXE Q2W | Continued  
N=1  
IXE Q4W |
| Self-reported IBD History  
N=0 | Self-reported IBD History  
N=1  
IXE Q4W (Continued) |
| Baseline PsA  
N=0 | Baseline PsA  
N=1  
IXE Q4W (Continued) |

**Crohn’s Disease**  
N=7  
(Probable and Definite Cases)

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*Adjudicated data shown for psoriasis trials only as no cases of IBD were reported for SPIRIT-P1;  
*Self-reported history of IBD and PsA was reported from one individual patient who continued with treatment;  
*History of IBD was not solicited from patients and only recorded if volunteered

**IBD**=inflammatory bowel diseases; **IXE**=ixekizumab; **Q2W**=80 mg ixekizumab every 2 weeks; **Q4W**=80 mg ixekizumab every 4 weeks; **PBO**=placebo; **PsA**=psoriatic arthritis
### Summary of Adjudicated Ulcerative Colitis Cases

All Ixekizumab-treated Patients – Integrated Psoriasis Trials

<table>
<thead>
<tr>
<th>Ulcerative Colitis</th>
<th>N=12</th>
</tr>
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<tbody>
<tr>
<td>(Probable and Definite Cases)</td>
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</tbody>
</table>

#### Probable
- **N=5**
  - **Discontinued**
    - **N=3**
      - IXE Q4W
  - **Continued**
    - **N=2**
      - IXE Q4W

<table>
<thead>
<tr>
<th>Self-reported IBD History</th>
<th>N=0</th>
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</table>

<table>
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<tr>
<th>Baseline PsA</th>
<th>N=1</th>
</tr>
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<tbody>
<tr>
<td>IXE Q4W (Continued)</td>
<td></td>
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</tbody>
</table>

#### Definite
- **N=7**
  - **Discontinued**
    - **N=5**
      - 1 IXE Q2W; 2 IXE Q12W; 2 IXE Q4W
  - **Continued**
    - **N=2**
      - 1 IXE Q2W; 1 IXE Q4W

<table>
<thead>
<tr>
<th>Self-reported IBD History</th>
<th>N=3</th>
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<table>
<thead>
<tr>
<th>Baseline PsA</th>
<th>N=3</th>
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*a Adjudicated data shown for psoriasis trials only as no cases of IBD were reported for SPIRIT-P1; b 1 IXE Q4W treated patient with a definite diagnosis of ulcerative colitis discontinued due to pregnancy; c History of IBD was not solicited from patients and only recorded if volunteered

*IBD=inflammatory bowel diseases; IXE=ixekizumab; Q2W=80 mg ixekizumab every 2 weeks; Q4W=80 mg ixekizumab every 4 weeks; PBO=placebo; PsA=psoriatic arthritis*
Conclusions

- IBD events were uncommon in ixekizumab-treated patients in an integrated dataset from seven psoriasis trials, and no cases were reported in the double-blind treatment period of a PsA clinical trial (SPIRIT-P1).

- For all psoriasis studies, the incidence rates of Crohn's disease and ulcerative colitis were 1.08 and 1.85 per 1000 patient-years, respectively.

- Rates of IBD were similar to those reported previously in patients with psoriasis. Patients with moderate-to-severe psoriasis or moderate-to-severe PsA should be monitored for onset or exacerbation of IBD during treatment with ixekizumab.