NICE National Institute for Health and Care Excellence

PART 1

Public observer slides

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia

Chair's presentation- Stephen O'Brien

Lead team: Prithwiraj Das, Derek Ward, Stella O'Brien

ERG: BMJ Technology Assessment Group (BMJ TAG)

Technical team: Stephen O'Brien, Sally Doss, Cameron Collins, Jasdeep Hayre

Company: Daiichi Sankyo

ACM 3 – 9th February 2021

Recap of the 1st committee meeting

(4th August 2020)

- The appraisal committee was unable to develop recommendations due to considerable uncertainty in the company network meta-analysis (NMA)
- NICE paused this appraisal pending further analyses being completed. NICE recommended that the company:
  - conduct a **primary analysis** where they build upon the NMAs conducted by the ERG
  - conduct **scenario analyses** using studies that reflect PCKS9i eligibility

Recap of the 2nd committee meeting

(5th November 2020)

- The appraisal committee concluded that bempedoic acid was not recommended as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia. Most notably:
  - the committee felt that the requested subgroup analyses relating to cardiovascular risk and HeFH status had not been appropriately done
  - the committee was concerned about the clinical effectiveness of bempedoic acid because of the lack of long-term data on cardiovascular outcomes in the pivotal trials.

ACD recommendation

- Bempedoic acid is not recommended, within its marketing authorisations, for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in adults

Bempedoic acid (Nilemdo/Nustendi, Daiichi Sankyo)

Marketing authorisation (received April 2020)	BA and BA/EZE FDC are indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet. **Insufficient response to statin population:** • BA with statin or statin + other lipid lowering therapies • BA/EZE FDC with statin (population has prior EZE therapy) **Statin intolerant population:** • BA alone or with other lipid lowering therapy • BA/EZE FDC alone (population has prior EZE therapy)
Description of technology	BA is a cholesterol synthesis inhibitor (inhibiting adenosine triphosphate citrate lyase). BA upregulates LDL receptors by suppression of cholesterol synthesis.
Administration	• BA – oral, once daily; 1 tablet containing 180 mg BA • FDC – oral, once daily; 1 tablet containing 180 mg BA FDC and 10 mg EZE.
List price	£55.44 (£1.98 per day, £723.20 per year) per 28-pack of BA £55.44 (£1.98 per day, £723.20 per year) per 28-pack of BA/EZE FDC £57.30 (£2.05 per day, £746.46 per year) per 28-pack of BA+EZE separate tablets

