Ixekizumab treatment for psoriasis: integrated efficacy analysis of three double-blinded, controlled studies (UNCOVER-1, UNCOVER-2, UNCOVER-3)*

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Summary

Background Ixekizumab, a high-affinity monoclonal antibody that selectively targets interleukin (IL)-17A, is approved for the treatment of moderate-to-severe psoriasis.

Objectives This analysis represents an overview of the efficacy outcomes from three phase III psoriasis studies.

Methods Data were integrated from the 12-week induction period of three studies in which patients received ixekizumab 80 mg every 2 weeks (IXE Q2W; n = 1169) or every 4 weeks (IXE Q4W; n = 1165) after an initial 160-mg dose for both; etanercept (50 mg biweekly; n = 740; two studies) or placebo (n = 792). The coprimary end points were the percentages of patients with response of static Physician’s Global Assessment (sPGA; score 0 or 1) and ≥ 75% improvement in baseline Psoriasis Area and Severity Index (PASI 75) at week 12. Response rates were compared between treatments using the Cochran–Mantel–Haenszel test stratified by study. Treatment comparisons with placebo included data from three studies, whereas etanercept comparisons were based on two studies.

Results Ixekizumab treatment was superior to placebo (P < 0.001) and etanercept (P < 0.001) on sPGA (0, 1) and PASI 75, with significant differences in PASI improvement at week 1. With IXE Q2W, at week 12, the frequencies of patients achieving PASI 75, 90 and 100 were nearly 90%, 70% and 40%, respectively. Ixekizumab–treated patients showed significantly greater improvement vs. placebo and etanercept in percentage body surface area involvement and fingernail psoriasis. IXE Q2W was superior to IXE Q4W on all treatment outcomes.

Conclusions Ixekizumab therapy at both dosing regimens demonstrated rapid onset and superior efficacy to placebo and etanercept, with IXE Q2W providing better outcomes than IXE Q4W during the first 12 weeks of treatment.

What’s already known about this topic?

- Study results have been reported from each of the pivotal phase III trials that compared two dose schedules of ixekizumab (a high-affinity anti-interleukin-17A...
Psoriasis is a common inflammatory skin disease characterized by red, scaly plaques that arise from a complex gene environment.\textsuperscript{1,2} Psoriasis is estimated to affect about 2–4\% of the population in Western countries,\textsuperscript{3} with rates varying across ethnic groups and geographical regions.\textsuperscript{3,4} Approximately 20\% of patients with psoriasis have moderate-to-severe disease and require systemic therapy to control its manifestations.\textsuperscript{5} The clinical manifestations of psoriasis and its comorbidities can be substantial and can negatively impact social relationships, mental health and work-related activities.\textsuperscript{6–8}

Several human genome studies have identified polymorphisms in immune-related genes, highlighting dysregulated cytokine networks as a possible aetiologic factor in the pathophysiology of psoriasis.\textsuperscript{9–12} Recent evidence has particularly implicated interleukin (IL)-17A as a cytokine integral to the pathogenesis of psoriasis.\textsuperscript{13–15}

Ixekizumab (IXE), a high-affinity monoclonal antibody that selectively targets IL-17A, is approved for the treatment of moderate-to-severe psoriasis. Three pivotal phase III studies have assessed the efficacy of IXE dose regimens compared with placebo (PBO), and two of the studies included the active comparator etanercept (ETN), a tumour necrosis factor-\(\alpha\) blocker.\textsuperscript{16,17} Etanercept was chosen as the active comparator because it is a commonly used, standard-of-care biological therapy, it is self-administered as a subcutaneous injection and it has a well-established safety and efficacy profile.

In this report, we provide an integrated overview of the efficacy outcomes from the IXE phase III programme, including comparisons with PBO and ETN. The integration not only allows for a comprehensive overview of the efficacy outcomes, but also allows for a comparison between the two IXE dose regimens during the 12-week induction period. We hypothesized that IXE would provide highly effective therapy for patients with moderate-to-severe plaque psoriasis that is superior to PBO and to ETN. In addition, we hypothesized that the response to IXE 80 mg every 2 weeks (Q2W) would be greater than the response to IXE 80 every 4 weeks (Q4W) across all efficacy measures.

