Biologics in Psoriasis: 2018 and Beyond

Jeffrey M. Sobell MD
Tufts University School of Medicine
SkinCare Physicians
Ora Clinical Research
Biologics in Psoriasis

- FDA approved
  - TNF inhibitors
    • Etanercept
    • Adalimumab
    • Infliximab
  - P40 inhibitors
    • Ustekinumab
  - IL-17 inhibitors
    • Secukinumab
    • Ixekizumab
    • Brodalumab
  - IL-23 inhibitors
    • Guselkumab

- Investigational
  - IL-23 inhibitors
    • Tildrakizumab
    • Risankizumab
    • Mirikizumab
  - TNF inhibitors
    • Certolizumab pegol
Key immune cells and mediators in psoriasis

Initiation

- Keratinocyte
- IL-1β
- IL-6
- TNF-α
- IFN-γ

Activation

- Natural killer T cell
- Plasmacytoid dendritic cell
- Myeloid dendritic cell
- Macrophage

Perpetuation

- Th1 cell
- TNF-α
- IFN-γ
- IL-12
- Th17 cell
- IL-17A
- IL-17F
- IL-22
- Antimicrobial peptides
  - IL-1β
  - IL-6
  - TNF-α
  - S100
  - CXCL8
  - CXCL9
  - CXCL10
  - CXCL11
  - CCL20

Hypothetical model based in part on non-clinical data

# Properties of TNF-α Inhibitors

<table>
<thead>
<tr>
<th>Property</th>
<th>Adalimumab</th>
<th>Etanercept</th>
<th>Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td><img src="image1" alt="Human (IgG1) Contains human CDR regions" /></td>
<td><img src="image2" alt="Fc region of Human IgG1" /></td>
<td><img src="image3" alt="Human (IgG1) Mouse (Binding site for TNF)" /></td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>10–20 days</td>
<td>4–5 days</td>
<td>8–9.5 days</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>• Self-administered subcutaneous injection</td>
<td>• Self-administered subcutaneous injection</td>
<td>• IV infusion over 1 to 2 hours</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>• 80 mg day 1, 40 mg days 8 and 22, then 40 mg eow thereafter</td>
<td>• 50 mg BIW for 3 months; 50 mg weekly thereafter</td>
<td>• 5 mg/kg via infusion at weeks 0, 2, 6, then every 8 weeks</td>
</tr>
</tbody>
</table>

IgG1 = immunoglobulin G subclass 1; EC = extracellular; CDR = complementarity-determining region; IV = intravenous; eow = every other week; biw = twice weekly.

Etanercept Step-Down Therapy: PASI Response Through Week 48

- **mITT** = modified intent to treat; **LOCF** = last observation carried forward
- *P < 0.0001 vs placebo.

<table>
<thead>
<tr>
<th>Week</th>
<th>Etanercept 50 mg BIW</th>
<th>Etanercept 25 mg BIW</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>77%</td>
<td>49%</td>
</tr>
<tr>
<td>12</td>
<td>79%</td>
<td>54%</td>
</tr>
<tr>
<td>24</td>
<td>77%</td>
<td>48%</td>
</tr>
<tr>
<td>36</td>
<td>74%</td>
<td>45%</td>
</tr>
<tr>
<td>48</td>
<td>23%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Adalimumab: PASI improvement at Week 16 (REVEAL)

Infliximab: PASI 75 Response Through Week 50

- 61% of randomized patients (including those who withdrew for any reason) maintained PASI 75 for the long term (n=281 at Week 50)*

- Ability to maintain detectable serum levels of infliximab is one of the factors associated with maintenance of response over time


*Pre-specified analysis; †Per protocol analysis
Psoriatic Arthritis: ACR 20 Week 24

- Adalimumab: n=151
  - Placebo: n=162
  - Adalimumab: 57%
- Etanercept: n=101
  - Placebo: n=104
  - Etanercept: 50%
- Infliximab: n=100
  - Placebo: n=100
  - Infliximab: 54%

TNF-α Inhibitor Safety Warnings

- Serious infections
- Malignancies
- Demyelinating disease
- Congestive heart failure
- Hepatitis B
- Hematologic
- Autoimmunity
- Live vaccines

PASI 75 Response at Week 12 (After 2 Doses of Ustekinumab)

PHOENIX 1

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>45 mg</th>
<th>90 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>255</td>
<td>255</td>
<td>256</td>
</tr>
<tr>
<td>Percent of Patients</td>
<td>3</td>
<td>67</td>
<td>66</td>
</tr>
</tbody>
</table>

PHOENIX 2

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>45 mg</th>
<th>90 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>410</td>
<td>409</td>
<td>411</td>
</tr>
<tr>
<td>Percent of Patients</td>
<td>4</td>
<td>67</td>
<td>76</td>
</tr>
</tbody>
</table>

*P*<0.001 vs placebo for each dose comparison

**Ustekinumab: Psoriatic Arthritis**

![Graph showing ACR 20 Responses* for Ustekinumab 45 mg and 90 mg compared to Placebo at Week 12 and Week 24.](chart)

- **Week 12**
  - Placebo: 20%
  - Ustekinumab 45 mg: 40%
  - Ustekinumab 90 mg: 42%
  - *P < 0.0001*

- **Week 24**
  - Placebo: 23%
  - Ustekinumab 45 mg: 42%
  - Ustekinumab 90 mg: 50%
  - *P < 0.0001*

*Nonresponder imputation (NRI) analysis.

