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Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial.

Mease PJ, et al.

Etanercept
ACR Response at 3 Months

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Etanercept</th>
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<tbody>
<tr>
<td>ACR 20</td>
<td>13%</td>
<td>73%*</td>
</tr>
<tr>
<td>ACR 50</td>
<td>3%</td>
<td>50%*</td>
</tr>
<tr>
<td>ACR 70</td>
<td>0%</td>
<td>13%</td>
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</table>

*P < .001

Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis.

van der Heijde DM, et al

Figure 1. Sites evaluated for radiographic evidence of erosions (●) and narrowing (●) in the hands and feet of patients with early rheumatoid arthritis.

Sharp score or van der Heijde score measures joint damage on x-ray: narrowing and erosions
Etanercept Inhibited Bone Erosion

*Mean Change in Erosion Score at 12 Months*

- **Placebo (n=104)**: ~0.66
- **Etanercept (n=101)**: ~-0.09

*stratified rank test

$p < 0.0001^*$

Etanercept Inhibited Joint Space Narrowing

Mean Change in JSN Score at 12 Months

- Placebo (n=104)
- Etanercept (n=101)

\[
p = 0.044^*\]

*stratified rank test

Etanercept Inhibited Structural Damage

Mean Change in Total Sharp Score at 12 Months

Primary Radiographic Endpoint

- Placebo (n=104)
- Etanercept (n=101)

*p = 0.0001*

*stratified rank test

Adalimumab Effectiveness in Psoriatic Arthritis Trial Study Group. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial.

Mease PJ, et al.

### Adalimumab

**Percent ACR Response at Weeks 12 and 24**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Adalimumab</th>
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<tbody>
<tr>
<td>Week 12</td>
<td>n=162</td>
<td>n=151</td>
</tr>
<tr>
<td>ACR20</td>
<td>14</td>
<td>58</td>
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<tr>
<td>ACR50</td>
<td>4</td>
<td>36</td>
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<tr>
<td>ACR70</td>
<td>1</td>
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<td>n=162</td>
<td>n=151</td>
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<tr>
<td>ACR20</td>
<td>15</td>
<td>57</td>
</tr>
<tr>
<td>ACR50</td>
<td>6</td>
<td>39</td>
</tr>
<tr>
<td>ACR70</td>
<td>1</td>
<td>23</td>
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</table>

All results p<0.001 placebo vs adalimumab

Mease P, et al. Presented at the 68th Annual Scientific Meeting of the American College of Rheumatology, October 19, 2004; San Antonio, Texas.
Mean Change in mTSS at Week 24

**Placebo**
- N: 152
- Baseline: 20.0
- Mean change: 1.0

**Adalimumab**
- N: 144
- Baseline: 22.3
- Mean change: -0.2***

***p≤0.001 vs placebo for ranked ANCOVA

The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year.

Kavanaugh A, et al.

Infliximab
ACR 20 at Week 14 and Week 24

<table>
<thead>
<tr>
<th></th>
<th>Primary Endpoint</th>
<th>Major Secondary Endpoint</th>
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<tr>
<td><strong>Week 14</strong></td>
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<tr>
<td>Placebo</td>
<td>11%</td>
<td>58%</td>
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<td><strong>Week 24</strong></td>
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<tr>
<td>Placebo</td>
<td>16%</td>
<td>54%</td>
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<tr>
<td>Infliximab</td>
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p < 0.001*

*Remains significant after multiple sensitivity analyses
European League Against Rheumatism 2004; Oral Presentation: OP0182.
Total vdh-S Score – Mean Change from Baseline at Week 24*

*Median Change in both groups was 0.0

Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA)


Ustekinumab, an anti-IL-12/23 p40 monoclonal antibody, inhibits radiographic progression in patients with active psoriatic arthritis: results of an integrated analysis of radiographic data from the phase 3, multicentre, randomised, double-blind, placebo-controlled PSUMMIT-1 and PSUMMIT-2 trials.

ACR20/50/70 Responders at Week 24

Primary Endpoint

Percent of Patients

- ACR20: 22.8, 42.4, 49.5
- ACR50: 8.7, 24.9, 27.9
- ACR70: 2.4, 12.2, 14.2

**PBO → UST 45 mg (n=189)**  **UST 45 mg (n=205)**  **UST 90 mg (n=204)**


*\( p < 0.001 \)
*Patients who did not receive UST are excluded
ACR20 Response Through Week 52

ACR20=American College of Rheumatology 20% improvement; SC=subcutaneous; TNFi=tumor necrosis factor inhibitor.

* P<0.0001; † P<0.001; ‡ P<0.01; § P<0.05 vs placebo.

Missing values were imputed as nonresponse (nonresponder imputation) through Week 52.

FUTURE 2
ACR50 and ACR70 Response Through Week 52

ACR50/70=American College of Rheumatology 50%/70% improvement; SC=subcutaneous; TNFi=tumor necrosis factor inhibitor.

*P<0.0001; †P<0.001; ‡P<0.01; §P<0.05 vs placebo. Missing values were imputed as nonresponse (nonresponder imputation) at Weeks 24 and 52.

FUTURE 1: Radiographic progression in PsA patients stratified by MTX use

Baseline to Week 24 (full analysis set)

Week 24 to Week 52 (X-ray completers)

*P<0.05 vs PBO
Change in mTSS >0.5 considered progression of radiographic disease

Gottlieb AB, et al. EADV 2015, P0348 Sponsored by Novartis Pharma AG
Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1.

