Ixekizumab Pharmacokinetics, Anti-Drug Antibodies, and Efficacy through 60 Weeks of Treatment of Moderate to Severe Plaque Psoriasis

Kristian Reich1, Kimberley Jackson2, Susan Ball3, Sandra Garces3, Lisa Kerr3, Laiyi Chua4, Talia M. Muram3 and Andrew Blauvelt5

Ixekizumab, a high-affinity monoclonal antibody that selectively targets IL-17A, is efficacious for moderate to severe plaque psoriasis. We examined relationships between serum ixekizumab concentrations, treatment-emergent anti-drug antibodies (TE-ADAs), and efficacy during 60 weeks of treatment in a randomized, controlled, phase 3 study. Steady-state ixekizumab serum trough concentrations were rapidly achieved and associated with high clinical responses at week 12 with a starting dose of 160 mg followed by 80 mg every 2 weeks. During the long-term extension period dosage of 80 mg every 4 weeks, stable serum trough concentrations maintained high clinical responses through week 60. Most (82.6%, 308/373) patients never developed TE-ADA. In TE-ADA positive patients (17.4%, n = 65), variations in ADA titers, neutralizing capacity, and persistence were observed. Fifty-six patients (15%) developed low or moderate maximum titers, with serum concentrations and efficacy comparable to those of TE-ADA negative patients. Nine patients (2.4%) developed high titers, with variable individual clinical responses; four of these nine patients achieved at least PASI 75 at week 60. Median serum concentrations in the TE-ADA-high titer group were generally comparable to the median serum concentrations in the lower titer groups. For most patients, TE-ADA had a negligible impact on ixekizumab serum concentrations and efficacy.

Clinicaltrials.gov: NCT01646177

INTRODUCTION

The efficacy of biologic therapies can be influenced by multiple factors, including the binding affinity to target, drug dose, dosing regimen, drug serum levels, and the development of anti-drug antibodies (ADAs), among others. Although not all ADAs may affect the efficacy of biologic therapy, associations between ADA, drug serum concentrations, and/or efficacy have been reported for biologics commonly used for moderate to severe psoriasis, such as adalimumab, infliximab, and ustekinumab (Chiu et al., 2015; Menter et al., 2007; 2008; Papp et al., 2008, 2011; Reich et al., 2005; Takahashi et al., 2013; Tsai et al., 2011). The clinical impact of ADAs is dependent on multiple interrelated factors, including the serum titer of ADAs, the persistence of ADAs over time, and their drug neutralizing capacity. Hence, ADAs (and neutralizing anti-drug antibodies [nADAs]) may have no clinically meaningful impact on efficacy unless they are present in sufficient concentrations to inhibit drug bioavailability or activity (Shankar et al., 2014).

Ixekizumab, a high-affinity monoclonal antibody that selectively targets IL-17A, is an efficacious treatment for moderate to severe plaque psoriasis (Blauvelt, 2016; Gordon et al., 2016; Griffiths et al., 2015; Liu et al., 2016). In this article, we describe the time course of ixekizumab serum drug levels; the incidence of treatment-emergent ADAs (TE-ADAs); and the relationship between TE-ADA, serum drug levels, and efficacy through 60 weeks of treatment in a randomized, phase 3 clinical trial of patients with moderate to severe psoriasis.

RESULTS

Patient characteristics

Baseline characteristics and patient disposition through 60 weeks of treatment in the UNCOVER-3 study were previously published (Gordon et al., 2016). Of 385 patients randomized to receive ixekizumab every 2 weeks (Q2W) during the 12-week induction dosing period, 363 (93.4%) completed week 12, and 325 (84.4%) were receiving ongoing treatment at the time of the 60-week database lock. Discontinuation rates were low for both the induction (5.7%) and long-term extension populations (10.2%). Baseline patient characteristics are provided in Table 1.
**Table 1. Baseline demographics and disease characteristics for patients receiving ixekizumab dosing Q2W/Q4W in the intent-to-treat population**

