NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the ACD** from Daiichi Sankyo UK

3. **Consultee and commentator comments on the ACD** from:
   a. British Cardiovascular Society
   b. Novartis

4. **Comments on the ACD received through the NICE website**

5. **Evidence Review Group critique of company comments on the ACD**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	Daiichi Sankyo	Daiichi Sankyo welcomes the opportunity to comment on the draft preliminary recommendations set out in the Appraisal Consultation Document (ACD) developed by the Appraisal Committee regarding the use of Bempedoic Acid for Treating Primary Hypercholesterolaemia or Mixed Dyslipidaemia [ID1515]. Despite treatment with oral lipid-lowering therapies, up to 80% of patients with hypercholesterolaemia and mixed dyslipidaemia do not reach guideline-recommended low-density lipoprotein cholesterol (LDL-C) goals.1-3 Bempedoic acid is a first-in-class (adenosine triphosphate (ATP)–citrate lyase inhibitor) oral, once-daily, lipid-lowering treatment option for patients with primary hypercholesterolaemia or mixed dyslipidaemia who are not reaching their therapeutic goals despite current oral lipid-lowering therapies. The ACD provides a thorough overview of the clinical and economic information submitted for this technology. Daiichi Sankyo agrees with the clinical and patient expert in Section 3.1 that "bempedoic acid is an inexpensive, oral preparation that is easy to use and suitable for people who cannot tolerate statins." Furthermore, Daiichi Sankyo agrees with the Appraisal Committee in their conclusion that "a new treatment option for managing cholesterol would be welcomed." Daiichi Sankyo has taken a responsible approach in focussing on the patient populations that will benefit most from bempedoic acid + ezetimibe, and in which the technology offers the most cost-effective use of NHS resources in accordance with the Appraisal Committee's comments. Daiichi Sankyo is seeking a positioning where statins are contraindicated or not tolerated, and ezetimibe alone does not appropriately control LDL-C (positions 2a and 2b). This position is supported by direct trial evidence from the Phase 3 Randomised Controlled Trial CLEAR Tranquillity. Recognising that the greater heterogeneity in the NMA was evident in the maximally tolerated network, focussing on the statin-intolerant population will substantially reduce the uncertainty in the evidence base for decision-making. Daiichi Sankyo is seeking a recommendation from NICE for bempedoic acid and bempedoic acid + EZE FDC based on the clinical and economic evidence submitted for: • bempedoic acid 180mg tablet (NILEMDO®▼) added to ezetimibe as separate tablets and, • bempedoic acid/ezetimibe (180mg/10mg) FDC tablet (NUSTENDI® ▼) Daiichi Sankyo agrees with the Appraisal Committee's comment that a number of uncertainties were addressed during Technical Engagement. In response to the ACD preliminary recommendations, Daiichi Sankyo is proposing to (i) focus on the most clinically and cost effective subgroups where there exists the highest unmet medical need, i.e., patients in whom statins are contraindicated or who cannot tolerate statin therapy and (ii) introduce a new net price which improves the cost-effectiveness of bempedoic acid + ezetimibe (EZE). The response is set out in three parts: (i) this cover letter, (ii) the ACD response letter, (iii) appendix I & II containing revised cost-effectiveness results at the new proposed net price based on the Appraisal Committee's preferred modelling assumptions. At the new proposed net price for bempedoic acid + EZE FDC, adopting the Appraisal Committee's preferred assumptions, the most plausible ICER for bempedoic acid + ezetimibe is [redacted] gained in position 2a and [redacted] lost in position 2b. Furthermore, deterministic sensitivity analysis (DSA) results remain below [redacted] in position 2a and above [redacted] lost in position 2b. Daiichi Sankyo is committed to working collaboratively with NICE to support access for patients to bempedoic acid, a first-in-class, oral once-daily treatment option, which can support the National Health Service's (NHS) Long Term Plan objectives in improving management of hypercholesterolaemia in England and keeping patients out of the hospital.	Comment noted. The committee considered the commercial access agreement which means that the ICERs for bempedoic acid and bempedoic acid-ezetimibe can be considered cost effective. Therefore, the committee has recommended bempedoic acid with ezetimibe for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in adults for whom statins are contraindicated or not tolerated, and ezetimibe alone does not control LDL-C well enough (see FAD sections 1.1 and 3.18).

			See full response in consultation response document from Daiichi Sankyo	
2	Consultee	Association of British Clinical Diabetologists	I am satisfied that all the relevant information has been taken into account	Comment noted.
3	Consultee	Association of British Clinical Diabetologists	The summaries of clinical and cost effectiveness are reasonable interpretation of the evidence, taking into account the confidential nature of discounts Alirocumab and Evolocumab which cannot be disclosed	Comment noted.
4	Consultee	Association of British Clinical Diabetologists	The current recommendation is sound and a suitable basis for guidance to the NHS	Comment noted.
5	Consultee	Association of British Clinical Diabetologists	There are no other aspects of the recommendation that require further consideration to avoid discrimination as far as I am aware	Comment noted.
6	Consultee	British Cardiovascular Society	Has all relevant information been taken into account? No – All relevant evidence has not been taken into account. In particular the current guidance is out of step with routine clinical practice and international guidelines. In this regard the NICE 2014 lipid guidance are behind other major guidelines in Europe which recommend LDl-C goals of below < 1.4 mmol/L (Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). European heart journal 2020; 41:111-88.). They do not take into account the fact that there is unequivocal evidence that cardiovascular benefits are identical irrespective of how LDL-C is lowered. This benefit relates to absolute reductions in LDL-C not percentage reductions which has implications for cost effectiveness assumptions. (Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. European heart journal 2017;38:2459-72. And Ference BA, Cannon CP, Landmesser U, Lüscher TF, Catapano AL, Ray KK. Reduction of low density lipoprotein-cholesterol and cardiovascular events with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and statins: an analysis of FOURIER, SPIRE, and the Cholesterol Treatment Trialists Collaboration. European heart journal 2018;39:2540-5.) Moreover the guidance does not recognise that wide distribution of event rates and in high risk patients, where even modest alsolute reductions in LDL-C can provide substantial absolute benefits (Annemans L, Packard CJ, Briggs A, Ray KK. ‘Highest risk–highest benefit’strategy: a pragmatic, cost-effective approach to targeting use of PCSK9 inhibitor therapies. European Heart Journal 2018;39:2546-50)	Comment noted. The committee noted and accepted the additional information supplied evidencing the association between LDL-C lowering and cardiovascular outcomes.
7	Consultee	British Cardiovascular Society	Are the summaries of cost effectiveness reasonable. • Not really- The reason they are not reasonable is that ezetimibe is being used as a comparator and not as standard of care. The comparator should only be monoclonal antibodies to PCSK9. However, the committee need to note that the threshold for patients to get access to PCSK9 is > 3.5mmol/L for very high risk CVD, > 4mmol/L for high risk CVD patients. Therefore, there are a body of patients who will not have access to PCSK9 inhibitors. Whilst the current cost effectiveness statements make sweeping statements like the fact that patients who are statin intolerant this is an over generalisation. For instance if a patient is statin intolerant and the LDL-C is for instance 3.0 mmol/L, the addition of bempedoic acid reduces LDL-C by 25%. If the patient were on high intensity statins and the LDL-C were 3.0mmol/L bempedoic acid would reduce LDL-C by 18%. The absolute reductions which drive benefit are statistically	Comment noted.

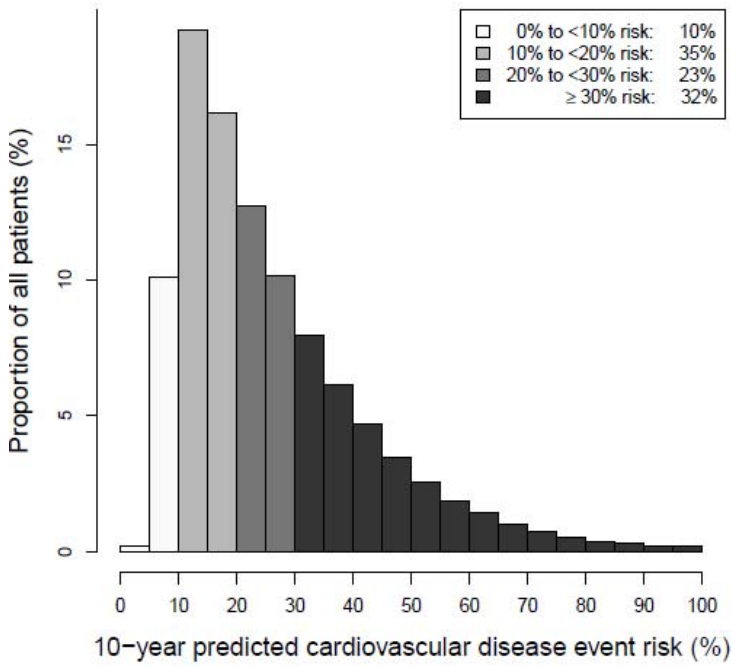
			almost identical. This is not something that is considered in the current document. Therefore, for both statin intolerant and statin tolerant patients, the guidelines should identify LDL-C cutoffs on a background of maximally tolerated statins and ezetimibe for instance 2.5-3.5 mmol/L where the estimated annual risk of a cardiovascular event is 2% per year or 10 year risk is 20%.	
8	Consultee	British Cardiovascular Society	Are the recommendations sound and a suitable basis for guidance to the NHS. • No – This is because they leave a large group of patients with an inadequately controlled LDL-C level, thus leaving them at higher than acceptable residual risk of CV events. The current evidence assumes that all patients with CVD are essentially the same which is clearly not the case. Contemporary data in the UK (using CPRD and ONS linked data) shows that observed 10-year event risks for males and females were 29.1% (95% confidence interval (CI) 28.8-29.4%) and 26.6% (26.2-27.0%), respectively. The average non HDL-C using in this population is 3.4mmol/L meaning the average LDL-C is around 2.6-2.8mmol/L. Moreover, approximately one third of CVD patients have 10 year risk > 30% despite usual clinical practice in the UK. See below. Fig 1  	Comment noted. The company has agreed a commercial access agreement which means that the ICERs for bempedoic acid and bempedoic acid-ezetimibe can be considered cost effective. Therefore, the committee has recommended bempedoic acid with ezetimibe for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in adults for whom statins are contraindicated or not tolerated, and ezetimibe alone does not control LDL-C well enough (see FAD sections 1.1 and 3.18).

