NICE National Institute for Health and Care Excellence

**Slides for public – all confidential data redacted**

# Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

# Lead team presentation

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ERG: Aberdeen

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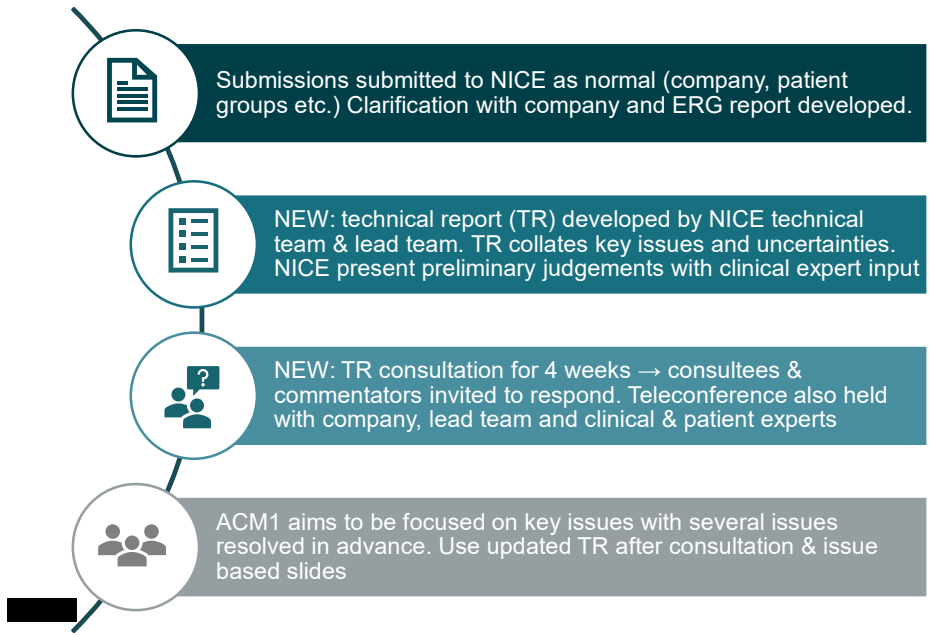
Company: Shire (now part of Takeda)

6th June 2019

# New STA process



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# Key issues

Model driver

## Issue 1: Positioning of lanadelumab [LANA] (generalisability)

- Should current C1-INH NHSE criteria for selected people only be used to define company's proposed lanadelumab positioning (severe disease)?
- Can results from HELP-03 be generalised to company's proposed positioning?
- Should subgroup results (≥8 attacks per month) be used for LANA cost-effectiveness?

## Issue 2: Comparator (C1-INH treatment)

- Is it plausible to assume [redacted] have Berinert and [redacted] have Cinryze?
- Should a weighted dose or fixed dose (1000IU) be assumed for Berinert?

## Issue 3: Long-term dose reduction for lanadelumab

- Is it plausible to assume 77% are on a lower dosing frequency after 1 year?
- Does this also apply to company's proposed positioning (severe disease)?

## Issue 4: Subsequent prophylactic treatment & continued treatment effect

- Is it appropriate to assume a continued treatment effect over time for LANA?
- Is it appropriate to assume all people having C1-INH will continue for a lifetime, and if LANA is stopped people will switch to C1-INH?
- Is it acceptable to use discontinuation rates from HELP-03?
- A stopping rule is used in current C1-INH NHSE criteria, does this need to be considered?

[redacted]

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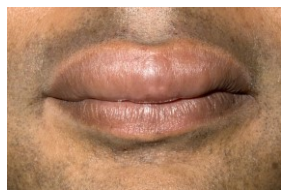
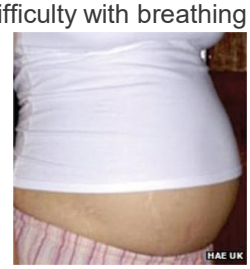
# Hereditary angioedema (HAE)

- HAE is a rare genetic disorder, associated with the deficiency of the protein C1-esterase inhibitor, which is a regulator of inflammatory pathways.
- It is estimated that HAE affects between 1 per 50,000 to 1 per 100,000 of the population.
- Most cases develop in childhood and some cases develop in early adulthood. HAE usually occurs during the first 10 to 20 years of life.
- In patients with HAE, at times of physiological or psychological stress, the function of the C1-esterase inhibitor is insufficient, resulting in the accumulation of excessive fluid (oedema) and localised oedematous swellings
- The swellings usually occur in the mouth, the gut (affecting the submucosal tissues) and the airway, causing difficulty with breathing (with potential asphyxia) and severe pain in the stomach





# Lanadelumab (Takhzyro, Shire)

Cross-reference

| | |
|---|---|
| **Marketing authorisation** | Routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older |
| **Administration** | Subcutaneous injection |
| **Dosing** | The recommended starting dose is 300 mg lanadelumab **every 2 weeks**. In patients who are stably attack free on treatment, a dose reduction to 300 mg lanadelumab **every 4 weeks** may be considered, especially in patients with low weight. |
| **Price** | List price of £12,420 per 300 mg vial has been approved by the Department of Health and Social Care. PAS (simple discount) approved |

| | Marketing authorisation | HELP-03 trial | NHS England commissioning policy for long-term prophylactic C1-INH |
|---|---|---|---|
| **Population** | Routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older. | Patients with type I and II disease with **at least 1 attack in the preceding 4 weeks**. | Recommends long-term prophylactic C1-INH in selected people with disease that is not controlled (**2 or more significant angioedema attacks per week over 8 weeks**) with oral prophylactic treatment, or if oral treatment is not suitable. |