Mease PJ, et al

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>IXEQ4W</th>
<th>IXEQ2W</th>
<th>Adalimumab 40 mg Q2W*</th>
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<tr>
<td><strong>LS mean change from baseline mTSS (SE)†</strong></td>
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<td>Week 16</td>
<td>0.36 (0.07)</td>
<td>0.13 (0.07)†</td>
<td>0.08 (0.07)§</td>
<td>0.12 (0.08)†</td>
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<tr>
<td>Week 24</td>
<td>0.49 (0.09)</td>
<td>0.17 (0.08)§</td>
<td>0.08 (0.08)¶</td>
<td>0.10 (0.09)¶</td>
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<td><strong>Percentage of patients with change in mTSS at week 24</strong></td>
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<tr>
<td>≤0</td>
<td>72.0</td>
<td>83.0</td>
<td>83.5</td>
<td>91.6¶</td>
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<td>≤0.5</td>
<td>77.4</td>
<td>89.0**</td>
<td>94.8¶</td>
<td>95.8¶</td>
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<td>≤0.95</td>
<td>83.9</td>
<td>94.0‡</td>
<td>96.9§</td>
<td>95.8§</td>
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</table>
Brodalumab Phase 2 PsA study: Clinical response and improvement in psoriasis in subjects with PsA

ACR20 response rate at Week 24

Mease P, et al. AAD 2014, P7605
Therapeutic response of PsA to TNFi and brodalumab

- No head-to-head trials
- BRO trial is Phase 2, not placebo controlled
- Others are Phase 3 and placebo controlled

ACR 20/50/70 Responses at Week 24

**Primary Endpoint**

- ACR20: 64.1 vs. 32.9 (p<0.001)
- ACR50: 31.5 vs. 14.2 (p<0.001)
- ACR70: 33.1 vs. 4.1 (p<0.001)

**Major Secondary Endpoints**

- PBO (n=246)
- GUS 100 mg q8w (n=248)
- GUS 100 mg q4w (n=245)

---

DISCOVER-2

ACR 20 Responses Through Week 24 (Secondary Endpoint)

All patients, including those with imputed data.

† Unadjusted (nominal) p-values vs. placebo.

* Adjusted p-value vs. placebo.

DISCOVER-2

LS Mean Change From Baseline in PsA-modified vdH-S Score at Week 24 (Controlled Major Secondary Endpoint)

- PBO (n=246)
- GUS 100 mg q8w (n=248)
- GUS 100 mg q4w (n=245)

p=0.072

p=0.011
Efficacy: ACR20, Primary Endpoint

Shown for randomised patients who received ≥1 dose of study drug. *P <0.05; †P <0.001; ‡P <0.0001 vs PBO.

ACR, American College of Rheumatology response criteria; PBO, placebo; Q4W, every 4 weeks; Q12W, every 12 weeks; TIL, tildrakizumab.
Efficacy: ACR50/70

Shown for randomised patients who received ≥1 dose of study drug. *P <0.05; †P <0.001; ‡P <0.0001 vs PBO.

ACR, American College of Rheumatology response criteria; PBO, placebo; Q4W, every 4 weeks; Q12W, every 12 weeks; TIL, tildrakizumab.
Efficacy: Enthesitis

**Total LEI Score**

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<th>Baseline, mean ± SD</th>
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<tbody>
<tr>
<td>TIL 200 mg Q4W</td>
<td>3.1 ± 1.7</td>
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<tr>
<td>TIL 200 mg Q12W</td>
<td>2.8 ± 1.7</td>
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<tr>
<td>TIL 100 mg Q12W</td>
<td>3.2 ± 1.8</td>
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<tr>
<td>TIL 20 mg Q12W</td>
<td>3.1 ± 1.7</td>
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<tr>
<td>PBO</td>
<td>2.8 ± 1.8</td>
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*P <0.05 compared with PBO. Data represents % change from baseline ± SD.

LEI, Leeds Enthesitis Index; PBO, placebo; Q4W, every 4 weeks; Q12W, every 12 weeks; SD, standard deviation; TIL, tildakizumab.
ACR50 response rates at Week 12 (NRI)

- There was a significant dose-response at Week 12 for ACR50 response rates (primary outcome; p=0.031‡)

*nominal p<0.05 vs placebo; **nominal p<0.01 vs placebo; ***nominal p<0.001 vs placebo. †Dose-response does not include 160 mg (320 mg LD) group. ‡The p value was calculated using a Cochran-Mantel-Haenszel test based on modified ridit scores and including geographic region and prior TNF inhibitor exposure as stratification factors. SE, standard error. NRI, non-responder imputation. FAS; patients with missing efficacy data were imputed as non-responders (NRI)
ACR50 response rates increased up to Week 24 and were maintained to Week 48 (NRI)
ACR20 and ACR70 response rates at Weeks 12 and 48 (NRI)

ACR20 response

- Placebo (FAS, n=42)
- BKZ 16 mg (FAS, n=41)
- BKZ 160 mg (FAS, n=41)

ACR70 response

- Placebo (FAS, n=42)
- BKZ 16 mg (FAS, n=41)

*nominal p<0.05 vs placebo; **nominal p<0.01 vs placebo; ***nominal p<0.001 vs placebo. The p values were derived at Week 12 from a logistic regression model including fixed effects for treatment, geographic region and prior TNF inhibitor exposure. The following data are not presented: placebo → BKZ 160 mg, placebo → BKZ 320 mg, BKZ 16 mg → BKZ 160 mg, BKZ 16 mg → BKZ 320 mg (Week 48)

FAS: Week 12; dose-blind set: Week 48 (NRI)
Bimekizumab BE ACTIVE study

PASI90 response rates increased up to Week 24 and were maintained through the study (NRI)

*Subgroup of patients with ≥3% BSA at baseline. The following data are not presented: placebo → BKZ 160 mg, placebo → BKZ 320 mg, BKZ 16 mg → BKZ 160 mg, BKZ 16 mg → BKZ 320 mg (Weeks 16–48).
Full data provided on slide 18. PASI, Psoriasis Area and Severity Index
FAS up to Week 12, dose-blind set Weeks 16–48 (NRI)
Percentage of patients with resolution of enthesitis at Weeks 12 and 48 (NRI)

