Tips on the use of anti-IL-17 Drugs in Psoriasis

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Dr. Lebwohl is also a consultant for Allergan, Almirall, Arcutis, Avotres, Birch biomed, Boehringer-Ingelheim, Bristol Myers Squibb, Cara, Castle Biosciences, Dermavant, Encore, Inozyme, LEO Pharma, Meiji, Menlo, Mitsubishi Pharma, Neuroderm LTD, Pfizer, Promius/Dr. Reddy, Theravance Biopharma, and Verrica.

Updated 04/23/19
Time to Achieve 50% Improvement in PASI

- **Brodalumab**: 1.8 (95% CI 1.8-1.9, n=1236)*
- **Ixekizumab**: 1.9 (one study, n=1469)*
- **Secukinumab (high dose)**: 3.0 (95% CI 2.8-3.2, n=323)*
- **Secukinumab (low dose)**: 3.9 (one study, n=327)*
- **Cyclosporine (high dose)**: 3.1 (Range 2.6-3.8, n=211)**
- **Cyclosporine (low dose)**: 5.4 (Range 3.5-9.7, n=359)**
- **Adalimumab**: 3.5 (one study, n=108)
- **Infliximab**: 3.7 (Range 3.2-4.3, n=21)**
- **Apremilast**: 4.3 (one study, n=68)
- **Ustekinumab (low dose)**: 4.4 (95% CI 4.2-4.7, one study, n=613)*
- **Tildrakizumab (high dose)**: 6.0 (one study, n=622)*
- **Tildrakizumab (low dose)**: 6.0 (one study, n=618)*
- **Certolizumab pegol (high dose)**: 7.0 (Range 6.0-7.5, n=342)**
- **Certolizumab pegol (low dose)**: 7.4 (Range 6.0-7.9, n=361)**
- **Etanercept (high dose)**: 6.5 (Range 6.0-6.7, n=226)**
- **Etanercept (low dose)**: 10.9 (Range 10.3-12.0, n=767)**
- **Methotrexate (high dose)**: 3.9 (Range 3.2-4.4, n=92)**
- **Methotrexate (low dose)**: 10.0 (Range 6.1-12.7, n=329)**
- **Actretin (high dose)**: 5.5 (Range 4.6-7.2, n=79)
- **Actretin (low dose)**: 25.4 (one study, n=18)*
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time to Achieve PASI 75 (Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brodalumab</td>
<td>2.1 (95% CI 2.01-2.26, n=1236)*</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>2.4 (one study, n=1469)*</td>
</tr>
<tr>
<td>Secukinumab (high dose)</td>
<td>3.0 (one study, n=323)*</td>
</tr>
<tr>
<td>Infliximab</td>
<td>3.5 (Range 3.3-4.1, n=1710)**</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>4.6 (Range 2.7-4.7, n=933)**</td>
</tr>
<tr>
<td>Tildrakizumab (high dose)</td>
<td>4.6 (one study, n=622)*</td>
</tr>
<tr>
<td>Tildrakizumab (low dose)</td>
<td>4.9 (one study, n=616)*</td>
</tr>
<tr>
<td>Ustekinumab (high dose)</td>
<td>4.6 (Range 4.3-5.4, n=1076)**</td>
</tr>
<tr>
<td>Ustekinumab (low dose)</td>
<td>5.0 (Range 4.8-6.4, n=1611)**</td>
</tr>
<tr>
<td>Cyclosporine (low dose)</td>
<td>6.0 (Range 3.8-7.0, n=339)**</td>
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<tr>
<td>Certolizumab pegol (high dose)</td>
<td>7.1 (Range 4.3-8.0, n=351)**</td>
</tr>
<tr>
<td>Certolizumab pegol (low dose)</td>
<td>6.9 (Range 4.1-8.0, n=342)**</td>
</tr>
<tr>
<td>Etanercept (high dose)</td>
<td>6.6 (Range 5.6-8.7, n=1177)**</td>
</tr>
<tr>
<td>Etanercept (low dose)</td>
<td>9.5 (Range 9.0-10.4, n=153)**</td>
</tr>
<tr>
<td>Methotrexate (high dose)</td>
<td>3.2 (one study, n=18)**</td>
</tr>
<tr>
<td>Methotrexate (low dose)</td>
<td>9.9 (Range 9.1-12.2, n=439)**</td>
</tr>
<tr>
<td>Acitretin (low dose)</td>
<td>25.3 (one study, n=18)*</td>
</tr>
</tbody>
</table>
Dear Dr. Lebwohl,
I prescribed Secukinumab for a 175 pound patient with severe psoriasis. We showed her how to administer the shots on Monday. She called me on Friday to say that she had administered two shots each day from Monday through Friday and was now out of Secukinumab. What should I do?
Sincerely,
Dr. XXXXXX

