Lead team presentation
Brodalumab for treating moderate to severe plaque psoriasis in adults [ID878]

1st Appraisal Committee meeting
Committee B
Chair: Amanda Adler
Lead team: Mark Chapman, Dani Preedy, Steve Smith
ERG: York Centre for Reviews and Dissemination
NICE technical team: Sharlene Ting, Ahmed Elsada
4th January 2018
Summary of evidence

**Clinical effectiveness**

AMAGINE randomised trials
- brodalumab vs. placebo and vs. ustekinumab: more people on brodalumab achieve PASI 75 at 12 weeks (and quicker) and maintain it up to 52 weeks

Network meta-analysis results after 10, 12 or 16 weeks depending on comparator
- brodalumab vs. all other treatments (apremilast, dimethyl fumarate, biologics): 2nd highest probability after ixekizumab of achieving PASI 75

**Cost effectiveness**

Presented in part 2 (confidential patient access schemes for apremilast, brodalumab, ixekizumab and secukinumab)
## Background

### Psoriasis

- common chronic inflammatory disease
- characterised by red, thick and scaly plaques on the skin
  - most common form: plaque psoriasis

### Brodalumab (Kyntheum, Leo Pharma)

- recombinant, fully human monoclonal immunoglobulin IgG2 antibody
- binds to interleukin-17 receptor-A
- inhibits inflammation
- **Marketing authorisation:** "moderate to severe plaque psoriasis in adults who are candidates for systemic therapy"
- Administration by subcutaneous injection. Dose:
  - **Weeks 1-3:** 210 mg every week
  - **Weeks 4 onwards:** 210 mg every 2 weeks
    - If no response, stop treatment after 12 to 16 weeks
    - If partial response, may see improvement after 16 weeks
**Patient and clinical perspective**

*Distressing and debilitating, need for a range of highly effective convenient treatments with minimal adverse reactions and impact on lifestyle*

**Impact of psoriasis**
- can be distressing at all levels of severity
- affects all aspects of life: physical, psychological, social, financial
- topical medicines and phototherapy are inconvenient

**People would like**
- range of effective options (people respond differently to treatments)
- reduces symptoms immediately
- no adverse reactions
- limited impact on lifestyle
- targets high impact sites

**Brodalumab**
- different mechanism of action
- very effective in clinical trials
- similar safety profile to other interleukin-17 inhibitors
- administration similar to other biologics
Measuring clinical effectiveness

Psoriasis Area and Severity Index (PASI)
- Weighted score (0 to 72) of 4 affected areas
  - 0 (no psoriasis); 10 (moderate); >10 (severe)
- Response considered as PASI 50, PASI 75, PASI 90, PASI 100
  - PASI 75: ≥75% reduction in PASI score from baseline (clinically important difference according to British Association of Dermatologists guidelines)
  - PASI 100: 100% reduction in PASI score (i.e. to 0)

Dermatology Life Quality Index (DLQI)
- 10 questions scored 0 to 3 (worst impact): symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment
- range from 0 to 30
- 5 point improvement (clinically important difference)
- DLQI 0 or 1: psoriasis has no effect on life at a specific visit

Static Physician Global Assessment (sPGA)
- measure physician’s impression of patient’s psoriasis based on severity of induration, scaling and erythema
- score: 0 (clear), 1 (almost clear) to 5 (severe)
### Topical therapy
- corticosteroid, vitamin D, vitamin D analogues, coal tar

### Phototherapy
- ultraviolet B (narrow and broad band), psoralen + ultraviolet A [PUVA]

### Systemic non-biological therapy
- methotrexate, ciclosporin, acitretin

### Systemic biological therapy

#### Severe (PASI ≥10 & DLQI >10)
- adalimumab (TA146)
- etanercept (TA103)
- ixekizumab (TA442)
- secukinumab (TA350)
- ustekinumab (TA180)

#### Very severe (PASI ≥20 & DLQI >18)
- infliximab (TA134)

#### Severe (PASI ≥10 & DLQI >10)
- apremilast (TA419)
- dimethyl fumarate (TA475)

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**Legend**
- TNF-α inhibitor
- IL-17 inhibitor
- IL-12/IL-23 inhibitor
- PDE-4 inhibitor
- Th1 and Th17 → Th2

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**Brodalumab for moderate to severe psoriasis?**

**Company’s positioning of brodalumab**
Decision problem – population

Company focuses on narrower population than NICE scope which reflects likely position of brodalumab in NHS clinical practice