**What does this study add?**

- We provide a comprehensive overview of ixekizumab therapy for moderate-to-severe plaque psoriasis by presenting integrated 12-week efficacy outcomes for two ixekizumab dosing regimens from the pivotal phase III studies.

**Patients and methods**

**Patients and study design**

Data were integrated from the 12-week induction phases of three phase III studies: UNCOVER-1, UNCOVER-2 and UNCOVER-3.\textsuperscript{16,17} Eligible patients (i) were aged \(\geq\) 18 years, (ii) had a diagnosis of chronic plaque psoriasis \(\geq\) 6 months before baseline (randomization), (iii) had involvement of \(\geq\) 10\% body surface area (BSA) at both screening and baseline visits, (iv) had at least moderate clinical severity as measured by a static Physician’s Global Assessment (sPGA; six-point scale) score of \(\geq\) 3, (v) had a Psoriasis Area and Severity Index (PASI) score of \(\geq\) 12 and (vi) were candidates for phototherapy, systemic therapy or both. Patients were randomized to receive IXE Q2W or IXE Q4W after an initial 160-mg dose, ETN (50 mg biweekly; in two of the three studies) or PBO.

Prior therapy with biologics was permitted with the exception of prior use of ETN, which was an exclusion criterion in UNCOVER-2 and UNCOVER-3. As aligned with other psoriasis phase III trials, there was no rescue therapy included. Patients were allowed to take mild topical corticosteroids for limited use on the face, axilla or genital areas; however, stronger topical corticosteroids were not allowed during the induction and maintenance treatment periods.

**Outcomes**

The studies assessed whether IXE Q2W or IXE Q4W was superior to PBO and noninferior or superior to ETN for two coprimary end points: the percentage of patients achieving sPGA scores of clear or minimal severity (0 or 1), and the percentage of patients achieving a reduction from baseline in PASI score of \(\geq\) 75\% (PASI 75) at week 12. Secondary end points included rates of higher clearance (PASI 90) and complete resolution of psoriasis plaques (sPGA 0, PASI 100), response rates for fingernail psoriasis measured by the Nail Psoriasis Severity Index (NAPSI 0) and improvement in percentage BSA involvement. In addition, we assessed the onset of efficacy in mean PASI improvement and time to achieving PASI 50 and 75.

Safety assessments were included in each of the studies. For this report, we provide an overview of the adverse events (AEs) observed in each treatment group and the percentage of discontinuations due to AEs.

**Statistical analyses**

Two datasets were defined for the integrated analyses through week 12: (i) a PBO-controlled integrated analysis set including
patient data from the IXE and PBO treatment arms from UNCOVER-1, -2 and -3; and (ii) the active-controlled integrated analysis set, which included patient data from the ETN group within the UNCOVER-2 and -3 studies. The integrated efficacy analyses were conducted on the randomized patients according to the assigned treatment regardless of compliance (intention to treat). Safety analyses were conducted on all randomized patients who received at least one dose of study treatment.

Treatment comparisons for categorical responses were based on the Cochran–Mantel–Haenszel (CMH) test stratified by study. Missing data were imputed using nonresponder imputation. Therefore, early discontinuations were considered treatment failures. Change-from-baseline analyses for BSA were conducted using a mixed-effects model of a repeated-measures model, including treatment, study, baseline value, visit and the interaction of treatment by visit as fixed factors. Times to first PASI 50 and PASI 75 were analysed using Kaplan–Meier estimates. Treatment comparisons were performed using the log-rank test stratified by study. A cumulative response plot of PASI percentage improvement at week 12 vs. percentage of patients was provided. Patient disposition and AEs were summarized and compared using the CMH test stratified by study.

The figures and tables in this paper present integrated data across all treatment arms and studies. For the majority of analyses, the PBO and IXE results are from the PBO-controlled integrated analysis set (UNCOVER-1, -2 and -3), whereas the ETN results are from the active-controlled integrated analysis set (UNCOVER-2 and -3). For mean change from baseline to week 12 in percentage BSA improvement and the percentage change from baseline in PASI score, the PBO, ETN and IXE results are from the active-controlled integrated analysis set.

These studies were registered with ClinicalTrials.gov: numbers NCT01474512 (UNCOVER-1), NCT01597245 (UNCOVER-2) and NCT01646177 (UNCOVER-3).

