H.14 Biological therapy

H.14.1 Stratified Case Series/Within-Group Comparisons

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>A. Mazzotta, M. Esposito, A. Costanzo, and S. Chimenti. Efficacy and safety of etanercept in psoriasis after switching from other treatments: an observational study. Am.J.Clin.Dermatol. 10 (5):319-324, 2009.

Ref ID: MAZZOTTA 2009</td>
<td>Observational: Prospective case series

Washout period: 4 weeks

Representative population sample: Recruited from academic dermatology out-patient clinic

Confounders adjusted for: not assessed

Minimal</td>
<td>N: 234</td>
<td>Inclusion criteria: Aged 18-80; moderate-to-severe plaque-type psoriasis; unsatisfactory clinical response/loss of efficacy (<PASI50) or resistance (AEs that could compromise treatment continuation or poor compliance) to traditional or biologic systemic agents

Exclusion criteria: Co-morbid conditions that were contraindications to anti-TNF-α treatment
<table>
<tr><th>Parameter</th><th>Psoriasis only (n=124)</th><th>Concomitant PsA (n-110)</th></tr>
<tr><td>Mean age – years (±SD)</td><td>44.0±13.5</td><td>50.4±12.3</td></tr>
<tr><td>Male (%)</td><td>65.3%</td><td>60.9%</td></tr>
</table>
</td>
<td>Etanercept (self-administered subcutaneously): 50 mg twice weekly for first 12 weeks reduced to 25 mg twice weekly for remaining 12 weeks</td>
<td>Treatment duration: 24 weeks</td>
<td>Change in PASI

PASI75

PASI50

AEs</td>
<td>None</td>
</tr>
</table>

	attrition bias: unclear **Outcomes adequately measured:** Yes **Appropriate statistical analysis:** yes		**Previous treatment**				
			CSA	104	66		
			PUVA	49	17		
			Retinoids	35	20		
			Corticosteroids	33	54		
			MTX	32	66		
			Biologics	**27**	**30**		
			Infliximab	23	30		
			Efalizumab	4	0		
			Fumaric acid esters	7	4		

Effect Size

Outcomes

Efficacy

Psoriasis only cohort

Parameter	**Patients (%)**		**p-value (between groups)**
	Previous biologic (n=26)	**No previous biologic (n=98)**	

Baseline PASI	14.5±5.2	16.1±7.1	NS
Week 12			
PASI score	5.4±3.8	4.9±4.0	NS
PASI50	18 (69.2%)	79 (80.2%)	NS
PASI75	8 (30.8%)	43 (43.7%)	NS
Week 24			
PASI score	4.0±4.5	2.8±3.4	NS
PASI50	18 (69.6%)	88 (89.9%)	0.013
PASI75	17 (65.2%)	74 (75.3%)	NS

Concomitant PsA cohort

Parameter	**Patients (%)**		**p-value (between groups)**
	Previous biologic (n=30)	**No previous biologic (n=80)**	
Baseline PASI	8.0±6.8	8.9±8.3	NS
Week 12			
PASI score	2.9±2.6	2.9±3.7	NS
PASI50	18 (59.3%)	53 (65.7%)	NS
PASI75	11 (37.0%)	36 (45.2%)	NS
Week 24			

PASI score	3.0±2.9	1.2±1.8	0.0010
PASI50	14 (45.8%)	74 (92.3%)	<0.0001
PASI75	9 (29.2%)	59 (73.8%)	<0.0001

Adverse events

- Not stratified by previous biologic exposure

Author's conclusion

- Etanercept may represent a valid, effective and well-tolerated therapeutic alternative treatment for patients with plaque-type psoriasis who have failed to respond to other biologic therapies
- However, etanercept had a lower efficacy in patients who have previously not responded to biologic therapy

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Van L, Modi SV, Yang DJ, Hsu S. Sustained Efficacy and Safety of Adalimumab in Psoriasis Treatment: A Retrospective Study of 49 Patients With and Without a History of TNF-Antagonist Treatment. Arch.Dermatol. 144 (6):804-806, 2008.

Ref ID: VAN2008</td>
<td>Observational:
Retrospective case series (medical chart review)

Washout period: Patients switched from infliximab therapy had a washout period of at least 2 months, and those switched from etanercept or efalizumab had a washout period of at least 2 weeks.

Representative population sample: Recruited from Baylor College of Medicine dermatology clinic; unclear how many (if any) had concomitant PsA

Confounders adjusted for: not assessed

Minimal attrition bias: borderline – 18.3%</td>
<td>N: 49

Drop-outs:

9 (18.3%) discontinued before 12 months:
3 due to AEs
3 due to primary lack of efficacy
2 due to secondary lack of efficacy
1 lost to follow-up</td>
<td>Inclusion criteria: moderate-to-severe plaque psoriasis; started treatment with adalimumab injections at least 12 months previously

Note: Patients who had undergone prior therapy with biological agents were switched to adalimumab therapy only after they had experienced lack or loss of efficacy with their prior treatment.

Exclusion criteria: Not stated

<table>
<tr><th>Parameter</th><th>All (n=49)</th></tr>
<tr><td>Biologics</td><td>39 (80%)</td></tr>
<tr><td>Anti-TNF-α</td><td>37 (76%)</td></tr>
<tr><td>Efalizumab</td><td>6 (12%)</td></tr>
<tr><td>Infliximab</td><td>29 (59%)</td></tr>
<tr><td>Etanercept</td><td>15 (31%)</td></tr>
</table>
</td>
<td>Adalimumab, 40 mg weekly

After 12 weeks patients whose disease was determined to be "clear" or "almost clear" by PGA had their doses decreased to once every 2 weeks, while the remainder continued weekly dosing for another 3 months. Patients were then reassessed at 3- to 6-month intervals, during which the dermatologist decreased the dosing frequency to once every 2 weeks or continued the weekly schedule, depending on individual response.</td>
<td>Treatment duration: up to 12 months</td>
<td>Clear or nearly clear on PGA

AEs</td>
<td>Not stated</td>
</tr>
</table>

	Outcomes adequately measured: unclear **Appropriate statistical analysis:** unclear						

Effect Size

Outcomes

Efficacy (ITT analysis)

Initial response (not stratified)

Overall	**All (n=49)**
Clear or nearly clear	
3 months	43 (88%)
6 months	3
9 months	1
Continued weekly dosing (no response at 9 months)	2

Sustained response (stratified)

Parameter	Patients (%)		
	Previous biologic (n=39)	**Previous anti-TNF-α (n=37)**	**No previous biologic (n=10)**
12 months (sustained efficacy)			
Clear or nearly clear	31 (79%)	29 (78%)	7 (70%)

Adverse events

- Not stratified by previous biologic exposure
- No complications were observed during transitions from prior biological agents

Author's conclusion

- Patients with psoriasis who have received prior anti-TNF-a can expect a sustained clinical response to adalimumab.

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>N. Cassano, A. Galluccio, Simone C. De, F. Loconsole, S. D. Massimino, A. Plumari, S. Dattola, Guerra A. Puglisi, L. Donato, F. Cantoresi, Pita O. De, G. Fenizi, V. Altamura, M. Congedo, R. Pellicano, and G. A. Vena. Influence of body mass index, comorbidities and prior systemic therapies on the response of psoriasis to adalimumab: an exploratory analysis from the APHRODITE data. J.Biol.Regul.Homeost.Agents 22 (4):233-237, 2008.

Ref ID: CASSANO2008

Based on the original study:
G. A. Vena, A. Galluccio, Simone C. De, V. Mastrandrea, R. Buquicchio, Greca S. La, S. Dattola, Guerra A. Puglisi, L. Donato, F. Cantoresi, Pita O. De, M. Pezza, D. Agostino, R. Vernaci, A. Miracapillo, G. Valenti, and N. Cassano. A</td>
<td>Observational: Open label prospective case series (multicentre)

Washout period: at least 2 weeks for topicals, 4 weeks for conventional systemics, and 12 weeks for biologics

Representative population sample: No – 100 % with concomitant PsA)

Confounders adjusted for: unclear

Minimal attrition bias: yes

Outcomes adequately measured: unclear (and PASI90 reported although explicitly said not to be</td>
<td>N: 147

Drop-outs:

3 (2.0%)</td>
<td>Inclusion criteria: adults with active PsA and chronic plaque psoriasis; moderate to severe disease (>10% BSA and PASI ≥10 or <10% BSA but lesions localised on visible difficult to treat sites e.g., hands and face)

Exclusion criteria: Pregnancy and lactation, any active infection, latent or recurrent infectious diseases (including latent TB or seropositivity for hepatitis B and C); history of demyelinating diseases, heart failure, lupus erythematosus, immunodeficiencies, cancer or lymphoproliferative disease (other than successfully treated BCC)

<table>
<tr><th>Parameter</th><th>All (n=144)</th></tr>
<tr><td>% male</td><td>51%</td></tr>
<tr><td>Mean age – years</td><td>48.6 (20-75)</td></tr>
<tr><td>Psoriasis duration, mean years</td><td>15.2</td></tr>
<tr><td>PsA duration,</td><td>7.6</td></tr>
</table>
</td>
<td>Adalimumab, (subcutaneously)

40 mg every other week

Note: concomitant therapies active in either PsA or psoriasis not permitted (except emollients and episodic administration of NSAIDs)</td>
<td>Treatment duration: up to 12 weeks</td>
<td>PASI75

PASI50

PASI90 not stated as an outcome in methods but reported in results</td>
<td>Not stated</td>
</tr>
</table>

<table>
<tr>
<td>multicentre open-label experience on the response of psoriasis to Adalimumab and effect of dose escalation in non-responders: the Aphrodite project. Int.J.Immunopathol.Pharmacol. 22 (1):227-233, 2009.