Safety of ustekinumab through up to 5 years

<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Infections</td>
<td>1.33</td>
<td>1.03</td>
<td>0.66</td>
<td>1.11</td>
<td>1.17</td>
</tr>
<tr>
<td>NMSC</td>
<td>0.94</td>
<td>0.49</td>
<td>0.4</td>
<td>0.42</td>
<td>0.16</td>
</tr>
<tr>
<td>Other Malignancies</td>
<td>0.39</td>
<td>0.4</td>
<td>0.77</td>
<td>0.59</td>
<td>0.46</td>
</tr>
<tr>
<td>MACE</td>
<td>0.47</td>
<td>0.36</td>
<td>0.46</td>
<td>0.56</td>
<td>0.37</td>
</tr>
</tbody>
</table>

* Adjudicated MACE included cardiovascular death, myocardial infarction and stroke

Secukinumab: ERASURE Study

Design

738 Subjects

Induction

BL
Week -4 to +1

Wk 8

Secukinumab 300 mg

Secukinumab 150 mg

Wk 12

Maintenance

Treatment Q4W

Wk 52

Q4W

Follow-up

Wk 60

Placebo


Placebo (responders only)
ERASURE: Results through 52 weeks

PASI 75 Response

- SEK 300 mg (n=245)
- SEK 150 mg (n=245)
- Placebo (n=247)

81.6% at Wk 12 for SEK 300 mg
71.6% at Wk 12 for SEK 150 mg
4.5% at Wk 12 for Placebo

* p<0.0001 vs placebo at Wk 12.

PASI 90 Response

- SEK 300 mg (n=245)
- SEK 150 mg (n=245)
- Placebo (n=247)

81.6% at Wk 12 for SEK 300 mg
71.6% at Wk 12 for SEK 150 mg
4.5% at Wk 12 for Placebo

* IGA score of 0 (clear) or 1 (almost clear) and an improvement of at least 2 points on the IGA scale compared with baseline;

b One subject did not sign informed consent before starting study procedures and was excluded from analyses.

**ERASURE: 52 Week Safety Data**

### AEs During entire treatment period (52 weeks)

<table>
<thead>
<tr>
<th></th>
<th>Any secukinumab 150 mg (n=353)</th>
<th>Any secukinumab 300 mg (n=349)</th>
<th>Placebo (n=247)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary of Crude Incidence of AEs, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with any AE(s)</td>
<td>287 (81.3)</td>
<td>286 (81.9)</td>
<td>124 (50.2)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>19 (5.4)</td>
<td>19 (5.4)</td>
<td>5 (2.0)</td>
</tr>
<tr>
<td>Discontinuations due to AEs</td>
<td>18 (5.1)</td>
<td>12 (3.4)</td>
<td>5 (2.0)</td>
</tr>
</tbody>
</table>

### Exposure-Adjusted Incidence of Most Common AEs, n (IR)*

<table>
<thead>
<tr>
<th></th>
<th>Any secukinumab 150 mg (n=353)</th>
<th>Any secukinumab 300 mg (n=349)</th>
<th>Placebo (n=247)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any AE(s)</td>
<td>287 (269.4)</td>
<td>286 (245.5)</td>
<td>124 (323.0)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>69 (26.2)</td>
<td>57 (20.9)</td>
<td>20 (30.8)</td>
</tr>
<tr>
<td>URTI</td>
<td>36 (12.7)</td>
<td>32 (11.1)</td>
<td>2 (3.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>24 (8.4)</td>
<td>31 (10.9)</td>
<td>10 (15.1)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>13 (4.4)</td>
<td>14 (4.7)</td>
<td>8 (12.0)</td>
</tr>
<tr>
<td>Psoriasis worsening</td>
<td>9 (3.0)</td>
<td>8 (2.6)</td>
<td>10 (15.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (2.7)</td>
<td>3 (1.0)</td>
<td>8 (12.0)</td>
</tr>
</tbody>
</table>

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**For the entire treatment period**

- Mean exposure: 313.0 (150 mg) and 320.7 (300 mg) days for secukinumab vs. 101.1 days for placebo
- No MACEs during the induction period. During the maintenance period, 4 adjudicated MACEs occurred in 3 subjects: ischemic stroke in one subject on secukinumab 150 mg; CVA in one subject (originally on placebo; re-randomized to secukinumab 300 mg at Wk 12) and 2 incidences of MI in one subject on secukinumab 300 mg
  - No definitive conclusions regarding secukinumab and MACE risk can be drawn due to the rarity of events and small exposure to placebo
- Treatment-emergent anti-drug antibodies were detected in 1 (0.14%) subject, who was receiving 150 mg secukinumab, among 738 subjects tested, and were transient (detected only at Wk 12)

Secukinumab: FIXTURE study design

Induction
Baseline

Week 8

Secukinumab 300 mg (n=327)
Secukinumab 150 mg (n=327)
Placebo (n=326)
Etanercept 50 mg BIW (n=326)

