The Logic Behind Biologics for Psoriasis

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Mechanism of Methotrexate

Mechanism of Cyclosporine

Monoclonal Antibodies, Fusion Proteins and Fab’ fragments against TNF: Structure


**Mechanism of TNF blockers**


**Infliximab Neutralization of TNFα**
Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial.


Infliximab in Psoriasis (N=33)
Mean PASI Score Through Week 10

PASI response rates at Week 16 of CHAMPION

- **PASI 50**: Placebo (20.2%), MTX (49.5%), Adalimumab (51.6%)
- **PASI 75**: Placebo (18.9%), MTX (39.5%), Adalimumab (51.6%)
- **PASI 90**: Placebo (11.3%), MTX (13.6%), Adalimumab (16.7%)
- **PASI 100**: Placebo (1.9%), MTX (7.3%), Adalimumab (16.7%)

*ITT, NRI
*P<0.001, adalimumab vs. placebo
†P<0.001, adalimumab vs. MTX
‡P<0.01, adalimumab vs. placebo
§P<0.05, adalimumab vs. MTX*
**PASI 75 Responder Rates from Baseline to Week 16**

Pooled Phase 3 Studies (CIMPASI-1/-2 and CIMPACT)

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo (N=157)</th>
<th>CZP 200 mg Q2W* (N=351)</th>
<th>CZP 400 mg Q2W (N=342)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0%</td>
<td>2.3%</td>
<td>2.6%</td>
</tr>
<tr>
<td>2</td>
<td>1.6%</td>
<td>19.4%</td>
<td>16.5%</td>
</tr>
<tr>
<td>4</td>
<td>3.9%</td>
<td>52.8%</td>
<td>52.8%</td>
</tr>
<tr>
<td>8</td>
<td>7.4%</td>
<td>68.9%</td>
<td>73.0%</td>
</tr>
<tr>
<td>12</td>
<td>7.5%</td>
<td>74.5%</td>
<td>80.1%</td>
</tr>
<tr>
<td>16</td>
<td><strong>80.1%</strong></td>
<td><strong>74.5%</strong></td>
<td><strong>80.1%</strong></td>
</tr>
</tbody>
</table>

**p<0.0001 versus placebo (not adjusted for multiplicity); *CZP 200 mg Q2W patients received loading dose of CZP 400 mg at Weeks 0, 2, and 4. Responder rates are the adjusted predicted probabilities based on logistic regression model with factors for treatment, region, study, prior biologic exposure (yes/no), study/region, and study/prior biologic exposure where missing data were imputed using NRI method (patients missing PASI response are considered to be nonresponders); CZP, certolizumab pegol; LD, loading dose of CZP 400 mg Q2W at Weeks 0, 2, and 4; NRI, nonresponder imputation; PASI 75, ≥75% reduction in psoriasis area and severity index; Q2W, every 2 weeks**

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**PGA 0/1 Responder Rates from Baseline to Week 16**

Pooled Phase 3 Studies (CIMPASI-1/-2 and CIMPACT)

<table>
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<tr>
<th>Week</th>
<th>Placebo (N=157)</th>
<th>CZP 200 mg Q2W* (N=351)</th>
<th>CZP 400 mg Q2W (N=342)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.4%</td>
<td>1.9%</td>
<td>1.7%</td>
</tr>
<tr>
<td>2</td>
<td>0.5%</td>
<td>13.0%</td>
<td>12.3%</td>
</tr>
<tr>
<td>4</td>
<td>4.7%</td>
<td>38.0%</td>
<td>39.7%</td>
</tr>
<tr>
<td>8</td>
<td>3.9%</td>
<td>48.2%</td>
<td>55.4%</td>
</tr>
<tr>
<td>12</td>
<td>2.8%</td>
<td>54.6%</td>
<td>63.7%</td>
</tr>
<tr>
<td>16</td>
<td><strong>63.7%</strong></td>
<td><strong>54.6%</strong></td>
<td><strong>63.7%</strong></td>
</tr>
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*p<0.05, **p<0.0001 versus placebo (not adjusted for multiplicity); *CZP 200 mg Q2W patients received loading dose of CZP 400 mg at Weeks 0, 2, and 4. Responder rates are the adjusted predicted probabilities based on logistic regression model with factors for treatment, region, study, prior biologic exposure (yes/no), study/region, and study/prior biologic exposure where missing data were imputed using NRI method (patients missing PGA 0/1 response are considered to be nonresponders); CZP, certolizumab pegol; LD, loading dose of CZP 400 mg Q2W at Weeks 0, 2, and 4; NRI, nonresponder imputation; PGA 0/1, 'clear' or 'almost clear' with ≥2-category improvement in physician's global assessment (5-point scale); Q2W, every 2 weeks**
Mechanism of ustekinumab

Revisiting human IL-12Rβ1 deficiency: a survey of 141 patients from 30 countries.
de Beaucoudrey L, et al
Medicine (Baltimore). 2010;89:381-402.