REF ID VENA2009</td>
<td>an outcome in the methods due to lack of statistical power)

Appropriate statistical analysis: unclear</td>
<td></td>
<td>
<table>
<tr><td>mean years</td><td></td></tr>
<tr><td>Mean PASI</td><td>18.8</td></tr>
<tr><td>Mean BSA</td><td>22.1%</td></tr>
<tr><td>Regular alcohol consumption</td><td>29%</td></tr>
<tr><td>Smokers</td><td>32%</td></tr>
<tr><td>Weight (kg)</td><td>74.8 (43-118)</td></tr>
<tr><td>Concomitant treatment for comorbidities</td><td>29%</td></tr>
<tr><td>Previous use of biologics*</td><td>56 (39%)</td></tr>
</table>
*Note: the previous biologics were infliximab and/or etanercept in all but 2 cases (who used efalizumab)
</td>
<td>Patients requiring other concomitant strategies were considered non-responders and were withdrawn from the study analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td colspan="8">Effect Size

Outcomes

<u>Efficacy (ACA); week 12</u>

<table>
<tr><th>Parameter</th><th>Patients (%)</th></tr>
</table>
</td>
</tr>
</table>

	All (n=144)
PASI75	65 (45%)

Note: response rates at week 12 in non-stratified sample independent of gender, smoking, alcohol consumption, hypertension and/or metabolic comorbidities (p>0.05)

- Total response rate: PASI50 = 111 (77%); PASI75 = 65 (45%)
- There was no consistent or significant differences in the PASI50 response rates between patients previously treated with only traditional systemics and those treated with biologics (p>0.05)
- Among **responders** (at least PASI50) the likelihood of achieving PASI75 was higher in patients who were naïve to biologics (47.5%) compared to those who had been treated with biologics in the past (26%); p=0.03

Author's conclusion

- Previous use of biologics did not appear to affect the rate of responders per se, although it was associated with a lower PASI75 rate among responders

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>K. Papp, V. Ho, H. D. Teixeira, K. Guerette, K. Chen, and C. Lynde. Efficacy and safety of adalimumab when added to inadequate therapy for the treatment of psoriasis: results of PRIDE, an open-label, multicentre, phase IIIb study [submitted]. J.Eur.Acad.Dermatol.Venereol., 2012.
REF ID PAPP2012</td>
<td>Observational: Open label prospective case series (multicentre; 23 sites in Canada – routine care)

Washout period: NA – concomitant therapies permitted

Representative population sample: Yes

Confounders adjusted for: unclear

Minimal attrition bias: yes

Outcomes adequately measured: yes</td>
<td>N: 203

Drop-outs:

11.8% (4.4% due to adverse events)</td>
<td>Inclusion criteria: Adult patients (at least 18 years of age) with a clinical diagnosis of psoriasis for at least 6 months and stable plaque psoriasis for at least 2 months prior to entry; moderate to severely active plaque psoriasis (BSA> 10% and a PASI score ≥12; active psoriasis despite treatment with topical agents; failure to respond to, intolerant to, or unable to access phototherapy; failure to respond to, intolerant to or contraindicated for at least two of the following therapies: Ciclosporine A, methotrexate and/or oral retinoids.

Exclusion criteria: Pregnancy,

other active skin diseases or infections present, erythrodermic,

pustular, medication-induced or -exacerbated psoriasis, or new onset guttate psoriasis as the primary morphology of psoriasis.

<table>
<tr><th>Parameter</th><th>All (n=203)</th></tr>
<tr><td>% male</td><td>61.1%</td></tr>
<tr><td>Mean age – years</td><td>45.5 (12.3)</td></tr>
</table>
</td>
<td>Adalimumab, self-

administered

Loading dose of 80 mg adalimumab

SC at baseline, followed by 40 mg SC every other week starting at

week 1

Note: concomitant therapies
Doses and regimens of concomitant medications and therapies for the treatment of</td>
<td>Treatment duration: min 24 weeks</td>
<td>PASI75</td>
<td>Abbott Laboratories</td>
</tr>
</table>

	Appropriate statistical analysis: yes: Comparisons between patient subgroups used ANOVA with subgroup as a main effect for continuous scale variables and the Fisher's Exact test for categorical variables. The 95% confidence intervals for binomial proportion are provided by exact (Clopper-Pearson) method. ITT analysis: yes (non-responder imputation)		(SD) | Psoriasis duration, mean years (SD) | 22.2 (11.5) Mean PASI (SD) | 20 (7.9) Mean BSA (SD) | 27.3% (17.1%) PsA | 75 (36.9%) Mean DLQI (SD) | 12.8 (6.98) Weight (kg), mean (SD) | 94.8 (23.9) Prior and concomitant psoriasis therapy (n [%]) Phototherapy (any time before baseline) | 169 (83.3) Topical treatments (within 12 months before baseline) | 109 (53.7)	psoriasis that the patient was receiving at baseline (topical, systemic or phototherapy) could be tapered off, stopped or remain stable from baseline until week 16. BUT The initiation of new topical therapies (with the exception of topical therapies for the palms, soles of feet, axilla and groin), the initiation of new systemic therapies or an increase in the dosing regimen of existing therapies, and the initiation of or an increase			

			Systemic non-biologic (any time before baseline) - corticosteroids - tazarotene - acitretin - ciclosporine - methotrexate - other Systemic Biologic (any time before baseline) - etanercept - infliximab - alefacept - efalizumab - ustekinumab - other **Note:** for subgroup analysis 'failure' of previous therapy was defined as	149 (73.4) 3 (1.5) 4 (2.0) 57 (28.1) 51 (25.1) 101 (49.8) 27 (13.3) 78 (38.4) 25 (12.3) 16 (7.9) 18 (8.9) 17 (8.4) 18 (8.9) 14 (6.4)	in the existing regimen and frequency of UVB phototherapy could not occur before the week 16 visit.			

			either never achieving a satisfactory response or achieving a satisfactory response but losing it over time				

Effect Size

Outcomes

Note: Biologic therapies, which had been used by 38.4% of patients, were discontinued largely due to lack of efficacy or the termination of the clinical study/investigation in which the biologic had been administered.

A total of 137 patients (67.5%) received concomitant therapies for psoriasis; the most commonly used medications (≥5% of patients) were corticosteroids (40.4%), vitamin D and analogues (17.7%), and methotrexate (11.3%). Ten patients (4.9%) received phototherapy during this study. The most commonly used (occurring in ≥5% of patients) concomitant medications were paracetamol (18.2%); acetylsalicylic acid (13.8%), ibuprofen (12.3%), atorvastatin (10.3%), hydrochlorothiazide (8.4%), and ramipril (8.9%).

PASI75 (ITT)

PASI75	**Patients (%)**						
	All (n=203)	**No prior biologics (N=125)**	**Prior biologics (N=78)**	**Prior anti-TNF (N=37)**	**Failed prior biologic (N=40)**	**Failed prior anti-TNF (N=17)**	**Failed ≥2 biologics (N=25)**
Week 16	144 (70.9%)	93 (74.4%)	51 (65.4%)	27 (73.0%)	24 (60.0%)	12 (70.6%)	17 (68.0%)
Week 24	140 (69.0%)	92 (73.6%)	48 (61.5%)	28 (62.2%)	24 (60.0%)	10 (58.8%)	14 (56.0%)

Author's conclusion

- In patients who had failed previous biologic treatment, PASI 75 response rates at weeks 16 and 24 were good, including patients who had failed previous treatment with etanercept

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>P.M. Laws , A.M. Downs, R. Parslew, B. Dever, C.H. Smith, J.N. Barker, B. Moriarty, R. Murphy, B. Kirby, A.D. Burden, S. McBride, A.V. Anstey, S. O'Shea, N. Ralph, C. Buckley, C.E.M. Griffiths, R.B. Warren. Practical experience of Ustekinumab in the treatment of psoriasis: experience from a multicentre, retrospective case cohort study across the U.K. and Ireland

Not yet published

RefID: LAWS2011</td>
<td>Observational: Open label retrospective case series; 10 centres in the UK and Ireland

Washout period: NA – concomitant therapies permitted

Representative population sample: Yes – included all who had completed 16 wk treatment (or stopped due to adverse events) between March 2009 and October 2010 outside clinical trials

Confounders adjusted for: no

Minimal attrition bias: NA</td>
<td>N: 129

Drop-outs:

NA</td>
<td>Inclusion criteria: included all who had completed 16 wk treatment (or stopped due to adverse events) between March 2009 and October 2010 outside clinical trials

Exclusion criteria: none stated

<table>
<tr><th>Parameter</th><th>All (N=129)</th></tr>
<tr><td>Age (years)</td><td>46.0 ± 11.4</td></tr>
<tr><td>Sex (male)</td><td>69 (53.5%)</td></tr>
<tr><td>Weight (kg)</td><td>93.7 ± 25.0</td></tr>
<tr><td>BMI (kg/m^2)</td><td>32.4 ± 8.7</td></tr>
<tr><td>Obesity (%)</td><td>51/93 (54.8%)</td></tr>
<tr><td>Smoking (yes)</td><td>51 (39.5%)</td></tr>
<tr><td>PsA</td><td>45 (34.9%)</td></tr>
<tr><td>Depression</td><td>35 (27.1%)</td></tr>
<tr><td>Disease duration (years)</td><td>24.3 ± 10.2</td></tr>
</table>
</td>
<td>Ustekinumab, induction therapy at weeks 0 and 4 and then every 12 weeks.

