Fremanezumab for preventing migraine

Lead team presentation

Malcolm Oswald (lay), Andrew Hitchings (clinical), Rob Hodgson (cost)

ERG: PenTAG

Technical team: Gary McVeigh, Thomas Paling, Caron Jones, Jasdeep Hayre

Company: Teva UK

22nd October 2019
Key issues

- Will fremanezumab treatment effect continue indefinitely after treatment is stopped?
- Would treatment be restarted if treatment effect (after stopping) diminishes?
- The model time horizon should be: 10 years or lifetime?
- How is the treatment effectiveness (effect on monthly migraine days) of fremanezumab and best supportive care expected to change after treatment stops?
- Are quality of life improvements beyond that achieved by reducing monthly migraine days plausible for people on treatment?
- Should the high frequency episodic migraine subgroup be considered separately to episodic and chronic migraine?
- What proportion of people will self-administer fremanezumab: 100%; 95%; 90%?
- Is there sufficient evidence to support a benefit for fremanezumab over onabotulinumtoxin A?
- Would fremanezumab be considered as an option once onabotulinumtoxin A has been used?
- Equality considerations
Migraine

- Headache disorder with recurring attacks usually lasting 4–72 hours
- Often accompanied by nausea, vomiting, sensitivity to light/sound
- Factors triggering attacks can include stress, change in sleep pattern, overtiredness, menstruation, caffeine/alcohol consumption
- Prevalence 5-25% in women; 2-10% in men

Classification

<table>
<thead>
<tr>
<th>Monthly headache days (MHD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 +</td>
</tr>
</tbody>
</table>

- **Whole population**
- **Episodic migraine: <15 MHD**
  - Low frequency: 0–7 MHD
  - High frequency: 8–14 MHD
- **Chronic migraine ≥15 MHD with ≥8 monthly migraine days (MMD)**
Fremanezumab (Ajovy, Teva)

<table>
<thead>
<tr>
<th>Description of technology</th>
<th>Fremanezumab (Ajovy, Teva) is a fully humanised monoclonal antibody that inhibits the action of calcitonin gene-related peptide (CGRP) which is believed to transmit signals that can cause severe pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marketing authorisation</td>
<td>Fremanezumab is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month</td>
</tr>
</tbody>
</table>
| Dosage and administration | Fremanezumab is administered by subcutaneous injection and has two dosing options available:  
• 225 mg once monthly (monthly dosing) or,  
• 675 mg every three months (quarterly dosing)  |
| List price                | The list price of fremanezumab is £450 per 225 mg injection (£1350 per 675 mg). Costs may vary in different settings because of negotiated procurement discounts |
# Background

<table>
<thead>
<tr>
<th>Comparators</th>
<th>Best supportive care episodic migraine [EM] and chronic migraine [CM] onabotulinumtoxin A [OBA] CM only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroups</td>
<td>High-frequency episodic migraine HFEM</td>
</tr>
<tr>
<td>Main clinical trial</td>
<td>FOCUS: compared fremanzumab with placebo in adults with migraine EM or CM who had 2 to 4 failed preventative therapies</td>
</tr>
</tbody>
</table>

## Key Results

**Comparison with OBA**

Network meta-analysis in chronic migraine

**Model**

Semi-Markov model. 28 MMD health states → model split by responders and non-responders → non-responders discontinue → exclusive cost and utilities for each MMD health state → MMDs driven by response status

**Company ICER**

|----------------|-------------|-------------|---------------|--------------|

**Technical teams most plausible ICER**

<table>
<thead>
<tr>
<th></th>
<th>EM: £53,309</th>
</tr>
</thead>
<tbody>
<tr>
<td>CM v BSC</td>
<td>£21,529</td>
</tr>
<tr>
<td>CM v OBA</td>
<td>Dominated</td>
</tr>
</tbody>
</table>
## Key trial results

