SUBMISSION TO POST-MARKET REVIEW OF USE OF BIOLOGICS IN THE TREATMENT OF SEVERE CHRONIC PLAQUE PSORIASIS

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ABBREVIATIONS

ADA	Adalimumab
BIW	Twice weekly
CI	Confidence interval
EOW / eow	Every other week
ETN	Etanercept
INF	Infliximab
IXE	Ixekizumab
LD	Loading dose
Log	Logarithmic
OR	Odds ratio
PASI	Psoriasis Area and Severity Index
PASI75	75% improvement in PASI
PBO	Placebo
OW	Once weekly
RD	Risk difference
RR	Relative risk
SEC	Secukinumab
UST	Ustekinumab
Wks	weeks
Wkly	weekly

Pfizer Australia welcomes the opportunity to provide an amended submission to the post-market review (hereinafter called the review) of biologics for severe chronic plaque psoriasis (CPP). These amendments are as a consequence of the inclusion of secukinumab and ixekizumab in the review as well as reference to Pfizer as a sponsor of a brand of infliximab. In addition, the latest Medicare 1 in 10 data are included.

PBS-listings of biologics for the treatment of CPP

Biologics currently listed on the Pharmaceutical Benefits Scheme (PBS) for CPP, including the basis of their listing, are included in **Figure 1 and Table 1**. As shown, efalizumab, which is no longer marketed was the first PBS-listed biologic. This was followed by:

- etanercept on the basis of cost-minimisation to efalizumab;
- infliximab on the basis of cost-effectiveness to both efalizumab and etanercept;
- adalimumab on the basis of cost-minimisation to etanercept; and
- ustekinumab on the basis of cost-effectiveness to etanercept.

More recently secukinumab was PBS-listed on the basis of cost-minimisation to adalimumab. This was followed by ixekizumab which was listed based on cost-minimisation to the least costly bDMARD (ixekizumab PSD page 15).

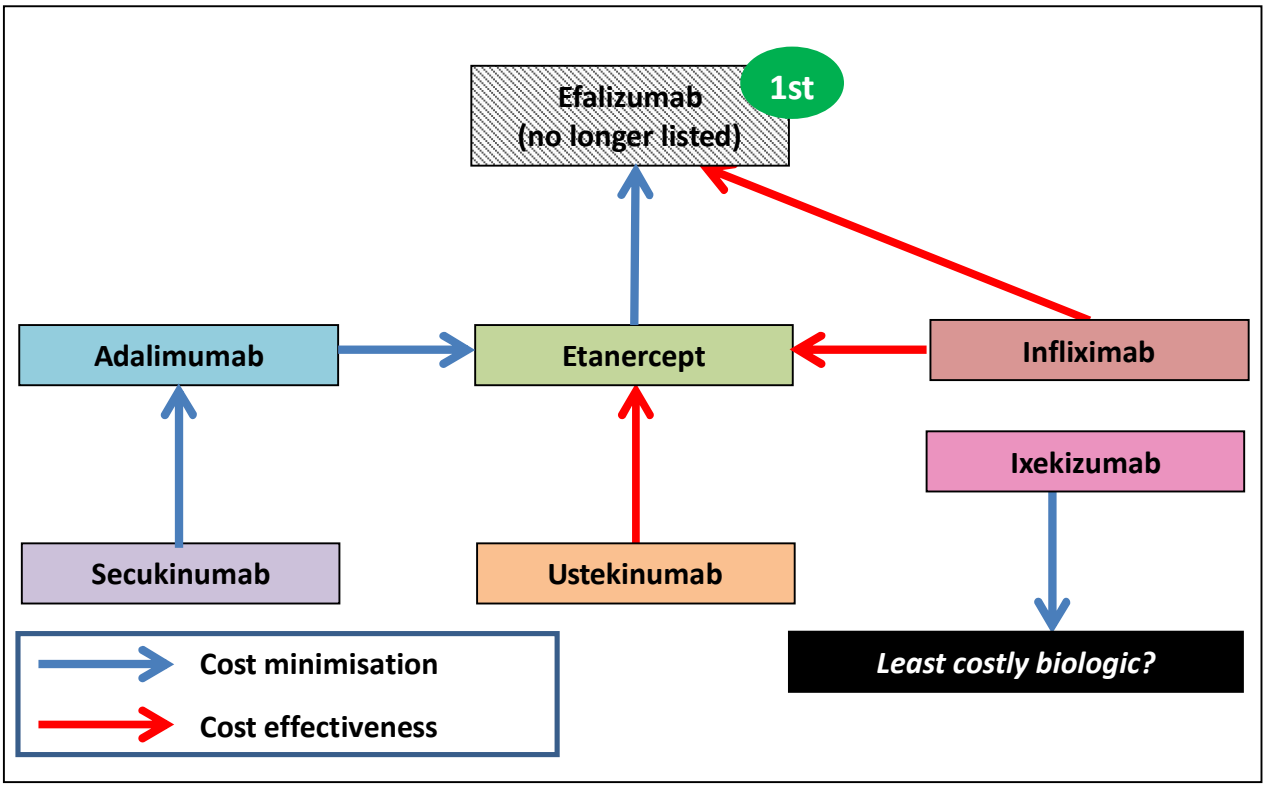


Figure 1: Biologics for severe chronic plaque psoriasis

Table 1: PBS-listing of biologics for PsO

Product	Basis of PBS-listing	Dosing relativities	Dosages in submission	Date of PBS-listing
Etanercept	Cost-minimisation to efalizumab	Etanercept 50 mg weekly (50 mg once weekly or 25 mg twice weekly)		1 August 2006
Infliximab	Cost-effectiveness to efalizumab and etanercept		Infliximab 5 mg/kg at day 0 then at 2 and 6 weeks,	1 December 2007

Product	Basis of PBS-listing	Dosing relativities	Dosages in submission	Date of PBS-listing
			then every 8 weeks	
Adalimumab	Cost-minimisation to etanercept	Adalimumab initial dose 80 mg, then 40 mg fortnightly starting one week after initial dose		1 June 2009
Ustekinumab	Cost-effectiveness to etanercept		45 mg at Weeks 0 and 4 then every 12 weeks thereafter. Alternative for patients ≥100 kg may be: 90 mg at Weeks 0 and 4, then every 12 weeks thereafter	1 March 2010
Secukinumab	Cost-minimisation to adalimumab	Secukinumab, 300 mg with initial dosing at weeks 0, 1, 2, and 3, then maintenance dosing of 300 mg every 4 weeks starting at week 4		1 September 2015
Ixekizumab	Cost-minimisation to least costly bDMARD	Ixekizumab, initial dose 160 mg, then 80 mg fortnightly from weeks 2 to 12, then 80 mg every 4 weeks		1 February 2017

Responses to the terms of reference for the review

1. ***Review current clinical guidelines for the treatment of severe chronic plaque psoriasis and compare to the Pharmaceutical Benefits Scheme (PBS) restrictions for use of biologics in this indication.***

A literature search was performed to identify clinical guidelines for the treatment of severe chronic plaque psoriasis.

American, Canadian and UK guidelines were identified, however, Australian guidelines are not available. The American, Canadian and UK Guidelines were generated between 2008 and 2010. Therefore they appear outdated. The American and Canadian Guidelines do not include ustekinumab, secukinumab and ixekizumab.

American Guidelines (Menter et al, 2008) and Canadian Guidelines (Canadian Dermatology Association, 2009; Papp et al, 2011) recommend biologics (adalimumab, etanercept, infliximab, alefacept) for moderate to severe plaque psoriasis.

UK Guidelines (NHS, 2010) recommend biologics (adalimumab, etanercept, infliximab and ustekinumab) for patients with severe psoriasis who fail to respond to have a contraindication to or are intolerant of phototherapy and systemic therapies, including ciclosporin and methotrexate, should be offered biologic therapy unless they have contraindications or are at increased risk of hazards from these therapies.

Therefore PBS restrictions differ from the American and Canadian Guidelines in only recommending biologics for severe psoriasis whereas these guidelines recommend biologics for moderate to severe psoriasis. However, they are similar to the UK guidelines which recommend biologics for severe psoriasis only.

2. Review and evaluate recent clinical evidence on the efficacy and safety of biologics used in the treatment of severe chronic plaque psoriasis and compare to the evidence considered by Pharmaceutical Benefits Advisory Committee (PBAC) in previous sponsor submissions.

Introduction

A network meta-analysis (mixed treatment comparison; MTC) of the biologics which are PBS-listed for severe CPP was performed to investigate the relative efficacy of biologics for severe CPP. A literature search was performed to identify the relevant publications reporting on the above-mentioned biologics for severe CPP. The inclusion criteria are outlined in **Table 2**.

Table 2: Inclusion and criteria for the MTC of biologics in severe CPP

Inclusion criteria
• Adalimumab or etanercept or infliximab or ustekinumab or secukinumab or ixekizumab; • RCTs; • Moderate to severe or severe CPP*; • Clinical endpoint of PASI75; • 12 week results for PASI75 reported or could be read off graph

**Note most publications were for moderate to severe CPP*

Abbreviations: CPP, chronic plaque psoriasis; PASI, psoriasis area and sensitivity index; PASI75, 75% reduction in PASI score; RCTs, randomised controlled trials

Studies included in MTC

The trials which were identified for inclusion in the MTC are included in **Table 3**.

Table 3: RCTs of biologics PBS-listed for severe CPP

Trial identifier	Population
Adalimumab	
Asahina 2010	Asahina A, Nakagawa H, Etoh T, Ohtsuki M, The Adalimumab M04-688 Study Group. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: Efficacy and safety results from a Phase II/III randomized controlled study. Journal of Dermatology, 2010; 37:299-310.
Cai 2017	Cai L, Gu H, Zheng J, Wang G, Zheng M, Wang G, Xi L-Y, Hao F, Liu X-M et al. Efficacy and safety of adalimumab in Chinese patients with moderate-to-severe plaque psoriasis: results from a phase 3, randomized, placebo-controlled, double-blind study. JEADV, 2017, 31, 89–95.
Gordon 2006	Gordon KB, Langley RG, Leonardi C, Toth D, Menter MA, Kang S, Heffernan M, Bruce Miller, Hamlin R, Lim L, Zhong J, Hoffman R and Okun MM. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: Double-blind, randomized controlled trial and open-label extension study. J Am Acad Dermatol 2006; 55:598-606.
Gordon 2015	Gordon KB, Langley RG, Leonardi C, Toth D, Menter MA, Kang S, Heffernan M, Bruce Miller, Hamlin R, Lim L, Zhong J, Hoffman R and Okun MM. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: Double-blind, randomized controlled trial and open-label extension study. J Am Acad Dermatol 2006; 55:598-606.
Menter 2008	Menter A, Tyring SK, Gordon K, MD, Kimball AB, Leonardi CL, MD, Langley RG, Strober BE, Kaul M, Gu Y, Okun M and Papp K. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. J Am Acad Dermatol 2008; 58:106-15
Saurat 2008	Saurat J-H, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne J-P, Unnebrink K, Kaul M and Camez A for the CHAMPION Study Investigators. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). British Journal of Dermatology, 2008; 158:558-566.

