Network meta-analysis to evaluate the efficacy of ixekizumab in the treatment of moderate-to-severe psoriasis

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INTRODUCTION

- Chronic plaque psoriasis (hereafter, psoriasis) is a persistent, chronic inflammatory skin disease, characterised by the presence of defined erythematosquamous plaques; it affects 2–4% of the global population.[1]
- Disease severity is commonly measured using the Psoriasis Area and Severity Index (PASI), which assesses four body regions for redness, thickness, and scaling of the skin, on a scale ranging from 0 to 72. Efficacy is reported as percentage improvement; e.g. PASI 75 indicates ≥ 75% improvement in PASI score.[2]
  - Symptoms and comorbidities associated with moderate-to-severe psoriasis result in impaired patient quality of life.[3-8]
  - 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.[9]
- A number of treatments are available for moderate-to-severe psoriasis, including several biologics;[10] nonetheless, many patients do not achieve their treatment goals.[11,12]
  - Less than half of patients (45%) receiving biologic treatments report feeling very satisfied; 85% of patients feel there is a need for better therapies.[3]
- Ixekizumab (Taltz®) is a new monoclonal antibody that binds with high affinity to interleukin 17A (IL-17A),[13] which plays a key role in psoriasis plaque formation.
- Ixekizumab has shown significantly greater efficacy in comparison to placebo and etanercept 50 mg twice a week (BIW) in pivotal UNCOVER trials.[14] 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 widely accepted by decision makers for generating comparative efficacy data for health technology assessment. For example, a previous NMA conducted by Reich *et al.*,[15] 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 (Q2W) versus other biologic treatments approved for moderate-to-severe psoriasis in Europe.

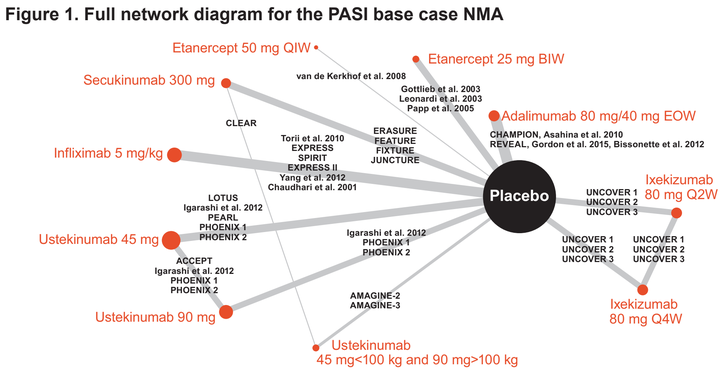
METHODS

- Input data for the NMA were identified through a systematic literature review (SLR) of published and grey literature (Jan 1990 to Nov 2015). This review included phase II, III, and IV randomised controlled trials (RCTs) of relevant conventional systemic and biologic therapies in moderate-to-severe psoriasis.
- Only EMA-approved doses of comparators were used to ensure findings were relevant to real-world scenarios.
  - Etanercept 50 mg BIW and apremilast were not included in the base case analysis as they are not recommended by NICE.
  - Although the approved induction dose for ixekizumab is 80 mg Q2W, a less frequent every fourth week (Q4W) induction dose was also analysed in pivotal clinical trials. These data were included in the NMA to highlight the improved outcomes achieved with the Q2W induction 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 week 10 and week 16 data were used, respectively).
- In line with NICE recommendations, the base-case analysis used a random-effects, conditional multinomial likelihood probit-link model to estimate the mean treatment difference (MTD) across all four PASI cut-offs.[16]
- A wide range of sensitivity analyses were designed to test the robustness of the base case network.
- Numbers needed to treat (NNT) were calculated based on the risk difference calculated from a multinomial likelihood with a probit link model.
- The comparability of the studies included in the NMA was explored by a comparison of baseline criteria (RCT design, patient characteristics, disease severity, etc.). Cochrane's Q test was used to test for heterogeneity in the RCTs included in the evidence network. A net heat map was used for consistency evaluation on the network of psoriasis treatments included in the NMA.[17]

RESULTS

- The following results reflect the base case PASI network diagram (see Figure 1); lines are weighted by the number and size of the studies.