Differences in population is covered in Issue 1 of the technical report (see slide 18)

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# Background

| | |
|---|---|
| **Comparators**<br>Issue 2 | **Company**: C1-INH only (position after oral therapy for those eligible for C1-INH)<br>**Technical team**: acceptable because:<br>• LANA is positioned after oral therapy or where oral therapy is not suitable<br>• No trial evidence for no long-term prophylactic & unlikely to be cost-effective |
| **Clinical trial** | HELP-03 RCT (N=125)<br>• compares LANA vs. placebo in people ≥ 12 years with type I or II HAE and at least 1 attack in last month<br>• 3 doses: 300 mg 4-weekly (low frequency, n=29), 300 mg 2-weekly (high frequency, n=27), 150 mg 4-weekly (not included in SmPC, n=28) |
| **Key results** | Investigator-confirmed monthly attack rates:<br>LANA 300 mg 2-weekly: **0.257** (0.145 to 0.458); LANA 300 mg 4-weekly: **0.526** (0.358 to 0.771); placebo: **1.970** (1.640 to 2.358) |
| **LANA vs. C1-INH** | Network meta-analysis using HELP-03 and CHANGE (cross-over trial) |
| **Key result** | HAE attack rate ratio (fixed effects model):<br>LANA 300 mg 2-weekly vs. C1-INH: [redacted]<br>LANA 300 mg 4-weekly vs C1-INH: [redacted] |
| **Model** | Cohort model. 2 health states: 'Alive with HAE' & 'Dead'. |
| **Preferred ICER** | **Company**: LANA dominant (compared with C1-INH)<br>**Tech team**: Agree, but uncertain for company's positioning (severe disease) |
| **ICER uncertainties** | *ICERs for severe disease (≥ 8 attacks per month) not robust → small sample.*<br>*All ICERs substantially higher if ↓ people use Berinert or ↓ have LANA low dose frequency. Berinert dosing has largest impact.* |

# Patient and carer perspectives

- HAE is characterised by unpredictable and sporadic attacks of subcutaneous swelling which can occur anywhere and varies from mild to life-threatening if it affects airways
- There are no confirmed triggers for attacks, but some common triggers appear to include hormonal changes, stress and anxiety invasive procedures such as dentistry, minor surgery, infections
- Swellings reach a very large size in a short time – around 30 to 40 minutes – and then take 2 or more days to resolve
- Current treatments may be effective, but can be problematic (long-term prophylactic C1-INH requires venepuncture twice weekly, which can lead to reduced venous access as veins become damaged, and doesn't prevent breakthrough attacks [attacks despite long-term prophylaxis])

[redacted]

# Patient and carer perspectives

- Unpredictable HAE attacks can affect every area of life. This uncertainty requires people with the condition to carry medications for emergencies and to plan carefully when travelling
- Whilst most live normal lives, people with the condition are more likely to suffer from anxiety and depression due to fear of future attacks. Daily activities can be hampered due to fear of attacks.
- Families with children with HAE have to develop a number of strategies – school life, sports, trips away as well as avoidance of certain triggers.
- Self-administration of long term prophylactic treatment would be in addition to the practical measures patients already have in place to try to manage their condition.

***"C1-INH is good treatment but the inconvenience it caused by having to have it administered in hospital was huge and it started to impact on my work and social life…Being able to self-administer C1-INH at home is a huge life-changer…means I can carry on my life as normal"***

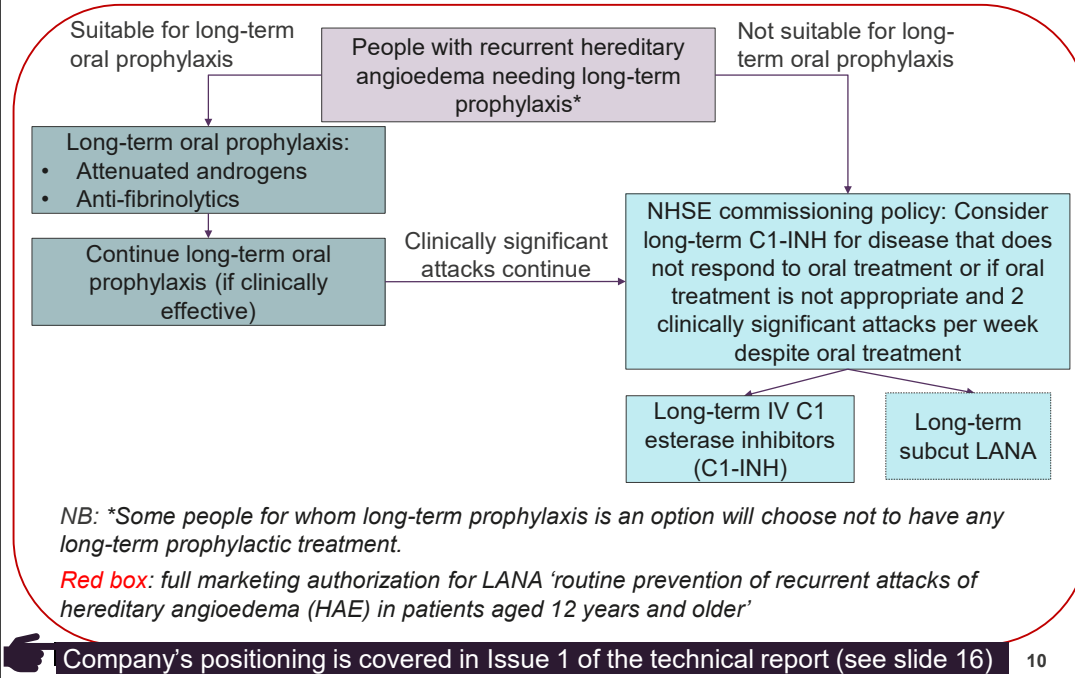
[redacted]