Trial identifier	Population
Etanercept	
Bachelez 2015	Bachelez H, van der Kerkhof PCM, Strohal R, Kubanov A, Valenzuela F, Lee J-H, Yakusevich V, Chimenti S, Papacharalambous J, Proulx J, Gupta P, Tan H, Tawadrous M, Valdez H, Wolk R, for the OPT Compare Investigators. Tofacitinib versus etanercept or placebo in moderate-to severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. The Lancet, 2015; 386:552-561.
Cassano 2006	Cassano N, Loconsole F, Galluccio A, Miracapillo A, Pezza M and Vena GA. Once-weekly administration of high-dosage etanercept in patients with plaque psoriasis: results of a pilot experience (power study). International Journal of Immunopathology and Pharmacology, 2006; 19(1): 225-229.
Cassano 2010	Cassano N, Loconsole F, Miracapillo A, Travaglin M, Digiusepp MD, Congedo M, Galluccio A, Buquicchio R, Mastrandrwa V, Filieri M, Raho G, Pezza M and Vena GA. Treatment of psoriasis with different dosage regimens of etanercept: preliminary results from the Tαranta plastic study group. International Journal of Immunopathology and Pharmacology, 2010; 23(3):797-802.
Gisondi 2008	Gisondi P, Del Giglio M, Cotena C and Girolomoni G. Combining etanercept and acitretin in the therapy of chronic plaque psoriasis: a 24-week, randomized, controlled, investigator-blinded pilot trial. British Journal of Dermatology, 2008; 158: 1345–1349.
Gottlieb 2003	Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, Gaspari AA, Ling M, Weinstein GD, Nayak A, Gordon KB and Zitnik R. A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol, 2003; 139:1627-1632.
Gottlieb 2011	Gottlieb AB, Leonardi C, Kerdel F, Mehlis S, Olds M and Williams DA. Efficacy and safety of briakinumab vs. etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. British Association of Dermatologists, 2011; 165:652–660.
Gottlieb 2012	Gottlieb AB, Langley RG, Strober BE, Papp KA, Klekotka P, Creamer K, Thompson EHZ, Hooper M and Kricorian G. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. British Association of Dermatologists, 2012; 167:649–657.
Lebwohl 2013	Lebwohl MG, Kircik L, Duffin KC, Pariser D, Hooper M, Wenkert D, Thompson EHZ, Yang J. Kricorian G and Koo J. A randomized study to evaluate the efficacy and safety of adding topical therapy to etanercept in patients with moderate to severe plaque psoriasis. J Am Acad Dermatol, 2013; 69(3):385-392.
Lee 2016	Lee J-H, Youn J-I, Kim T-Y, Choi J-H, Park C-J, Choe Y-B, Song H-J, Kim N-I, Kim K-J, Lee J-H and Yoo H-J. A multicenter, randomized, open-label pilot trial assessing the efficacy and safety of etanercept 50 mg twice weekly followed by etanercept 25 mg twice weekly, the combination of etanercept 25 mg twice weekly and acitretin, and acitretin alone in patients with moderate to severe psoriasis. BMC Dermatology, 2016; 16:11.
Leonardi 2003	Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A and Gottlieb AB for the Etanercept Psoriasis Study Group. Etanercept as monotherapy in patients with psoriasis. N Engl J Med, 2003; 349:2014-22.
Papp 2005	Papp KA, Tyring S, Lahfa M, Prinz J, Griffiths CEM, Nakanishi AM, Zitnik R and van der Kerkhof PCM for the Etanercept Psoriasis Study Group. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. British Journal of Dermatology, 2005; 152:1304–1312.
Reich 2016	Reich K, Soung J, Gooderham M, Zhang Z, Nograles K, Day RM, Ferris L, Goodfield M. 52-week efficacy and safety of apremilast and switch from etanercept in patients with moderate to severe psoriasis: results from the LIBERATE study. 2016
Sterry 2010	Sterry W, Ortonne J-P, Kirkham B, Brocq O, Robertson D, Pedersen RD, Estojak J, Molta CT, Freundlich B. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. BMJ, 2010;340:c147
Strober 2011	Sterry W, Ortonne J-P, Kirkham B, Brocq O, Robertson D, Pedersen RD, Estojak J, Molta CT, Freundlich B. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. BMJ, 2010;340:c147
Strohal 2013	Strohal R, Puig L, Chouela E, Tsai T-F, Melin J, Freundlich B, Molta CT, Fuiman J, Pedersen R and Roberson D. The efficacy and safety of etanercept when used with as-needed adjunctive topical therapy in a randomised, double-blind study in subjects with moderate-to-severe psoriasis (the PRISTINE trial). Journal of Dermatological Treatment, 2013; 24: 169–178.
Tyring 2006	Tyring S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-

Trial identifier	Population
	blind placebo-controlled randomised phase III trial. *Lancet*. 2006;367:29-35.
van der Kerkhof 2008	van der Kerkhof PCM, Segaert S, Lahfa M, Luger TA, Karolyi Z, Kaszuba A, Leigheb G, Camacho FM, Forsea D, Zang C, Boussuge MP, Paolozzi L and Wajdula J. Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. British Journal of Dermatology, 2008; 159:1177–1185
Zachariae 2008	Zachariae C, Mørk N-J, Reunala T, Lorentzen H, Falk E, Karvonen S-L, Johannesson A, Claréus B, Skov L, Mørk G, Walker S and Qvitzau S. The combination of etanercept and methotrexate increases the effectiveness of treatment in active psoriasis despite inadequate effect of methotrexate therapy. Acta Derm Venereol , 2008; 88:495–501
Infliximab	
Chaudhari 2001	Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG and Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. The Lancet, 2001; 357: 1842-1847.
Gottlieb 2004	Gottlieb AB, Evans R, Dooley LT, Guzzo CA, Baker D, Bala M, Marano CW and Menter A. Infliximab induction therapy for patients with severe plaque-type psoriasis: A randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol, 2004; 51(4):534-542.
Menter 2007	Menter A, Feldman SR, Weinstein GB, Papp K, Evans R, Guzzo C, Li S, Dooley LT, Arnold C, Gottlieb AB. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad, 2007; 56(31):.e1-31.e15.
Reich 2005	Reich K, Nestle FO, Papp K, Ortonne J-P, Evans R, Guzzo C, Li S, Dooley LT, Griffiths CEM for the EXPRESS study investigators. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. The Lancet, 2005; 366; 1367-1374.
Torii 2010	Torii H, Nakagawa H, the Japanese Infliximab Study Investigators. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. Journal of Dermatological Science , 2010; 59:40–49.
Yang 2012	Yang H-Z, Wang K, Jin H-Z, Gao T-W, Xiao S-X, Xu J-H, Wang B-X, Zhang F-R, Li C-Y, Liu X-M, Tu C-X, Ji S-Z, Shen Y and Zhu X-J. Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomized, double-blind, placebo-controlled multicenter trial. Chinese Medical Journal, 2012; 125(11):1845-1851
Ixekizumab	
Gordon 2016	Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, Reich K, Amato D, Ball SG, Braun DK, Cameron GS, Erickson J, Konrad RJ, Muram TM, Nickoloff BJ, Osuntokun OO, Secrest RJ, Zhao F, Mallbris L, and Leonardi CJ for the UNCOVER-1, UNCOVER-2, and UNCOVER-3 Study Groups. Phase 3 Trials of ixekizumab in moderate-to-severe plaque psoriasis. N Engl J Med, 2016; 375(4):345-356.
Griffiths 2015	Griffiths CEM, Strober BE, van der Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, Guzzo C, Xia Y, Zhou B, Li S, Dooley LT, Goldstein NH and Menter A, for the ACCEPT Study Group. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med, 2010; 362(2):118-128.
Secukinumab	
Bauvelt 2014	Blauvelt A, Prinz JC, Gottlieb AB, Kingo K, Sofen H, Ruer-Mulard M, Singh V, Pathan R, Papavassilis C and Cooper S for the FEATURE study group. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). British Journal of Dermatology, 2015; 172:484-493.
Langley 2014	Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CEM, Papp K, Puig L, Nakagawa H, Spelman L, Sigurgeirsson B, Rivas E, Tsai T-F, Wasel N, Tyring S, Salko T, Hampele I, Notter M, Karpov A, Helou S and Papavassilis C for the ERASURE and FIXTURE study groups. Secukinumab in plaque psoriasis — results of two phase 3 trials. N Engl J Med, 2014; 371(4):326-338.
Paul 2014	Paul C, Lacour J-P, Tedremets L, Kreutzer K, Jazayeri S, Adams S, Guindon C, You R, Papavassilis C for the JUNCTURE study group. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). European Academy of Dermatology , 2015; 29: 1082-1090
Ustekinumab	
Griffiths 2010	Griffiths CEM, Strober BE, van der Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, Guzzo C, Xia Y, Zhou B, Li S,

Trial identifier	Population
	Dooley LT, Goldstein NH and Menter A, for the ACCEPT Study Group. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med, 2010; 362(2):118-128.
Igarashi 2012	Igarashi A, Kato T, Kato M, Song M, Nakagawa H, the Japanese Ustekinumab Study Group. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: Long-term results from a phase 2 /3 clinical trial. Journal of Dermatology, 2012; 39: 242–252
Lebwohl 2015	Lebwohl M, Strober B, Menter A, Gordon K, Weglowska J, Puig L, Papp K, Spelman L, Toth D, Kerdel F, Armstrong AW, Stingl G, Kimball AB, Bachelez H, Wu JJ, Crowley J, Langley RG, Blicharski T, Paul C, Lacour J-P, Tyring S, Kircik L, Chimenti S, Duffin KC, Bagel J, Koo J, Aras G, Li J, Song W, Milmont CE, Shi Y, Erondu N, Klekotka P, Kotzin B and Nirula A. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. N Engl J Med, 2015; 373:1318-28.
Leonardi 2008	Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, Li S. Dooley LT, Gordon KB, for the PHOENIX 1 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet, 2008; 371: 1665–74.
Papp 2008	Papp KA, Langley RG, Lebwohl M, Krueger GG Szapary P, Yeilding N, Guzzo C, Hsu M-C, Wang Y, Li S, Dooley LT, Reich K, for the PHOENIX 2 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet, 2008; 371: 1675–84.
Paul 2014	Paul C, Puig L, Kragballe K, Luger T, Lambert J, Chimenti S. Girolomoni G, Nicolas J-F, Rizova E, Lavie F, Mistry S. Bergmans P, Barker J and Reich K, on behalf of the TRANSIT Investigators. Transition to ustekinumab in patients with moderate-to-severe psoriasis and inadequate response to methotrexate: a randomized clinical trial (TRANSIT). British Journal of Dermatology, 2014; 170:425–434.
Thaçi 2015	Thaçi D, Blauvelt A, Reich K, Tsai T-F, Vanaclocha F, Kingo K, Ziv M, Pinter A, Hugot S, You R and Milutinovic M. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. J Am Acad Dermatol, 2015; 73(3): 400-408
Tsai 2011	Tsai T-F, Ho J-C, Song M, Szapary P, Guzzo C, Shen Y-K, Li S, Kim K-J, Kim T-Y, Choi J-H, Young J-I on behalf of the PEARL Investigators. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: A phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). Journal of Dermatological Science, 2011; 63:154–163.
Zhu 2013	Zhu X, Zheng M. Song M, Shen Y-K, Chan D, Szapary PO and Wang B on behalf of LOTUS investigators. Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: results from a Phase 3 clinical trial (LOTUS). Journal of drugs in dermatology, 2013; 12(2): 166-174.