Weight dependent dosing: ≤100kg given 45mg >100kg given 90mg

Overlap therapy: medication co-prescribed during induction of ustekinumab therapy</td>
<td>Treatment duration: min 16 weeks</td>
<td>PASI75</td>
<td>None</td>
</tr>
</table>

	Outcomes adequately measured: yes **Appropriate statistical analysis:** yes **ITT analysis:** No: analysis performed on an available case basis throughout and therefore excludes 'drop outs' due to adverse events.		PASI: 22.9 ± 10.1 Alcohol Nil: 60 (48.8%) Up to weekly limit: 48 (39.0%) Excess: 9 (7.3%) **Number of previous systemics*** 0: 1.6 (2/129) 1-2: 33.3 (43/129) 3-4: 52.7 (68/129) ≥5: 12.4 (16/129) * Includes methotrexate, ciclosporin, acitretin, fumaric acid esters, hydroxycarbamide, mycophenolate mofetil, azathioprine.	**Rescue therapy:** was defined as additional medication required following the induction phase.			
Effect Size Outcomes **Note:** 10/80 who achieved PASI75 at week 16 received overlap therapy during induction; 4 of these were still on an additional systemic therapy at 16 weeks. Additional therapies included: ciclosporin (n=5), methotrexate (n=4) and acitretin (n=1). Of these 10, 7 had had previous biologic exposure and 3 were biologic naïve							

Also, of the 47 patients failed to achieve a PASI >75, 19 patients had additional systemic therapy (18 received treatment as overlap and 1 as rescue). Of the 19 patients 3 were biologic naïve. The patient who received rescue therapy was biologic naïve.

Efficacy at week 16 (ACA)

	Patients (%)			
	All (n=127)	**No prior biologics (N=21)**	**Prior biologics (N=106)**	**p-value (biologic vs naïve)**
PASI75	80 (63.0%)	16 (76.2%)	64 (60.4%)	0.14

	Patients (%)			
	All (n=127)	**None or 1 prior biologics (N=48)**	**2-4 prior biologics (N=79)**	**p-value (2-4 biologics vs 0-1 biologics)**
PASI75	80 (63.0%)	35 (72.9%)	45 (57.0%)	0.096

Efficacy at week 16 (ACA – excluding those who had overlap therapy)

	Patients (%)		
	All (n=98)	**No prior biologics (N=15)**	**Prior biologics (N=83)**
PASI75	70 (71.4%)	13 (86.7%)	57 (68.7%)

Author's conclusion

- Comparison of individuals who previously received 0 or 1 biologic agent with individuals who received 2-4 biologic agents prior to ustekinumab demonstrated a non-significant reduction in response (although the study may be underpowered to detect any differences)

H.14.2 Non-randomised comparison within RCT

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>J. P. Ortonne, S. Chimenti, K. Reich, R. Gniadecki, P. Sprogel, K. Unnebrink, H. Kupper, O. Goldblum, and D. Thaci. Efficacy and safety of adalimumab in patients with psoriasis previously treated with anti-tumour necrosis factor agents: subanalysis of BELIEVE.</td>
<td>Observational: prospective case series/ subanalysis of RCT data

Note: post-hoc analysis – not stated in initial study protocol

Blinding: patients blinded to topical treatment

Washout period: see exclusion criteria

Representativ</td>
<td>N: 730

Drop-outs (do not complete study)

54: 15 (5.3%) with prior anti-TNF and 39 (8.7%) anti-TNF naïve</td>
<td>Inclusion criteria: Aged 18 or over; diagnosis of chronic plaque-type psoriasis for at least 6 months; previous failure, intolerance of or contraindication to at least 2 traditional or biologic systemic agents (at least one of which was CSA, MTX or oral PUVA); disease severity that meets at least two of the following criteria: PASI ≥10, BSA ≥10% and DLQI ≥10

Exclusion criteria: Previous exposure to adalimumab; topical calcipotriol + betamethasone therapy within 2 weeks; systemic or topical corticosteroids within 4 or 2 weeks respectively; etanercept <3wks; infliximab <8wks; efalizumab<6wks; abatacept<65 days
<table>
<tr><th></th><th>Prior TNF-antagonist (n=282)</th><th>No prior TNF-antagonist (n=448)</th><th>All patients (n=730)</th></tr>
<tr><td>Mean age – years (±SD)</td><td>45.6±12.1</td><td>44.8±12.4</td><td>45.1±12.3</td></tr>
</table>
</td>
<td>Adalimumab (subcutaneously): 80 mg at wk 0, then 40 mg every other week to week 15

Note: 50% of patients self-administered concomitant topical calcipotriol 52.2 µg/g plus betamethasone dipropionate 0.64 mg/g once daily (application not to exceed 30% BSA or 100g per week); the other 50% received matching drug-free vehicle

(after wk 4 the dosing of topical switched from once daily to as needed – with the same restrictions on total dose)</td>
<td>Treatment duration

16 weeks</td>
<td>Primary (at wk 16): PASI75

Primary (at wk 16):

PASI90

PASI100

PGA – clear or minimal

DLQI

AEs (follow-up of up to 70 days post treatment)</td>
<td>Abbott Laboratories</td>
</tr>
</table>

J.Eur.Acad .Dermatol. Venereol., 2011. Ref ID: ORTONNE 2011	**e population sample:** yes **Confounders adjusted for:** yes **Confounders accounted for:** yes (see below) **Minimal attrition bias:** yes **Outcomes adequately measured:** Yes **Appropriate statistical analysis:** yes		Male (%)	64.9	71.0	68.6	Prior use of systemics within 12 months before study entry was recorded and reasons collected: i. Never responded ii. Lost response iii. Discontinued for intolerance/side effects iv. Other **Note:** there is lack of information to support these subjective ratings			
			BSA (%)	32.4±20.1	33.3±20.3	33.3±20.2				
			PASI	19.5±8.9	19.4±8.5	19.5±8.7				
			Mean duration of psoriasis – years (±SD)	22.4±11.8	20.3±11.5	21.1±11.7				
			History of PsA, n (%)	95 (33.7%)	110 (24.6%)	205 (28.1%)				
			Previous treatment							
			Methotrexate	214 (75.9%)	297 (66.3%)	511 (70.0%)				
			CSA	171 (60.6%)	227 (50.7%)	398 (54.5%)				
			Oral PUVA	132 (46.8%)	181 (40.4%)	313 (42.9%)				
			Biologics*			**47.7%**				
			Anti-TNF*			**38.6%**				
			Etanercept			29.9%				
			Infliximab			13.4%				
			Certolizumab			2.6%				

			*Includes 2.6% of the total population (5.5% of those previously using biologics) previously exposed to certolizumab				

Effect Size

Outcomes

Efficacy

PASI75 (ITT population – missing values imputed as non-response)	**Patients (%)**						**Odds ratio (95% CI)***	**p-value***
	ADA + vehicle		**ADA + topical**		**All ADA**			
	Prior TNF-antagonist (n=138)	**No prior TNF-antagonist (n=226)**	**Prior TNF-antagonist (n=144)**	**No prior TNF-antagonist (n=222)**	**Prior TNF-antagonist (n=282)**	**No prior TNF-antagonist (n=448)**		
Week 2	7 (5.1%)	14 (6.2%)	22	32	29 (10.3%)	46 (10.3%)	1.2 (0.7-2.0)	0.591
Week 4	41 (29.7%)	77 (34.1%)	53	96	94 (33.3%)	173 (38.6%)	0.8 (0.6-1.2)	0.252
Week 8	79 (57.2%)	139 (61.5%)	65	130	144 (51.1%)	269 (60.0%)	0.8 (0.6-1.1)	0.166
Week 12	99 (71.7%)	168 (74.3%)	71	141	170 (60.3%)	309 (69.0%)	0.8 (0.6-1.2)	0.339
Week 16	92 (66.7%)	166 (73.5%)	82	155	174 (61.7%)	321 (71.7%)	0.7 (0.5-1.1)	0.095

***Calculated by logistic regression adjusted for treatment group, number of prior systemics (>3, ≤3), age, duration of psoriasis, baseline PASI, baseline BSA affected, nail involvement, scalp involvement and presence of tender, swollen or stiff joints at baseline.

Note: no significant difference was revealed in this analysis between those using concomitant topical therapy and those using vehicle

Stratified efficacy rates at week 16

a) Prior anti-TNF treatment

ITT population – missing values imputed as non-response	Patients (%)			p-value vs no prior TNF antagonist*
	No prior TNF-antagonist (n=448)	Prior etanercept (n=170)	Prior infliximab (n=53)	
PASI75	321 (71.7%)	111 (65.3%)	31 (58.5%)	ETA = 0.361 INF = 0.174
PASI90	222 (49.6%)	63 (37.1%)	18 (34.0%)	ETA = 0.051 INF = 0.118
PASI100	102 (22.8%)	25 (14.7%)	8 (15.1%)	ETA = 0.173 INF = 0.576
PGA clear or minimal	293 (65.4%)	97 (57.1%)	25 (47.2%)	ETA = 0.385 INF = 0.058

b) Number of prior anti-TNF treatments

ITT population – missing values imputed as non-response	Patients (%)			p-value vs no prior TNF antagonist*
	No prior TNF-antagonist (n=448)	1 prior TNF-antagonist (n=231)	≥2 TNF-antagonist (n=51)	
PASI75	321 (71.7%)	149.0 (64.5%)	25.0 (49.0%)	1 = 0.234 ≥2 = 0.016
PASI90	94 (49.6%)	84.1 (36.4%)	19.0 (37.3%)	1 = 0.021 ≥2 = 0.276
PASI100	144 (22.8%)	34.0 (14.7%)	8.0 (15.7%)	1 = 0.166 ≥2 = 0.766
PGA clear or minimal	170 (65.4%)	128.0 (55.4%)	21.0 (41.2%)	1 = 0.176 ≥2 = 0.026

c) Reason for discontinuation of prior TNF-antagonist

ITT population – missing values imputed as non-response	Patients (%)				
	No prior TNF-antagonist (n=448)	**Prior TNF-antagonist (n=282)**	**Never responded (n=80)**	**Lost response (n=99)**	**Intolerance (n=16)**
PASI75	321 (71.7%)	174 (61.7%) p=0.095*	43 (53.8%) p=0.006*	65 (65.7%) p=0.673*	8 (50.0%) p=0.213*