## Clinical expert perspective

- Treatment is individualised with the aim to reduce attacks and, ideally, become attack-free.
- Acute attacks are exacerbated by stress, some predictable (for example exams, surgery and dental treatment) and some unpredictable (for example “good stress” life events, such as weddings and holidays).
- People who have regular swelling and those at risk of severe swelling would be considered to benefit from long-term prophylactic treatment
  - In clinical practice, many patients have oral prophylactic treatment, such as attenuated androgens, but this is associated with side effects and limited effectiveness
  - C1-INH is used in line with the NHSE commissioning policy. It is primarily used as short-term prophylaxis (for example before surgery). Only a minority of patients take C1-INH as a long-term prophylactic treatment
- Changes to dosing frequency are made iteratively, but long-term reductions are currently achieved with oral prophylactic treatments in most people

[redacted]

# Treatment pathway



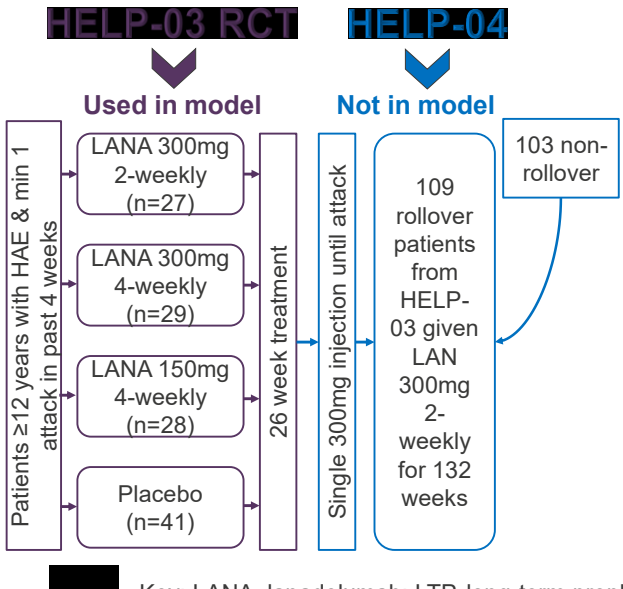

*NB: *Some people for whom long-term prophylaxis is an option will choose not to have any long-term prophylactic treatment.*

*Red box: full marketing authorization for LANA 'routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older'*

Company's positioning is covered in Issue 1 of the technical report (see slide 16)

# Clinical evidence summary (1)

Direct clinical trial evidence




Key: LANA, lanadelumab; LTP, long-term prophylactic

**HELP-03 RCT**

- 125 patients aged 12 years and older with types I or II HAE and **at least 1 attack (any severity)** in 4 week run-in period
- 4 treatment arms (3 LANA doses), no switches to alternative doses
- At baseline 90% type I HAE, mean 3.9 attacks in last month, 48% had previous C1-INH, 44% no previous LTP, 3% oral LTP and 52% have 3+ attacks in 4 week run-in
- Only 8% of attacks classed 'severe'

**HELP-04**

- On-going open-label extension from HELP-03 but also includes some new patients (non-rollover)
- Only used 2-weekly LANA dose (no lower dosing frequency arm)

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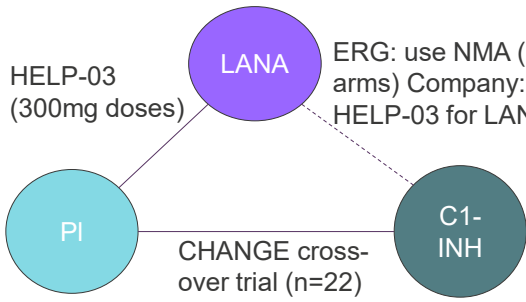
# Clinical evidence summary (2)

Indirect network meta-analysis (NMA)




- NMA diagram based on figure 13 in company submission (150mg dose not in SmPC)
- Company used Bayesian NMA of attack rate in fixed effects model (random effects not robust given small sample size). Use Woods (2010) adjustment to allow both HRs and count data in single analysis
- ERG not able to validate company's hazard ratios or standard errors for NMA, but broadly agree with approach

| | Monthly attack rate | |
|---|---|---|
| | HELP-03 (% change mean attack rate) | NMA (95% credible interval) |
| LANA 2-weekly vs. placebo | -86.9% (-92.8% to -76.1%) | [redacted] |
| LANA 4-weekly vs. placebo | -73.3% (-82.4% to -59.5%) | [redacted] |
| LANA 2-weekly vs. C1-INH | N/A | [redacted] |
| LANA 4-weekly vs. C1-INH | N/A | [redacted] |