Abbreviations: CPP, chronic plaque psoriasis; RCTs, randomised controlled trials

Network meta-analysis methodology

A network meta-analysis was performed using the methodology described by White (2011). The methodology is frequentist (as opposed to Bayesian) and is described by the author as "multivariate random-effects meta-regression" as it is an extension of conventional "random effects meta-analysis" comparing two treatments, to multiple treatments (eg, among treatments A, B, C, D and E). Multiple treatment effects (B vs A, C vs A, etc) can be estimated at the same time in a single statistical model.

The mvmeta command (from www.mrc-bsu.cam.ac.uk/IW_Stata/meta) of STATA 14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP.) was used to perform the network meta-analysis. In addition, various plots were produced using supporting routines in the network_graphs package (from www.mtm.uoi.gr).

The input data for the analysis are study level treatment contrasts (or relative treatment effects) between each comparator treatment against a reference treatment, typically placebo. If the effect measures are relative risk (RR) or odds ratio (OR), treatment contrasts are calculated on

the log scale, i.e. log(RR) or log(OR). If the effect measure is risk difference (RD), no log transformation is required. This analysis used RR as the effect measure.

The software allows estimation of treatment effects based on "fixed effects" or "random effects" model assumption. The "random effects" assumption is more general and was used in all analyses reported.

To explain the difference between "fixed effects" and "random effects", let $Y_{j,AvB}$ be the observed contrast between treatments A and B for trial j (say, on log(RR) scale) and consider the question of what $Y_{j,AvB}$ estimates. The answer provides the distinction between "fixed effects" and "random effects". The "fixed effects" model assumes there is a global true treatment effect θ_{AvB} (unobserved fixed value) which $Y_{j,AvB}$ estimates, ie, all trial level contrasts estimate the same θ_{AvB}. For this reason, the fixed effects model for data for trial j can be written as:

$$Y_{j,AvB} = \theta_{AvB} + \varepsilon_{j,AvB}$$

where $\varepsilon_{j,AvB}$ represents a random measurement error (assumed generated from a normal distribution with mean zero and variance estimated from the observed data).

Under the "random effects" assumption, true treatment effects differ from trial to trial; for trial j, there is a trial level true treatment effect $\theta_{j,AvB}$ (unobserved fixed value) which trial j's observed value $Y_{j,AvB}$ estimates. For another trial, say trial k, there is a different trial level true treatment effect $\theta_{k,AvB}$ (also unobserved fixed value) which trial k's observed value $Y_{k,AvB}$ (if indeed observed) will estimate. These trial level true treatment effects $\theta_{j,AvB}$ and $\theta_{k,AvB}$ are different – and unobserved – but are assumed to have been generated from a common normal distribution with mean θ_{AvB} and standard deviation τ, denoted as $N(\theta_{AvB}, \tau^2)$ – so called exchangeable assumption. Therefore, the random effects model for data can be written as:

$$Y_{j,AvB} = \theta_{j,AvB} + \varepsilon_{j,AvB}, \quad \theta_{j,AvB} \sim N(\theta_{AvB}, \tau^2)$$

where $\varepsilon_{j,AvB}$ represents a random measurement error as in the fixed effects case. The objective of the data analysis is to estimate θ_{AvB} and τ (tau).

The mean θ_{AvB} of the distribution is then interpreted as the true treatment difference between A and B. Tau is called the between-study heterogeneity parameter, it is assumed equal for any (A,B) pair, i.e. only one τ exists in the whole model. Theoretically this assumption is not required but is imposed to simplify the model and ensure estimability. When τ=0, "random effects" becomes "fixed effects".

An issue in network meta-analysis, which is not present in conventional meta-analysis is the potential for inconsistency between the direct and indirect evidence. For example, in a network that includes both A vs B, A vs C, and B vs C trials, the direct effect estimate between A and B (from A vs B trials) may be inconsistent with the indirect estimate (from A vs C and B vs C trials) i.e. the two estimates may be very different. Consistency or inconsistency models can be applied. A consistency model assumes θ_{AvB}, = θ_{AvC} - θ_{CvB} (e.g. the effect measure is in terms of log(RR) or log(OR)) – whereas an inconsistency model assumes θ_{AvB}, = θ_{AvC} - θ_{CvB} + w_{ABC}, where w_{ABC} represents an inconsistency parameter. A network may have many inconsistency parameters. More complicated situations involving inconsistency modelling are described in White et al (2012) e.g. a two-arm trial and a three-arm trial can be assumed to produce inconsistent treatment effects. The STATA command mvmeta can fit both consistency and inconsistency models. All key results were derived from consistency models, however, inconsistency models were also fitted and the test of inconsistency was reported. The

appropriate test is the omnibus test with the null hypothesis stating that all inconsistency parameters are zeros (i.e. the consistency model holds).

Analysis endpoint

The analysis endpoint included in the network met-analysis was PASI75 at week 12. If the study did not report the outcome at week 12, the closest time point at which PASI75 was reported was selected. This occurred in the adalimumab study Gordon 2015 where PASI75 results at week 16 were presented as well as a graph of PASI75 over time. As the graph was difficult to read, the week 16 result was extracted instead. In the infliximab studies the primary endpoint occurred at week 10 and the publications included PASI75 results over time. Therefore week 10 data were extracted (Chaudhari 2001, Gottlieb 2004, Menter 2007, Reich 2005, Torii 2010, and Yang 2012).

Data extraction

Summary data of PASI75 at week 12 (numbers of responses and numbers of patients) from treatment arms using TGA-approved dosages (co-treatments allowed) were extracted from the study publications. To qualify for inclusion, treatment arms only needed to have a TGA-approved dose up to week 12 thereafter the treatments could be changed. If placebo was included in the study, these data were extracted in all cases. Treatment arms with non-TGA-approved dosages were excluded. As a result of these selection criteria, some studies only had a single arm of relevant data and therefore could not be included in the network meta-analysis as no treatment contrasts could be computed. For example, Cassano 2006 was a two-arm study comparing two etanercept doses: ETN 50 mg BIW v ETN 100 mg OW. Since the latter dose was not a TGA-approved, that arm was deleted and therefore as one relevant arm remained, it could not be included in the analysis. TGA-approved dosages are tabulated in **Table 4**.

Table 4: Qualifying doses for active treatment arms in each study to be included in data extraction (placebo arm always included)

		Ustekinumab (UST)		Etanercept (ETN)	
Adalimumab (ADA)*	**Infliximab (INF)**	***Low dose (UST1)***	***High dose (UST2)***	***Low dose (ETN1)***	***High dose (ETN2)***
ADA 40 mg EOW	INF 5 mg/kg at weeks 0, 2 and 6	UST 45 mg at weeks 0 and 4	UST 90 mg at weeks 0 and 4	ETN 25 mg BIW	ETN 50 mg BIW
ADA 80 mg LD, 40 mg EOW			UST 45 or 90 mg per label	ETN 50 mg OW	ETN 50 mg BIW + clobetasol propionate§
			UST 45 or 90 mg per label + immediate withdrawal of methotrexate§		ETN 50 mg BIW + methotrexate§
			UST 45 or 90 mg per label + tapering of methotrexate§		ETN 50 mg BIW + placebo
Ixekizumab (IXE)	**Secukinumab (SEC)**				
IXE 160 mg followed by 80 mg every 2 wks	SEC 300 mg once wkly for 5 wks then every 4 wks				

*The recommended dose of adalimumab is an 80 mg loading dose followed by 40 mg eow. For the purposes of this analysis both this dose and 40 mg eow were included.

§Arms with methotrexate and clobetasol propionate were included as these therapies would be permitted on the PBS

Abbreviations: BIW = twice weekly; EOW = every other week; OW = once weekly; LD = loading dose; wks, weeks; wkly, weekly

Treatment group definitions

Main analysis

For the main analysis, seven treatment groups (including placebo) were defined according to the drug name, ie, PBO, ADA, INF, UST, ETN, IXE, SEC. For this analysis, treatments arms of the same drug but with different doses were combined at the study level. After combining arms, some studies became single-armed and therefore could not be used in the network meta-analysis, eg, Cassano 2010 had two etanercept arms, ETN 50 mg QW and ETN 50 BIW, these two were combined into a single "ETN" arm, and so the study could not be included in the analysis.

Sensitivity analysis

Where treatment groups could be included into low or high dose categories, based on their TGA-approved doses, these were included in treatment definitions for sensitivity analyses. This included doses of etanercept and ustekinumab. Thus for sensitivity analysis, for etanercept, two treatment groups were defined according to dosage:

- ETN1: ETN 25 mg BIW or ETN 50 mg OW
- ETN2: ETN 50 mg BIW ± any co-treatment

For ustekinumab, likewise, two treatment groups were defined according to dosage:

- UST1: UST 45 mg at weeks 0 and 4
- UST2: UST 90 mg at weeks 0 and 4, UST 45 or 90 mg per label, UST 45 or 90 mg per label + immediate withdrawal of methotrexate, UST 45 or 90 mg per label + tapering of methotrexate

For adalimumab and infliximab, treatment groups were defined as in the main analysis i.e. all arms of the same treatments were combined at study level, under treatment group labels ADA and INF, respectively.

Thus, in sensitivity analysis, nine treatment groups (including placebo) were identified: PBO, ADA, INF, UST1, UST2, ETN1, ETN2, IXE, SEC.

Note that some studies excluded in the main analysis were eligible for sensitivity analysis e.g. Cassano 2010 had two etanercept arms, ETN 50 mg OW and ETN 50 BIW. These two were combined into a single "ETN" arm in the main analysis making this study a one-armed study and therefore this study was excluded from the main analysis. However, in the sensitivity analysis, the two arms were not combined, and so the study contributed to the sensitivity analysis.

Effect measure

The effect measure for comparing treatments was based on relative risk (RR). For analysis, RRs were expressed on the logarithmic scale.

Network meta-analysis results (main analysis)

Network plot (main analysis)

The network plot in **Figure 2** shows all the unique treatments (represented as nodes) present in the studies included in the main analysis. A line connecting two nodes indicates that direct comparison between the two treatments is possible. Both nodes and edges are weighted according to the number of studies evaluating each treatment and direct comparison respectively. Thus for example, the placebo node is largest since it was included in the largest number of studies.