NICE scope: “adults with moderate to severe plaque psoriasis”

Company’s decision problem: candidates for systemic therapy and for whom standard systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated

ERG comments:
• Company’s decision problem appropriate and reflects likely position of brodalumab in NHS
• 17-35% of patients in AMAGINE trials had no prior systemic therapy or phototherapy

Where would brodalumab fit in the treatment pathway?
### NICE scope

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Company’s decision problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brodalumab</td>
<td>Brodalumab in a treatment sequence followed by ustekinumab then secukinumab then BSC</td>
</tr>
</tbody>
</table>

### Comparators

- TNF-alpha inhibitors (adalimumab, etanercept, infliximab)
- IL-17 inhibitors (ixekizumab, secukinumab)
- Ustekinumab
- Apremilast
- Dimethyl fumarate
- Best supportive care (BSC)

9 treatment sequences changing what goes 1<sup>st</sup>; mostly ustekinumab is 2<sup>nd</sup> and secukinumab is 3<sup>rd</sup>

<table>
<thead>
<tr>
<th>Sequence</th>
<th>1&lt;sup&gt;st&lt;/sup&gt;</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>1</td>
<td>Brodalumab</td>
<td>Ustekinumab</td>
<td>Secukinumab</td>
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**Is it more appropriate to compare**

- Brodalumab to other individual treatments, or
- Specific sequences of treatments with and without brodalumab?
Company clinical evidence

- 3 Phase III randomised controlled trials + open-label extension studies for all trials
  - AMAGINE-1: brodalumab (140 mg [not licensed] or 210 mg) vs placebo
  - AMAGINE-2
  - AMAGINE-3
    - identical in design
    - brodalumab (140 or 210 mg) vs ustekinumab (45 or 90 mg) and placebo

- Company
  - reported results only for licensed brodalumab dose (210 mg)
  - did not use results from open-label studies in economic model

- Network meta-analysis
  - ustekinumab only drug in ‘head-to-head’ trials with brodalumab
  - brodalumab vs
    - apremilast, dimethyl fumarate, fumaric acid esters, biologics (adalimumab, etanercept, infliximab, ixekizumab, secukinumab, ustekinumab) and common comparators (placebo, acitretin, methotrexate)
AMAGINE trials

Adults (18 to 75 years) with stable moderate to severe plaque psoriasis for ≥6 months (PASI ≥12, sPGA ≥3, involved body surface area ≥10%)

Brodalumab 210 mg at weeks 0, 1, 2, 4, 6, 8 and 10 (7 doses)

Phase III, international, multicentre, randomised, double-blind, parallel group

No UK sites

Key outcomes at 12 weeks
- Co-primary endpoints vs placebo:
  - PASI 75
  - sPGA 0 or 1
- Endpoint vs ustekinumab: PASI 100

ERG comments
- Available drugs or sequencing differ in other countries
- NHS patients eligible for brodalumab unlikely to have stable psoriasis
  - likely to have more severe psoriasis which responds less well to treatment

To what extent is response to treatment affected by whether or not psoriasis is stable?

PASI, Psoriasis Area and Severity Index (0-72); sPGA, Static Physician Global Assessment (0-5)
At end of induction, patients on brodalumab re-randomised if they achieved sPGA 0 or 1. Patients re-randomised to placebo could get brodalumab ‘rescue therapy’ if psoriasis worsened (sPGA ≥3).

n, number of people; Q2W, every 2 weeks; R, randomisation; sPGA, Static Physician Global Assessment.
AMAGINE-2 and -3 trial design

**Induction phase**
- Brodalumab 210 mg Q2W
- Brodalumab 140 mg Q2W
- Placebo

1. **Randomisation (2:2:1:1)**

2. **Maintenance phase**
- Brodalumab 210 mg Q2W
- Brodalumab 140 mg Q2W
- Ustekinumab

3. **Open-label extension phase**
- Brodalumab 210 mg Q2W

Legend:
- n, number of people; QnW, every n weeks; R, randomisation

Timeline:
- Day 1
- Week 12
- Week 52
- Week 108 / 120
ERG comments on trial design

- AMAGINE trials are of good quality and results likely to be reliable
- Re-randomisation design
  - cohorts at week 52 differ from week 12
  - no data on relapse rates → impossible to know if patients achieving PASI 75 response at end of induction:
    - maintained response or
    - stopped responding
  - At week 52, patients who discontinued were considered to be non-responders
- Discontinuation rates at 52 weeks for brodalumab were low (~20%)
  - similar to published rates for other biologics
## Baseline characteristics

