Contains redacted data

Slides for public – data redacted

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

ACM2 presentation (PART 1)

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ERG: Aberdeen

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Company: Shire (now part of Takeda)

7th August 2019

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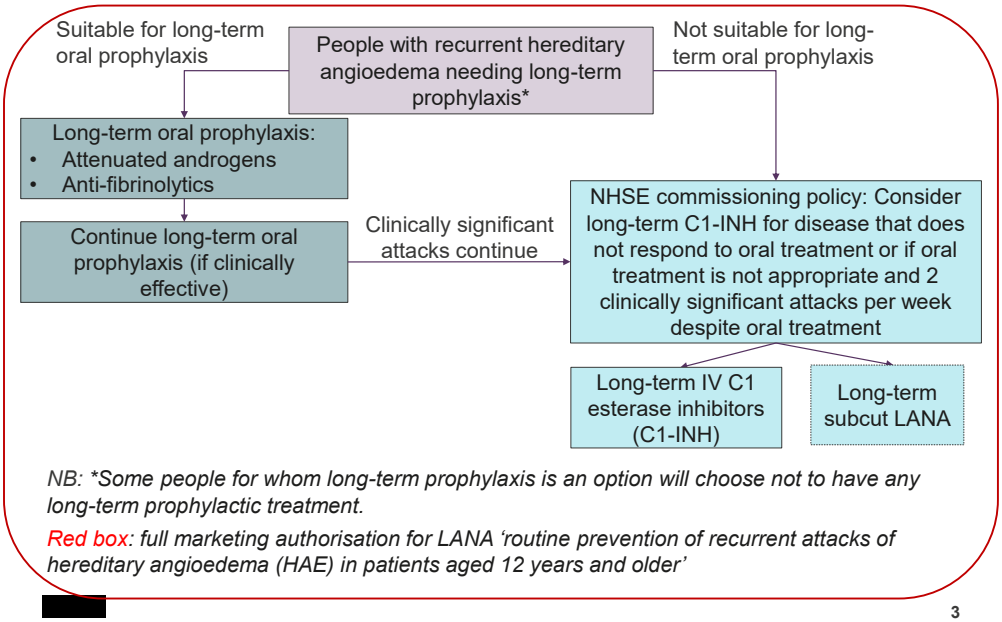
Key issues

- What is the most appropriate weekly dosing of Berinert?
  - Company's revised base case ([redacted] IU)
  - Company's clinical expert advisory board ([redacted] IU)
  - UKPIN data (2,781 IU)
- Are NHSE data on C1-INH use in line with committee's preferred assumption that 50% to 75% of people having C1-INH will have Berinert?
- Is 60.9% an appropriate lower bound for the proportion of people switching to a lower frequency of LANA dosing?

[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 authorisation for LANA 'routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older'

[redacted]

3

Lanadelumab (Takhzyro, Shire)

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. **Additional discount approved for ACM2**

	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.

[redacted]

4

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Cost effectiveness summary

	Company base case at ACM 1	Tech team
Pop	LANA vs. C1-INH only	Agree
Treatment	• C1-INH: Cinryze [redacted] Berinert [redacted] • 91% continue treatment for life (HELP-03) • 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. **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. • Correct acute attack costs if switching from LAN to C1-INH • £455 hospitalisation cost (for acute attack).	Accept base case

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

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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)

5

Summary of ACD

Section	Committee decision
Clinical effectiveness (3.4 to 3.7)	• The full HELP-03 population and the subgroup with 8 or more attacks over 4 weeks are relevant for decision making, but the latter is less robust • No long-term evidence on the use of LANA at its lower dosing frequency • indirect treatment comparison should be used to estimate the treatment effect for LANA and C1-INH
Cost effectiveness (3.8 to 3.14)	• A continued treatment effect for LANA is clinically plausible for most people, but assuming this for all people is optimistic • Plausible to assume 50% to 75% of people having C1-INH have Berinert • There is substantial uncertainty around the dosing schedule for Berinert and a fixed dose is clinically plausible • There is substantial uncertainty around the proportion of people having the lower dosing frequency of lanadelumab, but 77% would be the maximum
Results (3.17 & 3.18)	• The company's revised base case is not suitable for decision making • The estimates of cost effectiveness are considerably uncertain, and for some clinically plausible scenarios they are substantially higher than £30,000 per QALY gained
ACM2	Would like to see analyses with its preferred assumptions that incorporate the **lower price paid by the NHS for C1-INH** and **real-world data from NHS England about the dose and current use of Berinert**