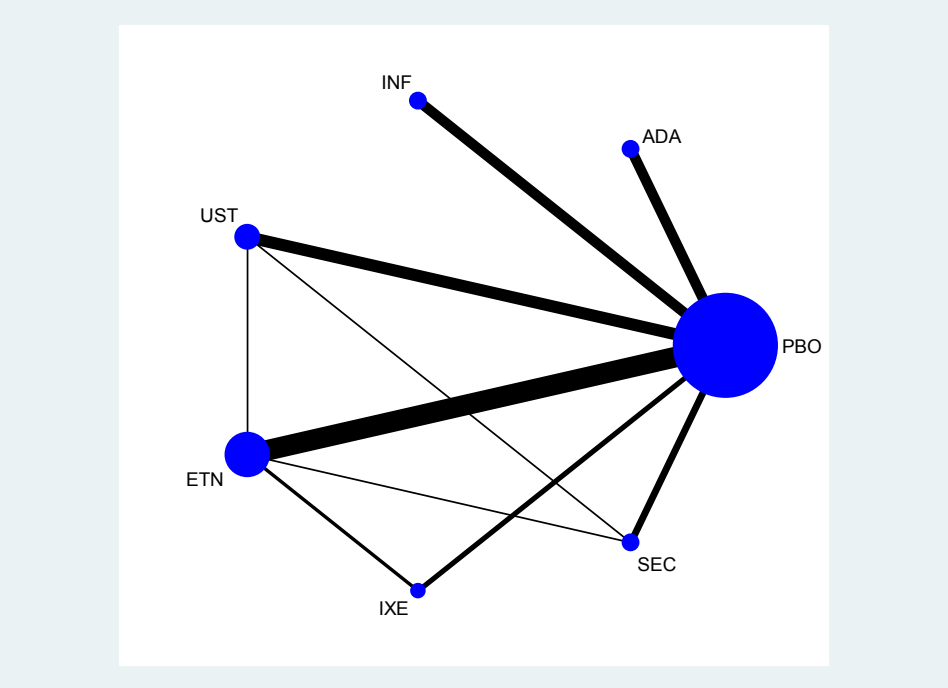


Figure 2: Network plot (main analysis)

To supplement interpretation of **Figure 2**, **Table 5** lists numbers of studies available for each direct comparison.

Table 5: Direct comparisons and number of included studies (main analysis)

Comparison	Number of studies	Comparison	Number of studies
ADA vs PBO	6	SEC vs PBO	4
INF vs PBO	6	ETN vs UST	1
UST vs PBO	7	SEC vs UST	1
ETN vs PBO	12	IXE vs ETN	2
IXE vs PBO	3	SEC vs ETN	1

Network meta-analysis results (main analysis)

A random effects network meta-analysis was fitted using log(RR) as the effect measure. The between study heterogeneity standard deviation was estimated to be 0.2294 ($p < 0.001$), indicating the presence of heterogeneity of treatment effects between studies in some comparisons. Therefore a random effects model is appropriate.

All pairwise relative risks of PASI75 at week 12 estimated from the network meta-analysis are shown in **Table 6**. To find the RR of a particular treatment X vs another treatment Y, locate the column labelled X and the row labelled Y, the table entry where these two intersect gives the required RR and its 95% confidence interval (CI). Since PASI75 is benefit, a relative risk >1 favours X, while a relative risk <1 favours Y.

Table 6: Relative risk (95% CI) of PASI75 at week 12 of treatment A (column label) vs treatment B (row label) (main analysis)

	ADA	INF	UST	ETN	IXE	SEC	PBO
ADA	ADA	*2.12 (1.06,4.22)*	1.29 (0.83,2.00)	0.97 (0.63,1.49)	*1.92 (1.17,3.13)*	*1.70 (1.04,2.78)*	*0.11 (0.07,0.15)*
INF	*0.47 (0.24,0.94)*	INF	0.61 (0.33,1.14)	*0.46 (0.25,0.85)*	0.90 (0.47,1.76)	0.80 (0.41,1.56)	*0.05 (0.03,0.09)*
UST	0.78 (0.50,1.20)	1.64 (0.88,3.07)	UST	*0.75 (0.58,0.98)*	*1.49 (1.03,2.15)*	1.32 (0.96,1.82)	*0.08 (0.07,0.10)*
ETN	1.03 (0.67,1.59)	*2.18 (1.18,4.06)*	*1.33 (1.02,1.74)*	ETN	*1.98 (1.48,2.65)*	*1.76 (1.27,2.44)*	*0.11 (0.09,0.14)*
IXE	*0.52 (0.32,0.85)*	1.11 (0.57,2.14)	*0.67 (0.47,0.97)*	*0.51 (0.38,0.68)*	IXE	0.89 (0.59,1.34)	*0.06 (0.04,0.08)*
SEC	*0.59 (0.36,0.96)*	1.24 (0.64,2.41)	0.76 (0.55,1.04)	*0.57 (0.41,0.79)*	1.12 (0.74,1.70)	SEC	*0.06 (0.05,0.09)*
PBO	*9.36 (6.46,13.58)*	*19.84 (11.12,35.41)*	*12.07 (9.57,15.22)*	*9.08 (7.31,11.29)*	*17.96 (13.03,24.74)*	*15.96 (11.61,21.95)*	PBO

Pink shading indicates 95% CI <1; blue shading indicates 95% CI >1 in cell with shading

In order to interpret the table, either select a column or row as a starting point. For example, select the ADA column and look down the rows. This will provide the relative risks of ADA vs treatments X where X = INF, UST, which shows the efficacy of ADA compared to other treatment. Alternative, a row can be selected and the RRs can be examined across the row. In this case, if the ADA row is selected the RR can be examined: for X vs ADA, where X = INF, UST, etc.

The table entries are colour coded. A cell with pink shading, means 95% CI <1; blue means 95% CI >1; no shading (or white) means 95% CI including the null value 1.

The following observations can be made after considering **Table 6**:

- The PBO row shows that all biologics are superior to PBO, with RR ranging from 9.08 (95% CI: 7.31 to 11.29) (ETN vs PBO) to 19.84 (95% CI: 11.12 to 35.54) (INF vs PBO). In terms of magnitude of point estimate of RR vs PBO, the treatments can be ranked as follows in decreasing order: INF, IXE, SEC, UST, ADA, ETN.
- Comparing the two columns ADA and ETN, it appears that ADA and ETN have similar efficacy on the endpoint PASI75 at week 12, with RR = 1.03, 95% CI: 0.67 to 1.59 (ADA vs ETN). Both treatments were significantly inferior to the other biologics (INF, UST, IXE, SEC) with the exception that ADA was only numerically, but not significantly, inferior to UST.
- For INF, IXE and SEC, the column entries are either shaded “blue” or “white”, indicating they were either significantly better, or there was no evidence of any difference, compared to their respective comparators. In other words, they were not significantly inferior to other treatments.
- INF was significantly superior to ADA (RR = 2.12, 95% CI: 1.06 to 4.22) and ETN (RR = 2.18, 95% CI: 1.18 to 4.06). However, the lower bound of the 95% CI against ADA was only 1.06 (i.e. 6% better) therefore the evidence for this comparison is not strong.
- IXE was significantly superior to ADA (RR = 1.92, 95% CI: 1.17 to 3.13) and ETN (RR = 1.98, 95% CI: 1.48 to 2.65), moreover it was significantly better than UST (RR = 1.49, 95% CI: 1.03, 2.15). Since the lower bounds of the 95% CIs all seem to be much larger than 1, it appears the evidence is quite convincing.

- SEC was significantly superior to ADA (RR = 1.70, 95% CI: 1.04 to 2.78) and ETN (RR = 1.76, 95% CI: 1.27 to 2.44). Similar to INF vs ADA, the lower bound of the 95% CI against ADA was only 1.04 (i.e. 4% better).
- UST was significantly better than ETN (RR = 1.33, 95% CI: 1.02 to 1.74), however the lower bound of the confidence interval is 1.02. It is only numerically superior to ADA. It was significantly inferior to IXE (RR = 0.67, 95% CI: 0.47 to 0.97) however the evidence is not strong since the upper confidence bound is close to 1. However, it was numerically, but not statistically inferior to INF and SEC.

As there are so many RRs in **Table 6**, plots are helpful to visualise the patterns of relative treatment effects. Relative risks and 95% CIs are shown in **Figure 3** for all combinations of treatments X and Y (X ≠ Y). Please note that if the RR of X vs Y is shown, the inverse (Y vs X) is not shown.

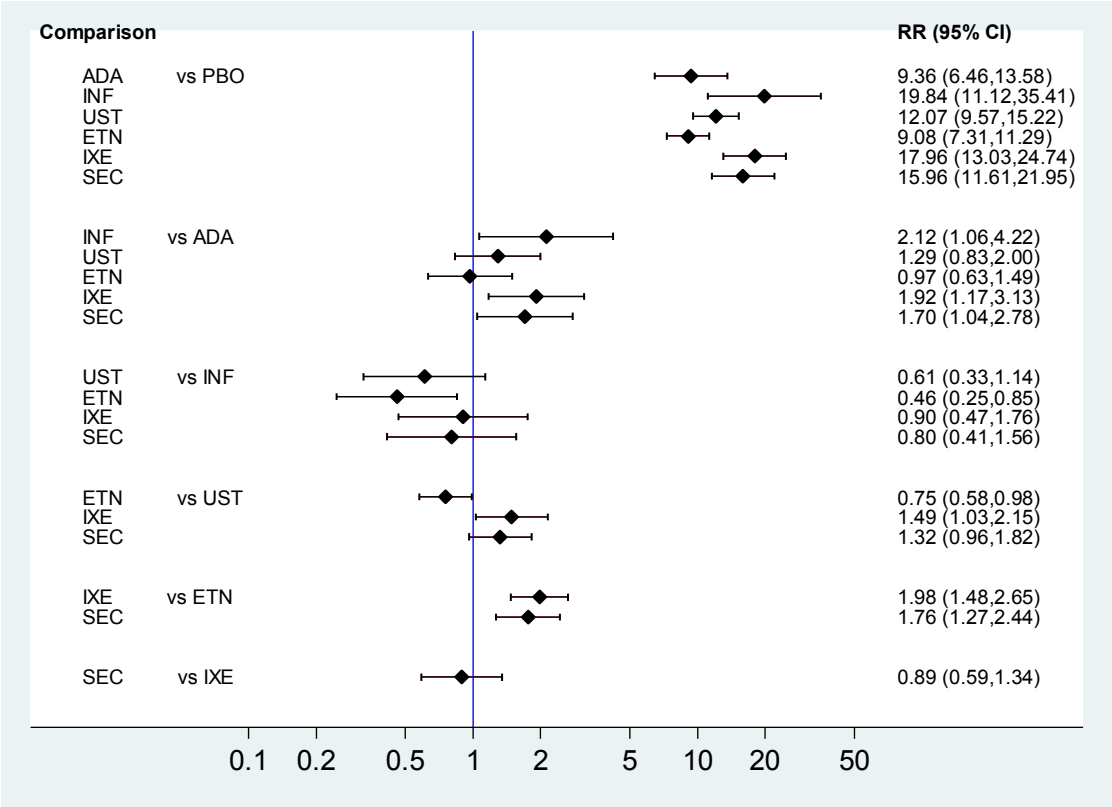


Figure 3: Relative risks of PASI75 at week 12 of all pairwise treatment combinations (main analysis)

Separate relative risk plots using each of the active treatments as reference are shown in **Figure 4**.