Resolution of enthesitis responders (%, SE)

- Placebo (FAS, n=21): 28.6 ± 59.1
- BKZ 160 mg (FAS, n=22; DBS, n=22): 59.1 ± 68.2
- BKZ 160 mg (320 mg LD) (FAS, n=22; DBS, n=20): 59.1 ± 70.0
- BKZ 320 mg (FAS, n=23; DBS, n=23): 34.8 ± 56.5

The following data are not presented: BKZ 16 mg (Week 12), placebo → BKZ 160 mg, placebo → BKZ 320 mg, BKZ 16 mg → BKZ 160 mg, BKZ 16 mg → BKZ 320 mg (Week 48)

Resolution of enthesitis (post hoc) was evaluated in patients with enthesitis at baseline using the Maastricht Ankylosing Spondylitis Entheses Score

FAS: Week 12, dose-blind set: Week 48 (NRI)
Adverse events for special monitoring up to Week 48

<table>
<thead>
<tr>
<th>Double-blind period (up to Week 12)</th>
<th>Placebo Q4W (n=42)</th>
<th>BKZ 16 mg Q4W (n=41)</th>
<th>BKZ 160 mg Q4W (n=41)</th>
<th>BKZ 160 mg (320 mg LD) Q4W (n=41)</th>
<th>BKZ 320 mg Q4W (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida infections</td>
<td>0</td>
<td>0</td>
<td>1 (2.4)</td>
<td>2 (4.9)</td>
<td>0</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>0</td>
<td>0</td>
<td>1 (2.4)</td>
<td>1 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Fungal oesophagitis †</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Malignancies</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neuropsychiatric events ‡</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic events ‡</td>
<td>1 (2.4)</td>
<td>0</td>
<td>5 (12.2)</td>
<td>3 (7.3)</td>
<td>1 (2.4)</td>
</tr>
</tbody>
</table>

- There were **no cases of inflammatory bowel disease**, major cardiovascular events or hypersensitivity and anaphylactic reactions during the study
- **All candida infections were of mild or moderate intensity and did not lead to treatment discontinuation**

*Five patients receiving bimekizumab withdrew prior to the dose-blind period, data from these patients are included in the overall treatment period columns; †Two patients receiving placebo withdrew without receiving a dose of bimekizumab; ‡Both cases were moderate; one resolved with oral anti-fungal treatment and the other was ongoing at the time of data cut-off. §Malignant melanoma in situ.

†One patient receiving bimekizumab 160 mg with 320 mg LD experienced suicidal ideation, accessed using e-SSRS, and was withdrawn from the study and referred to a mental health professional. ††The majority of hepatic events were liver enzyme elevations. TEAE, treatment-emergent adverse event. Safety set
Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3).

Longterm methotrexate therapy in psoriatic arthritis: clinical and radiological outcome.

- Abu-Shakra M, et al.
- *J Rheumatol* 1995 Feb;
  - 22(2):241-5.

- Mtx does not prevent joint damage on x-ray.
CHAMPION: Effect of BMI on the efficacy of adalimumab

- Weight response analysis of Comparative study of Humira vs Methotrexate vs Placebo in Psoriasis Patients (CHAMPION) trial
- Broken down into 3 groups:
  - Normal: BMI <25 kg/m²
  - Overweight: BMI 25–30 kg/m²
  - Obese: BMI >30 kg/m²
- Body weight correlated to lower levels of response in CHAMPION, including in placebo group

Prussick RB, et al. AAD 2015, P1350 Sponsored by AbbVie

*P<0.05 vs MTX, †P<0.05 vs placebo using Fisher exact test
Etanercept: PASI-75 at 12 weeks by weight quartiles

Pooled analysis of studies 200221632, 20021639, and 20021642

* P < 0.0001 compared with placebo
** P < 0.001 compared with placebo
Etanercept: PASI-75 at 12 weeks by 10 kg increments

Pooled analysis of studies 200221632, 20021639, and 20021642

- Placebo (N = 414)
- Linear (50 mg BIW) (N = 358)
- Linear (25 mg QW) (N = 160)
- Linear (25 mg BIW) (N = 415)

P-values are not available for subgroup analyses of weight in 10 kg increments.
Across all baseline body weight categories, IXE-treated patients achieved significantly greater PASI 75 response rates vs. PBO at Week 12.

PASI 75 Response by Treatment Week According to Baseline Body Weight Group, NRI
Induction Period, ITT Population (UNCOVER-2)

* p<.05 vs. PBO; † p<.001 vs. PBO; ‡ p<.001 vs. ETN.

ETN=Etanercept; ITT=Intent-to-Treat; IXE=Ixekizumab; IXE Q2W=80 mg of Ixekizumab Every 2 Weeks; IXE Q4W=80 mg of Ixekizumab Every 4 Weeks;
NRI=Nonresponder Imputation; PASI=Psoriasis Area and Severity Index; PBO=Placebo.
Across all baseline body weight categories, IXE-treated patients achieved significantly greater PASI 90 response rates vs. PBO at Week 12.
Across all baseline body weight categories, IXE-treated patients achieved significantly greater PASI 100 response rates vs. PBO at Week 12.
Etanercept vs Secukinumab

Nonresponder imputation at Week 12 from studies A2302 & A2303
Skin Clearance Response Rates improve over time on treatment with Brodalumab 210 mg Q2W in Non-obese and Obese Patients

- Rates of achieving sPGA 0/1, PASI 75, PASI 90, and PASI 100 were higher among nonobese patients than obese patients at weeks 12 and 52.
- The percentage of patients achieving PASI 100 increased from week 12 to week 52 in both nonobese and obese patients.
- The safety associated with brodalumab 210 mg Q2W was comparable between nonobese and obese patients (data not shown).