Inadvertent Overdose of Secukinumab, Consequences, and Cautions
Mark Taliercio, Dana Alessa, David B. Kessler,
JOURNAL OF PSORIASIS AND PSORIATRIC ARTHRITIS. 2016; V O L . 1.(4):147-9
Dr. Lebwhol,
Thank you for taking the time to speak to me at the Mt Sinai Winter meeting. I have reported to Novartis, my patient, a 70 year old white female with PMH of diabetes and hypertension with severe psoriasis with prior treatment of Enbrel, Humira, Stelara and methotrexate who was recently started on Cosentyx. Her medications included; Insulin, coreg, amlodipine, aspirin, citalopram, fenofibrate, and hydrochlorothiazide; She is 5'5", 190 lbs, bp 150/90.

She gave herself SQ shots of Cosentyx 150 mg x 2 daily on 8/11, 8/12, 8/13, 8/14, 8/15/2015. She called after one week complaining of her Skin "dry and peeling" and when was her next shot due. She had no adverse effects and her labs were normal except her usual elevated glucose. Her PGA went from 4->2 after 2 weeks. I restarted her next Cosentyx one month after her last dose and continues to do well.

Once again thank you for your time, I wish you and your family a Happy and healthy New Year.

Sincerely,
"In post-marketing database, we have 100+ cases of “overdoses” which are divided as unintentional, intentional and prescribed….there are no reports of unusual AEs – most times we don’t see any AE.” From Novartis

Pearl #2 Anti-IL-17 antibodies are safe
Maximum dose not known
10 OVERDOSAGE

Doses up to 30 mg/kg intravenously (i.e., approximately 2000 to 3000 mg) have been administered in clinical trials without dose-limiting toxicity. In the event of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.
Response to question about ixekizumab overdose

• Doses up to 180 mg have been administered subcutaneously in clinical trials without dose-limiting toxicity. Overdoses up to 240 mg, subcutaneously, have been reported without any serious adverse events.¹

• In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.²

Enclosed Prescribing Information
TALTZ® (ixekizumab) injection, for subcutaneous administration, Lilly

References
1. Data on file, Eli Lilly and Company and/or one of its subsidiaries.
Treatment of Moderate to Severe Psoriasis With High-Dose (450-mg) Secukinumab: Case Reports of Off-Label Use.

Immunity to infection in IL-17-deficient mice and humans.
Cypowyj S, Picard C, Maródi L, et al

Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity.
Puel A, Cypowyj S, Bustamante J, et al.
Oral fluconazole 150 mg single dose versus intra-vaginal clotrimazole treatment of acute vulvovaginal candidiasis.


Pearl #3 oral fluconazole for candidiasis
Late reactivation of spinal tuberculosis by low-dose methotrexate therapy in a patient with rheumatoid arthritis. Binymin K, Cooper RG


Methotrexate and reactivation tuberculosis.

Lamb SR.


Pearl #4 IL-17 not assoc. w/ TB reactivation

- “independent risk factors for post-transplant TB included cyclosporine-based immunosuppressant agents during the first year after kidney transplantation (odds ratio [OR]: 1.98, \( P = 0.001 \))”
- “high proportion of extrapulmonary spread”
Tuberculosis associated with infliximab, a tumor necrosis factor α -neutralizing agent.
Keane J, et al.
*N Eng J Med* 2001;345(15):1098-1104

- 70/147,000
- 48 ≤ 3 infusions
- Test for TB!
• Tb has occurred with all of the TNF blockers
• Tb is commonly extrapulmonary in patients on TNF blockers
• Test for Tb before starting anti-TNF therapy
Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden.

Askling J, Fored CM, Brandt L et al.