ACD consultation summary

- Responses from 8 stakeholders (company, patient and clinical experts, NHS England [NHSE], British Association of Dermatologists [BAD], HAE UK, Royal College of Pathologists [RCP] & UK United Kingdom Primary Immunodeficiency Network [UKPIN] and 9 web comments

Theme	Summary of responses	Tech team
Subcutaneous administration of LANA	Several responses including BAD, HAE UK & web that subcutaneous is easier and may lead to better QoL	Additional benefit for subcutaneous administration of LANA already captured in the model
Comparator	**BAD**: only licensed treatment for long-term prophylaxis in the UK is Cinryze so this should be the comparator	Berinert is used as a off-label treatment in clinical practice therefore Berinert is also included in the model
Additional costs	**BAD, HAE UK, UKPIN**: Still need treatment for acute breakthrough episodes (C1-INH, icatibant and oral therapy may also be used)	Costs for acute treatment in line with HELP-03 were included in the model
New medicines	**RCP**: oral Kallikrein inhibitors in Phase 2 & 3 trials for prophylaxis and acute attacks and may enter market in next 5 years	Cost effectiveness analyses only include treatments currently available and used in the NHS

7

ACD consultation summary

Theme	Summary of responses	Tech team
Optimised recommendation	**RCP**: use of LANA should be limited to very severe disease for which no alternative treatments	New evidence to be considered at ACM 2
C1-INH use in practice	**UKPIN**: carried out survey including 66 patients from 28 immunology centers and report average weekly doses for Berinert and Cinryze	Included in later slides
Innovation	**UKPIN**: LANA is innovative has the potential to reduce both burden of treatment (significantly less injections) and burden of illness (less attacks compared to IV C1-INH prophylaxis). This means less days off work/school (reduced economic impact) and reduced anxiety for patients – these are not necessarily accounted for in the model	The committee considered LANA to be innovative but agreed that all benefits were captured in the model
International evidence	**Web**: pharmaco-economic study from United States Hereditary Angioedema Association shows new subcutaneous prophylactic treatments associated with improved outcomes	Study may not be directly relevant to clinical practice in the NHS
Lack of alternative treatments	**Web**: LANA is effective treatment and should be available	New evidence to be considered at ACM 2

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Summary of new evidence

New evidence/analysis	Summary
NHSE data of C1-INH use	Data from 2016 to 2019 of 98 patients on Berinert vs Cinryze use. No data on dosing.
UKPIN survey	Snap survey of 34 immunology centres with 82% response rate, contributing data from 66 patients on prophylaxis with C1 inhibitor. Patients on Berinert (n=33) were using an average of **2,781** units per week for prophylaxis and patients on Cinryze (n=31) were using an average of **2,343** units per week for prophylaxis
Company's new data from clinical experts	Advisory board with 22 clinical experts (13 consultant immunologists, 9 nurse specialists) working in 16 centres in England and Wales. Their clinical practice included [redacted] patients who were on prophylactic treatment with Berinert
CMU information about C1-INH prices paid by NHS	Confidential prices treated as cPAS and included in part 2 slides only

[redacted]

9

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Slide updated after ACM 2

Company's revised base case

Assumption	Revised base case	Tech team/ERG
LANA attack rate	LANA attack rate estimated by applying rate ratios estimated from ITC to the placebo arm attack rate estimates from HELP-03	Agree this is in line with committee's preferred assumptions
Discontinuation	A proportion assumed to stop LANA. All patients having C1-INH stay on treatment	Agree this reflects clinical practice
Population	Full HELP-03 (n=97) & subgroup ≥ 8 attacks ([redacted])	Agree both groups relevant but subgroup results are less robust
Adjustments for discontinuation	The following are adjusted for treatment discontinuation: • Lanadelumab attack rate • Subcutaneous treatment utility benefit • Acute attack treatment costs	Agree this is in line with committee's preferred assumptions
Subsequent treatment	Patients who stop LANA have C1-INH	Agree this reflects clinical practice
Hospitalisation	A revised cost of £455 is applied	Agree
Berinert dosing	All patients have a target dose of [redacted] with pragmatic dose rounding applied to ensure there is no vial wastage ([redacted] IU weekly)	ERG: most plausible weekly dose is between 2781IU (UKPIN) and [redacted] IU (company advisory board)
LANA lower dosing freq	77% (no change from ACM1) but scenario assuming 61%	Committee preference: 77% was the upper limit
LANA price	Simple PAS discount increased to [redacted] (updated for ACM 2)	ICERs including all discounts in part 2 slides (treated as cPAS)