Nonresponder imputation was used to impute missing data.

PASI 75, 90, and 100, psoriasis area and severity index 75%, 90%, and 100% improvement; Q2W, every 2 weeks; sPGA, static physicians global assessment; TEAE, treatment-emergent adverse event.

Data on File, Valeant Pharmaceuticals North America LLC.
Figure 2. Proportions of Patients Achieving PASI 90 Response Weeks 16 and 24

GUSELKUMAB

\[ p < 0.001 \] for guselkumab or adalimumab vs placebo

76%

\[ n = 141 \]
\[ 53.2\% \]
\[ (45.0, 61.4) \]
\[ 1.1, 8.9 \]

\[ n = 105 \]
\[ 75.3\% \]
\[ (68.5, 79.9) \]
\[ 0.0, 6.1 \]

\[ n = 201 \]
\[ 72.9\% \]
\[ (64.2, 81.0) \]
\[ 0.8, 8.3 \]

\[ n = 205 \]
\[ 73.4\% \]
\[ (65.8, 80.2) \]
\[ 0.3, 6.3 \]

\[ p < 0.001 \] vs. adalimumab

65.2%

\[ n = 192 \]
\[ 79.7\% \]
\[ (74.0, 85.4) \]
\[ 5.0, 14.0 \]

\[ n = 201 \]
\[ 81.1\% \]
\[ (75.7, 86.9) \]
\[ 0.0, 4.6 \]

\[ n = 225 \]
\[ 75.1\% \]
\[ (69.4, 80.8) \]
\[ 0.7, 7.1 \]

\[ n = 207 \]
\[ 73.4\% \]
\[ (67.4, 79.4) \]
\[ 0.4, 9.3 \]

\[ p\text{-value based on the Cochran-Mantel-Haenszel chi-square test stratified by study.} \]

\[ \text{95\% confidence interval.} \]
Impact of body weight on efficacy of tildrakizumab at 12 weeks in moderate to severe chronic plaque psoriasis

• Pooled analysis from 3 RCTs: reSURFACE 1 and 2 and P05495

• 1° endpoints:
  • reSURFACE 1/2, PASI 75 and PGA 0/1 at Week 16
  • Study P05495, PASI 75 at Week 16

• Randomized patients stratified by body weight (≤90 kg, >90 mg; ≤100 kg, >100 mg)

• Authors concluded that PASI and PGA responses were numerically greater in patients with lower vs higher body weight
Figure 3. Mean PASI Improvement (%) From Baseline to Week 52 by Weight Deciles in Patients Treated With RZB (LOCF)

Weight deciles

- 1st: 43.5–63.3
- 2nd: 63.5–71.0
- 3rd: 71.1–77.4
- 4th: 77.7–82.1
- 5th: 82.2–86.8
- 6th: 87.0–92.6
- 7th: 92.7–98.6
- 8th: 98.8–107.5
- 9th: 107.6–120.6
- 10th: 121.6–170
## ESTEEM 1 & 2/PALACE 1–3: Long-term pooled safety of apremilast (≥156 weeks): Body weight assessments

<table>
<thead>
<tr>
<th>Assessment</th>
<th>APR-exposure period</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 to ≤52 wks n=1844</td>
<td>&gt;52 to ≤104 wks n=1161</td>
</tr>
<tr>
<td>Baseline weight, mean, kg</td>
<td>89.54 (21.54)</td>
<td>89.50 (21.61)</td>
</tr>
<tr>
<td>Mean (SD) change from baseline in weight, kg</td>
<td>-1.42 (4.85)</td>
<td>-1.64 (5.82)</td>
</tr>
<tr>
<td>Mean (SD) % change from baseline in weight</td>
<td>-1.48 (5.38)</td>
<td>-1.70 (6.17)</td>
</tr>
<tr>
<td>Patients with &gt;5% weight loss, n/m(^b) (%)</td>
<td>312/1843 (16.9)</td>
<td>284/1160 (24.5)</td>
</tr>
</tbody>
</table>

**APR-exposure periods** include all patients who received APR regardless of when APR exposure started

\(^a\)Cumulative APR exposure is based on each patient’s total exposure to APR through February 2015

\(^b\)n/m, number of patients with ≥1 occurrence at any time point/number of patients with ≥1 post-baseline value

- With longer-term exposure to APR, safety profile remains stable and favourable
- GI side-effects seem relatively persistent
- Unclear significance of decrease in lymphocyte counts
- Weight loss seems to be common in this population

Crowley J, et al. EADV 2016, P2052; Sponsored by Celgene Corporation
169 liver bx’s in 71 psoriasis pts on MTX

• Hepatic fibrosis: 71%
• In pts with risk fx: 96%
  - obesity  14/15
  - diabetes  7/7
  - ETOH  9/9
• ↑LFT’s not associated with fibrosis

Rosenberg P, et al

- TNF blocker x 24w; diet vs control
- PASI 75 was achieved by 85.9% in the diet group, and 59.3% in the control group (p < 0.001)
- w 24: mean ↓ wt = 12.9 ± 1.2 kg w diet
  -1.5 ± 0.5 kg control
Early increase of abdominal adiposity in patients with spondyloarthritis receiving anti-tumor necrosis factor-α treatment.

CONCLUSIONS

• In obese patients higher doses or stronger medications are more effective

• Weight loss helps
Risk of myocardial infarction in patients with psoriasis.
Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB.
JAMA 2006;296:1735-41

age 30, severe psoriasis
HR: 3.10
Association Between Tumor Necrosis Factor Inhibitor Therapy and Myocardial Infarction Risk in Patients With Psoriasis.


