Therapeutic Hotline
What’s New in Psoriasis

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Icahn School of Medicine at Mount Sinai
• Anti-IL-17 drugs
  Secukinumab
  Ixekizumab
  Brodalumab
• Anti IL-23
  Tildrakizumab
  Gusekumab
  BI 655066
• Certolizumab
• Biosimilars
Secukinumab

- 150 mg sc
- 300 mg w. 0, 1, 2, 3, 4 then q4w.
Doses & Regimen

**Secukinumab**
- 150 mg sc
- 300 mg w. 0, 1, 2, 3, 4 then q4w.

**Ixekizumab**
- 80 mg sc
- 160 mg day 1 then 80mg q2w. until w.12 then q4w
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secukinumab</td>
<td>150 mg sc</td>
<td>300 mg w. 0, 1, 2, 3, 4</td>
<td>then q4w.</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>80 mg sc</td>
<td>160 mg day 0 then 80 mg</td>
<td>q2w. until w.12 then 80 mg q4w</td>
</tr>
<tr>
<td>Brodalumab</td>
<td>210 mg sc</td>
<td>210 mg w.0,1,2 then q2w</td>
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</tbody>
</table>
Secukinumab was significantly superior to placebo in achieving clinical efficacy endpoints at Week 12.

Lebwohl M, et al. EADV 2014, P1652

- PASI 75 Response: 81.6%
- PASI 90 Response: 59.2%
- PASI 100 Response: 28.6%
ERASURE Study Results: Secukinumab rapidly improved plaque psoriasis, and sustained high efficacy up to 52 weeks

- The co-primary endpoints (PASI 75 and IGA 0/1 at Week 12) were met for both doses of secukinumab
- Differences in responses to secukinumab and placebo appeared early during therapy
- High responses to secukinumab were sustained up to Week 52, with maximal effect seen after 16 weeks

*P < 0.0001 versus placebo at Week 12.

aIGA score of 0 (clear) or 1 (almost clear) and an improvement of at least 2 points on the IGA scale compared with baseline.
bOne patient did not have informed consent and was excluded from analyses.
UNCOVER-1: Efficacy outcomes at Week 12

Ixekizumab

- PASI 75, NRI
  - Patients (%)
  - Weeks
  - PBO (n=431)
  - IXK q4w (n=432)
  - IXK q2w (n=433)
  - 89.1*
  - 82.6*
  - 3.9

- PASI 90, NRI
  - Patients (%)
  - Weeks
  - PBO (n=431)
  - IXK q4w (n=432)
  - IXK q2w (n=433)
  - 70.9*
  - 64.6*
  - 0.5

- sPGA (0,1) NRI
  - Patients (%)
  - Weeks
  - PBO (n=431)
  - IXK q4w (n=432)
  - IXK q2w (n=433)
  - 81.8*
  - 76.4*
  - 3.2

- PASI 100, NRI
  - Patients (%)
  - Weeks
  - PBO (n=431)
  - IXK q4w (n=432)
  - IXK q2w (n=433)
  - 35.3*
  - 33.6*
  - 0.0

*P<0.001 vs PBO based on logistic regression (Fisher’s exact test when PBO response was 0%)
NRI, nonresponder imputation
Gordon K, et al. WCD 2015 Sponsored by Eli Lilly
Ixekizumab in chronic plaque psoriasis: 52-week results from a Phase 2 study open-label study

PASI response rates over 52 weeks in OLE: all patients and those initially assigned to PBO

<table>
<thead>
<tr>
<th>PASI 100</th>
<th>PASI 90</th>
<th>PASI 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed</td>
<td>Nonresponder imputation</td>
<td></td>
</tr>
<tr>
<td>All patients (N=120)</td>
<td>Initially assigned to PBO</td>
<td></td>
</tr>
</tbody>
</table>

Gordon K, et al. AAD 2014, P8365
Brodalumab
Maintenance of clinical response with long-term brodalumab (AMG 827) for psoriasis: Week 144 results from an open label extension study
PASI 75/90/100 (as observed analysis)