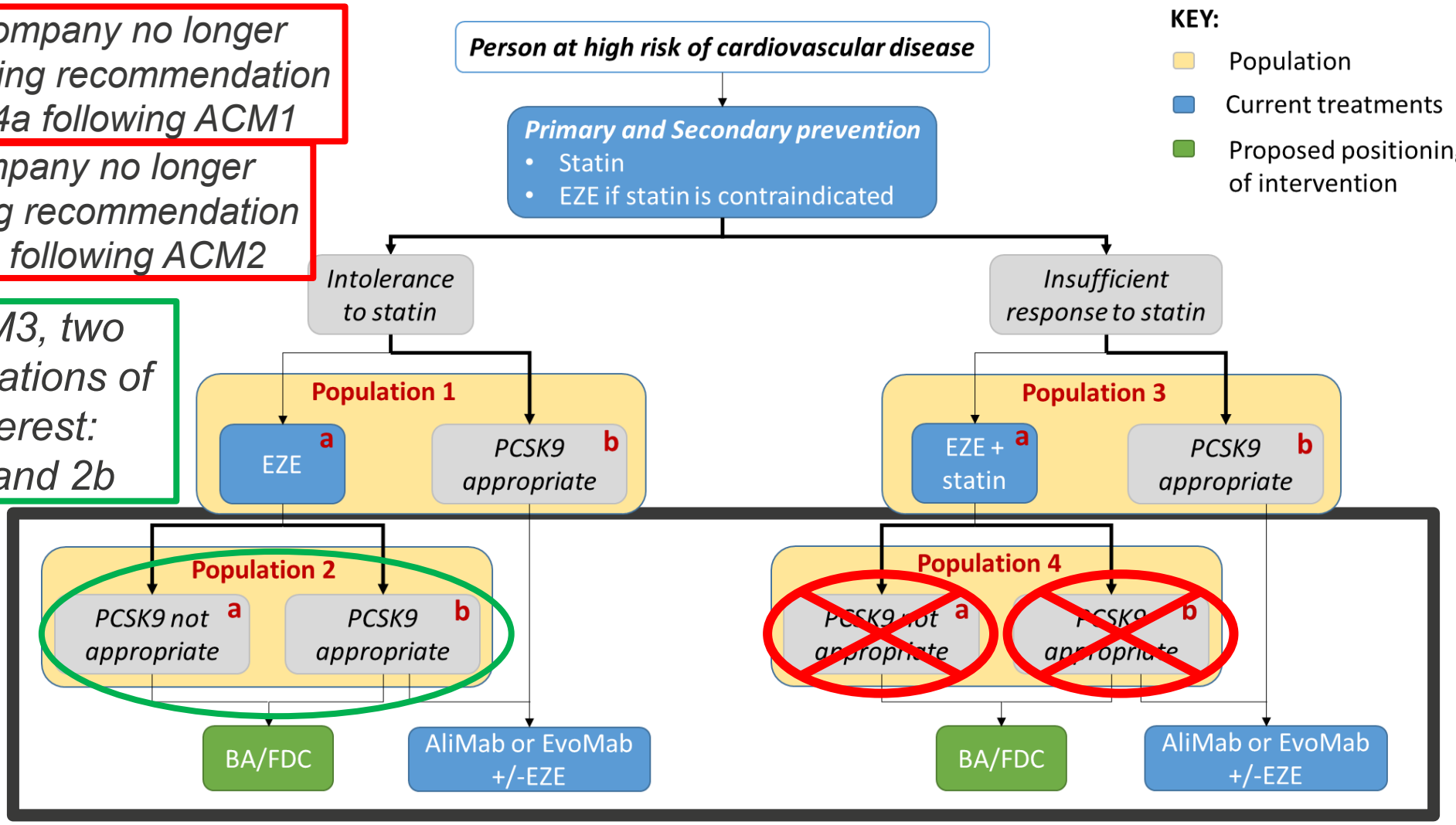
Treatment pathway

Position of BA/FDC in treatment pathway for hypercholesterolaemia and mixed dyslipidaemia

Company no longer seeking recommendation in 4a following ACM1

Company no longer seeking recommendation in 4b following ACM2

ACM3, two populations of interest: 2a and 2b



Note: Subpopulations labelled with 'a' relate to situations when alirocumab (ALI) and evolocumab (EVO) are not appropriate and 'b' for when ALI and EVO are appropriate.

ACM2: Cost-effectiveness results

- Results provided for BA/EZE FDC (cheaper combination and efficacy assumed equivalent)
- Results for EVO have not been presented, as a class-effect has been assumed and ALI is the cheaper PCKS9i (£4,437.79 for EVO and £4,383 for ALI)

Probabilistic results from ERG and Company for Company analyses (£/QALY)

Analysis	Statin intolerant		Maximally tolerated statin
	Position 2a	Position 2b (south-west quadrant)	Position 4b (south-west quadrant)
ERG NMA V2 (ERG preferred)	£23,824	£84,531*	£55,388*
Tech engagement analysis (Company preferred)	£23,969	£416,292 *	£114,181 *

Position 2a = FDC vs EZE
Position 2b and 4b = FDC vs ALI
*using list price for ALI