**FOCUS trial efficacy outcomes at week 12**

<table>
<thead>
<tr>
<th></th>
<th>Episodic migraine</th>
<th>Chronic migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=**)</td>
<td>Frem 3-mthly (n=**)</td>
</tr>
<tr>
<td><strong>Mean monthly migraine days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (SD)</td>
<td>****</td>
<td>****</td>
</tr>
<tr>
<td>LSM change (95% CI)</td>
<td>****</td>
<td>****</td>
</tr>
<tr>
<td>Difference vs placebo (95% CI)</td>
<td>****</td>
<td>****</td>
</tr>
<tr>
<td><strong>Patients with at least 50% reduction in monthly average migraine days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responder rate (n)</td>
<td>****</td>
<td>****</td>
</tr>
<tr>
<td>Odds ratio vs placebo (95% CI)</td>
<td>****</td>
<td>****</td>
</tr>
<tr>
<td><strong>Mean monthly days of use of any acute headache medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (SD)</td>
<td>****</td>
<td>****</td>
</tr>
<tr>
<td>LSM change (95% CI)</td>
<td>****</td>
<td>****</td>
</tr>
<tr>
<td>Difference vs placebo (95% CI)</td>
<td>****</td>
<td>****</td>
</tr>
</tbody>
</table>

Source: adapted from tables 25 and 29 company submission. Note: LSM = log-square mean
Economic model

- Semi-markov model
- EM and CM are analysed separately with dedicated input parameters for each
- People in the model are split into treatment responders and non-responders
  - Responders remain on treatment and non-responders discontinue
- Cost and utilities are exclusive to each health state
  - Separately calculated for responders and non-responders based on the proportion of patients in each MMD health state

![Diagram of the Markov Model with 28 health states](image)
Patient perspectives

Comments: Migraine Trust (based on 1,838 survey responses), OUCH (UK), patient

Migraine:
- Throbbing headaches with many other potential symptoms (e.g. visual, sensory, nausea, fatigue)

Especially debilitating when chronic:
- “I had to give up work because of chronic migraine four years ago. There are days when I feel useless, hopeless and a failure”
- “Chronic migraine infiltrates all parts of my life. On the odd day when I'm not in pain, I worry about being in pain.”
- “I developed bad anxiety and depression with suicidal thoughts”

Current treatment experience
- 67% of people living with migraine had tried five or more NHS treatments
- Only 19% of chronic migraine respondents were happy with treatment now
- “The preventative medicines have side effects which actually outweigh any positive impact they have on reducing the pain”
- There is a need a preventative treatment that reduces MMDs
Advantages of Fremanezumab
• “...can significantly reduce the frequency and severity of migraine attacks”
• faster rapidity of onset compared with current preventative treatments
• well tolerated → improves wellbeing and quality of life
• single monthly or quarterly treatment (unlike Botox, which requires multiple injections by a healthcare professional)
• Reduced use of acute treatments and painkillers → alleviates headaches induced by medication overuse

Disadvantages
• Potential injection site reactions and phobias
• Long-term tolerability unknown
Clinician perspectives

Submissions:
• Association of British Neurologists (ABN)
• British Association for Study of Headache (BASH), 2 submissions

Current treatment experience
• “very significant unmet need”
• “Headache services are extremely patchy... neurologists are extremely busy and oversubscribed”

Fremanezumab experience:
• Self-administered monthly injections: better compliance and less burden on healthcare resources compared to Botox
• “Patients will require injection training that could best be provided through industry support”
• “As the treatment is expensive, it is reasonable to restrict to those who have failed three treatments”
• Stop after three months if migraine days not reduced by 30%...re-evaluation after one year
• “Overall benefit will fall off following stopping”
Outstanding issues after technical engagement

- **Issue 1:** Treatment stopping rules [slides 12-14]
- **Issue 2:** Model time horizon [s15-17]
- **Issue 3:** Model utility values [s18]
- **Issue 4:** High frequency episodic migraine (HFEM) subgroup [s19]
- **Issue 5:** Resource use and costs [s20-21]
- **Issue 6:** Network-meta analysis in chronic migraine [s22-23]
- **Issue 7:** fremanezumab use post-onabotulinumtoxin A [s24]
**Issue 1: Treatment stopping rules**

**Background**

- **Company**: base-case assumes 20% stop treatment (every 64 weeks) following a positive response → indefinitely continuing treatment benefit (at zero cost) → reducing the ICER
  - **Technical team**: Lack of evidence to support the long-term efficacy and usage of fremanezumab → unrealistic to assume all treatment responders stop indefinitely
    - When migraines do not respond to treatment, treatment should be stopped