• ↑ TB risk up to 4x
Tumor necrosis factor blockade in chronic murine tuberculosis enhances granulomatous inflammation and disorganizes granulomas in the lungs. Chakravarty SD, et al

- Tumor necrosis factor-alpha is required in the protective immune response against Mycobacterium tuberculosis in mice.
  Flynn JL, et al

TNF is necessary for normal granuloma formation and function.
Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: the three-year prospective French research axed on tolerance of biotherapies registry. Tubach F et al. *Arthritis & Rheumatism* 2009;60:1884-94.

- IFX: SIR 18.6
- ADA: SIR 29.3
- ETN: SIR 1.8
WARNING
RISK OF INFECTIONS TUBERCULOSIS (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL (SEE WARNINGS). PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION WITH A TUBERCULIN SKIN TEST. ¹ TREATMENT OF LATENT TUBERCULOSIS INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE.
WARNING
RISK OF INFECTIONS
Cases of tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) have been observed in patients receiving HUMIRA. Patients should be evaluated for latent tuberculosis infection with a tuberculin skin test. Treatment of latent tuberculosis infection should be initiated prior to therapy with HUMIRA.
TB Rates in Adalimumab Clinical Studies

Pre-screening

<table>
<thead>
<tr>
<th>Rate per 100 pt-yrs</th>
<th>EU</th>
<th>North America</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3</td>
<td></td>
<td>0.08</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Post-screening

<table>
<thead>
<tr>
<th># cases</th>
<th>EU</th>
<th>North America</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td></td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

Exposure (pt-yrs)

<table>
<thead>
<tr>
<th></th>
<th>EU</th>
<th>North America</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>534</td>
<td></td>
<td>3978</td>
<td>4447</td>
</tr>
</tbody>
</table>
Patients need to be evaluated for tuberculosis risk factors and for latent or active tuberculosis infection with a tuberculin skin test both before and during treatment.

Cases of tuberculosis have occurred in patients who received etanercept; therefore, treatment of latent infection should be started before etanercept initiation.

Consider antituberculosis therapy before etanercept initiation in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Some patients who tested negative for latent tuberculosis before etanercept receipt have developed active tuberculosis.

- 41 patients - IL12 receptor β1 deficiency
- Salmonellosis
- Tuberculosis
“Individuals genetically deficient in interleukin (IL)-12/IL-23 are particularly vulnerable to disseminated infections from mycobacteria (eg, nontuberculous, environmental mycobacteria), salmonella (eg, nontyphi strains), and Bacillus Calmette-Guerin (BCG) vaccinations; consider appropriate diagnostic testing. Evaluate for tuberculosis (TB) infection prior to, during, and after treatment; do not administer to patients with active TB. Consider anti-TB therapy prior to initiation in patients with history of latent or active TB when an adequate course of treatment cannot be confirmed.”
Guselkumab PI

Tuberculosis
Evaluate all potential recipients of guselkumab for tuberculosis infection before initiating treatment. Do not administer guselkumab to patients with active tuberculosis infection. For patients with latent tuberculosis, antituberculosis therapy should be administered before initiating guselkumab. Consider antituberculosis treatment for patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Monitor patients closely for signs and symptoms of active tuberculosis infection during and after treatment.
Essential role of IL-17A in the formation of a mycobacterial infection-induced granuloma in the lung.


- IL-17A deficiency may reduce formation of granulomas
IL-23 compensates for the absence of IL-12p70 and is essential for the IL-17 response during tuberculosis but is dispensable for protection and antigen-specific IFN-γ responses if IL-12p70 is available.


- depletion of IL-17A–producing CD4+ T cells →no effect on disease progression during primary *M. tuberculosis* infection
Secukinumab in patients with LTBI

- At BL, 25 subjects who received SKB had a past history of either pulmonary TB, LTBI or a positive TB test
  Tested negative for LTBI by QFN Gold at screening
  None were on anti-TB medication during the psoriasis study
- None experienced reactivation of TB; median SKB treatment duration was 363 days

Tsai T-F, et al. AAD 2015, P607 Sponsored by Novartis Pharma AG
## Subjects diagnosed with LTBI during screening in Phase 3 SKB trials

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subjects diagnosed with LTBI in screening (n)</th>
<th>Median duration of treatment with SKB (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SKB 150 mg</td>
<td>52</td>
<td>364</td>
</tr>
<tr>
<td>Any SKB 300 mg</td>
<td>55</td>
<td>364</td>
</tr>
<tr>
<td>Any SKB</td>
<td>107</td>
<td>364</td>
</tr>
</tbody>
</table>
1 TB-negative subject (at BL; in ERASURE) was diagnosed with LTBI following retest according to local guidelines (Argentina) on Day 141 while on SKB 150 mg; treated with isoniazid 300 mg daily and completed the study without SKB dose interruption.