Table 1: ASCVD cohort baseline characteristics using UK data (n=244,578)

Risk factor	Median / n	IQR / %	Missing: n (%)
Age	67.3	59.2 - 74.0	0
Sex (Male)	151,888	62.1%	0
Date of cohort entry	01/01/2004	08/06/2000 – 21/05/2009	0
Vascular disease*			
Cerebrovascular Disease	73,520	30.1%	
Coronary Heart Disease	154,079	63.0%	
Peripheral Vascular Disease	32,459	13.3%	
Abdominal Aortic Aneurysm	7,048	2.9%	0
Years since first vascular event			
<1 yr before enrollment	150,557	61.6%	
1-2 yrs before enrollment	10,098	4.1%	
>2 yrs before enrollment	83,923	34.3%	0
Current smoking (Yes)	48,083	19.7%	24,449 (10.0%)
Diabetes mellitus	38,717	15.8%	0
Systolic blood pressure (mmHg)	140	126 - 150	12,605 (5.2%)
Total cholesterol (mmol/l)	4.7	4.0 - 5.6	28,610 (11.7%)
HDL cholesterol (mmol/l)	1.3	1.1 – 1.6	49,142 (20.1%)
hsCRP (mg/l)	N/A	N/A	244,578 (100.0%)
eGFR (ml/min/1.73m)	66.1	55.5 – 77.8	16,334 (6.7%)
BMI (kg/m2)	27.4	24.5 – 30.8	43,409 (17.7%)
Medication prescribed in the 6-months prior to cohort entry*			
Lipid-modifying therapy	148,414	60.7%	
Antihypertensive	187,052	76.5%	
Antiplatelet	168,588	68.9%	
Anticoagulant	18,690	7.6%	0
Ethnicity			
Asian	5,589	2.3%	
Black	1,985	0.8%	
Mixed	557	0.2%	
White	220,850	90.3%	
Other	2,215	0.9%	13,382 (5.5%)

* Individuals can have more than one

HDL: high density lipoprotein; hsCRP: high sensitivity C-reactive protein; eGFR: estimated glomerular filtration rate; BMI: body mass index; IQR: interquartile range

9	Consultee	British Cardiovascular Society	Addendum to above comments The relation to the above request for clarification the BCS makes the following points under the headings below. 1. Current care pathway and use of ezetimibe and PCSK9 inhibitors 2. Current event rates, risk distribution in ASCVD patients in the UK and level of lipid control 3. Determinants of absolute benefit from LDL-C lowering and hence potential to impact cost-effectiveness discussion. **Section 1** Ezetimibe is generic. In the past when this was used as a comparator for PCSK9 MAbs an ezetimibe comparison was appropriate and the threshold for Mabs for a single CV event >4mmol/L or >3.5mmol/L per litre and >5mmol/L for FH primary prevention were appropriate. As ezetimibe is generic and as there is no lower threshold for LDL-C for benefit it makes no sense to NOT have statins and ezetimibe as standard of care. However, because of the lack of update to NICE lipid guidance since 2014 and indeed for ACS patients these same guidance also refer to the 2009 ACS guidance. Therefore, UK lipid modification guidance is woefully out of date behind the rest of Europe and other countries where LDL goals are risk based and goals of < 1.4 mmmol/L are recommended (Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). European heart journal 2020;41:111-88). Current use of ezetimibe in the UK is < 10% and more like 7% from recent European wide registry data (Ray KK, Molemans B, Schoonen WM, et al. EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study. European Journal of Preventive Cardiology 2020). The comparison of bempedoic acid with PCSK9 MAbs is a complex one. Firstly, the majority of patients eligible for MAbs don't get them as most patients have LDL-C levels which are deemed not high enough, resulting in the Academic health sciences network rapid scramble to find patients. Even if all eligible patients were found eligible for MAbs there are a large group of patients with LDL-C levels for instance even with optimization of statins and ezetimibe with LDL-C levels between for instance 2-3.5 or 2-4mmol/L (Ray KK, Molemans B, Schoonen WM, et al. EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study. European Journal of Preventive Cardiology 2020). These people (see point 2) with sufficient comorbidities could have high residual risk which drives events which could in part be mitigated by LDL-C lowering **Section 2** Using linkage data from UK GPs and ONS/HES to create a retrospective cohort we can see that in approximately 250k individuals with established cardiovascular disease more than 6 months out from a diagnosis the average on treatment non-HDL is 3.4 mmol/L approximating to an average LDL-C of around 2.6 mmol/L (characteristics shown in Table 1). There were 244,578 patients from 393 practices included in the primary cohort, with a median follow-up of 5.25 years (interquartile range (IQR) 2.15-9.63; 23.3% followed-up for ≥10 years), during which 45,327 cardiovascular events were observed. Observed 10-year event risks for males and females were 29.1% (95% confidence interval (CI) 28.8-29.4%) and 26.6% (26.2-27.0%), respectively.	Comment noted. The committee discussed the evidence highlighting low uptake of the PCSK9i and agreed that bempedoic acid would be a welcomed treatment option for patients for whom statins are contraindicated or not tolerated, and ezetimibe alone does not control low-density lipoprotein cholesterol well enough (see FAD section 3.1). Comment noted.

There were 136,445 patients from 389 practices in a second cohort with a diagnosis of ASCVD in the preceding 6 months, with a median follow-up of 3.74 years (IQR 1.10-7.76; 14.4% followed-up for ≥10 years). During follow-up, 28,115 outcome events occurred and observed 10-year event risks for males and females were 29.6% (95% CI 29.2-30.1%) and 27.9% (27.4-28.4%), respectively. Among the secondary cohort, 14,865 patients (10.9%) had events within 6-months of diagnosis.

The 10 year risk of CVD among those with ASCVD is not homogeneous and varies widely and depends upon multiple variables (Fig 1)
Fig 1

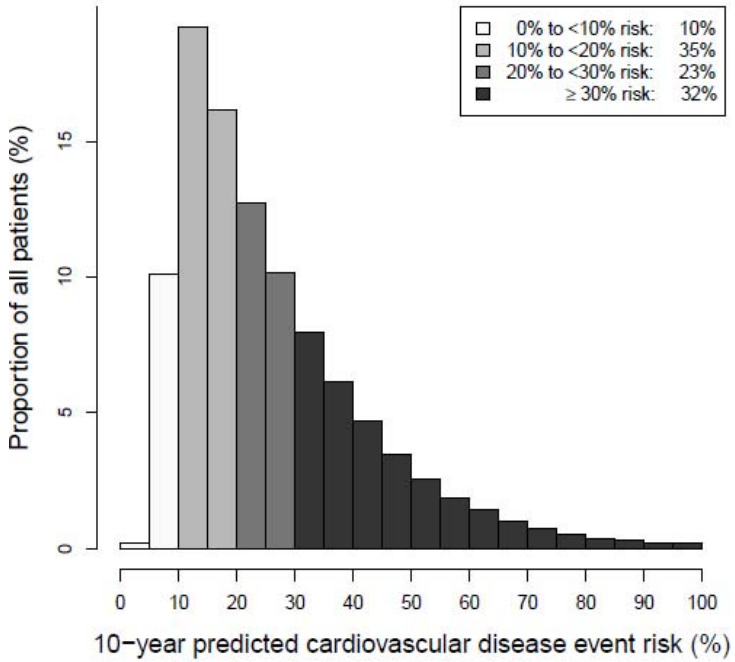
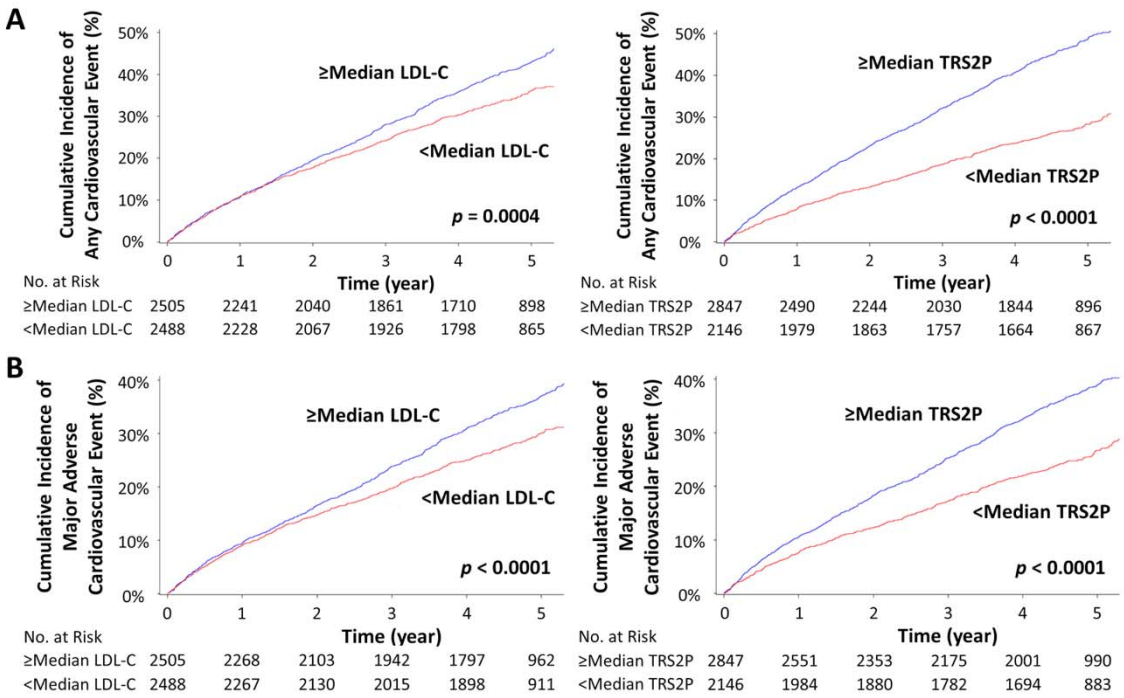


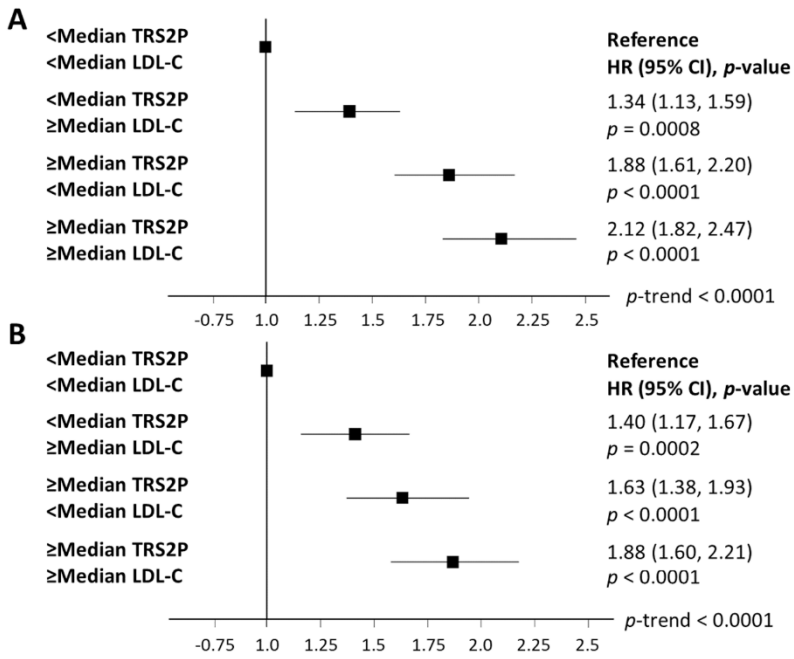
Table 1: Primary ASCVD cohort baseline characteristics using UK data (n=244,578)

Risk factor	Median / n	IQR / %	Missing: n (%)
Age	67.3	59.2 - 74.0	0
Sex (Male)	151,888	62.1%	0
Date of cohort entry	01/01/2004	08/06/2000 – 21/05/2009	0