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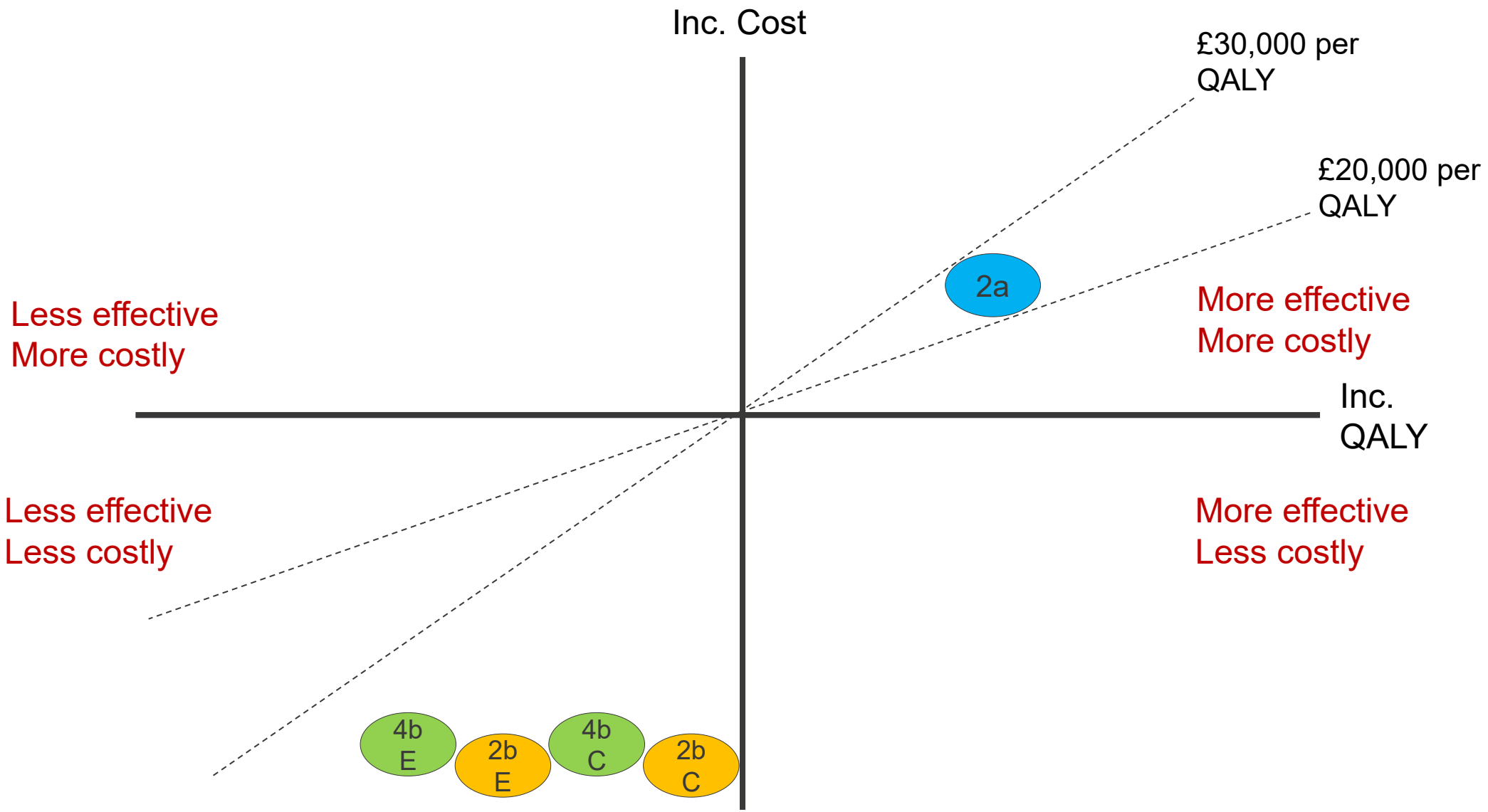
ACM2: Cost-effectiveness plane