Week 12

Treatment Q4W
Treatment Q4W

Maintenance

Secukinumab 300 mg
Secukinumab 150 mg
Placebo

Q4W
Q4W

Follow-up
Week 52
Week 60

Q4W

Placebo

50 mg QW

**FIXTURE: Response through 52 Weeks**

- **SEK 300 mg (n=323\(^a\))**
- **SEK 150 mg (n=327\(^a\))**
- **ETN (n=323\(^a\))**
- **PBO (n=324\(^a\))**

### PASI 75 response

- **SEK 300 mg**
  - 77%*
  - 44%*

- **SEK 150 mg**
  - 4.9%*

- **ETN**
  - 4.9%*

- **PBO**

### PASI 90 response

- **SEK 300 mg**
  - 77%*

- **SEK 150 mg**
  - 44%*

- **ETN**
  - 4.9%*

- **PBO**

---

*Primary endpoint

\(^a\)Number of evaluable subjects

Safety through Week 52
Incidences of total and serious AEs similar with SEK and ETN

<table>
<thead>
<tr>
<th></th>
<th>Entire Treatment</th>
<th>300 mg (n=467)</th>
<th>150 mg (n=469)</th>
<th>Etanercept (n=323)</th>
<th>Placebo (n=327)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean exposure, days</td>
<td></td>
<td>320.7</td>
<td>317.5</td>
<td>331.9</td>
<td>95.3</td>
</tr>
<tr>
<td>Any AEs, %</td>
<td></td>
<td>80.5</td>
<td>77.6</td>
<td>78.3</td>
<td>51.4</td>
</tr>
<tr>
<td>Death, %</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-fatal serious AEs, %</td>
<td></td>
<td>5.8</td>
<td>5.1</td>
<td>6.2</td>
<td>2.1</td>
</tr>
<tr>
<td>Discontinuations due to AEs, %</td>
<td></td>
<td>3.0</td>
<td>2.1</td>
<td>3.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Most common AEs, exposure-adjusted incidence rate*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>35.2</td>
<td>31.4</td>
<td>35.7</td>
<td>32.8</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>15.7</td>
<td>12.4</td>
<td>15.2</td>
<td>29.6</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>7.9</td>
<td>5.1</td>
<td>9.3</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9.9</td>
<td>9.3</td>
<td>7.9</td>
<td>8.4</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6.0</td>
<td>8.5</td>
<td>8.2</td>
<td>12.1</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>6.6</td>
<td>6.6</td>
<td>6.4</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>0.0</td>
<td>0.0</td>
<td>6.1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Adverse events (AEs) shown are those that occurred at an incidence rate >6.0 per 100 subject-years in combined secukinumab group or etanercept group

## Rare adverse events of special interest

<table>
<thead>
<tr>
<th>Serious AEs of special interest, n (%)(^a)</th>
<th>Secukinumab</th>
<th>Etanercept (n=323)</th>
<th>Placebo (n=327)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious infections</td>
<td>5 (1.1)</td>
<td>4 (1.2)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Malignant or unspecified tumors</td>
<td>3 (0.6)</td>
<td>2 (0.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>MACE</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

### Candida infections
- 12 (2.6%) subjects in secukinumab 150 mg group and 22 patients (4.7%) in 300 mg group; all mild or moderate
- 4 (1.2%) subjects in etanercept group; 3 out of 7 candida infections reported by the 4 patients were severe

### Treatment-emergent antidrug antibodies
- Detected in 4 (0.4%) out of 980 patients tested: 2 on 150 mg and 2 on 300 mg

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\(^a\)Not exposure adjusted


MACE, major adverse cardiac event.
Secukinumab safety in moderate-to-severe plaque psoriasis: Pooled subanalysis of 10 studies evaluating exacerbation of Crohn’s disease

• Entire treatment (randomization to Week 52) after induction, subjects in Phase 3 studies (>80% all subjects) received SKB q4w or RAN from Weeks 12 to 48, or ETN weekly from Weeks 12 to 51

Exposure-adjusted incidence of IBD during the entire treatment period

<table>
<thead>
<tr>
<th></th>
<th>SKB 300 mg\textsuperscript{a} (n=1410)</th>
<th>SKB 150 mg\textsuperscript{a} (n=1395)</th>
<th>SKB any dose\textsuperscript{b} (n=3430)</th>
<th>PBO (n=793)</th>
<th>ETN\textsuperscript{c} (n=323)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of exposure, days (mean ± SD)</td>
<td>305.0 ± 101.67</td>
<td>299.0 ± 103.89</td>
<td>290.1 ± 110.53</td>
<td>92.7 ± 57.05</td>
<td>331.9 ± 89.70</td>
</tr>
<tr>
<td>Incidence overall, n (%)</td>
<td>9 (0.33)</td>
<td>4 (0.35)</td>
<td>3 (0.11)</td>
<td>0</td>
<td>1 (0.34)</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>0</td>
<td>2 (0.18)</td>
<td>3 (0.11)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>2 (0.17)</td>
<td>2 (0.18)</td>
<td>4 (0.15)</td>
<td>0</td>
<td>1 (0.34)</td>
</tr>
<tr>
<td>Anal fistula\textsuperscript{d}</td>
<td>1 (0.08)</td>
<td>0</td>
<td>1 (0.04)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sclerosing cholangitis\textsuperscript{d}</td>
<td>0</td>
<td>0</td>
<td>1 (0.04)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Incidence in the subgroup with prior history of IBD, n (%) [95% CI]