**Stakeholder comments: Company**

- Conservative to assume only 20% stop treatment following a positive response → expert opinion is that the majority will stop treatment within 2yrs
- Expert opinion suggests fremanezumab will control migraines → once control is gained, improvements will be maintained
- Restarting treatment is plausible
- Non-responders will stop treatment

**Stakeholder comments: Allergan (OBA)**

- Assuming continued efficacy at zero cost is highly optimistic → underestimates the ICERs
- After a loss of efficacy there may be a need for people to restart treatment
Issue 1: Treatment stopping rules

Stakeholder comments: Novartis (erenumab)
- Positive discontinuation scenarios were considered inappropriate in the appraisal of erenumab
- Evidence demonstrating maintenance of treatment effect upon positive discontinuation has not been provided

Stakeholder comments: professional groups
- Treatment is stopped after negative response OR when MMDs fall below 8 or 10
- ‘Drug holidays’ are recommended to determine if continued treatment is necessary
- Limited data follow those who discontinue following a positive response
- Treatment would be restarted (for a further 6 – 12 months) if effect diminishes

Stakeholder comments: NHSE
- “…agreement of and adherence to stopping rules is important”
  - At a minimum people should be assessed 3 months after initiating treatment → treatment stopped in non-responders
**Issue 1: Treatment stopping rules**

ERG comments:
- For people who respond to treatment after 12 weeks the need to continue therapy would then be assessed annually → in line with OBA
- The following is reasonable given current clinical practice and experience
  - An assessment period of 3 months to monitor migraine frequency
  - A proportion with continued treatment effect after stopping treatment
- Satisfied with the approach used to estimate the proportion (20%) positively stopping treatment each year, however, this figure is still uncertain
- Highly uncertain whether treatment effect will continue after stopping treatment
- Response rates from FOCUS can be used to implement a negative stopping rule

Final technical report judgements:
- Assuming continued treatment effectiveness after stopping treatment is unrealistic and is not supported by evidence → assuming continued effectiveness at zero cost is optimistic and underestimates the ICER
- Treatment would likely be restarted if MMDs increase after stopping treatment

• After stopping treatment would the benefit continue indefinitely?
• Would treatment be restarted if treatment effect (after stopping) diminishes?
Issue 2: Model time horizon

Background
- Company used a 10 year time horizon in its base-case
- Tech team stated a preference for a lifetime time horizon
  - In the company’s model people discontinuing fremanezumab reverted to BSC MMDs → this is overly optimistic and resulted in unrealistic lifetime ICERs
  - The ERG explored the implications of using a lifetime horizon in 2 scenarios:
    - **Scenario A:** Assuming people who respond to fremanezumab revert to baseline fremanezumab MMDs after stopping treatment (with or without linear waning of the BSC effect over 5yrs)
    - **Scenario B:** Reverting to BSC MMDs after discontinuation but also applying BSC responder/non-responder rates where non-responders revert to baseline

Stakeholder comments: Company
- All meaningful benefits and costs are sufficiently captured by 10 years
- Data not available to model the natural history of migraine → extending time horizon increases modelling uncertainty
- The company considered the ERG scenarios (above) exploring a lifetime horizon:
  - **Scenario A:** “not clinically justifiable” that people who respond to frem would revert to baseline (non-responder) MMDs
  - **Scenario B:** “is a more reasonable and justifiable approach”
Issue 2: Model time horizon

Stakeholder comments: Allergan
- Lifetime model time horizon less appropriate given the uncertainty in key model assumptions → a shorter time horizon would result in more robust estimates

Stakeholder comments: Novartis
- Lifetime horizon was preferred in the appraisal of erenumab

Stakeholder comments: professional groups
- Lifetime horizon preferable, 5 yrs reasonable (difficult to model natural history)

Stakeholder comments: NHSE
- Lifetime horizon is reasonable

ERG comments:
- A 10-year time horizon is reasonable to capture most costs and benefits as longer time horizons require extrapolation of short term data
- Extending the time horizon exacerbates uncertainty in the model