Secukinumab shows no evidence for reactivation of previous or latent TB infection in psoriasis patients: Pooled Phase 3 safety

No reactivation of tuberculosis in psoriasis patients with latent tuberculosis infection while on ixekizumab treatment: a report from 11 clinical studies

Elisabeth Riedl¹,², Stefan Winkler³, Wen Xu², Noah Agada², Mark G Lebwohl⁴
Autosomal recessive deficiency in the receptor IL-17RA (due to mutations in the *IL17RA* gene) or autosomal dominant mutations in *IL17F* → Chronic mucocutaneous candidiasis
“Pre-treatment Evaluation for Tuberculosis
Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with SECUKINUMAB. Do not administer SECUKINUMAB to patients with active TB infection. Initiate treatment of latent TB prior to administering SECUKINUMAB. Consider anti-TB therapy prior to initiation of SECUKINUMAB in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving SECUKINUMAB should be monitored closely for signs and symptoms of active TB during and after treatment.”

Secukinumab PI
Safety in Psoriasis Patients with Latent Tuberculosis (TB) Treated with Guselkumab and Anti-TB Treatments in the Phase 3 VOYAGE Trials

Luis Puig, Tsen-fang Tsai, Tina Bhutani, Jonathan Uy, Paraneedharan Ramachandran, Michael Song, Yin You, Melinda Gooderham, Mark Lebwohl

130 patients randomized to PBO, GUS or ADA at baseline tested positive for LTBI & received concomitant anti-TB treatments.

No cases of TB reactivation

Presented at FC18
Tofacitinib Package Insert

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

*See full prescribing information for complete boxed warning.*

- Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving XELJANZ. (5.1)
- If a serious infection develops, interrupt XELJANZ until the infection is controlled. (5.1)
- Prior to starting XELJANZ, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting XELJANZ. (5.1)
- Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative (5.1)
- Lymphoma and other malignancies have been observed in patients treated with XELJANZ. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications. (5.2)
No mention of tuberculosis
IL-23 compensates for the absence of IL-12p70 and is essential for the IL-17 response during tuberculosis but is dispensable for protection and antigen-specific IFN-γ responses if IL-12p70 is available.


- depletion of IL-17A–producing CD4+ T cells →no effect on disease progression during primary *M. tuberculosis* infection

Pearl #4 IL-17 blockade not associated with Tb reactivation
FUTURE 2
ACR20 Response Through Week 52

Secukinumab

**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) vs Week 24 to Week 52 (X-ray completers)

Overall population
MTX: Yes
MTX: No

Mean change in vdH-mTSS

Pooled SKB doses vs PBO

Overall population
MTX: Yes
MTX: No

Mean change in vdH-mTSS

*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

### Effect on structural disease progression

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>IXE Q4W</th>
<th>IXE Q2W</th>
<th>Adalimumab 40 mg Q2W*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>N=106</td>
<td>N=107</td>
<td>N=103</td>
<td>N=101</td>
</tr>
<tr>
<td>LS mean change from baseline mTSS (SE)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>Percentage of patients with change in mTSS at week 24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0</td>
<td>72.0</td>
<td>83.0</td>
<td>83.5</td>
<td>91.6¶</td>
</tr>
<tr>
<td>≤0.5</td>
<td>77.4</td>
<td>89.0**</td>
<td>94.8¶</td>
<td>95.8¶</td>
</tr>
<tr>
<td>≤0.95</td>
<td>83.9</td>
<td>94.0‡</td>
<td>96.9§</td>
<td>95.8§</td>
</tr>
</tbody>
</table>
Brodalumab Phase 2 PsA study: Clinical response and improvement in psoriasis in subjects with PsA