*****All p-values calculated by logistic regression adjusted for treatment group, number of prior systemics (>3, ≤3), age, duration of psoriasis, baseline PASI, baseline BSA affected, nail involvement, scalp involvement and presence of tender, swollen or stiff joints at baseline.

d) ±PsA

ITT population – missing values imputed as non-response	Patients (%)			
	Prior TNF-antagonist (n=277)		**No prior TNF-antagonist (n=429)**	
	PsA (n=95)	**No PsA (n=187)**	**PsA (n=110)**	**No PsA (n=338)**
PASI75	51 (53.7%)	123 (65.8%)	77 (70.0%)	244 (72.2%)
PASI90	33 (34.7%)	70 (37.4%)	55 (50.0%)	167 (49.4%)
PASI100	14 (14.7%)	28 (15.0%)	23 (20.9%)	79 (23.4%)
PGA clear or minimal	49 (51.6%)	100 (53.5%)	72 (65.5%)	221 (65.4%)

DLQI

DLQI (ITT population – missing values imputed as non-response)	Prior TNF-antagonist (n=281)	No prior TNF-antagonist (n=446)	p-value*
Baseline	13.8	14.0	0.165
Week 16	4.5	3.4	0.199
Change	-9.3	-10.6	

*Analysis performed using ANCOVA adjusted for treatment group, number of prior systemics (>3, ≤3), age, duration of psoriasis, baseline PASI, baseline BSA affected, nail involvement, scalp involvement and presence of tender, swollen or stiff joints at baseline.

Adverse events and withdrawals:

	Prior TNF-antagonist (n=282)	No prior TNF-antagonist (n=448)
Withdrawal due to lack of efficacy	3 (1.06%)	5 (1.1%)
Withdrawal due to AEs	5 (1.8%)	22 (4.9%)
Serious AEs	11 (3.9%)	20 (4.5%)

Author's conclusion

- Adalimumab was effective and well tolerated in patients previously treated with anti-TNF therapy
- There was no statistically significant difference in PASI75 between patients with and without prior TNF therapy (based on pooled ADA group)

- Switching to adalimumab therapy will result in improved clinical response in a large proportion of patients who have previously failed, lost response to or been intolerant to a prior TNF antagonist
- Rates of AEs were similar between patients with and without prior TNF therapy (based on pooled ADA group)

H.14.3 RCT (randomised and non-randomised data available)

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>A. Menter, S. R. Feldman, G. D. Weinstein, K. Papp, R. Evans, C. Guzzo, S. Li, L. T. Dooley, C. Arnold, and A. B. Gottlieb. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis.</td>
<td>RCT (plus observational data)

Multicentre (63 sites in US, Canada and Europe)

• Randomised (minimisation with biased coin assignment)
• Double blind (adequate)
• Allocation concealment (independent external centre)
• Sample size calculation:</td>
<td>N: 835

Drop-outs (do not complete study to week 10)

62 (7.4%):

Placebo: 24 (11.5%)

INF 3 mg: 21 (6.7%)

INF 5 mg: 17 (5.4%)</td>
<td>Inclusion criteria: Aged 18 or over; moderate to severe plaque-type psoriasis; candidates for phototherapy or systemic therapy; previous; no history of serious infection, lymphoproliferative disease, or active TB; PASI ≥12 and BSA ≥10%

Exclusion criteria: Previous exposure to infliximab; concomitant topical therapy, phototherapy or systemic therapy for psoriasis (except low potency topical corticosteroids for face and groin after 10 weeks) or DMARDs (stable doses of NSAIDs permitted).
<table>
<tr><th></th><th>Placebo (n=208)</th><th>INF 3 mg (n=313)</th><th>INF 5 mg (n=314)</th></tr>
<tr><td>Mean age – years (±SD)</td><td>44.4±12.5</td><td>43.4±12.6</td><td>44.5±13.0</td></tr>
<tr><td>Male (%)</td><td>69.2</td><td>65.8</td><td>65.0</td></tr>
</table>
</td>
<td>Infliximab (intravenous infusion): 3 or 5 mg/kg at weeks 0, 2 and 6

N=627

Note: data from two dose groups pooled for our outcome</td>
<td>Placebo (n=208)</td>
<td>Treatment duration

10 weeks

Note: this was the induction phase</td>
<td>Primary (at wk 10): PASI75</td>
<td>Centocor and Schering-Plough</td>
</tr>
</table>

J.Am.Acad .Dermatol. 56 (1):31, 2007. Ref ID: MENTER2007	yes • ITT analysis: yes • Washout period: **For observational data:** **Representative population sample:** yes **Confounders adjusted for:** no **Minimal attrition bias:** yes **Outcomes adequately measured:** Yes **Appropriate**		BSA (%)	28.4±17.6	28.0±16.3	28.7±16.4				
			PASI	19.8±7.7	20.1±7.9	20.4±7.5				
			Mean duration of psoriasis – years (±SD)	17.8±10.8	18.1±11.8	19.1±11.7				
			PsA (%)	26	27.8	28.3				
			Caucasian (%)	90.9	93.0	93.3				
			Weight (kg)	91.1±22.6	92.0±22.5	92.2±23.3				
			Previous treatment (%)							
			Topicals	92.8	94.9	90.8				
			UVB	49.5	54.3	55.1				
			PUVA	29.8	28.4	27.4				
			MTX	33.7	32.6	34.7				
			Acitretin	14.4	15.0	15.6				
			CSA	13.5	13.4	11.1				
			Biologics	**13.0**	**15.7**	**14.3**				

	statistical analysis: yes							

Effect Size

Outcomes

Efficacy

PASI75 (ITT population); week 10

Subset	**Placebo (n=208)**	**Infliximab (combined 3 and 5 mg/kg) (n=627)**	**% Difference (95% CI)**	**p-value**
Total responders	4 (1.9%)	457 (72.9%)		
Prior use of biologics	0/27 (0%)	68/94 (72.3%)	72.3 (60.9-83.8)	<0.001
No prior use of biologics	4/181 (2.2%)	389/533 (73.0%)	70.8 (66.1-75.5)	<0.001

Adverse events and withdrawals (not stratified by previous treatment):

	Placebo (n=208)	**INF 3 mg (n=313)**	**INF 5 mg (n=314)**

Withdrawal due to lack of efficacy	10 (4.8%)	1 (0.3%)	0 (0%)
Withdrawal due to AEs	4 (1.9%)	13 (4.2%)	12 (3.8%)

Author's conclusion

- Prior biologic therapy did not have an effect on PASI75 response to infliximab at 10 weeks

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>C. E. Griffiths, B. E. Strober, P. C. van de Kerkhof, V. Ho, R. Fidelus-Gort, N. Yeilding, C. Guzzo, Y. Xia, B. Zhou, S. Li, L. T. Dooley, N. H. Goldstein, and A. Menter. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. New Engl.J.Med. 362 (2):118-128, 2010. Ref ID:</td>
<td>RCT

Multicentre (67 international sites)

• Randomised: 3:5:5 ratio (adequate: stratified by site and baseline weight <90 kg or ≥90kg)
• Single blind (investigator) – patients also blinded to UST dose (not adequately defined)
• Allocation concealment (not</td>
<td>N: 903

Drop-outs (do not complete study)

Week 12

ETA: 11 (3.2%)

UST 45 mg: 8 (3.8%)

UST 90 mg: 5 (1.4%)

Week 12 to end of study

ETA: 8/295 (2.7%)

UST 45</td>
<td>Inclusion criteria: ≥18 years of age, diagnosis of plaque psoriasis for at least 6 months earlier, candidates for phototherapy or systemic treatment, PASI ≥12 or PGA ≥ 3 (range 0-5), and BSA ≥10%. Inadequate response, intolerance, or contraindication to at least one conventional systemic agent for psoriasis and no previous treatment with ustekinumab or etanercept

Exclusion criteria: nonplaque (i.e., pustular, guttate, or erythrodermic) or drug-induced forms of psoriasis, recent serious infection or history of chronic or recurrent infectious disease, or a known malignant condition (except treated basal-cell or squamous-cell skin cancer or cervical cancer in situ with no evidence of recurrence for ≥5 years). Conventional systemic therapy or phototherapy within 4 weeks before enrolment, topical psoriasis agents within 2 weeks, investigational drugs within 4 weeks or five half-lives, or biologic agents within 3 months or five half-lives

<table>
<tr><th></th><th>ETA</th><th>UST 45</th><th>UST 90</th></tr>
</table>
</td>
<td>Ustekinumab 45 mg at weeks 0 and 4

(n=209)

Ustekinumab 90 mg at weeks 0 and 4

(n=347)

_____

Both UST arms:

If no response

(moderate, marked, or severe

psoriasis) to</td>
<td>Etanercept

(n=347)

50 mg twice weekly

Crossover:

If no response

(moderate, marked, or severe

psoriasis) at week 12 switched to 90 mg of

ustekinumab at weeks 16 and 20

If had response at wk 12 received 90</td>
<td>Treatment duration

Up to 44 weeks</td>
<td>Primary outcome: PASI75 at week 12

Secondary: PGA clear or minimal; PASI90 and change in PASI all at week 12 Change in PASI from week 12 to 12 weeks after re-treatment due to recurrence

AEs</td>
<td>Centocor R&D</td>
</tr>
</table>

<table>
<tr>
<td>GRIFFITHS2010

AND

Janssen Cilag. Clinical efficacy data from phase III study ACCEPT broken down into patients' medication history with biologic therapies [unpublished data]. Anonymous. Anonymous. 2011. 09-02-2011.