E is ERG preferred
C is Company preferred

ACD: Key points

Section	Committee decision
Clinical pathway (3.1-3.2)	• People with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia will welcome a new treatment option • The proposed position of BA with EZE in the treatment pathway reflects NHS clinical practice
Previous treatment with EZE (3.3)	• The network meta-analyses should include only trials in which all patients were having EZE at baseline
Baseline LDL-C levels (3.4)	• The cost-effectiveness estimates did not appropriately reflect the intended positioning of BA (for patients who had already had EZE and according to ALI or EVO eligibility) given the limitations of the trials informing baseline LDL-C levels
Subgroup analyses (3.5-3.7)	• Because of trial limitations, subgroup analyses could not be provided by HeFH and CV risk status • Because of trial limitations, it was not possible to use efficacy data directly related to the primary and secondary prevention populations
NMA (3.8)	• The ERG's updated network meta-analysis is the most suitable for decision making
Long-term effect (3.9-3.10)	• The latest available data should be used to inform long-term treatment effect • Evidence of the impact on cardiovascular outcomes should be provided

ACD consultation responses

- Stakeholder comments from:
  - Association of British Clinical Diabetologists
  - British Cardiovascular Society
  - Novartis Pharmaceuticals UK Ltd
- Web comments
- Company comments

Stakeholder comments

- Association of British Clinical Diabetologists
  - The current recommendation is a sound and a suitable basis for guidance to the NHS, and there are no other aspects of the recommendation that require further consideration to avoid discrimination
- British Cardiovascular Society
  - The recommendation is not suitable because it leaves a large group of patients with an inadequately controlled LDL-C level, thus leaving them at higher than acceptable residual risk of CV events
  - More accurate information of uptake of PCSK9i is required, as at present, we have a large group of patients with high risk and unsatisfactory LDL-C sitting in “no-man’s land”
  - The cardiovascular benefits of LDL-C lowering are independent of the methods by which it is achieved
- Novartis Pharmaceuticals UK Ltd
  - EZE is infrequently used in clinical practice across all subgroups of patients, and it has been observed that background EZE is not a treatment-effect modifier
  - Evidence from both patients who have, and have not previously received EZE should still be considered generalisable to clinical practice
  - Distinct cost-effectiveness analyses should be carried out by CV risk status and long-term data at 52 and 78 weeks should be provided to support treatment effect assumption

Web comments

Every comment references the group of patients with inadequately controlled LDL-C levels, but not eligible for PCSK9i

"I think they underestimate the significant issues we have with guidance as it stands, specifically the inability to use PCSK9i except for a very limited few patients with the highest cholesterol"

"found it very useful in statin intolerant patients who are not eligible under NICE criteria for PCSK9 inhibitor therapy"

"this drug would be a very helpful addition to approved lipid lowering drugs"