ACR20 response rate at Week 12

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients (%)</th>
<th>Placebo (n=55)</th>
<th>BRO 140 mg q2w (n=57)</th>
<th>BRO 280 mg q2w (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>18.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRO 140 mg q2w</td>
<td>* 36.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRO 280 mg q2w</td>
<td>* 39.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Double-blind, nonresponder imputation analysis
*P<0.05 vs placebo

Mease P, et al. AAD 2014, P7605
Brodalumab Phase 2 PsA study: Clinical response and improvement in psoriasis in subjects with PsA

**ACR20 response rate at Week 24**

<table>
<thead>
<tr>
<th></th>
<th>PBO (n=55)</th>
<th>BRO 140 mg q2w (n=57)</th>
<th>BRO 280 mg q2w (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 24</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patients (% ± SE)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ACR20</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>64.4</td>
<td>51.1</td>
<td>43.5</td>
</tr>
</tbody>
</table>

Indicates time point at which all subjects began receiving BRO 280 mg q2w

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

### Study design

<table>
<thead>
<tr>
<th>Key inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Active PsA</td>
</tr>
<tr>
<td>o TJC ≥3 out of 78</td>
</tr>
<tr>
<td>o SJC ≥3 out of 76</td>
</tr>
<tr>
<td>o CASPAR ≥3</td>
</tr>
<tr>
<td>• Patients with or without prior exposure to one anti-TNF therapy were permitted</td>
</tr>
</tbody>
</table>

#### Primary endpoint

ACR50 response

#### Efficacy and safety at Week 48

*Enrolled set. After Week 12, patients receiving placebo or bimekizumab 16 mg were re-randomized (1:1) to receive bimekizumab 160 mg or 320 mg; all other patients continued on their previous dose; †Patients with <10% improvement from baseline in TJC and SJC are eligible for rescue therapy. CASPAR, Classification Criteria for Psoriatic Arthritis; LD, loading dose; Q4W, every four weeks; SJC, swollen joint count; TJC, tender joint count; TNF, tumor necrosis factor

### Study design diagram

**Screening**

- n=42

**Double-blind period**

- Placebo Q4W
  - Bimekizumab 160 mg Q4W
  - Bimekizumab 320 mg Q4W
- Bimekizumab 16 mg Q4W
  - Bimekizumab 160 mg Q4W
  - Bimekizumab 320 mg Q4W
- Bimekizumab 160 mg Q4W
  - Bimekizumab 160 mg Q4W
- Bimekizumab 160 mg Q4W (320 mg LD at baseline)
  - Bimekizumab 160 mg Q4W
  - Bimekizumab 320 mg Q4W
- Bimekizumab 320 mg Q4W
  - Bimekizumab 320 mg Q4W

**Dose-blind period**

- n=36

**Extension study**

- Extension study to evaluate response to treatment and long-term safety

**Safety follow up visit**

- Safety follow up visit 20 weeks after last dose for patients not enrolling in extension study

**Weeks 16, 24 and 36:**

- evaluation for eligibility for rescue therapy

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Bimekizumab was supplied as a clear to opalescent, colorless to slightly brown, sterile, preservative free solution. Each single-use dose vial contained 160 mg/mL bimekizumab in 55 mM sodium acetate, 220 mM glycine and 0.04% (w/v) polysorbate 80 at pH 5.0. Placebo was supplied as a 0.9% sodium chloride aqueous solution.
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**

- Week 12
- Week 48

*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 16 mg, BKZ 16 mg → BKZ 160 mg, BKZ 16 mg → BKZ 320 mg (Week 48) FAS: Week 12; dose-blind set: Week 48 (NRI)
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)
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>n (%)</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>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 eC-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.
Pearl #6 IL-17 blockers are effective in obese patients