- MI incidence TNF inhibitor/ oral or photoRx /topical: 3.05, 3.85, and 6.73 per 1000 patient-years
- adjusted HR 0.50 vs topical Rx 95% CI, 0.32-0.7
Results: Unadjusted Cumulative Rates of MACE per 100 Patient-Years (PY)
Based on any Exposure to Therapy or Within 91 Days of Therapy Administration

Any Exposure

Unadjusted Rates of MACE per 100 PY (95% CI)

- Ustekinumab: 0.34 (0.23, 0.48)
- Infliximab/Golimumab*: 0.38 (0.22, 0.62)
- ADA/ETN**: 0.33 (0.24, 0.44)
- No Biologic: 0.45 (0.29, 0.66)
- All: 0.36 (0.30, 0.43)

Exposure Within 91 Days

- Ustekinumab: 0.29 (0.17, 0.47)
- Infliximab/Golimumab*: 0.31 (0.14, 0.62)
- Other Biologics**: 0.28 (0.19, 0.40)
- No Biologic: 0.45 (0.35, 0.58)
- All: 0.36 (0.30, 0.43)

*Denotes sponsor biologics, other than ustekinumab, approved for PsO &/or PsA; includes almost exclusively infliximab patients (n=1400); few patients were exposed to golimumab (n=35).
**95% (n=4374) are adalimumab &/or etanercept patients, with the remainder exposed to efalizumab, alefacept, or other non-sponsor biologic.
Association of Ustekinumab vs TNF Inhibitor Therapy With Risk of Atrial Fibrillation and Cardiovascular Events in Patients With Psoriasis or Psoriatic Arthritis.

Lee MP, Desai RJ, Jin Y, Brill G, Ogdie A, Kim SC.


<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>Favors Ustekinumab</th>
<th>Favors TNFi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>0.87 (0.58-1.29)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>≥60</td>
<td>1.46 (0.98-2.18)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.82 (0.49-1.39)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Male</td>
<td>1.21 (0.87-1.69)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.47 (0.93-2.31)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>No</td>
<td>0.88 (0.62-1.25)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Overall</td>
<td>1.08 (0.76-1.54)</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

Atrial fibrillation

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>Favors Ustekinumab</th>
<th>Favors TNFi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>1.08 (0.79-1.48)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>≥60</td>
<td>1.28 (0.84-1.94)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.91 (0.58-1.47)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Male</td>
<td>1.31 (0.97-1.76)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.08 (0.71-1.63)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>No</td>
<td>1.18 (0.86-1.62)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Overall</td>
<td>1.11 (0.80-1.52)</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

Major adverse cardiovascular event
Psoriasis Patients Treated With Biologics and Methotrexate Have a Reduced Rate of Myocardial Infarction: A Collaborative Analysis Using International Cohorts.

Gulliver WP, Young HM, Bachelez H, Randell S, Gulliver S, Al-Mutairi N.

Coronary artery plaque characteristics and treatment with biologic therapy in severe psoriasis: results from a prospective observational study.

Figure 1 Change in coronary plaque burden components over one-year by treatment. (A) Percent change in coronary plaque burden components over one-year by treatment. (B) Change in non-calcified plaque burden over one-year by treatment.
<table>
<thead>
<tr>
<th>Treatments</th>
<th>Change over one-year (mm²) (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF therapy (n = 48)</td>
<td>-0.06 (-5)</td>
<td>-</td>
</tr>
<tr>
<td>vs. Anti-IL12/23</td>
<td>-</td>
<td>-0.02 (-2)</td>
</tr>
<tr>
<td>vs. Anti-IL17</td>
<td>-</td>
<td>-0.15 (-12)</td>
</tr>
<tr>
<td>vs. NBT</td>
<td>-</td>
<td>0.06 (5)</td>
</tr>
<tr>
<td>Anti-IL12/23 therapy (n = 19)</td>
<td>-0.02 (-2)</td>
<td>-</td>
</tr>
<tr>
<td>vs. Anti-IL17</td>
<td>-</td>
<td>-0.15 (-12)</td>
</tr>
<tr>
<td>vs. NBT</td>
<td>-</td>
<td>0.06 (5)</td>
</tr>
<tr>
<td>Anti-IL17 therapy (n = 22)</td>
<td>-0.15 (-12)</td>
<td>-</td>
</tr>
<tr>
<td>vs. NBT</td>
<td>-</td>
<td>0.06 (5)</td>
</tr>
</tbody>
</table>

Values are reported as Mean (% change) for continuous data. Two-tailed P-values less than 0.05 significant (bold values). IL, interleukin; NBT, non-biologic treated.

Table 4 page 727 Elnabawi et al, Cardiovasc Res. 2019
Anti-TNF Antibody Therapy in Rheumatoid Arthritis and the Risk of Serious Infections and Malignancies: Systematic Review and Meta-analysis of Rare Harmful Effects in Randomized Controlled Trials

Tim Bongartz, MD
Alex J. Sutton, PhD
Michael J. Sweeting, MSc
Iain Buchan, MD, MPH
Eric L. Matteson, MD, MPH
Victor Montori, MD, MSc

Context: Tumor necrosis factor (TNF) plays an important role in host defense and tumor growth control. Therefore, anti-TNF antibody therapies may increase the risk of serious infections and malignancies.

Objective: To assess the extent to which anti-TNF antibody therapies may increase the risk of serious infections and malignancies in patients with rheumatoid arthritis by performing a meta-analysis to derive estimates of sparse harmful events occurring in randomized trials of anti-TNF therapy.

Data Sources: A systematic literature search of EMBASE, MEDLINE, Cochrane Library, and bibliographies of the relevant articles published from 1993 to August 4, 2011, was performed.