Papp K, et al. EADV 2014, FC05.03
Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis.
Puel A, 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?
FUTURE 2
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 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)

Mean change in vdH-mTSS

Overall population  MTX: Yes  MTX: No

Overall population  MTX: Yes  MTX: No

<table>
<thead>
<tr>
<th></th>
<th>Pooled SKB doses</th>
<th>PBO switched to SKB</th>
</tr>
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<tbody>
<tr>
<td>Week 24 to Week 52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX: Yes</td>
<td>0.21</td>
<td>0.29</td>
</tr>
<tr>
<td>MTX: No</td>
<td>-0.03</td>
<td>-0.18</td>
</tr>
</tbody>
</table>

*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>Effect on structural disease progression</th>
<th>Placebo</th>
<th>IXEQ4W</th>
<th>IXEQ2W</th>
<th>Adalimumab 40 mg Q2W*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LS mean change from baseline mTSS (SE)†</strong></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><strong>Percentage of patients with change in mTSS at week 24</strong></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 24

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

Mease P, et al. AAD 2014, P7605
Mechanism of Tildrakizumab, Guselkumab, BI655066

ReSURFACE 1: TIL in Plaque Psoriasis

- Randomized phase III trial of TIL vs placebo in moderate to severe plaque psoriasis

Stratified by body weight ≤ or > 90 kg, previous exposure to biologic therapy for psoriasis

Primary endpoint: Wk 12

- Wk 28

Pts with moderate to severe psoriasis ≥ 10% body surface area, ≥ 3 PGA, and PASI ≥12 (N = 772)

*Wks 0, 4, 16.
†Wks 0, 4.
‡Wks 12, 16.

Reich K, et al. EADV 2016. Abstract DT301.1I.
**reSURFACE 2: TIL in Plaque Psoriasis**

- Randomized phase III trial of TIL vs ETN or placebo in moderate to severe plaque psoriasis

- Stratified by body weight ≤ or > 90 kg, previous exposure to biologic therapy for psoriasis

- Pts with moderate to severe psoriasis ≥ 10% body surface area, ≥ 3 PGA, and PASI ≥ 12 (N = 1090)

- Primary endpoint:
  - Wk 12
  - Wk 28

- Wk 28

- 1:1

- Tildrakizumab 200 mg SC*
  - (n = 314)

- Tildrakizumab 100 mg SC*
  - (n = 307)

- Placebo†
  - (n = 156)

- Tildrakizumab 200 mg SC‡

- Tildrakizumab 100 mg SC‡

- Etanercept 50 mg SC§
  - (n = 313)

- 52 wks

- *Wks 0, 4, 16.
- †Wks 0, 4.
- ‡Wks 12, 16.
- §Twice weekly to Wk 12, once weekly to Wk 28.

Reich K, et al. EADV 2016. Abstract DT301.1I.
reSURFACE 1 and reSURFACE 2: TIL in chronic plaque psoriasis

PASI 90 and PASI 100

Modified ITT population (all randomized patients who received ≥1 dose of study medication). Figure represents observed data only; data shown for Week 12 are based on missing data being imputed as non-responders.

Reich K, et al. EADV 2016, D3T01.1I Late Breaker Sponsored by Sun Pharmaceutical
Voyage 1: Guselkumab Phase 3 for Psoriasis

<table>
<thead>
<tr>
<th>Screening</th>
<th>Placebo-controlled</th>
<th>Blinded Active Treatment</th>
<th>Open-Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n=329)</td>
<td>Gusekumab 100 mg Wk 0, 4 q8w</td>
<td>Placebo</td>
<td>Gusekumab 100 mg Wk 16, 20 q8w</td>
</tr>
<tr>
<td>Group 2 (n=174)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3 (n=334)</td>
<td></td>
<td>Adalimumab (ADA) qow</td>
<td></td>
</tr>
</tbody>
</table>

Weeks: 0, 4, 16, 24, 48

Primary Endpoint vs. PBO
Secondary Endpoint vs. ADA
DBL Secondary Endpoint vs. ADA