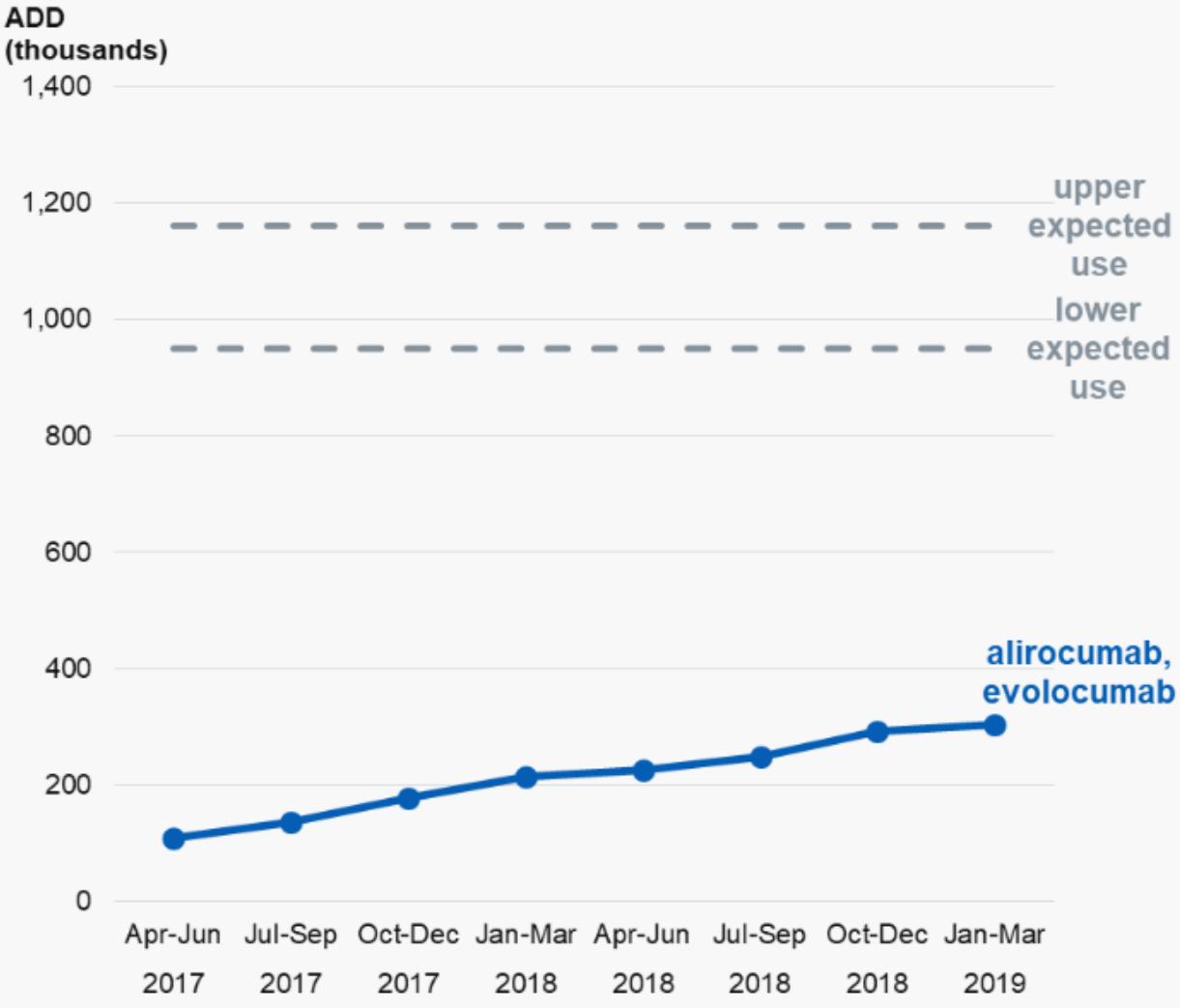
"Unfortunately there are high risk patients who are currently ineligible for alirocumab or evolocumab on NICE criteria, or do not tolerate or respond adequately to this medication. This is when there is a particular need for another cholesterol lowering agent such as bempedoic acid."

"I believe there remains a significant cohort of statin-intolerant individuals who currently can't access PCSK9i based therapies."

Access to PCSK9i

- October 2018 to September 2019, the annual volume of ALI/EVO used was between 65% and 72% lower than expected.
- The NHS accelerated access collaborative Rapid Uptake Working Group suggest patients are not navigated through the lipid management pathway appropriately and therefore very few actually get to the stage where a PCSK9i is considered.

Chart 7a: Alirocumab and evolocumab - observed use and range of expected use in primary and secondary care prescribing from April 2017 to March 2019



Source: NHS Digital

Company comments

- Updated positioning in treatment pathway
  - Now only seeking recommendation where statins are contraindicated or not tolerated, and ezetimibe alone does not appropriately control LDL-C (**positions 2a and 2b**).
- Commercial arrangement
  - Agreed a confidential commercial access arrangement with NHSE which offers BA with EZE at a lower price
- Updated cost-effectiveness results
  - Provided revised cost-effectiveness results at the new proposed net price based on the Appraisal Committee's preferred modelling assumptions
- COVID-19 context
  - The accessibility of BA in primary and secondary care provides an additional convenient, oral therapeutic option in lipid lowering management, allowing more patient care outside of the hospital setting