Company argued population similar to BADBIR registry population (UK and Ireland)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Age (years)$^\wedge$</th>
<th>Psoriasis duration (years)$^\wedge$</th>
<th>PASI$^\wedge$</th>
<th>DLQI$^\wedge$</th>
<th>% prior systemic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMAGINE-1</td>
<td>Brodalumab* (n=222)</td>
<td>46 ± 12</td>
<td>20 ± 13</td>
<td>19.4 ± 6.6</td>
<td>14.2 ± 7.3</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=220)</td>
<td>47 ± 13</td>
<td>21 ± 12</td>
<td>19.7 ± 7.7</td>
<td>13.9 ± 6.8</td>
<td>83</td>
</tr>
<tr>
<td>AMAGINE-2</td>
<td>Brodalumab* (n=612)</td>
<td>45 ± 13</td>
<td>19 ± 12</td>
<td>20.3 ± 8.3</td>
<td>XXX</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>Ustekinumab (n=300)</td>
<td>45 ± 13</td>
<td>19 ± 13</td>
<td>20.0 ± 8.4</td>
<td>XXX</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=309)</td>
<td>44 ± 13</td>
<td>18 ± 12</td>
<td>20.4 ± 8.2</td>
<td>XXX</td>
<td>74</td>
</tr>
<tr>
<td>AMAGINE-3</td>
<td>Brodalumab* (n=624)</td>
<td>45 ± 13</td>
<td>18 ± 12</td>
<td>20.4 ± 8.3</td>
<td>XXX</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Ustekinumab (n=313)</td>
<td>45 ± 13</td>
<td>18 ± 12</td>
<td>20.1 ± 8.4</td>
<td>XXX</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=315)</td>
<td>44 ± 13</td>
<td>18 ± 12</td>
<td>20.1 ± 8.7</td>
<td>XXX</td>
<td>65</td>
</tr>
</tbody>
</table>

*210mg every 2 weeks, $^\wedge$mean ± standard deviation
BADBIR, British Association of Dermatologists Biologic Interventions Register; DLQI, Dermatology Life Quality Index (0-30); PASI, Psoriasis Area and Severity Index (0-72); n, number of people
ERG comments on characteristics of populations in AMAGINE trials

- Similar baseline characteristics across different treatment groups
- AMAGINE-1 had more patients with psoriasis of longer duration, with psoriasis arthritis and who had previous treatments, than AMAGINE-2 and -3
- AMAGINE included patients with PASI ≥12 and mean baseline DLQI >12
  - higher than treatment threshold in current NICE guidance for severe psoriasis (PASI ≥10 and DLQI >10)
- 17-35% patients in AMAGINE had no previous systemic treatment or phototherapy and AMAGINE excluded patients on previous ustekinumab or anti-interleukin-17 therapy
  - inconsistent with proposed positioning of brodalumab

- Is AMAGINE population representative of moderate to severe psoriasis as defined in the NHS?
- Are results from AMAGINE generalisable to target population of patients with prior systemic therapy?
### Key results at end of induction (12 weeks)

<table>
<thead>
<tr>
<th>Study</th>
<th>Brodalumab (n)</th>
<th>Placebo (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AMAGINE-1</strong></td>
<td>83 (78–88)</td>
<td>3 (1–6)</td>
</tr>
<tr>
<td>Brodalumab (n=222)</td>
<td>76 (70–81)</td>
<td>1 (0, 4)</td>
</tr>
<tr>
<td>Placebo (n=220)</td>
<td>56 (NR)</td>
<td>5 (NR)</td>
</tr>
<tr>
<td><strong>AMAGINE-2</strong></td>
<td>86 (83–89)</td>
<td>70 (65–75)</td>
</tr>
<tr>
<td>Brodalumab (n=612)</td>
<td>79 (75–82)</td>
<td>61 (NR)</td>
</tr>
<tr>
<td>Ustekinumab (n=300)</td>
<td>61 (55–67)</td>
<td>44 (NR)</td>
</tr>
<tr>
<td>Placebo (n=309)</td>
<td>56 (NR)</td>
<td>4.5 (NR)</td>
</tr>
<tr>
<td><strong>AMAGINE-3</strong></td>
<td>85 (82–88)</td>
<td>69 (64–74)</td>
</tr>
<tr>
<td>Brodalumab (n=624)</td>
<td>80 (76–83)</td>
<td>57 (52–63)</td>
</tr>
<tr>
<td>Ustekinumab (n=313)</td>
<td>59 (NR)</td>
<td>44 (NR)</td>
</tr>
<tr>
<td>Placebo (n=315)</td>
<td>6 (4–9)</td>
<td>7 (NR)</td>
</tr>
</tbody>
</table>