Results

Demographics, baseline clinical characteristics and disease severity

A total of 3866 patients were randomized to treatment in the three phase III studies from 21 countries. During the 12-week induction phase, 1169 patients were treated with IXE 80 mg Q2W, 1165 patients with IXE 80 mg Q4W, 740 patients with ETN and 792 patients with PBO.

The baseline patient demographics, patient characteristics and disease severity were consistent across the four treatment groups (Table 1). On average, the patients were aged approximately 46 years, with the majority being white (93%) and male (68%). Patients reported a mean duration of psoriasis of 19 years, with 55% reporting previous nonbiological systemic therapy, 26% reporting previous biological therapy and 44% reporting phototherapy. The patients had a mean PASI score of 20, a mean NAPSI score of 26 and a mean BSA involvement of 27%.

Patient disposition

The majority of patients (95%) completed the induction phase. There were no significant differences among the treatment groups for early study discontinuation. A significantly greater percentage of patients in the PBO group discontinued due to a lack of efficacy compared with the IXE treatment arm from two studies: UNCOVER-2 and -3. Previous nonbiological systemic therapy includes methotrexate, ciclosporin, retinoids, other nonbiological systemic agents and psoralen–ultraviolet A.

| Variable                                      | PBO (n = 792) | ETN (n = 740) | IXE Q2W (n = 1165) | IXE Q4W (n = 1169) | Total (n = 3866) |
|-----------------------------------------------|---------------|---------------|-------------------|-------------------|-----------------|
| Age (years), mean ± SD                        | 46.2 ± 12.8   | 45.5 ± 13.3   | 45.4 ± 13.1       | 45.1 ± 12.9       | 45.5 ± 13.0     |
| Male, n (%)                                   | 560 (70.7)    | 505 (68.2)    | 791 (67.9)        | 766 (65.5)        | 2622 (67.8)     |
| Race – white, n (%)                           | 726 (91.7)    | 682 (92.7)    | 1072 (92.3)       | 1092 (93.5)       | 3572 (92.6)     |
| Weight (kg), mean ± SD                        | 91.6 ± 23.5   | 92.5 ± 23.4   | 92.1 ± 23.5       | 90.8 ± 22.7       | 91.7 ± 23.2     |
| BSA involvement (%), mean ± SD                | 27.7 ± 17.8   | 26.8 ± 16.6   | 27.6 ± 16.6       | 27.2 ± 17.1       | 27.3 ± 17.0     |
| PASI, mean ± SD                               | 20.6 ± 8.5    | 19.9 ± 7.5    | 20.4 ± 7.5        | 20.1 ± 7.9        | 20.2 ± 7.8      |
| NAPSI, mean ± SD                              | 26.3 ± 20.4   | 27.6 ± 20.5   | 24.6 ± 19.0       | 25.6 ± 19.7       | 25.8 ± 19.8     |
| sPGA, mean ± SD                               | 3.6 ± 0.6     | 3.5 ± 0.6     | 3.6 ± 0.6         | 3.5 ± 0.6         | 3.6 ± 0.6       |
| Psoriasis duration (years), mean ± SD         | 19.1 ± 12.1   | 18.5 ± 12.1   | 18.9 ± 12.4       | 18.8 ± 12.1       | 18.8 ± 12.2     |
| Previous psoriasis therapy, n (%)             | 416 (52.5)    | 388 (52.4)    | 643 (55.2)        | 662 (56.6)        | 2109 (54.6)     |
| Nonbiological systemic therapy                 | 257 (32.4)    | 136 (18.4)    | 311 (26.7)        | 315 (26.9)        | 1019 (26.4)     |
| Phototherapy                                  | 319 (40.3)    | 330 (44.6)    | 519 (44.5)        | 515 (44.1)        | 1683 (43.5)     |

BSA, body surface area; PASI, Psoriasis Area and Severity Index; NAPSI, Nail Psoriasis Severity Index; sPGA, static Physician’s Global Assessment; PBO, placebo; ETN, etanercept; IXE Q2W, ixekizumab 80 mg every 2 weeks; IXE Q4W, ixekizumab 80 mg every 4 weeks. ETN treatment arm is from two studies: UNCOVER-2 and -3. Previous nonbiological systemic therapy includes methotrexate, ciclosporin, retinoids, other nonbiological systemic agents and psoralen–ultraviolet A.
groups (Table 2), whereas the two IXE treatment groups were similar with regard to reasons for early discontinuation.