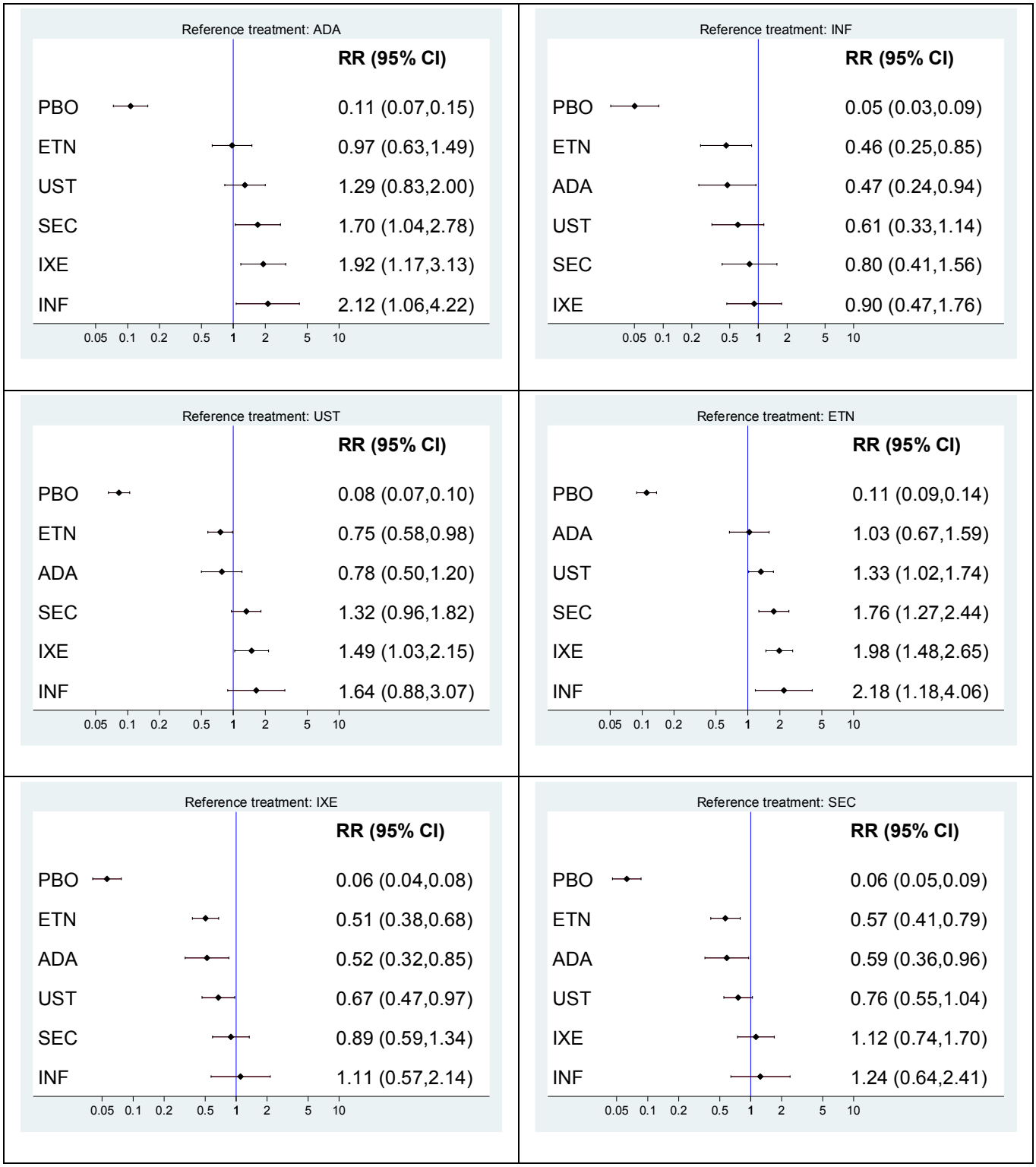


Figure 4: Relative risks of PASI75 at week 12 of other treatments vs an active treatment as reference (main analysis)

Testing for inconsistency (main analysis)

In a separate network meta-analysis model allowing for inconsistency, the test for inconsistency resulted in a p-value of 0.9641 (based on a chi-square test with 6 degrees of freedom of value 1.43). This means that there was no evidence to reject the null hypothesis “model is consistent”. This gives some confidence of the findings based on consistency model.

Conclusion (main analysis)

This network meta-analysis compared six biologics (ADA, INF, UST, ETN, IXE, SEC) and placebo based on the efficacy of treatments on the outcome PASI75 at week 12, using relative risk (RR) as effect measure. In the main analysis, treatment groups were not defined by dose. At study level, treatment arms using the same biologic but at different doses were combined. Arms that did not include TGA-approved doses were excluded from extraction.

In this analysis, ADA and ETN were found to have similar efficacy on PASI75 at week 12, since RR = 1.03, 95% CI: 0.67 to 1.59 (ADA vs ETN). Both treatments were significantly inferior to the other biologics (INF, UST, IXE and SEC) with the exception that ADA was numerically, but not significantly, inferior to UST.

The three treatments INF, IXE and SEC were significantly superior to both ADA and ETN. In addition, IXE was significantly superior to UST, while INF and SEC were only numerically superior to UST.

UST was significantly superior to ETN (RR 1.33, 95% CI: 1.02 to 1.74) – with the caveat that as the lower bound of the 95% CI was close to 1, the evidence was not that convincing. UST was only numerically superior to ADA. Moreover, UST was significantly inferior to IXE.

Network meta-analysis (Sensitivity analysis)

As mentioned previously, nine treatment groups were included in the sensitivity analysis: PBO, ADA, INF, UST1, UST2, ETN1, ETN2, IXE, SEC, i.e. a placebo group and nine active biologic groups. Etanercept doses were divided into two groups (low dose and high dose) as were ustekinumab doses. In contrast, in the main analysis, all doses for a particular treatment were combined.

Network plot (sensitivity analysis)

As with the main analysis, the network plot for the sensitivity analysis in **Figure 5** shows all the unique treatments (represented as nodes) present in the studies included in the main analysis. As before, a line connecting two nodes indicates that direct comparison between the two treatments is possible and both nodes and edges are weighted according to the number of studies evaluating each treatment and direct comparison, respectively.

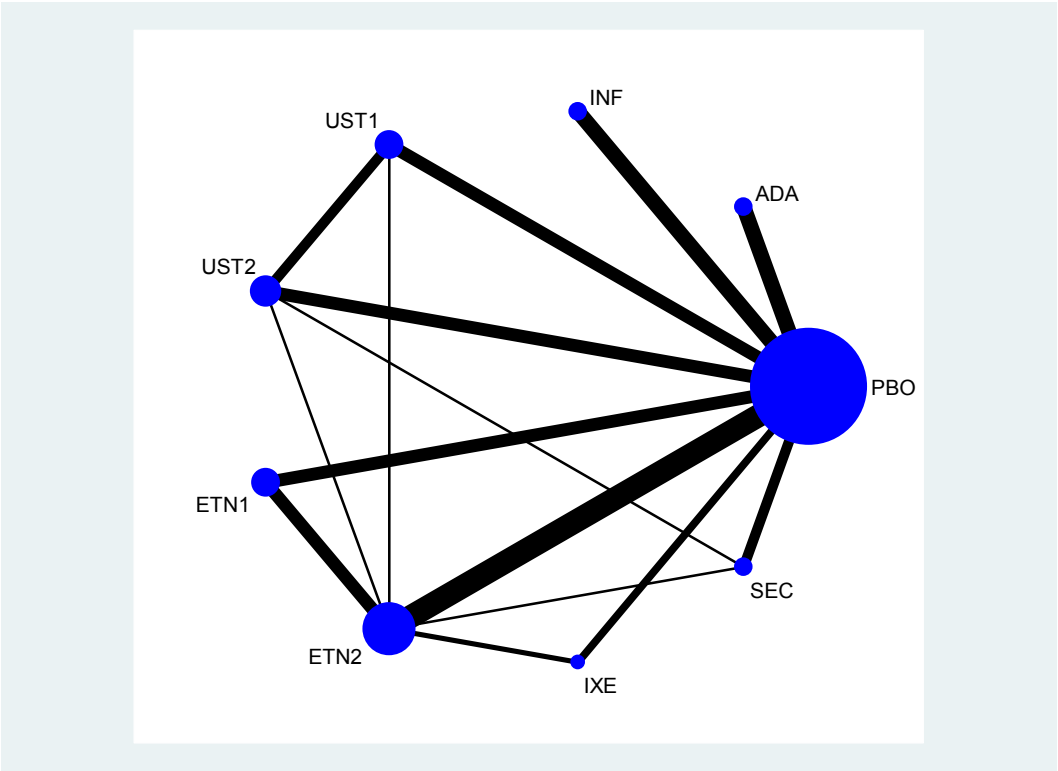


Figure 5: Network plot (sensitivity analysis)

As before, to supplement interpretation of **Figure 5**, **Table 7** lists numbers of studies available for each direct comparison.

Table 7: Direct comparisons and number of included studies (sensitivity analysis)

Comparison	Number of studies	Comparison	Number of studies
ADA vs PBO	6	UST2 vs UST1	4
INF vs PBO	6	ETN2 vs UST1	1
UST1 vs PBO	5	ETN2 vs UST2	1
UST2 vs PBO	5	SEC vs UST2	1
ETN1 vs PBO	5	ETN2 vs ETN1	5
ETN2 vs PBO	9	IXE vs ETN2	2
IXE vs PBO	3	SEC vs ETN2	1
SEC vs PBO	4		

Network meta-analysis results (sensitivity analysis)

As in the main analysis, a random effects network meta-analysis was fitted using log(RR) as effect measure. The between study heterogeneity standard deviation was estimated to be 0.1004 (p =0.003), indicating the presence of heterogeneity of treatment effects between studies in some comparisons between some treatment pairs. Heterogeneity is slightly less than in main analysis, possibly as a result of refining the treatment groups.

All pairwise relative risks of PASI75 at week 12 estimated from network meta-analysis are shown in **Table 8**. As before, to find the RR of a particular treatment X vs treatment Y, locate the column labelled X and the row labelled Y, the table entry where these two intersect gives

the required RR and its 95% confidence interval (CI). Since PASI75 is a positive outcome or benefit, a relative risk >1 favours X, while a relative risk <1 favours Y.