Final technical report judgements:
- Lifetime time horizon is preferred

• The model time horizon should be: 10 years or lifetime?
### Issue 2: Model time horizon

*Post all-cause discontinuation scenarios*

#### Background
- Lifetime ICERs using the company model were unrealistic
- After discontinuation (per-cycle) treatment effectiveness was maintained long-term
- ERG scenarios adjust treatment effect after stopping → more realistic ICERs

<table>
<thead>
<tr>
<th>Scenario A</th>
<th>Scenario A (BSC effect waning)</th>
<th>Scenario B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fremazumab non-responder</strong></td>
<td>Residual effect over frem baseline MMDs (1 fewer MMDs than baseline)</td>
<td></td>
</tr>
<tr>
<td><strong>Fremazumab responder</strong></td>
<td>Continues treatment full fremazumab effect (-7 MMDs [EM]; -9 MMDs [CM])</td>
<td></td>
</tr>
</tbody>
</table>
| **Fremazumab responder: following per cycle discontinuation** | Revert to baseline fremazumab MMD  
  • baseline = 16 MMDs for responders | Revert to BSC responder/non-responder MMDs  
  • responders (see below)  
  • non-responders revert to BSC baseline |
| **BSC responder** | Maintain BSC responder MMDs (-7 MMDs [EM]; -8 MMDs [CM]) | Revert to baseline BSC non-responder MMDs (effect linearly waned over 5 years) |
| **BSC non-responder** | Remain at baseline BSC MMDs | Maintain BSC responder MMDs (-7 MMDs [EM]; -8 MMDs [CM]) |

*What is the most plausible assumption after all-cause discontinuation?*
### Issue 3: Model utility values

**Company**
- Mapped from the Migraine-Specific Quality of Life Questionnaire (MSQoL) to EQ-5D-3L
- Clinical experts stated there was anecdotal evidence to support an additional utility premium (benefit) for people on treatment

**Technical team**
- Insufficient evidence to support an on treatment utility benefit
- Requested utility values at engagement:
  1. Re-analysed base-case utility values accounting for baseline characteristics
  2. EQ-5D-5L mapped to EQ-5D-3L

**Company**
- MSQoL is the most appropriate quality of life (QoL) measure
- EQ-5D misses QoL impacts
- Evidence of on treatment utility benefits from FOCUS and experts

**Allergan**
- Improvements in QoL beyond reductions in MMDs on OBA

**Professional groups**
- Preventatives reduce severity and duration of migraines
- HIT-6 and MIDAS are preferred

**ERG comments:**
- MSQoL is more appropriate than HIT-6 and MIDAS in this population
- Using utility data mapped from MSQoL instead of EQ-5D-5L is reasonable
- Unclear if additional HRQoL benefits were not captured by the MSQoL

**Final technical report judgements:**
- On and off treatment utility values should be equivalent → no additional benefit

**Are on treatment QoL improvements beyond that achieved by reducing MMDs plausible?**
**Issue 4: High-frequency episodic migraine subgroup**

**Background**
- The HFEM subgroup has particularly high unmet need as they are not eligible for OBA (CM only)
- No consensus on the definition of HFEM
- HFEM subgroup from FOCUS is from a post-hoc analyses

**Stakeholder comments: Company**
- HFEM can be defined as between 8 and 14 MMDs
- HFEM subgroup is recognised and clinically distinct
- HFEM has a substantial QoL impact with limited treatment options → high unmet need
- Lack of definition should not prevent consideration

**Stakeholder comments: Allergan**
- There is no agreed definition for HFEM

**Stakeholder comments: Novartis**
- HFEM not considered in the erenumab appraisal

**Stakeholder comments: Professional groups**
- HFEM is recognised and is challenging to treat
- HFEM is believed to cause similar disability to CM

**Stakeholder comments: NHS England**
- HFEM is 10 or more (within the EM definition < 15)

**ERG comments:**
- Experts advice: HFEM is clinically relevant and biologically distinct from CM

**Final technical report judgements:**
- HFEM does not need separate consideration

*Should HFEM be considered separately to episodic and chronic migraine?*
**Issue 5: Resource use and costs**

**Background**
- Company: assumed that 100% of people self-administer fremanezumab
- Technical team: it’s appropriate to assume an administration cost for (10%) of people receiving fremanezumab