Company additional information

- Evidence of long-term impact
  - Although LDL-C reduction at 12 weeks was presented as part of the primary trial endpoints, LDL-C reduction with BA is sustained beyond 12 weeks as demonstrated in analyses presented for 24 and 52 weeks, through at least 78 weeks of treatment in the trials
- CV outcomes data for BA and the association of LDL-C reduction with CV risk reduction
  - A global, randomised, double-blind, placebo-controlled study is fully recruited and ongoing to assess the effect of BA on CV outcomes in patients with statin intolerance, and is expected to report in 2023
  - The EAS/ESC consensus panel reinforces that any mechanism of lowering plasma LDL particle concentration should reduce the risk of atherosclerotic cardiovascular disease events proportional to the absolute reduction in LDL-C and the cumulative duration of exposure to lower LDL-C
  - In addition, Mendelian randomisation studies showed that genetic variants that mimic the effect of ATP citrate lyase inhibitors (such as BA) and statins appeared to lower plasma LDL-C levels by the same mechanism of action and were associated with similar effects on the risk of cardiovascular disease per unit decrease in the LDL-C level

ACM2 committee preferred analysis

Model driver | Small impact | Unknown impact

Relating issue from ACM1	Committee preferred analysis in ACM2	Included at ACM3 company analysis	Impact
Issue 2. Previous and/or concomitant therapy	To be only patients with prior EZE	Implemented	
Issue 3. Baseline LDL-C from PCSK9i eligibility	Population 2a to be adjusted by PCKS9i eligibility	No adjustment made	
Issue 4. Subgroup analyses by CV risk and HeFH	If possible, present appropriate subgroup analysis	No update Trial data limitation	
Issue 5. Primary and secondary prevention subpopulation	If possible, present appropriate subgroup analysis	No update Trial data limitation	
Issue 5a. CV event history and risk data	Cannot be taken from CLEAR trials, accepted alternative	No update	
Issue 6: Preferred NMA	ERG NMA V2 • SI V2 for population 2 • MTD V2 for population 4	Implemented	
Issue 7. 12-week study data cut off and long term impact	No additional data provided	Sources provided evidencing long-term impact	

ACM3: Cost-effectiveness results

- Results provided for BA/EZE FDC (cheaper combination and efficacy assumed equivalent)
- Results for EVO have not been presented, as a class-effect has been assumed and ALI is the cheaper PCKS9i (£4,437.79 for EVO and £4,383 for ALI

Probabilistic results from ACM2 and ACM3 updated CCA price (£/QALY)

Analysis	Statin intolerant		Maximally tolerated statin
	Position 2a	Position 2b (south-west quadrant)	Position 4b (south-west quadrant)
ACM2 committee preferred results	£23,824	£84,531*	£55,388*
ACM3 including confidential discount	XXXX	XXXX	No longer seeking recommendation

Position 2a = FDC vs EZE
Position 2b and 4b = FDC vs ALI
*using list price for ALI