<table>
<thead>
<tr>
<th>Variable</th>
<th>IXE Q2W/IXE Q4W (N = 385)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>45.6 (13.1)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>254 (66.0)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>361 (93.8)</td>
</tr>
<tr>
<td>Weight in kg, mean (SD)</td>
<td>90.4 (23.4)</td>
</tr>
<tr>
<td>&lt;100, n (%)</td>
<td>275 (71.6)</td>
</tr>
<tr>
<td>≥100, n (%)</td>
<td>109 (28.4)</td>
</tr>
<tr>
<td>Duration of psoriasis in years, mean (SD)</td>
<td>17.8 (12.2)</td>
</tr>
<tr>
<td>% BSA involvement, mean (SD)</td>
<td>28.0 (17.3)</td>
</tr>
<tr>
<td>sPGA  150, n (%)</td>
<td>20.7 (8.2)</td>
</tr>
<tr>
<td>≥4, n (%)</td>
<td>178 (46.2)</td>
</tr>
<tr>
<td>Previous biologic therapy, n (%)</td>
<td>58 (15.1)</td>
</tr>
</tbody>
</table>

Abbreviations: BSA, body surface area; IXE, ixekizumab; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation; sPGA, Static Physician’s Global Assessment.

Table 1 Data in this table have been previously published by Gordon et al. (2016).

**Ixekizumab pharmacokinetics (PK) and efficacy**

With induction dosing (160-mg starting dose, then 80 mg ixekizumab Q2W through week 12), steady-state ixekizumab serum trough concentrations were quickly achieved, with a week 12 median concentration of 8.84 μg/ml. These concentrations were associated with a rapid attainment of high clinical response rates. During long-term extension dosing of 80 mg every 4 weeks (Q4W) dosing, median ixekizumab serum trough concentrations reached a new steady-state level by the week 24 assessment and remained stable to week 60, with median concentrations ranging from a minimum of 3.03 μg/ml to a maximum of 3.31 μg/ml during this period. These concentrations were associated with maintenance of high responses that persisted through week 60 (Figure 1). In addition, clinical response stratified by serum trough concentration quartiles was evaluated at week 60. PASI 75 and Static Physician’s Global Assessment 0/1 response rates for each quartile are provided in Table 2. High clinical response was achieved across all concentration quartiles. The lowest quartile was associated with numerically lower rates of response.

**Anti-drug antibodies**

**Incidence of ADAs.** Subjects were divided into four TE-ADA analysis populations depending on their maximum TE-ADA titer reached during 60 weeks of treatment. Titer subgroups included TE-ADA negative, TE-ADA low (maximum titer < 1:160), TE-ADA moderate (maximum titer ≥ 1:160 and < 1:1,280), and TE-ADA high (maximum titer ≥ 1:1,280). If TE-ADA titer observations were within the range of their TE-ADA titer subgroup at more than one visit (regardless of whether these were consecutive visits or not), their maximum titer was conservatively defined as “persistent.”

The incidence of TE-ADAs and nADAs through week 60 is summarized in Table 3. Briefly, most (82.6%) patients were TE-ADA negative through week 60. With increasing TE-ADA

**Figure 1. Time course of ixekizumab serum trough concentrations and clinical response rates for patients receiving ixekizumab Q2W/Q4W.**

Patients received an initial dose of 160 mg ixekizumab, then 80 mg ixekizumab every 2 weeks (Q2W) through week 12, followed by 80 mg every 4 weeks (Q4W) through week 60. Observed clinical response rates (left y-axis) are shown as the percentage of patients achieving (a) PASI 75, 90, and 100 and (b) Static Physician’s Global Assessment 0/1 and 0. Serum trough concentration (μg/ml, right y-axis) is shown at each PK visit as box-and-whisker plots, providing 5th, 25th, median, 75th, and 95th percentiles. Analysis includes all patients in the PK population with one or more samples qualifying as a serum trough sample (N = 372).