[redacted] Key: LANA, lanadelumab; PI, placebo

*Note: Slide has been amended after Appraisal Committee Meeting*

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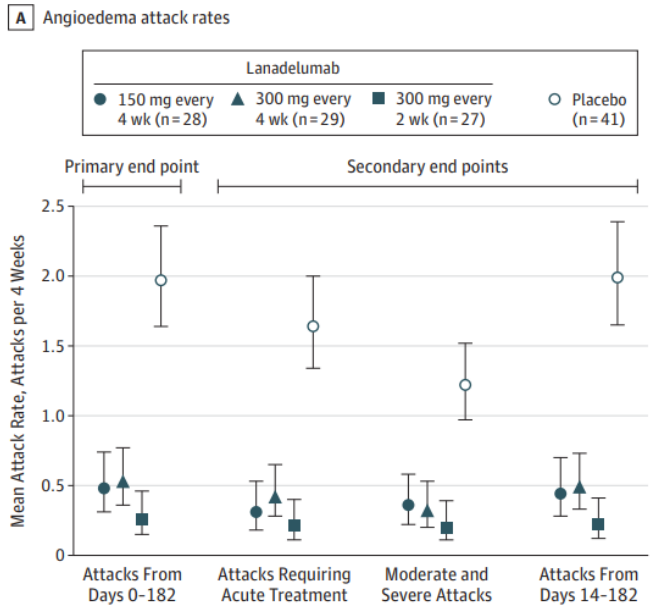
# Clinical evidence summary (3)




- Figure 3 in ERG report: primary and secondary endpoints in ITT population
- Attack rates are model-based mean attacks per month (error bar = 95%CI)
- Both 300mg doses of LANA met primary endpoint and showed statistically significant and clinically meaningful (>50%) reductions in number of HAE attacks during the treatment period compared with placebo

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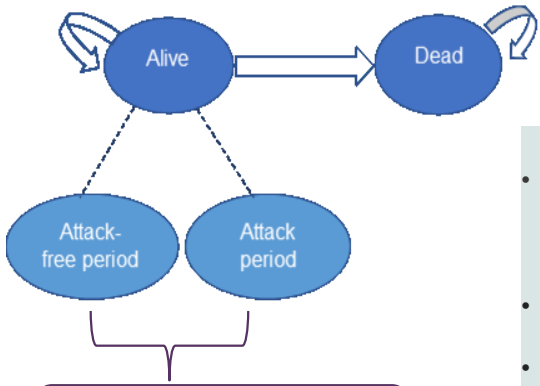
# Cost effectiveness summary (1)




1. Tech team prefer attack rates from NMA for both arms. Company use HELP-03

2. Company adjust attack rate ↑ if stop & switch treatment (instead of treatment specific rates for all)

[redacted]

## Company model

- Cohort approach with 2 heath states. Only attack frequency used (location of attack does not have important impact on quality of life)
- Attack disutility is based on average attack rate and severity (not location)
- After clarification, model allows subsequent treatment with C1-INH (if LANA is stopped)
- Model uses lifetime horizon (41 years at start from HELP-03 and run for 60 years)
- Discount rate 3.5%

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# Cost effectiveness summary (2)

| | Company revised base case | Tech team |
|---|---|---|
| Pop | LANA vs. C1-INH only | Agree |
| Treatment | • C1-INH: Cinryze [redacted], Berinert [redacted]<br>• 91% continue treatment for life (HELP-03)<br>• C1-INH stay on treatment. If LANA stopped, switch to C1-INH (no utility benefit for subcut admin) | Company assumption clinically plausible |
| Dose | **LANA lower dose frequency**: 44% after 6 months & 77% after 1 year.<br>**C1-INH**: no dose changes | Company assumption clinically plausible |
| Utility | Nordenfelt (2014) with added benefit for subcut admin. EQ-5D from HELP-03 is limited | Agree |
| Cost | • Resource use from clinical experts.<br>• Correct acute attack costs if switching from LAN to C1-INH<br>• £455 hospitalisation cost (for acute attack)<br>• Acute icatibant costs excluded. | Accept revised base case |

The only difference between company's revised base case & tech team preferred analysis is LANA treatment effect

⇩

**Company**: use HELP-03 data
**ERG:** concerned company apply rate ratio for C1-INH vs. placebo to estimate attack rate in C1-INH arm but use regression based attack rates from HELP-03 to estimate attack rate in LANA arm. Creates inconsistency in percentage reduction of attacks for LANA vs. C1-INH (company base case: [redacted] vs. [redacted] reduction in NMA). ERG prefer to use NMA for best estimate of treatment effect for LANA vs. C1-INH

⇩

**Tech team**: use NMA for both arms (attack rate adjusted for discontinuation/switching in LANA arm)

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# Issues resolved after technical engagement

| | Summary | Stakeholder responses | Technical team consideration | In updated base case? |
|---|---|---|---|---|
| 2 | **Comparator (positioning)**<br>**Company:** position LANA after oral therapy therefore only consider C1-INH a comparator.<br>**Clinical experts:** LANA could be used earlier in treatment pathway as an alternative to oral therapy<br>**NICE tech team:** Is no long-term prophylactic (LTP) an appropriate comparator? | ***Oral therapy***<br>**Company:** submitted new evidence showing cost-effectiveness [redacted]<br>***No LTP***<br>**Clinical experts:** although many patients may prefer no LTP to oral therapy, only small % eligible for C1-INH would choose not to have it<br>**Patient expert:** majority (85%) will choose to have long-term C1-INH | ***Oral therapy***<br>No trial evidence for oral LTP. Accept company's positioning after oral therapy<br>***No LTP***<br>Only small % choose not to have C1-INH, no trial evidence for no LTP & not cost-effective (see slide 24) | Company **x**<br>ERG **x**<br><br>Company **x**<br>ERG **x** |