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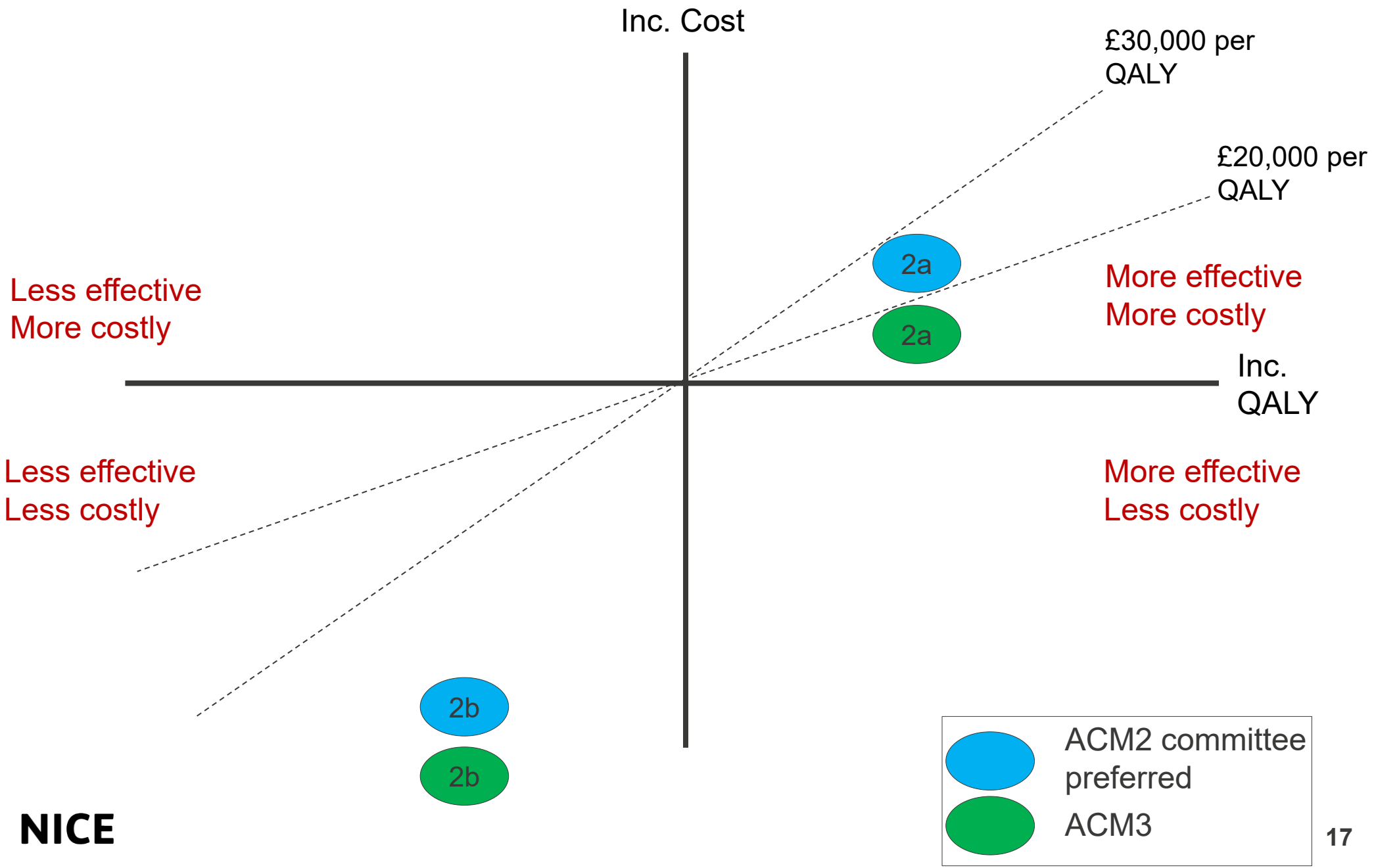
ACM3: Cost-effectiveness plane



Decision-making: south-west quadrant ICERs

- **In position 2b (when PCSK9i are appropriate), Bempedoic acid accrues fewer costs than the PCSK9i (Alirocumab and Evolocumab) but also fewer QALYs (south-west ICERs)**
- South-west quadrant ICERs are presented as costs saved per QALY lost
- The higher the ICER, the more cost is saved per QALY lost, so high ICERs are better here and the commonly assumed decision rule of accepting ICERs below a given threshold is reversed
- Positive recommendations are made when the costs saved are sufficient to cover the QALY loss
- Usually, south-west quadrant ICERs have led to positive recommendations when ICERs are substantially above £30,000 per QALY lost
- As with other decision-making, more certainty is needed the closer to the margins of cost-effectiveness the ICERs are i.e. QALYs lost and costs saved are both considered as well as the ICERs themselves
- **At ACM2, the committee agreed that conservative thresholds for populations 2a and 2b should be adopted given the high level of uncertainty. For population 2b, this meant an acceptable ICER would be above £30,000 per QALY lost**

ERG comments

- The 78 week data referred to by the company relate to data from the CLEAR Harmony open-label extension (OLE) study (NCT03067441) and they have not been discussed previously
- The ERG notes that the OLE study provides efficacy data for BA after approximately 2.5 years of treatment for some patients and the ERG considers it important to consider these data given that the data for the statin intolerant population are limited to a maximum follow-up of 24 weeks.
- **ERG provided cost-effectiveness results exploring the impact of treatment waning, and the impact of adjusting baseline LDL-C by PCSK9i eligibility in population 2a (as recommended by committee at ACM2)**