<table>
<thead>
<tr>
<th></th>
<th>SKB 300 mg\textsuperscript{a} (n=1410)</th>
<th>SKB 150 mg\textsuperscript{a} (n=1395)</th>
<th>SKB any dose\textsuperscript{b} (n=3430)</th>
<th>PBO (n=793)</th>
<th>ETN\textsuperscript{c} (n=323)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with prior IBD history, n</td>
<td>15</td>
<td>14</td>
<td>39</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>IBD overall</td>
<td>0 (0) [0.00–30.90]</td>
<td>2 (18.76) [2.27–67.78]</td>
<td>3 (10.53) [2.17–30.76]</td>
<td>0 (0) [0.00–139.33]</td>
<td>–</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>0 (0) [0.00–30.90]</td>
<td>1 (9.28) [0.23–51.70]</td>
<td>2 (6.99) [0.85–25.25]</td>
<td>0 (0) [0.00–139.33]</td>
<td>–</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>0 (0) [0.00–30.90]</td>
<td>1 (9.23) [0.23–51.42]</td>
<td>1 (3.47) [0.09–19.32]</td>
<td>0 (0) [0.00–139.33]</td>
<td>–</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Includes subjects from Phase 3 studies only who received the specified SKB dose (300 or 150 mg) regardless of dosing interval (ie, q4w, RAN); PBO subjects who were re-randomized to SKB at Week 12 are also included, and had an induction period with weekly SKB doses from Weeks 12 to 16; \textsuperscript{b}Includes subjects from Phase 2 and 3 studies who received any dose of SKB; \textsuperscript{c}ETN data are from one pivotal Phase 3 trial, FIXTURE; \textsuperscript{d}“Anal fistula” and “Sclerosing cholangitis” are not true IBD, they were retrieved because of the broader search criteria applied

Ward N, et al. AAD 2014, P8233

RAN, retreatment-as-needed
Secukinumab for psoriatic arthritis: ACR 20

**ACR 20 Responses**

- **Placebo**
  - Week 12: 25%
  - Week 24: 15%

- **Secukinumab**
  - Week 12: 56%
  - Week 24: 54%

*Nonresponder imputation (NRI) analysis.*

Ixekizumab: UNCOVER 1-3 study design

UNCOVER-1

Induction dosing:
- IXK 80 mg q2w (n=433)
- IXK 80 mg q4w (n=432)
- PBO q2w (n=431)

Week 0 → Induction dosing → Week 12

Maintenance dosing:
- IXK q4w
- IXK q12w
- PBO q4w

Week 0 (followed by a maintenance period for a total of 60 weeks)

UNCOVER-2 and 3

Induction dosing:
- IXK q4w (n=347)
- PBO q4w
- ETN 50 mg biw (n=358)

Week 0 → Double-blind induction dosing → Week 12

NRI, nonresponder imputation; sPGA, static PGA
Ixekizumab: Efficacy (UNCOVER-1)

Co-primary endpoints

Gated secondary endpoints

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

NRI, nonresponder imputation; sPGA, static PGA

Gordon K, et al. WCD 2015
Ixekizumab: Efficacy Week 60

UNCOVER-1

sPGA (0,1) through Week 60 among IXK-treated patients with sPGA (0,1) at Week 12 (NRI)*

*Patients with sPGA >2 at any timepoint between Weeks 12 and 60 were considered nonresponders at all subsequent visits.

Leonardi C, et al. WCD 2015

NRI, nonresponder imputation; sPGA, static PGA
UNCOVER-3: Continuous ixekizumab for 60 weeks


NRI based on treatment groups at Week 0

*N=386 for induction period; †N=385 for induction period

PASI 75

Response rate (%)

Weeks

PASI 90

Response rate (%)

Weeks

PASI 100

Response rate (%)

Weeks

IXE q4w/IXE q4w

IXE q2w/IXE q4w
Ixekizumab: Safety through Week 60

## UNCOVER-1

### Safety Weeks 1–12

<table>
<thead>
<tr>
<th></th>
<th>PBO N=431</th>
<th>IXK q4w N=432</th>
<th>IXK q2w N=433</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAE</td>
<td>210 (48.7)</td>
<td>264 (61.1)*</td>
<td>257 (59.4)*</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SAE</td>
<td>5 (1.2)</td>
<td>12 (2.8)</td>
<td>6 (1.4)</td>
</tr>
</tbody>
</table>