**Table 2. Clinical response rates at week 60 stratified by ixekizumab serum trough concentration quartiles for patients receiving ixekizumab Q2W/Q4W**

<table>
<thead>
<tr>
<th>Quartile</th>
<th>N = 69</th>
<th>N = 73</th>
<th>N = 71</th>
<th>N = 72</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI 75</td>
<td>62 (89.9)</td>
<td>72 (98.6)</td>
<td>69 (97.2)</td>
<td>72 (100.0)</td>
</tr>
<tr>
<td>sPGA 0/1</td>
<td>47 (68.3)</td>
<td>65 (89.0)</td>
<td>63 (88.7)</td>
<td>70 (97.2)</td>
</tr>
<tr>
<td>sPGA 0</td>
<td>56.4–79.8</td>
<td>81.2–96.9</td>
<td>80.7–96.8</td>
<td>92.7–100.0</td>
</tr>
</tbody>
</table>

Abbreviations: PASI, Psoriasis Area and Severity Index; Q1, quartile 1 (<2.18 μg/ml); Q2, quartile 2 (≥2.18 to <3.20 μg/ml); Q4, every 2 weeks; Q3, quartile 3 (≥3.20 to <4.35 μg/ml); Q4, every 4 weeks; sPGA, Static Physician’s Global Assessment.

Values are provided as n (%) and 95% confidence interval.
ADA results were unavailable for two TE-ADAs.

For all subgroups, most (24 weeks of the study (76.9% of TE-ADA determined. Most TE-ADAs were first detected during the first 60 weeks of treatment. A transient decrease in median concentration at week 60. Three patients in titer over time to either a negative titer or to a titer within the range of a lower titer category at week 60. Three patients in the TE-ADA—high population tended to have lower mean clinical responses (Figure 2a and b). In addition, a wide range of serum trough concentrations were observed within each TE-ADA subgroup. As a result, overlap in the distribution of concentrations was considerable when comparing TE-ADA titer groups.

### Relationship between ADAs and ixekizumab serum concentrations.

Overall, the time course of median ixekizumab serum trough levels was similar across titer groups through week 60, and considerable overlap in concentrations was observed. However, a transient decrease in median concentration in the TE-ADA—high population was observed at week 48 (Figure 2a and b). In addition, a wide range of serum trough concentrations were observed within each TE-ADA subgroup. As a result, overlap in the distribution of concentrations was considerable when comparing TE-ADA titer groups.

### Relationship between ADAs and ixekizumab efficacy.

Like serum drug levels, clinical responses were similar between the TE-ADA—negative, TE-ADA—low, and TE-ADA—moderate populations (Figure 2c and d). Although the TE-ADA—high population tended to have lower mean clinical responses, there was high variability among individual patients in this group (four achieved at least a 75% decline in Psoriasis Area and Severity Index [PASI] score [PASI 75], and five failed to achieve PASI 75 at week 60). Of the four TE-ADA—high patients who achieved PASI 75, three achieved a 90% reduction or greater in PASI score (PASI 90), two of whom achieved complete resolution (PASI 100) at week 60. All five TE-ADA—high patients who did not achieve PASI 75 at week 60 had either persistent high titers (two patients), high titers with coexisting nADAs (two patients), or both persistent high titers and coexisting nADAs (one patient). The two patients with transient high titer TE-ADAs with a reduced clinical response (<PASI 75) also had persistent moderate titer TE-ADAs. However, across TE-ADA subgroups, there was no relationship between persistent moderate titer and decreased efficacy.

There were 13 nADA-positive patients across all TE-ADA titer groups, nine of whom achieved at least PASI 75 at week 60 (4/4 nADA-positive TE-ADA—low patients, 4/5 nADA-positive TE-ADA—moderate patients, and 1/4 TE-ADA—high patients). Of these patients, eight achieved at least PASI 90, six of whom achieved complete clearance (PASI 100) at week 60.

### DISCUSSION

Steady-state ixekizumab serum drug trough concentrations and clinically meaningful response was rapidly achieved with induction dosing. During long-term extension maintenance dosing, stable serum drug concentrations and clinical response were maintained through 60 weeks of treatment. Most (82.6%) evaluable patients never developed TE-ADAs during the 60-week treatment period, and varying patterns of ADAs (titer, neutralizing capacity, and kinetics) were observed in the 17.4% of patients who developed TE-ADAs. Most TE-ADA—positive patients (86.2%) had low or moderate titers with similar serum trough concentrations and efficacies to those observed in TE-ADA—negative patients. Only nine patients (2.4%) had high titer TE-ADAs.