**Improvement in disease severity**

Both IXE treatment groups were superior to PBO on the coprimary end points of PASI 75 and sPGA 0 or 1 (P < 0.001) (Figs 1, 2). Each IXE treatment group was also superior to ETN with regard to PASI 75 and sPGA 0 or 1 (P < 0.001) (Figs 1, 2). Clinical response rates for sPGA and PASI at 12 weeks are provided in Table S1 (see Supporting Information).

Both IXE treatment groups were superior to PBO in achieving a high level of clinical response and complete resolution of psoriatic plaques, as measured by PASI 90, PASI 100 and sPGA 0 (P < 0.001) (Figs 1, 2). Each IXE treatment group was also superior to ETN in achieving a high level of clinical response and complete resolution of psoriatic plaques (P < 0.001) (Figs 1, 2).

Mean improvements from baseline to week 12 in percentage BSA involvement for patients treated with IXE Q2W or IXE Q4W were significantly greater than in patients treated with PBO or ETN. The least-squares mean changes ± SE from baseline were PBO −0.1 ± 0.73, ETN −14.4 ± 0.51, IXE Q4W −21.8 ± 0.51 and IXE Q2W −21.9 ± 0.51; P < 0.001 for all comparisons; only in studies with an ETN comparator. Similar results were seen in the PBO-controlled integrated studies (data not shown).

Both IXE treatment groups had significantly greater response rates for NAPSI 0 compared with PBO or ETN, indicating greater improvement in fingernail psoriasis. The response rates for NAPSI 0 at week 12 were as follows: PBO 4.9%, ETN 10.3%, IXE Q4W 14.8% and IXE Q2W 16.6% (P < 0.001 vs. PBO; P ≤ 0.01 vs. ETN).

**Early onset of efficacy**

IXE demonstrated statistically significant separation from PBO and ETN as early as week 1 in mean improvement in PASI score (Fig. 3). Mean changes in PASI were significantly greater and occurred earlier in patients treated with IXE compared

### Table 2: Study treatment discontinuation, intention-to-treat population

| Variable                                | PBO (n = 792) | ETN (n = 740) | IXE Q4W (n = 1165) | IXE Q2W (n = 1169) |
|-----------------------------------------|--------------|--------------|--------------------|--------------------|
| Number of patients (%)                  | 748 (94-4)   | 702 (94-9)   | 1096 (94-1)        | 1120 (95-8)        |
| Completed period                         | 44 (5-6)     | 38 (5-1)     | 69 (5-9)           | 49 (4-2)           |
| Discontinued from period                 |              |              |                    |                    |
| Reasons for discontinuation, n (%)      |              |              |                    |                    |
| Adverse event                            | 9 (1-1)      | 9 (1-2)      | 24 (2-1)           | 22 (1-9)           |
| Protocol violation                       | 6 (0-8)      | 7 (0-9)      | 19 (1-6)           | 9 (0-8)            |
| Patient decision                         | 11 (1-4)     | 10 (1-4)     | 16 (1-4)           | 11 (0-9)           |
| Lost to follow-up                        | 5 (0-6)      | 7 (0-9)      | 4 (0-3)            | 2 (0-2)            |
| Lack of efficacy                         | 10 (1-3)     | 3 (0-4)      | 4 (0-3)**          | 1 (0-1)*           |
| Investigator decision                   | 2 (0-3)      | 2 (0-3)      | 1 (0-1)            | 3 (0-3)            |
| Sponsor decision                         | 1 (0-1)      | 0 (0)        | 1 (0-1)            | 1 (0-1)            |

PBO, placebo; ETN, etanercept; IXE Q2W, ixekizumab 80 mg every 2 weeks; IXE Q4W, ixekizumab 80 mg every 4 weeks. *ETN treatment arm is from two studies: UNCOVER-2 and -3. *P = 0.001 vs. PBO; **P < 0.05 vs. PBO.
with ETN or PBO, with a median time to onset of PASI 50 response of 2.1 weeks for IXE compared with 8.1 weeks for ETN.