### Selection of AEs of special interest

#### Infection-related SAE
- PBO: 1 (0.2)
- IXK q4w: 3 (0.7)
- IXK q2w: 3 (0.7)

#### Any candida
- PBO: 2 (0.5)
- IXK q4w: 3 (0.6)
- IXK q2w: 4 (0.9)

#### Malignancy
- PBO: 2 (0.5)
- IXK q4w: 3 (0.7)
- IXK q2w: 0

#### MACE
- PBO: 0
- IXK q4w: 2 (0.7)
- IXK q2w: 0

#### Crohn’s disease
- PBO: 0
- IXK q4w: 1 (0.2)
- IXK q2w: 0

#### Ulcerative colitis
- PBO: 0
- IXK q4w: 0
- IXK q2w: 1 (0.2)

### Safety Weeks 12–60

<table>
<thead>
<tr>
<th></th>
<th>PBO N=226, pt-y=102.9</th>
<th>IXK q12w N=227, pt-y = 155.2</th>
<th>IXK q4w N=229, pt-y=187</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAE</td>
<td>123 (119.5)</td>
<td>168 (108.2)</td>
<td>182 (97.1)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>SAE</td>
<td>7 (6.8)</td>
<td>9 (5.8)</td>
<td>15 (8.0)</td>
</tr>
</tbody>
</table>

### Selection of AEs of special interest

#### Infection-related SAE
- PBO: 1 (1.0)
- IXK q12w: 1 (0.6)
- IXK q4w: 3 (1.6)

#### Any candida
- PBO: 2 (1.9)
- IXK q12w: 4 (2.6)
- IXK q4w: 8 (4.3)

#### Malignancy
- PBO: 0
- IXK q12w: 2 (1.3)
- IXK q4w: 0

#### Crohn’s disease
- PBO: 1 (1.0)
- IXK q12w: 0
- IXK q4w: 0

#### Ulcerative colitis
- PBO: 0
- IXK q12w: 0
- IXK q4w: 0

---

*P≤0.05 vs PBO

*Among patients with an static PGA (0,1) at Week 12

*b1 death from unknown cause presumed to be cardiovascular death due to lack of other information

IR, incidence rate; MACE, major cardiovascular adverse event; pt-y, patient-years

Leonardi C, et al. WCD 2015
SPIRIT-P1: ACR responders at Week 24

*P≤0.01, †P≤0.001 vs placebo
Nonresponder imputation; ADA was active control
Mease P, et al. AAD 2016, P2515

Placebo (n=106)
ADA 40 mg q2w (n=101)
IXE 80 mg q4w (n=107)
IXE 80 mg q2w (n=103)
Brodalumab: AMAGINE-2 and 3 study design


Day 1

Screening
≥7 days, ≤30 days

Day 1

Induction

UST

Week 12

PGA ≥3 or persistent sPGA ≥2 x 4 week

Week 52

Maintenance

UST

R

2:2:1:1N

210 mg q2w BRO

140 mg q2w BRO

140 mg q4w BRO

140 mg q8w BRO

210 mg q2w BRO

R

2:2:2:1

R

2:2:1:1N

PBO

210 mg q2w BRO

UST

UST

a

45 mg if ≤100 kg, 90 mg if >100 kg

AMAGINE-2 and 3: PASI 75 Week 12

PASI 75 response rates (NRI) by week in the induction phase

Coprimary endpoint: PASI 75 at Week 12 BRO vs PBO—adjusted P<0.001 for both dosages
Secondary endpoint: BRO 210 mg q2w vs UST—adjusted P=0.007; weight-based BRO subgroup vs UST—adjusted P=0.007

AMAGINE-2 and 3: PASI Responses for 210 mg q2w

PASI response rates (NRI after treatment change) by week for constant BRO 210 mg through the maintenance phase

- Constant 210 mg q2w defined as patients randomized to BRO 210 mg q2w for both induction and maintenance phases
- Patients with inadequate response are not imputed further and observed data were used

## Brodalumab: Suicidal Ideation and behavior AEs

<table>
<thead>
<tr>
<th></th>
<th>52-week pool&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Long-term pool&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ustekinumab (n=613; pt-y=503.6)</td>
<td>Brodalumab (n=4019; pt-y=3545.7)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>1 (0.20) [0.01–1.11]</td>
<td>3 (0.08) [0.02–0.25]</td>
</tr>
<tr>
<td>Suicidal behavior</td>
<td>1 (0.20) [0.01–1.11]</td>
<td>4 (0.11) [0.03–0.29]</td>
</tr>
<tr>
<td><strong>Completed suicide&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td>0 (0.00) [0.00–0.73]</td>
<td>2 (0.06) [0.01–0.20]</td>
</tr>
<tr>
<td>Intentional self-injury</td>
<td>0 (0.00) [0.00–0.73]</td>
<td>1 (0.03) [&lt;0.01–0.16]</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>1 (0.20) [0.01–1.11]</td>
<td>1 (0.03) [&lt;0.01–0.16]</td>
</tr>
<tr>
<td>Suicidal behavior</td>
<td>0 (0.00) [0.00–0.73]</td>
<td>0 (0.00) [0.00–0.10]</td>
</tr>
<tr>
<td>Overall suicidal ideation and behavior</td>
<td>2 (0.40) [0.05–1.44]</td>
<td>7 (0.20) [0.08–0.41]</td>
</tr>
</tbody>
</table>

<sup>a</sup>Cumulative events through 52-week, controlled treatment period

<sup>b</sup>Includes events in the 52-week treatment period and uncontrolled OLE

<sup>c</sup>Includes fatal event reported as intentional overdose that was adjudicated as indeterminate
Guselkumab: VOYAGE 1 study design

