Part 1 slide handouts for public [redacted]

Tildrakizumab for treating moderate to severe plaque psoriasis [ID1060]

2nd Appraisal Committee meeting

Committee B, 22nd January 2018

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Key issues for consideration

- Is 28 weeks the appropriate time point to assess tildrakizumab treatment response?
  - If not:
    - When is the appropriate time point to assess treatment response?

[redacted]

Tildrakizumab (Ilumetri, Almirall)

Mechanism of action	• Tildrakizumab is a monoclonal antibody that is a selective inhibitor of the p19 subunit of interleukin-23. This inhibits inflammatory pathway in psoriasis biological mechanism
Marketing authorisation	• The marketing authorisation (October 2018) is for: "adults with moderate to severe psoriasis who are candidates for systemic therapy"
Administration and dose	• Subcutaneous injection of **100mg** at weeks 0, 4 and every 12 weeks thereafter • **200mg** dose may be appropriate for patients with certain characteristics (high disease burden, ≥90kg body weight), **both doses are presented** for this appraisal • Self-administration may be appropriate with training
List price	• A confidential discount to the list price has been agreed
Stopping treatment (from SmPC)	• Consideration should be given to discontinuing treatment in patients who have shown no response after 28 weeks of treatment

Treatment Pathway

1st

Topical therapy
corticosteroid, vitamin D, vitamin D analogues, coal tar

2nd

Phototherapy
ultraviolet B (narrow and broad band), psoralen + ultraviolet A

3rd

Systemic non-biological therapy
methotrexate, ciclosporin, acitretin

4th

Systemic biological therapy
Severe (PASI ≥10 & DLQI >10)
adalimumab (TA146)
etanercept (TA103)
ustekinumab (TA180)
ixekizumab (TA442)
secukinumab (TA350)
brodalumab (TA511)
guselkumab (TA521)

Tildrakizumab

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

Proposed position

Systemic non-biological therapy
Severe (PASI ≥10 & DLQI >10)
apremilast (TA419)
dimethyl fumarate (TA475)

LEGEND
TNF-α inhibitor
IL-12/IL-23 inhibitor
IL-17 inhibitor
IL-23 inhibitor

Full marketing authorisation

BSC

Best supportive care

[redacted]

ACD preliminary recommendation

Tildrakizumab is not recommended for treating moderate to severe plaque psoriasis in adults for whom systemic treatment is appropriate.

ACD committee conclusions (1)

Clinical need	• Having a choice of treatments is especially important to people with psoriasis • Both lower and higher doses appropriate for consideration
Comparators	• Systemic biological treatments including infliximab • Apremilast and dimethyl fumarate are not relevant comparators
Trial data (reSURFACE trials)	• Compared 2 doses of tildrakizumab (100 mg and 200 mg) with placebo, reSURFACE 2 had etanercept arm • Tildrakizumab more effective than placebo or etanercept at 12 weeks and 28 weeks • No difference between 100 mg and 200 mg doses
Network meta-analysis	• Tildrakizumab PASI 75 response at 12 to 16 weeks: higher than etanercept, similar to adalimumab and ustekinumab, and lower than other targeted biologicals • Tildrakizumab PASI 75 response at 24 to 28 weeks: higher than etanercept and adalimumab, similar to other biologicals at 12 to 16 weeks (i.e. time of stopping rules for those treatments in NHS) • Infliximab should be included in the NMA
Stopping treatment	• Response to tildrakizumab should be assessed at 28 weeks in line with marketing authorisation and noticeably better PASI 75 response rate at 28 weeks compared to 12 weeks

ACD committee conclusions (2)

Assumptions in model	• Tildrakizumab with both a 14-week and 28-week assessment point should be compared with other biologicals at the induction periods that reflect the stopping rules used in NHS
Utility values	• Absolute utility scores without adjustment for age appropriate • For best supportive care, utility should return to baseline rather than the utility of patients with the lowest response to treatment (which might represent some improvement in symptoms)
Costs	• Induction and maintenance costs should be based on recommended stopping rules for all treatments and costs for people that did not respond to treatment should be included • Fonia et al. costs better reflect cost of best supportive care
Cost-effectiveness estimates	• Treatment sequences may result in misleading cost-effectiveness estimates, comparison of individual treatments to best supportive care alone is more appropriate • Incremental net monetary benefit in addition to ICERs should be considered
Results	• Tildrakizumab is less cost effective than other biological treatments when assessed either at week 28 or 14 and not a cost effective use of NHS resources