Ref ID: JANSSENCILAG2011A</td>
<td>stated)
• Sample size calculation: yes
• ITT analysis: yes for efficacy (assumptions not stated)
• Washout period: see exclusion criteria</td>
<td>mg: 2/174 (1.1%)

UST 90 mg: 7/270 (2.6%)</td>
<td>
<table>
<tr><td></td><td>(n=347)</td><td>mg (n=209)</td><td>mg (n=347)</td></tr>
<tr><td>Mean age – years (±SD)</td><td>45.7±13.4</td><td>45.1±12.6</td><td>44.8±12.3</td></tr>
<tr><td>Male (%)</td><td>70.9</td><td>63.6</td><td>67.4</td></tr>
<tr><td>BSA (%)</td><td>23.8±13.9</td><td>26.7±17.8</td><td>26.1±17.6</td></tr>
<tr><td>PASI</td><td>18.6±6.2</td><td>20.5±9.2</td><td>19.9±8.4</td></tr>
<tr><td>Mean duration of psoriasis – years (±SD)</td><td>18.8±12.2</td><td>18.9±11.8</td><td>18.7±11.8</td></tr>
<tr><td>PsA (%)</td><td>27.4</td><td>29.7</td><td>27.4</td></tr>
<tr><td>Caucasian (%)</td><td>91.1</td><td>92.3</td><td>89.0</td></tr>
<tr><td>Weight (kg)</td><td>90.8±20.9</td><td>90.4±21.1</td><td>91.0±22.8</td></tr>
<tr><td colspan="4">Previous treatment (%)</td></tr>
<tr><td>Topicals</td><td>96.8</td><td>96.7</td><td>96.8</td></tr>
</table>
</td>
<td>ustekinumab at week 12 received

one additional dose of ustekinumab at week

16

All arms:

Treatment interrupted at week 12 in all patients with cleared, minimal, or

mild psoriasis; patients retreated with

ustekinumab if moderate, marked, or severe psoriasis recurred</td>
<td>mg of

ustekinumab at weeks 0 and 4 when psoriasis recurred</td>
<td></td>
<td></td>
<td></td>
</tr>
</table>

			<table><tr><td>Photo</td><td>64.6</td><td>66.0</td><td>66.3</td></tr><tr><td>Conventional systemics</td><td>57.3</td><td>61.7</td><td>52.4</td></tr><tr><td>Biologics</td><td>11.8</td><td>12.4</td><td>10.4</td></tr></table> **Note:** for subgroup analysis, disease severity similar in biologic ever and never used groups, but longer duration (by 3.5 years) and 5% more males in those with prior biologic exposure.					

Effect Size

Outcomes

Note: of those randomised to etanercept 336 completed 12-wk treatment and 41 did not cross over to 90 mg of ustekinumab after wk 12 (23 of whom completed treatment without requiring further intervention). Of the 295 who crossed over 50 did not have PGA response at wk 12 and received 90 mg of ustekinumab at wk 16 and 20, 245 had a PGA response at wk 12 and received 90 mg of ustekinumab at wk 0 and 4 when psoriasis recurred

Of those randomised to ustekinumab 45 mg 27 did not receive re-treatment with 45 mg of ustekinumab after wk 12 (17 of whom completed treatment without requiring additional treatment). Of the 174 who received additional ustekinumab treatment 20 did not have PGA response at wk 12 and received an additional dose at wk 16 and 154 had a PGA response at wk 12 and received two re-treatment doses when psoriasis recurred.

Of those randomised to ustekinumab 90 mg 72 did not receive re-treatment with 90 mg of ustekinumab after wk 12 (47 of whom completed treatment without requiring further intervention). Of the 270 Received additional ustekinumab treatment 25 did not have PGA response at wk 12 and received an additional dose at wk 16; 245 had a PGA response at wk 12 and received two re-treatment doses when psoriasis recurred.

Efficacy

Week 12 – initial randomised phase (ITT population)

	ETA (n=347)	**UST 45 mg (n=209)**	**UST 90 mg (n=347)**	**% treatment difference between UST and ETA (95% CI)**	**p-value (between UST and ETA)**
PASI75	197 (56.8%)	141 (67.5%)	256 (73.8%)	45 mg: 10.7 (2.4-19.0) 90 mg: 17.0 (10.0-24.0)	45 mg: 0.01 90 mg: <0.001
PASI90	80 (23.1%)	76 (36.4%)	155 (44.7%)	45 mg: 13.3 (5.8-20.7) 90 mg: 21.6 (14.6-28.5)	45 mg: <0.001 90 mg:<0.001
PGA (clear or minimal)	170 (49.0%)	136 (65.1%)	245 (70.6%)	45 mg: 16.1 (7.6-24.4) 90 mg: 21.6 (14.4-28.6)	45 mg: <0.001 90 mg:<0.001

Week 16 to 28 – crossover (ITT population)

	ETA non responders who crossed over to UST 90 mg (n=50)
PASI75	24 (48.9%)
PASI90	12 (23.4%)
PGA (clear or minimal)	20 (40.4%)

Withdrawals:

	UST 90 mg 0-12 weeks (n=347)	**UST 90 mg 16-44 weeks (n=295)**
Serious adverse events	4 (1.1%)	10 (3.4%)
Withdrawal due to AEs	4 (1.2%)	2 (0.68%)

Additional unpublished data from call for evidence (data stratified for those who have ever of never used biologics before – adalimumab, etanercept and/or infliximab)

Week 12

Proportion of subjects achieving a PASI 50 response at week 12

	Etanercept			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	347	286	(82.4%)	556	501	(90.1%)	7.7%	3.0%	12.4%	<0.001
Never used	319	265	(83.1%)	519	473	(91.1%)	8.1%	3.3%	12.9%	<0.001
Ever used	27	20	(74.1%)	36	28	(77.8%)	3.7%	-17.7%	25.1%	0.735

Proportion of subjects achieving a PASI 75 response at week 12

	Etanercept			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	347	197	(56.8%)	556	397	(71.4%)	14.6%	8.2%	21.1%	<0.01
Never used	319	186	(58.3%)	519	377	(72.6%)	14.3%	7.7%	21.0%	<0.01
Ever used	27	10	(37.0%)	36	20	(55.6%)	18.5%	-5.9%	42.9%	0.149

Proportion of subjects achieving a PASI 90 response at week 12

	Etanercept			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	347	80	(23.1%)	556	231	(41.5%)	18.5%	12.5%	24.5%	<0.001
Never used	319	76	(23.8%)	519	221	(42.6%)	18.8%	12.4%	25.1%	<0.001
Ever used	27	4	(14.8%)	36	10	(27.8%)	13.0%	-6.9%	32.8%	0.224

Mean of percent improvement in PASI from baseline at week 12

	Etanercept		Ustekinumab					
	N	change	N	change	Diff	95% CI		p-value
All subjects	339	72.06 ± 25.947	544	81.10 ± 21.919	9.04	5.84	12.24	<0.001
Never used	311	72.59 ± 25.953	508	82.05 ± 20.799	9.46	6.22	12.70	<0.001
Ever used	27	65.55 ± 25.870	35	68.30 ± 31.676	2.75	-12.26	17.76	0.715

Proportion of subjects achieving PGA score of cleared (0) or minimal (1) at week 12

	Etanercept			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	347	170	(49.0%)	556	381	(68.5%)	19.5%	13.0%	26.1%	<0.001
Never used	319	159	(49.8%)	519	362	(69.7%)	19.9%	13.1%	26.7%	<0.001
Ever used	27	10	(37.0%)	36	19	(52.8%)	15.7%	-8.7%	40.2%	0.219

Author's conclusion

- Those who had failed to respond to etanercept could still respond to subsequent ustekinumab 90 mg, although at a lower rate than patients who had not previously failed a biologic