<table>
<thead>
<tr>
<th>Screening</th>
<th>Placebo-controlled</th>
<th>Blinded active treatment</th>
<th>Open label</th>
</tr>
</thead>
</table>

Group 1  
(n=300)

Group 2  
(n=150)

Group 3  
(n=300)

Week 0  
4  
16  
24  
48  
1° EP  
vs PBO  
2° EP  
vs ADA  
DBL 2° EP  
vs ADA

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>GUS 100 mg Week 0, 4, q8w</td>
<td>ADA q2w</td>
</tr>
<tr>
<td>GUS 100 mg Week 16, 20, q8w</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GUS injection  
Placebo → GUS injection  
ADA injection  
ADA q2w
**VOYAGE 1: IGA 0/1 and PASI 90**

**IGA 0/1 at Week 16**

- Placebo (n=174): 6.9%
- Guselkumab (n=329): 85.1%

*(P<0.001 vs placebo)*

**PASI 90 at Week 16**

- Placebo (n=174): 2.9%
- Guselkumab (n=329): 73.3%

*(P<0.001 vs placebo)*
VOYAGE 1: PASI response

**PASI 75 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
### VOYAGE 1: AEs of interest through Week 16

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Placebo (n=174)</th>
<th>Guselkumab (n=329)</th>
<th>Adalimumab (n=333)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 AE</td>
<td>86 (49.4)</td>
<td>170 (51.7)</td>
<td>170 (51.1)</td>
</tr>
<tr>
<td>≥1 SAE</td>
<td>3 (1.7)</td>
<td>8 (2.4)</td>
<td>6 (1.8)</td>
</tr>
<tr>
<td>Discontinued due to ≥1 AE</td>
<td>2 (1.1)</td>
<td>4 (1.2)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections treated with antibiotics</td>
<td>44 (25.3)</td>
<td>85 (25.8)</td>
<td>85 (25.5)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>13 (7.5)</td>
<td>20 (6.1)</td>
<td>24 (7.2)</td>
</tr>
<tr>
<td>MACE</td>
<td>0</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Malignancies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMSC</td>
<td>0</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Malignancy other than NMSC</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥1 injection site reaction (ISR)</td>
<td>–</td>
<td>8 (2.4)</td>
<td>25 (7.5)</td>
</tr>
<tr>
<td>Total number of injections</td>
<td>–</td>
<td>975</td>
<td>3262</td>
</tr>
<tr>
<td>Injections with ISR</td>
<td>–</td>
<td>11 (1.1)</td>
<td>51 (1.6)</td>
</tr>
</tbody>
</table>
Tildrakizumab: reSURFACE 1 & 2 study design

**reSURFACE 1**
- **Screening**
- **BL**
- **Day –28**
  - Visit 1
- **Day 1**
  - Visit 2
- **End Part 1**
  - 1° endpoint
  - Week 12
  - Visit 5
- **End Part 2**
  - Week 28
  - Visit 8
- **TIL 100 mg sc**
- **TIL 200 mg sc**
- **Placebo**

**reSURFACE 2**
- **Screening**
- **BL**
- **Day –28**
  - Visit 1
- **Day 1**
  - Visit 2
- **End Part 1**
  - 1° endpoint
  - Week 12
  - Visit 6
- **End Part 2**
  - Week 28
  - Visit 9
- **TIL 200 mg sc**
- **TIL 100 mg sc**
- **Placebo**

**Treatment Assignment**
- **Part 1**
  - 2:2:1
  - TIL 200 mg sc
  - TIL 100 mg sc
  - Placebo
- **Part 2**
  - 2:2:1:2
  - TIL 200 mg sc
  - TIL 100 mg sc
  - Placebo

**Endpoints**
- **Screening**
- **End Part 1 1° endpoint**
- **End Part 2**

Reich K, et al. EADV 2016, D3T01.11
reSURFACE 1 and 2: PASI 75 and PGA 0/1

PASI 75

PGA 0/1

<table>
<thead>
<tr>
<th>Weeks</th>
<th>TIL 100 mg</th>
<th>TIL 200 mg</th>
<th>Placebo</th>
<th>Placebo → TIL 100 mg</th>
<th>Placebo → TIL 200 mg</th>
<th>ETN 50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20</td>
<td>60</td>
<td>0</td>
<td>22</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>64*</td>
<td>62*</td>
<td>3</td>
<td>66*</td>
<td>77</td>
<td>82*</td>
</tr>
<tr>
<td>8</td>
<td>59*</td>
<td>58*</td>
<td>7</td>
<td>76</td>
<td>71</td>
<td>69</td>
</tr>
<tr>
<td>12</td>
<td>76</td>
<td>71</td>
<td>7</td>
<td>76</td>
<td>71</td>
<td>69</td>
</tr>
<tr>
<td>16</td>
<td>86</td>
<td>82*</td>
<td>8</td>
<td>86</td>
<td>82*</td>
<td>80*</td>
</tr>
<tr>
<td>22</td>
<td>86</td>
<td>82*</td>
<td>8</td>
<td>86</td>
<td>82*</td>
<td>80*</td>
</tr>
<tr>
<td>28</td>
<td>86</td>
<td>82*</td>
<td>8</td>
<td>86</td>
<td>82*</td>
<td>80*</td>
</tr>
</tbody>
</table>