Table 8: Relative risk (95% CI) of PASI75 at week 12 of treatment A (column label) vs treatment B (row label) (sensitivity analysis)

	ADA	INF	UST1	UST2	ETN1	ETN2	IXE	SEC	PBO
ADA	ADA	*2.10 (1.12,3.95)*	1.21 (0.85,1.73)	1.33 (0.93,1.88)	*0.66 (0.46,0.96)*	1.00 (0.71,1.42)	*1.89 (1.30,2.75)*	*1.65 (1.14,2.39)*	*0.11 (0.08,0.14)*
INF	*0.48 (0.25,0.89)*	INF	0.58 (0.32,1.03)	0.63 (0.35,1.12)	*0.31 (0.17,0.56)*	*0.48 (0.27,0.84)*	0.90 (0.50,1.62)	0.79 (0.44,1.41)	*0.05 (0.03,0.09)*
UST1	0.82 (0.58,1.18)	1.74 (0.97,3.09)	UST1	1.09 (0.97,1.23)	*0.54 (0.44,0.68)*	*0.82 (0.70,0.98)*	*1.56 (1.25,1.95)*	*1.36 (1.12,1.65)*	*0.09 (0.07,0.10)*
UST2	0.75 (0.53,1.07)	1.59 (0.90,2.82)	0.92 (0.81,1.03)	UST2	*0.50 (0.41,0.61)*	*0.75 (0.65,0.88)*	*1.43 (1.16,1.77)*	*1.25 (1.05,1.48)*	*0.08 (0.07,0.09)*
ETN1	*1.51 (1.04,2.19)*	*3.18 (1.77,5.72)*	*1.84 (1.48,2.28)*	*2.01 (1.63,2.46)*	ETN1	*1.51 (1.31,1.74)*	*2.87 (2.33,3.52)*	*2.50 (2.00,3.12)*	*0.16 (0.13,0.20)*
ETN2	1.00 (0.71,1.42)	*2.10 (1.19,3.73)*	*1.21 (1.02,1.44)*	*1.33 (1.14,1.55)*	*0.66 (0.57,0.76)*	ETN2	*1.89 (1.62,2.21)*	*1.65 (1.39,1.97)*	*0.11 (0.09,0.12)*
IXE	*0.53 (0.36,0.77)*	1.11 (0.62,2.00)	*0.64 (0.51,0.80)*	*0.70 (0.57,0.87)*	*0.35 (0.28,0.43)*	*0.53 (0.45,0.62)*	IXE	0.87 (0.70,1.09)	*0.06 (0.05,0.07)*
SEC	*0.61 (0.42,0.88)*	1.27 (0.71,2.28)	*0.73 (0.60,0.89)*	*0.80 (0.68,0.95)*	*0.40 (0.32,0.50)*	*0.61 (0.51,0.72)*	1.15 (0.92,1.44)	SEC	*0.06 (0.05,0.08)*
PBO	*9.48 (6.97,12.90)*	*19.96 (11.54, 34.54)*	*11.51 (9.61,13.78)*	*12.57 (10.63, 14.86)*	*6.27 (5.10,7.70)*	*9.49 (8.05,11.17)*	*17.97 (14.59, 22.13)*	*15.68 (12.82, 19.16)*	PBO

Pink shading indicates 95% CI <1; blue shading indicates 95% CI >1 in cell with shading

From **Table 8**, and as found in the main analysis, it is clear that all biologics are superior to placebo with RR ranging from 6.27 (95% CI: 5.10 to 7.70) (ETN1 vs PBO) to 19.96 (95% CI: 11.54 to 34.54) (INF vs PBO). In terms of magnitude of the point estimate of RR vs placebo, the treatments can be ranked as follows in decreasing order: INF, IXE, SEC, UST2, UST1, {ETN2, ADA}, ETN1 – note that as ETN2 and ADA have almost identical point estimates they were placed inside brackets as a group.

The main finding in the sensitivity analysis is that ETN1 and ETN2 have clear differences in efficacy on the outcome PASI75 at week 12 with ETN2 clearly superior to ETN1, with RR (ETN2 vs ETN1) = 1.51, 95% CI: 1.31 to 1.74. Therefore, splitting the ETN doses into two groups reflected the superiority of the increased dose of etanercept for CPP. The recommended dosages from the TGA-approved PI indicate that superior efficacy can be achieved by administration of etanercept 50 mg twice weekly for the first twelve weeks.

Note that in the main analysis, RR (ETN vs PBO) was 9.08, whereas in the sensitivity analysis, RR (ETN1 vs PBO) was only 6.27, while RR (ETN2 vs PBO) was 9.49. So, it appears ETN2 (high dose) is more reflective of the combined dose (ETN).

On the other hand, UST2 and UST1 were similar, RR = 1.09 (UST2 vs UST1) with UST2 slightly better; therefore splitting the doses into 2 groups was probably unnecessary.

In **Table 8,** if we remove ETN1, and use either UST1 or UST2, it is very similar to the corresponding table (**Table 6**) under the main analysis – in terms of conclusions about the relative efficacy of the treatments. The only exception is that in the sensitivity analysis, there were more significant findings where previously there were only numerical findings. Specifically,

- SEC was significantly better than both UST1 and UST2; RR (vs UST1) = 1.36, 95% CI: 1.12,1.65, while RR = (vs UST2) 1.25, 95% CI: 1.05,1.48 – *this finding is more conclusive than main analysis which only showed a numerical advantage of SEC over UST*.

As before, as there are so many RRs in **Table 8** plots assist in showing the patterns of relative treatment effects. Relative risks and 95% CIs are shown in the following plot for all combinations of treatments X and Y (X ≠ Y). Please note that if the RR of X vs Y is shown, the inverse (Y vs X) is not shown. Separate relative risk plots using each of the active treatments as reference are shown in **Figure 7**.

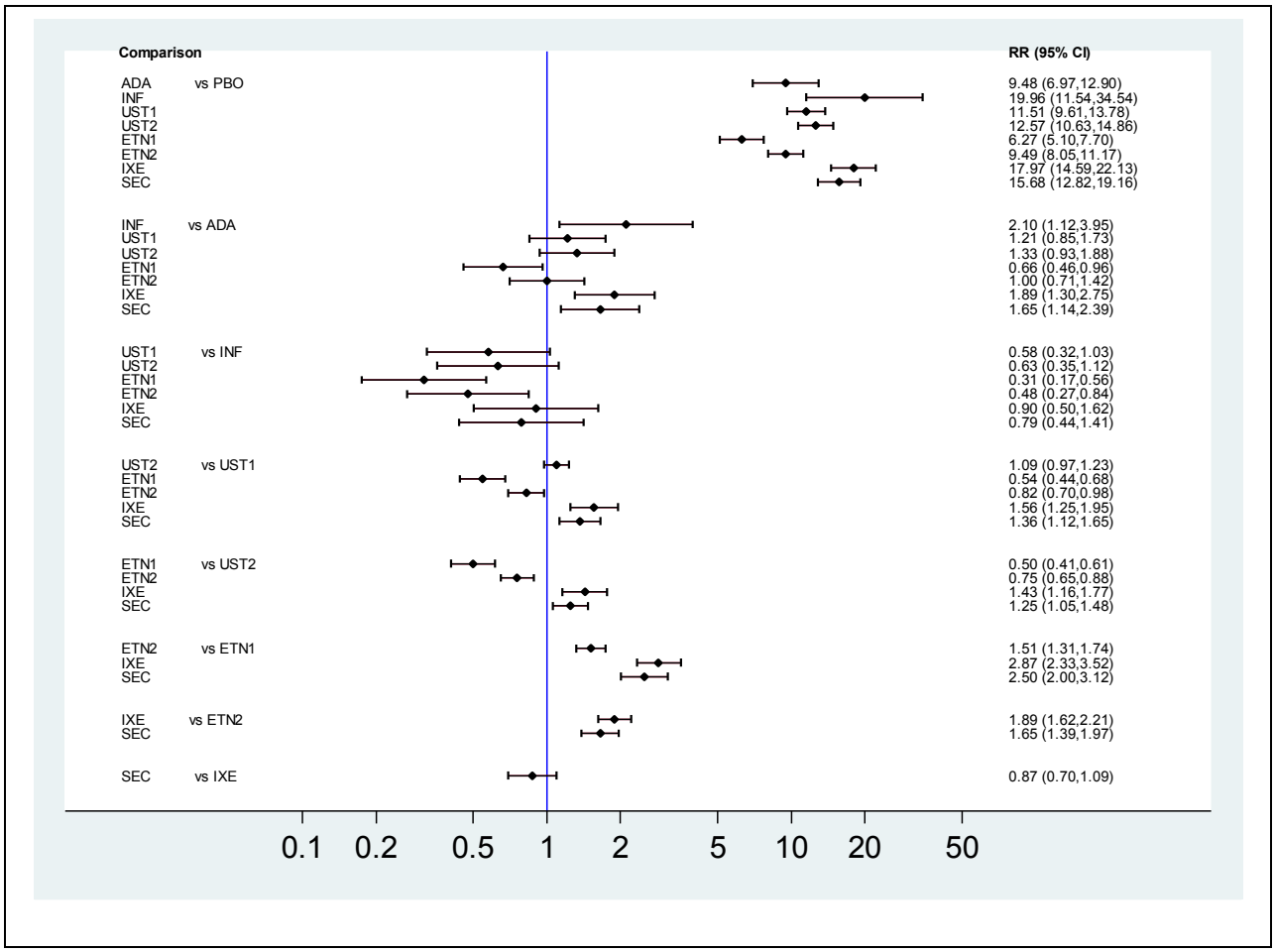


Figure 6: Relative risks of PASI75 at week 12 of other treatments vs an active treatment as reference (sensitivity analysis)