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C. L. Leonardi, A. B. Kimball, K. A. Papp, N. Yeilding, C. Guzzo, Y. Wang, S. Li, L. T. Dooley, K. B. Gordon, and Investigators Study. 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	**RCT:** multicentre – 48 sites in USA, Canada and Belgium (Dec 2005-Sept 2007) • Randomised: 1:1:1 ratio (adequate: minimisation) Baseline randomisation was stratified by investigational site, weight (≤90 kg or >90 kg), and the number of conventional systemic therapies to which patients had	N: 766 **Drop-outs (do not complete study)** **Up to week 12** Ust 45: 1 Ust 90: 11 (1 received no Tx; 1 lack of efficacy; 2 AEs; 7 other) Placebo: 12 (3 lack of efficacy; 6 AE; 3 other) **Week 12-40** Ust 45: 38 (19 lack of efficacy; 11 AE) Ust 90: 19 (6 lack of efficacy; 7	**Inclusion criteria:** Aged 18 or over; diagnosis of plaque-type psoriasis for at least 6 months; PASI ≥12; BSA ≥10%; candidates for phototherapy or systemic therapy **Exclusion criteria:** History or symptoms of active tuberculosis; non-plaque psoriasis; recent systemic or local infection; known malignancy (except treated BCC or SCC of at least 5 years duration); treatment with agents targeting IL-12 or -23, biological or investigational agents within 3 months (or 5 drug half lives), conventional systemics or phototherapy within 4 weeks, topicals for psoriasis within 2 weeks	**Ustekinumab** (subcutaneously): 45 or 90 mg at weeks 0 and 4 and then every 12 weeks At week 40 those who achieved long-term response (at least PASI 75 at weeks 28 and 40) were re-randomised to continue maintenance treatment with ustekinumab or were withdrawn from active treatment (placebo). Patients withdrawn from treatment at week 40 were retreated when they lost at least 50% of PASI	**Placebo**, weeks 0 and 4 then crossover to ustekinumab (half to 90 and half to 45 mg) at weeks 12 and 16 then every 12 weeks Placebo controlled phase is 0-12 weeks	Treatment duration Placebo-controlled phase (0-12 weeks) Placebo crossover and active treatment phase (12-40 weeks) Randomised withdrawal phase (40-76 weeks)	PASI90 PASI75 PASI50 % change in PASI PGA (clear/minimal on 6-pt scale (0), minimal (1), mild (2), moderate (3), marked (4), or severe (5)) Change in DLQI	Centocor Inc

trial (PHOENIX 1).[Erratum appears in Lancet. 2008 May 31;371(9627):1838]. Lancet 371 (9625):1665-1674, 2008. Ref ID: LEONARDI 2008 AND Janssen Cilag. Clinical efficacy data from phase III study PHOENIX 1, broken down into patients' medication history with biologic therapies [unpublished data]. Anonymous. Anonymous. 2011. 09-	an inadequate response, intolerance, or contraindication (<3 or ≥3). Week 40 randomisation was stratified by investigational site and baseline weight (≤90 kg or >90 kg). • Double blind (adequate) • Allocation concealment: adequate (centralised interactive voice response system) • Sample size calculation: yes • ITT analysis:	AEs;) Placebo-> Ust 45: 11/123 (7 lack of efficacy; 2 AE) Placebo-> Ust 90: 5/120 (2 lack of efficacy; 1 AE)		improvement. Patients not achieving PASI 75 at week 28 or 40 were not re-randomised, and their dosing was discontinued or modified				

02-2011. Ref ID: JANSSEN CILAG2011	yes for efficacy (non-responder imputation for dichotomous data at week 12 [but for other efficacy analyses missing data were not imputed and were treated as missing] ACA for continuous); safety analyses based on actual treatment received • Washout period: see exclusion criteria							
Demographics								

	Ustekinumab 45 mg (n=255)	**Ustekinumab 90 mg (n=256)**	**Placebo (n=255)**
Mean age – years (±SD)	44.8±12.5	46.2±11.3	44.8±11.3
Male (%)	68.6	67.6	71.8
Weight (kg)	93.7±23.8	93.8±23.9	94.2±23.5
PASI	20.5±8.6	19.7±7.6	20.4±8.6
PGA (marked or severe)	114 (44.7%)	109 (42.6%)	112 (43.9%)
DLQI	11.1±7.1	11.6±6.9	11.8±7.4
Mean duration of psoriasis – years (±SD)	19.7±11.7	19.6±11.1	20.4±11.7
PsA, n (%)	74 (29.0%)	94 (36.7%)	90 (35.3%)
Previous treatment			
Topicals	245	239	242
Photo	173	169	150
Conventional systemics	141	141	142
Biologics*	**134 (52.5%)**	**130 (50.8%)**	**128 (50.2%)**
*Includes etanercept, alefacept, efalizumab, infliximab and adalimumab			

Note: for subgroup analysis, disease slightly more severe, (PASI [2 pt higher], PGA [3.6% more marker or severe], BSA [4% higher], DLQI [1 pt higher]) and longer duration (by 1 year) in those with prior biologic exposure.

Also, slightly higher weight (by 3 kg but all means >90kg) and greater proportion male (7% higher) in those with prior exposure

Effect Size

Outcomes

Additional unpublished data from call for evidence (data stratified for those who have ever of never used biologics before – adalimumab, etanercept and/or infliximab)

Week 12

Proportion of subjects achieving a PASI 50 response at week 12

	Placebo			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	255	26	(10.2%)	511	433	(84.7%)	74.5%	69.7%	79.4%	<0.001
Never used	150	24	(16.0%)	299	262	(87.6%)	71.6%	64.7%	78.6%	<0.001
Ever used	105	2	(1.9%)	212	171	(80.7%)	78.8%	72.8%	84.7%	<0.001

Proportion of subjects achieving a PASI 75 response at week 12

	Placebo			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	255	8	(3.1%)	511	341	(66.7%)	63.6%	59.0%	68.2%	<0.001
Never used	150	8	(5.3%)	299	213	(71.2%)	65.9%	59.6%	72.2%	<0.001
Ever used	105	0	(0.0%)	212	128	(60.4%)	60.4%	53.8%	67.0%	<0.001

Proportion of subjects achieving a PASI 90 response at week 12

	Placebo			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	255	5	(2.0%)	511	200	(39.1%)	37.2%	32.6%	41.7%	<0.001
Never used	150	5	(3.3%)	299	125	(41.8%)	38.5%	32.2%	44.8%	<0.001
Ever used	105	0	(0.0%)	212	75	(35.4%)	35.4%	28.9%	41.8%	<0.001

Mean of percent improvement in PASI from baseline at week 12

	Placebo		Ustekinumab					
	N	change	N	change	Diff	95% CI		p-value
All subjects	253	6.98 ± 30.773	506	76.41 ± 25.414	69.43	65.30	73.56	<0.001

Never used	148	12.69 ± 32..248	298	78.69 ± 23.338	66.00	60.74	71.26	<0.001
Ever used	105	-1.07 ± 26.701	208	73.14 ± 27.856	74.21	67.74	80.68	<0.001

Proportion of subjects achieving PGA score of cleared (0) or minimal (1) at week 12

	Placebo			Ustekinumab					
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	255	10	(3.9%)	511	312	(61.1%)	57.1%	52.3%	62.0%	<0.001
Never used	150	8	(5.3%)	299	190	(63.5%)	58.2%	51.7%	64.8%	<0.001
Ever used	105	2	(1.9%)	212	122	(57.5%)	55.6%	48.5%	62.8%	<0.001

Mean of improvement in DLQI from baseline at week 12

	Placebo		Ustekinumab				
	N	change	N	change	Diff	95% CI		p-value
All subjects	252	-0.6 ± 5.97	503	-8.3 ± 6.68	-7.70	-8.68	-6.72	<0.001
Never used	147	-1.07 ± 6.08	296	-8.0 ± 6.31	-6.93	-8.17	-5.69	<0.001
Ever used	105	0.14 ± 5.78	207	-8.9 ± 7.15	-9.04	-10.62	-7.46	<0.001

Week 24/28

Proportion of subjects achieving a PASI 50 response at week 24

	Ustekinumab		
	N	n	(%)
All subjects	497	461	(92.8%)
Never used	290	275	(94.8%)
Ever used	207	186	(89.9%)

Proportion of subjects achieving a PASI 75 response at week 24

	Ustekinumab		
	N	n	(%)
All subjects	497	400	(80.5%)
Never used	290	245	(84.5%)
Ever used	207	155	(74.9%)

Proportion of subjects achieving a PASI 90 response at week 24

	Ustekinumab		
	N	n	(%)
All subjects	497	296	(59.6%)
Never used	290	182	(62.8%)
Ever used	207	114	(55.1%)

Mean of percent improvement in PASI from baseline at week 24

	Ustekinumab	
	N	change (m±SD)
All subjects	497	85.14 ± 21.28
Never used	290	86.96 ± 19.36
Ever used	207	82.59 ± 23.52

Proportion of subjects achieving PGA score of cleared (0) or minimal (1) at week 24

	Ustekinumab		
	N	n	(%)
All subjects	497	350	(70.4%)
Biologics (etanercept, infliximab, or adalimumab)			
Never used	290	213	(73.4%)
Ever used	207	137	(66.2%)

Mean of improvement in DLQI from baseline at week 28

	Ustekinumab	
	N	change (m±SD)
All subjects	490	-8.8 ± 7.23
Never used	286	-8.7 ± 7.03
Ever used	204	-9.1 ± 7.52

Week 52

Proportion of subjects achieving a PASI 50 response at week 52

	Ustekinumab		
	N	n	(%)
All subjects	162	158	(97.5%)
Never used	103	101	(98.1%)
Ever used	59	57	(96.6%)

Proportion of subjects achieving a PASI 75 response at week 52

	Ustekinumab		
	N	n	(%)
All subjects	162	144	(88.9%)
Never used	103	93	(90.3%)
Ever used	59	51	(86.4%)

Proportion of subjects achieving a PASI 90 response at week 52

	Ustekinumab		
	N	n	(%)
All subjects	162	105	(64.8%)
Never used	103	66	(64.1%)
Ever used	59	39	(66.1%)

Mean of percent improvement in PASI from baseline at week 52

	Ustekinumab	
	N	change (m±SD)
All subjects	162	89.90 ± 14.62
Never used	103	90.15 ± 14.62
Ever used	59	89.45 ± 14.73

Proportion of subjects achieving PGA score of cleared (0) or minimal (1) at week 52

	Ustekinumab		
	N	n	(%)

All subjects	162	115	(71.0%)
Never used	103	72	(69.9%)
Ever used	59	43	(72.9%)

Mean of percent improvement in DLQI from baseline at week 52

	Ustekinumab	
	N	change (m±SD)
All subjects	162	-9.6 ± 6.83
Never used	103	-9.0 ± 6.84
Ever used	59	-10.6 ± 6.73