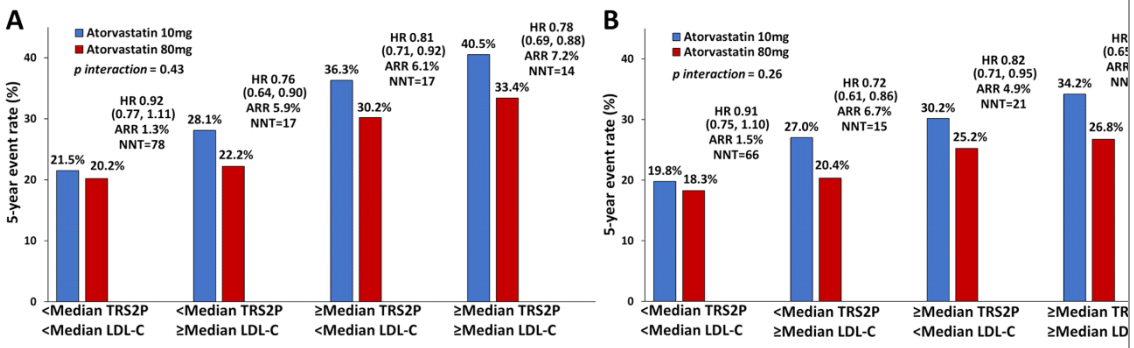
			Vascular disease* Cerebrovascular Disease Coronary Heart Disease Peripheral Vascular Disease Abdominal Aortic Aneurysm	 73,520 154,079 32,459 7,048	 30.1% 63.0% 13.3% 2.9%	 0	
			Years since first vascular event <1 yr before enrollment 1-2 yrs before enrollment >2 yrs before enrollment	 150,557 10,098 83,923	 61.6% 4.1% 34.3%	 0	
			Current smoking (Yes)	48,083	19.7%	24,449 (10.0%)	
			Diabetes mellitus	38,717	15.8%	0	
			Systolic blood pressure (mmHg)	140	126 - 150	12,605 (5.2%)	
			Total cholesterol (mmol/l)	4.7	4.0 - 5.6	28,610 (11.7%)	
			HDL cholesterol (mmol/l)	1.3	1.1 – 1.6	49,142 (20.1%)	
			hsCRP (mg/l)	N/A	N/A	244,578 (100.0%)	
			eGFR (ml/min/1.73m)	66.1	55.5 – 77.8	16,334 (6.7%)	
			BMI (kg/m2)	27.4	24.5 – 30.8	43,409 (17.7%)	
			Medication prescribed in the 6-months prior to cohort entry* Lipid-modifying therapy Antihypertensive Antiplatelet Anticoagulant	 148,414 187,052 168,588 18,690	 60.7% 76.5% 68.9% 7.6%	 0	
			Ethnicity Asian Black Mixed White Other	 5,589 1,985 557 220,850 2,215	 2.3% 0.8% 0.2% 90.3% 0.9%	 13,382 (5.5%)	
			* Individuals can have more than one HDL: high density lipoprotein; hsCRP: high sensitivity C-reactive protein; eGFR: estimated glomerular filtration rate; BMI: body mass index; IQR: interquartile range Section 3 We have overwhelming evidence that cardiovascular benefits of LDL-C lowering and independent of the methods by which it achieved. Trials (Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. European heart journal 2017;38:2459-72. And Ference BA, Cannon CP, Landmesser U, Lüscher TF, Catapano AL, Ray KK. Reduction of low density lipoprotein-cholesterol and cardiovascular events with proprotein				Comment noted. The company has agreed a commercial access agreement which means that the ICERs for bempedoic acid and bempedoic

			convertase subtilisin-kexin type 9 (PCSK9) inhibitors and statins: an analysis of FOURIER, SPIRE, and the Cholesterol Treatment Trialists Collaboration. European heart journal 2018;39:2540-5.) comparing annualised relative benefits per 1mmol/L lowering of PCSK9 MAbs versus statins or ezetimibe versus statins show that the relative benefits standardised per unit change in LDL-C and duration of exposure are indistinguishable. Although we do not have outcomes data for bempedoic acid in this regard, using mendellian randomization data and the genetic proxy for bempedoic acid (ACLY), would produce the same cardiovascular benefit per unit lowering of LDL-C through HMGCoA (statin target), NCP1L1 (ezetimibe), PCSK9 (Mabs) (Ference, B.A., Ray, K.K., Catapano, A.L., Ference, T.B., Burgess, S., Neff, D.R., Oliver-Williams, C., Wood, A.M., Butterworth, A.S., Di Angelantonio, E. and Danesh, J., 2019. Mendelian randomization study of ACLY and cardiovascular disease. *New England Journal of Medicine*, *380*(11), pp.1033-1042). Hence what determines likely benefit with bempedoic acid is not percentage (%) reduction in LDL-C but absolute reduction. A further nuance is that because bempedoic acid works through the same pathway as statins, the background dose of statins influences bempedoic acid efficacy. Hence saturation of the cholesterol synthesis pathway by targeting HMGCoA pathway with say 20-80 mg of atorvastatin will have a different effect on the efficacy of bempedoic acid if say 0mg or 10mg atorvastatin were used. Because the people receiving 20-80mg of atorvastatin would have a lower on treatment LDL-C, the absolute reduction in LDL-C from bempedoic acid and hence potential cost effectiveness less, than a patient who is on low or no statin who would have a much higher starting level of LDL-C. Here the greater efficacy and also higher LDL-C translate in greater absolute reductions in LDL-C and hence greater relative risk reduction. Finally, while the above demonstrates how even modest relative reductions in LDL-C could translat into meaningful relative benefits based on absolute LDL-C lowering for estimations of absolute benefits and hence cost effectiveness, it is essential to look at absolute risk (residual risk on treatment). This can be explained by looking at a 5 year trial of 10 vs 80mg atorvastatin (TNT – need reference) in stable coronary disease. The trial showed that an additional reduction of LDL-C of about 0.6 mmol/l (2.6 vs 2.0) reduced cardiovascular events by 22% in relative terms and about 2.2% in absolute terms over 5 years. Among the 10 mg atorvastatin patients, you can divide the patients into 4 groups using combinations of LDL-C above and below the median and residual risk above and below the median (TRS2P score). Risk is highest when residual risk and LDL-C are highest at baseline and lowest when both are low with intermediate risk when only one is high. When looking at benefit the additional benefit of atorvastatin 80mg is greatest when both residual risk and LDL-C are high (see below). In parallel with this line of thinking in a patient with an LDL-C of 3 mmol/L a 25% lowering of LDL-C with bempedoic acid would be expected to reduce LDL-C by 0.75mmmol/L offering about a 18% relative risk reduction. This could be applied to a range of scenarios of baseline risk ranging from 10%, 10 year risk to higher levels to more appropriately narrow down the treatment group where there is an unmet need but also value from this novel therapy. In summary rather than saying bempedoic acid per se is not cost effective for anyone, due consideration is needed for care pathways, current real life use of treatments, current real like LDL-C levels and real life residual risk and more accurate information of exactly how many people are getting Mabs. At present we have a large group of patients with high risk and unsatisfactory LDL-C sitting in “no-man’s land.” Determinants of risk in CAD patients on atorvastatin 10mg for different cardiovascular MACE outcomes	acid-ezetimibe can be considered cost effective. Therefore, the committee has recommended bempedoic acid with ezetimibe for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in adults for whom statins are contraindicated or not tolerated, and ezetimibe alone does not control LDL-C well enough (see FAD sections 1.1 and 3.18).

			 Incremental impact of residual risk and LDL-C alone or in combination	



Incremental benefit of atorvastatin 80 on risk among patients stratified by residual risk and LDL-C alone or in combination



10	Commentator	Novartis Pharmaceuticals UK Ltd	Paragraph 3.3 – Novartis is concerned about the request suggested in the ACD to restrict the network meta-analyses to only patients having ezetimibe at baseline. The rationale mentioned by the ERG is that patients would be expected to have previously had ezetimibe according to the treatment pathway. However, ezetimibe is infrequently used in UK clinical practice despite having been approved by NICE for several years. Low usage of ezetimibe applies to all subgroups of patients, including patients for whom statins are contraindicated or not tolerated. In the CPRD analysis conducted by Novartis recently, we observed the use of ezetimibe in secondary prevention without HeFH and primary prevention with HeFH to be 4.1% and 5.4% respectively. This argument is further substantiated by clinical input, Novartis internal market research and publication.[1] Since it is not the case that all patients for whom maximally tolerated statins do not adequately control LDL-C levels, will receive ezetimibe, evidence from patients who have not previously received ezetimibe should still be considered generalisable to clinical practice. Furthermore, it has been observed that background ezetimibe is not a treatment-effect modifier. For example in the ODYSSEY Long term trial, results in percentage change in LDL-C for alircocumab vs. placebo was -53.6% and -61.3% for patients on ezetimibe and without ezetimibe, respectively.[2] Therefore it is appropriate to consider aggregate data on clinical efficacy, from both patients who have, and have not, previously received ezetimibe. 1. Steen DL, Khan I, Ansell D, Sanchez RJ, Ray KK. Retrospective examination of lipid-lowering treatment patterns in a real-world high-risk cohort in the UK in 2014: comparison with the National Institute for Health and Care Excellence (NICE) 2014 lipid modification guidelines. BMJ Open. 2017;7(2):e013255. 2. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. New England journal of medicine. 2015;372(16):1489-99.	Comment noted and acknowledged in the third appraisal committee meeting. However, the committee continues to take the view that the network meta-analyses should be restricted to include only patients having ezetimibe at baseline.
11	Commentator	Novartis Pharmaceuticals UK Ltd	Paragraph 3.5 and 3.6 – Novartis acknowledge the difficulty in providing subgroup analyses by cardiovascular risk status i.e. separately for patients being treated for primary versus secondary prevention. In the company's submission, the proportions of primary and secondary prevention are only reported for CLEAR Serenity and not reported for other CLEAR trials. Evidently, there are clear limitations of the CLEAR trials due to unclear reporting of previous cardiovascular events, despite this being a clear modifier of treatment effect on risk reduction. Novartis is concerned with the company's approach in assuming the same treatment effect on cardiovascular prevention for bempedoic acid irrespective of CVD status, and distinct cost-effectiveness analyses should be carried out for these two populations. In particular, Novartis agree with the clinical expert that 'it is not reasonable to assume a similar treatment effect on cardiovascular prevention, because cardiovascular risk is higher in secondary prevention patients'.	Comment noted. The committee agreed that the company's subgroup analysis were not sufficient.
12	Commentator	Novartis Pharmaceuticals UK Ltd	Paragraph 3.9 – The company's model assumes that treatment effect at week 12 is sustained over the lifetime of the model, despite mean treatment duration in the trials being less than 12 weeks. However, as highlighted in page 14 of the SMC advice "the secondary outcome of LDL-C reduction to week 24 has indicated that the bempedoic acid treatment effect may diminish slightly". Therefore, Novartis agree with the comments in the ACD that long-term data for bempedoic acid at 52 and 78 weeks should be provided to support this assumption.	Comment noted. The committee discussed additional evidence provided by the company on the long-term treatment effect of bempedoic acid at the third

				appraisal committee meeting (see FAD section 3.9).
13	Public	(Web commenter 1)	**Has all of the relevant evidence been taken into account?** I am not sure the entire picture and unmet need is fully considered **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** I am sure there are price points that could be debated and I am not an expert in this area. I do spend a lot of time rejecting referrals who need escalation but aren't eligible for anything and it is difficult to take into account the time the GP and I and admin staff and patient waste as they are just a bit too good for a PCSK9i. **Are the recommendations sound and a suitable basis for guidance to the NHS?** 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 therefore significantly disadvantaging those with an LDL of 3.4 for example.	Comment noted. The company has agreed a commercial access agreement which means that the ICERs for bempedoic acid and bempedoic acid-ezetimibe can be considered cost effective. Therefore, the committee has recommended bempedoic acid with ezetimibe for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in adults for whom statins are contraindicated or not tolerated, and ezetimibe alone does not control LDL-C well enough (see FAD sections 1.1 and 3.18).
14	Public	(Web commenter 2)	**General Comment:** On behalf of the many patients who are still unable to achieve optimal cholesterol levels with the currently available/allowable medications I was disheartened to read the initial recommendations of TA10534. If appropriate reductions in cholesterol are not achieved on maximally tolerated doses of statins current initial recomendation within the NHS is to add/use Ezetimibe. If this does not achieve goal or is not tolerated then a patient should be considered for alirocumab or evolocumab if their LDLcholesterol results/clinical history meets the appropriate NICE TA. 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.	Comment noted. The company has agreed a commercial access agreement which means that the ICERs for bempedoic acid and bempedoic acid-ezetimibe can be considered cost effective. Therefore, the committee has recommended bempedoic acid with