**Stakeholder comments: Company**
- Assuming 10% need their treatment administered is too high → 5%, in line with expert opinion, should be explored
- Changing this assumption has a negligible impact on the ICER

**Stakeholder comments: Allergan**
- A better reflection of real world resource use would assume:
  1. people won’t self-administered from the start
  2. some will need treatment administering for them
  3. compliance and response will be monitored

**Stakeholder comments: Novartis**
- Needle phobic patients won’t be able to self administer
- The clinical trials do not demonstrate any self administration
- Fremanezumab needs appropriate storage (refrigeration)

**Stakeholder comments: Professional groups**
- 5% / 10% may need their treatment administered
- Vast majority will self-administer (>95%)

**Stakeholder comments: NHS England**
- Reasonable to assume some will not be able/willing to self-administer → exact proportion unknown
Issue 5: Resource use and costs

ERG comments:
• Scenarios provided where:
  – 5% or 10% cannot self-administer fremanezumab
  – A weighted cost for oral and injectable triptan was modelled

Final technical report judgements:
• Assuming all people receiving fremanezumab will be able/willing to self-administering treatment is unrealistic → assuming 10% of people have their treatment administered is reasonable
• Applying an administration cost has a minimal impact on the ICER

What proportion of people will self-administer treatment: 100%; 95%; 90%?
Issue 6: Network meta-analysis for chronic migraine

**Background**
- No direct comparison of frem and OBA in CM
- Concerns with the evidence in the NMA limit its robustness
  - Placebo-adjusted analysis requested
- Improvements estimated from the NMA are not statistically significant
  - Equal efficacy should be considered
- Concern that prior OBA use could bias results
- Assuming equivalence in monthly headache days (MHDs) and MMDs may flatten response

**Stakeholder comments**

**Company**
- No RCT data → NMA is the best evidence available
- Placebo-adjusted NMA was not feasible
- Different assessment time points (24 weeks [OBA] and 12 weeks [FOCUS) and outcomes (reduction in MHDs [OBA] and reduction in MMDs [FOCUS]) favour OBA → NMA effect estimate is conservative
- NMA shows additional benefit for frem across all endpoints despite data limitations → assuming equal efficacy is unreasonable
- NMA effect estimates which were not statistically significant have been accepted in previous appraisals
- Concern that prior OBA use could bias results
- Assuming equivalence in monthly headache days (MHDs) and MMDs may flatten response
- Due to data limitations MHDs and MMDs assumed equivalent → reduction in MHDs is easier to achieve than MMDs → this assumption could underestimate frem relative efficacy
Is there sufficient evidence to support a benefit for fremanezumab over OBA?

**Issue 6: Network meta-analysis for chronic migraine**

**Stakeholder comments: Allergan**
- No robust evidence that fremanezumab is more clinically effective than OBA
- Data limitations prevent a robust indirect comparison

**Stakeholder comments: Novartis**
- Same NMA limitations as in erenumab v OBA NMA (not accepted by committee)
- No robust evidence of a treatment benefit over OBA

**Stakeholder comments: Professional groups**
- No head to head studies → relative efficacy is unknown
- Assuming equivalence of MHDs and MMDs is unreasonable → different severity
- No evidence of benefit, however patients may prefer frem administration

**ERG comments:**
- Frem effectiveness (compared to OBA) appears reduced for people previously treated with OBA
- Reasonable to assume MHDs are equivalent to MMDs
- Scenario provided assuming equal the efficacy of frem and OBA

**Final technical report judgements:**
- Estimates from the NMA are not robust
- The possibility of no comparative benefit cannot be ruled out
Issue 7: Use of fremanezumab after OBA (CM)

Background
- Fremanezumab is positioned as a treatment option after 3 or more failed preventative therapies
- FOCUS included patients who had previously received OBA at various lines of treatment that may not be available in England
- At technical engagement, company provided subgroup analyses of effectiveness of fremanezumab in those previously treated with OBA
  - Results: similar efficacy to full trial population; however, small patient numbers and uncertainty relating to how many preventative treatments those with prior-OBA exposure have failed