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
K. A. Papp, R. G. Langley, M. Lebwohl, G. G. Krueger, P. Szapary, N. Yeilding, C. Guzzo, M. C. Hsu, Y. Wang, S. Li, L. T. Dooley, K. Reich, and Investigators Study. 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	**Observational:** prospective case series/prognostic study based on RCT data (70 sites in Europe and North America) **Note:** post-hoc analysis – not stated in study protocol **Washout period:** 4 weeks for conventional systemics; 2 weeks for topicals; 3 months for biologics **Representative**	N: 1230 (N=820 for our cohort of which 84 (10.2%) dropped out) 40 due to lack of efficacy; 16 AEs; 28 'other' **Up to week 12** Ust 45: 6 (0 lack of efficacy; 2 AEs) Ust 90: 9 (0 lack of efficacy; 5 AEs) Placebo: 18 (2 lack of efficacy; 8 AE) **Week 12-28**	**Inclusion criteria:** Aged 18 or over; diagnosis of plaque-type psoriasis for at least 6 months; PASI ≥12; BSA ≥10%; candidates for phototherapy or systemic therapy **Note:** data on switching biologics only available for those initially randomised to ustekinumab (and both doses are pooled together) **Exclusion criteria:** History or symptoms of active tuberculosis; non-plaque psoriasis; recent systemic or local infection; known malignancy (except treated BCC or SCC of at least 5 years duration); treatment with agents targeting IL-12 or -23, biological or investigational agents within 3 months (or 5 drug	**Ustekinumab** (subcutaneously): 40 or 90 mg at weeks 0 and 4 and then every 12 weeks	Placebo	Treatment duration Placebo-controlled phase (0-12 weeks) Placebo crossover and active treatment phase (12-28 weeks) Randomised dose intensification phase (28-52 weeks) Note: data for switching biologics only available	PASI90 PASI75 PASI50 % change in PASI PGA (clear/minimal on 6-pt scale (0), minimal (1), mild (2), moderate (3), marked (4), or severe (5)) Change in DLQI	Centocor Inc

trial (PHOENIX 2). Lancet 371 (9625):1675-1684, 2008. Ref ID: PAPP2008 AND Janssen Cilag. Clinical efficacy data from phase III study PHOENIX 2 broken down into patients' medication history with biologic therapies [unpublished data]. Anonymous. Anonymous. 2011. 09-02-2011. REF ID JANSSENCILAG2011B	**population sample:** yes **Confounders accounted for:** unclear (see below) **Minimal attrition bias:** yes **Outcomes adequately measured:** Yes **Appropriate statistical analysis:** yes (but post-hoc) **For randomised data** • Randomised:	Ust 45: 37 (25 lack of efficacy; 2 AEs) Ust 90: 32 (15 lack of efficacy; 7 AEs) Placebo-> Ust 45: 22/197 (9 lack of efficacy; 4 AE) Placebo-> Ust 90: 17/195 (7lack of efficacy; 2 AE)	half lives), conventional systemics or phototherapy within 4 weeks, topicals for psoriasis within 2 weeks			for those who had a constant dose of ustekinumab for 28 weeks		

	1:1:1 ratio (adequate: minimisation) Baseline randomisation was stratified by investigational site, weight (≤90 kg or >90 kg), and the number of conventional systemic therapies to which patients had an inadequate response, intolerance, or contraindication (<3 or ≥3). Second randomisation was stratified by investigational site and baseline							

	weight (≤90 kg or >90 kg). • Double blind (not explained) • Allocation concealment: adequate (centralised interactive voice response system) • Sample size calculation: yes • ITT analysis: yes for efficacy (non-responder imputation for dichotomous data at week 12 and dose intensification phase [but for other efficacy analyses missing data were not							

	imputed and were treated as missing]); safety analyses based on actual treatment received • Washout period: see exclusion criteria							

Demographics

	Ustekinumab 45 mg (n=409)	**Ustekinumab 90 mg (n=411)**	**Placebo (n=410)**
Mean age – years (±SD)	45.1±12.1	46.6±12.1	47.0±12.5
Male (%)	69.2	66.7	69.0
BSA (%)	25.9±15.5	27.1±17.4	26.1±17.4
PASI	19.4±6.8	20.1±7.5	19.4±7.5
Mean duration of psoriasis – years (±SD)	19.3±11.7	20.3±12.3	20.8±12.2
PsA, n (%)	107 (26.2%)	94 (22.9%)	105 (25.6%)
Previous treatment			

Topicals	393	384	396
Photo	286	267	276
Conventional systemics	223	224	241
Biologics*	**157 (38.4%)**	**450 (36.5%)**	**159 (38.8%)**
*Includes etanercept, alefacept, efalizumab, infliximab and adalimumab			

Note: for subgroup analysis, disease slightly more severe, (PASI [1 pt higher], PGA [9% more marker or severe], BSA [1.4% higher], DLQI [1 pt higher]) and longer duration (by 2 years) in those with prior biologic exposure.

Also, slightly higher weight (by 5 kg but all means >90kg)

Effect Size

Outcomes

Efficacy – post hoc analysis of baseline factors predictive of week 28 response (PASI75) vs partial responders (PASI50, but not PASI75) **for those treated with either dose of ustekinumab**

Predictive characteristic	**Patients, n (%)**	
	PASI 75 responders at week 28 (n=589)	**Partial responders at week 28 (n=158)**

Patients with PsA	131 (22.2%)	54 (34.8%)
Patients treated previously with biologic agents	209 (35.5%)	71 (44.9%)
Failed at least one previous biologic	71 (12.1%)	34 (21.5%)
Total sample	*590/797 (74%)*	*159/797 (19.9%)*

Parameter	**Patients (%)**	
	Previous biologic (n=307)	**No previous biologic (n=513)**
28 weeks		
PASI75	209 (68.1%)	380 (74.1%)

Note: Logistic regression analysis revealed that inadequate response to at least one biologic agent was an independent predictor of partial response (p=0.024), as was a history of psoriatic arthritis (p=0.047)

Potential predictive factors included in the model: age, sex, bodyweight, duration of psoriasis, BSA affected, PGA marked or severe, history of PsA, use of phototherapy, traditional systemics or biologics and inadequate response to at least one conventional systemic or one biologic agent, but it is unclear whether the results have been adjusted for these covariates.

Adverse events

- Not stratified by previous biologic exposure

Additional data for call for evidence (data stratified for those who have ever of never used biologics before – adalimumab, etanercept and/or infliximab)

Week 12

Proportion of subjects achieving a PASI 50 response at week 12

	Placebo			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	410	41	(10.0%)	820	709	(86.5%)	76.5%	72.7%	80.2%	<0.001
Never used	286	33	(11.5%)	570	496	(87.0%)	75.5%	70.9%	80.1%	<0.001
Ever used	124	8	(6.5%)	250	213	(85.2%)	78.7%	72.6%	84.9%	<0.001

Proportion of subjects achieving a PASI 75 response at week 12

	Placebo			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	410	15	(3.7%)	820	584	(71.2%)	67.6%	64.0%	71.2%	<0.001
Never used	286	11	(3.8%)	570	426	(74.7%)	70.9%	66.7%	75.1%	<0.001
Ever used	124	4	(3.2%)	250	158	(63.2%)	60.0%	53.2%	66.7%	<0.001

Proportion of subjects achieving a PASI 90 response at week 12

	Placebo			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	410	3	(0.7%)	820	382	(46.6%)	45.9%	42.3%	49.4%	<0.001
Never used	286	2	(0.7%)	570	288	(50.5%)	49.8%	45.6%	54.0%	<0.001
Ever used	124	1	(0.8%)	250	94	(37.6%)	36.8%	30.6%	43.0%	<0.001

Mean of percent improvement in PASI from baseline at week 12

	Placebo		Ustekinumab				
	N	change	N	change	Diff	95% CI	p-value
All subjects	404	4.91 ± 34.784	812	79.52 ± 24.342	74.61	71.24 77.98	<0.001
Never used	281	7.54 ± 35.168	564	80.80 ± 24.558	73.26	69.17 77.35	<0.001
Ever used	123	-1.10 ± 33.256	248	76.61 ± 23.638	77.71	71.81 83.61	<0.001

Proportion of subjects achieving PGA score of cleared (0) or minimal (1) at week 12

	Placebo			Ustekinumab					
	N	n	(%)	N	n	(%)	Diff	95% CI	p-value
All subjects	410	20	(4.9%)	820	580	(70.7%)	65.9%	62.1% 69.6%	<0.001
Never used	286	17	(5.9%)	570	418	(73.3%)	67.4%	62.8% 71.9%	<0.001
Ever used	124	3	(2.4%)	250	162	(64.8%)	62.4%	55.9% 68.9%	<0.001

Mean of improvement in DLQI from baseline at week 12

	Placebo		Ustekinumab					
	N	change	N	change	Diff	95% CI		p-value
All subjects	400	-0.5 ± 5.66	803	-9.6 ± 6.90	-9.10	-9.88	-8.32	<0.001
Never used	277	-0.9 ± 5.95	560	-9.3 ± 6.74	-8.40	-9.34	-7.46	<0.001
Ever used	123	0.3 ± 4.88	243	-10.3 ± 7.24	-10.60	-12.02	-9.18	<0.001

Week 24/28

Proportion of subjects achieving a PASI 50 response at week 24

	Ustekinumab		
	N	n	(%)
All subjects	800	742	(92.8%)
Never used	558	517	(92.7%)
Ever used	242	225	(93.0%)

Proportion of subjects achieving a PASI 75 response at week 24

	Ustekinumab		
	N	n	(%)
All subjects	800	627	(78.4%)
Never used	558	446	(79.9%)
Ever used	242	181	(74.8%)