⚠ NICE accept most relevant comparator is C1-INH → oral or no LTP not included in technical team's preferred assumptions for company's proposed positioning (severe disease)

[redacted] Proportion using Berinert vs Cinryze covered in issue 2, slide 23

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## Outstanding issues after technical engagement

- **Issue 1:** Positioning of LANA (generalisability)
- **Issue 2:** Comparator (C1-INH treatment) 
- **Issue 3:** Long-term dose reduction for LANA 
- **Issue 4:** Subsequent prophylactic treatment & continued treatment effect

# **Issue 1:** Positioning of LANA (generalisability)

**Background**

- Company position LANA after oral therapy (those currently eligible for C1-INH in the NHS England commissioning policy) but the full MA for LANA is wider (covered in slide 10)
- NHSE commissioning policy only recommends C1-INH in a severe disease group (≥2 attacks per week over 8 weeks). This definition differs compared with HELP-03 (at least 1 attack in last 4 weeks)
- HELP-03 did not specify previous treatment

See next slide for baseline characteristics in HELP-03

**Stakeholder comments**

- **Clinical experts:** Criteria for C1-INH in NHSE policy is well defined and followed in clinical practice. In HELP-03 some patients would have >1 attack in last 4 weeks and some people at baseline were having long-term prophylactic C1-INH at baseline (stopped for trial)
- **Royal College of Pathologists (RCPth):** should use same criteria as NHSE
- **UKPIN:** studies used to support NHSE policy had similar attack frequency to HELP-03

[redacted]

*Note: Slide has been amended after Appraisal Committee Meeting*

# **Issue 1:** Positioning of LANA (generalisability)

- In the HELP-03 trial, the average number of attacks of unspecified severity at baseline was 3.9 in the previous 4 weeks
- Inclusion criteria did not specify previous oral therapy or contraindication to oral therapy.

| Baseline characteristic | | Lanadelumab | | | |
|---|---|---|---|---|---|
| **HELP-03** | **Placebo** | **300mg q2w** | **300mg q4w** | **All LANA*** | **Total*** |
| Mean (SD) attacks in last 4 wks | 4.15 (3.98) | 2.96 (2.79) | 3.76 (3.51) | 3.79 (4.31) | 3.90 (4.19) |
| 1 to <2 run-in attack rate/month | 12 (29.3%) | 7 (25.9%) | 9 (31.0%) | 26 (31.0%) | 38 (30.4%) |
| 2 to <3 run-in attack rate/month | 8 (19.5%) | 6 (22.2%) | 5 (17.2%) | 14 (16.7%) | 22 (17.6%) |
| ≥ 3 run-in attack rate/month | 21 (51.2%) | 14 (51.9%) | 15 (51.7%) | 44 (52.4%) | 65 (52.0%) |
| Prior long term C1-INH only (%) | 22 (53.7%) | 9 (32.1%) | 18 (62.1%) | 38 (45.2%) | 60 (48.0%) |
| Oral therapy | 1 (2.4%) | 0 | 1 (3.4%) | 3 (3.6%) | 4 (3.2%) |
| C1-INH and oral therapy | 1 (2.4%) | 3 (11.1%) | 1 (3.4%) | 5 (6.0%) | 6 (4.8%) |
| No LTP use | 17 (41.5%) | 16 (57.1%) | 9 (31.0%) | 38 (45.2%) | 55 (44%) |
| * Includes 150mg q4w arm (not in MA and not considered relevant) | | | | | |

[redacted]

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# **Issue 1:** Positioning of LANA (generalisability)

**Company**

- Appropriate to position LANA for same population who would receive C1-INH (high unmet need). If NHSE criteria becomes less stringent over time, NICE rec and LANA data still relevant
- Efficacy not expected to vary by baseline attack rate (confirmed by clinical experts). Subgroup analyses from HELP-03 confirm this, but small patient numbers (not presented here).
- Scenario analysis using company's revised base case shows LANA is more cost-effective as baseline attacks increases

| Baseline attack rate (per 28 day cycle) | Incremental costs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|
| ≥ 8 attack | [redacted] | [redacted] | Dominant |

[redacted]

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# **Issue 1:** Positioning of LANA (generalisability)

## ERG comments

**Subgroup analyses**

- [redacted] from HELP-03 would be potentially eligible for C1-INH in the NHS England policy.
- Company's subgroup analyses (≥8 attacks per month) based on very small patient numbers

**Scenario analyses**

- ERG scenario analyses using NICE preferred assumptions and subgroup (≥8 attacks per month) show improved cost-effectiveness of LANA compared with full HELP-03 population
-  (see slides 35 and 36 for ICERs)

**Implementation issues**

- May be difficult for commissioners to monitor or enforce use of LANA for population currently eligible for C1-INH

[redacted]

*Note: Slide has been amended after Appraisal Committee Meeting*

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Key issue for cttee

# **Issue 1:** Positioning of LANA (generalisability)

**Technical report**

- Unclear whether NHSE criteria for long-term C1-INH reflects severe disease
- HELP-03 is the best available data source but uncertain whether results can be generalised to company's proposed positioning for those currently eligible for C1-INH
- The company's ICER for severe disease (8+ attacks per month) show LANA is dominant but may not be robust because of small patient numbers & did not include all tech team preferred assumptions

**NHSE criteria for long-term prophylactic C1-INH**

a) Individuals who fail, or are intolerant of oral prophylaxis and who experience **2 or more clinically significant attacks per week**, despite oral prophylaxis over a period of at least 56 days requiring treatment with c1 esterase inhibitor or icatibant.

b) Individuals in whom oral prophylaxis is contraindicated for example pregnant women, recognising that there are currently no other prophylactic treatment options during pregnancy and that there is increased risk of rapid deterioration in condition and additional risks to women during pregnancy.