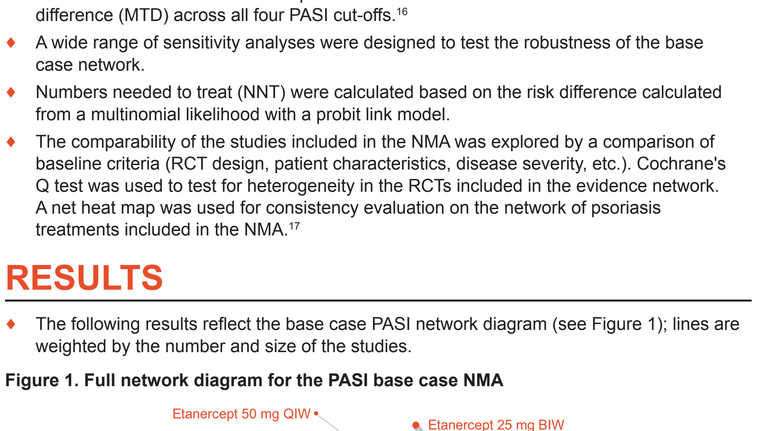
Figure 1. Full network diagram for the PASI base case NMA



Note: Week 12 data used for all treatments, except infliximab and adalimumab, for which week 10 and week 16 data were included, respectively. BIW=Twice a week dosing regimen; EOW=Every other week dosing regimen; PASI=Psoriasis Area Severity Index; Q2W=Every second week dosing regimen; Q4W=Every fourth week dosing regimen; QIW=Once weekly dosing regimen.

- Results from the NMA include MTD across all PASI levels based on the probit link model. Estimates of MTD demonstrated that ixekizumab 80 mg Q2W was more efficacious than each of the comparators included in the base case (as shown in Figure 2).

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

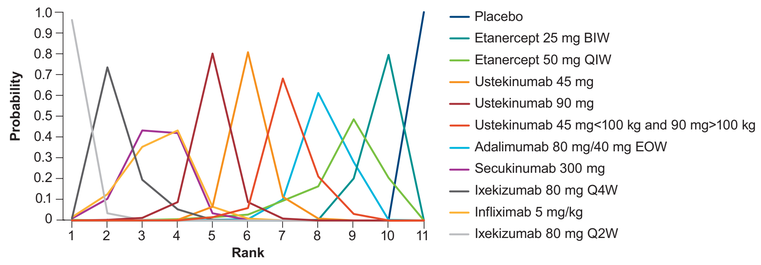


Ixekizumab 80 mg Q4W was excluded from this analysis.

BIW=Twice a week dosing regimen; EOW=Every other week dosing regimen; IXE=Ixekizumab; LCL=Lower credibility interval; MTD=Mean treatment difference on the Z score scale for PASI 50/75/90/100; Q2W=Every second week dosing regimen; QIW=Once weekly dosing regimen; UCL=Upper credibility interval.

- Ixekizumab 80 mg Q2W had the highest likelihood (96.3%) 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 3).

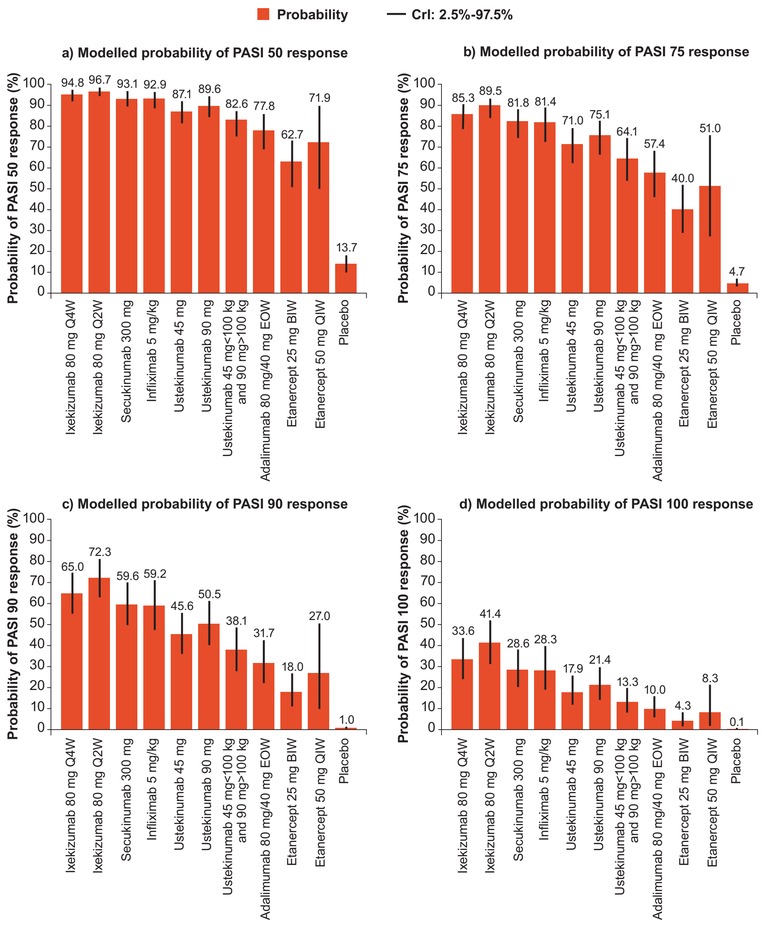
Figure 3. Rankogram for the PASI base case NMA