Proportion of subjects achieving a PASI 90 response at week 24

	Ustekinumab		
	N	n	(%)
All subjects	800	442	(55.3%)
Never used	558	329	(59.0%)
Ever used	242	113	(46.7%)

Mean of percent improvement in PASI from baseline at week 24

	Ustekinumab

	N	change (m±SD)
All subjects	406	84.25 ± 21.613
Never used	283	85.07 ± 21.640
Ever used	123	82.38 ± 21.478

Proportion of subjects achieving PGA score of cleared (0) or minimal (1) at week 24

	Ustekinumab		
	N	n	(%)
All subjects	800	578	(72.3%)
Never used	558	419	(75.1%)
Ever used	242	159	(65.7%)

Mean of improvement in DLQI from baseline at week 28

	Ustekinumab	
	N	change (m±SD)
All subjects	793	-9.9 ± 7.12

Biologics (etanercept, infliximab, or adalimumab)		
Never used	555	-9.7 ± 7.01
Ever used	238	-10.2 ± 7.36

Week 24/28

Proportion of subjects achieving a PASI 50 response at week 52

	Ustekinumab		
	N	n	(%)
All subjects	537	532	(99.1%)
Never used	389	386	(99.2%)
Ever used	148	146	(98.6%)

Proportion of subjects achieving a PASI 75 response at week 52

	Ustekinumab		
	N	n	(%)

All subjects	537	487	(90.7%)
Never used	389	360	(92.5%)
Ever used	148	127	(85.8%)

Proportion of subjects achieving a PASI 90 response at week 52

	Ustekinumab		
	N	n	(%)
All subjects	537	362	(67.4%)
Never used	389	276	(71.0%)
Ever used	148	86	(58.1%)

Mean of percent improvement in PASI from baseline at week 52

	Ustekinumab	
	N	change (m±SD)
All subjects	537	90.83 ± 13.280-

Never used	389	91.86 ± 12.670
Ever used	148	88.12 ± 14.464

Proportion of subjects achieving PGA score of cleared (0) or minimal (1) at week 52

	Ustekinumab		
	N	n	(%)
All subjects	537	389	(72.4%)
Never used	389	291	(74.8%)
Ever used	148	98	(66.2%)

Author's conclusion

- Partial responders to ustekinumab were more likely than responders to have failed a previous biologic
- The majority of patients who had received a previous biologic (but not necessarily failed to respond to it) achieved PASI75 on ustekinumab

H.14.4 Cohort Study

Reference	Study type	Number of patients	Patient characteristics	Intervention	Cohorts – previous treatment	Length of follow-up	Outcome measures	Source of funding
B. E. Strober, Y. Poulin, F. A. Kerdel, R. G. Langley, Y. Gu, S. R. Gupta, M. M. Okun, and K. A. Papp. Switching to adalimumab for psoriasis patients with a suboptimal response to etanercept, methotrexate, or phototherapy: efficacy and safety results from an open-label study. J.Am.Acad. Dermatol.	**Prospective cohort study** Multicentre (24 in Canada and USA) • Nonrandomised • Blinding: open label • Sample size calculation: yes • ITT analysis: yes for efficacy (non-responder imputation for dichotomous and LOCF for continuous) • Washout	N: 152 **Drop-outs (do not complete study): 16** E: 9 (11.0%) M: 2 (4.9%) P: 5 (17.2%)	**Inclusion criteria:** ≥18 years of age, diagnosis of chronic plaque psoriasis for at least 6 months earlier; contraception for women of childbearing age; suboptimal response* to prior psoriasis therapy ***Note:** Definition of **suboptimal response** Substudy E: PGA mild or worse following etanercept treatment for at least 6 months or at least 3 months of etanercept therapy with deterioration of efficacy (as determined by treating physician) Substudy M: PGA mild or worse following methotrexate treatment for at least 4 months Substudy P: PGA of moderate or worse after at least 2 months of NB-UVB phototherapy **PGA definitions** Mild=slight plaque elevation, fine scale covering lesions and erythema up to definite red colouration Moderate= moderate degree of plaque elevation, coarse scale covering lesions and erythema with definite red colouration	**Adalimumab** **(n=152)** 80 mg at week 0 and 40mg every other week beginning at week 1 through to week 15 Self-administered using pre-filled auto-injection device --- **All arms:** Concomitant therapy with	**Etanercept (n=82)** (substudy E) 50 mg twice weekly or 25 mg twice weekly (data pooled) **Methotrexate (n=41)** (substudy M) Various regimens median maximum dose = 15 mg/wk (IQR: 10-20 mg/wk) **NB-UVB phototherapy(n=29)** (substudy P) Median	Treatment duration 16 weeks (safety data collected up to 70 days after last treatment)	Primary outcome: PGA clear or minimal at 16 weeks Secondary: PASI DLQI AEs	Abbott Laboratories

64 (4):671-681, 2011. Ref ID: STROBER 2011 B. Strober, J. Weisman, Y. Gu, and M. Okun. Adalimumab is Effective for Psoriasis Patients Who Are Primary Nonresponders to Etanercept: Subanalysis of an Open-Label Clinical Trial [submitted]. American Academy of Dermatology.70th Annual Meeting, 16-20th March, 2012. Ref ID: STROBER	period: Etanercept= 11-17 days; MTX or NB-UVB = 4-10 days (i.e. at least 4 half lives) • Standard washout for other concomitant interventions **Representative population sample:** yes **Confounders adjusted for:** no **Minimal attrition bias:** yes **Outcomes adequately measured:** Yes		**Exclusion criteria:** history of neurological symptoms suggestive of CNS demyelinating disease; history of cancer or lymphoproliferative disease (except successfully treated non-melanoma skin cancer or localised carcinoma in situ of the cervix)	previously prescribed topical therapies permitted (but no new prescriptions or changes in concentrations were permitted)	highest dose 725 mJ (IQR: 447-1000 mJ) Median number of session = 33			

2012	**Appropriate statistical analysis:** yes							

Demographics

	Etanercept (n=82)	**Methotrexate (n=41)**	**NB-UVB (n=29)**
Mean age – years (±SD)	48.3±13.7	47.4±13.1	47.5±14.6
Male (%)	57.3	68.3	55.2
BSA (%)	11.6±10.3	10.9±7.3	14.5±12.6
PASI	10.0±6.3	10.2±5.5	12.8±5.7
Mean duration of psoriasis – years (±SD)	17.2±12.0	19.8±13.5	23.0±14.1
PsA (%)	57.3	41.5	24.1
Caucasian (%)	84.1	95.1	86.2
Weight (kg)	96.4±23.4	89.5±17.5	86.0±17.8
Median duration of suboptimal therapy, months	20.0	8.0	4.0
DLQI (0-30) (mean ±SD)	8.8±6.0	10.9±6.3	10.4±6.9

PGA (%)			
Clear or minimal	1.2	2.4	0
Mild	20.7	19.5	3.4
Moderate	62.2	63.4	75.9
Severe	15.9	12.2	20.7
Very severe	0	2.4	0

Effect Size

Outcomes

Efficacy

Week 16 (ITT population)

Patients, n (%)	**All** **(n=152)**	**Etanercept (n=82)**	**Methotrexate (n=41)**	**NB-UVB (n=29)**
Week 16 PGA (clear or minimal)	79 52 (44-66)%	40 49 (38-60)% *Note: lower dose 47% and higher dose 50%*	25 61 (25-76)%	14 48 (29-67)%

Week 16 PGA (clear)	31 20 (14-28)%	10 (12%) *Note: lower dose 8% and higher dose 16%*	15 (37%)	6 (21%)
DLQI *Screening mean* Change to week 16	**N=149** *9.6* -5.2	**N=80** *8.9* -3.8	**N=40** *10.5* -7.0	**N=29** *10.4* -6.5

Additional information from conference abstract submitted by Abbott in call for evidence (STROBER2012): summary evidence for subgroups of primary nonresponders (never achieved satisfactory response to the prior therapy) and secondary nonresponders (achieved satisfactory response initially but lost it over time).

Note: Patients who reported both primary and secondary non-response were included in both subgroups; patients who discontinued their prior therapies due to reasons other than efficacy were not included in either subgroup

ITT analysis.

Patients, n (%)	**Etanercept (n=82)**		**Methotrexate (n=41)**		**NB-UVB (n=29)**	
N (%)	Primary N=26	Secondary N=58	Primary N=27	Secondary N=12	Primary N=18	Secondary N=11
Week 16 PGA (clear or minimal)	15	27	17	6	11	3

Note: the discrepancy in number of primary and secondary non-responders and total numbers is due to some people being included in both categories

Withdrawals and AEs:

	Etanercept (n=82)	**Methotrexate (n=41)**	**NB-UVB (n=29)**
Withdrawal due to AEs	0 (0%)	0 (0%)	1 (3.4%)
Withdrawal due to lack of efficacy	4 (4.9%)	1 (2.4%)	2 (6.9%)
Serious AEs	4 (4.9%)	0 (0%)	1 (3.4%)

Author's conclusion

- Patients who previously experienced suboptimal response to MTX treatment had the most robust response to adalimumab, but etanercept treated patients may also experience improvement in psoriasis symptoms upon switching to adalimumab
- Switching from etanercept to adalimumab was an effective therapeutic approach in approximately half of patients with prior suboptimal response to etanercept
- Adalimumab treatment led to clinical response in the majority of patients who had been suboptimally controlled on etanercept, methotrexate, or narrow-band ultraviolet B phototherapy. The majority of patients who had never achieved satisfactory response with etanercept were able to achieve clinical response after switching to adalimumab.