Presented are the two subgroups used for stratification in the studies

<table>
<thead>
<tr>
<th>SKB 300 mg</th>
<th>SKB 150 mg</th>
<th>Etanercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI 90</td>
<td>PASI 100</td>
<td>PASI 100</td>
</tr>
<tr>
<td>&lt;90kg</td>
<td>≥90kg</td>
<td>&lt;90kg</td>
</tr>
<tr>
<td>67.7</td>
<td>54.5</td>
<td>30.7</td>
</tr>
<tr>
<td>66.2</td>
<td>53.8</td>
<td>16.7</td>
</tr>
<tr>
<td>63.2</td>
<td>51.6</td>
<td>15.7</td>
</tr>
<tr>
<td>60.2</td>
<td>49.8</td>
<td>14.7</td>
</tr>
<tr>
<td>57.2</td>
<td>49.2</td>
<td>13.7</td>
</tr>
<tr>
<td>54.2</td>
<td>47.8</td>
<td>12.7</td>
</tr>
<tr>
<td>51.2</td>
<td>45.6</td>
<td>11.7</td>
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<td>48.2</td>
<td>44.4</td>
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<td>45.2</td>
<td>43.2</td>
<td>9.7</td>
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<td>42.2</td>
<td>41.6</td>
<td>8.7</td>
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<td>39.2</td>
<td>40.0</td>
<td>7.7</td>
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<td>36.2</td>
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<td>6.7</td>
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<td>33.2</td>
<td>34.6</td>
<td>5.7</td>
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<td>30.2</td>
<td>32.6</td>
<td>4.7</td>
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<tr>
<td>27.2</td>
<td>29.6</td>
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<tr>
<td>24.2</td>
<td>26.6</td>
<td>2.7</td>
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<tr>
<td>21.2</td>
<td>23.6</td>
<td>1.7</td>
</tr>
<tr>
<td>18.2</td>
<td>21.6</td>
<td>0.7</td>
</tr>
<tr>
<td>15.2</td>
<td>18.6</td>
<td>1.7</td>
</tr>
<tr>
<td>12.2</td>
<td>15.6</td>
<td>2.7</td>
</tr>
<tr>
<td>9.2</td>
<td>12.6</td>
<td>3.7</td>
</tr>
<tr>
<td>6.2</td>
<td>9.6</td>
<td>4.7</td>
</tr>
<tr>
<td>3.2</td>
<td>6.6</td>
<td>5.7</td>
</tr>
<tr>
<td>0</td>
<td>3.6</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Nonresponder imputation at Week 12 from studies A2302 & A2303
Across all baseline body weight categories, IXE-treated patients achieved significantly greater PASI 75 response rates vs. PBO at Week 12.

*<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.

**Graphs**

- **<80 kg**
  - PBO (n=50)
  - ETN (n=111)
  - IXE Q4W (n=97)
  - IXE Q2W (n=123)

- **≥80 to <100 kg**
  - PBO (n=61)
  - ETN (n=121)
  - IXE Q4W (n=130)
  - IXE Q2W (n=133)

- **≥100 kg**
  - PBO (n=55)
  - ETN (n=125)
  - IXE Q4W (n=119)
  - IXE Q2W (n=95)

**Abbreviations**
- PASI: Psoriasis Area and Severity Index
- PBO: Placebo
- ETN: Etanercept
- IXE: Ixekizumab
- NRI: Nonresponder Imputation
- ITT: Intent-to-Treat
- Q2W: Every 2 Weeks
- Q4W: Every 4 Weeks

**Statistical Significance**
- *p<.05 vs. PBO
- †p<.001 vs. PBO
- ‡p<.05 vs. ETN
- ¶p<.001 vs. ETN

Across all baseline body weight categories, IXE-treated patients achieved significantly greater PASI 100 response rates vs. PBO at Week 12.

**<80 kg**
- PBO (n=50)
- ETN (n=111)
- IXE Q4W (n=97)
- IXE Q2W (n=123)

**≥80 to <100 kg**
- PBO (n=61)
- ETN (n=121)
- IXE Q4W (n=130)
- IXE Q2W (n=133)

**≥100 kg**
- PBO (n=55)
- ETN (n=125)
- IXE Q4W (n=119)
- IXE Q2W (n=95)

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

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.
TNF neutralization in MS: results of a randomized, placebo-controlled multicenter study.

- MS exacerbations ↑ with lenercept.
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
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?*
Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis.
Puel A, et al.
Secukinumab

PUBMED search

1/10/18

NO ↑ MALIGNANCIES
Ixekizumab

PUBMED search
1/10/18

NO ↑ MALIGNANCIES
Brodalumab

PUBMED search

1/10/18

NO ↑ MALIGNANCIES
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.