ACD consultation responses

- **Consultee comments from:**
  - Almirall
  - Psoriasis and Psoriatic Arthritis Alliance
  - British Association of Dermatologists (BAD)

- **Commentator comments from:**
  - Celgene
  - LEO Pharma
  - Novartis

Value of tildrakizumab as a new treatment option

Psoriasis and Psoriatic Arthritis Alliance:

- people with psoriasis need access to a wide range of therapies as efficacy wanes

British Association of Dermatologists:

- experience with TNF and IL17 inhibitors have shown how important it is in practice to have more than one agent in a therapeutic class
- the importance to patients and carers of the less frequent dosing scheduled compared with other biologics should be considered

Treatment response assessment

ACD: *response to tildrakizumab at 28 weeks higher than at 12 weeks; effect was not seen with other biologicals. Committee considered that tildrakizumab's less frequent dosing meant that this late treatment effect was more noticeable.*
Clinical expert: *assessment at 12 weeks premature.* ***Committee*** *concluded that response to tildrakizumab should be assessed at 28 weeks to avoid the possibility of people switching from effective treatment*

Comparator companies:

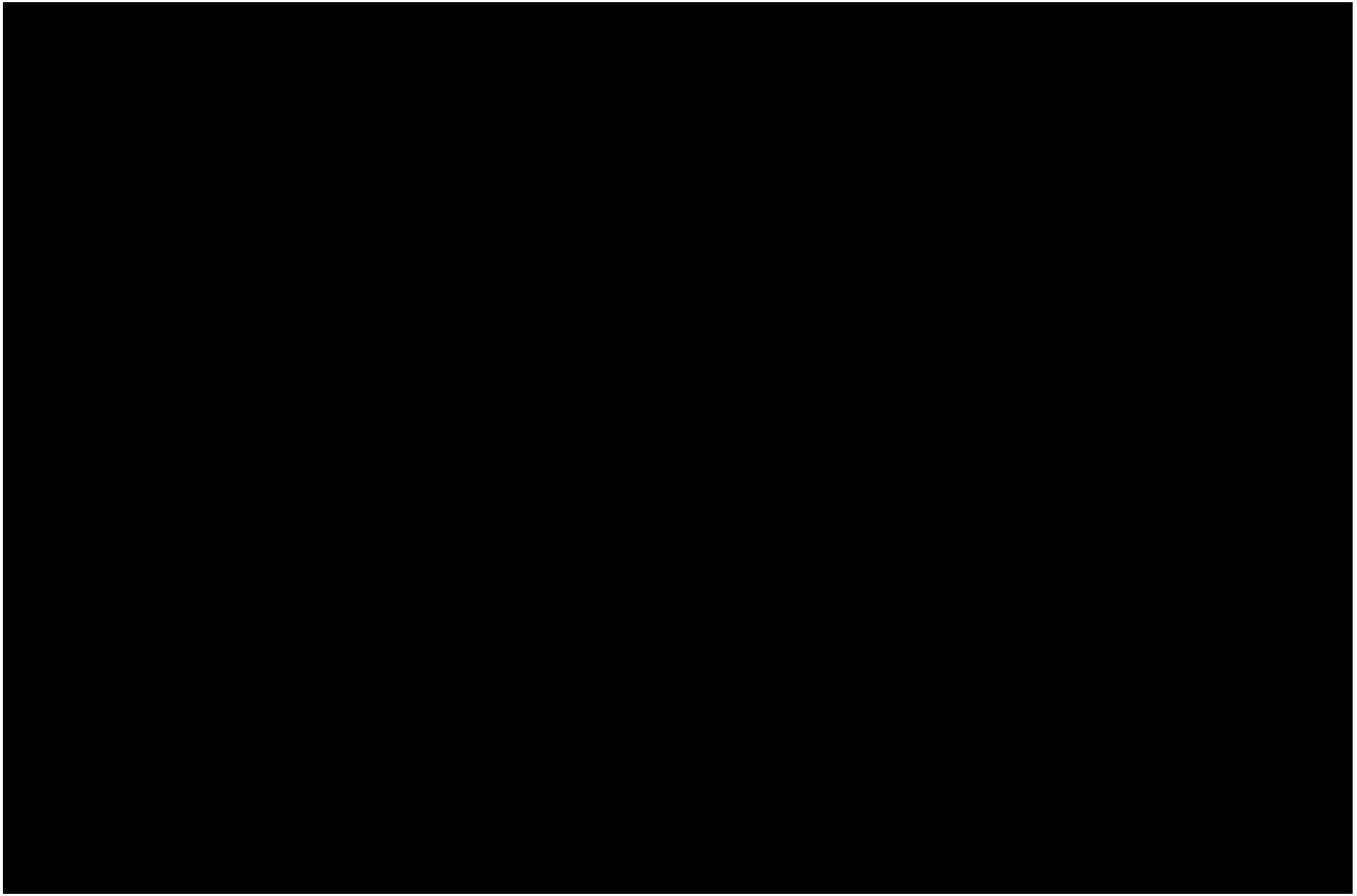
- NICE recommended timing of response assessment has differed from MA in past appraisals (TA442 ixekizumab MA:16 to 20 wks vs. guidance: 12 wks)
- Ustekinumab also has the same dosing frequency and an earlier response assessment (16 weeks, TA180)
- Other biologicals also had increases in efficacy in trials after the recommended time point of assessment
- Time points of assessment have been consistent with the timings used to determine the primary end-point within their clinical trials in past appraisals