ERG comments:
- Efficacy appears reduced for participants who have had prior OBA treatment in the fremanezumab monthly group → differences in MMD changes versus placebo
  - Prior OBA use (****** v placebo); no prior OBA use (****** v placebo)

Final technical report judgements:
- There is clinical evidence to suggest that fremanezumab may be effective in a subgroup of people with CM who have had prior OBA
- No cost-effectiveness evidence provided to support this positioning

Would fremanezumab be considered as an option in those who have had OBA?
## Cost effectiveness results (1):

### Episodic migraine (frem v BSC)

<table>
<thead>
<tr>
<th>Scenario (issue)</th>
<th>Incremental costs (£)</th>
<th>Incremental QALYs</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company base case</td>
<td>❁❁❁❁</td>
<td>❁❁❁❁</td>
<td>£13,954</td>
</tr>
<tr>
<td>ERG fixes</td>
<td>❁❁❁❁</td>
<td>❁❁❁❁</td>
<td>£13,535</td>
</tr>
<tr>
<td>No positive stopping rule (1)</td>
<td>❁❁❁❁</td>
<td>❁❁❁❁</td>
<td>£20,214</td>
</tr>
<tr>
<td>Lifetime time horizon (2) [see slides 15,17]</td>
<td>❁❁❁❁</td>
<td>❁❁❁❁</td>
<td></td>
</tr>
<tr>
<td>Scenario A</td>
<td>❁❁❁❁</td>
<td>❁❁❁❁</td>
<td>£71,789</td>
</tr>
<tr>
<td>Scenario A (BSC effect waning)</td>
<td>❁❁❁❁</td>
<td>❁❁❁❁</td>
<td>£25,957</td>
</tr>
<tr>
<td>Scenario B</td>
<td>❁❁❁❁</td>
<td>❁❁❁❁</td>
<td>£8,933</td>
</tr>
<tr>
<td>No additional on treatment utility benefit (3)</td>
<td>❁❁❁❁</td>
<td>❁❁❁❁</td>
<td>£16,435</td>
</tr>
<tr>
<td>Administration costs for 10% (5)</td>
<td>❁❁❁❁</td>
<td>❁❁❁❁</td>
<td>£14,022</td>
</tr>
<tr>
<td>Technical team’s preferred ICER (all above + scenario A)</td>
<td>❁❁❁❁</td>
<td>❁❁❁❁</td>
<td>£243,684*</td>
</tr>
<tr>
<td>Technical team’s preferred ICER (all above + scenario A [BSC waning])</td>
<td>❁❁❁❁</td>
<td>❁❁❁❁</td>
<td>£53,309*</td>
</tr>
<tr>
<td>Technical team’s preferred ICER (all above + scenario B)</td>
<td>❁❁❁❁</td>
<td>❁❁❁❁</td>
<td>£16,902*</td>
</tr>
</tbody>
</table>

*probabilistic ICERs consistent with deterministic
# Cost effectiveness results (2):
*Chronic migraine (frem v BSC)*

<table>
<thead>
<tr>
<th>Scenario (issue)</th>
<th>Incremental costs (£)</th>
<th>Incremental QALYs</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company base case</td>
<td>*****</td>
<td>*****</td>
<td>£11,825</td>
</tr>
<tr>
<td>ERG fixes</td>
<td>*****</td>
<td>*****</td>
<td>£11,487</td>
</tr>
<tr>
<td>No positive stopping rule (1)</td>
<td>*****</td>
<td>*****</td>
<td>£16,951</td>
</tr>
<tr>
<td>Lifetime time horizon (2) [see slides 15,17]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scenario A</td>
<td>*****</td>
<td>*****</td>
<td>£194,498</td>
</tr>
<tr>
<td>Scenario A (BSC effect waning)</td>
<td>*****</td>
<td>*****</td>
<td>£12,078</td>
</tr>
<tr>
<td>Scenario B</td>
<td>*****</td>
<td>*****</td>
<td>£23,464</td>
</tr>
<tr>
<td>No additional on treatment utility benefit (3)</td>
<td>*****</td>
<td>*****</td>
<td>£13,363</td>
</tr>
<tr>
<td>Administration costs for 10% (5)</td>
<td>*****</td>
<td>*****</td>
<td>£11,881</td>
</tr>
<tr>
<td>Technical team’s preferred ICER (all above + scenario A)</td>
<td>*****</td>
<td>*****</td>
<td>Dominated</td>
</tr>
<tr>
<td>Technical team’s preferred ICER (all above + scenario A [BSC waning])</td>
<td>*****</td>
<td>*****</td>
<td>£21,529*</td>
</tr>
<tr>
<td>Technical team’s preferred ICER (all above + scenario B)</td>
<td>*****</td>
<td>*****</td>
<td>£43,754*</td>
</tr>
</tbody>
</table>