Figure. Malignancy events in psoriasis studies (52-week results).
Secukinumab, Ixekizumab & Brodalumab Package Inserts

No mention of Malignancy as Contraindication
Safety of Secukinumab in Hepatitis B Virus
SL Bevans, TT Mayo, BE Elewski, in press

• Reports of HBV infection (5 patients), HCV infection (3 patients), and HBV and HCV co-infection (1 patient), all without viral reactivation or significant elevation in liver enzymes.

Pearl #9 IL-17 blockers have been used in hepatitis/HIV; anecdata
Impact of Secukinumab on Endothelial Dysfunction and Other Cardiovascular Disease Parameters in Psoriasis Patients over 52 Weeks.


• At w. 52 “secukinumab might have a beneficial effect on CV risk by improving the endothelial function of patients with plaque psoriasis” as measured by flow mediated dilation.

Pearl #10 Do IL-17 blockers protect against cardiovascular disease?
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 4 Change in non-calcified coronary plaque burden over one-year between treatment groups

<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.
• Contribute to education/clinical knowledge of the psoriasis community
• Opportunity to establish a database of your patient population
• Academic recognition and publication opportunities
• Supplement existing insurance fee schedules
  – Site compensation is $525 (including $25 for patient) per Enrollment visit and $350 (including $25 for patient) per biannual Follow Up visit

If you are interested in participating in the Registry as a research investigator,

Email: psoriasis@corrona.org
Website: www.corrona.org
Call: 508.408.5415
Suicidal ideation and behavior, including 4 completed suicides, occurred in subjects treated with SILIQ in the psoriasis clinical trials. There were no completed suicides in the 12-week placebo-controlled portion of the trials. SILIQ users with a history of suicidality or depression had an increased incidence of suicidal ideation and behavior as compared to users without such a history [see Adverse Reactions (6.1)]. A causal association between treatment with SILIQ and increased risk of suicidal ideation and behavior has not been established.

Pearl #11: REMS program is easy and worthwhile; only for brodalumab
### RESULTS (cont)

<table>
<thead>
<tr>
<th>Age, y/ Sex</th>
<th>Brodalumab dose</th>
<th>Clinical response (PASI score)</th>
<th>Clinical information</th>
</tr>
</thead>
</table>
| 59/Male     | 210 mg          | 100                           | ● 329 days after first dose of brodalumab  
● History of financial stressors (lost disability due to brodalumab response and unable to find work) |
| 39/Male     | 210 mg          | 73                            | ● 140 days after first dose of brodalumab  
● Informed investigator he had legal difficulties and was likely to be incarcerated  
● Family reported he killed himself, means unknown |
| 56/Male     | 210 mg          | 100                           | ● 845 days after first dose of brodalumab  
● Ongoing treatment for depression and anxiety  
● Described recent stress and isolation due to relocation |
| Indeterminate case | 56/Male | 210 mg | 100 | ● History of depression; on antidepressant and benzodiazepine  
● 97 days after first dose of brodalumab  
● Toxic levels of mixed opiates compatible with ingestion of poppy seed tea and methadone; therapeutic level of citalopram, elevated alprazolam, and alcohol  
● HADS baseline depression and anxiety score decreased from 15 to 2 and 14 to 6, respectively, 2 weeks before the event  
● Ruled indeterminate by C-CASA adjudication |

C-CASA, Columbia classification algorithm of suicide assessment; HADS, hospital anxiety and depression scale; PASI, psoriasis area and severity index.
### RESULTS

**Table 1. Changes in Depression and Anxiety as Measured by HADS During Short-term Psoriasis Treatment in the AMAGINE-1 Trial**