Median serum trough concentrations were generally comparable across titer groups over time, with the exception of a transient decrease in median concentration at week 48 in the TE-ADA—high population. Furthermore, variability in ixekizumab serum trough concentrations was

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**Table 3. Incidence and persistence of TE-ADAs for patients receiving ixekizumab Q2W/Q4W**

<table>
<thead>
<tr>
<th>TE-ADA Subgroup1</th>
<th>n (% of evaluable patients) (N = 373)</th>
<th>Transient2</th>
<th>TE-ADA titer category at week 60</th>
<th>n (% of TE-ADA subgroup)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TE-ADA negative</td>
<td>308 (82.6)</td>
<td>—</td>
<td>Negative</td>
<td>—</td>
</tr>
<tr>
<td>TE-ADA positive</td>
<td>65 (17.4)</td>
<td>—</td>
<td>Low</td>
<td>—</td>
</tr>
<tr>
<td>TE-ADA low</td>
<td>38 (10.2)</td>
<td>20 (52.6)</td>
<td>Moderate</td>
<td>6 (33.3)</td>
</tr>
<tr>
<td>TE-ADA moderate</td>
<td>18 (4.8)</td>
<td>7 (38.9)</td>
<td>High</td>
<td>6 (33.3)</td>
</tr>
<tr>
<td>TE-ADA high</td>
<td>9 (2.4)</td>
<td>5 (55.6)</td>
<td>Low</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>nADA positive</td>
<td>13 (3.5)</td>
<td>—</td>
<td>Moderate</td>
<td>—</td>
</tr>
<tr>
<td>TE-ADA low6</td>
<td>4 (1.1)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>TE-ADA moderate</td>
<td>5 (1.3)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>TE-ADA high</td>
<td>4 (1.1)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Abbreviations:** nADA, neutralizing anti-drug antibody; Q2W, every 2 weeks; Q4W, every 4 weeks; TE-ADA, treatment-emergent anti-drug antibody.

1 Participants were assigned to TE-ADA subgroups based on their maximum TE-ADA titer reached during 60 weeks of treatment. Titer subgroups were TE-ADA low (maximum titer <1:160), TE-ADA moderate (maximum titer $\geq$1:160 and <1:1,280), and TE-ADA high (maximum titer $\geq$1:1,280).

2 Titers were defined as transient if a maximum titer group observation was detected at only a single visit during the first 60 weeks of treatment. Titers were defined as persistent if a maximum titer group observation was detected at more than one visit, regardless of whether these were consecutive visits or not.

3 Frequencies include all subjects in each TE-ADA subgroup with an observed evaluable sample collected at week 60.

4 nADA results were unavailable for two TE-ADA—low patients.
considerable, resulting in overlap in the distribution of concentrations between titer groups. Overall, the TE-ADA-positive population exhibited lower mean clinical response rates compared with the TE-ADA-negative population. However, a more detailed evaluation of individual patients in the TE-ADA-positive population showed a high individual variability of clinical responses (ranging from no response to achieving PASI 100). Patient-level data in this population suggested that reduced clinical response was associated with patients with persistent high titer and/or high titers with coexisting nADAs. Both patients who had transient high titer TE-ADAs and lower efficacy (<PASI 75) also had persistent moderate titer TE-ADAs. However, persistent moderate titer TE-ADAs did not exhibit a relationship with lower efficacy overall. Neutralizing ADAs were only consistently associated with reduced clinical responses in patients with high TE-ADA titers.

Our findings suggest that the presence of TE-ADAs, the titer of TE-ADAs, and the presence of detectable nADAs are not sufficient on their own to predict reduced clinical response of ixekizumab. This is consistent with the concept that multiple patient-specific and drug-specific factors influence immunogenicity and its clinical impact (Shankar et al., 2014). In this study, only some individuals with TE-ADAs had decreased clinical efficacy, particularly those with persistent high TE-ADA titers or those with high TE-ADA titers and coexisting nADAs. Thus, a combination of multiple ADA attributes (e.g., titer magnitude and persistence) appeared to be important for an effect on efficacy of ixekizumab. Indeed, most TE-ADA-positive patients did not exhibit these ADA attributes and maintained clinically meaningful responses to ixekizumab throughout 60 weeks of treatment.