*probabilistic ICERs consistent with deterministic*
## Cost effectiveness results (3): 
### Chronic migraine (frem v OBA)

<table>
<thead>
<tr>
<th>Scenario (issue)</th>
<th>Incremental costs (£)</th>
<th>Incremental QALYs</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company base case</td>
<td>*****</td>
<td>*****</td>
<td>£16,227</td>
</tr>
<tr>
<td>ERG fixes</td>
<td>*****</td>
<td>*****</td>
<td>£16,118</td>
</tr>
<tr>
<td>No positive stopping rule (1)</td>
<td>*****</td>
<td>*****</td>
<td>£24,756</td>
</tr>
<tr>
<td>Lifetime time horizon (2) [see slides 15,17]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scenario A</td>
<td>*****</td>
<td>*****</td>
<td>£17,905</td>
</tr>
<tr>
<td>Scenario A (BSC effect waning)</td>
<td>*****</td>
<td>*****</td>
<td>£17,905</td>
</tr>
<tr>
<td>Scenario B</td>
<td>*****</td>
<td>*****</td>
<td>£18,700</td>
</tr>
<tr>
<td>No additional on treatment utility benefit (3)</td>
<td>*****</td>
<td>*****</td>
<td>£20,681</td>
</tr>
<tr>
<td>Administration costs for 10% (5)</td>
<td>*****</td>
<td>*****</td>
<td>£16,332</td>
</tr>
<tr>
<td>Equal efficacy frem v OBA (6)</td>
<td>*****</td>
<td>*****</td>
<td>Dominated</td>
</tr>
<tr>
<td>Technical team’s preferred ICER (all above + scenario A)</td>
<td>*****</td>
<td>*****</td>
<td>Dominated</td>
</tr>
<tr>
<td>Technical team’s preferred ICER (all above + scenario A [BSC waning])</td>
<td>*****</td>
<td>*****</td>
<td>Dominated</td>
</tr>
<tr>
<td>Technical team’s preferred ICER (all above + scenario B)</td>
<td>*****</td>
<td>*****</td>
<td>Dominated</td>
</tr>
</tbody>
</table>
## Scenario analyses: scenario A

<table>
<thead>
<tr>
<th>Scenario (issue)</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EM: frem v BSC</td>
</tr>
<tr>
<td></td>
<td>CM: frem v BSC</td>
</tr>
<tr>
<td></td>
<td>CM: frem v OBA</td>
</tr>
<tr>
<td>Company base case</td>
<td>£13,954</td>
</tr>
<tr>
<td></td>
<td>£11,825</td>
</tr>
<tr>
<td></td>
<td>£16,227</td>
</tr>
<tr>
<td>Tech team assumptions</td>
<td>£243,684</td>
</tr>
<tr>
<td></td>
<td>Dominated</td>
</tr>
<tr>
<td></td>
<td>Dominated</td>
</tr>
</tbody>
</table>

Starting from the technical teams preferred assumptions

<table>
<thead>
<tr>
<th>Scenario (issue)</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive stoppers restart if effect diminishes by 50%</td>
<td>Not reported</td>
</tr>
<tr>
<td>No administration costs</td>
<td>£242,644</td>
</tr>
<tr>
<td></td>
<td>Dominated</td>
</tr>
<tr>
<td>Administration cost for 5%</td>
<td>£243,134</td>
</tr>
<tr>
<td></td>
<td>Dominated</td>
</tr>
<tr>
<td>Weighted oral and injectable triptan costs</td>
<td>£240,933</td>
</tr>
<tr>
<td></td>
<td>Dominated</td>
</tr>
<tr>
<td>Use NMA frem v OBA effectiveness estimate</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
</tr>
</tbody>
</table>
## Scenario analyses: scenario A, BSC waning