BAD: Not possible in clinical practice to keep patient with severe disease on a drug for 28 weeks in hope of efficacy which is not materialising. A decision will be made earlier than this (e.g.12 weeks), based perhaps on lesser degree of response

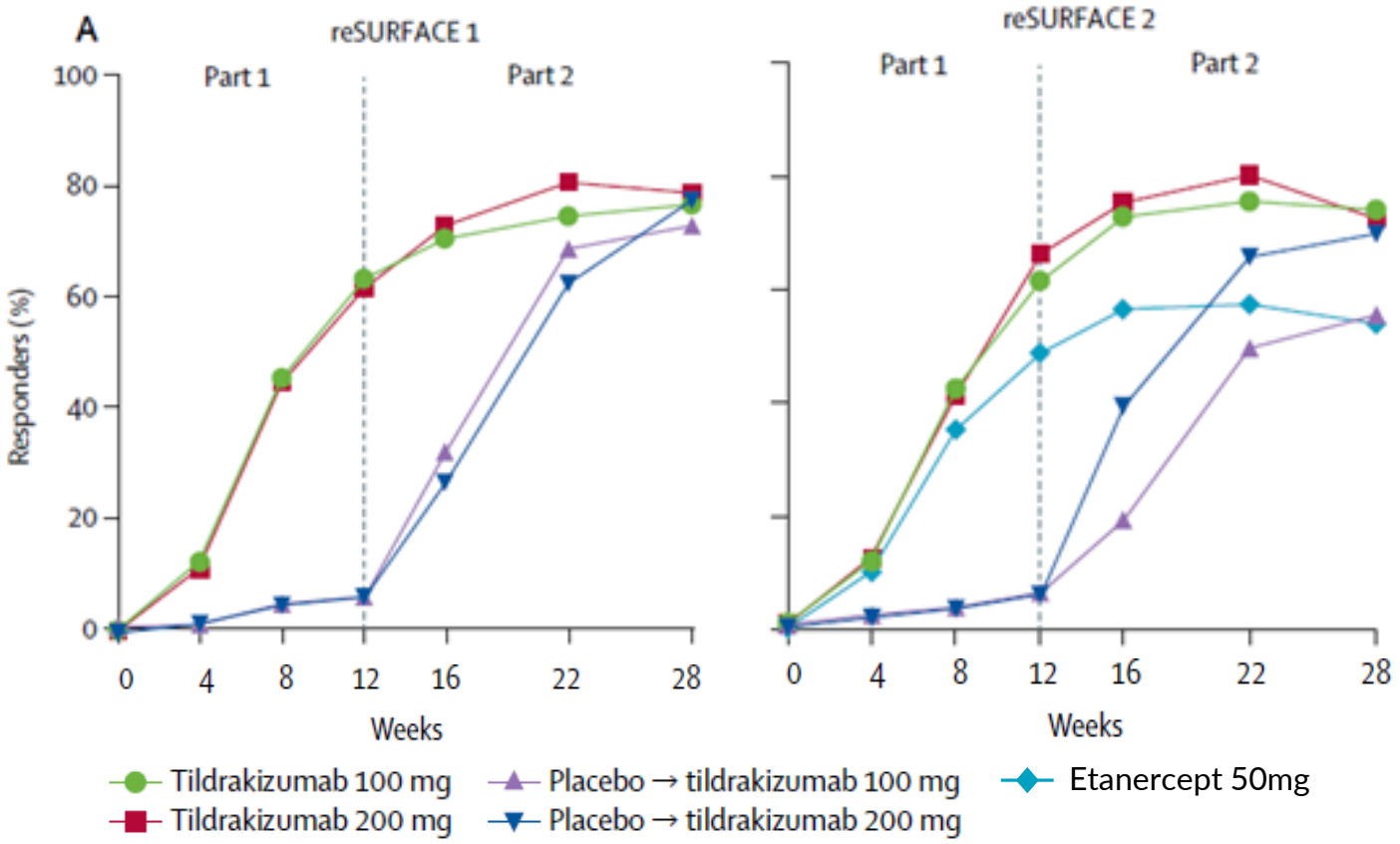
Treatment response assessment: ustekinumab