Comparisons between ixekizumab dose regimens

In the PBO-controlled integrated analysis set, comparisons between the two IXE dosing regimens revealed significantly greater response rates for the coprimary end points of PASI 75 and sPGA 0 or 1 (P < 0.001 for both) and for the PASI 90 (P < 0.001), PASI 100 (P = 0.026) and sPGA 0 (P = 0.009) end points for patients in the IXE Q2W treatment group compared with those in the IXE Q4W treatment group (Fig. 4). Although numerically greater, the response rate of the IXE Q2W treatment group for NAPSI 0 did not differ significantly from the rate observed in the IXE Q4W treatment group (P = 0.35). There was no significant difference between IXE Q4W and IXE Q2W in the mean improvement in percentage BSA (P = 0.51).

Percentage improvement in Psoriasis Area and Severity Index at week 12

In contrast to categorical improvements in PASI, Figure 5 shows continuous improvement in PASI by a plot of the cumulative response of PASI percentage improvement over treatment weeks. The median improvements were 95.9%, 94.2%, 73.3% and 4.1% for IXE Q2W, IXE Q4W, ETN and PBO, respectively.

Safety profile

An overview of AEs from the 12-week induction phase is presented in Table 3. The percentage of patients reporting at least one treatment-emergent AE was similar between the IXE treatment groups and ETN and greater than with PBO. Events reported at a significantly greater frequency in the total IXE group compared with PBO were nonspecified injection-site reaction (ISR), injection-site erythema, nausea and oropharyngeal pain. Events reported significantly more frequently by IXE-treated patients than by ETN-treated patients were injection-site pain and nausea. ISRs led to discontinuation of study in 0.3% of IXE-treated patients and 0.4% of ETN-treated patients. Only two patients who received IXE used premedication for ISRs for future injections.

The rate of any Candida infection was 0.5% with PBO, 0.7% with ETN, 0.6% with IXE Q4W and 1.4% with IXE Q2W. Oral Candida or oral fungal infection occurred in 0.1% of patients treated with ETN, 0.2% of patients treated with IXE Q4W, 0.7% of patients treated with IXE Q2W and no patients treated with PBO. The rate of oral Candida was significantly greater for the IXE Q2W vs. the PBO group (P < 0.05).
Of the AEs reported by IXE-treated patients, 94-4% were rated as mild or moderate in severity, including events of ISR and oral Candida. The frequency of AEs reported as severe did not differ significantly between IXE treatment groups and PBO (Table 3). The percentage of patients reporting severe treatment-emergent AEs was significantly greater for ETN-treated patients than for IXE Q2W-treated patients (4.9% vs. 3.1%, respectively).

No significant differences were found between IXE treatment groups and PBO or between IXE treatment groups and ETN for the percentage of patients with at least one serious AE (Table 3). The rate of discontinuation due to AEs did not differ significantly among the treatment groups (Table 3).

Discussion

This integrated analysis of efficacy outcomes from the IXE phase III psoriasis programmes reinforces the significant findings from the individual studies demonstrating that IXE treatment is effective in improving psoriasis severity in patients with moderate-to-severe disease. In addition to reinforcing the efficacy demonstrated in the individual studies, the integrated analyses provide a reliable estimate of the overall efficacy outcomes expected with IXE therapy. With the IXE 80 mg Q2W dose regimen, nearly 90% of patients achieved the clinically meaningful response of PASI 75, 70% achieved PASI 90 and almost 40% had complete resolution of psoriasis (PASI 100). Furthermore, patients experienced substantial and meaningful improvements in associated symptoms, including reductions in BSA involvement and fingernail psoriasis. In contrast to the above rates for IXE, the rates of these outcomes for patients treated with ETN were 48% for PASI 75, 22% for PASI 90 and 6% for complete resolution. Significant differences between IXE treatment groups and ETN or PBO were evident as early as week 1, with the magnitude of these differences continuing to increase over the 12-week induction phase.