VOYAGE 1: GUS vs ADA in moderate-to-severe psoriasis
PASI 75, PASI 90 and PASI 100

Guselkumab

PASI 75 at Week 16*

PASI 90 at Week 16*

PASI 100 at Week 16†

*Week 16, 24 and 48 P<0.001 vs ADA; †Week 24 and 48 P<0.001 vs ADA

Blauvelt A, et al. EADV 2016, D3T01.1D Sponsored by Janssen Global Services LLC
Mean PASI Improvement in Patients Treated with Subcutaneous BI 655066 (0.25 and 1.0 mg/kg)

6/9 (66%) of patients who entered long term follow up maintained PASI 100 for 41–66 weeks.

Primary Endpoint

Optional Follow Up

Krueger et al. J. Allergy Clinical Immunology. Published on line 12 March 2015
Clinical response to selective IL-23p19 inhibitor (BI 655066) vs UST in moderate-to-severe chronic plaque psoriasis

Papp K, et al. EADV 2015, FC03.06 Sponsored by Boehringer Ingelheim

*18 mg BI 655066 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.
Safety, efficacy and PK of a p19-directed IL-23 antibody (LY3074828) in patients with plaque psoriasis and healthy subjects

- Phase 1, placebo-controlled, 40 patients, 5 healthy volunteers, 12 weeks; 4% BSA, PASI 6.6

**Study Design**

- **Cohort 1:** 3 patients LY3074828 (LY), 1 patient placebo (4 patients)
- **Cohort 2-7:** 5 patients LY, 1 patient placebo in each cohort (36 patients)

**Subcutaneous Administration Cohort:**

- 5 healthy volunteers
- 120 mg SC
- Day 1 Dose
- Follow-up period (Post-dose – Day 64)

**PASI Change (Mean) From Baseline by LY Dose**

- Placebo
- 5 mg
- 23 mg
- 50 mg
- 120 mg
- 200 mg
- 350 mg
- 500 mg

- Mean Change in PASI (%)
- Baseline is defined as the last non-missing value prior to the first dose of study drug

- **LY=LY3074828; PASI=Psoriasis Area and Severity Index**

- **Another a p19-directed IL-23 antibody effective in phase 1**

Tuttle J, et al. EADV 2016, P0456 Sponsored by Eli Lilly and Company
Successful treatment of moderate to severe plaque psoriasis with the PEGylated Fab certolizumab pegol: results of a phase II randomised, placebo-controlled trial with a re-treatment extension.

Reich K, et al.

Percentage of Subjects with PASI75 at Week 12 – ITT Population

- Placebo, N=59: 6.8%
- Certolizumab 400mg week 0→200 mg eow, N=59: 74.6%*
- Certolizumab 400mg week 0→400 mg eow, N=58: 82.8%*

* Versus placebo, p<0.001
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)


ACR20 response rate to Week 96 by dose [NRI]

Mease P, et al. AAD 2015, P877 Sponsored by UCB Pharma
• Will they be as effective?
• Will the side effect profile be the same? Or better? Or worse?
• How much less expensive will they be?
• Will insurers force our patients to fail the least expensive biosimilar before moving to another biologic?
Biosimilar Experience in India: Rituximab

- Branded rituximab introduced
- 2007 Generic rituximab introduced in India
  - price: 1/3
  - number of patients treated ↑ 6-fold

Data from Dr. Reddy’s laboratories
April 8, 2009

Dear RAPTIVA Patient,

Re: VOLUNTARY U.S. MARKET WITHDRAWAL OF RAPTIVA® (efalizumab)

Patient safety is a top priority for Genentech. Since September 2008, Genentech has received 3 reports of progressive multifocal leukoencephalopathy (PML), a serious and almost always fatal brain infection caused by a virus, in patients taking RAPTIVA (efalizumab). Because of the following key aspects of PML and our commitment to safety, Genentech has decided to voluntarily stop selling RAPTIVA.

- Although we believe that there are many psoriasis patients who benefit from RAPTIVA, there is no way to know ahead of time who will get PML.
- There is no treatment or cure for PML. People who do live with PML are severely disabled.