			There are no trials comparing bempedoic acid plus ezetimibe versus alirocumab or evolocumab however one would not normally expect the combination efficacy to be as good. The comparison is however not clinically relevant in the currently expected use of bempedoic acid. If the patient meets NICE criteria for use of alirocumab or evolocumab after statin and/or ezetimibe then this treatment would be tried, not bempedoic acid. Hopefully the cost effectiveness estimates can be adapted to allow the appropriate use of this significant addition to cholesterol treatment options. This will allow more patients to benefit from the reductions in cardiovascular disease which are associated with lowering of cholesterol levels and help the UK to achieve the aspirations set in the NHS long term plan and associated initiatives.	ezetimibe for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in adults for whom statins are contraindicated or not tolerated, and ezetimibe alone does not control LDL-C well enough (see FAD sections 1.1 and 3.18).
15	Public	(Web commenter 3)	**Has all of the relevant evidence been taken into account?** The committee concluded that the cost-effective estimates for bempedoic acid with ezetimibe are not what NICE normally considers an acceptable use of NHS resources. However, considerations need to be made for patients with unmet needs such statin intolerant Type 2 Diabetics with uncontrolled lipid levels (6-8 mmol/l) that are at high or very high CVD risk . These patients have tried all statins and are unable to tolerate them, and ezetimibe and/or fibrates alone or in combination are not efficacious enough to lower their CVD risk. If we had bempodoic acid this would give us as clinicians an avenue to explore without moving to a PCSK9 inhibitor which is not only an expensive route, but may cause anxiety with patients with needle phobia. If tragically an event was to take place what would be the cost implications, let alone the impact to the patients lives and their families, versus giving them an alternative such as bempedoic acid. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Although the ICER, is coming slightly higher than the threshold (£23,824 per QALY), in my opinion the benefits of bempedoic acid in achieving unmet needs of a select group of patients for example my type 2 diabetics as mentioned above, will counteract the initial cost of the product and the long term benefits to the patient and to the NHS in terms of reduced CVD events, therefore a wise use of NHS resources. Penny wise pound foolish is not the way I would look at this. **Are the recommendations sound and a suitable basis for guidance to the NHS?** Bempedoic acid, I believe is an important treatment option for primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet, and NICE as a body have acknowledged that a new treatment option for managing cholesterol would be welcomed. Therefore I believe the recommendation is not sound, and should be reversed so that this becomes a treatment option for my patients who sadly fall under the unmet need category in lipid management and do not qualify for a PCSK9 inhibitor and therefore are sitting in limbo waiting for an event. This is not good medicine and we should have the option to actively treat and minimise the risk of a CVD event. In my practice alone we have 25 patients who would greatly benefit from this option!	Comment noted. The company has agreed a commercial access agreement which means that the ICERs for bempedoic acid and bempedoic acid-ezetimibe can be considered cost effective. Therefore, the committee has recommended bempedoic acid with ezetimibe for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in adults for whom statins are contraindicated or not tolerated, and ezetimibe alone does not control LDL-C well enough (see

				FAD sections 1.1 and 3.18).
16	Public	(Web commenter 4)	**General Comments:** Dear Committee, In response to your draft document for Bempedoic acid, I would like to support the comments raised by your expert in the document. As a clinician running a district General Hospital lipid service I would agree there are a number of high cardiovascular risk (secondary prevention or genetic cause of high cholesterol) patients who do not meet the NICETA 393/394 criteria for PCSK9i but are statin intolerant and either do not respond adequately or have side effects to Ezetimibe. Therefore the Bempedoic acid treatment would provide another valuable risk reduction option for these groups of patients. I would therefore reinforce the importance clinically of this option. In the last month from my lipid clinic list of around 400 patients I have already identified around 8 who think would benefit from this treatment of those I have been reviewing recently.	Comment noted. The company has agreed a commercial access agreement which means that the ICERs for bempedoic acid and bempedoic acid-ezetimibe can be considered cost effective. Therefore, the committee has recommended bempedoic acid with ezetimibe for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in adults for whom statins are contraindicated or not tolerated, and ezetimibe alone does not control LDL-C well enough (see FAD sections 1.1 and 3.18).
17	Public	(Web commenter 5)	**Has all of the relevant evidence been taken into account?** Yes it has **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The summaries need review in the context of filling a gap with lipid lowering therapy in high Cardiovascular risk patients whom they cannot achieve their LDL-C targets. **Are the recommendations sound and a suitable basis for guidance to the NHS?** Bempedoic acid should help to fill the treatment gap in lipid-lowering therapy for high risk patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia unable to reach LDL C goals after maximum tolerated doses of statins, with or without ezetimibe or in patients in eligible (PCSK9) inhibitors . Patients may not achieve their target lipids this could be either they are unable to tolerate an appropriate lipid therapy dose or they have very high levels of LDL-C that cannot be sufficiently lowered with existing	Comment noted. The company has agreed a commercial access agreement which means that the ICERs for bempedoic acid and bempedoic acid-ezetimibe can be considered cost effective. Therefore, the committee has recommended bempedoic acid with ezetimibe for treating

			therapies. Significant number of patients cannot meet their LDL-C targets despite current lipid lowering therapies. Failing to reach LDL-C targets leaves patients at increased cardiovascular risk. High CV risk patients who fail to achieve low LDL-C <2.0 mmol/L may not meet criteria for PCSK9 inhibitor therapy. Poor LDL-C control despite current oral lipid-lowering therapies underlines the need for more intensive cholesterol management.	primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in adults for whom statins are contraindicated or not tolerated, and ezetimibe alone does not control LDL-C well enough (see FAD sections 1.1 and 3.18).

11th January 2021

Dear [redacted],

Re: Comment on the National Institute for Health and Care Excellence (NICE) Appraisal Consultation Document (ACD): Bempedoic Acid▼ for Treating Primary Hypercholesterolaemia or Mixed Dyslipidaemia [ID1515]

Daiichi Sankyo welcomes the opportunity to comment on the draft preliminary recommendations set out in the Appraisal Consultation Document (ACD) developed by the Appraisal Committee regarding the use of Bempedoic Acid for Treating Primary Hypercholesterolaemia or Mixed Dyslipidaemia [ID1515].

Despite treatment with oral lipid-lowering therapies, up to 80% of patients with hypercholesterolaemia and mixed dyslipidaemia do not reach guideline-recommended low-density lipoprotein cholesterol (LDL-C) goals.[1-3] Bempedoic acid is a first-in-class (adenosine triphosphate (ATP)–citrate lyase inhibitor) oral, once-daily, lipid-lowering treatment option for patients with primary hypercholesterolaemia or mixed dyslipidaemia who are not reaching their therapeutic goals despite current oral lipid-lowering therapies.

The ACD provides a thorough overview of the clinical and economic information submitted for this technology. Daiichi Sankyo agrees with the clinical and patient expert in Section 3.1 that *"bempedoic acid is an inexpensive, oral preparation that is easy to use and suitable for people who cannot tolerate statins."* Furthermore, Daiichi Sankyo agrees with the Appraisal Committee in their conclusion that *"a new treatment option for managing cholesterol would be welcomed."*

Daiichi Sankyo has taken a responsible approach in focussing on the patient populations that will benefit most from bempedoic acid + ezetimibe, and in which the technology offers the most cost-effective use of NHS resources in accordance with the Appraisal Committee's comments. Daiichi Sankyo is seeking a positioning where statins are contraindicated or not tolerated, and ezetimibe alone does not appropriately control LDL-C (positions 2a and 2b). This position is supported by direct trial evidence from the Phase 3 Randomised Controlled Trial CLEAR Tranquillity. Recognising that the greater heterogeneity in the NMA was evident in the maximally tolerated network, focussing on the statin-intolerant population will substantially reduce the uncertainty in the evidence base for decision-making.

Daiichi Sankyo is seeking a recommendation from NICE for bempedoic acid and bempedoic acid + EZE FDC based on the clinical and economic evidence submitted for:

- bempedoic acid 180mg tablet (NILEMDO®▼) added to ezetimibe as separate tablets and,
- bempedoic acid/ezetimibe (180mg/10mg) FDC tablet (NUSTENDI® ▼)

Daiichi Sankyo agrees with the Appraisal Committee's comment that a number of uncertainties were addressed during Technical Engagement. In response to the ACD preliminary recommendations, Daiichi Sankyo is proposing to (i) focus on the most clinically and cost effective subgroups where there exists the highest unmet medical need, i.e., patients in whom statins are contraindicated or who cannot tolerate statin therapy and (ii) introduce a new net price which improves the cost-effectiveness of bempedoic acid + ezetimibe (EZE).

The response is set out in three parts: (i) this cover letter, (ii) the ACD response letter, (iii) appendix I & II containing revised cost-effectiveness results at the new proposed net price based on the Appraisal Committee's preferred modelling assumptions.

At the new proposed net price for bempedoic acid + EZE FDC, adopting the Appraisal Committee's preferred assumptions, the most plausible ICER for bempedoic acid + ezetimibe is £[redacted] gained in position 2a and £[redacted] lost in position 2b. Furthermore, deterministic sensitivity analysis (DSA) results remain below £[redacted] in position 2a and above £[redacted] lost in position 2b.

Daiichi Sankyo is committed to working collaboratively with NICE to support access for patients to bempedoic acid, a first-in-class, oral once-daily treatment option, which can support the National Health Service's (NHS) Long Term Plan objectives in improving management of hypercholesterolaemia in England and keeping patients out of the hospital.

Regards,

[redacted]

[redacted], **Daiichi Sankyo UK Ltd**

Cardiovascular Disease – The NHS Policy context

It is a national health policy priority in England to improve the prevention of cardiovascular disease (CVD) events over the course of the next decade. This is outlined within the NHS Long Term Plan, which outlines the ambition to prevent up to 150,000 CVD events over the next 10 years, and to improve the detection and treatment of high-risk conditions such as raised cholesterol. The Long Term Plan also aims to reduce avoidable outpatient appointments and to strengthen the role of primary care professionals to keep patients out of hospital.[4]

Cardiovascular disease is the underlying cause of 26% of all deaths in the United Kingdom, which includes heart attacks and strokes. This equates to approximately 160,000 deaths each year or an average of 435 people each day. At least, 42,000 of these deaths occur prematurely and, in many cases, can be prevented. CVD remains the leading cause of premature mortality in England and is one of the conditions most strongly associated with health inequalities, with people living in England's most deprived areas being almost four times more likely to die prematurely of CVD than those in the least deprived areas.[5]. LDL-C is an important medically treatable and modifiable risk factor.[6-9] Extensive evidence from epidemiologic, genetic, and clinical intervention studies has indisputably shown that LDL-C is causal in the development of atherosclerotic CVD and its major clinical sequelae.[10]

As NICE currently updates its methods, a consideration of the associated health inequalities with this disease area is important. Its case for change proposals rightly acknowledge that a technology that can reduce health inequalities associated with socioeconomic status or other factors may offer additional value. It is recognised that, based on public data, the uptake of PCSK9 inhibitors within the NHS in England is very low compared to estimated eligible patients[11,12]; this has been largely attributed to inefficient referral pathways to secondary care. Indeed, section 3.1 of the ACD details the patient and clinical expert views that uptake of alirocumab and evolocumab in clinical practice is between 65% and 72% lower than expected.

Daiichi Sankyo believes that the accessibility of bempedoic acid in primary and secondary care will provide health care professionals with an additional convenient, oral therapeutic option in lipid lowering management, allowing more patient care outside of the hospital setting and helping to reduce the health inequalities associated with CVD. In the context of the burden that the pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), has had on NHS resources, the delivery of this priority is more important than ever.

Oral, once-daily bempedoic acid

Daiichi Sankyo is seeking a recommendation from NICE for bempedoic acid for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia or mixed dyslipidaemia in adults in whom statin therapy is contraindicated or who cannot tolerate statin therapy, and serum total or LDL-C concentration is not appropriately controlled with ezetimibe alone.

This equates to positions 2a and 2b in the submission. These patient groups reflect the

populations in which patient and clinical experts have indicated that bempedoic acid has most clinical value and where there exists the highest unmet medical need.

- Population 2a: statins are contraindicated or not tolerated, and ezetimibe alone does not appropriately control LDL-C and alirocumab or evolocumab are not appropriate

  This group of patients currently have no NICE recommended treatment options and there exists a high medical unmet need.

- Population 2b: statins are contraindicated or not tolerated, and ezetimibe alone does not appropriately control LDL-C and alirocumab or evolocumab are appropriate

  Bempedoic acid can offer a convenient, once-daily oral treatment option, which some patients may prefer to injectable treatments such as alirocumab or evolocumab

In order to optimise clinical value and cost-effectiveness, the Company is no longer pursuing a recommendation in position 4b (people who do not have appropriately controlled LDL-C with the maximally tolerated statin dose in combination with ezetimibe, and for whom it is appropriate to take evolocumab or alirocumab).