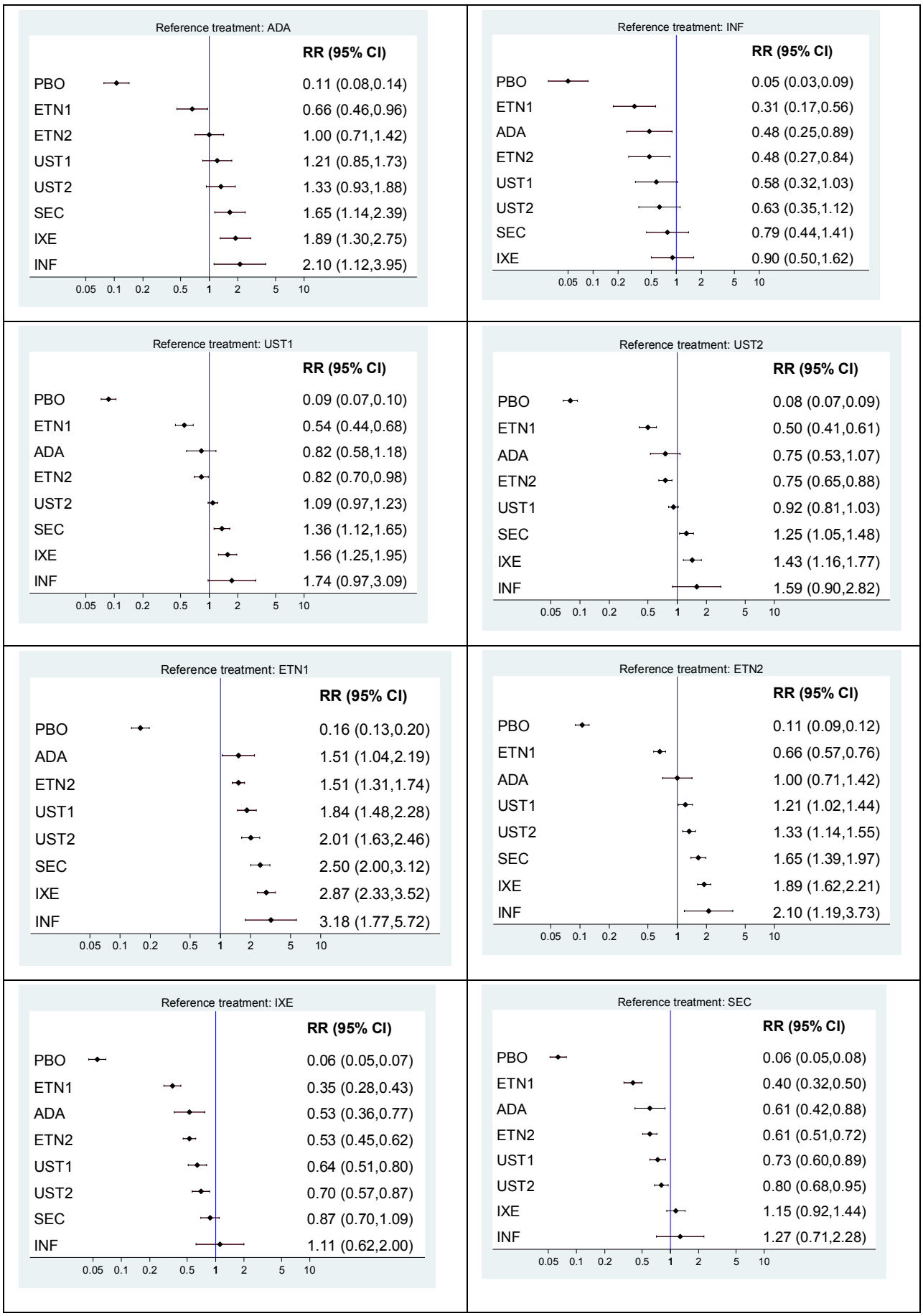


Figure 7: Relative risks of PASI75 at week 12 of other treatments vs an active treatment as reference (sensitivity analysis)

Testing for inconsistency (sensitivity analysis)

In a separate network meta-analysis model allowing for inconsistency, the test for inconsistency resulted in a p-value of 0.2415 (based on a chi-square test with 12 degrees of freedom of value 15.00). As in the main analysis, this means that there was no evidence to reject the null hypothesis “model is consistent”. This provides confidence of the findings based on the consistency model reported here.

Conclusion (sensitivity analysis)

The sensitivity analysis largely confirms and supports the findings of the main analysis.

Discussion of findings of the network meta-analysis

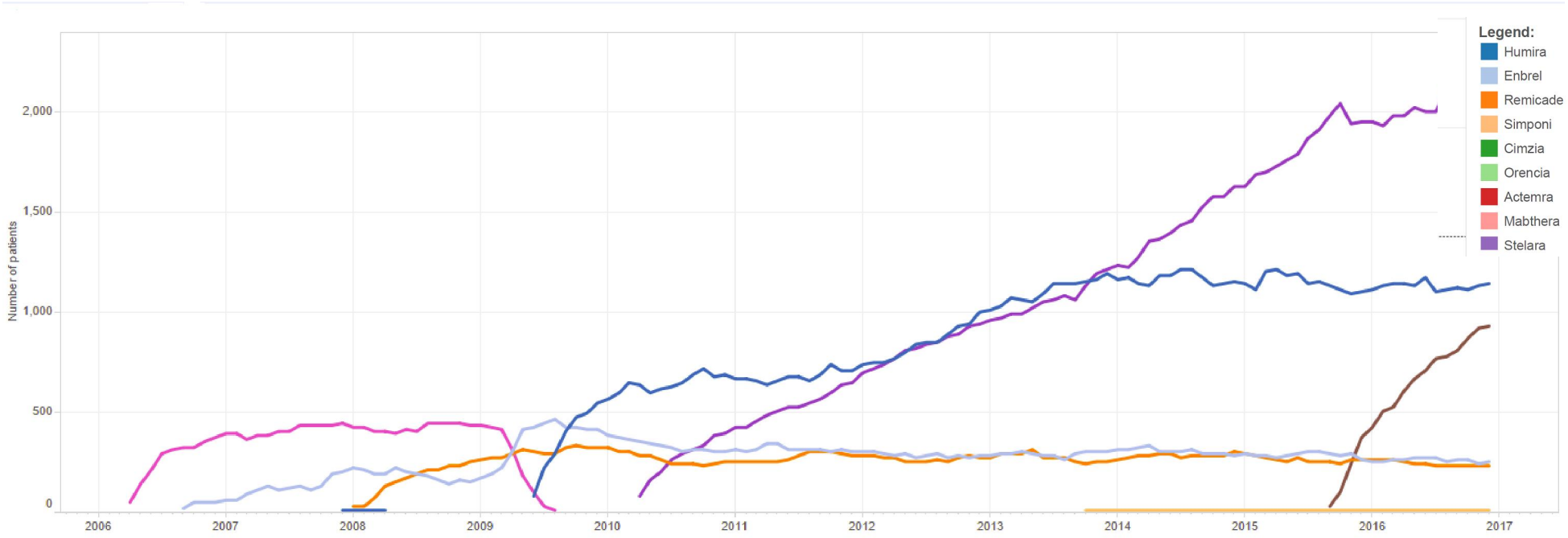
The network meta-analysis confirms the basis of the PBS-listings of adalimumab, etanercept, infliximab and ustekinumab. Infliximab and ustekinumab were PBS-listed based on cost-effectiveness relative to etanercept, whereas adalimumab was PBS-listed based on cost-minimisation vs etanercept. This reflects the relative efficacy of these biologics.

In terms of the most recently listed biologics, in the main network meta-analysis, secukinumab was shown to be superior to adalimumab and ixekizumab was superior to both adalimumab and ustekinumab. In the sensitivity analysis, when ustekinumab was divided into UST1 and UST2, secukinumab was superior to both dosages.

3. Review the utilisation of PBS biologics for the treatment of chronic plaque psoriasis including time on treatment and discontinuation from treatment, and compare this with that observed in the clinical trial evidence considered by the PBAC.

Medicare 1 in 10 data of biologics for CPP are show in **Figure 8** and **Figure 9** in terms of patients and scripts. As shown, the most widely used biologic is ustekinumab, followed by adalimumab. Secukinumab has had rapid uptake and is the third most widely used biologic. This is followed by etanercept and infliximab. The lower usage of infliximab is likely to be due to the fact that it is an intravenous infusion, therefore it is less convenient to use.

As ixekizumab has only been PBS-listed recently, its usage is not reflected in the Medicare 1 in 10 data.

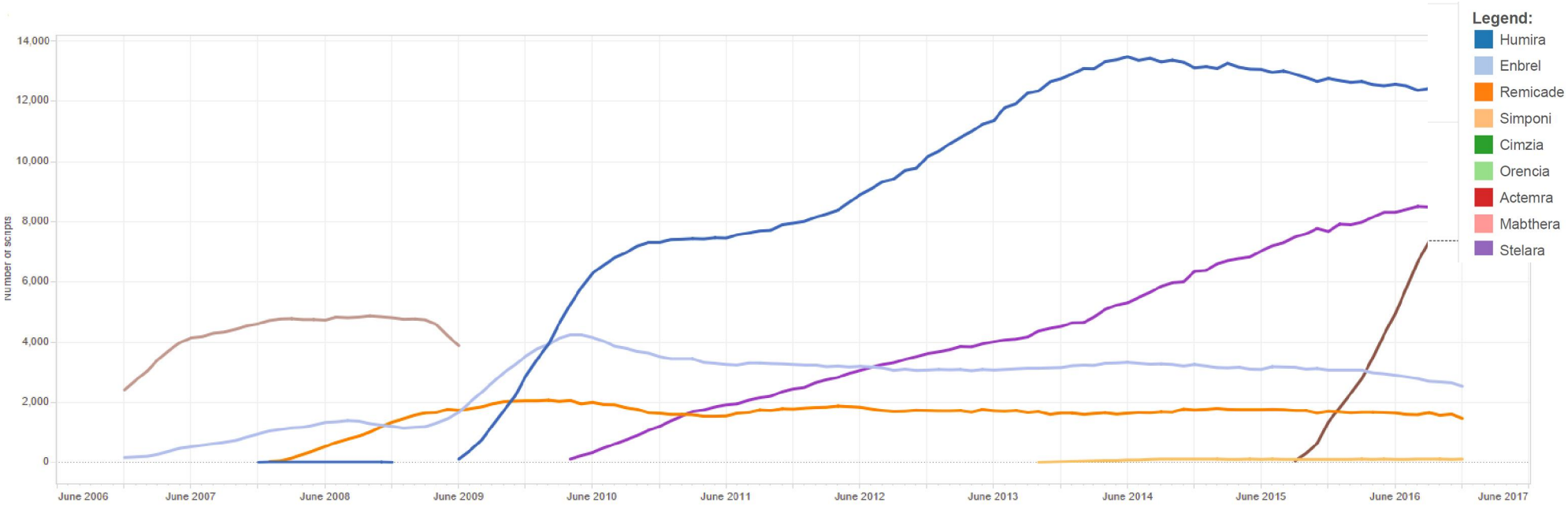


Data: Patients on therapy

	2013 Q4	2014 Q1	2014 Q2	2014 Q3	2014 Q4	2015 Q1	2015 Q2	2015 Q3	2015 Q4	2016 Q1	2016 Q2	2016 Q3	2016 Q4
Humira	1,194	1,143	1,184	1,173	1,153	1,204	1,194	1,133	1,103	1,143	1,173	1,123	1,143
Enbrel	303	324	303	293	283	283	293	293	263	263	273	263	253
Remicade	253	283	293	283	303	273	273	253	263	263	243	233	233
Simponi	10	10	10	10	10	10	10	10	10	10	10	10	10
Stelara	1,214	1,275	1,396	1,527	1,629	1,699	1,790	1,983	1,952	1,983	2,003	2,124	2,276
Cosentyx								30	374	526	708	809	931
Grand Total	2,974	3,035	3,186	3,288	3,379	3,470	3,561	3,702	3,965	4,188	4,410	4,562	4,845

A patient is defined to be on therapy if they have purchased a biologic script in the previous 4 months (or 6 months for Stelara or 15 months for MabThera) or if they have purchased a DMARD / immunosuppressant script in the previous 6 months (or 13 months for Methotrexate 1623K and 9 months for other Methotrexate)

Figure 8: Patients on therapy with biologics for CPP



ata: Biologics scripts

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Humira		10	10	2,883	7,314	7,951	10,156	12,746	13,110	12,756	12,462
Enbrel	172	951	1,204	3,540	3,520	3,257	3,075	3,156	3,257	3,075	2,539
Remicade			1,345	2,053	1,639	1,780	1,730	1,649	1,750	1,710	1,467
Simponi								30	121	111	121
Stelara					1,204	2,448	3,621	4,522	6,353	7,678	8,821
Cosentyx										1,345	8,507
Raptiva	2,418	4,613	4,815	1,325							
Grand Total	2,590	5,574	7,374	9,802	13,676	15,436	18,582	22,103	24,591	26,675	33,918

Figure 9: Biologics scripts for CPP

Discontinuation rates of biologics for CPP from Medicare 1 in 10 data compared to pooled rates from clinical studies are shown in **Table 9.** As shown, the discontinuation rates in clinical practice are higher for all biologics than seen in clinical studies.