Should current C1-INH NHSE criteria for selected people only be used to define company's proposed lanadelumab positioning (severe disease)?
Can results from HELP-03 be generalised to people with severe disease?
Should subgroup results (≥8 attacks per month) be used for LANA cost-effectiveness?

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# **Issue 2:** Comparator (C1-INH treatment)

**Background**
- Company assumes [redacted] have Berinert and [redacted] have Cinryze using hospital dispensing data from Jul-Sep 2018
- NICE technical team: based on short-term data but clinically plausible

**Stakeholder comments**
- **UKPIN:** varies between hospitals, no data but ongoing HAE network survey will capture this
- **Clinical experts**: varies, but likely to be used in approximately equal proportions

**Company**
- Aware of variation, base case assumptions using 3-month hospital dispensing data considered most robust but also report scenario analyses using 3-year data from the Hospital Pharmacy Audit ([redacted] for Berinert and [redacted] for Cinryze)

| Proportions | Revised base case ICER (£/QALY) |
|---|---|
| Base-case ([redacted] Cinryze IV: [redacted] Berinert IV) | Dominant |
| ([redacted] Cinryze IV: [redacted] Berinert IV) | Dominant |
| ([redacted] Cinryze IV: [redacted] Berinert IV) | Dominant |

In ERG model, when assume [redacted] have Berinert, ICER switches from being dominant to over £30,000 per QALY gained

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# **Issue 2:** Comparator (C1-INH treatment)

**ERG**:

- Agree C1-INH is comparator but some people eligible for C1-INH may not use or tolerate it and have no long-term prophylactic treatment. Consultation response from patient expert suggests 15% of those eligible for C1-INH may not use it
  - ICER for LANA vs. no long-term prophylactic treatment: >£2,500,000 per QALY gained

ERG identified additional issue relating to dosing of Berinert that has large impact on ICER (not covered in technical report at consultation stage, but covered in final technical report)

| Company | ERG |
|---|---|
| Berinert cost is based on dose [redacted] compared with 1000IU Cinryze (2 x 500IU vials) | • CHANGE trial used 1000IU dose of Cinryze → used to inform efficacy data for C1-INH<br>• Question whether same fixed dose (1000IU) would be used for Berinert & Cinryze long-term prophylaxis as they are both C1-INH<br>• Clinical expert to ERG: use 1000IU regardless of Berinert/Cinryze for long-term prophylaxis. Resistant symptoms may need higher dose<br>• Identified publication reporting Berinert Patient Registry data which identified 47 patients from USA and Europe having long-term prophylaxis with Berinert: median dose 1000IU (range 500 to 3000IU) or 13.77IU/kg<br>• ERG scenario analyses using 1000IU fixed dose & NICE preferred assumptions is £1,463,662 per QALY gained |

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# Issue 2: Comparator (C1-INH treatment)

**Additional clinical expert input (after technical engagement)**

- In clinical practice have used 1000IU dose for long-term prophylaxis with Berinert. When considering weight based dosing, would take into account vial sizes – would under-dose rather than use only part of a vial
- C1-INH prescribed in secondary care only (not prescribed or dispensed in primary care). Estimate around 15-25 people eligible for C1-INH in England.

**Other potential data sources**

- Prescribing data – company use HPAI data (prescribing in secondary care)
- NHS England – does NHSE collect any data around C1-INH use to monitor the commissioning policy?
- HAE network survey – raised as potential data source at technical engagement by UKPIN but no published data or details about this

**Technical report**

- There is variation in clinical practice but the company's base case (assumes that most people having C1-INH have Berinert instead of Cinryze as a long-term prophylactic treatment) is clinically plausible.
- It is unclear whether the company's long-term prophylactic dosing regimen for Berinert (based on weight) reflects current clinical practice. Using a fixed dose 1000IU is also clinically plausible

Is it plausible to assume [redacted] have Berinert and [redacted] have Cinryze?
Should Berinert be dosed by weight or as a fixed 1000IU dose?