Daiichi Sankyo is seeking a recommendation from NICE for bempedoic acid and bempedoic acid + EZE FDC based on the clinical and economic evidence submitted for:

- bempedoic acid 180mg tablet (NILEMDO®▼) added to ezetimibe as separate tablets and,
- bempedoic acid/ezetimibe (180mg/10mg) FDC tablet (NUSTENDI® ▼)

Bempedoic acid is a first-in-class, oral, once-daily, lipid-lowering treatment option for patients with primary hypercholesterolaemia or mixed dyslipidaemia who are not reaching their therapeutic goals despite current oral lipid-lowering therapies.[13,14]

- Upon activation in the liver, bempedoic acid acts as an adenosine triphosphate (ATP)–citrate lyase inhibitor that significantly reduces low-density lipoprotein cholesterol (LDL-C) levels by acting two steps upstream in the same cholesterol biosynthesis pathway as statins.[15]
- Unlike statins, bempedoic acid is not activated in skeletal muscle because the enzyme needed for its activation is not present in skeletal muscle cells. This feature therefore offers an alternative oral treatment for those patients who have experienced muscular adverse events with statins which may have affected treatment compliance and subsequent lipid control.[15,16]
- Bempedoic acid may also provide additional benefits by reducing inflammation markers, as evidenced by consistent reductions in the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP).[17-19]

- Bempedoic acid has been shown to be well tolerated among patients with hypercholesterolaemia who require additional lipid-lowering therapy, as studied within the CLEAR trial programme.[20]

Bempedoic acid offers the flexibility of a once-daily oral option (Nilemdo®) as an add on to existing lipid lowering treatment such as ezetimibe or as a single, once-daily fixed-dose combination (FDC) tablet with ezetimibe (Nustendi®). It can be taken with or without food at a time that is convenient for the patient.

Effect of bempedoic acid in LDL-C reduction is sustained beyond 12 weeks and has been demonstrated to be consistent across the majority of demographic and disease-related subgroups

Treatment with bempedoic acid, as demonstrated in four phase 3 randomised clinical trials in 3,623 enrolled adults with hypercholesterolaemia/mixed dyslipidaemia,[21] was associated with significantly decreased LDL-C levels compared with placebo (in statin-intolerant patients or those on maximally tolerated lipid-lowering therapies, including statins of any intensity).[21] The primary LDL-C lowering effect was further supported by significant reductions for other lipid parameters, including non–high-density lipoprotein cholesterol (non–HDL-C), total cholesterol (TC), and apoB ($P < 0.001$) after 12 weeks of treatment. The LDL-C reduction was maintained throughout the treatment period, and observed on a background of lipid-lowering therapies,[21] including statins, ezetimibe,[22] or other non-statin agents.[23]

In addition, a decrease in the LDL-C level associated with bempedoic acid versus placebo was consistent in all individual clinical trial pre-specified subgroup analyses (presented previously),[24-27] supporting the consistency of the treatment effect associated with BA across the majority of demographic and disease-related subgroups, including those on primary versus secondary prevention.

The Phase 3 CLEAR trial programme is consistent, in terms of background therapy at baseline (and in particular referring to the proportion of patients on ezetimibe), with other large scale clinical trials in hypercholesterolemia and real-world data,[9,28-32] showing that among patients with hypercholesterolaemia and LDL-C ≥ 70 mg/dL (1.8 mmol/L) ezetimibe usage is very low. A subgroup analysis of the CLEAR data published by Catapano et al. (2020)[22] demonstrated that treatment effect of bempedoic acid (in terms of relative % LDL-C reduction) is consistent in patients regardless of whether they have received prior ezetimibe, in both patients who were statin-intolerant or on maximally tolerated statin treatment. There was no significant treatment-by-subgroup interaction for background ezetimibe in either the ASCVD/HeFH on statins ($P = 0.146$) or the statin-intolerant pooled population ($P = 0.120$). Bempedoic acid inhibits cholesterol synthesis through ACL inhibition in the liver, unlike ezetimibe, which blocks reabsorption of cholesterol in the small intestine. Therefore, there is no plausible mechanistic reason to expect that the effect of bempedoic acid would vary by prior ezetimibe. Indeed the dedicated trial on the efficacy of FDC that combines bempedoic acid and ezetimibe in a single pill showed that, at week 12, the FDC lowered LDL-C (−36.2%) significantly more than placebo (1.8% (placebo-corrected difference −38.0%); $P < 0.001$), ezetimibe alone (−23.2%;

P < 0.001) or bempedoic acid alone (−17.2%; *P* < 0.001.[33] It has also been shown that bempedoic acid treatment significantly lowered LDL-C levels versus placebo in both patients with and without HeFH receiving maximally tolerated statins with or without other LLTs.[34]

Although LDL-C reduction at 12 weeks was presented as part of the primary trial endpoints, LDL-C reduction with bempedoic acid is sustained beyond 12 weeks as demonstrated in analyses presented for 24 and 52 weeks[20,24,25] through at least 78 weeks of treatment in the trials. All 1,462 patients with atherosclerotic cardiovascular disease (ASCVD) with hypercholesterolaemia and/or heterozygous-familial hypercholesterolaemia (HeFH) who completed 52 weeks of treatment in CLEAR Harmony including those of the CLEAR Harmony placebo arm, were enrolled in the open-label extension (OLE) study and received bempedoic acid for an additional 78 weeks and then underwent a 4-week off treatment follow-up period.[35] Sustained LDL-C lowering on top of maximally tolerated statins was observed through 78 weeks of bempedoic acid treatment, which was comparable between the former bempedoic acid group and former placebo group, and demonstrated reversibility after patients who completed the follow-up period were off the drug for 4 weeks.[35] bempedoic acid resulted in a reduction in non–HDL-C, apoB, TC, and hsCRP levels from baseline. These improvements were sustained through 78 weeks of bempedoic acid treatment.[35]. As demonstrated in clinical trials on the efficacy of bempedoic acid in LDL-C lowering and given the mechanism of action of bempedoic acid as presented in pharmacodynamic and pharmacokinetic studies in the EMA regulatory file and described in the EPAR report, there is no plausible reason for a waning of effect as raised in a concern in the ACD. The effect of bempedoic acid in decreasing LDL-C levels remains consistent as shown in all individual clinical trial pre-specified subgroup analyses across the majority of demographic and disease-related subgroups.[24-27] Any apparent fluctuations in LDL-C reduction over time (which are non-significant and not clinically meaningful in absolute LDL levels) may reflect provision in the trial protocol for adjustment of background treatment for some of the patients beyond the 12-week endpoint as well as reflecting the mean LDL-C reduction from the totality of patients (ITT population) including those who discontinued or paused treatment.

Cardiovascular risk of patients from the CLEAR trials has been collected and data have been presented

The Phase 3 bempedoic acid program evaluated over 3,600 unique patients including over 3,000 high-risk patients with LDL-C ≥ 70 mg/dL (1.8 mmol/L) who had ASCVD and/or HeFH, a high prevalence of other CVD risk factors, and were receiving maximally tolerated statin therapy. An additional 614 patients had hypercholesterolaemia with a history of statin intolerance and a broader range of risk factors for cardiovascular disease. Detailed information were collected to describe CV risk and results were stratified by CV risk. However, it was not possible to calculate QRISK3 scores from the data collected as these multinational trials did not collect all of the necessary variables.

Regarding the concern on the lack of CV outcomes data for bempedoic acid and the association of LDL-C reduction with CV risk reduction

A global, randomised, double-blind, placebo-controlled study (ClinicalTrials.gov Identifier: NCT02993406) is fully recruited and ongoing[36] to assess the effect of bempedoic acid in CV outcomes in patients with statin intolerance. The study randomized 14,014 patients to treatment with bempedoic acid 180 mg daily or matching placebo on a background of guideline-directed medical therapy. The primary outcome is a composite of the time to first CV death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization. The trial is an events-driven trial with a projected median treatment exposure of 42 months and is expected to report in [redacted].

The current pivotal LDL-C reduction trials were not designed and powered to assess CV outcomes and thus such data cannot be provided currently as raised by the Appraisal Committee in the ACD. However, as noted by the EAS/ESC consensus panel,[10] LDL-C has been unequivocally recognised as the principal causal factor in the development of ASCVD and its major clinical sequelae. Meta-analyses of over 200 prospective cohort studies, Mendelian randomisation studies, and randomised trials including more than 2 million participants with over 20 million person-years of follow-up and over 150,000 cardiovascular events demonstrate a remarkably consistent dose-dependent log-linear association between the absolute magnitude of exposure of the vasculature to LDL-C and the risk of ASCVD; and this effect appears to increase with increasing duration of exposure to LDL-C.[37-39] The EAS/ESC consensus panel reinforces that the naturally randomised genetic studies and the randomised intervention trials consistently demonstrate that any mechanism of lowering plasma LDL particle concentration should reduce the risk of ASCVD events proportional to the absolute reduction in LDL-C and the cumulative duration of exposure to lower LDL-C, provided that the achieved reduction in LDL-C is concordant with the reduction in LDL particle number and that there are no competing deleterious off-target effects.[37] In addition, Mendelian randomisation studies showed that genetic variants that mimic the effect of ATP citrate lyase inhibitors (such as bempedoic acid) 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.[40] To date, all cholesterol lipid-lowering drug approvals in the United States and European Union have been initially based on LDL-C lowering without confirmed CV outcomes benefits. Initial approvals of PCSK9is, based on an LDL-C lowering mechanism through the LDL receptor and validation by human genetics, provide the most recent evidence of the continued acceptance of LDL-C lowering as a validated surrogate.[41-44]

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Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

Consultation on the appraisal consultation document – deadline for comments 5pm on Monday 4 January **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Cardiovascular Society
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

Consultation on the appraisal consultation document – deadline for comments 5pm on Monday 4 January **email:** NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Has all relevant information been taken into account? No – All relevant evidence has not been taken into account. In particular the current guidance is out of step with routine clinical practice and international guidelines. In this regard the NICE 2014 lipid guidance are behind other major guidelines in Europe which recommend LDl-C goals of below < 1.4 mmol/L (Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). European heart journal 2020; 41:111-88.). They do not take into account the fact that there is unequivocal evidence that cardiovascular benefits are identical irrespective of how LDL-C is lowered. This benefit relates to absolute reductions in LDL-C not percentage reductions which has implications for cost effectiveness assumptions. (Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. European heart journal 2017;38:2459-72. And Ference BA, Cannon CP, Landmesser U, Lüscher TF, Catapano AL, Ray KK. Reduction of low density lipoprotein-cholesterol and cardiovascular events with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and statins: an analysis of FOURIER, SPIRE, and the Cholesterol Treatment Trialists Collaboration. European heart journal 2018;39:2540-5.) Moreover the guidance does not recognise that wide distribution of event rates and in high risk patients, where even modest alsolute reductions in LDL-C can provide substantial absolute benefits (Annemans L, Packard CJ, Briggs A, Ray KK. 'Highest risk–highest benefit'strategy: a pragmatic, cost-effective approach to targeting use of PCSK9 inhibitor therapies. European Heart Journal 2018;39:2546-50)
2	Are the summaries of cost effectiveness reasonable . • Not really- The reason they are not reasonable is that ezetimibe is being used as a comparator and not as standard of care. The comparator should only be monoclonal antibodies to PCSK9. However, the committee need to note that the threshold for patients to get access to PCSK9 is > 3.5mmol/L for very high risk CVD, > 4mmol/L for high risk CVD patients. Therefore, there are a body of patients who will not have access to PCSK9 inhibitors. Whilst the current cost effectiveness statements make sweeping statements like the fact that patients who are statin intolerant this is an over generalisation. For instance if a patient is statin intolerant and the LDL-C is for instance 3.0 mmol/L, the addition of bempedoic acid reduces LDL-C by 25%. If the patient were on high intensity statins and the LDL-C were 3.0mmol/L bempedoic acid would reduce LDL-C by 18%. The absolute reductions which drive benefit are statistically almost identical. This is not something that is considered in the current document. Therefore, for both statin intolerant and statin tolerant patients, the guidelines should identify LDL-C cutoffs on a background of maximally tolerated statins and ezetimibe for instance 2.5-3.5 mmol/L where the estimated annual risk of a cardiovascular event is 2% per year or 10 year risk is 20%.
3	Are the recommendations sound and a suitable basis for guidance to the NHS. • • No – This is because they leave a large group of patients with an inadequately controlled LDL-C level, thus leaving them at higher than acceptable residual risk of CV events. The current evidence assumes that all patients with CVD are essentially the same which is clearly not the case. Contemporary data in the UK (using CPRD and ONS linked data) shows that observed 10-year event risks for males and females were 29.1% (95% confidence interval (CI) 28.8-29.4%) and 26.6% (26.2-27.0%), respectively. The average non HDL-C using in this population is 3.4mmol/L meaning the average LDL-C is around 2.6-2.8mmol/L. Moreover, approximately one third of CVD patients have 10 year risk > 30% despite usual clinical practice in the UK. See below. Fig 1