*210mg every 2 weeks; ^(95% confidence intervals); DLQI, Dermatology Life Quality Index (0-30); PASI, Psoriasis Area and Severity Index (0-72); sPGA, Static Physician Global Assessment (0-5); n, number of patients; NR, Not reported
Treatment effect up to 52 weeks
PASI response rates largely maintained up to 52 weeks

Similar results observed for AMAGINE-2 (not shown here)

n, number of patients; PASI, Psoriasis Area and Severity Index (0-72); Q2W, every 2 weeks
Base case network diagram

59 trials (n=28,346): moderate to severe plaque psoriasis, eligible for systemic therapy

BID, 2 times a day; DMF, dimethyl fumarate; QnW, every n weeks
### Company’s network meta-analysis – base case and sensitivity analyses

#### Base case: PASI response rates at induction
- Dosages and duration of induction therapy per licence of each treatment
- Company included unlicensed doses and (conventional) non-biologics only if contributed to evidence for relevant therapies
- Omitted comparators: non-biologics, best supportive care

#### Sensitivity analyses

- **Sensitivity analysis 1:** Including EMA licensed dose recommended by NICE
- **Sensitivity analysis 2:** 16 week outcomes from 1 of the 59 trials (CLEAR) used (primary endpoint of trial) vs 12-week outcomes used in base case
- **Sensitivity analysis 3:** trials <100 patients randomised excluded
- **Sensitivity analysis 4:** trials >30% randomised patients had previous biologics excluded (30% pragmatically chosen to include as many brodalumab trials as possible)
- **Sensitivity analysis 5:** trials with mean baseline PASI >25 excluded

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*Which analysis is most appropriate?*

EMA, European Medicines Agency; PASI, Psoriasis Area and Severity Index (0-72)
## Company’s network meta-analysis results

Results for unadjusted base case and sensitivity analyses are consistent

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median probability of PASI 75 response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Company base case (unadjusted)</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Ixekizumab 80mg Q2W</td>
<td>90.4%</td>
</tr>
<tr>
<td>Brodalumab 210mg</td>
<td>XXX</td>
</tr>
<tr>
<td>Secukinumab 300mg</td>
<td>83.6%</td>
</tr>
<tr>
<td>Infliximab 5mg/kg</td>
<td>79.2%</td>
</tr>
<tr>
<td>Ustekinumab 45mg</td>
<td>71.6%</td>
</tr>
<tr>
<td>Ustekinumab 90mg</td>
<td>75.3%</td>
</tr>
<tr>
<td>Ustekinumab (in-label dose)</td>
<td>71%</td>
</tr>
<tr>
<td>Adalimumab 40mg Q2W</td>
<td>66%</td>
</tr>
<tr>
<td>Etanercept 50mg / week</td>
<td>39.1%</td>
</tr>
<tr>
<td>Apremilast 30mg BID</td>
<td>27.3%</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>19.3%</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.7%</td>
</tr>
</tbody>
</table>

BID, 2 times a day; PASI, Psoriasis Area and Severity Index (0-72); Q2W, every 2 weeks
ERG comments on network meta-analysis

- Trials similar enough to pool
- Network meta-analysis well conducted
- Quality of life in AMAGINE poorer than comparator trials and higher proportion received previous biologics
- Company presented only PASI response rates
- PASI response rates of placebo groups varied significantly across 49 trials:
  - PASI 50 response rates: 5.1–33.3%
  - PASI 75 response rates: 0–20% (AMAGINE trials: 2.7–8.1%)
- Results for placebo-adjusted and placebo-unadjusted models consistent
  - However, ERG prefers placebo-adjusted model
    - this reduces difference between studies and ensures that relative treatment outcomes across trials are not biased

🤔 Which model is preferred? Unadjusted or placebo-adjusted?
# NMA results – ERG placebo-adjusted model