BIW=Twice a week dosing regimen; EOW=Every other week dosing regimen; PASI= Psoriasis Area Severity Index; Q2W=Every second week dosing regimen; Q4W=Every fourth week dosing regimen; QIW=Once weekly dosing regimen.

- The probabilities of the various therapies of achieving each of the different PASI levels were derived using probit analyses (Figure 4a–d). The point estimates of achieving one of the PASI cut-off values were consistently highest 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 4. Modelled PASI probability response distribution for all biologics included in the base case network based on a Bayesian NMA[16]



BIW=Twice a week dosing regimen; CrI=Credible intervals; EOW=Every other week dosing regimen; PASI=Psoriasis Area Severity Index; PASI 50=≥50% improvement in Psoriasis Area and Severity Index; PASI 75=≥75% improvement in Psoriasis Area and Severity Index; PASI 90=≥90% improvement in Psoriasis Area and Severity Index; PASI 100=100% improvement in Psoriasis Area and Severity Index; Q2W=Every second week dosing regimen; Q4W=Every fourth week dosing regimen; QIW=Once weekly dosing regimen.

- Numbers needed to treat (NNT) are lower for ixekizumab 80 mg Q2W compared to other treatments included in the NMA, for all PASI thresholds (as shown in Table 1).

Table 1. Number needed to treat per PASI (placebo as the reference) score

	PASI 50			PASI 75			PASI 90			PASI 100		
		CrI			CrI			CrI			CrI	
	NNT	2.5%	97.5%	NNT	2.5%	97.5%	NNT	2.5%	97.5%	NNT	2.5%	97.5%
Ixekizumab 80 mg Q2W	1.21	1.17	1.25	1.18	1.13	1.25	1.41	1.26	1.61	2.46	1.93	3.19
Ixekizumab 80 mg Q4W	1.23	1.19	1.28	1.24	1.17	1.34	1.57	1.37	1.85	3.05	2.29	4.10
Secukinumab 300 mg	1.26	1.22	1.31	1.30	1.21	1.41	1.72	1.47	2.04	3.60	2.64	4.87
Infliximab 5 mg/kg	1.26	1.21	1.33	1.31	1.20	1.45	1.74	1.44	2.14	3.67	2.53	5.28
Ustekinumab 45 mg	1.36	1.30	1.44	1.51	1.37	1.71	2.27	1.85	2.84	5.82	4.04	8.37
Ustekinumab 90mg	1.32	1.26	1.39	1.43	1.30	1.60	2.04	1.68	2.54	4.87	3.40	7.01
Ustekinumab 45 mg<100 kg and 90 mg>100 kg	1.46	1.35	1.59	1.70	1.47	2.00	2.75	2.11	3.64	7.95	5.05	12.35
Adalimumab 80 mg/40 mg EOW	1.57	1.42	1.76	1.92	1.60	2.36	3.35	2.43	4.66	10.82	6.42	17.85
Etanercept 25 mg BIW	2.06	1.72	2.57	2.90	2.16	4.01	6.20	3.93	9.79	26.80	13.46	50.65
Etanercept 50 mg QIW	1.78	1.32	2.71	2.34	1.42	4.25	4.59	2.02	10.47	18.07	4.70	54.87

BIW=Twice a week dosing regimen; CrI=Credible interval; EOW=Every other week dosing regimen; NNT=Number Needed to Treat; PASI=Psoriasis Area Severity Index; PASI 50=≥50% improvement in Psoriasis Area and Severity Index; PASI 75=≥75% improvement in Psoriasis Area and Severity Index; PASI 90=≥90% improvement in Psoriasis Area and Severity Index; PASI 100=100% improvement in Psoriasis Area and Severity Index; QIW=Once weekly dosing regimen; Q2W=Every second week dosing regimen; Q4W=Every fourth week dosing regimen.

- 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.