A limitation of this study is that it includes post hoc analyses in a limited number of patients from a single study and

Figure 2. PK and clinical response by TE-ADA status over time for patients receiving ixekizumab Q2W/Q4W. (a) Median observed ixekizumab serum trough concentrations (µg/ml ± standard deviation) by TE-ADA status for PK population patients with at least one sample qualifying as a serum trough sample (n = 372). The number of serum trough samples at each PK visit for each TE-ADA subgroup are provided below the x-axis. (b) Box-and-whisker plots of ixekizumab serum trough concentrations (µg/ml) by TE-ADA status at weeks 12 and 60. Plots show 5th, 25th, median, 75th, and 95th percentiles. (c) Mean percent change from baseline in PASI score (last observation carried forward) by TE-ADA status. (d) Bar graphs of mean percent change from baseline in PASI ± standard deviation at weeks 12 and 60. Analysis included all patients in the ADA-evaluable population (n = 373). Patients were grouped into TE-ADA subpopulations based on their highest observed TE-ADA titer during the first 60 weeks of treatment. TE-ADA populations: TE-ADA neg (negative), TE-ADA low (<1:160), TE-ADA mod (moderate, ≥1:160 and <1:1,280), and TE-ADA high (≥1:1,280). ADA, anti-drug antibody; mod, moderate; neg, negative; PASI, Psoriasis Area and Severity Index; PK, pharmacokinetics; Q2W, every two weeks, Q4W, every four weeks, TE-ADA, treatment-emergent anti-drug antibody.
disease state, which precluded a comprehensive statistical analysis to compare parameters among subgroups. In addition, this study did not explicitly investigate every potential factor that could influence PK, clinical responses, and TE-ADA development (such as patient demographics, concomitant medications, disease status, environmental factors, and others). The analysis approach used here, defining subgroups based on maximum TE-ADA titer reached during the study period, had the advantage of being a conservative and objective method of evaluating the relationship between TE-ADAs, PK, and efficacy. Nevertheless, this approach does have the limitation of not capturing fluctuations in titer and other characteristics over time. The relationship between TE-ADAs, ixekizumab serum concentration, and efficacy will continue to be monitored in the UNCOVER-3 clinical trial.

Despite these limitations, this study provides important insight into the PK of ixekizumab and its relationship with clinical response over time. In addition, this study provides an in-depth analysis of the prevalence, characteristics, and clinical impact of ixekizumab ADAs. In particular, we show that the presence of ADAs alone, including nADAs, had minimal clinical relevance to the efficacy of ixekizumab. Overall, TE-ADA development had a negligible impact on ixekizumab serum concentrations and clinical responses during the first 60 weeks of treatment in this study of patients with moderate to severe plaque psoriasis.

MATERIALS AND METHODS

Study design

UNCOVER-3 is a randomized, placebo- and active-controlled, double-blinded, multicenter phase 3 clinical trial to evaluate the efficacy and safety of ixekizumab in patients with moderate to severe plaque psoriasis. A detailed summary of the study design and patient inclusion criteria have been previously reported (Gordon et al., 2016; Griffiths et al., 2015). Briefly, during a 12-week induction dosing period, patients eligible for inclusion were randomized in a 2:2:2:1 ratio to treatment groups receiving 80 mg of ixekizumab Q2W or Q4W after an initial dose of 160 mg ixekizumab, 50 mg etanercept twice weekly, or placebo, respectively. Patients entered the long-term extension period after week 12, during which all patients received 80 mg ixekizumab Q4W.

The UNCOVER-3 trial is conducted in accordance with the ethical principles of the Declaration of Helsinki. Eligible patients provided written informed consent before undergoing study-related procedures. The trial protocol was approved by the institutional review board or ethics committee at each participating site. UNCOVER-3 is registered at clinicaltrials.gov under registration number NCT01646177.

Efficacy assessments

Efficacy outcomes were reported as the observed percentage of patients achieving PASI 75, PASI 90, or PASI 100, as well as the percentages of patients with a Static Physician's Global Assessment score of 0 or of either 0 or 1. For plots of efficacy by TE-ADA titer group, efficacy was summarized as the mean percentage of improvement from baseline in PASI for each analysis group.

PK assessment

Izekizumab serum concentration was determined from serum samples that were collected for ADA testing during patient visits at weeks 4, 12, 24, 36, 48, and 60 using an ELISA method at Intertek Pharmaceutical Services (San Diego, CA), with quantification limits ranging from 7.5–300 ng/ml. Samples above the limit of quantification were diluted to provide results within the calibrated range. All samples were diluted to a minimum of 1:5. Inter-assay precision (percentage relative standard deviation) ranged from 11.8%–17.3%.