• 141 patients
• mycobacterial infections & salmonella
Ixekizumab, Secukinumab,

Key Cells and Mediators in Psoriasis

**Innate immunity**
- Keratinocyte
- Natural killer T cell
- Myeloid dendritic cell
- Plasmacytoid dendritic cell
- Macrophage

**Adaptive immunity**
- T cell
- IL-1β
- IL-6
- TNF-α
- INF-γ

**Antimicrobial peptides**
- IL-12
- IL-23
- IL-17A
- IL-17F

**Activation**
- IL-20
- INF-α
- S100
- CXCL8
- CXCL9
- CXCL10
- CXCL11
- CCL20

**Th1 cell**
- IL-22

**Th2 cell**
- IL-10

**Th17 cell**
- IL-21

**Th22 cell**
- IL-23

**Secukinumab**
- Ixekizumab


Secukinumab was significantly superior to placebo in achieving clinical efficacy endpoints at Week 12

- **PASI 75 Response**: 81.6%
- **IGA mod 2011 0/1 Response**
  - Secukinumab 150 mg: 65.3%
  - Secukinumab 100 mg: 51.2%
- **PASI 90 Response**: 59.2%
- **PASI 100 Response**: 28.6%

Lebwohl M, et al. EADV 2014, P1652
UNCOVER-1: Efficacy outcomes at Week 12

Ixekizumab

**PASI 75, NRI**

- PBO (n=431)
- IXK q4w (n=432)
- IXK q2w (n=433)

*P<0.001 vs PBO based on logistic regression (Fisher's exact test when PBO response was 0%)

NRI, nonresponder imputation

**PASI 90, NRI**

**PASI 100, NRI**

**Mechanism of Brodalumab**

Pearl #1 Anti-IL-17 antibodies are fast
Treatment effects at week 4

**PASI 75**

**PASI 90**

**IL-17 Inhibitors**

Lower treatment effect  
Relative Effect (Proportion)  
Greater treatment effect

Week 4

Density

0 20 40

0.2 0.4 0.6

0 30 60

0.0 0.1 0.2 0.3 0.4

Subject #9: Close Up View of Buttocks - Baseline and Week 1

Baseline

Week 1
Ixekizumab Q2W

Subject #9: Close Up View of Buttocks - Baseline and Week 2

Baseline

Week 2
Ixekizumab Q2W
Subject #9: Close Up View of Buttocks - Baseline and Week 4

Baseline

Week 4
Izekizumab Q2W
PASI 75 and sPGA 2

Subject #9: Close Up View of Buttocks - Baseline and Week 8

Baseline

Week 8
Izekizumab Q2W
Subject #9: Close Up View of Buttocks - Baseline and Week 12

Baseline and Week 12
Ixekizumab Q2W
PASI 75 and sPGA 1

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.
*Science.* 2011;332(6025):65-68.
Mechanism of Guselkumab, Tilkdrakizumab, Risankizumab, Mirikizumab


VOYAGE 1: Prespecified endpoints of PASI 90 and PASI 100 response with guselkumab through 2 years

Griffiths CEM, et al. EADV 2017; D3T01.I Sponsored by Janssen Clinical Research and Development LLC
Tildrakizumab-PASI 75; PGA 0/1

Reich K, et al. EADV 2016, D3T01.1I Late Breaker Sponsored by Sun Pharmaceutical

PASI 75

PGA 0/1

Weeks

Responders (%)

Tildrakizumab-PASI 90 and 100

Reich K, et al. EADV 2016, D3T01.1I Late Breaker Sponsored by Sun Pharmaceutical
Risankizumab

*18 mg BI 65506 only given once at Week 0. Analysis includes all patients who were randomised and who received at least one dose of assigned therapy during the study with non-responder imputation.

ultIMMa-1 and ultIMMa-2:
PASI 90 responses with risankizumab through Week 52

**ultIMMa-1**
PASI 90 response over 52 weeks (NRI):

- RZB (n=304)
- Placebo → RZB (n=97)
- UST (n=100)

**ultIMMa-2**
Maintenance of PASI 90 in those who achieved PASI 90 at w.16 (NRI): integrated

*P<0.001 vs placebo; †P<0.05, ‡P<0.01, §P<0.001 vs UST

Gordon KB, et al. AAD 2018, Late-breaking Research: Clinical Trials; Sponsored by AbbVie and Boehringer Ingelheim
Mirikizumab through Week 16