<table>
<thead>
<tr>
<th>Scenario (issue)</th>
<th>ICER (£/QALY)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EM: frem v BSC</td>
<td>CM: frem v BSC</td>
<td>CM: frem v OBA</td>
</tr>
<tr>
<td>Company base case</td>
<td>£13,954</td>
<td>£11,825</td>
<td>£16,227</td>
</tr>
<tr>
<td>Tech team assumptions</td>
<td>£53,309</td>
<td>£21,529</td>
<td>Dominated</td>
</tr>
</tbody>
</table>

### Starting from the technical teams preferred assumptions

<table>
<thead>
<tr>
<th>Positive stoppers restart if effect diminishes by 50%</th>
<th>Not reported</th>
<th>£28,501</th>
<th>Not reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>No administration costs</td>
<td>£53,701</td>
<td>£21,432</td>
<td>Dominated</td>
</tr>
<tr>
<td>Administration cost for 5%</td>
<td>£53,190</td>
<td>£21,481</td>
<td>Dominated</td>
</tr>
<tr>
<td>Weighted oral and injectable triptan costs</td>
<td>£50,856</td>
<td>£19,239</td>
<td>Dominated</td>
</tr>
<tr>
<td>Use NMA frem v OBA effectiveness estimate</td>
<td>N/A</td>
<td>N/A</td>
<td>£40,053</td>
</tr>
</tbody>
</table>
## Scenario analyses: scenario B

<table>
<thead>
<tr>
<th>Scenario (issue)</th>
<th>ICER (£/QALY)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EM: frem v BSC</td>
<td>CM: frem v BSC</td>
<td>CM: frem v OBA</td>
</tr>
<tr>
<td>Company base case</td>
<td>£13,954</td>
<td>£11,825</td>
<td>£16,227</td>
</tr>
<tr>
<td>Tech team assumptions</td>
<td>£16,902</td>
<td>£43,754</td>
<td>Dominated</td>
</tr>
</tbody>
</table>

### Starting from the technical teams preferred assumptions

<table>
<thead>
<tr>
<th>Positive stoppers restart if effect diminishes by 50%</th>
<th>Not reported</th>
<th>£57,049</th>
<th>Not reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>No administration costs</td>
<td>£16,818</td>
<td>£43,568</td>
<td>Dominated</td>
</tr>
<tr>
<td>Administration cost for 5%</td>
<td>£16,860</td>
<td>£43,661</td>
<td>Dominated</td>
</tr>
<tr>
<td>Weighted oral and injectable triptan costs</td>
<td>£14,352</td>
<td>£41,677</td>
<td>Dominated</td>
</tr>
<tr>
<td>Use NMA frem v OBA effectiveness estimate</td>
<td>N/A</td>
<td>N/A</td>
<td>£42,179</td>
</tr>
</tbody>
</table>
Equality

*Migraine trust*
- Migraine can be classed as a disability
- Women are 3 times more likely to be affected by migraine
- Current access to migraine treatments varies across regions in England

*Company*
- Migraine is more common in women → approximately twice the migraine prevalence compared to men (18% vs 7%)
- Restricting access to fremanezumab disadvantages women to a greater extent

*Technical team*
- The technical team concluded that these are not issues that can be addressed by NICE guidance on fremanezumab
Key issues

• Will fremanezumab treatment effect continue indefinitely after treatment is stopped?
• Would treatment be restarted if treatment effect (after stopping) diminishes?
• The model time horizon should be: 10 years or lifetime?
• How is the treatment effectiveness (effect on monthly migraine days) of fremanezumab and best supportive care expected to change after treatment stops?
• Are quality of life improvements beyond that achieved by reducing monthly migraine days plausible for people on treatment?
• Should the high frequency episodic migraine subgroup be considered separately to episodic and chronic migraine?
• What proportion of people will self-administer fremanezumab: 100%; 95%; 90%?
• Is there sufficient evidence to support a benefit for fremanezumab over onabotulinumtoxin A?
• Would fremanezumab be considered as an option once onabotulinumtoxin A has been used?
• Equality considerations