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Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

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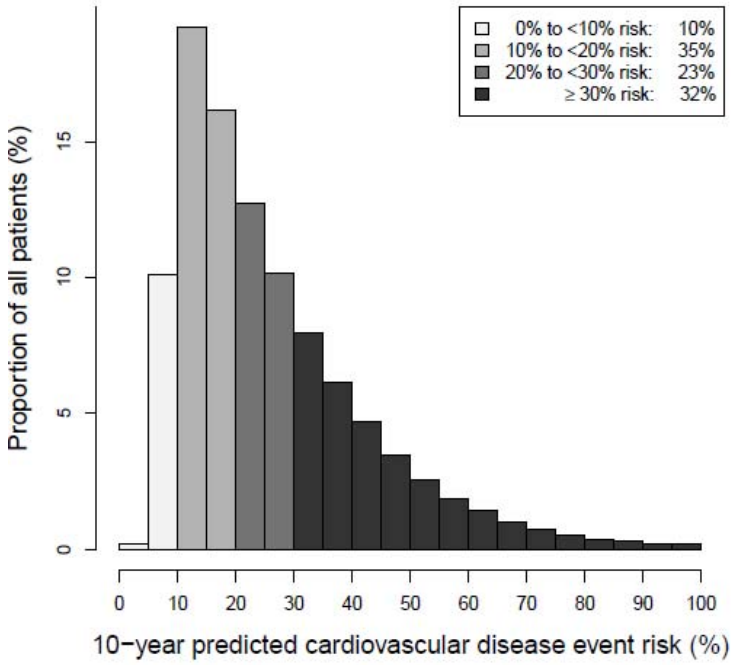


Table 1: ASCVD cohort baseline characteristics using UK data (n=244,578)

Risk factor	Median / n	IQR / %	Missing: n (%)
Age	67.3	59.2 - 74.0	0
Sex (Male)	151,888	62.1%	0
Date of cohort entry	01/01/2004	08/06/2000 – 21/05/2009	0
Vascular disease*			
Cerebrovascular Disease	73,520	30.1%	
Coronary Heart Disease	154,079	63.0%	
Peripheral Vascular Disease	32,459	13.3%	
Abdominal Aortic Aneurysm	7,048	2.9%	0
Years since first vascular event			
<1 yr before enrollment	150,557	61.6%	
1-2 yrs before enrollment	10,098	4.1%	
>2 yrs before enrollment	83,923	34.3%	0
Current smoking (Yes)	48,083	19.7%	24,449 (10.0%)
Diabetes mellitus	38,717	15.8%	0
Systolic blood pressure (mmHg)	140	126 - 150	12,605 (5.2%)
Total cholesterol (mmol/l)	4.7	4.0 - 5.6	28,610 (11.7%)
HDL cholesterol (mmol/l)	1.3	1.1 – 1.6	49,142 (20.1%)
hsCRP (mg/l)	N/A	N/A	244,578 (100.0%)
eGFR (ml/min/1.73m)	66.1	55.5 – 77.8	16,334 (6.7%)
BMI (kg/m2)	27.4	24.5 – 30.8	43,409 (17.7%)

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

Consultation on the appraisal consultation document – deadline for comments 5pm on Monday 4 January **email:** NICE DOCS

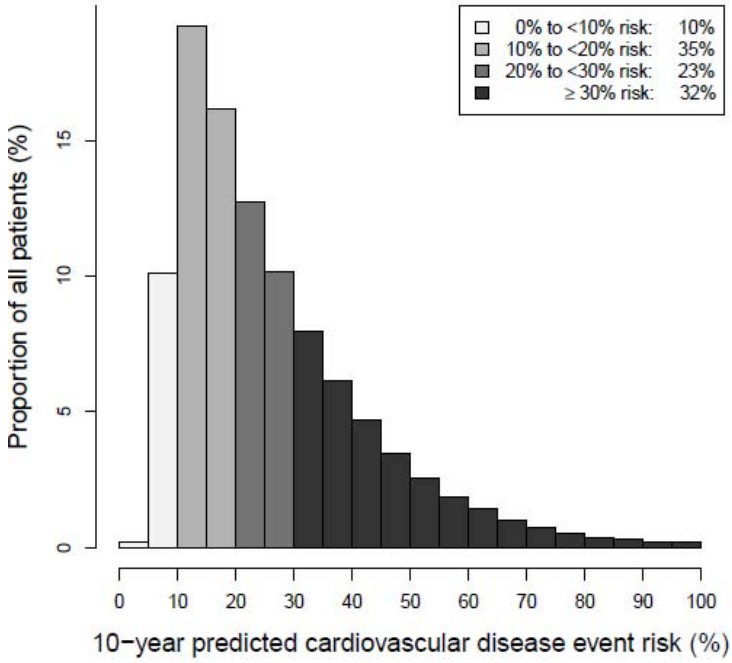
	Medication prescribed in the 6-months prior to cohort entry*			
	Lipid-modifying therapy	148,414	60.7%	
	Antihypertensive	187,052	76.5%	
	Antiplatelet	168,588	68.9%	
	Anticoagulant	18,690	7.6%	0
	Ethnicity			
	Asian	5,589	2.3%	
	Black	1,985	0.8%	
	Mixed	557	0.2%	
	White	220,850	90.3%	
	Other	2,215	0.9%	13,382 (5.5%)
	* Individuals can have more than one			
	HDL: high density lipoprotein; hsCRP: high sensitivity C-reactive protein; eGFR: estimated glomerular filtration rate; BMI: body mass index; IQR: interquartile range			
4	Addendum to above comments The relation to the above request for clarification the BCS makes the following points under the headings below. 1. Current care pathway and use of ezetimibe and PCSK9 inhibitors 2. Current event rates, risk distribution in ASCVD patients in the UK and level of lipid control 3. Determinants of absolute benefit from LDL-C lowering and hence potential to impact cost-effectiveness discussion. **Section 1** Ezetimibe is generic. In the past when this was used as a comparator for PCSK9 MAbs an ezetimibe comparison was appropriate and the threshold for Mabs for a single CV event >4mmol/L or >3.5mmol/L per litre and >5mmol/L for FH primary prevention were appropriate. As ezetimibe is generic and as there is no lower threshold for LDL-C for benefit it makes no sense to NOT have statins and ezetimibe as standard of care. However, because of the lack of update to NICE lipid guidance since 2014 and indeed for ACS patients these same guidance also refer to the 2009 ACS guidance. Therefore, UK lipid modification guidance is woefully out of date behind the rest of Europe and other countries where LDL goals are risk based and goals of < 1.4 mmmol/L are recommended (Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). European heart journal 2020;41:111-88). Current use of ezetimibe in the UK is < 10% and more like 7% from recent European wide registry data (Ray KK, Molemans B, Schoonen WM, et al. EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study. European Journal of Preventive Cardiology 2020). The comparison of bempedoic acid with PCSK9 MAbs is a complex one. Firstly, the majority of patients eligible for MAbs don't get them as most patients have LDL-C levels which are deemed not high enough, resulting in the Academic health sciences network rapid scramble to find patients. Even if all eligible patients were found eligible for MAbs there are a large group of patients with LDL-C levels for instance even with optimization of statins and ezetimibe with LDL-C levels between for instance 2-3.5 or 2-4mmol/L (Ray KK, Molemans B, Schoonen WM, et al. EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study. European Journal of Preventive Cardiology 2020). These people (see point 2) with sufficient comorbidities could have high residual risk which drives events which could in part be mitigated by LDL-C lowering **Section 2** Using linkage data from UK GPs and ONS/HES to create a retrospective cohort we can see that in approximately 250k individuals with established cardiovascular disease more than 6 months out from			

a diagnosis the average on treatment non-HDL is 3.4 mmol/L approximating to an average LDL-C of around 2.6 mmol/L (characteristics shown in Table 1).

There were 244,578 patients from 393 practices included in the primary cohort, with a median follow-up of 5.25 years (interquartile range (IQR) 2.15-9.63; 23.3% followed-up for ≥10 years), during which 45,327 cardiovascular events were observed. Observed 10-year event risks for males and females were 29.1% (95% confidence interval (CI) 28.8-29.4%) and 26.6% (26.2-27.0%), respectively.

There were 136,445 patients from 389 practices in a second cohort with a diagnosis of ASCVD in the preceding 6 months, with a median follow-up of 3.74 years (IQR 1.10-7.76; 14.4% followed-up for ≥10 years). During follow-up, 28,115 outcome events occurred and observed 10-year event risks for males and females were 29.6% (95% CI 29.2-30.1%) and 27.9% (27.4-28.4%), respectively. Among the secondary cohort, 14,865 patients (10.9%) had events within 6-months of diagnosis.

The 10 year risk of CVD among those with ASCVD is not homogeneous and varies widely and depends upon multiple variables (Fig 1)
Fig 1



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Other	2,215	0.9%	13,382 (5.5%)

* Individuals can have more than one

HDL: high density lipoprotein; hsCRP: high sensitivity C-reactive protein; eGFR: estimated glomerular filtration rate; BMI: body mass index; IQR: interquartile range

Section 3

We have overwhelming evidence that cardiovascular benefits of LDL-C lowering and independent of the methods by which it achieved. Trials (Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. European heart journal 2017;38:2459-72. And Ference BA, Cannon CP, Landmesser U, Lüscher TF, Catapano AL, Ray KK. Reduction of low density lipoprotein-cholesterol and cardiovascular events with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and statins: an analysis of FOURIER, SPIRE, and the Cholesterol Treatment Trialists Collaboration. European heart journal 2018;39:2540-5.) comparing annualised relative benefits per 1mmol/L lowering of PCSK9 MAbs versus statins or ezetimibe versus statins show that the relative benefits standardised per unit change in LDL-C and duration of exposure are indistinguishable. Although we do not have outcomes data for bempedoic acid in this regard, using mendellian randomization data and the genetic proxy for bempedoic acid (ACLY), would produce the same cardiovascular benefit per unit lowering of LDL-C through HMGCoA (statin target), NCP1L1 (ezetimibe), PCSK9 (Mabs) (Ference, B.A., Ray, K.K., Catapano, A.L., Ference, T.B., Burgess, S., Neff, D.R., Oliver-Williams, C., Wood, A.M., Butterworth, A.S., Di Angelantonio, E. and Danesh, J., 2019. Mendelian randomization study of ACLY and cardiovascular disease. *New England Journal of Medicine*, *380*(11), pp.1033-