In patients on biologics, for which malignancies is there evidence of an increase?

- NMSC
- MM
- Lung ca in COPD
- Lymphoma
- NOT in most solid tumors
What do package inserts say? TNF blockers

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

See full prescribing information for complete boxed warning.

SERIOUS INFECTIONS (5.1, 6.1):
- Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.
- Discontinue HUMIRA if a patient develops a serious infection or sepsis during treatment.
- Perform test for latent TB; if positive, start treatment for TB prior to starting HUMIRA.
- Monitor all patients for active TB during treatment, even if initial latent TB test is negative.

MALIGNANCY (5.2):
- Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA.
- Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in adolescent and young adults with inflammatory bowel disease treated with TNF blockers including HUMIRA.

Lymphoma, new primary malignancy
Lymphoma and other new primary malignancy have been reported in adults and pediatric patients; fatal cases have been reported in children and adolescents. Use of etanercept by patients with a history of malignancy or current malignancy may be unadvisable. The effect of TNF inhibition on the development and course of malignancies is not fully understood.
Results: Age and Gender Adjusted Cumulative Rates of Malignancies (excluding NMSC) per 100 Patient-Years (PY) Based on Any Exposure to Therapy (Figure 1)

Figure 1. Cumulative Rates of Malignancies

*This group includes (n=36) patients exposed to golimumab only. **95.7% (n=4067) are adalimumab &/or etanercept patients, with the remainder exposed to other biologics. ***Adjustment used All population as reference.
IL-17 Mediated Inflammation Promotes Tumor Growth and Progression in the Skin

D. He, et al

IL-23 → ↑IL-17 → ↑tumor growth

Could blocking IL-17 be protective against cancer?
Secukinumab

PUBMED search
1/1/19
NO report of
↑ MALIGNANCIES
Ixekizumab

Pubmed search 1/1/19

No report of ↑ Malignancies
Brodalumab

PUBMED search
1/2/19 NO report of ↑ MALIGNANCIES

Search results
Items: 2

   Kaushik SB, Lebwohl MG.
   PMID: 30017705
   Similar articles

   PMID: 29271481
   Similar articles
Exposure-Adjusted Malignancy Event Rates Through 52 Weeks Were Lower in the All-Brodalumab Group Than Those in the Ustekinumab Group

The all-brodalumab group includes all patients who received ≥1 dose of brodalumab. AE, adverse event; n, number of AEs; NMSC, nonmelanoma skin cancer; PY, total patient-years of exposure through week 52; Q2W, every 2 weeks; SEER, Surveillance, Epidemiology, and End Results.
Secukinumab, Ixekizumab & Brodalumab Package Inserts

No mention of Malignancy as Contraindication
Guselkumab

PUBMED search

1/2/19 NO report of ↑ MALIGNANCIES
Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis.
PMID: 29271481

Tildrakizumab
PUBMED search
1/2/19
NO report of ↑ MALIGNANCIES
IL-23 is increased in colon adenocarcinoma
a, Quantitative mRNA expression of IL-23p19 in human colon tumour (red) compared to normal adjacent tissue of the same individual (green, connected by a line), or tissue from cancer-free individuals (black, yellow). b, Significant upregulation of IL-23p19 expression in


<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Number of paired (tumour and normal) samples</th>
<th>Fold increase in expression</th>
<th>Number &gt;5x</th>
<th>Number &gt;10x</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>36</td>
<td>15.33</td>
<td>23</td>
<td>17</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ovarian</td>
<td>32</td>
<td>9.45</td>
<td>12</td>
<td>4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Head and neck</td>
<td>44</td>
<td>3.41</td>
<td>11</td>
<td>4</td>
<td>0.01</td>
</tr>
<tr>
<td>Lung</td>
<td>114</td>
<td>3.03</td>
<td>20</td>
<td>8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Breast</td>
<td>78</td>
<td>2.86</td>
<td>16</td>
<td>6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Stomach</td>
<td>64</td>
<td>2.13</td>
<td>9</td>
<td>3</td>
<td>0.001</td>
</tr>
<tr>
<td>Melanoma</td>
<td>89</td>
<td>1.47</td>
<td>5</td>
<td>0</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

↑IL-23 in many cancers

IL-23 promotes tumour incidence and growth

Mouse carcinogenesis model

Recurrence of Melanoma after Starting Apremilast for Psoriasis.

Salopek TG.

h/o 2 melanomas:
2009 - 1.53mm Clark IV
2012 - 0.9mm Clark IV
2015 started apremilast
>4mos. later→recurrence near first MM
Apremilast Package Insert

No mention of malignancy

• RA pts started on MTX pre 1986
• State cancer registry (not NMSC)
• 4,145 person-years (avg. 9.3 yrs)
MTX associated with:
• 50% ↑ risk of malignancy
• 3-fold ↑ in melanoma
• 5-fold ↑ in non-Hodgkins lymphoma
• 3-fold ↑ in lung ca.

Buchbinder R et al.  
Incidence and prediction of nonmelanoma skin cancer post-renal transplantation: a prospective study in Queensland, Australia.

- 18.8%, <5 years
- 24.8%, 5-10 years
- 33.3%, 10-20 years
- 47.1%, >20 years
Skin Cancer in Organ Transplant Patients

Immunosuppressive Drugs
- Cyclosporine A
- Tacrolimus

Berg and Otley, JAAD 47:1-17, 2002
Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 y cohort study.

- 1252 patients for up to 5 years (average 1.9)
- 6-fold ↑ skin cancer
- No ↑ nonskin cancer
Metastatic melanoma after solid organ transplantation: An interdisciplinary, institution-based review of management with systemic and targeted therapies.

Tripathi SV, Morris CR, Alhamad T, Fields RC, Linette GP, Cornelius LA.