*a PGA score of clear or minimal with ≥2-grade reduction from baseline

*P<0.001 vs placebo; †P<0.05, ‡P<0.001 vs ETN; P-values unadjusted for multiplicity; calculated using the Cochran-Mantel-Haenszel test stratified by body weight (≤90kg, >90kg) and prior biologic exposure for psoriasis. Data as observed; NRI at Week 12

Reich K, et al. EADV 2016, D3T01.11
**reSURFACE 1 and 2: PASI 90 and 100**

![Graphs showing PASI 90 and 100 responders over weeks for reSURFACE 1 and reSURFACE 2.](image)

*P<0.001 vs placebo
Data as observed; NRI at Week 12
Reich K, et al. EADV 2016, D3T01.1I
Patients who took ≥1 dose of Part 1 study medication based on the treatment actually received

Patient on TIL 100 mg died: had alcoholic cardiomyopathy and hepatic steatosis, although adjudication was unable to determine cause of death

Reich K, et al. EADV 2016, D3T01.1I

---

### reSURFACE 2: Safety

<table>
<thead>
<tr>
<th></th>
<th>Part 1 (Weeks 0–12)</th>
<th></th>
<th>Part 2 (Weeks 12–28)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TIL 200 mg (n=314)</td>
<td>TIL 100 mg (n=307)</td>
<td>Placebo (n=156)</td>
<td>Placebo/TIL 200 mg (n=299)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ETN 50 mg (n=313)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ETN/ETN 50 mg (n=289)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo/TIL 100 mg (n=72)</td>
<td></td>
</tr>
<tr>
<td>≥1 AEs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>155 (49.4)</td>
<td>136 (44.3)</td>
<td>86 (55.1)</td>
<td>169 (54.0)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>6 (1.9)</td>
<td>4 (1.3)</td>
<td>4 (2.6)</td>
<td>7 (2.2)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>1 (0.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Discontinued&lt;sup&gt;b&lt;/sup&gt; due to AEs</td>
<td>3 (1.0)</td>
<td>3 (1.0)</td>
<td>2 (1.3)</td>
<td>6 (1.9)</td>
</tr>
<tr>
<td></td>
<td>2 (0.6)</td>
<td>2 (0.7)</td>
<td>1 (0.6)</td>
<td>27 (8.6)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>34 (10.8)</td>
<td>41 (13.4)</td>
<td>12 (7.7)</td>
<td>36 (11.5)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2 (0.6)</td>
<td>2 (0.7)</td>
<td>1 (0.6)</td>
<td>42 (14.0)</td>
</tr>
<tr>
<td>URTI</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>6 (2.0)</td>
</tr>
<tr>
<td>Most common AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Patients who took ≥1 dose of Part 1 study medication based on the treatment actually received

<sup>b</sup>Patent on TIL 100 mg died: had alcoholic cardiomyopathy and hepatic steatosis, although adjudication was unable to determine cause of death

Reich K, et al. EADV 2016, D3T01.1I
Risankizumab Phase II Study

- Treatment arms
  - RKZ 18 mg at Week 0 (PBO at Weeks 4 and 16)
  - RKZ 90 mg at Weeks 0, 4 and 16
  - RKZ 180 mg at Weeks 0, 4 and 16
  - UST (45 or 90 mg) at Weeks 0, 4 and 16

- Prespecified primary analysis:
  - PASI 90 at Week 12, comparing RZK (90 mg + 180 mg pooled) with UST

Papp K, et al. AAD 2015, Late breaker
### Risankizumab Primary Endpoint: PASI 90

**Week 12 analysis**

<table>
<thead>
<tr>
<th></th>
<th>RKZ 18 mg</th>
<th>RKZ 90 mg</th>
<th>RKZ 180 mg</th>
<th>RKZ 90 mg + 180 mg</th>
<th>UST</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>43</td>
<td>41</td>
<td>42</td>
<td>83</td>
<td>40</td>
</tr>
<tr>
<td>PASI 90 (LOCF)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders, n (%)</td>
<td>14 (32.6)</td>
<td>30 (73.2)</td>
<td>34 (81.0)</td>
<td>64 (77.1)</td>
<td>16 (40.0)</td>
</tr>
<tr>
<td>Difference from UST</td>
<td>–8.1%</td>
<td>33.0%</td>
<td>39.5%</td>
<td>36.4%</td>
<td>N/A</td>
</tr>
<tr>
<td>P-value</td>
<td>0.4337</td>
<td>0.0013</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>N/A</td>
</tr>
<tr>
<td>PASI 90 (NRI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders, n (%)</td>
<td>13 (30.2)</td>
<td>30 (73.2)</td>
<td>33 (78.6)</td>
<td>63 (75.9)</td>
<td>16 (40.0)</td>
</tr>
<tr>
<td>Difference from UST</td>
<td>–10.4%</td>
<td>33.0%</td>
<td>37.2%</td>
<td>35.2%</td>
<td>N/A</td>
</tr>
<tr>
<td>P-value</td>
<td>0.3089</td>
<td>0.0013</td>
<td>0.0002</td>
<td>&lt;0.0001</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Papp K, et al. AAD 2015, Late breaker
Risankizumab: Adverse Events Through Week 12