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median probability of PASI response</th>
<th>Ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PASI 50</td>
<td>PASI 75</td>
</tr>
<tr>
<td>Ixekizumab (80 mg Q2W)</td>
<td>96.1%</td>
<td>89.1%</td>
</tr>
<tr>
<td>Brodalumab (210 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secukinumab (300 mg)</td>
<td>92.5%</td>
<td>81.8%</td>
</tr>
<tr>
<td>Infliximab (5 mg/kg)</td>
<td>90.9%</td>
<td>78.9%</td>
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<tr>
<td>Ustekinumab (90 mg)</td>
<td>87.0%</td>
<td>72.5%</td>
</tr>
<tr>
<td>Ustekinumab (in-label dose)</td>
<td>85.8%</td>
<td>70.6%</td>
</tr>
<tr>
<td>Ustekinumab (45 mg)</td>
<td>85.2%</td>
<td>69.7%</td>
</tr>
<tr>
<td>Adalimumab (40 mg)</td>
<td>85.0%</td>
<td>69.5%</td>
</tr>
<tr>
<td>Etanercept (100 mg/week)</td>
<td>71.2%</td>
<td>51.2%</td>
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<td>39.0%</td>
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<td>51.9%</td>
<td>31.5%</td>
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BID, 2 times a day; PASI, Psoriasis Area and Severity Index (0-72); Q2W, every 2 weeks

**Is brodalumab clinically effective?**
Cost effectiveness
Where do QALY gains come from?

Company assumes NO association

Company assumes all QALY gains here

Increase in QALYs comes only from improvement in quality of life, rather than increasing length of life
Company model

ERG: model meets requirements of NICE reference case; high quality; similar to recent technology appraisals. Uncertainty in assuming that patients stop all treatments at the same rate

- Markov state transition model: 40 year time horizon, 2 week cycle length, treatment-specific duration of ‘induction’ (10, 12 or 16 weeks). Serious adverse events (infections) included. Perspective from NHS/PSS. 3.5% discount

- Baseline characteristics (similar to trials in network meta-analysis and AMAGINE): 45 years, mean weight 85.8kg, 68% men

Ada, Adalimumab; Apr, Apremilast; Brod, Brodalumab; BSC, Best supportive care; DMF, dimethyl fumarate; Etan, Etanercept; Infl, Infliximab; Ixe, Ixekizumab; PASI, Psoriasis Area and Severity Index (0-72); Sec, Secukinumab; Ust, Ustekinumab
## Treatment sequences

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- Sequences based on: British Association of Dermatologists guidelines, expert opinion
- Therapies selected to have different mechanism of action
- Experts suggest likeliest 1<sup>st</sup>, 2<sup>nd</sup> & 3<sup>rd</sup> treatments: adalimumab, ustekinumab, secukinumab
  - TNF-α inhibitor, IL-17 inhibitor, IL-12/IL-23 inhibitor, PDE-4 inhibitor, Th1 and Th17 $\rightarrow$ Th2

BSC, Best supportive care
Treatment sequences – **ERG comments**

*Limited number of sequences provides misleading cost-effectiveness estimates. ERG’s alternative base case using net monetary benefit framework is preferred*

- Modelling treatment sequences vs comparison of single lines of therapy followed by best supportive care → reflects clinical practice
- Limited number of sequences and positions of brodalumab
- Modelling selective sequences provide misleading cost-effectiveness estimates, especially if included treatments are also not cost effective

- **ERG alternative approach:** net monetary benefit framework with rankings of each treatment compared with best supportive care
  - Treatment rankings from ERG’s alternative base case are identical to company’s base case → provides significant reassurance and confirmation on robustness of company’s results
Incremental cost-effectiveness ratios (ICERs) vs net monetary benefit framework (NMB)

**ICER:** What is the extra cost per unit of extra benefit?
ICER decision rule: recommend technology if
\[ \frac{\Delta \text{Costs}}{\Delta \text{QALYs}} < \text{threshold} \]

But, ICER > 0 can mean:

**NMB**
- Value of an intervention in monetary terms at a willingness-to-pay threshold (NHS opportunity cost)
- For NMB, ICER decision rule is rearranged:
  \[ (\Delta \text{QALYs} \times \text{threshold}) - \Delta \text{Costs} > 0 \]
- Incremental NMB: difference in NMB between alternative interventions
- Positive incremental NMB: intervention is cost-effective compared with alternative at given willingness-to-pay threshold