Invasive Melanomas ↑2 fold
M:F ratio 14:1


- Acitretin 30 mg/d
- 2/19 ➔ 2 SCCs vs 9/19 ➔ 18 SCCs
Chemoprevention of skin cancer in xeroderma pigmentosum.

- 121 BCCs or SCCs in 5 patients 2 years prior to Rx
- Isotretinoin 2 mg/kg/d → 25 tumors over 2 years of Rx
The role of antinuclear autoantibodies in patients with psoriasis treated with anti-tumor necrosis factor-alpha agents: a retrospective long-term study.

Autoimmunity
Treatment with ENBREL® may result in the formation of autoantibodies (see ADVERSE REACTIONS: Autoantibodies) and, rarely, in the development of a lupus-like syndrome (see ADVERSE REACTIONS: Adverse Reaction Information from Spontaneous Reports) which may resolve following withdrawal of ENBREL®. If a patient develops symptoms and findings suggestive of a lupus-like syndrome following treatment with ENBREL®, treatment should be discontinued and the patient should be carefully evaluated.
Antinuclear antibodies associate with loss of response to antitumour necrosis factor-α therapy in psoriasis: A retrospective, observational study.
Pink AE et al.  
*Br J Dermatol* 2009 Oct 26; [e-pub ahead of print].  
(http://dx.doi.org/10.1111/j.1365-2133.2009.09563.x)

- 60 on 1st agent ➔ ANA 16.7%
- 22 stopped 1st agent ➔ ANA 54.5%
- 9 stopped 2 agents ➔ ANA 77.8%
- 6 stopped 3 agents ➔ ANA 83.3%
Drug-Induced SLE Associated with Etanercept Therapy

- 4 patients.
- Manifestations including fever, arthritis, discoid skin changes, rash, pleuritic pain, ANA, anti-dsDNA, anti-histone, hypocomplementemia, anti-Sm, anti-RNP.
- No baseline serologies.
- All resolved with discontinuation of etanercept and/or addition of corticosteroids.

Regression of subacute cutaneous lupus erythematosus in a patient with rheumatoid arthritis treated with a biologic tumor necrosis factor alpha-blocking agent: comment on the article by Pisetsky and the letter from Aringer et al.

Fautrel B, Foltz V, Frances C, Bourgeois P, Rozenberg S.

Aringer M et al.
*Arthritis Rheum.*

• ↓proteinuria, arthritis, C4
• ↑autoantibodies
<table>
<thead>
<tr>
<th></th>
<th>Classic DILE(^1)</th>
<th>TNF-α inhibitor DILE(^2)</th>
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</thead>
<tbody>
<tr>
<td>ANA</td>
<td>&gt;95%</td>
<td>100%</td>
</tr>
<tr>
<td>dsDNA</td>
<td>&lt;1%</td>
<td>91%</td>
</tr>
<tr>
<td>Antihistone</td>
<td>&gt;95%</td>
<td>57%</td>
</tr>
<tr>
<td>Decreased complement</td>
<td>&lt;1%</td>
<td>59%</td>
</tr>
<tr>
<td>Rash</td>
<td>27%</td>
<td>72%</td>
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</tbody>
</table>

1. Benucci et al Clin Rheumatol 27:91-95
Treatment of coexistent psoriasis and lupus erythematosus.

“Anti-TNF-α agents, ustekinumab, and abatacept may be valid treatment options for patients with concomitant LE and psoriasis. Clinical lupus flares in LE patients treated with TNF-α inhibitors were infrequent.”
Anti-nuclear antibody positivity and the use of certolizumab in inflammatory bowel disease patients who have had arthralgias or lupus-like reactions from infliximab or adalimumab. Verma HD, Scherl EJ, Jacob VE, Bosworth BP. J Dig Dis 2011;12:379-83.

- 5/6 patients → arthralgias or lupus-like symptoms resolved after being switched to certolizumab (P < 0.001)
- 2/4 ANA positive patients → ANA negative
Efficacy and safety of ustekinumab, an IL-12 and IL-23 inhibitor, in patients with active systemic lupus erythematosus: results of a multicentre, double-blind, phase 2, randomised, controlled study.

- 62% of ustekinumab treated patients reported response vs 33% in the placebo group (P=0.006) at week 24
Apremilast for discoid lupus erythematosus: results of a phase 2, open-label, single-arm, pilot study.

De Souza A, Strober BE, Merola JF, Oliver S, Franks AG Jr.

A 2 year, open ended trial of methotrexate in systemic lupus erythematosus.
Wilson K, Abeles M.

Discoid lupus erythematosus: successful treatment with oral methotrexate.
Goldstein E, Carey W.
Hypertrophic lupus erythematosus treated successfully with acitretin as monotherapy.
Al-Mutairi N, Rijhwani M, Nour-Eldin O. 

Efficiency of acitretin in the treatment of cutaneous lupus erythematosus.
Ruzicka T, Meurer M, Bieber T. 
Low dose cyclosporine A in the treatment of resistant proliferative lupus nephritis.
Sheikholeslami M, et al.  
*Mod Rheumatol.* 2017:1-7 [Epub ahead of print].

Therapeutic drug monitoring of cyclosporine microemulsion in patients with corticosteroid-resistant systemic lupus erythematosus. 
Wada Y, et al.  
TNF neutralization in MS: results of a randomized, placebo-controlled multicenter study.

- MS exacerbations ↑ with lenercept.
Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides.  
Mohan N, et al.  

- 17 – etanercept, 2 – infliximab
- partial or complete resolution on d/c
- 1 positive rechallenge

- UST → no effect on MS
Activity of secukinumab, an anti-IL-17A antibody, on brain lesions in RRMS: results from a randomized, proof-of-concept study.

Havrdová E, et al
Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial.