<table>
<thead>
<tr>
<th>n (%)</th>
<th>RZK 18 mg (n=43)</th>
<th>RZK 90 mg (n=41)</th>
<th>RZK 180 mg (n=42)</th>
<th>UST (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE&lt;sup&gt;a&lt;/sup&gt;</td>
<td>31 (72.1)</td>
<td>27 (65.9)</td>
<td>24 (57.1)</td>
<td>24 (60.0)</td>
</tr>
<tr>
<td>Severe AE</td>
<td>2 (4.7)</td>
<td>1 (2.4)</td>
<td>1 (2.4)</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>AE considered drug related by investigator</td>
<td>6 (14.0)</td>
<td>8 (19.5)</td>
<td>6 (14.3)</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>AE leading to D/C</td>
<td>1 (2.3)</td>
<td>1 (2.4)</td>
<td>0 (0)</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Serious AE&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2 (4.7)</td>
<td>2 (4.9)</td>
<td>0 (0)</td>
<td>1 (2.5)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Most common AEs were nasopharyngitis and headache. <sup>b</sup>BI 18 mg: allergy to arthropod bite and erythema multiforme prolonging hospitalization; pelvic/rib fracture. BI 90 mg: GI bleed and resulting iron deficient anemia; cerebrovascular accident (stroke); patient had pre-existing cerebral aneurysm that required clipping and had a stroke in the immediate postop period. UST: diverticulitis unrelated to study medication. MedDRA v17.1

Papp K, et al. AAD 2015,
Risankizumab: ultiMMa-1&2

• Treatment arms
  – Risankizumab 150 mg  (n=304, 294)
  – Ustekinumab 45/90 mg (n=100, 99)
  – Placebo            (n=102, 98)

• Regimen
  – Week 0, 4 then every 12 weeks

• Primary endpoint
  – Week 16: PASI 90 and PGA 0/1
<table>
<thead>
<tr>
<th></th>
<th>PASI 90</th>
<th>PASI 100</th>
<th>PGA 0,1</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RKZ</td>
<td>UST</td>
<td>RKZ</td>
<td>UST</td>
</tr>
<tr>
<td><strong>ultiMMa-1</strong></td>
<td>75</td>
<td>42</td>
<td>88</td>
<td>63</td>
</tr>
<tr>
<td><strong>ultiMMa-2</strong></td>
<td>75</td>
<td>48</td>
<td>84</td>
<td>62</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>5</td>
<td>2</td>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>

**PASI** stands for Psoriasis Area and Severity Index, and **PGA** stands for Physician's Global Assessment.
Certolizumab pegol: CAMPASI 1&2 study design

**Screening**

**Initial treatment period** (double-blind)

**Maintenance period**

**Open-label treatment**

**Safety follow-up**

- **Placebo q2w**
- **CZP 200 mg q2w**
- **CZP 400 mg q2w**
- **Escape CZP 400 mg q2w**

**LD**, loading dose of CZP 400 mg q2w at Weeks 0, 2, and 4 or Weeks 16, 18, and 20

**PGA responder** defined as PGA 0/1 with $\geq 2$-category improvement

**CZP 400 mg q2w**

**CZP 200 mg q2w**

**1:2:2**

- **<PASI 50**
- **$\geq$PASI 50**: withdrawn

**Coprimary endpoints**

- PASI 75 and PGA$^b$

**Gottlieb AB, et al. AAD 2017, Late-breaking Research: Clinical Trials, 5077**
Based on logistic regression model with factors for treatment, region, and prior biologic exposure (yes/no) using multiple imputation

Defined as PGA 0/1 with ≥2-category improvement

Gottlieb AB, et al. AAD 2017, Late-breaking Research: Clinical Trials, 5077
# CIMPASI-1&2: Adverse events of interest reported through Week 16

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=51)</th>
<th>CIMPASI-1</th>
<th>CIMPASI-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CZP 200 mg (n=95)</td>
<td>CZP 400 mg (n=88)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0</td>
<td>30 (31.6)</td>
<td>39 (44.3)</td>
</tr>
<tr>
<td><em>Candida</em> infections</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oral fungal infection</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fungal skin infection</td>
<td>0</td>
<td>0</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Herpes dermatitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Epstein-Barr viral infection</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- **Serious infections**: 0, 0, 0
- **Malignancy**: 0, 0, 0
- **Depression**: 0, 1 (1.1), 0

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*Vulvovaginal candidiasis; Abdominal abscess and hematoma infection; Basal cell carcinoma*

Gottlieb AB, et al. AAD 2017, Late-breaking Research: Clinical Trials, 5077
Conclusions

• Currently 8 FDA approved biologics for psoriasis
• New targets in development in response to advancements in basic science
• Therapies targeting IL-17 and IL-23 exhibit promising potential thus far
• Further study is necessary to eludate the long term efficacy and safety characteristics of these categories of drugs