In addition, the integrated analyses allowed for comparison between the IXE Q4W and IXE Q2W dosing regimens during the induction treatment period. Administration of IXE Q2W resulted in better treatment outcomes than with IXE Q4W,
although both dosing regimens produced significantly better treatment outcomes than either PBO or ETN. Patients treated with IXE Q2W had significantly greater response rates for the coprimary end points of sPGA 0 or 1 and PASI 75 and for the secondary end points of PASI 90, PASI 100 and sPGA 0 compared with patients who were treated with IXE Q4W. Within the integrated analyses, both IXE dose schedules showed a similar safety profile to that shown in the individual studies, with the exception of oral Candida. Whereas there was no difference among treatment groups for any type of Candida infection, treatment with IXE Q2W was associated with a higher frequency of oral Candida compared with PBO; most oral infections were mild to moderate in severity and were managed with standard therapies. IL-17 plays a key role in host mucocutaneous defence against extracellular pathogens, including the yeast Candida albicans. The differences between the two induction doses of IXE in the percentage of patients experiencing treatment success were 6.8% [95% confidence interval (CI) 3.4–10.1] for sPGA 0 or 1, 7.1% (95% CI 4.2–9.9) for PASI 75, 6.5% (95% CI 2.7–10.4) for PASI 90 and 4.4% (95% CI 0.5–8.3) for PASI 100. The additional benefit provided with the highest dose of IXE corresponds to one additional patient reaching treatment success after induction treatment with the highest dose of IXE vs. the lowest dose for every 14 (95% CI 10–24) patients treated. In clinical practice, a physician could see each week approximately 20 patients with psoriasis who had moderate-to-severe disease, and who were candidates for biological therapy. Therefore the difference of efficacy between the lowest and the highest dose of IXE represents one to two additional patients experiencing treatment success every week. However, the clinical relevance of Q2W dosing during induction was based on the totality of evidence across induction and maintenance, in which Q2W dosing yielded significantly better outcomes on multiple measures after short-term treatment that were then maintained with long-term treatment of 80 mg Q4W dosing. The increased understanding of the pathophysiology of psoriasis has led to treatment advances, particularly biological therapies that selectively target key cytokines involved in psoriasis pathogenesis, including tumour necrosis factor-α, IL-23 and IL-17A. The efficacy and safety profiles vary among the biologics, with many patients not achieving optimal resolution of psoriasis, or experiencing slow onset of effect and diminishing efficacy over time with older biologics. IXE treatment provides a significant reduction of clinical symptoms of psoriasis within a short time in patients with moderate-to-severe disease. Compared with ETN, patients were five times more likely to achieve complete resolution of psoriasis within 12 weeks of starting IXE, while having similar safety outcomes. The majority of IXE-treated patients achieved minimal severity or complete clearance at 12 weeks, suggesting that this outcome becomes realistic for patients with plaque psoriasis. As treatments become more effective, these higher rates of clearance may be considered the expectation for treatment objectives.

Safety data also support IL-17A inhibition as a highly favourable therapeutic strategy in patients with psoriasis. The overall safety profile of IXE is consistent with expected outcomes associated with its mechanism of action. The most common events include infections and ISRs. Oral Candida was also associated with IXE Q2W induction therapy. IXE therapy was well tolerated as indicated by the low rate of discontinuation, and the similar rates of serious AEs across all treatment groups, including PBO. For further information on the safety profile of IXE therapy and its relationship with AEs of interest, the reader is directed to a recent publication of the outcomes from the integrated safety database across seven trials in psoriasis with IXE therapy.

This report focused on the integrated analysis of data from the 12-week induction phase of three phase III studies. Therefore, the outcomes reported are limited to this initial duration of treatment. The study population was primarily white and male, also limiting the generalizability of these results to other demographic populations. However, this integrated analysis of data has several strengths, including comparisons with PBO and an active comparator, ETN, as well as a large sample size (integrating data across three clinical studies), providing statistical power to compare IXE Q4W and IXE Q2W doses. The three phase III studies were conducted across multiple countries, representing a varied treatment population, and the inclusion criteria reflected most patients affected by moderate-to-severe plaque psoriasis.

In conclusion, consistently with the individual studies, the integrated analysis reported here replicates the rapid onset and the superiority of IXE treatment over ETN or PBO. The majority of patients achieved minimal disease severity, with approximately 40% achieving complete resolution of psoriasis after 12 weeks of IXE Q2W treatment. Patients treated with the IXE Q2W dosing regimen had significantly better treatment outcomes than those treated with IXE Q4W.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

Table S1 Clinical response rates for static Physician’s Global Assessment and Psoriasis Area and Severity Index at 12 weeks, nonresponder imputation.
Video S1. Author Video.
Powerpoint S1 Journal Club Slide Set.