Hueber W, Sands BE, et al

Secukinumab not effective
Secondary area under the curve analysis (weeks 4-10) showed a significant difference (mean $\Delta$CDAI=49; 95% CI (2 to 96), $p=0.043$) in favour of placebo. Post hoc subgroup analysis showed that unfavourable responses on SEK were driven by patients with elevated inflammatory markers (CRP≥10 mg/l and/or faecal calprotectin≥200 ng/ml; mean $\Delta$CDAI=62; 95% CI (-1 to 125), $p=0.054$ in favour of placebo.
No Definitive Role of Secukinumab in Crohn’s Disease

*Entire treatment period – exposure-adjusted (52 weeks)*

- Phase III incidence rate as expected with psoriasis
  - No dose relationship between secukinumab doses
  - All cases with Crohn’s disease had prior history

<table>
<thead>
<tr>
<th>Based on all AEs</th>
<th>AIN457 300 mg (n=1410)</th>
<th>AIN457 150 mg (n=1395)</th>
<th>Placebo (n=793)</th>
<th>Etanercept (n=323)</th>
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<tbody>
<tr>
<td><strong>Inflammatory bowel disease</strong></td>
<td>n (IR)</td>
<td>n (IR)</td>
<td>n (IR)</td>
<td>n (IR)</td>
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<tr>
<td>3 (0.26)</td>
<td>4 (0.35)</td>
<td>0 (0.00)</td>
<td>1 (0.34)</td>
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<tr>
<td>[0.05, 0.75]</td>
<td>[0.10, 0.90]</td>
<td>[0.0, 1.83]</td>
<td>[0.01, 1.90]</td>
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<tr>
<td><strong>Colitis ulcerative</strong></td>
<td>2 (0.17)</td>
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<td>1 (0.34)</td>
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<td>[0.02, 0.61]</td>
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<tr>
<td>AIN457 150 mg (n=1395)</td>
<td>n (IR)</td>
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<tr>
<td><strong>Crohn’s disease</strong></td>
<td>0 (0.00)</td>
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<td><strong>Anal fistula</strong></td>
<td>1 (0.08)</td>
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<td>[0.0, 1.26]</td>
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</tbody>
</table>

IR=Exposure-adjusted incidence rate per 100 patient-years.

A third case of Crohn’s disease occurred in study A2211E1- 150 mg Start of Relapse arm

** Not associated with inflammatory bowel disease
Inflammatory bowel disease among patients with psoriasis treated with ixekizumab: A presentation of adjudicated data from an integrated database of 7 randomized controlled and uncontrolled trials.


APREMILAST FOR UC: PROPORTION OF SUBJECTS ACHIEVING CLINICAL REMISSION BY TMS* AT WEEK 12 (ITT, NRI)

Δ = 17.8%

Δ = 8.0%

P = 0.0301

P = 0.4240

*TMS ≤2, with no individual subscore >1.

ITT=intent to treat; NRI=non-responder imputation.
PROPORTION OF APREMILAST 30 MG BID SUBJECTS ACHIEVING ENDOSCOPIC SUBSCORE ≤1, CLINICAL REMISSION BY PMS*, AND CLINICAL RESPONSE§ BY TMS AT WEEK 12 (ITT, NRI)

*PMS ≤2 with no individual subscore >1. §Decrease from baseline in the TMS ≥3 points and ≥30%, along with a reduction in the rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore ≤1.

PMS=Partial Mayo Score.
PROPORTION OF SUBJECTS ACHIEVING HISTOLOGICAL REMISSION (GEBOES <2) AT WEEK 12 (ITT, NRI)

- Placebo: 29.3%, 17/58
- Apremilast 30 mg BID: 43.9%, 25/57
- Apremilast 40 mg BID: 41.8%, 23/55

Δ=14.5% for Placebo vs Apremilast 30 mg BID
Δ=12.5% for Placebo vs Apremilast 40 mg BID

P=0.1073 for Placebo vs Apremilast 30 mg BID
P=0.1671 for Placebo vs Apremilast 40 mg BID
EXPLORATORY END POINT: PROPORTION OF SUBJECTS ACHIEVING MUCOSAL HEALING \((\text{MES} \leq 1 \text{ AND GEBOES} < 2)\) AT WEEK 12 (ITT, NRI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion Achieving Mucosal Healing</th>
<th>Δ</th>
<th>P</th>
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<tr>
<td>Placebo</td>
<td>15.5%</td>
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<tr>
<td>Apremilast 30 mg BID</td>
<td>33.3%</td>
<td>17.8%</td>
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<td>Apremilast 40 mg BID</td>
<td>21.8%</td>
<td>6.3%</td>
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\(\Delta = 17.8\%\)

\(\Delta = 6.3\%\)
**MEDIAN PERCENT CHANGE FROM BASELINE (LOCF) IN HSCRP**

- Placebo
- Apremilast 30 mg BID
- Apremilast 40 mg BID

*P*<0.05 for treatment comparison vs. placebo.

LOCF=last observation carried forward; hsCRP=high-sensitivity C-reactive protein.
Does exposure to isotretinoin increase the risk for the development of inflammatory bowel disease?
A meta-analysis.


NO
Isotretinoin and inflammatory bowel disease: trial lawyer misuse of science and FDA warnings.

Tenner S.

Isotretinoin, acne, and Crohn's disease: a convergence of bad skin, bad science, and bad litigation creates the perfect storm.
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<th>PsA</th>
<th>OBESITY</th>
<th>CARDIAC</th>
<th>CA</th>
<th>+ANA</th>
<th>LUPUS</th>
<th>MS</th>
<th>CROHN</th>
<th>HEPATITIS C Ab +</th>
<th>HBsAg+</th>
<th>Anti-HBc+</th>
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