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## **Issue 3:** Long-term dose reduction for lanadelumab

**Background**

- Company assumes 77% have lower frequency dosing (q4w) of LANA after 1 year using short-term freedom from attack data from HELP-03
- SmPC "lower dosing frequency may be considered in patients who are stably attack-free on treatment…especially in patients with low weight"

**Stakeholder comments**

- **Clinical experts, UKPIN:** can't predict accurately, but 77% is plausible.
- HAE attack rates vary over a patient's lifetime and dose frequency may need to be ↑ if HAE becomes more active, but would expect to lower again in future

**Company**

- 77% likely to be representative of more severe disease (NHSE criteria), based on new HELP-03 analysis of time to 1st attack after steady state with LANA is achieved (day 70 onwards) split by baseline attack risk (< 3 attacks vs. >3 attacks)
- Provides evidence that LANA is effective to treat more severe disease (also addresses Issue 1: generalisability of LANA evidence)

[redacted]

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# **Issue 3:** Long-term dose reduction for lanadelumab

For LANA → no diff between less severe (blue) and more severe group (green) in % staying attack-free

For placebo → more severe group (green) less likely to stay attack-free

[redacted]

## **Issue 3:** Long-term dose reduction for lanadelumab

**ERG**:

- This proportion is an assumption and was not directly observed in the clinical trial. Assumption based on short-term data from HELP-03 and there is no other external supporting or confirmatory evidence
- Company submitted figures only show no difference when defining severe disease as < 3 or > 3 attacks per month and highlight small numbers matching NHSE criteria

**Technical report**

- Company base case does not explicitly model changes in dosing frequency over time, but given that attack rates vary over a patients lifetime, it's reasonable to assume that at any given time, the majority of people having LANA with be on the lower frequency after 1 year
- Uncertain whether this can be generalised to patients with severe disease, which reflects the company's proposed positioning of LANA

Is it plausible to assume 77% having LANA are on a lower dosing frequency after 1 year? Does this also apply to company's proposed positioning (severe disease)?

[redacted]

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## **Issue 4:** Subsequent prophylactic treatment & continued treatment effect

**Background**

- Company assume LANA won't lose effectiveness over time. ERG, tech team & experts agree this is plausible for most people → optimistic CE results
- Company's revised base case:
  - If stop LANA, switch to C1-INH
  - Continue C1-INH in comparator arm
- Company assume 91% continue treatment over lifetime. ERG unclear why HELP-04 not used to inform discontinuation rates

**Stakeholder comments**

- **Clinical experts, UKPIN:** only small proportion develop non-response over time (5-10%).
- Agree no alternatives after C1-INH but if LANA is stopped C1-INH would be used

**Company**

- C1-INH rarely stopped because achieving a sub-optimal response still beneficial for patients with severe disease and no other treatment options (confirmed by experts)
- Discontinuation rates were based on HELP-03 but new evidence from longer-term HELP-04 show most people stayed on treatment

[redacted]

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## **Issue 4:** Subsequent prophylactic treatment & continued treatment effect

**HELP-04 discontinuation (interim data: May 2016 to Sept 2017)**

| HELP-04 | Rollover | Non-rollover | Total |
|---|---|---|---|
| **Number treated** | 109 | 103 | 212 |
| **Completed study** | 0 (0%) | 2 (1.9%) | 2 (0.9%) |
| **Ongoing (active study participation)** | 102 (93.6%) | 95 (92.2%) | 197 (92.9%) |
| **Discontinued** | 7 (6.4%) | 6 (5.8%) | 13 (6.1%) |

**ERG comments**

Continued treatment effect

- Optimistic to assume no one will lose treatment effect over time (for example due to antibodies) but company scenarios show results relatively robust to more pessimistic assumptions (see table 18 in company response to clarification, all ICERs dominant)

Subsequent treatment

- No change in ERG preferred assumptions

Discontinuation

- No change in ERG preferred assumptions

[redacted]

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## **Issue 4:** Subsequent prophylactic treatment & continued treatment effect

**Technical report**

- Only a small proportion are likely to develop non-response to lanadelumab, therefore it is acceptable to assume a continued treatment effect for lanadelumab over time. However, the model does not account for this non-response, therefore this assumption will result in optimistic cost-effectiveness results for LANA
- It is appropriate to assume C1-INH is continued over a lifetime
- If lanadelumab is stopped, it is acceptable to assume people will switch to C1-INH
- It is reasonable to use discontinuation rates from HELP-03 because the results are similar to longer-term data from HELP-04

[redacted]

## **Issue 4:** Subsequent prophylactic treatment & continued treatment effect

**NHSE criteria for long-term prophylactic C1-INH**

- After the first 6 months of treatment, the time between dosing should be gradually increased. If, at a dosing interval of one treatment per week, the symptoms remain below two or more clinically significant attacks per week a trial of treatment discontinuation should be commenced. If breakthrough attacks present above this level, the time between dosing should be reduced to regain adequate symptom control.
- If treatment is ineffective after two months (defined as a lack of reduction in attack frequency despite optimised treatment) then treatment with prophylactic C1-inhibitor should be discontinued and alternative therapy options considered.

1) Is it appropriate to assume a continued treatment effect over time for LANA?
2) Is it appropriate to assume all people having C1-INH will continue for a lifetime and if LANA is stopped, people will switch to C1-INH?
3) Is it acceptable to use discontinuation rates from HELP-03?
4) A stopping rule is used in NHSE criteria for using C1-INH, does this need to be considered for LANA (not included in model)?