	1042). Hence what determines likely benefit with bempedoic acid is not percentage (%) reduction in LDL-C but absolute reduction. A further nuance is that because bempedoic acid works through the same pathway as statins, the background dose of statins influences bempedoic acid efficacy. Hence saturation of the cholesterol synthesis pathway by targeting HMGCoA pathway with say 20-80 mg of atorvastatin will have a different effect on the efficacy of bempedoic acid if say 0mg or 10mg atorvastatin were used. Because the people receiving 20-80mg of atorvastatin would have a lower on treatment LDL-C, the absolute reduction in LDL-C from bempedoic acid and hence potential cost effectiveness less, than a patient who is on low or no statin who would have a much higher starting level of LDL-C. Here the greater efficacy and also higher LDL-C translate in greater absolute reductions in LDL-C and hence greater relative risk reduction. Finally, while the above demonstrates how even modest relative reductions in LDL-C could translat into meaningful relative benefits based on absolute LDL-C lowering for estimations of absolute benefits and hence cost effectiveness, it is essential to look at absolute risk (residual risk on treatment). This can be explained by looking at a 5 year trial of 10 vs 80mg atorvastatin (TNT – need reference) in stable coronary disease. The trial showed that an additional reduction of LDL-C of about 0.6 mmol/l (2.6 vs 2.0) reduced cardiovascular events by 22% in relative terms and about 2.2% in absolute terms over 5 years. Among the 10 mg atorvastatin patients, you can divide the patients into 4 groups using combinations of LDL-C above and below the median and residual risk above and below the median (TRS2P score). Risk is highest when residual risk and LDL-C are highest at baseline and lowest when both are low with intermediate risk when only one is high. When looking at benefit the additional benefit of atorvastatin 80mg is greatest when both residual risk and LDL-C are high (see below). In parallel with this line of thinking in a patient with an LDL-C of 3 mmol/L a 25% lowering of LDL-C with bempedoic acid would be expected to reduce LDL-C by 0.75mmmol/L offering about a 18% relative risk reduction. This could be applied to a range of scenarios of baseline risk ranging from 10%, 10 year risk to higher levels to more appropriately narrow down the treatment group where there is an unmet need but also value from this novel therapy. In summary rather than saying bempedoic acid per se is not cost effective for anyone, due consideration is needed for care pathways, current real life use of treatments, current real like LDL-C levels and real life residual risk and more accurate information of exactly how many people are getting Mabs. At present we have a large group of patients with high risk and unsatisfactory LDL-C sitting in “no-man’s land.” Determinants of risk in CAD patients on atorvastatin 10mg for different cardiovascular MACE outcomes

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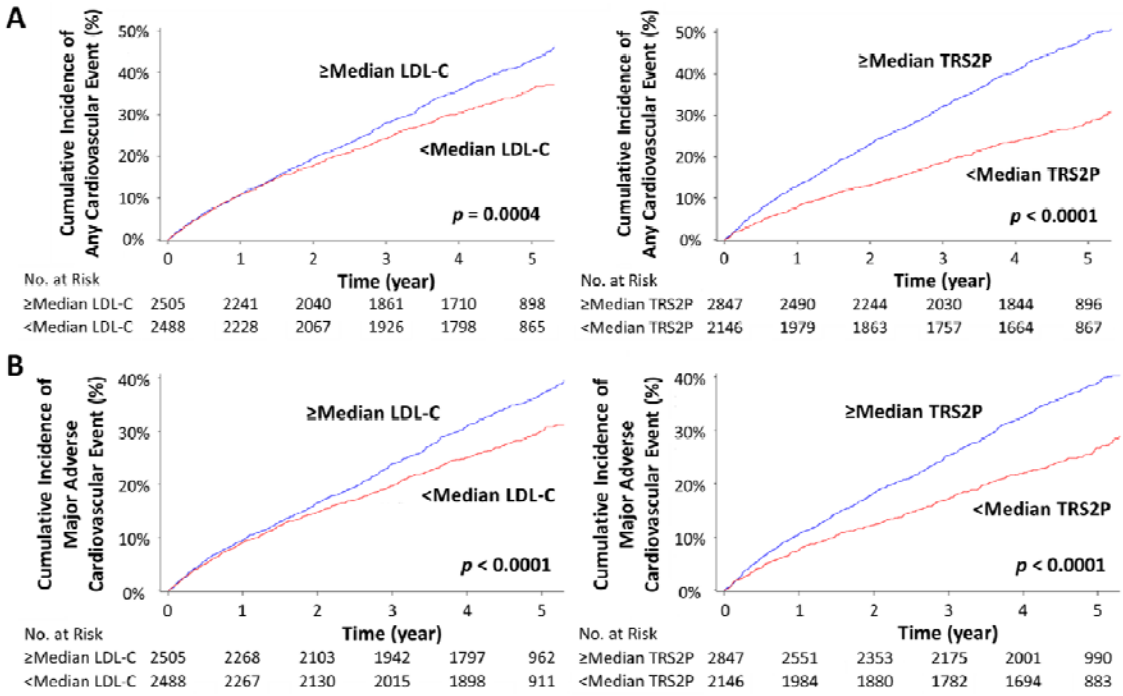
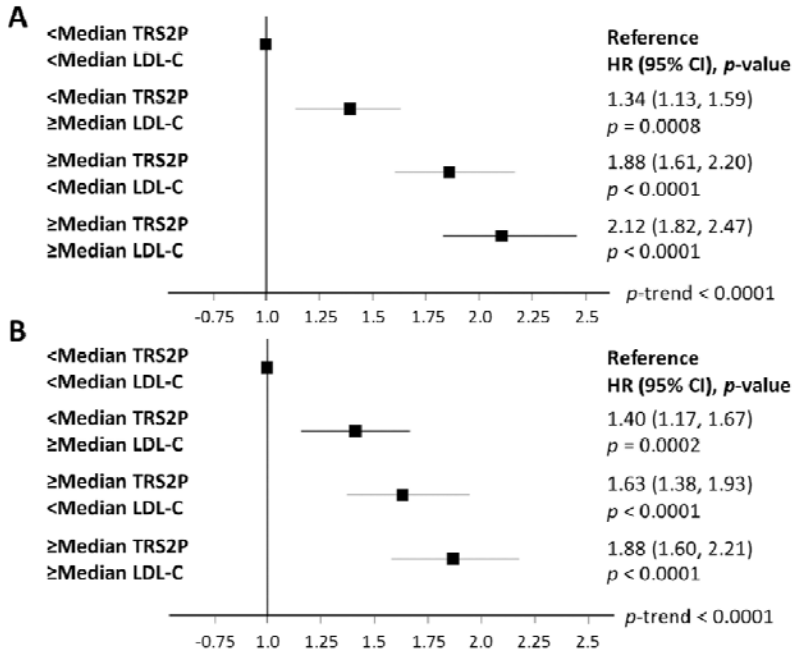


Incremental impact of residual risk and LDL-C alone or in combination



Incremental benefit of atorvastatin 80 on risk among patients stratified by residual risk and LDL-C alone or in combination

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	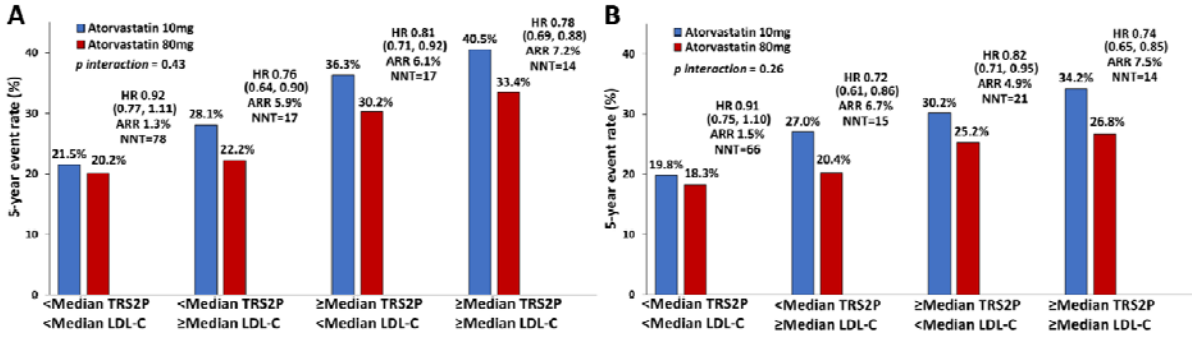

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Novartis Pharmaceuticals UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable
Name of commentator person completing form:	[redacted]
Comment number	**Comments**

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Paragraph 3.3 – Novartis is concerned about the request suggested in the ACD to restrict the network meta-analyses to only patients having ezetimibe at baseline. The rationale mentioned by the ERG is that patients would be expected to have previously had ezetimibe according to the treatment pathway. However, ezetimibe is infrequently used in UK clinical practice despite having been approved by NICE for several years. Low usage of ezetimibe applies to all subgroups of patients, including patients for whom statins are contraindicated or not tolerated. In the CPRD analysis conducted by Novartis recently, we observed the use of ezetimibe in secondary prevention without HeFH and primary prevention with HeFH to be 4.1% and 5.4% respectively. This argument is further substantiated by clinical input, Novartis internal market research and publication.[1] Since it is not the case that all patients for whom maximally tolerated statins do not adequately control LDL-C levels, will receive ezetimibe, evidence from patients who have not previously received ezetimibe should still be considered generalisable to clinical practice. Furthermore, it has been observed that background ezetimibe is not a treatment-effect modifier. For example in the ODYSSEY Long term trial, results in percentage change in LDL-C for alircocumab vs. placebo was -53.6% and -61.3% for patients on ezetimibe and without ezetimibe, respectively.[2] Therefore it is appropriate to consider aggregate data on clinical efficacy, from both patients who have, and have not, previously received ezetimibe. 1. Steen DL, Khan I, Ansell D, Sanchez RJ, Ray KK. Retrospective examination of lipid-lowering treatment patterns in a real-world high-risk cohort in the UK in 2014: comparison with the National Institute for Health and Care Excellence (NICE) 2014 lipid modification guidelines. BMJ Open. 2017;7(2):e013255. 2. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. New England journal of medicine. 2015;372(16):1489-99.
2	Paragraph 3.5 and 3.6 – Novartis acknowledge the difficulty in providing subgroup analyses by cardiovascular risk status i.e. separately for patients being treated for primary versus secondary prevention. In the company's submission, the proportions of primary and secondary prevention are only reported for CLEAR Serenity and not reported for other CLEAR trials. Evidently, there are clear limitations of the CLEAR trials due to unclear reporting of previous cardiovascular events, despite this being a clear modifier of treatment effect on risk reduction. Novartis is concerned with the company's approach in assuming the same treatment effect on cardiovascular prevention for bempedoic acid irrespective of CVD status, and distinct cost-effectiveness analyses should be carried out for these two populations. In particular, Novartis agree with the clinical expert that 'it is not reasonable to assume a similar treatment effect on cardiovascular prevention, because cardiovascular risk is higher in secondary prevention patients'.
3	Paragraph 3.9 – The company's model assumes that treatment effect at week 12 is sustained over the lifetime of the model, despite mean treatment duration in the trials being less than 12 weeks. However, as highlighted in page 14 of the SMC advice "the secondary outcome of LDL-C reduction to week 24 has indicated that the bempedoic acid treatment effect may diminish slightly". Therefore, Novartis agree with the comments in the ACD that long-term data for bempedoic acid at 52 and 78 weeks should be provided to support this assumption.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Association of British Clinical Diabetologists
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Name of commentator person completing form:	[redacted]

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I am satisfied that all the relevant information has been taken into account
2	The summaries of clinical and cost effectiveness are reasonable interpretation of the evidence, taking into account the confidential nature of discounts Alirocumab and Evolocumab which cannot be disclosed
3	The current recommendation is sound and a suitable basis for guidance to the NHS
4	There are no other aspects of the recommendation that require further consideration to avoid discrimination as far as I am aware
5	
6	

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ERG review of the company's response to ACM2

February 2021

1. Introduction

The ERG notes that the company, Daiichi Sankyo, is now only seeking a recommendation from NICE for bempedoic acid (BA) and BA + ezetimibe (EZE) fixed dose combination (FDC) in the statin intolerant population (position 2) rather than also in patients on maximally tolerated statin dose (position 4). The ERG considers the only new clinical evidence on the effectiveness of BA presented in the company's response to the ACD to be results from the CLEAR Harmony open label extension (OLE) study, which was a study of BA that relates to position 4. 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. The ERG, therefore, provides a summary of the CLEAR Harmony OLE study results in Section 3. The company also provided revised cost-effectiveness analyses and these are discussed further in Section 2.