<table>
<thead>
<tr>
<th>Depression</th>
<th>Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td><strong>Brodalumab 140 mg Q2W</strong></td>
<td><strong>Brodalumab 140 mg Q2W</strong></td>
</tr>
<tr>
<td><strong>Brodalumab 210 mg Q2W</strong></td>
<td><strong>Brodalumab 210 mg Q2W</strong></td>
</tr>
<tr>
<td><strong>Improvement, n/N (%)</strong></td>
<td><strong>Improvement, n/N (%)</strong></td>
</tr>
<tr>
<td><strong>Any improvement</strong></td>
<td></td>
</tr>
<tr>
<td>• Any depression/anxiety to none</td>
<td>• None to any depression/anxiety</td>
</tr>
<tr>
<td>≥2-point improvement</td>
<td>≥2-point worsening</td>
</tr>
<tr>
<td>Any to none and ≥2-point improvement</td>
<td>None to any and ≥2-point worsening</td>
</tr>
<tr>
<td>82/184 (44.6)</td>
<td>123/185 (66.5)</td>
</tr>
<tr>
<td>9/53 (17.0)</td>
<td>34/52 (65.4)</td>
</tr>
<tr>
<td>46/168 (27.4)</td>
<td>89/156 (57.1)</td>
</tr>
<tr>
<td>8/53 (15.1)</td>
<td>31/52 (59.6)</td>
</tr>
<tr>
<td>127/185 (67.2)</td>
<td>94/169 (55.6)</td>
</tr>
<tr>
<td>37/60 (61.7)</td>
<td>37/60 (61.7)</td>
</tr>
<tr>
<td>8/53 (15.1)</td>
<td>122/197 (61.9)</td>
</tr>
<tr>
<td>77/204 (37.7)</td>
<td>45/78 (57.7)</td>
</tr>
<tr>
<td>21/151 (13.8)</td>
<td>97/196 (52.2)</td>
</tr>
<tr>
<td>55/204 (27.0)</td>
<td>39/78 (50.0)</td>
</tr>
<tr>
<td>19/151 (12.6)</td>
<td></td>
</tr>
<tr>
<td>37/204 (18.1)</td>
<td>76/203 (37.4)</td>
</tr>
<tr>
<td>10/152 (6.6)</td>
<td>13/134 (9.7)</td>
</tr>
<tr>
<td>24/204 (11.8)</td>
<td>34/203 (16.7)</td>
</tr>
<tr>
<td>8/152 (5.3)</td>
<td>16/132 (12.1)</td>
</tr>
<tr>
<td>39/208 (18.8)</td>
<td>11/134 (8.2)</td>
</tr>
<tr>
<td>5/148 (3.4)</td>
<td>42/207 (20.3)</td>
</tr>
<tr>
<td>12/208 (5.8)</td>
<td>10/130 (7.7)</td>
</tr>
<tr>
<td>5/148 (3.4)</td>
<td>22/206 (10.7)</td>
</tr>
<tr>
<td>7/130 (5.3)</td>
<td>9/130 (6.9)</td>
</tr>
</tbody>
</table>

**Worsening, n/N (%)**

| **Any worsening**                   |                                  |
| • None to any depression/anxiety   |                                  |
| ≥2-point worsening                  |                                  |
| None to any and ≥2-point worsening  |                                  |
| 77/204 (37.7)                      | 76/203 (37.4)                    |
| 21/151 (13.8)                      | 13/134 (9.7)                     |
| 55/204 (27.0)                      | 34/203 (16.7)                    |
| 19/151 (12.6)                      | 11/134 (8.2)                     |
| 37/204 (18.1)                      | 53/203 (26.1)                    |
| 10/152 (6.6)                       | 13/134 (9.7)                     |
| 24/204 (11.8)                      | 34/203 (16.7)                    |
| 8/152 (5.3)                        | 16/132 (12.1)                    |
| 39/208 (18.8)                      | 11/134 (8.2)                     |
| 5/148 (3.4)                        | 42/207 (20.3)                    |
| 12/208 (5.8)                       | 10/130 (7.7)                     |
| 5/148 (3.4)                        | 22/206 (10.7)                    |
| 7/130 (5.3)                        | 9/130 (6.9)                      |

*In the AMAGINE-1 study, the proportion of patients who experienced improvement in depression or anxiety, as determined by HADS, was appreciably greater with brodalumab than with placebo.*

HADS, hospital anxiety and depression scale; Q2W, every 2 weeks.

*Data are through week 12 of the AMAGINE-1 study. *b*Baseline to endpoint. *c*Baseline to highest score.*
Pearl #13 Getting approvals for biologics isn’t that hard

70 yo ♂, Psoriasis 15% BSA & PSA

- Prescribe etanercept
National Psoriasis Foundation
Leah McCormick Howard
Health Policy Manager
Lhoward@psoriasis.org
(503) 546-5553
AAD Practice Management Center
Office of Access to Care and Treatment
Rachna Chaudhari

www.aad.org/priorauth