**PASI 90**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Week 16</th>
<th>Week 24</th>
<th>Week 32</th>
<th>Week 40</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>MKZ 300 mg q8w  (n=51)</td>
<td>67%</td>
<td>71%</td>
<td>74%</td>
<td>76%</td>
<td>73%</td>
</tr>
<tr>
<td>MKZ 100 mg q8w  (n=51)</td>
<td>65%</td>
<td>69%</td>
<td>72%</td>
<td>75%</td>
<td>72%</td>
</tr>
<tr>
<td>MKZ 30 mg q8w  (n=51)</td>
<td>37%</td>
<td>31%</td>
<td>35%</td>
<td>38%</td>
<td>35%</td>
</tr>
<tr>
<td>Placebo (n=52)</td>
<td>0%</td>
<td>2%</td>
<td>6%</td>
<td>10%</td>
<td>12%</td>
</tr>
</tbody>
</table>

**DLQI 0/1**

<table>
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<tr>
<th>Treatment</th>
<th>Week 16</th>
<th>Week 24</th>
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<th>Week 40</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>MKZ 300 mg q8w  (n=51)</td>
<td>49%</td>
<td>46%</td>
<td>47%</td>
<td>49%</td>
<td>48%</td>
</tr>
<tr>
<td>MKZ 100 mg q8w  (n=51)</td>
<td>45%</td>
<td>42%</td>
<td>45%</td>
<td>47%</td>
<td>46%</td>
</tr>
<tr>
<td>MKZ 30 mg q8w  (n=51)</td>
<td>35%</td>
<td>31%</td>
<td>35%</td>
<td>37%</td>
<td>36%</td>
</tr>
<tr>
<td>Placebo (n=52)</td>
<td>0%</td>
<td>2%</td>
<td>6%</td>
<td>10%</td>
<td>12%</td>
</tr>
</tbody>
</table>

**sPGA 0/1**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Week 16</th>
<th>Week 24</th>
<th>Week 32</th>
<th>Week 40</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>MKZ 300 mg q8w  (n=51)</td>
<td>71%</td>
<td>69%</td>
<td>68%</td>
<td>67%</td>
<td>64%</td>
</tr>
<tr>
<td>MKZ 100 mg q8w  (n=51)</td>
<td>65%</td>
<td>63%</td>
<td>62%</td>
<td>61%</td>
<td>59%</td>
</tr>
<tr>
<td>MKZ 30 mg q8w  (n=51)</td>
<td>37%</td>
<td>35%</td>
<td>34%</td>
<td>33%</td>
<td>32%</td>
</tr>
<tr>
<td>Placebo (n=52)</td>
<td>0%</td>
<td>2%</td>
<td>6%</td>
<td>10%</td>
<td>12%</td>
</tr>
</tbody>
</table>

**sPGA 0**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Week 16</th>
<th>Week 24</th>
<th>Week 32</th>
<th>Week 40</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>MKZ 300 mg q8w  (n=51)</td>
<td>66%</td>
<td>64%</td>
<td>63%</td>
<td>62%</td>
<td>60%</td>
</tr>
<tr>
<td>MKZ 100 mg q8w  (n=51)</td>
<td>57%</td>
<td>55%</td>
<td>54%</td>
<td>53%</td>
<td>51%</td>
</tr>
<tr>
<td>MKZ 30 mg q8w  (n=51)</td>
<td>31%</td>
<td>29%</td>
<td>27%</td>
<td>26%</td>
<td>24%</td>
</tr>
<tr>
<td>Placebo (n=52)</td>
<td>0%</td>
<td>2%</td>
<td>6%</td>
<td>10%</td>
<td>12%</td>
</tr>
</tbody>
</table>

*P<0.05, †P<0.01, ‡P<0.001 vs placebo. Logistic regression analysis with treatment, geographic region, and previous biologic therapy in the model; NRI


OASIS-2: PASI 90 responses with mirikizumab at Week 16 and Week 52, with reference to the results of ECLIPSE and IMMerge

**OASIS-2**

(Primary outcome measure: PASI 90)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Week 16</th>
<th>Week 24</th>
<th>Week 32</th>
<th>Week 40</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKB 300 mg</td>
<td>73%</td>
<td>69%</td>
<td>82%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIR 250 mg q4w</td>
<td>74%</td>
<td>67%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ECLIPSE**

(Primary outcome measure: PASI 90)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Week 12</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKB 300 mg (n=514)</td>
<td>76%</td>
<td>84%</td>
</tr>
<tr>
<td>GUS 100 mg q8w (n=534)</td>
<td>70%</td>
<td>87%</td>
</tr>
</tbody>
</table>