How should cost effectiveness of brodalumab be assessed?
**Key model parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Company’s source</th>
<th>ERG comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI response achieved after induction and maintenance on an active treatment</td>
<td>Base-case network meta-analysis</td>
<td>ERG prefers placebo-adjusted network meta-analysis</td>
</tr>
<tr>
<td>PASI response achieved for best supportive care</td>
<td>Base-case network meta-analysis for placebo</td>
<td></td>
</tr>
<tr>
<td>Mortality rate</td>
<td>UK life tables, age and sex specific adjusted for increased risk of death by 42% associated with psoriasis (based on UK GPRD study), not affected by treatment or level of PASI response</td>
<td>Appropriate</td>
</tr>
</tbody>
</table>

*Is a relative risk of death of 1.42 plausible?*

PASI, Psoriasis Area and Severity Index (0-72); GPRD, General Practice Research Database
## Key model assumption

<table>
<thead>
<tr>
<th>Assumption</th>
<th>ERG comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment effectiveness does not depend on previous use of therapies →</td>
<td>Consistent with previous appraisals</td>
</tr>
<tr>
<td>placement of drug in sequence has no impact on drug’s effectiveness</td>
<td></td>
</tr>
<tr>
<td>Treatment waning: same effect maintained with ongoing treatment until</td>
<td>Consistent with previous appraisals</td>
</tr>
<tr>
<td>discontinuation</td>
<td></td>
</tr>
<tr>
<td>Discontinuation annual rate assumed to be the same for all treatments</td>
<td>Consistent with previous appraisals but uncertainty around the appropriateness</td>
</tr>
<tr>
<td></td>
<td>of using a constant rate for all treatments</td>
</tr>
<tr>
<td>On best supportive care, patients continue until end of the modelled time</td>
<td>Appropriate</td>
</tr>
<tr>
<td>horizon or death</td>
<td></td>
</tr>
<tr>
<td>Patients can move to the death state from any health state at any time</td>
<td>Appropriate</td>
</tr>
</tbody>
</table>

**How should treatment discontinuation be modelled?**
Utility values

• Utility values based on EQ-5D-3L data from AMAGINE-1 subgroup DLQI >10
  – change in EQ-5D-3L from baseline to week 12 stratified by PASI response
  – company explored relationship between change in EQ-5D-3L score, PASI response and baseline DLQI using regression model

• Utility decreased to account for serious infection (multiplier calculated using data from Diamantopoulos 2014 on utility for pneumonia, adjusted for expected duration of event, baseline age and sex of Sisk 1997 cohort)

• **Base case:** patients with PASI ≥12 and DLQI >10 (moderate to severe); regression model adjusted for baseline DLQI

• **4 scenario analyses** to address uncertainty of generalisability of data:
  1. all patients in AMAGINE-1
  2. 4th quartile of DLQI from TA103 (etanercept)
  3. DLQI >10 estimates from TA350 (secukinumab)
  4. median values from previous appraisals

DLQI, Dermatology Life Quality Index (0-30); PASI, Psoriasis Area and Severity Index (0-72)
Utility values – ERG comments

- Company should adjust regression model for baseline EQ-5D (better goodness of fit), not baseline DLQI
- Consistent results in DLQI >10 subgroup and all patients → data from AMAGINE-1 generalisable to AMAGINE-2 and -3
- Uncertainty about generalisability of utility values to other trials in network meta-analysis: other appraisals have higher baseline utility and smaller increments