Relating issue from ACM1	Committee preferred analysis in ACM2	Included at ACM3 company analysis	ERG ACM3 analysis
Issue 3. Baseline LDL-C from PCSK9i eligibility	Population 2a to be adjusted by PCKS9i eligibility	No adjustment made	Adjusted by PCKS9i eligibility in population 2a
Issue 7. 12-week study data cut off and long term impact	No additional data provided	Sources provided evidencing long-term impact	Explored potential treatment waning impact on ICERs

ERG scenario: baseline LDL-C adjusted

Issue 3: Scenario Analysis - Deterministic ICERs (£/QALY)

Analysis	Position 2a
New company baseline Baseline LDL-C levels = (XXXX)	XXXX
ERG scenario Baseline LDL-C levels = (XXXX)	XXXX

- The company used different mean baseline LDL-C levels in its economic model depending on the position of BA in the treatment pathway:
  - In patients who were eligible to receive ALI or EVO, the company used mean baseline LDL-C levels from patients having ALI or EVO treatment in the CLEAR trials
  - However, in patients who were ineligible for ALI or EVO, baseline LDL-C levels were taken from all patients in the CLEAR trials and did not distinguish between those who could have ALI or EVO and those who could not
- Therefore, baseline LDL-C levels in people not eligible for ALI or EVO (XXXX) were lower than baseline LDL-C levels in all patients (XXXX)

Important to note that uptake of ALI and EVO in clinical practice is between 65% and 72% lower than expected. **Therefore, the scenario presented here is conservative.**

ERG treatment waning results

- The 78 week data referred to by the company relate to data from the CLEAR Harmony open-label extension (OLE) study, **which was a study of BA that relates to position 4**
- The ERG considers the efficacy results of the OLE are potentially confounded due to the mix of patients continuing on long term treatment of BA and patients newly starting BA (nearly 1/3 originating from placebo arm of CLEAR Harmony).
- The ERG considers that there may be a slight waning of treatment effect with bempedoic acid beyond 12-weeks and is unable to comment as to whether similar waning would be seen for the comparators

Mean LDL-C reduction from baseline in CLEAR Harmony and CLEAR Harmony open label extension

	CLEAR Harmony			Open Label Extension	
Time period (cumulative)	12-weeks (12)	24-weeks (24)	52-weeks (52)	12-weeks (64)	78-weeks (130)
Mean LDL-C reduction from baseline	-16.5%	-14.9%	-12.6%	-14.9%	-14.4%
Size	BA n=1,488 Placebo n=742			BA n=970 Placebo n=492	

ERG treatment waning results

- Given that the company has still not used the latest available data to inform the long-term treatment effect of BA in the economic analyses, the ERG has explored two scenarios to show what impact a treatment waning effect on LDL-C could have on the cost-effectiveness results.
- Based on CLEAR Serenity, the % reduction in LDL-C from week 12 to week 24 in the BA treatment arm equates to an absolute increase in LDL-C of 2.4%, and a relative increase of approximately 10%.
- When the relative increase (10%) is applied to the NMA results, the BA treatment effect on LDL-C changes from XXXX to XXXX. For ALI+EZE, the treatment effect changes from XXXX to XXXX, if a similar waning of treatment effect is assumed.

Issue 7: Scenario Analysis – Deterministic ICERs (£/QALY)

Analysis	Position 2a	Position 2b (south-west quadrant)
New company baseline	XXXX	XXXX
ERG scenario: Benefit reduction applied to all treatment arms	XXXX	XXXX
ERG scenario: Benefit reduction applied only to FDC (conservative)	XXXX	XXXX

Key issues

- Is BA with EZE cost-effective where statins are contraindicated or not tolerated, and ezetimibe alone does not appropriately control LDL-C (**positions 2a and 2b**)?