2. Company's revised cost-effectiveness analyses

In response to the ACD, the company presented updated base case analyses for positions 2a (when statins are contraindicated or not tolerated and EZE does not appropriately control LDL-C: ALI and EVO are not appropriate) and 2b (when statins are contraindicated or not tolerated and EZE does not appropriately control LDL-C: ALI and EVO are appropriate).

One change that has been made to the company's base case analyses includes the network meta-analysis (NMA) suggested by the ERG. This analysis reflects the proposed positioning of BA in the treatment pathway and, therefore, only includes patients receiving EZE at baseline. This analysis was referred to as "ERG SI NMA V2" in the ERG's previous response documents. As a result of this change, the company's preferred assumptions generally align with the ERG's preferred assumptions. Additional areas of uncertainty that still warrant further exploration are discussed in the next section.

Furthermore,

[redacted]

[redacted] The company's revised cost-effectiveness results including these changes are given in Table 2 to Table 4.[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		

Table 2. Company's revised base case, position 2a, comparison with EZE

Results per patient	FDC	EZE*	Incremental value
Deterministic			
Total costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (cost per QALY)	-	-	[redacted]
Probabilistic (10,000 simulations)^			
ICER (cost per QALY)	-	-	[redacted]

Abbreviations: EZE, ezetimibe; FDC, bempedoic acid in a fixed dose combination with ezetimibe; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years
*No further treatment/placebo with background EZE
^Total costs and QALYs not reported

Table 3. Company's revised base case, position 2b, comparison with ALI+EZE

Results per patient	FDC	ALI + EZE	Incremental value
Deterministic			
Total costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (cost per QALY)	-	-	[redacted]
NMB at £20,000 per QALY	-	-	[redacted]
NMB at £30,000 per QALY	-	-	[redacted]
Probabilistic (10,000 simulations)^			

ICER (cost per QALY)	-	-	[redacted]

Abbreviations: Ali, alirocumab; EZE, ezetimibe; FDC, bempedoic acid in a fixed dose combination with ezetimibe; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years

[redacted]

^Total costs and QALYs not reported

Table 4. Company's revised base case, position 2b, comparison with EVO+EZE

Results per patient	FDC	EVO + EZE	Incremental value
Total costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (cost per QALY)	-	-	[redacted]
NMB at £20,000 per QALY	-	-	[redacted]
NMB at £30,000 per QALY	-	-	[redacted]

Abbreviations: EVO, evolocumab; EZE, ezetimibe; FDC, bempedoic acid in a fixed dose combination with ezetimibe; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years

[redacted]

The company also conducted one-way sensitivity analyses in positions 2a (vs EZE) and 2b (vs ALI+EZE). In position 2a, results were most sensitive to the mean baseline LDL-C level, average reduction in LDL-C (FDC), risk factor (all risks varied simultaneously) and annual cost of treatment (FDC) (Figure 1). In position 2b, results were most sensitive to the annual cost of treatment (ALI), average reduction in LDL-C (ALI+EZE), risk factor (all risks varied simultaneously) and average reduction in LDL-C (FDC) (Figure 2).

Figure 1. Deterministic Sensitivity Analysis: Appraisal Committee-Preferred Settings: Position 2a: BA + EZE FDC versus EZE

Figure 2. Deterministic Sensitivity Analysis: Appraisal Committee-Preferred Settings: Position 2b: Alirocumab + EZE versus BA + EZE FDC

3. ERG comment

One limitation of the company's revised model is that probabilistic analyses cannot be generated in position 2b for the comparison with EVO+EZE, based on the updated NMA. However, given that a class effect is assumed for ALI and EVO, and ALI and EVO have similar acquisition costs, the ERG does not consider this to be a major issue.

In the company' revised model, the ERG also found that the total cost for EVO+EZE in position 2b did not include the acquisition cost of EZE. Results including the acquisition cost of EZE are provided by the ERG in Table 5.

Table 5. Cost-effectiveness results in position 2b, comparison with EVO+EZE, including the cost of EZE

Results per patient	FDC	EVO + EZE	Incremental value
Total costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (cost per QALY)	-	-	[redacted]
NMB at £20,000 per QALY	-	-	[redacted]
NMB at £30,000 per QALY	-	-	[redacted]

Abbreviations: EVO, evolocumab; EZE, ezetimibe; FDC, bempedoic acid in a fixed dose combination with ezetimibe; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years [redacted]

The company noted in their response to the ACD that although the 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.[1,2,3,4] The ERG notes that the 78 week data referred to by the company relate to data from the CLEAR Harmony open-label extension (OLE) study (NCT03067441)[4] and that they have not been discussed previously. The ERG also notes that they relate to the maximally tolerated statin population rather than the statin intolerant population in which the company is now focusing its positioning of BA, and they also include patients who have not received prior EZE.

Nevertheless, the ERG considers the results from CLEAR Harmony OLE to be of relevance as they provide data on the longer-term efficacy of BA. The ERG notes, from the reference supplied in the company response to the ACD, that the publication for the OLE is a conference abstract and so there are limited data available to the ERG. The CLEAR Harmony OLE comprised up to a further 78 weeks of treatment with BA for patients who completed CLEAR Harmony and the primary objective of the study was to establish the long-term safety rather than efficacy of BA. CLEAR Harmony was a 52-week placebo controlled randomised controlled trial of BA and so in total patients completing the OLE could have approximately 2.5 years of BA treatment and follow-up. In contrast, the data used in the economic model for the statin intolerant population comprises just 12 weeks of follow-up.

A total of 1,462 patients enrolled in the CLEAR Harmony OLE (BA n=970; placebo n=492) and the ERG considers it important to highlight that nearly one third of patients in the OLE only started treatment with BA at the start of the OLE as they originate from the placebo arm of CLEAR Harmony. The ERG therefore 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.

The 78-week completion rate in the OLE was reasonably high (86.2%, n=1260) and the results from the OLE at 12- and 78-weeks of follow-up (from start of OLE) show a mean LDL-C reduction from baseline in CLEAR Harmony of –14.9% and –14.4%, respectively. In comparison, the results from CLEAR Harmony for % LDL-C reduction at 12-, 24- and 52-weeks were -16.5%, -14.9% and -12.6%, respectively. The ERG notes that the percentage (%) LDL-C reductions in the OLE differ slightly to those in CLEAR Harmony, with a greater % reduction in LDL-C at 12-weeks in CLEAR Harmony. The

ERG also notes that it is reported that the overall safety during the OLE was consistent with the safety findings from the other Phase 3 BA studies with no new safety issues identified.[4]

As explained in the main ERG report and discussed further in the ERG's response to technical engagement, data are mostly limited to 12-weeks in the company's NMAs, although treatment with BA is likely to be long-term depending on a patient response and tolerance. 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. The ERG would therefore prefer to see data from the latest timepoints with data (24 weeks for the SI NMA) given the possible treatment waning effect with BA and the long-term nature of expected treatment with BA in clinical practice. The ERG's clinical experts also affirmed that the response at week 12 would be expected to be larger than the sustained response in terms of reduction in LDL-C. However, the ERG also considers it important to highlight that its clinical experts also reported that if a sustained response is achieved from lipid-lowering therapies, further waning effects may be seen when patients relax their healthy habits on diet and exercise. Thus, treatment waning effects can be due other factors and not just lipid-lowering drug efficacy.

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 (Laufs *et al.* 2019)[5], the % reduction in LDL-C changes from -23.6% at week 12 to -21.2% at week 24 in the BA treatment arm. This equates to an absolute increase in LDL-C of 2.4% between week 12 and week 24, 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 [redacted] to [redacted]. For ALI+EZE, the treatment effect changes from [redacted] to [redacted], if a similar waning of treatment effect is assumed.

Table 6 shows results when the relative increase in LDL-C is applied to all treatment arms (from cycle 0). The results in Table 7 are more conservative and show the impact when the increase is only applied to the FDC (from cycle 0). As mentioned earlier, the ERG is unable to comment as to whether similar waning would be seen for the comparators thus these analyses are purely exploratory. Additionally, the waning effect calculated from CLEAR Serenity is not limited to patients with prior

EZE and based on the wording in Laufs *et al.* 2019 the ERG is unsure whether the data the ERG has used to calculate the relative change consistently includes the placebo-corrected change from baseline mentioned in the statistical methods of the paper.

Table 6. ERG scenario: 10% reduction in LDL-C benefit applied to all treatment arms

Results per patient	FDC	Comparator	Incremental value
Position 2a: FDC vs EZE^			
Total costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (cost per QALY)	-	-	[redacted]
Position 2b: FDC vs ALI+EZE			
Total costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (cost per QALY)	-	-	[redacted]
NMB at £20,000 per QALY	-	-	[redacted]
NMB at £30,000 per QALY	-	-	[redacted]

Abbreviations: Ali, alirocumab; EZE, ezetimibe; FDC, bempedoic acid in a fixed dose combination with ezetimibe; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years

[redacted]

^No reduction in LDL-C for EZE (no further treatment/placebo with background EZE) assumed in the base case

Table 7. ERG scenario: 10% reduction in LDL-C benefit applied to the FDC

Results per patient	FDC	Comparator	Incremental value
Position 2a: FDC vs EZE^			
Total costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (cost per QALY)	-	-	[redacted]
Position 2b: FDC vs ALI+EZE			
Total costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]

ICER (cost per QALY)	-	-	*******
NMB at £20,000 per QALY	-	-	*******
NMB at £30,000 per QALY	-	-	*******

Abbreviations: Ali, alirocumab; EZE, ezetimibe; FDC, bempedoic acid in a fixed dose combination with ezetimibe; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years

[redacted]

^No reduction in LDL-C for EZE (no further treatment/placebo with background EZE) assumed in the base case

One other area the ERG would like to explore further, is the baseline LDL-C level in position 2a. As explained in the ACD and main ERG report, 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. Following this, baseline LDL-C levels in people not eligible for ALI or EVO ([redacted]) were lower than baseline LDL-C levels in all patients ([redacted]). In the ACD, it is noted that the clinical experts agreed that the baseline LDL-C levels will differ across these subpopulations and that committee wanted to see results based on the appropriate mean baseline LDL-C levels for the appropriate subpopulations. The ERG has provided these results for position 2a in Table 8 and caveats this analysis with patient and clinical expert opinion in the ACD that uptake of ALI and EVO in clinical practice is between 65% and 72% lower than expected.

The ERG has not provided results where baseline LDL-C levels reflect the intended positioning for bempedoic acid (that is, patients who had already had EZE and according to ALI or EVO eligibility) because these results are not reliable for decision making. Further details can be found in the ERG's response to ACM1.

Table 8. ERG scenario: baseline LDL-C level in position 2a

Results per patient	FDC	EZE*	Incremental value
Total costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (cost per QALY)	-	-	[redacted]

Abbreviations: EZE, ezetimibe; FDC, bempedoic acid in a fixed dose combination with ezetimibe; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years
*No further treatment/placebo with background EZE

Other areas of uncertainty in the ACD include subgroup analyses by cardiovascular (CV) risk and heterozygous familial hypercholesterolaemia, efficacy data directly related to the appropriate subpopulations, the source of primary CV risks and CV event history, and the lack of long-term data on cardiovascular outcomes in the pivotal trials. However, the ERG notes that the available data on BA for these subgroups and outcomes are limited.

4. References

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2 Ray KK, Bays HE, Catapano AL, Lalwani ND, Bloedon LT, Sterling LR, et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. N Engl J Med. 2019 Mar;380(11):1022-32.

3 Goldberg AC. Efficacy and safety of bempedoic acid added to maximally tolerated statins in patients with hypercholesterolemia and high cardiovascular risk: the CLEAR Wisdom trial. Presented at the 68th Annual Scientific Session and Exposition of the American College of Cardiology; 16-18 March 2019. New Orleans, LA.

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