	Tildrakizumab	Ustekinumab
NICE stopping rule	• ACD: 28 weeks	• 16 weeks
Dosing schedule	• 0, 4, 16, 28 weeks…	• 0, 4, 16, 28 weeks…
SmPC	'*Consideration should be given to discontinuing treatment in patients who have shown no response after 28 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 28 weeks.'*	'*Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.'*
Primary outcome (pivotal trials)	• Assessed at 12 weeks	• Assessed at 12 weeks
Model (time point of assessment)	• 14 and 28 weeks	• 16 weeks
Rationale	ACD: '…*evidence of clinically and statistically significant improvement in outcomes with tildrakizumab at 28 weeks compared with 12 weeks… response to tildrakizumab should be assessed at 28 weeks to avoid the possibility of people switching from effective treatment*.'	'*the Committee noted that the response should be measured at 16 weeks for ustekinumab, rather than at 12 weeks as defined for etanercept in TA103, and that this measurement should be carried out before the third (16-week) dose is given*.'

Meta-analysis results – ERG PASI75 forest plot



Proportion of patients achieving PASI 75



Part 1: placebo-controlled. **Part 2**: participants in placebo arms switch to tildrakizumab.

Tildrakizumab PASI75 response rate increases between week 12 and week 28

Stopping rule 12 weeks vs 28 weeks

- Summary of Product Characteristics: "*Consideration should be given to discontinuing treatment in patients who have shown no response after 28 weeks of treatment"*
- Company comment:
  "*it would be biologically implausible, evidentially premature, and clinically burdensome to specialists and patients, to implement an assessment and stopping rule at week 12*"
- The primary endpoints of both trials are measured at 12 weeks
- Economic analysis uses treatment assessment at 28 weeks

Considering the transitions between PASI groups at the 2 time points, many people who do not achieve PASI75 score at week 12 go on to achieve PASI75 by week 28

Results from pooled reSURFACE1 and 2 population who received tildrakizumab 100mg

Comparators

ACD: *"The clinical expert explained that these options [apremilast and dimethyl fumarate] were rarely used in practice because they are perceived to be less effective than biologicals. The committee concluded that apremilast and dimethyl fumarate were not relevant comparators to tildrakizumab."*

Comparator companies:

- Apremilast and dimethyl fumarate should be included as comparators
  - They have a significant market share. *IQVIA syndicated patient record service moving annual total* data to October 2018 indicates that almost [redacted]
  - of patients starting a targeted systemic therapy (including biologics, apremilast and dimethyl fumarate) for the first time, started on apremilast.
  - They are recommended by NICE for the same patient population
  - They have been included in recent appraisals as comparators (TA511)
  - Apremilast is an established treatment the NHS with real-world evidence supporting its effectiveness

Company: revised base case

Company revised base case:

- Takes into account all committee preferences
- **Includes a revised and approved Patient Access Scheme**

No cost effectiveness results presented in public part of meeting because there are confidential patient access schemes available for brodalumab, ixekizumab, secukinumab and guselkumab