# Outstanding uncertainties in evidence base

From table 10 in technical report → these are areas of uncertainty that cannot be resolved. Committee should be aware of these when making its recommendations.

| Issue | Why issue is important | Impact on ICER |
|---|---|---|
| Lack of direct comparative data | • no comparative data that directly compares LANA with C1-INH.<br>• The clinical effectiveness is uncertain because an indirect comparison was needed. | Results may be more uncertain→ the company used a fixed effects model due to small sample size, but random effects models show wider credible intervals. This uncertainty is not accounted for in the model. |
| Lack of long-term data on lower LANA dosing frequency | • no evidence on the long-term use of a lower lanadelumab dosing frequency because the HELP-04 open-label extension study did not use this dosing regimen. | The cost-effectiveness results may be optimistic. |

[redacted]

# Technical report summary of cost-effectiveness (section 1.6)

- **Technical team's preferred cost-effectiveness analysis**
  - LANA is dominant compared with C1-INH for the overall HELP-03 population with less severe disease (at least 1 attack per month).
  - ICERs for severe disease (8+ attacks per month) show improved cost-effectiveness for LANA but this is based on very few patient numbers so unlikely to be robust.
- **Uncertainty around ICER**
  - ICER for severe disease (8+ attacks per month) is similar to current C1-INH NHSE criteria but includes small patient numbers and may not be robust
  - The ICER for the overall HELP-03 population could be substantially higher if Berinert is given as a fixed 1000IU dose, if fewer people use Berinert, or if fewer people having LANA use lower dosing frequency
- **Overall conclusion**
  - Despite some uncertainty LANA could be cost-effective compared with C1-INH but some clinically plausible scenarios show ICERs substantially >£30,000 per QALY gained

[redacted]

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# Cost effectiveness results (with PAS) LANA vs. C1-INH

## Full HELP-03 population

| Scenario | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|
| **Company revised base case (ERG run)** | [redacted] | [redacted] | Dominant |
| Use rate ratios for LANA vs. placebo from NMA including adjusted attack rate (not HELP-03) | | | |
| **Technical team's preferred assumptions** | [redacted] | [redacted] | Dominant |
| Clinically plausible scenario issue 2 (comparator: [redacted] have Berinert) | | | |
| a) ERG scenario: [redacted] have Berinert | [redacted] | [redacted] | Dominant |
| b) ERG scenario: [redacted] have Berinert | [redacted] | [redacted] | £87,949 |
| c) ERG scenario: [redacted] have Berinert | [redacted] | [redacted] | £345,040 |
| d) Fixed 1000IU per Berinert infusion | [redacted] | [redacted] | £1,463,662 |
| Clinically plausible scenario issue 3 (long-term dose reduction for LANA: 77%) | | | |
| a) ERG scenario: 70% | [redacted] | [redacted] | Dominant |
| b) ERG scenario: 60% | [redacted] | [redacted] | £186,148 |
| c) ERG scenario: 50% | [redacted] | [redacted] | £593,866 |

*Company report incremental costs [redacted] and incremental QALYs [redacted] in revised base case but ERG could not replicate this

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# Cost effectiveness results (with PAS) LANA vs. C1-INH

## Subgroup with ≥8 attacks per month at baseline

| Scenario | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|
| **Company scenario** ≥8 attacks (per month) | [redacted] | [redacted] | Dominant |
| Use rate ratios for LANA vs. placebo from NMA including adjusted attack rate (not HELP-03) | | | |
| **Technical team's preferred assumptions** | | | |
| a) ≥8 attacks (per month) at baseline | [redacted] | [redacted] | Dominant |
| Clinically plausible scenario issue 2 (comparator: [redacted] have Berinert) | | | |
| a) ERG scenario: [redacted] have Berinert | [redacted] | [redacted] | Dominant |
| b) ERG scenario: [redacted] have Berinert | [redacted] | [redacted] | Dominant |
| c) ERG scenario: [redacted] have Berinert | [redacted] | [redacted] | £11,504 |
| d) Fixed 1000IU per Berinert infusion | [redacted] | [redacted] | £799,381 |
| Clinically plausible scenario issue 3 (long-term dose reduction for LANA: 77%) | | | |
| a) ERG scenario: 70% | [redacted] | [redacted] | Dominant |
| b) ERG scenario: 60% | [redacted] | [redacted] | Dominant |
| c) ERG scenario: 50% | [redacted] | [redacted] | £99,684 |

# Innovation and Equality

## Technical report

- The company considers lanadelumab to be innovative.
  - The technical team considers that all relevant benefits associated with lanadelumab are adequately captured in the model.
- The company states that C1-INH treatment is based on human or animal products that may not be acceptable to some people. No other equality issues were anticipated by the company, consultees and their nominated clinical and patient experts.
  - The committee will consider this issue when making its recommendations

[redacted]

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# Key issues

Model driver

## Issue 1: Positioning of lanadelumab [LANA] (generalisability)

- Should current C1-INH NHSE criteria for selected people only be used to define company's proposed lanadelumab positioning (severe disease)?
- Can results from HELP-03 be generalised to company's proposed positioning?
- Should subgroup results (≥8 attacks per month) be used for LANA cost-effectiveness?

## Issue 2: Comparator (C1-INH treatment)

- Is it plausible to assume [redacted] have Berinert and [redacted] have Cinryze?
- Should a weighted dose or fixed dose (1000IU) be assumed for Berinert?

## Issue 3: Long-term dose reduction for lanadelumab

- Is it plausible to assume 77% are on a lower dosing frequency after 1 year?
- Does this also apply to company's proposed positioning (severe disease)?

## Issue 4: Subsequent prophylactic treatment & continued treatment effect

- Is it appropriate to assume a continued treatment effect over time for LANA?
- Is it appropriate to assume all people having C1-INH will continue for a lifetime, and if LANA is stopped people will switch to C1-INH?
- Is it acceptable to use discontinuation rates from HELP-03?
- A stopping rule is used in current C1-INH NHSE criteria, does this need to be considered?

[redacted]

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