Table 2. Results of the NMA sensitivity analyses (probability of ranking 1st, 2nd and 3rd best therapy)

Sensitivity analysis	1st therapy	2nd therapy	3rd therapy
1. "Placebo-controlled" studies	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Secukinumab 300 mg
2. Time points – 12 weeks data versus 16 weeks data		Ixekizumab 80 mg Q4W	Secukinumab 300 mg
3. Study differentiation / effect modification based on patients' weight		Ixekizumab 80 mg Q4W	Secukinumab 300 mg
4. Study differentiation / effect modification based on dosing (secukinumab)		Ixekizumab 80 mg Q4W	Secukinumab 300 mg
5. Exclusion of Asian studies		Ixekizumab 80 mg Q4W	Secukinumab 300 mg
6. Biologics and systemic therapies		Ixekizumab 80 mg Q4W	Infliximab 5 mg/kg
7. Ixekizumab 80 mg Q4W dosing regimen excluded from sensitivity analysis 6		Secukinumab 300 mg	Infliximab 5 mg/kg
8. Biologics (excluding etanercept 50 mg BIW and apremilast) + systemic therapies (methotrexate and ciclosporin)		Ixekizumab 80 mg Q4W	Secukinumab 300 mg
9. Sensitivity analysis 8 + etanercept 50 mg BIW		Ixekizumab 80 mg Q4W	Secukinumab 300 mg
10. Sensitivity analysis 8 + apremilast		Ixekizumab 80 mg Q4W	Secukinumab 300 mg
11. Sensitivity analysis 8 + brodalumab		Ixekizumab 80 mg Q4W	Brodalumab 210 mg
12. Sensitivity analysis 8 + brodalumab + apremilast		Ixekizumab 80 mg Q4W	Brodalumab 210 mg
13. Ixekizumab (80 mg Q2W or 80 mg Q4W) + systemic therapies (methotrexate / ciclosporin)		Ixekizumab 80 mg Q4W	Ciclosporin 2.5 mg/kg/day
14. As the different dosing schedules of etanercept with 25 mg BIW and 50 mg QIW should result in similar clinical efficacy the two dosages were pooled in sensitivity analysis 14 to analyse the impact on the base case results (etanercept 25 mg BIW and etanercept 50 mg QIW as one etanercept treatment arm)		Ixekizumab 80 mg Q4W	Secukinumab 300 mg

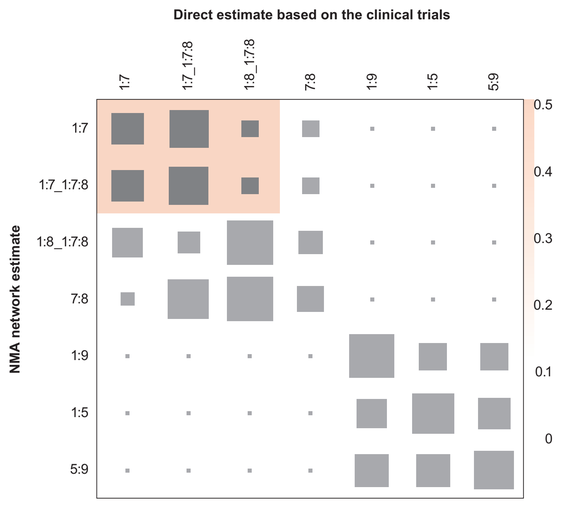
BIW=Twice a week dosing regimen; Q2W=Every second week dosing regimen; Q4W=Every fourth week dosing regimen; QIW=Once weekly dosing regimen.

- Finally, none of the diagnostic tests, outlined in the methodology section, detected any significant heterogeneity, inconsistencies or autocorrelation issues. Cochrane's Q test to assess heterogeneity was not significant for the base case NMA (Table 3), and the net heat plot did not highlight any inconsistencies (Figure 5).[17]

Table 3. Cochrane's Q as a heterogeneity test for the base case NMA

	Cochrane's Q	Degrees of freedom	p-value
Whole network	26.54	27	0.4889
Within-designs	25.73	24	0.3668
Between-designs	0.81	3	0.8481

Figure 5. Net heat plot for consistency evaluation of the full network of treatments in the NMA



1=Placebo, 2=Adalimumab 80 mg/40 mg EOW, 3=Etanercept 25 mg BIW, 4=Etanercept 50 mg QIW, 5=Secukinumab 300 mg, 6=Infliximab 5 mg/kg, 7=Ustekinumab 45 mg, 8=Ustekinumab 90 mg, 9=Ustekinumab 45 mg<100 kg and 90 mg>100 kg, 10=Ixekizumab 80 mg Q4W, 11=Ixekizumab 80 mg Q2W.

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 being the best therapy.
- 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 patient HRQoL.[9]
- One limitation of the NMA was that it was based on induction dosing period data only. A lack of long-term placebo-controlled RCT data data meant 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 doses), are available.

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