**IMMerge**

(open-label; ITT NRI)

(Primary outcome measure: PASI 90)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Week 16</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKB 300 mg (n=163)</td>
<td>66%</td>
<td>57%</td>
</tr>
<tr>
<td>RZB 150 mg q12w (n=164)</td>
<td>74%</td>
<td>87%</td>
</tr>
</tbody>
</table>

*Data imputation method not available

IL-17F and IL-17A are cytokines central to the pathophysiology of PSO

**Role of IL-17 in disease:** IL-17A and IL-17F are key cytokines that are central to pathobiology in psoriasis, PsA, axSpA and HS.1-3

**Role of IL-17F:** IL-17F has overlapping biology with IL-17A. While IL-17A is more potent, IL-17F is more abundant in psoriatic lesions and can drive inflammation independently of IL-17A.4-7

**IL-23-independent IL-17 production:** IL-17 can be produced independently of IL-23 regulation by some immune cells which can contribute to the pathobiology of IL-17-mediated diseases.8

**Bimekizumab** is an investigational humanized monoclonal IgG1 antibody that selectively inhibits both IL-17F and IL-17A, suppressing inflammation to a greater extent than IL-17A inhibition alone.7,9

The safety and efficacy of bimekizumab have not been established and it is not approved by any regulatory authority worldwide.

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Response at week 4 and complete clearance at week 16 (ITT, NRI)

76.9% of bimekizumab-treated patients achieved PASI 75 after one dose, with 58.6% achieving PASI 100 at week 16.

Week 4 PASI 75

- Placebo (N=83): 2.4%
- Bimekizumab 320 mg Q4W (N=321): 76.9%
- Ustekinumab (N=163): 15.3%

Week 16 PASI 100

- Placebo (N=83): 0%
- Bimekizumab 320 mg Q4W (N=321): 58.6%
- Ustekinumab (N=163): 20.9%

For PASI 75 at Week 4 and PASI 100 at Week 16 (versus placebo only), the p value for the comparison of treatment groups was based on the Cochran–Mantel–Haenszel test from the general association, for PASI 100 at Week 16 (versus ustekinumab), the p value for a general association was based on a stratified Cochran–Mantel–Haenszel test where region and prior biologic exposure were used as stratification variables, is considered nominal, and was not controlled for multiplicity. Proportions were calculated using non-responder imputation (NRI). ITT: intent-to-treat; PASI 75/100: ≥75/100% improvement from Baseline in Psoriasis Area and Severity Index; Q4W: every four weeks.

Durability at week 52: PASI 90 and IGA 0/1 (ITT, NRI)

Weeks

- Placebo (N=83): 3.1% (p<0.001)
- Bimekizumab 320 mg Q4W (N=321): 43.6% (p<0.001)
- Ustekinumab (N=163): 81.6%

Weeks

- Placebo (N=83): 12.9% (p<0.001)
- Bimekizumab 320 mg Q4W (N=321): 49.8% (p<0.001)
- Ustekinumab (N=163): 77.9%

PASI 90: ≥90% improvement from Baseline in Psoriasis Area and Severity Index; IGA 0/1: score of 0 (clear) or 1 (almost clear) with ≥2-category improvement relative to Baseline in Investigator's Global Assessment, scored on a 5-point scale; ITT: intent-to-treat; Q4W: every four weeks.
Complete clearance: PASI 100 over 52 weeks (ITT, NRI)

The p-value for a general association was based on a stratified Cochran-Mantel-Haenszel test where region and prior biologic exposure were used as stratification variables, is considered nominal, and was not controlled for multiplicity. Proportions were calculated using non-responder imputation (NRI). At Week 16, patients receiving placebo were switched to bimekizumab 320 mg Q4W. ITT: intent-to-treat; PASI 100: 100% improvement in psoriasis area severity index (PASI) score; Q4W: every four weeks.

The graph shows the proportion of patients achieving PASI 100 (%)

- Placebo (N=83)
- Bimekizumab 320 mg Q4W (N=321)
- Ustekinumab (N=163)

Weeks

PASI 100

- 15.0%
- 1.2% Δ 13.8%
- 64.2% p<0.001
- 38.0% Δ 26.2%

The p-value for a general association was based on a stratified Cochran-Mantel-Haenszel test where region and prior biologic exposure were used as stratification variables, is considered nominal, and was not controlled for multiplicity. Proportions were calculated using non-responder imputation (NRI). At Week 16, patients receiving placebo were switched to bimekizumab 320 mg Q4W. ITT: intent-to-treat; PASI 100: 100% improvement in psoriasis area severity index (PASI) score; Q4W: every four weeks.