ADA assessments

ADAs were identified using an ELISA-based affinity capture elution assay with a sensitivity of 4.6 ng/ml and a drug tolerance of 480.5 μg/ml. ADA titers were determined by serial dilution of serum samples. Patients were classified as TE-ADA positive if they had a 4-fold or greater increase in ADA titer from baseline. If patients were negative for ADA at baseline and they developed a posttreatment titer of 1:10 or greater, they were classified as TE-ADA positive. Confirmed ADA-positive samples were characterized for production of nADAs using a direct competition immunoassay on a MesoScale Discovery platform (MesoScale Discovery, Rockville, MD). Assay sensitivity was 768.6 ng/ml, and drug tolerance was 622 ng/ml.

Statistical analysis

Patient populations in this study included (i) subjects randomized to the Q2W/Q4W treatment regimen (intent-to-treat population), (ii) ADA-evaluable subjects (evaluable population), and (iii) PK population. Evaluable subjects included patients with either an evaluable baseline sample and at least one evaluable postbaseline sample, or patients with no evaluable baseline sample whose evaluable postbaseline samples are all ADA negative. The PK population included all patients with at least 1 observed ixekizumab concentration that met trough criteria.

PK samples were included in the analyses only if they met the criteria for being a trough sample. A trough sample for the Q2W dosing regimen had to be collected between 7 and 21 days after the prior dose aligned with the ±7-day visit interval for dosing specified in the study protocol. Similarly, for the Q4W dosing regimen, samples had to be collected between 21 and 35 days after the prior dose aligned with the ±7-day visit interval for dosing specified in the study protocol.

Patients in the PK population who were positive for TE-ADAs were grouped into low (<1:160), moderate (≥1:160 but <1:1,280), or high (≥1:1,280) titer groups based on the maximum titer they reached between weeks 0 and 60. For the purposes of this study, TE-ADA maximum titers were defined as persistent if they were within the cutoff of the maximum titer group at more than one visit, even if they were observed at nonconsecutive visits. TE-ADA maximum titers were defined as transient if the maximum titer group observation occurred at only one visit. Analyses of the time of first occurrence of TE-ADA included all evaluable samples from patients in the evaluable population and were summarized as the first visit at which patients were observed to be positive for TE-ADA.

Efficacy values (PASI and Static Physician's Global Assessment) corresponding to each PK/ADA sampling visit were summarized as observed data when plotted with serum trough concentrations for the PK population. Clinical response was also assessed for subgroups of patients in serum trough concentration quartiles as the number of patients, percentage of patients, and 95% confidence intervals in each quartile subgroup achieving PASI 75 or Static Physician's Global Assessment 0/1. Serum trough quartiles were Q1 (<2.18 μg/ml), Q2 (≥2.18 μg/ml, <3.20 μg/ml), Q3 (≥3.20 μg/ml, <4.35 μg/ml), and Q4 (≥4.35 μg/ml). Mean percent PASI response from baseline was summarized using last observation carried forward. All other data were summarized using descriptive statistics.
CONFLICT OF INTEREST
KR has been an advisory board member, and/or speaker, and/or consultant, and/or has participated in clinical studies for AbbVie, Affibody, Amgen, Biogen, Boehringer Ingelheim, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, Leo Pharma, Eli Lilly and Company, Medac, Merck Sharp and Dohme Corp., Novartis, Ocean Pharma, Pfizer, Regeneron, Sanofi, Takeda, UCB Pharma, and Xenopoint. AB has served as a scientific adviser/c Clinical study investigator for AbbVie, Aclaris, Allergan, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly and Company, Genentech/Roche, GlaxoSmithKline, Janssen, Leo, Meiiji, Merck Sharp and Dohme, Novartis, Pfizer, Purdue Pharma, Regeneron, Sandoz, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, UCB, Valeant, and Vifor and as a paid speaker for Eli Lilly and Company, Janssen, Regeneron, and Sanofi Genzyme. KJ, SB, SG, LK, LC, and TMM own stock and are employees of Eli Lilly and Company.

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REFERENCES

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