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Company new evidence: Berinert dosing

ACD: there is substantial uncertainty around the dosing schedule for Berinert but a fixed dose of 1,000 IU is mostly likely to reflect NHS practice

Company	NHSE	UKPIN	ERG

Further clinical input from 2 online advisory board meetings:
• [redacted]
• [redacted]
  • [redacted]
  • [redacted]
• [redacted]
	No further data on dosing	Report survey of 34 immunology centres (82% response rate) that includes 66 patients. Of 33 patients on prophylaxis with Berinert the average dose was 2,781 units per week.	• Data from UKPIN is [redacted] lower than base case in company submission (unclear if accounts for dose rounding to avoid wastage)
			• Unclear if overlap between company advisory board & UKPIN survey

Company's clinical input → [redacted] IU per week Company's revised base case → [redacted] IU per week (target [redacted] but with pragmatic dose rounding)		NHSE: no data UKPIN: 2,781IU per week	ERG: most plausible dose range 2,781IU to [redacted] IU per week

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Company new evidence: Berinert dosing

Company carried out advisory board with 22 clinical experts (13 consultant immunologists, 9 nurse specialists) working in 16 centres in England and Wales. This represents 72% of specialist centres. Their clinical practice included [redacted] patients who were on prophylactic treatment with Berinert; dosing information was available for [redacted]

Berinert Dosing	Total no patients	Infusion weekly total (units)	Total weekly units (units, all patients)	ERG
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	Where actual doses were calculable, [redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	

ERG: It is not clear how more evidence could be collected to resolve this uncertainty other than to survey the doses for all patients on Berinert in England, taking account of whether they would be candidates for lanadelumab or not

[redacted]

12

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Company new evidence: LANA dosing freq

ACD: there is substantial uncertainty around the proportion of people having the lower dose frequency of lanadelumab, and 77% is the upper limit on this value

Company

- Assumed 77% of patients would switch to dosing every four weeks (Q4W) after 1 year
- Further clinical input from 22 clinical experts confirmed they would offer a less frequent dose if appropriate. For those able to predict a percentage [redacted] the range was [redacted]
- In clinical practice, clinicians also consider [redacted], therefore estimate may be >77%

77% → Proportion on higher (Q2W) dose of LANA in HELP-03 and stably attack-free (would be eligible for lower freq dose)

↓

Company's revised base case (no change from ACM 1)

[redacted]

60.9% → Midpoint of patients stably attack-free from both the higher dose freq (Q2W) and lower dose freq (Q4W) arms of HELP-03

↓

Company's scenario at ACM 2 (pragmatic approach as not all patients stably attack free on Q2W switch to Q4W)

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Company new evidence: LANA dosing freq

ERG

- Only [redacted] of the 22 clinical experts made an estimate ([redacted]) and for those who did make an estimate, it was not clear what they based their estimate upon
  - the ERG would prefer to give more weight to the answers of those who have prescribed lanadelumab
- Suggest retaining 77% as upper bound (none of company's experts suggested values above this)
- Lower bound still unknown. Company's clinical input suggest reducing dosing frequency of LANA would be discussed with patients and decision would be joint taking account of many different factors. Therefore company's lower bound may still be high

[redacted]

Company: other issues

LANA effectiveness *ACD: The committee considered both approaches and concluded that using the indirect treatment comparison to inform attack rates for both lanadelumab and C1-INH is the more consistent and robust approach. The committee concluded that the indirect treatment comparison should be used to estimate the treatment effect for both LANA and C1-INH.*