Table 9: Discontinuation rates of biologics in CPP

Discontinuation rates	Adalimumab	Etanercept	Infliximab	Secukinumab	Ustekinumab
Medicare 1 in 10 data	17.5%	26.3%	16%	17.8%	9.7%
Clinical trials	3.9%	7.0%	8.9%	3.6%	2.6%

The results in the above table are not unexpected. Firstly, in the controlled setting of a clinical study discontinuation rates can be expected to be higher. Secondly, the discontinuation rate for etanercept can be expected to be higher as, if adequate resolution of the psoriasis is not achieved, then it is appropriate that the more effective agent, ustekinumab is initiated.

Summary and conclusion

Etanercept was PBS-listed for severe CPP based on cost-minimisation vs efalizumab. This was followed by PBS-listing of infliximab on the basis of cost-effectiveness vs both etanercept and efalizumab. Adalimumab was PBS-listed based on cost-minimisation vs etanercept. Thereafter ustekinumab was PBS-listed based on cost-effectiveness vs etanercept. More recently secukinumab was PBS-listed on the basis of cost-minimisation to adalimumab. This was followed by ixekizumab which was listed based on cost-minimisation to the least costly bDMARD.

American, Canadian and UK Guidelines for CPP were identified. These guidelines appear outdated. American and Canadian Guidelines recommend use of biologics (adalimumab, etanercept and infliximab) for moderate to severe CPP. The UK guidelines recommend adalimumab, etanercept, infliximab and ustekinumab for severe CPP. This is similar to the PBS restrictions for these agents.

A network meta-analysis shows that adalimumab and etanercept have similar efficacy. Both treatments were inferior to infliximab and ustekinumab. This confirms the basis on which these biologics was PBS-listed. In the main network meta-analysis, secukinumab was shown to be superior to adalimumab and ixekizumab was superior to both adalimumab and ustekinumab.

Utilisation from Medicare 1 in 10 data show that ustekinumab is used most commonly followed by adalimumab. Infliximab is used less which probably is due to the administration by IV infusion.

Discontinuation rates are higher in clinical practice than in clinical studies. This is expected. The higher discontinuation rate for etanercept is likely to occur due to switching to a superior agent if the CPP does not resolve.

Appendix to network meta-analysis

Network meta-analysis data (main analysis)

Tables for each biologic under investigation are provide below. PASI75 response data from each study are included in the relevant table. For studies investigating more than one active drug, the data were arbitrarily included in one of the tables so that the study appears once only.

Etanercept studies – PASI75 at week 12 data (main analysis)								
	Treatment and statistics							
	PBO		ETN		IXE		SEC	
Study identifier	**r**	**n**	**r**	**n**	**r**	**n**	**r**	**n**
Bachelez 2015	6	107	197	335				
Langley 2014 (FIXTURE)	16	324	142	323			249	323
Gottlieb 2003	1	55	17	57				
Gottlieb 2011	5	68	79	141				
Leonardi 2003	6	166	136	326				
Papp 2005	6	193	163	390				
Reich 2016	10	84	40	83				
Strober 2011	5	72	55	139				
Tyring 2006	15	307	147	311				
Griffiths 2015 (UNCOVER-2)	4	168	149	358	315	351		
Griffiths 2015 (UNCOVER-3)	14	193	204	382	336	385		
van der Kerkhof 2008	1	46	36	96				

R, number of responses; n, number of subjects

Abbreviations: ETN, etanercept; IXE, ixekizumab; PBO, placebo; sec, secukinumab

Adalimumab studies – PASI75 at week 12 data (main analysis)				
	Treatment and statistics			
	PBO		ADA	
Study	**r**	**n**	**r**	**N**
Asahina 2010	1	46	40	81
Cai 2017	10	87	263	338
Gordon 2006	2	52	24	45
Gordon 2015	2	42	30	43
Menter 2008	20	398	554	814
Saurat 2008	8	53	83	108

R, number of responses; n, number of subjects

Abbreviations: ADA, adalimumab; PBO, placebo

Infliximab studies – PASI75 at week 12 data				
	Treatment and statistics			
	PBO		INF	
Study	**r**	**n**	**r**	**n**
Chaudhari 2001	2	11	9	11
Gottlieb 2004	3	51	87	99

Infliximab studies – PASI75 at week 12 data				
	Treatment and statistics			
	PBO		INF	
Menter 2007	4	208	237	314
Reich 2005	2	77	242	301
Torii 2010	0.5	20	24.5	36
Yang 2012	1	45	68	84

R, number of responses; n, number of subjects

Abbreviations: INF, infliximab; PBO, placebo

Ixekizumab studies – PASI75 at week 12 data				
	Treatment and statistics			
	PBO		IXE	
Study	**r**	**n**	**r**	**n**
Gordon 2016	17	431	386	433

R, number of responses; n, number of subjects

Abbreviations: IXE, ixekizumab; PBO, placebo

Secukinumab studies – PASI75 at week 12 data						
	Treatment and statistics					
	PBO		UST		SEC	
Study	**r**	**n**	**r**	**n**	**r**	**n**
Blauvelt 2014	0.5	60			44.5	59
Langley 2014 (ERASURE)	11	246			200	245
Paul 2015	2	61			52	60
Thaçi 2015			265	335	304	334

R, number of responses; n, number of subjects

Abbreviations: PBO, placebo; SEC, secukinumab; UST, ustekinumab

Ustekinumab studies – PASI75 at week 12 data						
	Treatment and statistics					
	PBO		UST		ETN	
Study	**r**	**n**	**r**	**n**	**r**	**n**
Lebwohl 2015 (AMAGINE-2)	25	309	210	300		
Lebwohl 2015 (AMAGINE-3)	19	315	217	313		
Griffiths 2010			397	556	197	347
Igarashi 2012	2	31	80	126		
Leonardi 2008	8	255	341	511		
Papp 2008	15	410	584	820		
Tsai 2011	3	60	41	61		
Zhu 2013	18	162	132	160		

R, number of responses; n, number of subjects

Abbreviations: ETN, etanercept; PBO, placebo; UST, ustekinumab

Network meta-analysis data (sensitivity analysis)

As in the main analysis, tables for each biologic under investigation are provide below. PASI75 response data from each study are included in the relevant table. For studies investigating more than one active drug, the data were arbitrarily included in one of the tables so that the study appears once only.

Etanercept studies – PASI75 at week 12 data (sensitivity analysis)										
	Treatment and statistics									
	PBO		ETN1		ETN2		IXE		SEC	
Study	**r**	**n**	**r**	**n**	**r**	**n**	**r**	**n**	**r**	**n**
Bachelez 2015	6	107			197	335				
Cassano 2010			13	36	19	36				
Gottlieb 2003	1	55	17	57						
Gottlieb 2011	5	68			79	141				
Griffiths 2015 (UNCOVER-2)	4	168			149	358	315	351		
Griffiths 2015 (UNCOVER-3)	14	193			204	382	336	385		
Langley 2014 (FIXTURE)	16	324			142	323			249	323
Leonardi 2003	6	166	55	162	81	164				
Papp 2005	6	193	67	196	96	194				
Reich 2016	10	84	40	83						
Sterry 2010			135	371	207	377				
Strober 2011	5	72			55	139				
Strohal 2013			51	137	85	136				
Tyring 2006	15	307			147	311				
van der Kerkhof 2008	1	46	36	96						

R, number of responses; n, number of subjects

Abbreviations: ETN1, low dose etanercept; ETN2, high doses etanercept; IXE, ixekinumab PBO, placebo; SEC, secukinumab

Adalimumab studies – PASI75 at week 12 data (sensitivity analysis)				
	Treatment and statistics			
	PBO		ADA	
Study	**r**	**n**	**r**	**n**
Asahina 2010	1	46	40	81
Cai 2017	10	87	263	338
Gordon 2006	2	52	24	45
Gordon 2015	2	42	30	43
Menter 2008	20	398	554	814
Saurat 2008	8	53	83	108

R, number of responses; n, number of subjects

Abbreviations: ADA, adalimumab; PBO, placebo

Infliximab studies – PASI75 at week 12 data (sensitivity analysis)				
	Treatment and statistics			
	PBO		INF	
Study	**r**	**n**	**r**	**n**
Chaudhari 2001	2	11	9	11
Gottlieb 2004	3	51	87	99
Menter 2007	4	208	237	314
Reich 2005	2	77	242	301
Torii 2010	5	20	24.5	36
Yang 2012	1	45	68	84

R, number of responses; n, number of subjects

Abbreviations: INF, infliximab; PBO, placebo

Ixekizumab studies – PASI75 at week 12 data (sensitivity analysis)				
	Treatment and statistics			
	PBO		IXE	
Study	**r**	**n**	**r**	**n**
Gordon 2016	17	431	386	433

R, number of responses; n, number of subjects

Abbreviations: IXE, ixekizumab; PBO, placebo

Secukinumab studies – PASI75 at week 12 data (sensitivity analysis)						
	PBO		UST2		SEC	
Study	**r**	**n**	**r**	**n**	**r**	**n**
Blauvelt 2014	0.5	60			44.5	59
Langley 2014 (ERASURE)	11	246			200	245
Paul 2015	2	61			52	60
Thaçi 2015			265	335	304	334

R, number of responses; n, number of subjects

Abbreviations: PBO, placebo; SEC, secukinumab; UST2, high dose ustekinumab

Ustekinumab studies – PASI75 at week 12 data (sensitivity analysis)								
	Treatment and statistics							
	PBO		UST1		UST2		ETN2	
Study	**r**	**n**	**r**	**n**	**r**	**n**	**r**	**n**
Griffiths 2010			141	209	256	347	197	347
Igarashi 2012	2	31	38	64	42	62		
Lebwohl 2015 (AMAGINE-2)	25	309			210	300		
Lebwohl 2015 (AMAGINE-3)	19	315			217	313		
Leonardi 2008	8	255	171	255	170	256		
Papp 2008	15	410	273	409	311	411		
Tsai 2011	3	60	41	61				
Zhu 2013	18	162	132	160				

R, number of responses; n, number of subjects

Abbreviations: ETN2, high dose etanercept; PBO, placebo; UST1, low dose ustekinumab; UST2, high dose ustekinumab

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