<table>
<thead>
<tr>
<th>PASI response</th>
<th>Adjusted for baseline DLQI</th>
<th>Adjusted for baseline EQ-5D (ERG’s base case)</th>
<th>e.g. TA350 (secukinumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DLQI&gt;10 (base case)*</td>
<td>DLQI&gt;10</td>
<td>DLQI &gt;10</td>
</tr>
<tr>
<td></td>
<td>All patients^</td>
<td>All patients</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.5206</td>
<td>0.5206</td>
<td>0.6402</td>
</tr>
<tr>
<td></td>
<td>0.6105</td>
<td>0.6105</td>
<td></td>
</tr>
<tr>
<td>PASI &lt;50</td>
<td>(0.0158)</td>
<td>(0.0035)</td>
<td>(-0.0037)</td>
</tr>
<tr>
<td></td>
<td>(0.0044)</td>
<td>(-0.0044)</td>
<td>(0.109)</td>
</tr>
<tr>
<td>PASI 50–74</td>
<td>(0.1898)</td>
<td>(0.2337)</td>
<td>(0.1574)</td>
</tr>
<tr>
<td></td>
<td>(0.1349)</td>
<td>(0.1349)</td>
<td>(0.193)</td>
</tr>
<tr>
<td>PASI 75–89</td>
<td>(0.2946)</td>
<td>(0.3411)</td>
<td>(0.2631)</td>
</tr>
<tr>
<td></td>
<td>(0.2441)</td>
<td>(0.2441)</td>
<td>(0.226)</td>
</tr>
<tr>
<td>PASI 90–99</td>
<td>(0.3552)</td>
<td>(0.3608)</td>
<td>(0.2895)</td>
</tr>
<tr>
<td></td>
<td>(0.2798)</td>
<td>(0.2798)</td>
<td>NR</td>
</tr>
<tr>
<td>PASI 100</td>
<td>(0.3680)</td>
<td>(0.3774)</td>
<td>(0.2986)</td>
</tr>
<tr>
<td></td>
<td>(0.2897)</td>
<td>(0.2897)</td>
<td>NR</td>
</tr>
</tbody>
</table>

Increments in parentheses; *n=401; ^n=621; aUsed EQ-5D-3L as in AMAGINE-1, n=3,286; DLQI, Dermatology Life Quality Index (0-30); PASI, Psoriasis Area and Severity Index (0-72); NR, Not reported

How should utility values be modelled? Adjusted for baseline DLQI or baseline EQ-5D?
## Resource use and costs

<table>
<thead>
<tr>
<th>Cost parameter</th>
<th>Company assumption</th>
<th>ERG comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>Brodalumab: 7 doses for induction (12 weeks) Other drugs: list price, lowest priced biosimilars if available</td>
<td>Brodalumab: 8 doses (unit packs of 2 cannot be split) Other drugs: appropriate</td>
</tr>
<tr>
<td>Administration</td>
<td>Only infliximab (intravenous infusion)</td>
<td>Previous appraisals include costs for subcutaneous treatments; little impact</td>
</tr>
<tr>
<td>Monitoring visits</td>
<td>Exclude additional resource use for dimethyl fumarate</td>
<td>Include additional 2 outpatient visits and associated blood tests for dimethyl fumarate</td>
</tr>
<tr>
<td>Non-responder</td>
<td>Exclude: already included in best supportive care costs</td>
<td>Include non-responder costs of £128 per 2 week cycle, based on TA475 (dimethyl fumarate) and TA442 (ixekizumab)</td>
</tr>
<tr>
<td>Best supportive care</td>
<td>Based on Fonia 2010 £5,283 per year</td>
<td>Appropriate</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Based on 6 serious infections: £2,653</td>
<td>Appropriate</td>
</tr>
</tbody>
</table>
ERG base case

• Analysis: Net monetary benefit of each treatment vs best supportive care
  – addresses ‘misleading’ estimates of cost effectiveness from restricted treatment sequences that may include options that are not cost effective

• Clinical effectiveness input: derived from placebo-adjusted network meta-analysis
  – improved goodness of fit

• Utility: regression model adjusted for baseline EQ-5D for DLQI >10 subgroup
  – improved goodness of fit

• Brodalumab dosing assumptions for induction (12 weeks) from 7 to 8 doses
  – more appropriate given the inability to split packs

• Inclusion of non-responder costs
  – consistent with recent appraisals
Results in Part 2 only

- Confidential PAS for apremilast, brodalumab, ixekizumab and secukinumab

- Results for company’s base case, scenario and sensitivity analyses are largely consistent

- Committee will see:
  - Company’s base case deterministic and probabilistic results
  - ERG’s base case probabilistic results
Company comments on innovation

• Brodalumab:
  – has the potential to deliver complete skin clearance for many patients
  – treats nail and scalp psoriasis
  – is associated with rapid responses
  – requires fewer induction doses than anti-TNF therapies
  – delivers sustained responses, even after interrupting treatment
  – provides clinicians and patients with a choice within the interleukin-17 class of biological therapies

❖ Is brodalumab innovative?
Equality considerations

- As in previous appraisals, the following issues have been identified:
  - Psoriasis Area and Severity Index (PASI) may underestimate disease severity in people with darker skin as redness may be less evident (key component of PASI)
  - Dermatology Life Quality Index (DLQI) underestimates the impact of people who are not sexually active or older or socially isolated and does not capture anxiety and depression
End of Part 1