C1-INH prices *The committee noted that at the next appraisal committee meeting, it would like to see analyses with its preferred assumptions that incorporate the lower price paid by the NHS for C1-INH and real-world data from NHS England about the dose and current use of Berinert*

ITC vs. HELP-03 regression	• Company disagree with committee's preferred approach using ITC but use this in revised base case (scenario: regression based on HELP-03 data)
Tender prices C1-INH	• Tender price is applied for a limited period of time and subject to fluctuation. This may be particularly relevant for plasma-derived C1-INHs where supply constraints may have an impact on pricing. • There will be a new C1-INH tender in place for the start of 2020 therefore current tender process considered unreliable to inform long-term cost-effectiveness analyses

[redacted]

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NHSE new evidence: C1-INH use

ACD: The committee concluded that it is reasonable to assume between 50% and 75% of people having C1-INH will have Berinert, and the rest will have Cinryze

NHS England provided data on C1-INH use in line with the NHS England commissioning policy. The average number per year

- Berinert 73%
- Cinryze 27%

	Number of patients (%)				
	2016 Total	2017 Total	2018 Total	2019 Total	Grand Total
Berinert	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cinryze	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Data available		[redacted]	[redacted]	[redacted]	[redacted]
No data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total returns	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Company's revised base case unchanged from ACM1 and assumes [redacted] Berinert

16

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Slide updated after ACM 2

Company's results for LANA vs. C1-INH

Only includes LANA PAS (see part 2 slides for cPAS)

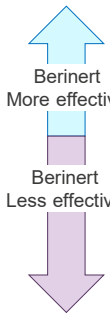
Company analysis	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (£)
Revised base case (full pop; n=97)	[redacted]	[redacted]	Dominant	£379,506
Revised base case (≥8 attacks; [redacted])	[redacted]	[redacted]	Dominant	£654,306
Company scenario: LANA switching to lower freq dosing (revised base case 77%)				
60.9% (full pop; n=97)	[redacted]	[redacted]	£31,061	-£674
60.9% (≥8 attacks; [redacted])	[redacted]	[redacted]	Dominant	£292,249
Company scenario: Apply HELP-03 regression for LANA attack rate (revised base case uses rate ratios from ITC)				
HELP-03 regression (full pop; n=97)	[redacted]	[redacted]	Dominant	£432,600
HELP-03 regression (≥8 attacks; [redacted])	[redacted]	[redacted]	Dominant	£837,664
Company scenario: Berinert clinical practice dosing from advisory board (revised base case used [redacted] per week)				
[redacted] IU per week (full pop; n=97)	[redacted]	[redacted]	Dominant	£166,024
[redacted] IU per week (≥8 attacks; [redacted])	[redacted]	[redacted]	Dominant	£444,840

[redacted]

17

Company's additional scenario for LANA vs. C1-INH
Only includes LANA PAS (see part 2 slides for cPAS)

Company reported this scenario analysis varying the effectiveness of Berinert to reflect a potentially higher average dose compared to the dose for which effectiveness data is available



Rate ratio vs placebo	HELP-03		≥ 8 attacks	
	ICER	NMB	ICER	NMB
0.1	Dominant	£172,081	Dominant	£203,369
0.2	Dominant	£226,763	Dominant	£320,241
0.3	Dominant	£279,869	Dominant	£435,521
0.4	Dominant	£332,096	Dominant	£549,908
Base case (0.492)	Dominant	£379,506	Dominant	£654,306
0.5	Dominant	£383,780	Dominant	£663,738
0.6	Dominant	£435,106	Dominant	£777,196
0.7	Dominant	£486,183	Dominant	£890,391
0.8	Dominant	£537,079	Dominant	£1,003,392
0.9	Dominant	£587,839	Dominant	£1,116,243
1.0 (equal to placebo)	Dominant	£638,495	Dominant	£1,228,976

[redacted]

18

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Key issues

- What is the most appropriate weekly dosing of Berinert?
  - Company revised base case ([redacted] IU)
  - Company's clinical expert advisory board ([redacted] IU)
  - UKPIN data (2,781 IU)
- Are NHSE data on C1-INH use in line with committee's preferred assumption that 50% to 75% of people having C1-INH will have Berinert?
- Is 60.9% an appropriate lower bound for the proportion of people switching to a lower frequency of LANA dosing?

[redacted]