**INTRODUCTION**

- Chronic plaque psoriasis (hereafter, psoriasis) is a persistent, chronic inflammatory skin disease, characterized by the presence of defined erythematosquamous plaques; it affects 2–4% of the global population.
- Disease severity is commonly measured using the Psoriasis Area and Severity Index (PASI), which assesses four body regions (face, truncal, and both arms and legs), and grading of the skin, on a scale ranging from 0 to 72. Efficacy is reported as percentage improvement; e.g. PASI 20 indicates a 20% improvement in PASI score.
- Symptoms and comorbidities associated with moderate-to-severe psoriasis result in impaired patient quality of life.
- Clinical studies have demonstrated a link between the degree of skin clearance, health-related quality of life (HRQoL), and productivity outcomes. Patients who achieve PASI 90 and PASI 100 have substantially greater improvements in HRQoL.
- A number of treatments are available for moderate-to-severe psoriasis, including several biologics; nonetheless, many patients do not achieve their treatment goals.
- Less than half of patients (45%) receiving biologic treatments report feeling very satisfied. 85% of patients feel there is a need for better therapies.
- Ixekizumab (Ikea) is a novel monoclonal antibody that binds with high affinity to interleukin 17A (IL-17A), which plays a key role in psoriasis plaque formation.
- Ixekizumab has shown significantly greater efficacy in comparison to placebo and adalimumab (Humira) in several clinical trials. However, data comparing the relative efficacy of ixekizumab to other biologics are not currently available.
- Given the scarcity of head-to-head trials, network meta-analysis (NMA) is a valuable decision maker for comparing effectiveness data for health technology assessment. For example, a previous NMA conducted by Rech et al. comparing the efficacy of biologic agents used in moderate-to-severe psoriasis, was used in an economic model to quantify the benefit of ustekinumab in a NICE submission.

**OBJECTIVE**

- The aim of this study was to determine the relative clinical efficacy of ixekizumab 80 mg every two weeks compared to other biologic treatments approved for moderate-to-severe psoriasis in EU.

**METHODS**

- Input data for the NMA were identified through a systematic literature review (SLR) of published and grey literature (January 1990 to Nov 2015). This review included phase II, III, and IV randomized controlled trials (RCTs) of relevant conventional systemic and biologic therapies in moderate-to-severe psoriasis.
- Only 28% of doses of comparators were used to ensure findings were relevant to real-world scenarios.  
  - Etanercept 50 mg QIW and adalimumab were not included in the base case analysis as they are not recommended by NICE.
  - Although the same induction dose of ixekizumab 80 mg was used every fourth week (Q4W) induction dose was also analyzed in pivotal clinical trials. These dose were included in the NMA to highlight the improved outcomes achieved with the ixekizumab Q4W dosing regimen.
- PASI score improvements of ≥ 50%, ≥ 75%, ≥ 90%, and 100% (PASI 50, 75, 90, and 100) were included as efficacy outcomes in the NMA, at the end of the respective, drug-specific induction period.
- Due to a lack of long-term placebo-controlled RCT data the NMA was limited to induction dosing periods only (i.e. first 12 weeks of treatment for all comparators, except for infliximab and adalimumab, for which weeks 12 and weeks 168 data were used, respectively).
- In line with NICE recommendations, the base-case analysis used a random-effects, conditional multivariate hierarchical probability model to estimate the mean treatment effect (MTE) across all four PASI cut-offs.
- A wide range of sensitivity analyses were designed to test the robustness of the base case analysis.
- Numbers needed to treat (NNT) were calculated based on the risk difference calculated from a multivariate logistic model with a placebo control risk.
- The comparability of the studies included in the NMA was explored by a comparison of baseline characteristics (i.e. RCT design, patient characteristics, disease severity, etc.). Cochran’s Q test was used to test for heterogeneity in the RCTs included in the evidence network. A net health benefit was used for consistency evaluation on the network of pairwise treatments included in the NMA.

**RESULTS**

- The following results reflect the base case PASI network diagram (see Figure 1). Lines are weighted by the absolute and relative risk data.

**Figure 1. Full network diagram for the PASI base case NMA**

- ixekizumab 80 mg Q2W had the highest likelihood (96.2%) of being the best therapy in the base case followed by ixekizumab 80 mg Q4W with a probability of 74% of being the second best therapy (see Figure 2).
- The probabilities of the various therapies of achieving each of the different PASI levels were derived using probit analysis (Figure 4–6). The point estimates of achieving one of the PASI cut-off values were consistently higher for ixekizumab 80 mg Q2W, when compared to the other therapies included in the base case, thus corroborating the results of the MTD analysis.

**Figure 2. MTDs of achieving a given PASI relief at week 12 (ixekizumab 80 mg Q2W as the reference)**

- Sensitivity analyses conducted to test the robustness of the base case network are shown in Table 2.
  - The results of these analyses were consistent with the base case results.

**Figure 3. Rankogram for the PASI base case NMA**

- Finally, none of the diagnostic tests, outlined in the methodology section, detected any significant heterogeneity, inconsistencies or autocorrelation issues. Cochrane’s Q test led to significant heterogeneity was not significant for the base case (NMA Table 2), and the net health plot did not highlight any inconsistencies (Figure 5).

**Table 3. Cochran’s Q as a heterogeneity test for the base case NMA**

**CONCLUSIONS**

- The results of the base case and the sensitivity analyses consistently demonstrated that ixekizumab 80 mg Q2W was superior to other biologic treatments currently available for moderate-to-severe psoriasis in Europe.
- The MTD results demonstrated the robustness of the analyses and further corroborated ixekizumab 80 mg Q2W being the best treatment among comparators included.
- In the rankogram, ixekizumab 80 mg Q2W had the highest probability of achieving a PASI response across all thresholds; this included PASI 90 and 100, which have been linked to significant improvements in HRQoL.
- One limitation of the NMA was that it was based on induction dosing period only. A lack of long-term placebo-controlled RCT data measurement that the relative efficacy of ixekizumab 80 mg Q2W could not be analysed over prolonged time-frames.
- The NMA was also limited by the absence of head-to-head data for ixekizumab versus a newer biologic treatment, which would allow comparison (and validation) of estimates from indirect comparisons. This can be addressed once data from the IXORA-S trial, which directly compares the efficacy of ixekizumab 80 mg Q2W versus ustekinumab (approved dose), are available.

**REFERENCES**